# Selective Electrocatalytic reduction mediated by Sm(II) : Application to nitroarenes, sulfoxides and phthalimides

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# Selective Electrocatalytic reduction mediated by Sm(II) : Application to nitroarenes, sulfoxides and phthalimides

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**Yu-Feng ZHANG**

Composition du Jury :

| | |
|---|---|
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| Mohamed MELLAH<br>Maitre de Conférences, Université Paris-Sud (ICMMO UMR 8182) | Directeur de thèse |

**Titre :** Réduction électrocatalytique sélective médiée par Sm（II）: application aux nitroarènes, aux sulfoxydes et aux phtalimides

**Mots clés :** divalents de samarium, réduction, électrocatalyse, nitroarènes, sulfoxydes, phtalimides

**Résumé :** Le $SmI_2$ en tant que réactif de transfert monoélectronique a été largement utilisé en chimie organique depuis les premiers travaux de Kagan. Cependant, la quantité stoechiométrique ou en excès de $SmI_2$ et d'additifs toxique tels que HMPA sont utilisés normalement pour améliorer la réactivité. de plus, du a la sensibilité à l'oxygène, le stockage de la solution de $SmI_2$ est difficile.
Récemment, nous avons développé une nouvelle méthode électrocatalytique basée sur la régénération électrochimique de $Sm^{2+}$. Par rapport à la réaction $SmI_2$ classique, notre processus s'est produit avec une quantité catalytique de Sm.
Premierement, pour la réduction de Nitroarenes, la reaction a sélectivement fourni les composés aromatiques azoïques et les anilines en fonction du solvent choisi. Notamment, c'est la première fois que la réaction $Sm^{2+}$ se produit dans le methanol dans le cas des anilines.
Deuxiement, dans le cas de la réduction des sulfoxydes par $SmI_2$, en general, l'HMPA était necessaire comme additif. Dans notre procédé électrocatalytique, les sulfoxydes ont été transformés en sulfures avec une chimiosélectivité élevée et des excellents rendements toujours à température ambiante sans besoin ni de HMPA ni d'atmosphère protectrice.
Enfin, les dérivés d'isoindolinone sont des séries de produits importants en chimie organique, la réduction des phtalimides est l'approche la plus pratique pour les obtenir. Avec les alcools, l'alcoxylation réductrice de phtalimides a eu lieu pour la premiere fois avec le $Sm^{2+}$ électrocatalytique dans nos conditions. Et si on ajoute d'autres sources de protons, ce procédé a fourni les ω-hydroxylactames et isoindolinones correspondants avec des rendements eleves.

**Title :** Selective Electrocatalytic reduction mediated by Sm(II) : Application to nitroarenes, sulfoxides and phthalimides

**Keywords :** divalent of samarium, reduction, eletrocatalyst, nitroarenes, sulfoxides, phthalimides

**Abstract :** The $SmI_2$ as a single electron transfer reagent has been widely used in organic chemistry since the pioneering works by Kagan. However, the stoichiometric or excess amount of $SmI_2$ and harmful additives such as HMPA are used normally to enhance the reactivity, moreover, due to the oxygen sensitive, the storage of $SmI_2$ solution is difficult.
Recently, we have developed a new electrocatalytic method based on the electrochemical regeneration of $Sm^{2+}$. Compared to the classic $SmI_2$ reaction, our process occurred with a catalytic amount of Sm. In the reduction of Nitroarenes, it selectively afforded the azo aromatic compounds and anilines depending on different solvents system. Notably, it's the first time that the $Sm^{2+}$ reaction occurred in the methanol.
Normally, the HMPA was the additive in the reduction of sulfoxides by $SmI_2$. Under our electrocatalytic process, the sulfoxides were converted into sulfides in high chemoselectivity and yield at room temperature without HMPA and protecting atmosphere.
The isoindolinone derivatives are series of important products in organic chemistry, the reduction of phthalimides is the most convenient approach to provide them. With alcohols, the unprecedented $Sm^{2+}$ electrocatalyzed reductive alkoxylation of phthalimides was established. Moreover, adding other proton sources, this process afforded the corresponding ω-hydroxylactams and isoindolinones.

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# Content

# Résumé

Le diiodure de samarium ($SmI_2$), décrit pour la première fois par H. B. Kagan en 1977, est connu comme étant un des agents réducteurs des plus utiles et des plus polyvalents en synthèse organique. Son importance et son application ont été démontrées par la publication de très nombreux articles, ce qui prouve le rôle prédominant de ce réactif en synthèse. Cependant, la majorité des réactions organiques médiées par le diiodure de samarium ($SmI_2$) en tant que réducteur, nécessitent toujours l'emploi d'une quantité sur-stœchiométrique de ce réactif. Cet inconvénient diminue fortement le potentiel d'applications synthétiques à plus grande échelle voir à l'échelle industrielle. Plusieurs groupes de recherche ont envisagé l'emploi de co-réducteurs pour rendre l'utilisation du $SmI_2$ catalytiques. Cependant, bien que les co-réducteurs proposés pour des applications catalytiques représentent des progrès significatifs, leur utilisation n'en est pas moins restée que marginale, probablement en raison de l'incompatibilité entre les co-réducteurs utilisés en large excès et les substrats couramment utilisés pour les réactions induites par $SmI_2$. Récemment, notre groupe a rapporté une nouvelle méthode pour générer le $SmI_2$ par dissolution électrochimique directe d'une anode en samarium métallique. Son application s'est révélée très efficace dans des procédures électrosynthétiques et électrocatalytiques pour la formation de liaisons carbone-carbone. Dans le cadre de cette thèse, les investigations sont orientées vers la réduction catalytique de groupes fonctionnels variés. En effet, sur la base des résultats antérieurs et les conditions électrocatalytiques établies, le sujet de ma thèse portait sur le potentiel d'application de cette nouvelle procédure catalytique pour la réduction chimiosélectives de différents groupes fonctionnels en chimie organique.

Ainsi à partir des nitrobenzènes, nous avons développé une alternative facile, efficace et sûre pour la synthèse d'une grande variété de dérivés d'azobenzène symétriques et dissymétriques. L'efficacité et la grande tolérance fonctionnelle de cette procédure fournissent un nouvel outil pour accéder à des azobenzènes variés. L'utilisation de l'électrochimie pour effectuer des réactions catalytiques dans des conditions douces utilisant $SmI_2$ comme réducteur, l'absence de métaux précieux, de bases fortes et de substances non dangereuses font de notre protocole une excellente alternative aux méthodes décrites. Nous avons examiné de près le mécanisme réactionnel en identifiant clairement différents intermédiaires dans le processus catalytique.

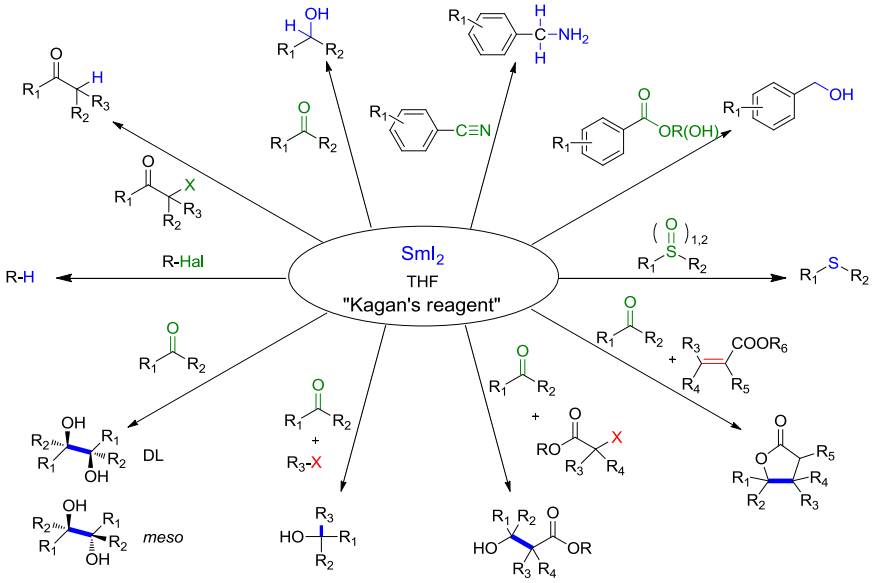
La réduction électrocatalysée de nitrobenzènes fonctionnalisés en anilines correspondantes a également été réalisée en changeant simplement de solvant. Ainsi, pour la première fois la réaction de réduction par le samarium divalent est réalisée dans le méthanol pur. Cette procédure de réduction catalytique a montré une chimiosélectivité élevée, une grande tolérance fonctionnelle et toutes les anilines et aminopyridines escomptées sont obtenus avec de très bons rendements isolés.

La réduction électrocatalytique des sulfoxydes a également été envisagée. Nous avons montré que la réduction dans ce cas pouvait avoir lieu soit dans le méthanol soit dans le THF. Néanmoins, le THF a été choisi pour réaliser cette transformation sur une plus large gamme de substrats. Enfin, la réduction chimiosélective électrocatalytique des phtalimides a été également testé pour la production de produits alcoxylés, de ω-Hydroxylactames et/ou d'isoindolinones. Nous avons mis en place pour la première fois une procédure de réduction électrocatalytique séléctive présentant une grande tolérance fonctionnelle et une totale chimiosélectivité. Grâce à l'électrochimie, cette approche évite avec succès les conditions usuelles de hautes températures et hautes pressions d'hydrogène. Les alcools primaires ou secondaires réagissent très efficacement avec les phtalimides, pour obtenir les isoindolinones 2-substituées correspondantes avec des rendements de bons à excellents. En outre, il n'y a aucune réduction du cycle aromatique, des liaisons insaturées, des groupements nitriles, esters, amides ou hydroxyles présentes sur la structure initialement.

# Chapter I. Introduction of $SmI_2$ chemistry

## I. 1. The use of $SmI_2$ in organic chemistry

$SmI_2$ was first reported in 1906, but for a long time, it was only researched in inorganic chemistry.[1] In 1977, Kagan and co-workers published the first article on preparation and application of $SmI_2$ (Kagan's reagent) in organic chemistry.[2] This reagent can be easily prepared at room temperature by simply mixing Sm powder and 1,2-diiodoethane under inert atmosphere. This process makes possible the use of $SmI_2$ in the laboratory. Over the years, $SmI_2$ has become one of the most important reducing agent in organic chemistry.[3] As a single electron transfer reagent, it was not only able to reduce a range of functional groups but also to perform numerous C-C bond formations (Scheme 1.1).




Scheme **1.1** The general application of $SmI_2$ in organic chemistry

[1] Matignon, C. A.; Caze, E. *Ann. Chim. Phys.* **1906,** *8,* 417-426.
[2] Namy, J.-L.; Girard, P.; Kagan, H. B. *Nouv. J. Chim.* **1977,** *1,* 5-7.
[3] For reviews, see: (a) Soderquist, J. A. *Aldrichimica Acta,* **1991,** *24,* 15-23. (b) Molander, G.A., *Chem. Rev.* **1992,** *92,* 29-68. (c) Molander, G. A. *Org. React.* **1994,** *46,* 211-367. (d) Molander, G.A.; Harris, C. R. *Chem. Rev.* **1996,** *96,* 307-338. (e) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998,** *54,* 3321-3354. (f) Krief, A.; Laval, A. M. *Chem. Rev.* **1999,** *99,* 745-778. (g) Kagan, H. B. *Tetrahedron* **2003,** *59,* 10351-10372. (h) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004,** *104,* 3371-3404. (i) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem., Int. Ed.* **2009,** *48,* 7140-7165. (j) Procter, D. J.; Flowers, R. A., II; Skrydstrup, T. *Organic Synthesis Using Samarium Diiodide: A Practical Guide;* RSC Publishing: Cambridge, U.K., 2010. (k) Szostak, M.; Spain, M.; Parmar, D.; Procter, D. J. *Chem. Commun.* **2012,** *48,* 330-346. (l) Szostak, M.; Spain, M.; Procter, D. J. *Chem. Soc. Rev.* **2013,** *42,* 9155-9183. (m) Szostak, M.; Fazakerley, N. J.; Parmar, D.; Procter, D. J. *Chem. Rev.* **2014,** *114,* 5959-6039.

## I. 2. Reduction of functional groups

Functional group transformations by reductants are one of the most fundamental conversion in organic synthesis. In 1980, Kagan's group introduced the application of $SmI_2$ in a variety of functional group transformations such as deoxygenation of epoxides and sulfoxides, reduction of conjugated double bonds, reduction of carbonyl derivatives and dehalogenation.[4] From then on, $SmI_2$ is widely used as a versatile reducing reagent and has captured the imagination of organic chemists and become one of the most important single electron transfer (SET) reagent for organic functional groups transformation (Table 1.1).

The dehalogenation[5] and β-elimination[6] by $SmI_2$ were performed in high temperature or HMPA (Table 1.1, entry **1**). Adding the alcohol or water as proton donor, the $SmI_2$ reduction of aldehydes and ketones affords the corresponding alcohols (Table 1.1, entry **2**),[7] also deoxygenation of acids[8] (Table 1.1, entry **3**) and amides[9] (Table 1.1, entry **4**) produce the corresponding alcohols and amines. Interestingly, the $SmI_2$ mediated reduction of aryl esters provided a deoxygenation protocol (Table 1.1, entry **5**),[10] but the lactones afforded the corresponding diols (Table 1.1, entry **6**).[11] As an important application, the reduction of α-heteroatom-substituted carbonyl compounds to the parent carbonyl compound is the most common chemoselective transformation mediated by $SmI_2$ (Table 1.1, entry **7-9**).[12,13,14]

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[4] Girard, P.; Namy, J.-L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980,** *102,* 2693-2698.

[5] (a) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987,** 1485-1486. (b) Kagan, H. B.; Namy, J.-L.; Girard, P. *Tetrahedron,* **1981,** *37,* 175-180. (c) Curran, D. P.; Fevig, T. L.; Jasperse, C. P.; Totleben, M. J. *Synlett.* **1992,** 943-961. (d) Hasegawa, E.; Curran, D. P. *Tetrahedron Lett.* **1993,** *34,* 1717-1720.

[6] (a) Concellón, J. M.; Rodríguez-Solla, H. *Chem. Soc. Rev.* **2004,** *33,* 599-609. (b) Concellón, J. M.; Bernad, P. L.; Pérez-Andrés, J. A. *Angew. Chem., Int. Ed.* **1999,** *38,* 2384-2386. (c) Concellón, J. M.; Bernad, P. L.; Bardales, E. *Org. Lett.* **2001,** *3,* 937-939.

[7] (a) Keck, G. E.; Wager, C. A.; Sell, T.; Wager, T. T. *J. Org. Chem.* **1999,** *64,* 2172-2173. (b) Keck, G. E.; Wager, C. A. *Org. Lett.* **2000,** *2,* 2307-2309. (c) Chopade, P. R.; Davis, T. A.; Prasad, E.; Flowers II, R. A. *Org. Lett.* **2004,** *6,* 2685-2688. (d) Davis, T. A.; Chopade, P. R.; Hilmersson, G.; Flowers II, R. A. *Org. Lett.* **2005,** *7,* 119-122. (e) Keck, G. E.; Truong, A. P. *Org. Lett.* **2002,** *4,* 3131-3134. (f) Keck, G. E.; Giles, R. L.; Cee, V. J.; Wager, C. A.; Yu, T.; Kraft, M. B. *J. Org. Chem.* **2008,** *73,* 9675-9691. (g) Huang, L.-L.; Xu, M.-H. Lin, G.-Q. *J. Am. Chem. Soc.* **2006,** *128,* 5624-5625.

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[9] Kamochi, Y.; Kudo, T. *Chem. Lett.* **1993,** 1495-1498.

[10] Lam, K.; Markó, I. E. *Org. Lett.* **2008,** *10,* 2773-2776.

[11] Duffy, L. A.; Matsubara, H.; Procter, D. J. *J. Am. Chem. Soc.* **2008,** *130,* 1136-1137.

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[13] (a) Kusuda, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1989,** *30,* 2945-2948. (b) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987,** *28,* 4437-4440.

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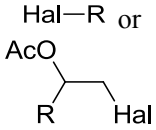
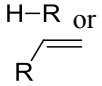
The reduction of nitrogen-containing compounds are very important transformation in organic chemistry. For the reduction of nitro[15] and cyano[16] groups, the $SmI_2$ presented high reactivity, furthermore, the cleavage of N-O[17] and N-N[18] bonds by $SmI_2$ have been a routine process. Moreover, the hydrogenation of electron-deficient alkenes by $SmI_2$ was also demonstrated with high functional group tolerance.[19] Kagan reported the reduction of sulfoxides and sulfones but long reaction times and an excess of $SmI_2$ was needed.[4] The addition of HMPA accelerated the reaction greatly.[20] However, the carbon-sulfur bond of alkyl or alkenyl phenyl sulfones was cleaved under the $SmI_2$-HMPA system.[21] In 2011, Procter's group demonstrated that the use of $SmI_2$-$Et_3N$-$H_2O$ system could directly reduce the acyclic esters[22] and amides[23] into the alcohols. The $SmI_2$-base-ROH system has exhibited the superiority and more extensive in the future.

**Table 1.1** The reduction of functional groups by $SmI_2$.

| entry | SM | Additive | product | Ref. |
|---|---|---|---|---|
| **1** |  | 1. None (long time and high temp.)<br>2. HMPA |  | 5, 6 |

[15] (a) Souppe, J.; Danon, L.; Namy, J. L.; Kagan, H. B. *J. Organomet. Chem.* **1983**, *250,* 227-236. (b) Kende, A. S.; Mendoza, J. S. *Tetrahedron Lett.* **1991,** *32,* 1699-1702. (c) Brady, E. D.; Clark, D. L.; Keogh, D. W.; Scott, B. L.; Watkin, J. G. *J. Am. Chem. Soc.* **2002,** *124,* 7007-7015.

[16] Szostak, M.; Sautier, B.; Spain, M.; Procter, D. J. *Org. Lett.* **2014,** *16,* 1092−1095.

[17] (a) Keck, G. E.; McHardy, S. F.; Wager, T. T. *Tetrahedron Lett.* **1995,** *36,* 7419-7422. (b) Zhang, Y.; Lin, R. *Synth. Commun.* **1987,** *17,* 329-332. (c) Natale, N. R. *Tetrahedron Lett.* **1982,** *23,* 5009-5012. (d) Bode, J. W.; Carreira, E. M. *Org. Lett.* **2001,** *3,* 1587-1590. (e) Fader, L. D.; Carreira, E. M. *Org. Lett.* **2004,** *6,* 2485-2488.

[18] (a) Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992,** *114,* 6266-6267. (b) Enders, D.; Funabiki, K. *Org. Lett.* **2001,** *3,* 1575-1577. (c) Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004,** *126,* 5686-5687. (d) Chowdari, N. S.; Barbas III, C. F. *Org. Lett.* **2005,** *7,* 867-870.

[19] (a) Inanaga, J.; Handa, Y.; Tabuchi, T.; Otsubo, K.; Yamaguchi, M.; Hanamoto, T. *Tetrahedron Lett.* **1991,** *32,* 6557-6558. (b) Cabrera, A.; Alper, H. *Tetrahedron Lett.* **1992,** *33,* 5007-5008. (c) Fujita, Y.; Fukuzumi, S.; Otera, J. *Tetrahedron Lett.* **1997,** *38,* 2121-2124. (d) Dahlen, A.; Hilmersson, G. *Tetrahedron Lett.* **2003,** *44,* 2661-2664. (e) Dahlen, A.; Hilmersson, G. *Chem. Eur. J.* **2003,** *9,* 1123-1128. (f) Keck, G. E.; McLaws, M. D. *Tetrahedron Lett.* **2005,** *46,* 4911-4914. (g) Davies, S. G.; Rodríguez-Solla, H.; Tamayo, J. A.; Garner, C. Smith, A. D. *Chem. Commun.* **2004,** 2502-2503. (h) Davies, S. G.; Rodríguez-Solla, H.; Tamayo, J. A.; Cowley, A. R.; Concellón, C.; Garner, A. C.; Parkes, A. L.; Smith, A. D. *Org. Biomol. Chem.* **2005,** *3,* 1435-1447.

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[21] (a) Kunzer, H.; Stahnke, M.; Sauer, G.; Wiechert, R. *Tetrahedron Lett.* **1991,** *32,* 1949-1952. (b) Eckelbarger, J. D.; Wilmot, J. T.; Gin, D. Y. *J. Am. Chem. Soc.* **2006,** *128,* 10370-10371.

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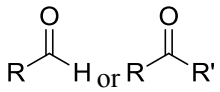
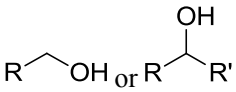
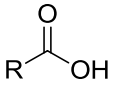
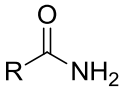
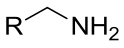
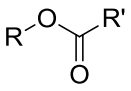
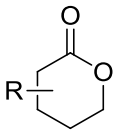
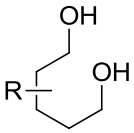
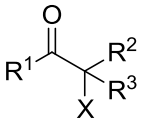
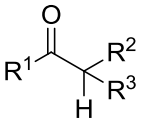
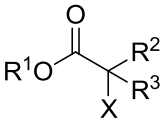
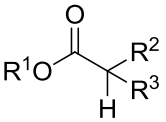
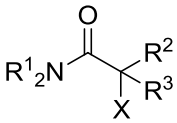
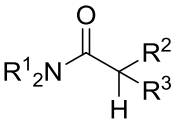
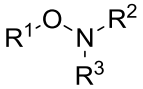
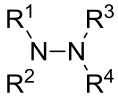
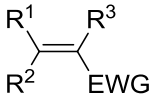
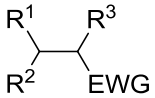
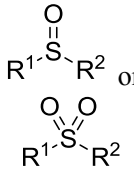
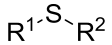
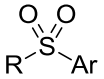
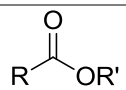
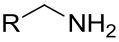
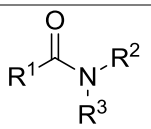
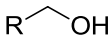
[23] Szostak, M.; Spain, M.; Eberhart, A. J.; Procter, D. J. *J. Am. Chem. Soc.* **2014,** *136,* 2268-2271.

| | | | | |
|---|---|---|---|---|
| **2** |  | ROH or $H_2O$ |  | 7 |
| **3** |  | 1. NaOH, $H_2O$<br>2. $H_2O$ |  | 8 |
| **4** |  | $H_2O$ |  | 9 |
| **5** |  | HMPA | R−H | 10 |
| **6** |  | $H_2O$ |  | 11 |
| **7** |  | ROH |  | 12 |
| **8** |  | HMPA and ROH |  | 13 |
| **9** |  | None, HMPA or DMPU or LiCl |  | 14 |
| **10** | $R-NO_2$ | ROH | R−NHOH or $R-NH_2$ | 15 |
| **11** |  | None | $R^1$−OH and H−$NR^2R^3$ | 17 |
| **12** |  | None, DMPU | H−$NR^1R^2$ and H−$NR^3R^4$ | 18 |
| **13** |  | ROH or $H_2O$ and HMPA or DMA or $NEt_3$-$H_2O$ |  | 19 |
| **14** |  or | HMPA or DMPU |  | 20 |
| **15** |  | HMPA | R−H | 21 |
| **16** |  | $NEt_3$ and $H_2O$ |  | 22 |
| **17** | R−CN | $NEt_3$ and $H_2O$ |  | 16 |

| | | | | |
|---|---|---|---|---|
| **18** |  | $NEt_3$ and $H_2O$ |  | 23 |

Although, the results illustrated that the $SmI_2$ reagent can reduce a large range of organic functional groups, generally excess amounts of $SmI_2$ and several additives were needed in most of the transformations.

## I. 3. $SmI_2$ mediated Carbon-carbon bonds formation

The carbon-carbon bond formation by $SmI_2$ is another significant application in organic chemistry, one of the best known reaction is the pinacol coupling (Table 1.2, entry **1**).[24] In General, the coupling was carried out in high chemoselectivity. Using tetraglyme as the additive, the stereoselectivity was increased obviously.[24a, b] Furthermore, the pinacol cross coupling between imine derivatives and ketones mediated by $SmI_2$ efficiently provided the vicinal amino alcohols[25] or diamines[26] (Table 1.2, entry **2**, **3**). Notably, the reductive coupling of carbonyls/imines and alkenes was also efficiency and versatility (Table 1.2, entry **4**-**6**).[27, 28, 29] Besides, the $SmI_2$ intramolecular radical cyclization can be used to construct the five member ring efficiently (Table 1.2, entry **7**) without any toxic reagent (Sn reagents).[30]

[24] (a) Namy, J.-L.; Souppe, J.; Kagan, H. B. *Tetrahedron Lett.* **1983,** *24,* 765-766. (b) Fürstner, A.; Csuk, R.; Rohrer, C.; Weidmann, H. *J. Chem. Soc., Perkin Trans. 1* **1988,** 1729-1734.

[25] (a) Chiara, J. L.; Marco-Contelles, J.; Khiar, N.; Gallego, P.; Destabel, C.; Bemabe, M. *J. Org. Chem.* **1995,** *60,* 6010-6011. (b) Sturino, C. F.; Fallis, A. G. *J. Am. Chem. Soc.* **1994,** *116,* 7447-7448. (c) Burchak, O. N.; Philouze, C.; Chavant, P. Y.; Py, S. *Org. Lett.* **2008,** *10,* 3021-3023.

[26] (a) Enholm, E. J.; Forbes, D. C.; Holub, D. P. *Synth. Commun.* **1990,** *20,* 981-987. (b) Imamoto, T.; Nishimura, S. *Chem. Lett.* **1990,** 1141-1142. (c) Zhong, Y.-W.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2004,** *6,* 4747-4750. (d) Zhong, Y.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2004,** *6,* 3953-3956. (e) Ebran, J.-P.; Hazell, R. G.; Skrydstrup, T. *Chem. Commun.* **2005,** 5402-5404.

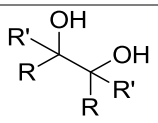
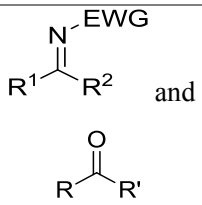
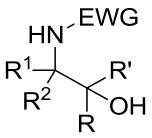
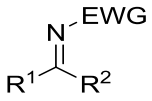
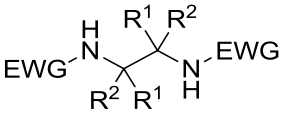
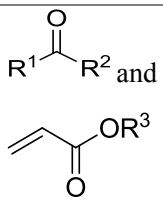
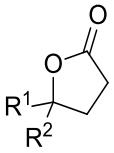
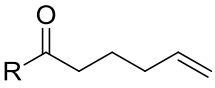
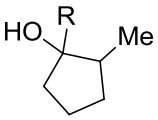
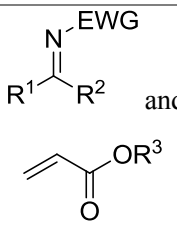
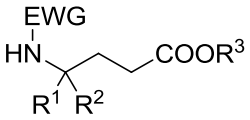
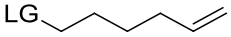
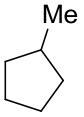
[27] (a) Johnston, D. J.; Couché, E.; Edmonds, D. J.; Muir, K. W.; Procter, D. J. *Org. Biomol. Chem.* **2003,** *1,* 328-337. (b) Hutton, T. K.; Muir, K. W.; Procter, D. J. *Org. Lett.* **2003,** *5,* 4811-4814.

[28] (a) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1995,** *60,* 872-882. (b) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1992,** *57,* 3132-3139.

[29] (a) Riber, D.; Skrydstrup, T. *Org. Lett.* **2003,** *5,* 229-231. (b) Peltier, H. M.; McMahon, J. P.; Patterson, A. W.; Ellman, J. A. *J. Am. Chem. Soc.* **2006,** *128,* 16018-16019.

[30] (a) Fukuzawa, S.; Tsuchimoto, T. *Synlett* **1993,** 803-804. (b) de Pouilly, P.; Chénedé, A.; Mallet, J.-M.; Sinaÿ, P. *Tetrahedron Lett.* **1992,** *33,* 8065-8068.

**Table 1.2** The carbon-carbon bonds formations by $SmI_2$

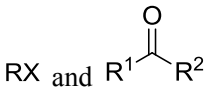
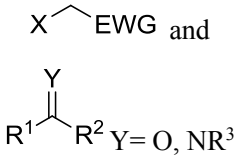
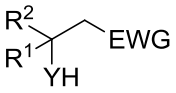
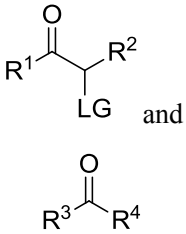
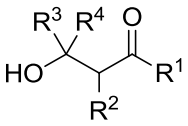
| entry | SM | Condition | product | Ref. |
|---|---|---|---|---|
| **1** |  | None or tetraglyme or HMPA or *t*BuOH |  | 24 |
| **2** |  | None or *t*BuOH or MeOH or HMPA |  | 25 |
| **3** |  | None or *t*BuOH or MeOH or HMPA |  | 26 |
| **4** |  | ROH or HMPA |  | 27 |
| **5** |  | ROH or/and HMPA |  | 28 |
| **6** |  | tBuOH or $H_2O$ or LiBr |  | 29 |
| **7** |  | HMPA, HMPA and ROH, $NiI_2$ and ROH |  | 30 |

Similar to the Grignard reaction, the Barbier reaction was one of the most useful transformation for carbon-carbon bonds. Both intra- and intermolecular couplings can be carried out by using $SmI_2$ (Table 1.3, entry **1**).[31] Over the past 40 years, the use of $Sm^{2+}$ in organic synthesis has brought the $Sm^{3+}$ enolates which are important

[31] (a) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999,** *99,* 745-788. (b) Molander, G. A.; Machrouhi, F. *J. Org. Chem.* **1999,** *64,* 4119-4123.

intermediates in $SmI_2$ reactions.[32] The Reformatsky (Table 1.2, entry **2**)[33] and aldol type (Table 1.2, entry **3**)[34] reactions mediated by $SmI_2$ are representative examples.

**Table 1.3** The Barbier type reactions by $SmI_2$

| entry | SM | Condition | product | Ref. |
|---|---|---|---|---|
| **1** |  | None or HMPA or Fe(III) or Ni (II) |  | 31 |
| **2** |  | None or HMPA or DMPU |  | 33 |
| **3** |  | None or ROH or HMPA |  | 34 |

However, a number of reports demonstrated that the $SmI_2$ can conduct varieties of carbon-carbon bond formations, in this case, these processes still need an excess of $SmI_2$ and harmful additives.

The significance and diverse applications of $SmI_2$ have been highlighted, however, the majority of organic reactions mediated by samarium diiodide ($SmI_2$) as reductive reagent require a stoichiometric or even a large excess amounts. Due to the high molecular mass of $SmI_2$ (MW: 404 g/mol) and low concentration in THF ($c$= 0.1 M), a large amount of metal and solvent are required. This drawback confine the scale of the reactions and the application in industry.

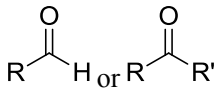
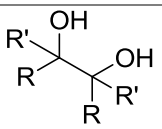
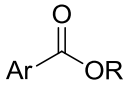
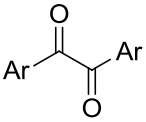
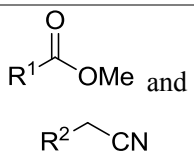
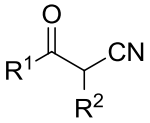
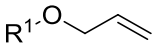
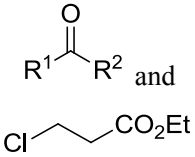
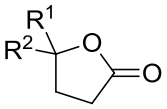
## I. 4. The use of $SmI_2$ in catalytic fashion

Therefore, using a $SmI_2$ catalyzed process is an excepted method to avoid the economic and environmental problem. In 1989, Duñach and co-workers firstly reported the samarium electrocatalyzed pinacol coupling of aldehydes and ketones with the Mg

[32] Rudkin, I. M.; Miller, L. C.; Procter, D. J. *Organomet. Chem.* **2008,** *34,* 19-45.
[33] (a) Utimoto, K.; Matsui, T.; Takai, T.; Matsubara, S. *Chem. Lett.* **1995,** *24,* 197-198. (b) Tabuchi, T.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986,** *27,* 3889-3890.
[34] (a) Enholm, E. J.; Jiag, S.; Abboud, K. *J. Org. Chem.* **1993,** *58,* 4061-4069.

or Al as the sacrificial anode (Table 1.4, entry **1**).[35] Furthermore, they successfully extended this process to perform the reductive dimerization of aromatic esters into the 1,2-diketones (Table 1.4, entry **2**),[36] cyanomethylation of esters (Table 1.4, entry **3**),[37] cleavage of allyl ethers into alcohols (Table 1.4, entry 4)[38] and the cross coupling between 3-chloroesters and carbonyl compounds into the butyrolactones (Table 1.4, entry **5**)[39]. With the aid of electrochemistry, the Mg anode was oxidized to the $Mg^{2+}$ while the $Sm^{3+}$ was reduced to the $Sm^{2+}$. This process presented the possibility to use the $SmI_2$ in a catalytic amount.

**Table 1.4** $SmI_2$ catalytic system based on Mg sacrificial anode

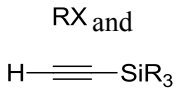
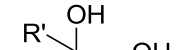
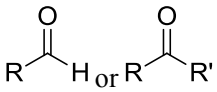
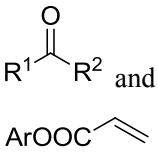
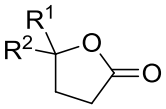
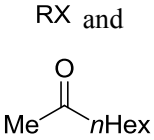
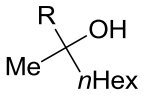
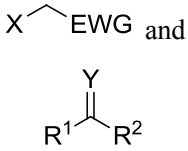
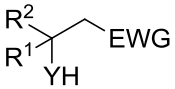
| entry | SM | Condition | product | Ref. |
|---|---|---|---|---|
| **1** |  | cat. $SmCl_3$, Mg or Al as the sacrificial anodes |  | 35 |
| **2** |  | cat. $SmCl_3$, Mg as the sacrificial anode |  | 36 |
| **3** |  | cat. $SmCl_3$, *t*BuOH, Mg as the sacrificial anode |  | 37 |
| **4** |  | cat. $SmCl_3$, Mg as the sacrificial anode |  | 38 |
| **5** |  | cat. $SmCl_3$, Mg as the sacrificial anode |  | 39 |

Later on, Murakami and Ito reported a $SmI_2$-Sm system to synthesize the alkynylsilanes (Table 1.5, entry **1**).[40] In this process, the Sm(0) reduced the Sm(III) into the Sm(II). Instead of metallic Sm, Endo's group developed the $SmI_2$ catalyzed pinacol

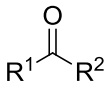
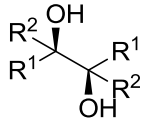
[35] Léonard, E.; Duñach, E.; Périchon, J. *J. Chem. Soc., Chem. Commun.* **1989,** 276-277.
[36] Hébri, H.; Duñach, E.; Heintz, M.; Troupel, M.; Périchon, J. *Synlett* **1991,** 901-902.
[37] Hébri, H.; Duñach, E.; Périchon, J. *Synlett* **1992,** 293-294.
[38] Espanet, B.; Duñach, E.; Périchon, J. *Tetrahedron Lett.* **1992,** *33,* 2485-2488.
[39] Hébri, H.; Duñach, E.; Périchon, J. *J. Chem. Soc., Chem. Commun.* **1993,** 499-500.
[40] Murakami, M.; Hayashi, M.; Ito, Y. *Synlett* **1994,** 179-180.

coupling with Mg as the co-reductant (Table 1.5, entry **2**).[41] In 1997, Corey's group reported a $SmI_2$ catalytic intramolcular of ketones to γ-lactones with zinc amalgam (Table 1.5, entry **3**).[42] Two years later, Namy and co-workers introduced the $SmI_2$ catalytic Barbier reaction with mischmetall and summarized some other conversions by this system (Table 1.5, entry **4**)[43]. Besides, Orsini's group successfully accomplished the Reformatsky reaction by a $SmI_2$ catalytic system (Table 1.5, entry **5**).[44] Notably, Greeves's group developed a $SmI_2$-Mg/tetraglyme catalyzed pinacol coupling in high diastereoselectivity (Table 1.5, entry **6**).[45]

**Table 1.5** $SmI_2$ catalytic system based on the use of co-reducing reagents

| entry | SM | Condition | product | Ref. |
|---|---|---|---|---|
| **1** |  | cat. $SmI_2$, Sm |  | 40 |
| **2** |  | cat. $SmI_2$, Mg, TMSCl |  | 41 |
| **3** |  | cat. $SmI_2$, Zn•Hg, LiI, TMSOTf |  | 42 |
| **4** |  | cat. $SmI_2$, mischmetall |  | 43 |
| **5** |  $Y= O, NR^3$ | cat. $SmI_2$, Mg |  | 44 |

[41] Nomura, R.; Matsuno, T.; Endo, T. *J. Am. Chem. Soc.* **1996,** *118,* 11666-11667.
[42] Corey, E. J.; Zheng, G. Z. *Tetrahedron Lett.* **1997,** *38,* 2045-2048.
[43] (a) Hélion, F.; Namy, J.-L. *J. Org. Chem.* **1999,** *64,* 2944-2946. (b) Lannou, M.-I.; Hélion, F.; Namy, J.-L. *Tetrahedron* **2003,** *59,* 10551-10565.
[44] Orsini, F.; Lucci, E. M. *Tetrahedron Lett.* **2005,** *46,* 1909-1911.
[45] Aspinall, H. C.; Greeves, N.; Valla, C. *Org. Lett.* **2005,** *7,* 1919-1922.

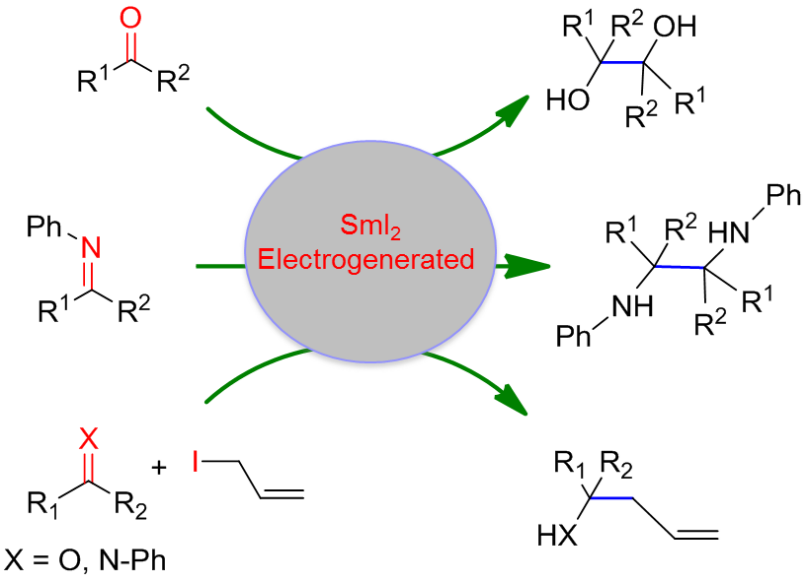
| | | | | |
|---|---|---|---|---|
| **6** |  | cat. $SmI_2$, $Me_2SiCl_2$, Mg, tetraglyme |  up to 90% de | 45 |

The proposed metals as co-reductants for catalytic applications represent significant advances, however, due to the incompatibility between the co-reductants and the substrates, they have not been extensively used. In addition, the presence of additional metals in the reaction medium may favor ligand redistribution, this is supported by the fact that lower chemoselectivities and stereoselectivities were generally observed in reactions involving catalytic $SmI_2$ by comparison with the stoichiometric system.

## I. 5. The use of electrogenerated $SmI_2$

In 2012, our group developed a new method to generate $SmI_2$ by electrochemistry. They described the first electrochemical preparation of samarium diiodide by direct oxidation of a "sacrificial" samarium anode. This alternative route for the synthesis of $Sm^{II}$ species is particularly efficient and can be carried out with routine methods in a galvanostatic mode. The electrogenerated $SmI_2$ was well characterized by electrochemistry and UV/Vis analysis. The beneficial effects of this new methodology in terms of reactivity and solvent economy have been highlighted in several organic reactions induced by $SmI_2$ as reducing reagent (pinacolization, imine homocoupling, barbier type reaction). After that, they demonstrated the potential of this method, in particularly for selective cross-coupling reactions (Scheme 1.2).[46]

[46] Sahloul, K.; Sun, L.; Requet, A.; Chahine, Y.; Mellah, M. *Chem. Eur. J.* **2012,** *18,* 11205-11209.




**Scheme 1.2** The C-C bond formations mediated by electrogenerated $SmI_2$

This original in situ synthesis of $SmI_2$ by electrochemistry also offered an important way to prepare various sensitive lanthanide reagents for organic applications as $SmCl_2$, $SmBr_2$ and $Sm(OTf)_2$.[47] This electrosynthetic procedure avoids the presence of additional metals such as Li and Mg.

Later on, they have discovered a novel and reliable $SmI_2$ catalytic system based on the use of a samarium electrode as co-reductant. $SmI_2$ can act as a catalyst through the use of a samarium cathode, which effectively reduces the trivalent samarium, formed during the chemical reaction, to regenerate the divalent samarium catalytic species. Various transformations mediated by this useful reagent were conducted under the established electrocatalytic conditions, and this method potentially provides an approach to catalytic Sm(II)-based reductants and reductive coupling reactions.

To establish this catalytic procedure, they have investigated the properties of several electrodes to reduce the trivalent into divalent samarium species. All attempts to reduce a suspension of $SmI_3$ using cathodes based on platinum, carbon, nickel, lead, or stainless steel were not conclusive. Indeed, the initial $SmI_3$ suspension remained unchanged after the electrolysis. Interestingly, they discovered that the use of a samarium metal as the cathode effectively reduces $SmI_3$ to provide divalent samarium species (Table 1.6, entry **6**).

[47] Sun, L.; Mellah, M. *Organometallics* **2014,** *33,* 4625-4628.

**Table 1.6** the Screening of Cathode Materials for Reduction of $SmI_3$ Salts in THF/$n$Bu$_4$NPF$_6$[a]

$$SmI_3 \xrightarrow[THF,\ nBu_4NPF_6]{M\ cathode} SmI_2$$

| entry | Cathode | current density (mA/cm$^2$) | UV−vis ($\lambda_{max}$, nm) |
|---|---|---|---|
| **1** | Pt | 1.52 | n. d. |
| **2** | C | 2.10 | n. d. |
| **3** | Pb | 2.87 | n. d. |
| **4** | Ni | 1.80 | n. d. |
| **5** | SS[b] | 8.06 | n. d. |
| **6** | Sm | 1.25 | 612-557 |

[a]Conditions: electrolyte 0.04 M $n$Bu$_4$PF$_6$ in THF, 0.1 mmol of $SmI_3$, I = $5\cdot10^{-2}$ A, standard vitreous carbon anode. [b]SS: stainless steel contains 72% Fe, 18% Cr, and 10% Ni.

This procedure presented a novel and reliable $SmI_2$ catalytic system based on the samarium electrode as the cathode to perform the $Sm^{2+}/Sm^{3+}$ regeneration. Thanks to the use of a samarium cathode, which effectively reduces the trivalent samarium, $Sm^{2+}$ can act as a catalyst regenerated during the chemical reaction under the electrochemistry. (Figure 1.1)

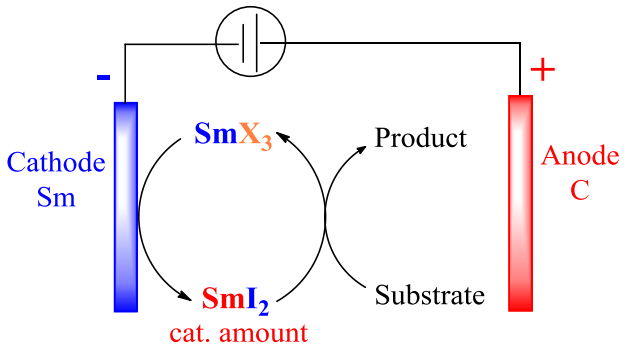
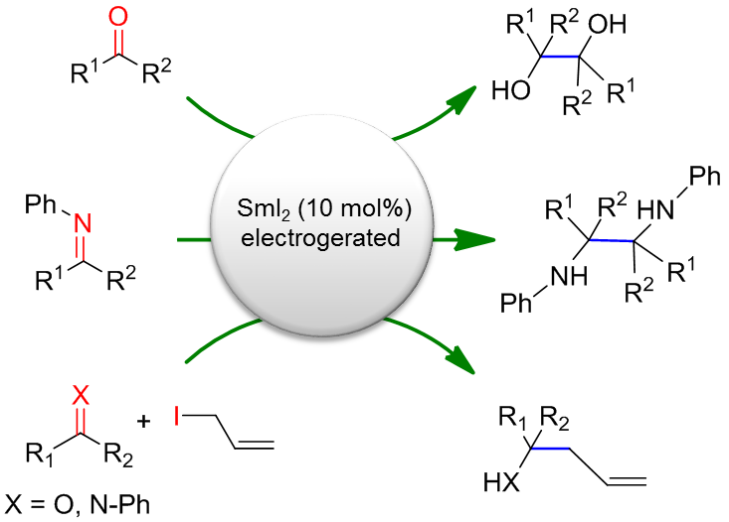


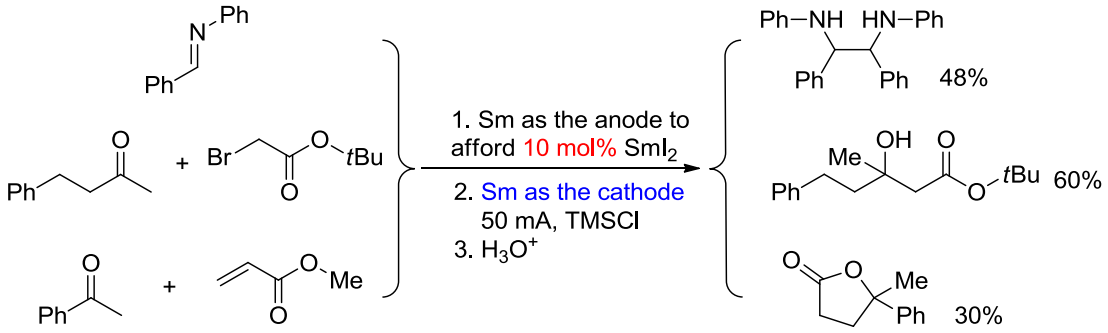

**Figure 1.1** the $Sm^{2+}$ electrocatalytic process

In the presence of catalytic amounts of $SmI_2$, the pinacolization provided the vicinal diols in moderate to good yields (Scheme 1.3). Diastereoselectivities are generally the same as the stoichiometric $SmI_2$ conditions (meso/dl ratio close to 1:1). Besides, carbonyl substrates and allyl iodide afforded the corresponding homoallylic alcohols in good yields under the optimized conditions that the trimethylsilyl chloride and carbonyl compound diluted in dry THF were introduced dropwise by a syringe pump during the electrolysis.




**Scheme 1.3** The $SmI_2$ electrocatalyzed pinacol coupling reaction

To extend the application of this Sm electrocatalyzed system, other reactions mediated by samarium diiodide were performed (Scheme 1.4). This electrocatalytic procedure could also be applied to the reductive coupling of *N*-benzylideneaniline, which provided the corresponding diamine in 48% yield (Scheme 1.4). Furthermore, Reformatsky type reaction between tert-butylbromoacetate and 4-phenyl-2-butanone gave the desired cross-coupling product in 60% yield (Scheme 1.4). Finally, the crosscoupling between acetophenone and methyl acrylate leaded to the corresponding lactone in 30% isolated yield.




**Scheme 1.4** other applications by $SmI_2$ electrocatalytic system

## I. 6. Conclusion

Samarium diiodide ($SmI_2$), first described by Kagan in 1977 is recognized to be one of the most useful and versatile reducing agent in organic synthesis. Its importance and application has been highlighted by several important reports, which demonstrate the prominent role of $SmI_2$ in synthesis. However, the majority of organic reactions

mediated by samarium diiodide ($SmI_2$) as reductive reagent require a stoichiometric amount or even a large excess of $SmI_2$.This drawback tends to decrease the synthetic potential of the reactions promoted by $SmI_2$ in large scale. Several research groups have investigated potential solutions that would allow the use of catalytic amounts of $SmI_2$ by employing co-reductants.

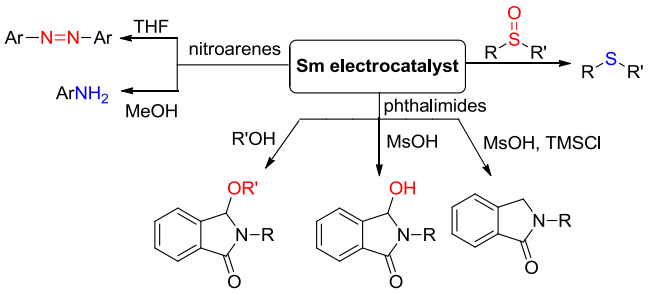
Although the proposed metals co-reductant for catalytic applications represent significant advances, they have not been extensively used, probably because of the incompatibility between the co-reductants used in large excess and the substrates commonly encountered in $SmI_2$-induced reactions.

Recently, our group reported a new method to generate $SmI_2$ by direct electrochemical dissolution of a samarium metal anode. Its efficient application in organic electrosynthetic and electrocatalytic procedures encouraged us to pursue the investigations toward the catalytic reduction of functional groups mediated by $SmI_2$ with the aid of electrochemistry.

Indeed, based on the previous results mediated by the electrocatalytic condition, the subject of my PhD focused on the potential of the application on chemoselective functional group transformations.

Starting from the nitrobenzenes, the Sm electrocatalyzed system selectively afforded either the azo aromatic compounds or amino aromatics in high chemoselectivity and functional group tolerance depending on the electrochemical conditions (Chapter II, III). Moreover, without any additives as HMPA, the electrocatalytic system that we developed could reduce efficiently the sulfoxides into the corresponding sulfides (Chapter IV). Finally, we developed a new catalytic $SmI_2$ reduction of phthalimides (Chapter V) which was never reported before. Under the electrocatalytic condition, the unprecedented reductive alkoxylation of phthalimides by $Sm^{2+}$ was performed in high chemoselectivity and functional group tolerance. In the last chapter, we also developed the efficient reductive conditions of phthalimides into the corresponding aza-hemiacetals or isoindolinones, respectively. (Scheme 1.5)

Compared with the classic $SmI_2$ reaction, the advantages such as the catalytic amount of Sm, less solvent and no protecting gas used, higher chemoselectivity and functional group tolerance illustrated the electrocatalytic process was a better choice.




**Scheme 1.5** The application of $SmI_2$ electrocatalytic system in other substrates

# Chapter II. The Sm electrocatalytic reductive coupling of nitrobenzenes

## II. 1. Introduction

Since their discovery in the early 19th century, azobenzenes are considered as one of the largest and most versatile class of organic dyes, accounting for approximatively 70% of worldwide production of industrial dyes. Azo(hetero)arenes are currently widely used in textile, food, cosmetic and pharmaceutical industries.[48] The *E*/*Z* photoisomerization of the azo functionality induces a remarkable change in their physical properties (e.g. electronic, geometry and polarity),[49] from which chemists have taken advantage to develop sophisticated protein probes,[50] organic dyes,[51] chemosensors,[52] smart surface materials[48] and molecular machines.[53]

Despite the significant efforts devoted to the preparation of diverse substituted azo-photoswitches,[54] accessing sterically constrained azobenzenes using common synthetic procedures still remains a challenge, not only in terms of efficiency, robustness and versatility, but also in terms of sustainability and environmental considerations. Although asymmetrical and symmetrical azobenzenes can be readily prepared through azo coupling, Mills reaction, oxidative or reductive dimerization, these methods are often fraught with major drawbacks such as the use of an excess of reducing or oxidizing agents and/or of hazardous reactants (e.g. aromatic amines). Furthermore, their efficiency lowers with increasing steric congestion, so that their versatility is determined by the capacity of both substrates and products to endure harsh reaction conditions. In order to avoid these limitations, several catalytic strategies have been developed, relying either on a catalytic oxidation of anilines or reduction of nitroarenes.

---

[48] Bafana, A.; Devi, S.; Chakrabarti, T. *Environmental Reviews* **2011**, *19*, 350-371.
[49] Merino, E.; Ribagorda, M. *Beilstein Journal of Organic Chemistry* **2012**, *8*, 1071-1090.
[50] For significant examples, see: (a) Lim, S.; Hong, K.; Kim, D.; Kwon, H.; Kim, H. *J. Am. Chem. Soc.* **2014**, *136*, 7018-7025. (b) Kienzler, M.; Reiner, A.; Trautman, E.; Yoo, S.; Trauner, D.; Isacoff, E. *J. Am. Chem. Soc.* **2013**, *135*, 17683-17686.
[51] Isaad, J.; Perwuelz, A. *Tetrahedron Lett.* **2010**, *51*, 5810-5814.
[52] Lim, H.; Han, J.; Kwak, D.; Jin, M.; Cho, K. *J. Am. Chem.* Soc. **2006**, *128*, 14458-14459.
[53] Baroncini, M.; Bergamini, G. in *Discovering the Future of Molecular Sciences*, Pignataro, B. Ed. (Wiley-VCH: Weinheim, **2014**), pp 379-397.
[54] For recent reviews, see: (a) Léonard, E.; Mangin, F.; Villette, C.; Billamboz, M.; Len, C. *Catal. Sci. Technol.* **2016**, *6*, 379-398. (b) Merino, E. *Chem. Soc. Rev.* **2011**, *40*, 3835-3853. (c) Reuter, R.; Wegner, H. *Chem. Commun.* **2011**, *47*, 12267-12276. (d) Hamon, F.; Djedaini-Pilard, F.; Barbot, F.; Len, C. *Tetrahedron* **2009**, *65*, 10105-10123. (e) Beharry, A. A.; Woolley, G. A. *Chem. Soc. Rev.*, **2011**, *40*, 4422-4437.

To date, only a few examples have been reported to produce efficiently various symmetrical and asymmetrical azobenzenes using catalytic aerobic oxidation of anilines.

## II. 2. 1. Catalytic synthesis of azobenzenes from anilines

Initially, the catalytic oxidation of anilines was major processes to synthesize the azo aromatic compounds.

In 2008, Corma's group reported the gold-catalyzed oxidative synthesis of azo compounds from anilines.[55] The reaction presented that gold nanoparticles supported on titanium dioxide ($TiO_2$), 1 wt % of catalyst under 5 bar of dioxygen catalyze the aerobic oxidation of aromatic anilines to symmetric and asymmetric azo compounds with yields above 99% (Scheme 2.1 (**1**)).

Then, it was demonstrated in literatures that copper could be a good source of catalyst for this kind of oxidation. In this context, Xi's group developed a CuCl-catalyzed (20 mol% CuCl) oxidative coupling reaction of primary aromatic amines under atmospheric conditions to afford azo compounds (Scheme 2.1 (**2**)).[56] This approach was easy handing and low cost. And two years later, Jiao's group published a novel copper-catalyzed approach (10 mol% CuBr and 30 mol% pyridine) to aromatic azo compounds, which are highly valued chemicals and widely used in industry. Both symmetric and unsymmetric substituted azobenzenes can be conveniently prepared by this method in good to excellent yield (Scheme 2.1 (**3**)).[57] Another possibility for the red copper catalyzed oxidiation was published by Gu and co-worker in 2014 (Scheme 2.1 (**5**)).[58] They developed a red copper as the catalyst to synthesize both symmetric and asymmetric aromatic azo compounds under mild reaction conditions. Low reaction temperature and high catalytic efficiency render this system potential for industrial and synthetic applications.

Meanwhile, some other groups showed that the Mn catalyst was another choice for the synthesis of azobenzenes by oxidation of anilines. Indeed, Wang's group reported a

---

[55] (a) Grirrane, A.; Corma, A.; Garcia, H. *Science* **2008**, *322*, 1661-1664. (b) Grirrane, A.; Corma, A.; Garcia, H. *Nat. Protoc.* **2010**, *11*, 429-438. (c) Corma, A.; Concepción, P.; Serna, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7266-7269. (d) Combita, D.; Concepción, P.; Corma, A. *Journal of Catalysis* **2014**, *311*, 339-349.

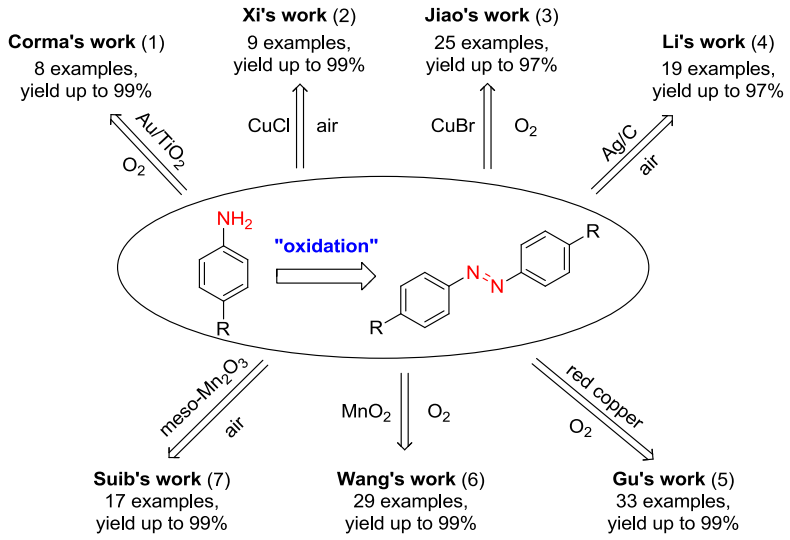
[56] Lu, W.; Xi, C. *Tetrahedron Lett.* **2008**, *49*, 4011-4015.

[57] Zhang, C.; Jiao, N. *Angew. Chem. Int. Ed.* **2010**, *49*, 6174-6177.

[58] Wang, J.; He, J.; Zhi, C.; Luo, B.; Li, X.; Pan, Y.; Cao, X.; Gu, H. *RSC Adv.* **2014**, *4*, 16607-16611.

highly active, selective and recyclable manganese oxide catalyst in the oxidative coupling of anilines for the synthesis of symmetric and unsymmetric azobenzenes (Scheme 2.1 (**6**)).[59] Notably, the asymmetric azo compounds were afforded in high efficiency. Recently, Suib's group developed a meso-$Mn_2O_3$ catalyst for oxidative synthesizing diverse symmetrical and unsymmetrical aromatic azo compounds (Scheme 2.1 (**7**)).[60] Air as the terminal oxidant, the absence of precious metals and additives, and the atmospheric conditions with proper reusability are the superiority.

Besides, the monodispersed Ag NPs was also reported by Li's group to activate $O_2$ in air at room temperature and under atmospheric pressure, to oxidate the anilines into both symmetric and asymmetric azobenzenes under mild conditions (Scheme 2.1 (**4**)).[61]




**Scheme 2.1** General procedures to catalyzed synthesis of azo compounds by anilines oxidation.

## II. 2. 2. Catalytic synthesis of azobenzenes from nitrobenzenes

In contrast to the anilines, the nitrobenzenes are less noxious and more convenient to save, therefore, the reductive catalysis to synthesize the azo compounds is advantageous.

[59] Wang, M.; Ma, J.; Yu, M.; Zhang, Z.; Wang, F. *Catal. Sci. Technol.* **2016**, *6*, 1940-1945.
[60] Dutta, B.; Biswas, S.; Sharma, V.; Savage, N. O.; Alpay, S. P.; Suib, S. L. *Angew. Chem. Int. Ed.* **2016**, *55*, 2171-2175.
[61] Cai, S.; Rong, H.; Yu, X.; Liu, X.; Wang, D.; He, W.; Li, Y. *ACS Catal.* **2013**, *3*, 478-486.

In 2010, Zhu's group revealed a reduction of nitrobenzenes on supported gold nanoparticles by visible and ultraviolet light.[62] Even though only 5 examples were presented, this process is greener than thermal processes, has the potential to utilize solar energy, and can be applied in temperature-sensitive synthesis. Similarly, Guo and co-workers reported a Copper-photocatalytic reduction of nitroaromatics to synthesize azo compounds in visible light.[63] This study provided a green photocatalytic route for the production of azo compounds with a low-cost metal.

In 2011, Gu and co-workers developed a novel worm-like Pd nanomaterial which shows high catalytic activity toward the formation of azo compounds directly from the corresponding nitroaromatic compounds.[64] Without harmful transition metals, the reaction was efficient and this preparation was much easier and more environmentally friendly. Later on, Chung's group developed a catalytic system that can produce an azo compound, an azoxy compound, or an amine as a major product just by changing the reaction conditions.[65]

In the same time, Sakai's group demonstrated that a reduction step composed of $In(OTf)_3$ and $Et_3SiH$ with a subsequent oxidation step enabled a highly selective and a catalytic conversion of aromatic nitro compounds into both symmetrical and unsymmetrical azobenzenes.[66] Moreover, they disclosed that this simple catalytic system appears to be remarkably tolerant of a variety of functional groups.

Notably, Cao's group used the $Au/Mg_4Al$ HT catalyst to reduce directly the nitroarenes into the azo compounds without any external base or additives.[67] This reaction proceeded chemoselectively in a highly efficient manner under mild reaction conditions using $H_2$ as a clean reductant. This catalytic protocol provided a variety of symmetrical and asymmetrical aromatic azo compounds in good to excellent yields.

One year later, they developed the gold-catalyzed approach for the synthesis of aromatic azo compounds directly from reductive coupling of the corresponding nitroarenes by using CO as the sole reductant.[68] The reaction is very mild, general, scalable, and tolerant of various functionalities.

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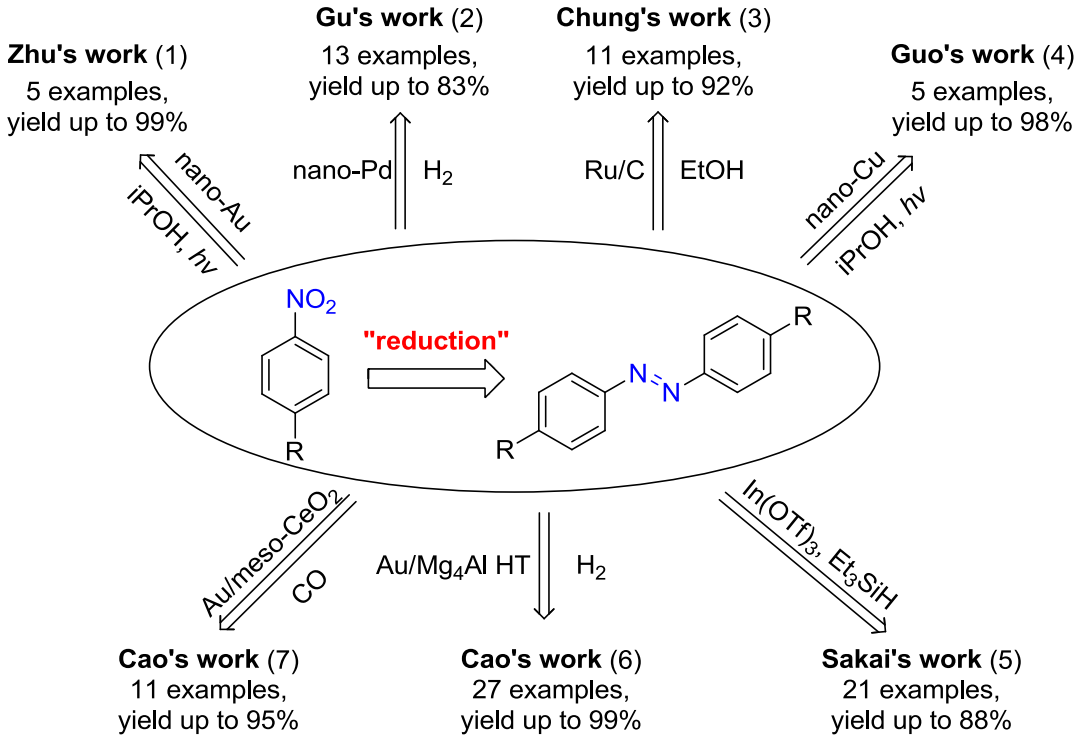
[62] Zhu, H.; Ke X.; Yang, X.; Sarina, S.; Liu, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 9657-9661.
[63] Guo, X.; Hao, C.; Jin, G.; Zhu, H.-Y.; Guo, X.-Y. *Angew. Chem. Int. Ed.* **2014,** *53,* 1973-1977.
[64] Hu, L.; Cao, X.; Shi, L.; Qi, F.; Guo, Z.; Lu, J.; Gu, H. *Org. Lett.* **2011**, *13*, 5640-5643.
[65] Kim, J. H.; Park, J. H.; Chung, Y. K. *Adv. Synth. Catal.* **2012**, *354*, 2412-2418.
[66] Sakai, N.; Asama, S.; Anai, S.; Konakahara, T. *Tetrahedron* **2014**, *70*, 2027-2033.
[67] Liu, X.; Li, H.-Q.; Ye, S.; Liu, Y.-M.; He, He.-Y.; Cao, Y. *Angew. Chem. Int. Ed.* **2014,** *53,* 7624-7628.
[68] Li, H.-Q.; Liu, X.; Zhang, Q.; Li, S.-S.; Liu, Y.-M.; He, He.-Y.; Cao, Y. *Chem. Commun.,* **2015,** *51,* 11217-11220.



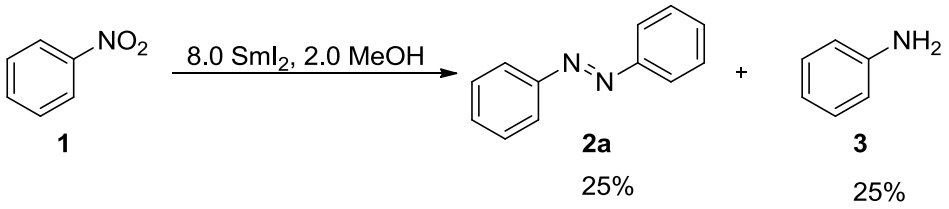

**Scheme 2.2** General procedures to catalyzed synthesis of azo compounds by nitrobenzenes reduction.

Under those catalytic conditions, various symmetrical and asymmetrical azobenzenes were generated, but the yields are moderate and the chemoselectivity is in general low. In this context, devising novel catalytic methods to achieve this type of reaction are still of great importance with the aim of being effective, selective, tolerant to manifold functional groups and easy to implement.

## II. 3. Stoichiometric synthesis of azobenzenes from nitrobenzenes using electrogenerated $SmI_2$

In a seminal study from Kagan's group, it was reported that $SmI_2$ was capable of promoting the reductive coupling of nitrobenzene into the corresponding azobenzene.[69] However, the reaction required the use of 8.0 equivalents of $SmI_2$ and 2.0 equivalents of MeOH, while providing only a mixture of aniline **3** and azobenzene **2a** with a low conversion (50%).

[69] Souppe, J.; Danon, L.; Namy, J. L.; Kagan, H. B. *J. Organomet. Chem.* **1983**, *250*, 227-236.




**Scheme 2.3** The reduction of nitrobenzene by $SmI_2$

Based on these results, we decided to explore the reduction of nitrobenzene **1** by electrogenerated $SmI_2$ instead of Kagan's reagent for a selective access to azobenzenes.

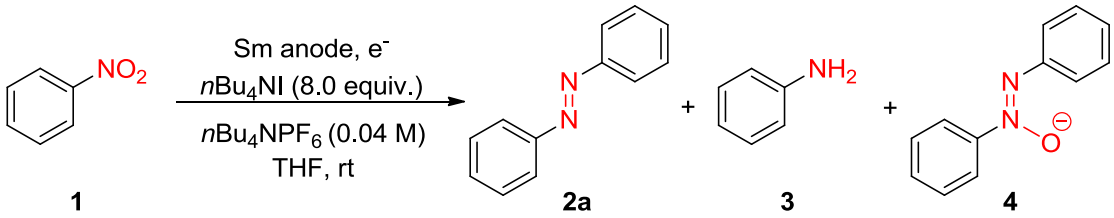
## II. 3. 1. Electrochemical conditions optimization

Firstly, the electrochemical process was conducted using a samarium anode to generate continuously a stoichiometric amount of $SmI_2$ (Table 2.1). To produce $SmI_2$ from a samarium anode, 4.0 Equivalents of $Sm^{II}$ are theoretically needed to ensure the formation of the desired azobenzene. Therefore, under imposed current intensity of $50x10^{-3}$ A, the transformation of 1 mmol of nitrobenzene would take around 5 hours of electrolysis.

Referring to the Kagan's report,[69] we demonstrated the effect of proton donors as additives on the selectivity (Table 2.1). In the presence of 10.0 equivalents of MeOH, complete conversion was achieved within 5 hours to give the desired azobenzene **2a** as a major product (49%). Aniline **3** and azoxybenzene **4** were also obtained in 35 % and 16 % yields, respectively. On the other hand, with 100.0 equivalents of MeOH, the selectivity of the reaction decreased dramatically providing azobenzene **2a** in 23% yield along with aniline **3** (75%). In contrast, when the electrolysis was performed without proton donor, azobenzene **2a** was obtained as the sole product in 95 % yield. The same reaction was attempted using $SmI_2$ (8.0 equivalents) prepared according to Kagan's method in anhydrous THF. However, only 35% conversion was observed after 60 hours with a poor selectivity towards aniline **3** (54%) (Entry 4, table 1). This result is in agreement with the results reported by Kagan et al.[69] This difference of behavior, when compared to our method, can be attributed to the specific reactivity of the electrogenerated $SmI_2$, which is freshly produced in the electrolytic medium. As noted in a previous report on the homocoupling of aliphatic ketone and the reduction of 1-

chlorododecane,[70, 71] it proved to be also more reactive. Control experiments were then performed. First of all, the samarium anode was replaced by an inert carbon anode and electrolysis was strictly performed in the established conditions. After the electrolysis time estimated (5 h), nitrobenzene **1** was fully recovered indicating that the direct reduction at the cathode did not occur. We also checked that no chemical transformation took place without application of any current intensity. Both control experiments confirm that the coupling is mediated by electrogenerated $SmI_2$.

**Table 2.1** Optimization of the reductive coupling of nitrobenzene by electrogenerated $SmI_2$.




**1** **2a** **3** **4**

| Entry | MeOH (equiv.) | t(h) | Conv [%] | Yield[b] | | |
|---|---|---|---|---|---|---|
| | | | | **2a** | **3** | **4** |
| **1** | 10 | 5 | 100 | 42 | 35 | 16 |
| **2** | 100 | 5 | 100 | 23 | 75 | 0 |
| **3** | 0 | 5 | 100 | 95 | 0 | 0 |
| **4** | 0[a] | 60 | 35 | 37 | 54 | 9 |

Reaction conditions: $PhNO_2$ (1.0 mmol, 1.0 equiv.), $nBu_4NI$ (8.0 mmol, 8.0 equiv.) and $nBu_4NPF_6$ (0.04 M) in THF (50 mL) at r.t. for 5 h. [a] 6 eq. $SmI_2$ prepared by Kagan's method. [b]Isolated yield.

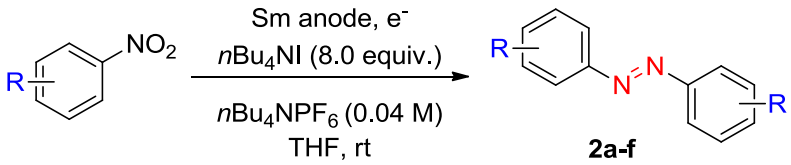
## II. 3. 2. Reductive synthesis of symmetrical azo compounds using stoichiometric amount of electrogenerated $SmI_2$

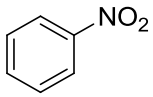
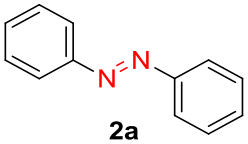
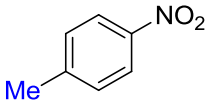
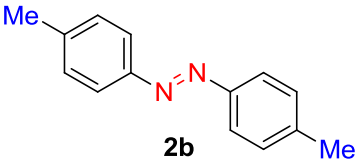
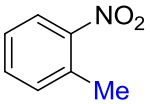
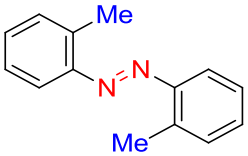
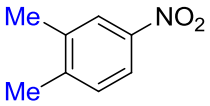
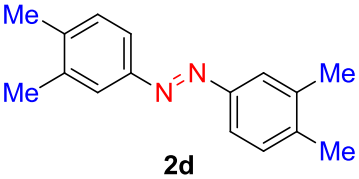
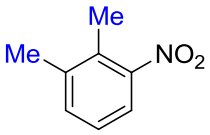
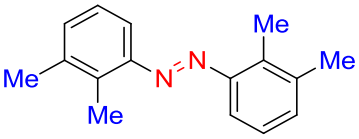
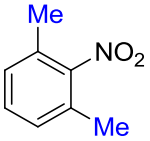
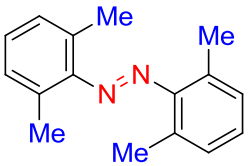
In order to further verify the reactivity of this method, under the optimized reaction condition, the scope of different nitroarenes was investigated. The methyl aryl-substituted nitrobenzenes (Table 2.2, entry **2-6**) easily reacted under the optimized

[70] Sun, L.; Sahloul, K.; Mellah, M. *ACS Catal.* **2013**, *3*, 2568-2573.
[71] (a) Sahloul, K.; Sun, L.; Requet, A.; Chahine, Y.; Mellah, M. *Chem. Eur. J.* **2012**, *18*, 11205-11209. (b) Sun, L.; Mellah, M. *Organometallics* **2014**, *33*, 4625-4628.

reaction condition to afford respective azo compound derivatives in excellent yields. Ortho and even diortho methyl substituents were no influence to this reaction.

**Table 2.2** Reduction of alkyl nitroarenes into azobenzenes



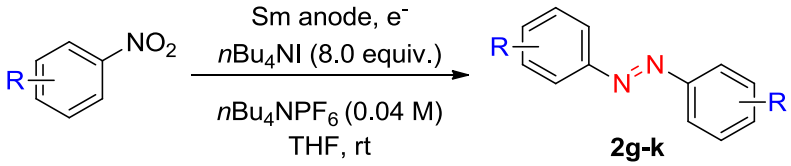

| entry | $ArNO_2$ | Product | Yield %[b] |
|---|---|---|---|
| 1 |  |  **2a** | 98 |
| 2 |  |  **2b** | 95 |
| 3 |  |  **2c** | 98 |
| 4 |  |  **2d** | 95 |
| 5 |  |  **2e** | 91 |
| 6 |  |  **2f** | 80 |

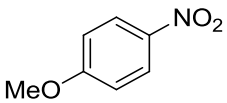
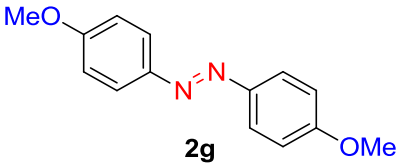
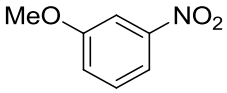
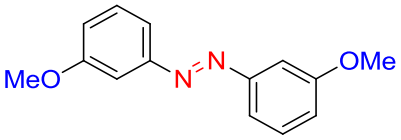
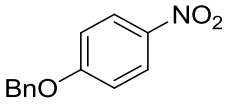
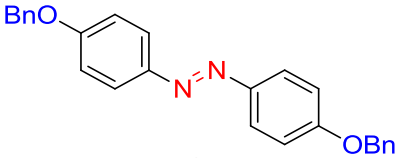
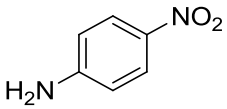
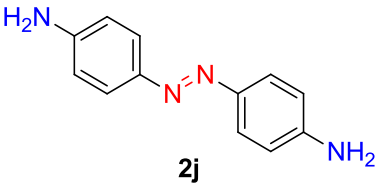
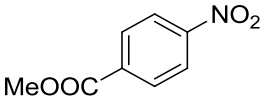
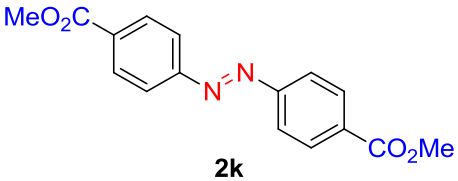
Reaction conditions: R-$ArNO_2$ (1.0 mmol, 1 equiv.), $n$Bu$_4$NI (8.0 mmol, 8 equiv.) and $n$Bu$_4$NPF$_6$ (0.04 M) in THF (50 mL) at r.t. for 5 h. [b]Isolated yield.

Then, we investigated the reductive coupling of various nitrobenzenes with sensitive functional groups. To our delight, all the substrates tested in this reaction gave

the expected azobenezenes in good isolated yields. The substrates with the electron-donating groups as methoxyl (Table 2.3, entry **1**, **2**), benzoxyl (Table 2.3, entry **3**), amino (Table 3.2, entry **4**) provided the corresponding products as well as methyl substituted. Slightly differently, methyl 4-nitrobenzoate ((Table 3.2, entry **5**) with the electron withdrawing group gave a relatively low yield (61%).

**Table 2.3** Reduction of nitrobenzenes with sensitive functional group into azobenzenes.

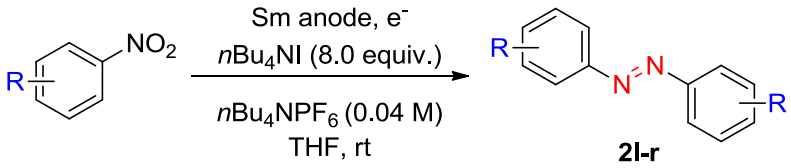


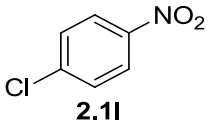
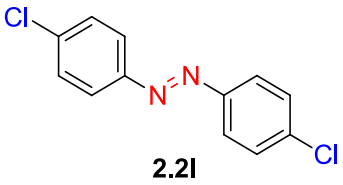
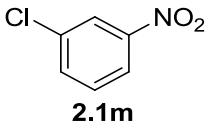
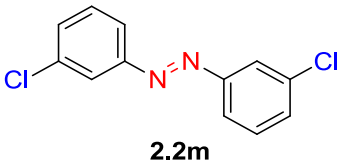
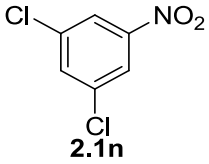
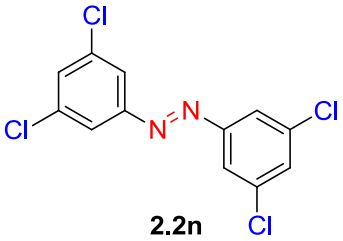
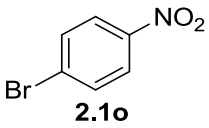
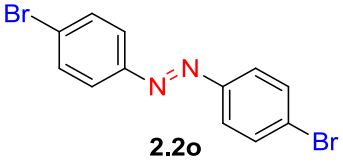
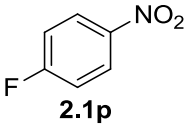
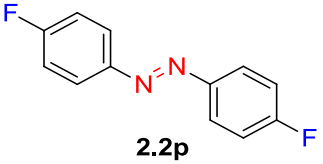

| entry | $ArNO_2$ | Product | Yield %[b] |
|---|---|---|---|
| **1** |  |  **2g** | 99 |
| **2** |  |  **2h** | 94 |
| **3** |  |  **2i** | 91 |
| **4** |  |  **2j** | 90 |
| **5** |  |  **2k** | 61 |

Reaction conditions: R-$ArNO_2$ (1.0 mmol, 1 equiv.), $n$Bu$_4$NI (8.0 mmol, 8 equiv.) and $n$Bu$_4$NPF$_6$ (0.04 M) in THF (50 mL) at r.t. for 5 h. [b]Isolated yield.

Furthermore, the halogenated compounds were induced to this electrochemical process. The chloro, bromo and fluro substrates all afforded the corresponding products without dehalogenation (Table 2.4, entry **1-6**). Interestingly, the electron withdrawing trifluromethyl group gave the product in 93% yield (Table 2.4, entry **7**).

**Table 2.4** Reduction of halogenated nitrobenzenes into azobenzenes.




| entry | $ArNO_2$ | Product | Yield %[b] |
|---|---|---|---|
| 1 |  2.1l |  2.2l | 92 |
| 2 |  2.1m |  2.2m | 94 |
| 3 |  2.1n |  2.2n | 88 |
| 4 |  2.1o |  2.2o | 77 |
| 5 |  2.1p |  2.2p | 91 |

| | | | |
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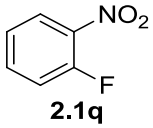
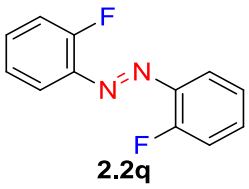
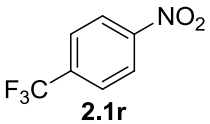
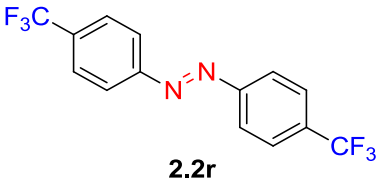
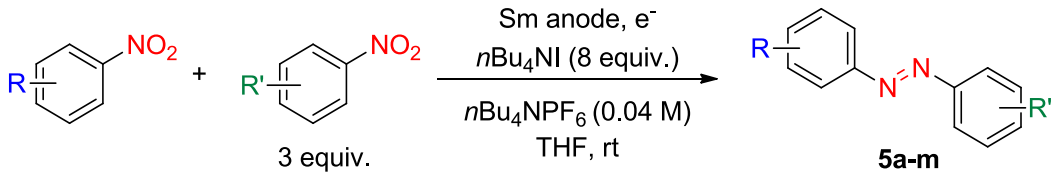
| 6 |  2.1q |  2.2q | 31 |
| 7 |  2.1r |  2.2r | 93 |

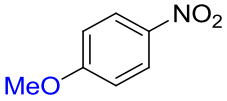
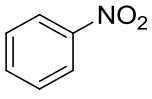
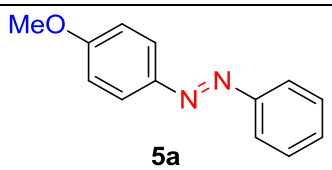
Reaction conditions: R-Ar$NO_2$ (1.0 mmol, 1 equiv.), *n*$Bu_4NI$ (8.0 mmol, 8 equiv.) and *n*$Bu_4NPF_6$ (0.04 M) in THF (50 mL) at r.t. for 5 h. [b]Isolated yield.

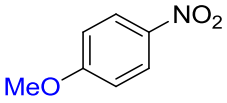
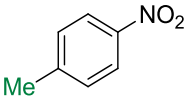
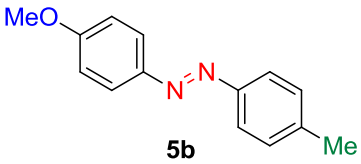
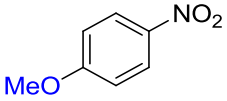
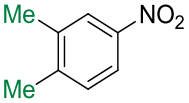
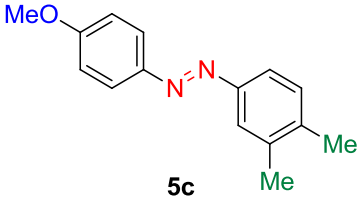
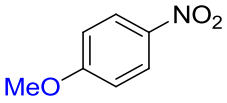
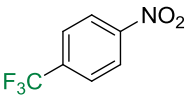
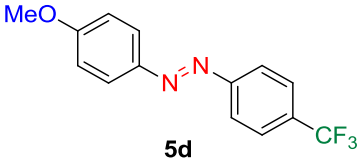
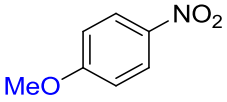
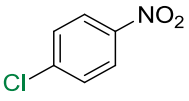
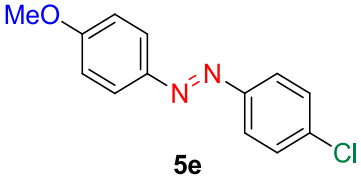
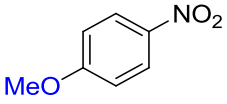
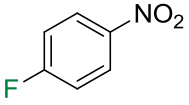
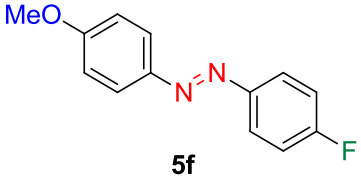
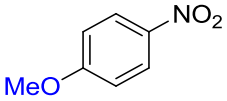
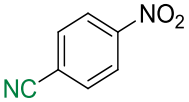
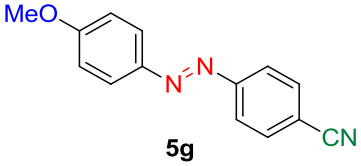
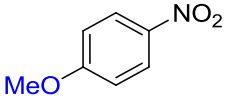
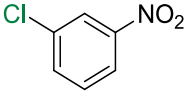
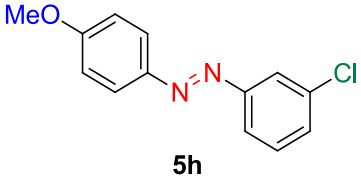
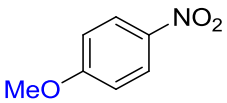
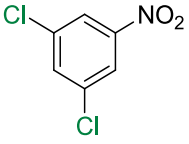
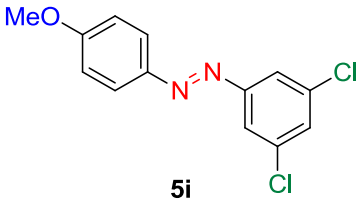
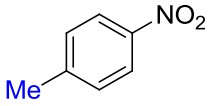
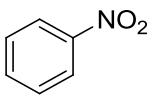
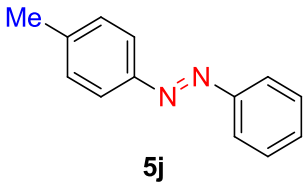
## II. 3. 3. The electrogenerated stoichiometric $SmI_2$ reductive synthesis of asymmetrical azo compounds

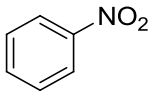
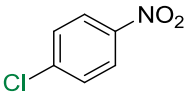
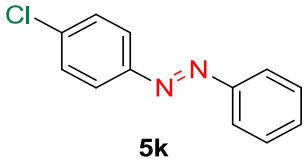
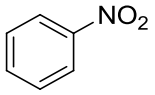
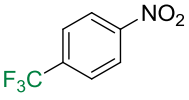
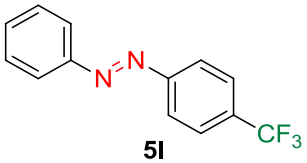
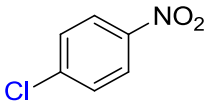
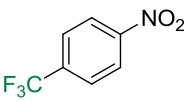
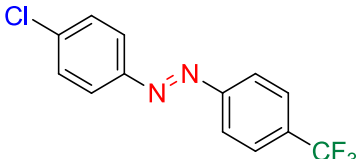
The synthesis of asymmetrical azo compounds is a challenge. Following the previous reports, we chose a 1:3 ratio of two nitroarenes to synthesize the asymmetrical azo compounds. Using 1.0 equivalent *p*-methoxynitrobenzene and another 3.0 equivalents, the asymmetrical azo products were afforded high yields. The entries 10-13 illustrated that the 1.0 equivalent electron-rich nitrobenzene could provide a high yield.

**Table 2.5** electrogenerated $SmI_2$ reduction of nitroarenes into asym metrical azobenzenes.




| entry | $ArNO_2$ 1.0 eq. | $Ar'NO_2$ 3.0 eq. | product | Yield %[b] |
|---|---|---|---|---|
| 1 |  |  |  5a | 96 |

| | | | | |
|---|---|---|---|---|
| **2** |  |  |  **5b** | 98 |
| **3** |  |  |  **5c** | 96 |
| **4** |  |  |  **5d** | 80 |
| **5** |  |  |  **5e** | 96 |
| **6** |  |  |  **5f** | 90 |
| **7** |  |  |  **5g** | 85 |
| **8** |  |  |  **5h** | 89 |
| **9** |  |  |  **5i** | 86 |
| **10** |  |  |  **5j** | 86 |

| | | | | |
|---|---|---|---|---|
| **11** |  |  |  **5k** | 89 |
| **12** |  |  |  **5l** | 92 |
| **13** |  |  |  **5m** | 78 |

[a]Reaction conditions: R-ArNO$_2$ (0.25 mmol, 1 equiv.), R'-ArNO$_2$ (0.75 mmol, 3 equiv.), *n*Bu$_4$NI (8.0 mmol, 8.0 equiv. of R-ArNO$_2$ and R'-ArNO$_2$) and *n*Bu$_4$NPF$_6$ (0.04 M) in THF (50 mL) in the presence of 10 mol% of SmI$_2$ (determined by coulometry) at r.t. for 5 h. [b]Yields given are isolated yields.

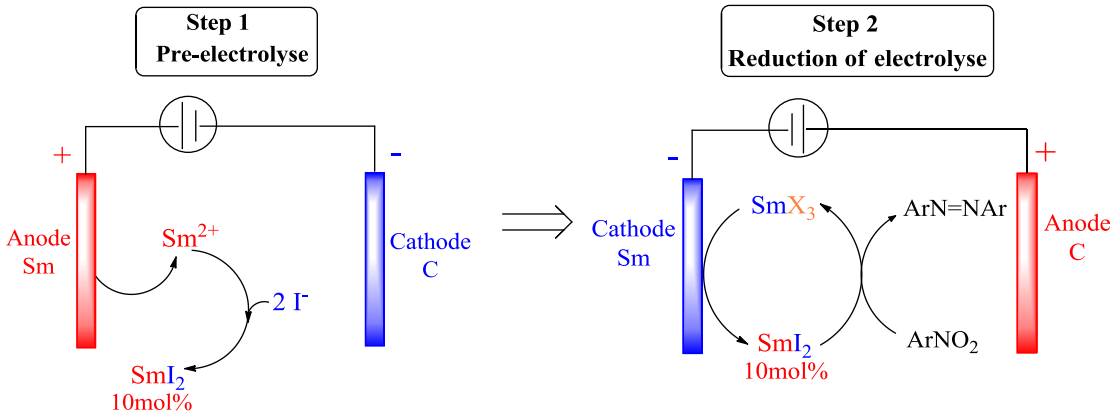
# II. 4. The Sm$^{II}$ electrocatalytic synthesis of azo compounds from nitrobenzenes

## II. 4. 1. Probe of Sm$^{2+}$ electrocatalytic reductive process

After demonstrating that electrogenerated SmI$_2$ can be a powerful reductant for the conversion of nitroarenes into corresponding azo compounds, we turned our attention to the development of a catalytic version.

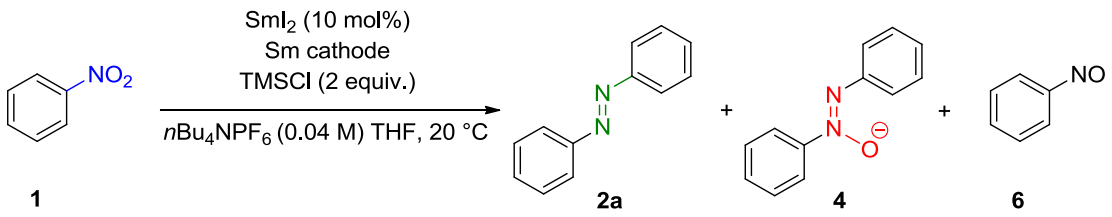
For its implementation, the catalytic procedure was accomplished in two steps as previously reported for various C-C bond forming reactions.[22] The first step consists in the *in situ* electrogeneration of SmI$_2$ from the samarium electrode used as an anode in the presence of *n*Bu$_4$NI. This pre-electrolysis was achieved in an undivided cell charged with anhydrous THF containing *n*Bu$_4$NPF$_6$ under argon at a constant current intensity of $50\times10^{-3}$ A, which prevents any manipulation of the sensitive catalyst out of the electrochemical cell. In order to perform the second electrolysis step, nitrobenzene **1** and 2.0 equivalents of trimethylsilyl chloride (TMSCl) were then introduced. In a precedent report, we demonstrated that TMSCl was able to promote the cleavage the Sm$^{III}$-O bonds by metal exchange, providing the corresponding silyl ether and Sm$^{III}$X$_3$.[22] A subsequent electron transfer from the samarium cathode allows ultimately the regeneration of the Sm$^{II}$X$_2$ active species from Sm$^{III}$X$_3$ free in solution. The polarity

of the samarium electrode is then simply reversed to act as a cathode during the whole electrolysis process. Electrocatalysis is therefore carried out by applying a constant current intensity of 50 mA. Gratifyingly, nitrobenzene led selectively to the desired azobenzene **2a** in 88 % yield.




**Figrure 2.1** The two steps of this $Sm^{2+}$ electrocatalytic process.

Figure 2.2 depicts the evolution of the various species during the course of the electrocatalytic reduction of nitrobenzene **1**. Based on the retention times of pure samples, three compounds were clearly identified, namely nitrobenzene **1a**, azoxybenzene **4**, and azobenzene **2a**. On the other hand, no other potential intermediates, such as nitrosobenzene **6** or aniline **3**, were detected by this method. The concentration of nitrobenzene **1** was found to decrease continuously during the electrolysis process, while the concentration of azobenzene **2a** increased over the same period, but after a delayed time of 60 minutes. Meanwhile, the formation of azoxybenzene **4** reached a threshold of 40% conversion after 140 minutes, before its concentration decreases in the second half of the electrocatalysis. The evolution of the concentration of azoxybenzene **4** suggests a reaction pathway, in which the nitroaromatic compound is initially reduced to the azoxy compound and then to the corresponding azobenzene (Figure 2.2).



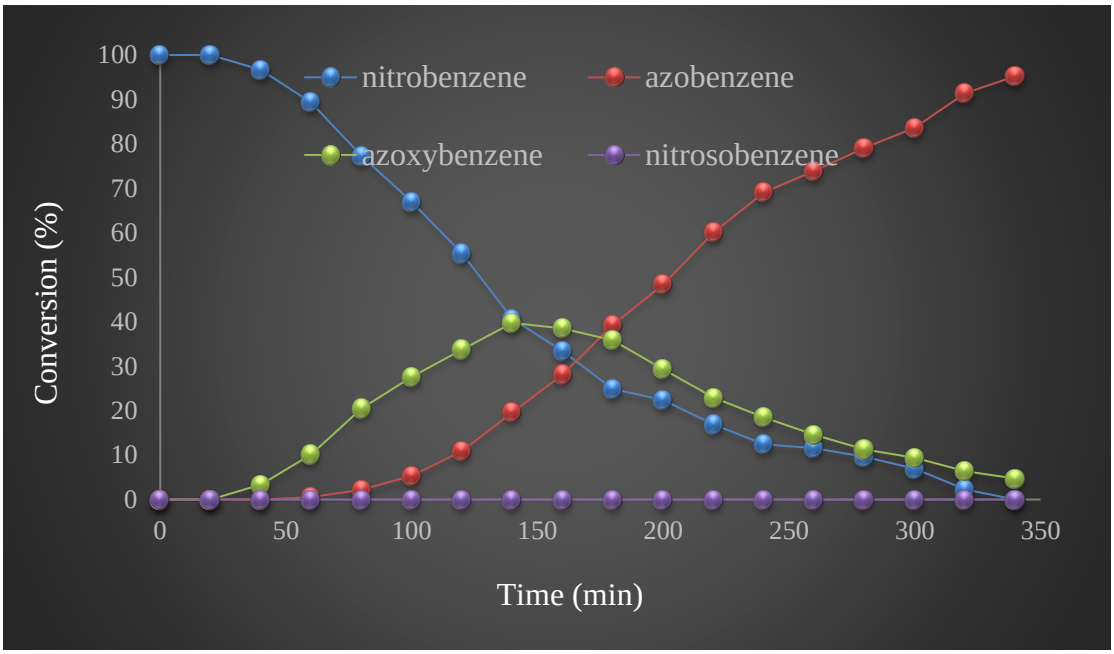
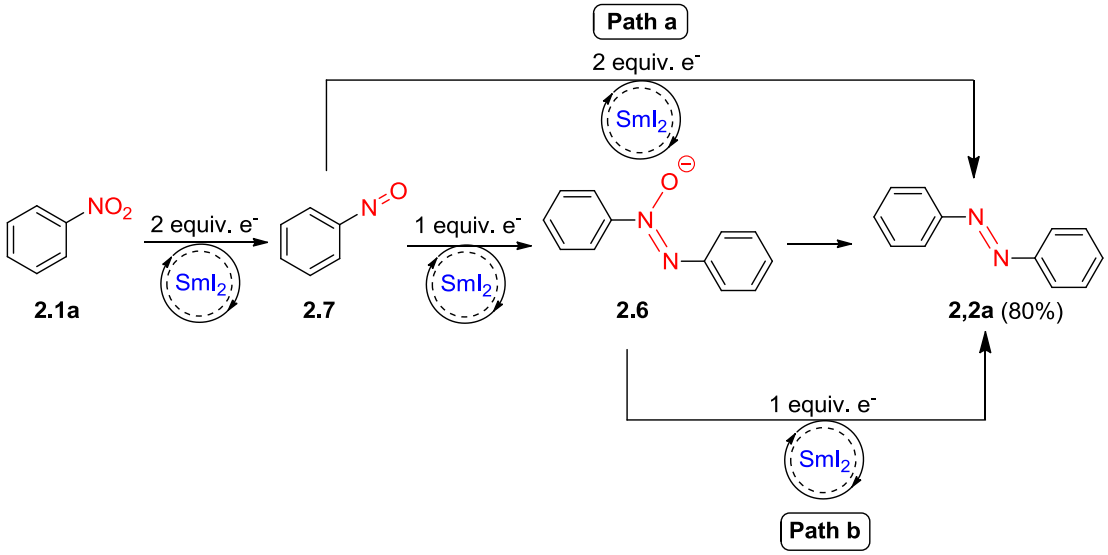




**Figure 2.2** Time-conversion plot for the catalytic reduction of nitrobenzene into azobenzene in anhydrous THF (0.02 M) by electrogenerated $SmI_2$ (10 mol%).

Besides, when azoxybenzene **4** or nitrosobenzene **6** were subjected independently to the same reaction conditions (Scheme 2.4, paths **a** and **b**), they both led to azobenzene **2a** as a sole product within one and four hours (1 and 3 equivalents of electrons), respectively. We observed that azoxybenzene **4** was converted into azobenzene **2a** at a rate four times faster than nitrosobenzene **6**, which is in agreement with their respective reactivities. These experiments confirm that nitrosobenzene **6** might be the first intermediate in the catalytic process, but would react too quickly to be detected by GC analysis.




**Path a**: experiment using nitrosobenzene as starting material under electrocatalytic homocoupling conditions mediated by $SmI_2$. **Path b**: experiment using azoxybenzene as starting material under electrocatalytic homocoupling conditions mediated by $SmI_2$.

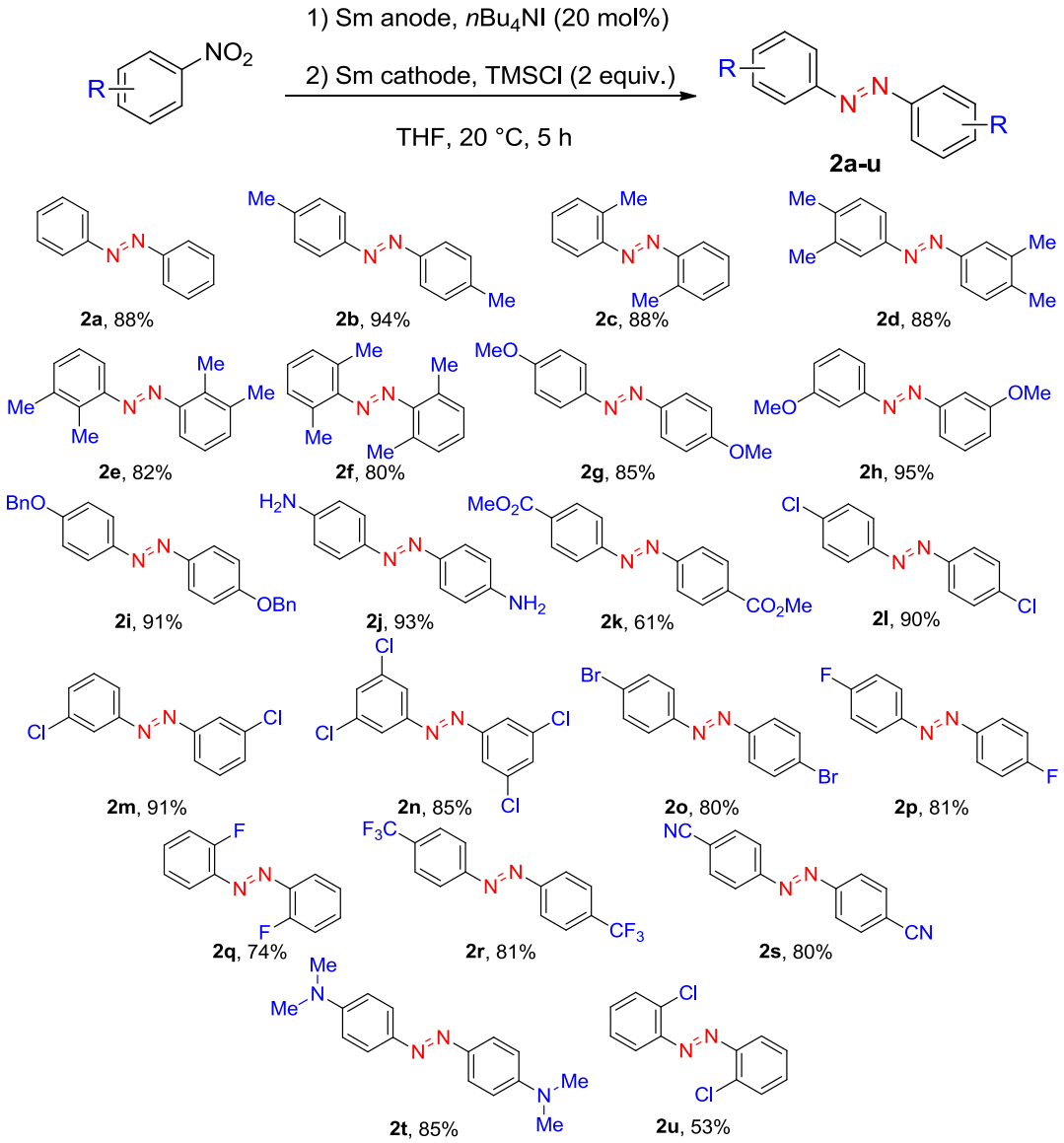
**Scheme 2.4** Probing mechanism intermediates for the catalytic reduction of nitrobenzene.

## II. 4. 2. $SmI_2$-electrocatalyzed reduction of nitroarenes into symmetrical azobenzenes

We turned our attention on assessing the scope and the limitations of this catalytic procedure. Using our optimized electrolysis conditions, diverse nitrobenzene derivatives were converted into the corresponding azobenzenes in high yields (up to 95%) with an excellent selectivity (> 99%) (Table 2.6). Nitrobenzene, nitrotoluenes and dimethylnitrobenzenes were examined and gave the corresponding azobenzenes (Table 2.6, **2a-f**) in excellent yields (80-94%). The reaction was compatible with both electron-rich (Table 2.6, **2g**, **2h**, **2i**, **2j**, **2t**) and electron-poor (Table 2.6, **2k**, **2p-s**) arenes, providing the desired azobenzenes in yields ranging from 53% to 95%. Nitroaromatics bearing halogen substituents were also converted into the corresponding azobenzenes without observing any dehalogenation process (Table 2.6, **2l-q**, **2u**). Of note, our procedure can be performed on a large-scale without decreasing the yield. Thus, 10 mmol of *p*-methoxynitrobenzene gave the azo product (Table 2.6, **2g**) in 85% yield (1.02 g) after 50 hours of electrolysis. The established catalytic procedure proved to be versatile and efficient for the synthesis of various functionalized symmetrical

azobenzenes. These results encouraged us to apply this procedure to the synthesis of unsymmerical azobenzenes, which is much more challenging. The method of choice involves usually the treatment of diazonium salts with electron-rich aromatic compounds in a stoichiometric manner.[54, 72]

**Table 2.6** $SmI_2$-catalyzed reduction of nitroarenes into symmetrical azobenzenes.



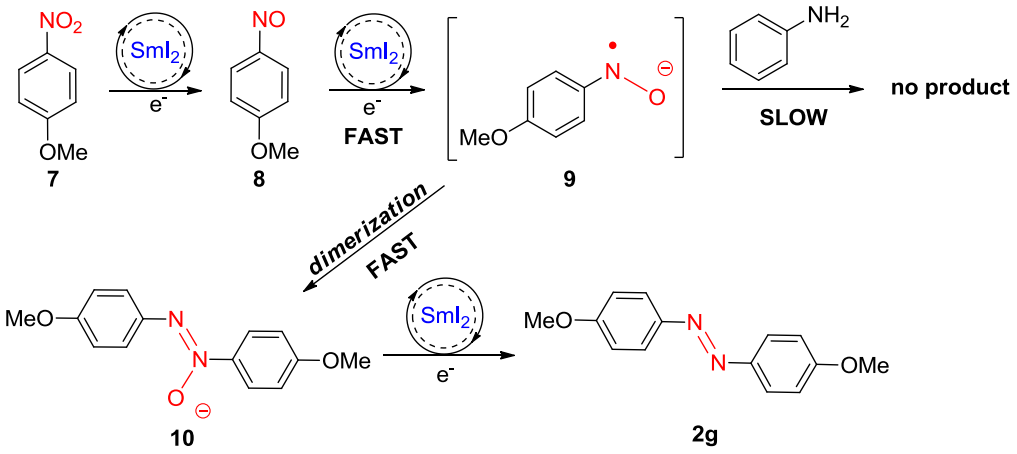

Reaction conditions: R-Ar$NO_2$ (1 mmol, 1 equiv.), TMSCl (2 mmol, 2 equiv.) and $n$Bu$_4$N$PF_6$ 0.04 M in THF (50 mL) in the presence of 10 mol% of $SmI_2$ (determined by coulometry) at 20 °C for 5 h. Yields given are isolated yields.

[72] Hansen, M. J.; Lerch, M. M.; Szymanski, W.; Feringa, B. L. *Angew. Chem. Int. Ed,* **2016**, *55*, 13514-13518.

## II. 4. 3. $SmI_2$-electrocatalyzed reduction of nitroarenes into unsymmetrical azobenzenes

Since we were able to isolate *p*-methoxynitrosobenzene **8** via a stoichiometric reduction of *p*-methoxynitrobenzene **7**, this reaction was also attempted in the presence of aniline to get the unsymmetrical azobenzene by condensation (Scheme 2.5). However the cross-coupling product was never detected and only symmetrical 1,2-bis(4-methoxyphenyl)diazene was isolated after full conversion. This result supports the hypothesis that the dimerization is favored and implies the existence of a radical intermediate **9**, which results from the nitrosobenzene monoelectronic reduction. It then gives rise to a fast radical process instead of a condensation between azoxybenzene and aniline (Mills reaction)[54].

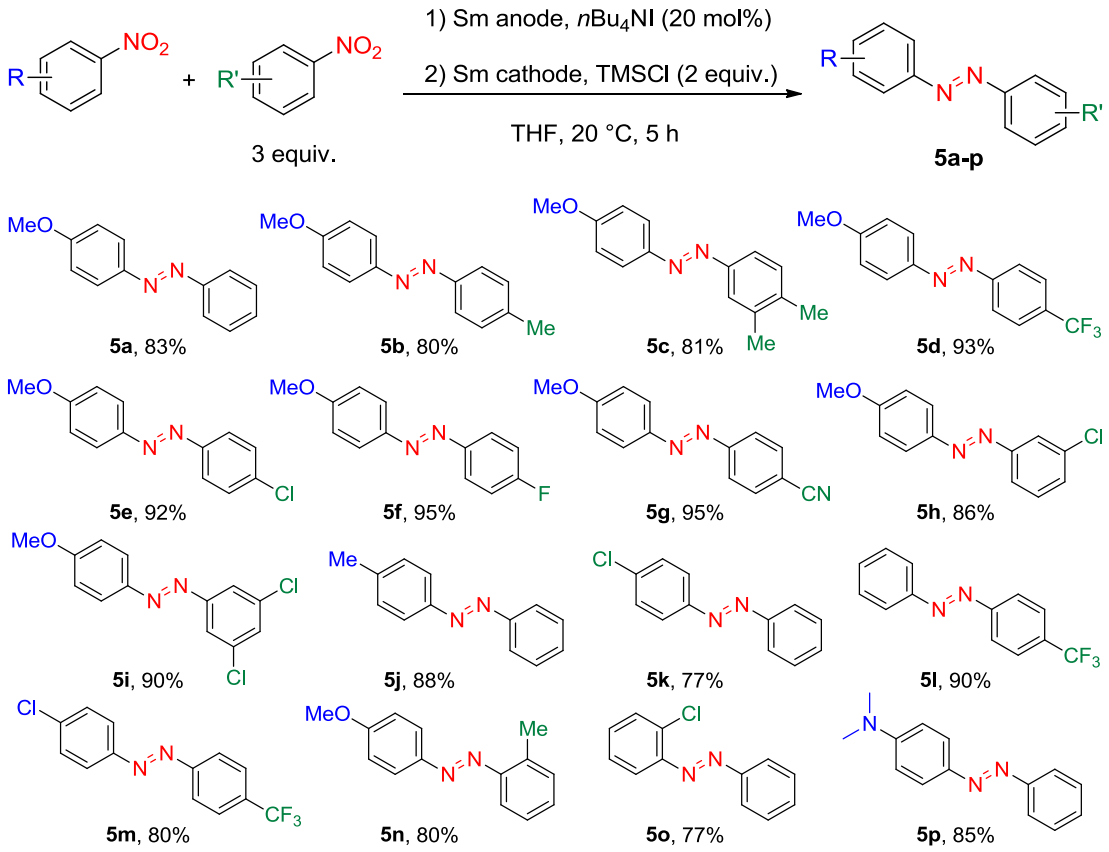
Once formed, nitrosobenzene **8** should be even more easily reduced than the parent nitrobenzene **7** to be rapidly converted into the corresponding azoxybenzene **10**, following a pathway that involves successive transfer of electrons (Scheme 2.5). To ascertain this radical pathway, we carried out the catalytic reduction of nitrobenzene **7** in the presence of 2,6-di-*tert*-butyl-4-methylphenol and TEMPO as radical inhibitors. In both cases, no traces of azobenzene **2g** were observed. Furthermore, the reaction did not give any product resulting from the trapping of radical intermediates by 2,6-di-*tert*-butyl-4-methylphenol or by TEMPO. We assumed that the radical species **9** formed from nitrosobenzene **8** quickly dimerize to form azoxybenzene **10** (intermediate clearly detected by GC analysis) through successive electron transfers, delivering finally azobenzene **2g**.




**Scheme 2.5** Proposed mechanism based on a radical process and successive electron transfers mediated by $SmI_2$.

Therefore, a 1:3 molar ratio was employed according to the nature of electronic substituents to furnish the corresponding products in high yields (77-90%) (Table 2.7, **34-39**).To illustrate this method, methyl yellow (Table 2.7, **5p**), which can be used as a pH indicator, was prepared in 85% yield from a direct cross-coupling between nitrobenzene and *N,N*-dimethyl-4-nitroaniline.

**Table 2.7** $SmI_2$-catalyzed reduction of nitroarenes into asymmetrical azobenzenes.




Reaction conditions: R-Ar$NO_2$ (0.25 mmol, 1 equiv.), R'Ar$NO_2$ (0.75 mmol, 3 equiv.), TMSCl (2.0 mmol, 2 equiv.) and $n$Bu$_4$N$PF_6$ (0.04 M) in THF (50 mL) in the presence of 10 mol% of $SmI_2$ (determined by coulometry) at 20 °C for 5 h. Yields given are isolated yields.

## II. 5. Conclusion

We have developed a facile, efficient and safe alternative for synthesizing a wide variety of azobenzene derivatives, including symmetrical and asymmetrical ones, is possible. The efficiency and the wide functional tolerance of this procedure provide a new tool in our arsenal to access azobenzenes. The use of electrochemistry to perform

catalytic reactions in mild conditions employing $SmI_2$ as a reductant, the absence of precious metals, bases, and non-hazardous substances make our protocol a great alternative to current methods. During the screening of the substrate scope (Table 2.6), we found that electron-donating substituents in *ortho* position were not reactive in dimerization step. We looked closely to the reaction mechanism, which allow us to identify clearly various intermediates in the catalytic process. Results from preliminary mechanistic experiments suggest that the formation of azobenzenes is accomplished by successive monoelectronic reductions. The key step is the reduction of nitrosobenzene into a radical anionic intermediate. The fast dimerization of this intermediate to generate an azoxybenzene followed by a subsequent monoelectronic transfert mediated by $Sm^{II}X_2$ catalyst seems to be the reaction pathway in this catalytic process.

# II. 6. Experiment

## II. 6. 1. General Information

THF was distilled from sodium metal/benzophenone before use. All commercially available chemicals were used without purification. $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded on either a Bruker AM 360 (360 MHz), AM 300 (300 MHz), or AM 250 (250 MHz) instrument with samples dissolved in $CDCl_3$. Mass spectra were recorded on a microTOF-q Brucker Daltonics spectrometer. The gas chromatography (GC) were performed on a spectrometer Varian GC-430 (injection: split/splitless, FID detector, column VF1-MS: 15m x 0.25 mm x 0.25 microns, program: 1 min 50 °C, 10 °C/min to 250 °C, 250 °C 2 min, 23 min total). Electrolysis were performed with a AUTOLAB potentiostat/galvanostat (model: PGSTAT302N), in an undivided three-electrodes cell containing samarium rod working electrode, a standard glassy carbon counter electrode and a saturated calomel electrode (SCE) as reference.

The chemical $SmI_2$ is prepared using Kagan's method.[73] The dark blue solution obtained is used at the concentration of 0.1 mol/L in $SmI_2$.

The samarium electrode used is based on a samarium rod of 12.7 mm (0.5 in) diameter and 5 cm length, directly connected to a copper wire to ensure current conductivity. This self-made electrode is stored under inert atmosphere when it is not used. All the samarium rods are purchased from Alfa Aesar (99.9 % metals basis excluding Ta).

## II. 6. 2. General procedure for the synthesis of symmetrical azo compounds

### II. 6. 2. 1. Stoichiometric conditions

Under argon, reactions were carried out in a one compartment cell containing a magnetic stirring bar, samarium anode (20 $cm^2$ area), glassy carbon cathode (20 $cm^2$ area) and SCE as reference electrode. The cell is then charged with 50mL of electrolyte solution containing 0.04 M $n$Bu$_4$NPF$_6$ in degassed anhydrous THF, $n$Bu$_4$NI (8.0 mmol) as the source of iodide and 1 mmol of nitrobenzene. The electrolysis was performed at i = 50 mA during 16200 seconds (time estimated for generating 4 mmol of $SmI_2$).

[73] Souppe, J.; Danon, L.; Namy, J. L.; Kagan, H. B. *J. Organomet. Chem.* **1983**, *250*, 227-236.

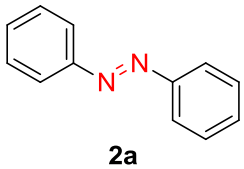
During the electrolysis, the samarium rod act as anode and glassy carbon as cathode. The mixture was then diluted by $Et_2O$ (50 mL), quenched with $NaHCO_3$ (20 mL) and extracted with diethylether (3×20 mL). The combined extracts were washed with sodium thiosulfate and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel. The resulting compounds were identified by comparison of their physical and spectral data with those given in the literature.

## II. 6. 2. 2. Catalytic conditions for symmetrical azo compounds

Under argon, reactions were carried out in a one compartment cell containing a magnetic stirring bar, samarium anode (20 $cm^2$ area), glassy carbon cathode (20 $cm^2$ area) and SCE as reference electrode. The cell is then charged with 50mL of electrolyte solution containing 0.04 M $n$Bu$_4$NPF$_6$ in degassed anhydrous THF and $n$Bu$_4$NI (6.0 mmol) as the iodide source. The pre-electrolysis was performed at i = 50 mA during 500 seconds (time estimated for generating 0.1 mmol $SmI_2$). After the pre-electrolysis a dark blue solution was observed and corresponding nitrobenzene (1.0 mmol) and trimethylsilyl chloride (2.0 mmol) were then added in the mixture. The polarity of electrodes is then reversed, that means, samarium rod act as cathode and glassy carbon as anode. The electrolysis was then performed at i = 50 mA during 3 hours. The mixture was then diluted by $Et_2O$ (50 mL), quenched with $NaHCO_3$ (20 mL) and extracted with diethyl ether (3×20 mL). The combined extracts were washed with sodium thiosulfate and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel. The resulting compounds were identified by comparison of their physical and spectral data with those given in the literature.

## II. 6. 2. 3. Characterization data of symmetrical azo compounds

**(*E*)-1, 2-diphenyldiazene (2a)**



**2a**

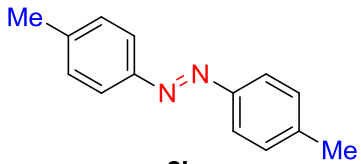
Purified directly by flash column chromatography (On silica gel, 98 / 2 pentane / ethyl acetate eluent) to give an orange crystal (80 mg, 0.44 mmol, 88 % yield). The spectral data matched that reported in the literature.[74]

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 8.02-7.97 (m, 4H), 7.62-7.50 (m, 6H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 152.8, 131.2, 129.3, 123.0.

**HRMS (ESI)** m/z Calcd for $C_{12}H_{11}N_2$ ($M+H^+$): 183.0917. Found: 183.0918.

**(*E*)-1, 2-di-*p*-tolyldiazene (2b)**




**2b**

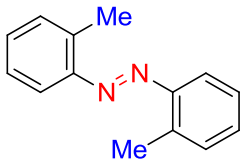
Purified directly by flash column chromatography (On silica gel, 98 / 2 pentane / ethyl acetate eluent) to give an orange crystal (99 mg, 0.47mmol, yield: 94%).The spectral data matched that reported in the literature.[75]

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.86 (d, $J$ = 8.3 Hz, 4H), 7.34 (d, $J$ = 8.3 Hz, 4H), 2.47 (s, 6H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 151.0, 141.4, 129.9, 122.9, 21.7.

**HRMS (ESI)** Calcd for $C_{14}H_{15}N_2$ ($M+H^+$): 211.1230. Found: 211.1228.

**(*E*)-1, 2-di-*o*-tolyldiazene (2c)**




**2c**

Purified directly by flash column chromatography (On silica gel, 98 / 2 pentane / ethyl acetate eluent) to give an orange crystal (92 mg, 0.44 mmol, yield: 88%). The spectral data matched that reported in the literature.[75]

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.74-7.65 (m, 2H), 7.45-7.37 (m, 4H), 7.36-7.30 (m, 2H), 2.81 (s, 6H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 151.3, 138.2, 131.5, 130.9, 126.6, 116.1, 17.8.

**HRMS (ESI)** Calcd for $C_{14}H_{15}N_2$ ($M+H^+$): 211.1230. Found: 211.1230.

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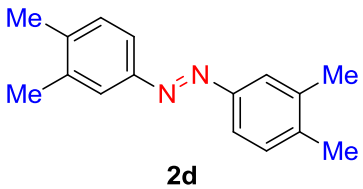
[74] Cepanec, I.; Litvic, M.; Udikovic, J.; Pogorelic, I.; Lovric, M. *Tetrahedron* **2007**, *63*, 5614–5621.
[75] Zhang, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 6174–6177.

**(*E*)-1, 2-bis(3,4-dimethylphenyl)diazene (2d)**




**2d**

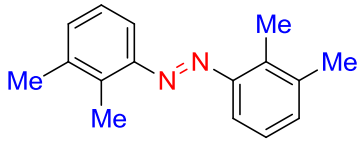
Purified directly by flash column chromatography (On silica gel, 98 / 2 pentane / ethyl acetate eluent) to give an orange crystal (105 mg, 0.44 mmol, yield: 88%). The spectral data matched that reported in the literature.[76]

**$^1$H NMR (300 MHz, $CDCl_3$)** δ 7.80-7.65 (m, 4H), 7.32-7.21 (m, 2H), 2.39 (s, 3H), 2.37 (s, 3H).

**$^{13}$C NMR (75 MHz, $CDCl_3$)** δ 151.4, 140.0, 137.5, 130.4, 123.5, 120.9, 20.1, 20.1.

**HRMS (ESI)** Calcd for $C_{16}H_{19}N_2$ ($M+H^+$): 239.1543. Found: 239.1537.

**(*E*)-1, 2-bis(2, 3-dimethylphenyl)diazene (2e)**




**2e**

Purified directly by flash column chromatography (On silica gel, 98 / 2 pentane / ethyl acetate eluent) to give an orange crystal (98 mg, 0.41 mmol, yield: 82%).

**Melting point:** 108- 110 °C

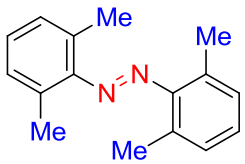
**IR (film) $\nu_{max}$:** 2923, 2855, 1657, 1459, 1380, 1155, 1067, 949 $cm^{-1}$.

**$^1$H NMR (300 MHz, $CDCl_3$)** δ 7.56-7.50 (m, 2H), 7.32-7.28 (m, 2H), 7.25-7.17 (m, 2H), 2.71 (s, 3H), 2.43 (s, 3H).

**$^{13}$C NMR (75 MHz, $CDCl_3$)** δ 151.5, 138.4, 137.0, 132.0, 125.9, 113.7, 20.2, 13.5.

**HRMS (ESI)** Calcd for $C_{16}H_{19}N_2$ ($M+H^+$): 239.1543. Found: 239.1538.

**(*E*)-1,2-bis(2,6-dimethylphenyl)diazene (2f)**




**2f**

[76] Okumura, S.; Lin, C. –H.; Takeda, Y.; Minakata S. *J. Org. Chem*. **2013**, *78*, 12090-12105.

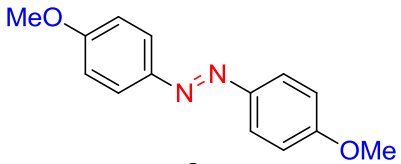
Purified directly by flash column chromatography (On silica gel, 99 / 1 pentane / ethyl acetate eluent) to give an orange crystal (95.2 mg, 0.40 mmol, yield: 80%). The spectral data matched that reported in the literature.[77]

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.21-7.15 (m, 6H), 2.45 (s, 12H).

**$^{13}$C NMR (100 MHz, $CDCl_3$)** δ131.3, 129.4, 128.4, 19.8.

**HRMS (ESI)** Calcd for $C_{16}H_{19}N_2$ ($M+H^+$): 239.1543. Found: 239.1541.

**(*E*)-1, 2-bis(4-methoxyphenyl)diazene (2g)**




**2g**

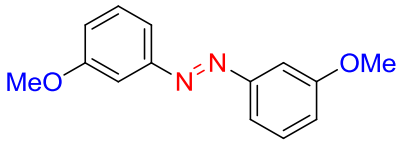
Purified directly by flash column chromatography (On silica gel, 95 / 5 pentane / ethyl acetate eluent) to give an orange crystal (103 mg, 0.43 mmol, yield: 85%). The spectral data matched that reported in the literature.[75]

**$^1$H NMR (250 MHz, $CDCl_3$)** δ 7.92 (d, $J$ = 9.3 Hz, 4H), 7.04 (d, $J$ = 9.3 Hz, 4H), 3.91 (s, 6H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 161.7, 147.2, 124.5, 114.3, 55.7.

**HRMS (ESI)** Calcd for $C_{14}H_{15}N_2O_2$ ($M+H^+$): 243.1128. Found: 243.1126.

**(*E*)-1, 2-bis(3-methoxyphenyl)diazene (2h)**




**2h**

Purified directly by flash column chromatography (On silica gel, 95 / 5 pentane / ethyl acetate eluent) to give an orange crystal (115 mg, 0.48 mmol, yield: 95%). The spectral data matched that reported in the literature.[78]

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.62 (d, $J$ = 7.6 Hz, 2H), 7.51 (app t, $J$ = 2.3 Hz, 2H), 7.46 (app t, $J$ = 7.9 Hz, 2H), 7.08 (dd, $J$ = 7.9, 2.3 Hz, 2H), 3.92 (s, 6H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 160.5, 153.9, 129.9, 118.0, 117.3, 105.9, 56.0.

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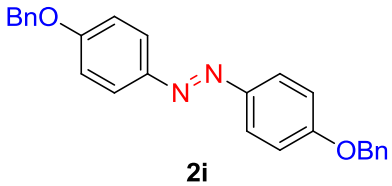
[77] Zhang, L.; Xia, J.; Li, Q.; Li, X.; Wang, S. *Organometallics* **2011**, *30*, 375–378.
[78] Singh, S.; Chauhan, P.; Ravi, M.; Taneja, I.; Wahajuddin; Yadav, P. P. *RSC. Adv.* **2015**, *5*, 61876-61880.

**HRMS (ESI)** Calcd for $C_{14}H_{15}N_2O_2$ ($M+H^+$): 243.1128. Found: 243.1123.

**(*E*)-1,2-bis(4-(benzyloxy)phenyl)diazene (2i)**




**2i**

Purified directly by flash column chromatography (On silica gel, 95 / 5 pentane / ethyl acetate eluent) to give an orange crystal (179 mg, 0.46 mmol, yield: 91%).

**Melting point:** 195- 197 °C

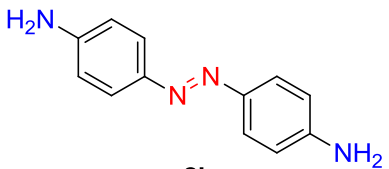
**IR (film) $\nu_{max}$:** 3092, 3061, 3033, 2944, 2916, 2859, 1602, 1496, 1452, 1315, 1245, 1151, 1108, 1015, 843, 733, 691 $cm^{-1}$.

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.86 (d, *J* = 9.0 Hz, 4H), 7.48-7.30 (m, 10H), 7.06 (d, *J* = 9.0 Hz, 4H), 5.13 (s, 4H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 161.0, 147.4, 136.8, 128.9, 128.4, 127.7, 124.6, 115.3, 70.5.

**HRMS (ESI)** Calcd for $C_{26}H_{23}N_2O_2$ ($M+H^+$): 395.1754. Found: 395.1733.

**(*E*)-4, 4'-(diazene-1,2-diyl)dianiline (2j)**




**2j**

Purified directly by flash column chromatography (On silica gel, 30 / 70 pentane / ethyl acetate eluent) to give a brown crystal (99 mg, 0.47 mmol, yield: 93%). The spectral data matched that reported in the literature.[79]

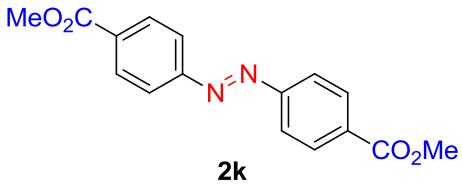
**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.72 (d, *J* = 8.5 Hz, 4H), 6.71 (d, *J* = 8.5 Hz, 4H), 3.93 (s, 4H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 148.7, 146.0, 124.6, 115.0.

**HRMS (ESI)** Calcd for $C_{12}H_{13}N_4$ ($M+H^+$): 213.1135. Found: 213.1135.

**(*E*)-dimethyl 4,4'-(diazene-1,2-diyl)dibenzoate (2k)**

[79] Ma, H.; Li, W.; Wang, J.; Xiao, G.; Gong, Y.; Qi, C.; Feng, Y.; Li, X.; Bao, Z.; Cao, W.; Sun, Q.; Veaceslav, C.; Wang, F.; Lei, Z. *Tetrahedron*, **2012**, *68*, 8358-8366.




**2k**

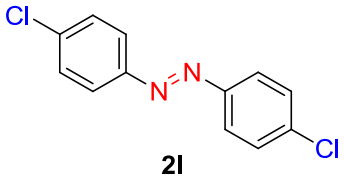
Purified directly by flash column chromatography (On silica gel, 80 / 20 pentane / ethyl acetate eluent) to give a yellow crystal (92 mg, 0.31 mmol, yield: 61%). The spectral data matched that reported in the literature.[80]

**$^1$H NMR (250 MHz, $CDCl_3$)** δ 8.19 (d, *J* = 8.5 Hz, 4H), 7.97 (d, *J* = 8.5 Hz, 4H), 3.95 (s, 6H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 166.6, 155.1, 132.7, 130.9, 123.2, 52.6.

**HRMS (ESI)** Calcd for $C_{16}H_{15}N_2O_4$ ($M+H^+$): 299.1026. Found: 299.1027.

**(*E*)-1, 2-bis(4-chlorophenyl)diazene (2l)**




**2l**

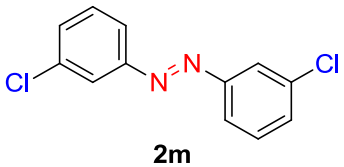
Purified directly by flash column chromatography (On silica gel, 99 / 1 pentane / ethyl acetate eluent) to give a yellow crystal (113 mg, 0.45 mmol, yield: 90%). The spectral data matched that reported in the literature.[75]

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.88 (d, *J* = 8.8 Hz, 4H), 7.51 (d, *J* = 8.8 Hz, 4H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 151.0, 137.4, 129.6, 124.4.

**HRMS (ESI)** Calcd for $C_{12}H_9Cl_2N_2$ ($M+H^+$): 251.0137. Found: 251.0130.

**(*E*)-1, 2-bis(3-chlorophenyl)diazene (2m)**




**2m**

Purified directly by flash column chromatography (On silica gel, 99 / 1 pentane / ethyl acetate eluent) to give a yellow crystal (114 mg, 0.46 mmol, yield: 91%). The spectral data matched that reported in the literature.[81]

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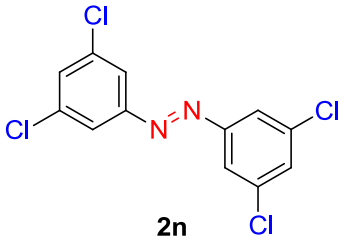
[80] Hu, L; Cao, X.; Shi, L.; Qi, F.; Guo, Z.; Lu, J.; Hu, H. *Org. Lett.*, **2011**, *13*, 5640–5643.
[81] Thorwirth, R.; Brnhardt, F.; Stolle, A.; Ondruschka, B.; Asghari, J. *Chem. Eur. J.* **2010**, *16*, 13236-13242.

**$^1$H NMR (300 MHz, $CDCl_3$)** δ 7.91 (s, 2H), 7.88-7.78 (m, 2H), 7.51-7.40 (m, 4H).

**$^{13}$C NMR (75 MHz, $CDCl_3$)** δ 153.3, 135.4, 131.4, 130.4, 122.8, 122.1.

**HRMS (ESI)** Calcd for $C_{12}H_9Cl_2N_2$ ($M+H^+$): 251.0137. Found: 251.0130

**(*E*)-1, 2-bis(3,5-dichlorophenyl)diazene (2n)**




**2n**

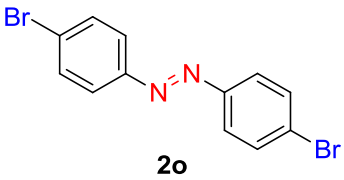
Purified directly by flash column chromatography (On silica gel, 99 / 1 pentane / ethyl acetate eluent) to give a yellow crystal (135 mg, 0.43 mmol, yield: 85%). The spectral data matched that reported in the literature.[82]

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.80 (s, 4H), 7.48 (s, 2H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 153.3, 136.1, 131.5, 122.1.

**HRMS (ESI)** Calcd for $C_{12}H_7Cl_4N_2$ ($M+H^+$): 318.9358. Found: 318.9363

**(*E*)-1,2-bis(4-bromophenyl)diazene (2o)**




**2o**

Purified directly by flash column chromatography (On silica gel, 99 / 1 pentane / ethyl acetate eluent) to give a yellow crystal (135 mg, 0.40 mmol, yield: 80%). The spectral data matched that reported in the literature.[82]

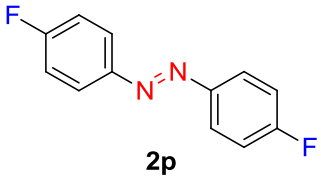
**$^1$H NMR (300 MHz, $CDCl_3$)** δ 7.77 (d, $J$ = 8.6 Hz, 4H), 7.63 (d, $J$ = 8.6 Hz, 4H).

**$^{13}$C NMR (75 MHz, $CDCl_3$)** δ 151.4, 132.6, 126.0, 124.7.

**HRMS (ESI)** Calcd for $C_{12}H_9Br_2N_2$ ($M+H^+$): 338.9127. Found: 338.9120.

**(*E*)-1, 2-bis(4-fluorophenyl)diazene (2p)**

[82] Liu, X.; Li, H. Q.; Ye, S.; Liu, Y. M.; He, H. Y.; Cao, Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 7624-7628.



**2p**

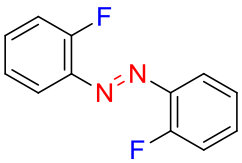
Purified directly by flash column chromatography (On silica gel, 99 / 1 pentane / ethyl acetate eluent) to give a yellow crystal (88 mg, 0.41 mmol, yield: 81%). The spectral data matched that reported in the literature.[75]

**$^{1}$H NMR (250 MHz, $CDCl_3$)** δ8.00-7.80 (m, 4H), 7.26-7.15 (m, 4H).

**$^{13}$C NMR (63 MHz, $CDCl_3$)** δ 164.6 (d, $J$ = 250.3 Hz), 149.2, 125.0 (d, $J$ = 9.1 Hz), 116.3 (d, $J$ = 22.8 Hz).

**HRMS (ESI)** Calcd for $C_{12}H_9F_2N_2$ ($M+H^+$): 219.0728. Found: 219.0723.

**(*E*)-1, 2-bis(2-fluorophenyl)diazene (2q)**



**2q**

Purified directly by flash column chromatography (On silica gel, 99 / 1 pentane / ethyl acetate eluent) to give a yellow crystal (81 mg, 0.37 mmol, yield: 74%). The spectral data matched that reported in the literature.[83]

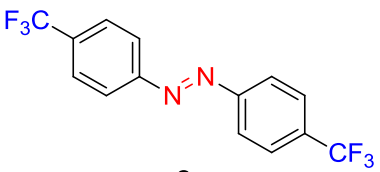
**$^{1}$H NMR (300 MHz, $CDCl_3$)** δ 7.85-7.77 (m, 2H), 7.60-7.42 (m, 2H), 7.38-7.20 (m, 4H), 7.16-6.82 (m, 2H).

**$^{13}$C NMR (75 MHz, $CDCl_3$)** δ 160.4 (d, $J$ = 257.4 Hz), 140.8 (d, $J$ = 6.3 Hz), 133.0 (d, $J$ = 8.1 Hz), 124.4 (d, $J$ = 3.6 Hz), 117.9, 117.1 (d, $J$ = 18.9 Hz).

**$^{19}$F NMR (235 MHz, $CDCl_3$)** δ = -124.1 (s).

**HRMS (ESI)** Calcd for $C_{12}H_9F_2N_2$ ($M+H^+$): 219.0728. Found: 219.0727.

**(*E*)-1, 2-bis(4-(trifluoromethyl)phenyl)diazene (2r)**



**2r**

[83] Geng, X; Wang, C. *Org. Lett*. **2015**, *17*, 2434−2437.

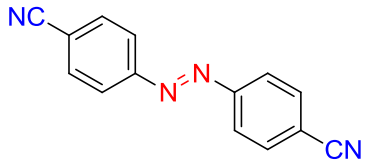
Purified directly by flash column chromatography (On silica gel, 99 / 1 pentane / ethyl acetate eluent) to give a yellow crystal (129 mg, 0.41 mmol, yield: 81%). The spectral data matched that reported in the literature.[84]

**$^1$H NMR (360 MHz, CDCl3)** δ 8.05 (d, *J* = 8.3 Hz, 4H), 7.82 (d, *J* = 8.3 Hz, 4H).

**$^{13}$C NMR (90 MHz, CDCl3)** δ 154.3, 133.2 (q, *J* = 32.8 Hz), 126.6 (d, *J* = 3.9 Hz), 124.0 (d, *J* = 270.5 Hz), 123.6.

**HRMS (ESI)** Calcd for $C_{14}H_9F_6N_2$ ($M+H^+$): 319.0664. Found: 319.0658.

**(*E*)-4,4'-(diazene-1,2-diyl)dibenzonitrile (2s)**




**2s**

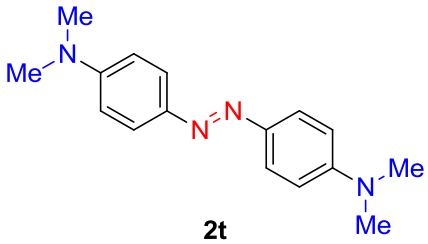
Purified directly by flash column chromatography (On silica gel, 80 / 20 pentane / ethyl acetate eluent) to give a yellow crystal (93 mg, 0.40 mmol, yield: 80%). The spectral data matched that reported in the literature.[85]

**$^1$H NMR (360 MHz, CDCl$_3$)** δ 8.06 (d, *J* = 8.4 Hz, 4H), 7.87 (d, *J* = 8.5 Hz, 4H).

**$^{13}$C NMR (90 MHz, CDCl$_3$)** δ 154.0, 133.4, 123.8, 118.2, 115.1.

**HRMS (ESI)** Calcd for $C_{14}H_9N_4$ ($M+H^+$): 233.0822. Found: 233.0826.

**(*E*)-4,4'-(diazene-1,2-diyl)bis(*N*,*N*-dimethylaniline) (2t)**




**2t**

Purified directly by flash column chromatography (On silica gel, 65 / 35 pentane / ethyl acetate eluent) to give an orange crystal (118 mg, 0.43 mmol, yield: 85%). The spectral data matched that reported in the literature.[76]

**$^1$H NMR (250 MHz, CDCl$_3$)** δ 7.85 (d, *J* = 9.0 Hz, 4H), 6.79 (d, *J* = 9.1 Hz, 4H), 3.09 (s, 12H).

**$^{13}$C NMR (63 MHz, CDCl$_3$)** δ 151.5, 144.1, 124.0, 111.8, 40.4.

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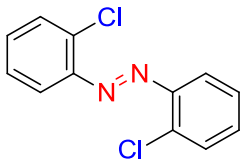
[84] Abramovitch, R. A.; Challand, S. R.; Scriven, E. F. V. *J. Org. Chem*. **1972**, *37*, 2705-2710.
[85] Sakai, N.; Fujii, K.; Nabeshima, S.; Ikeda, R.; Konakahara, T. *Chem. Commun*. 2010, **46**, 3173-3175.

**HRMS (ESI)** Calcd for $C_{16}H_{21}N_4$ ($M+H^+$): 269.1761. Found: 269.1748.

**(*E*)-1, 2-bis(2-chlorophenyl)diazene (2u)**



**2u**

Purified directly by flash column chromatography (On silica gel, 99 / 1 pentane / ethyl acetate eluent) to give a yellow crystal (67 mg, 0.27 mmol, yield: 53%). The spectral data matched that reported in the literature.[83]

**$^1$H NMR (300 MHz, $CDCl_3$)** δ 7.76 (dd, *J* = 7.5, 1.9 Hz, 2H), 7.55 (dd, *J* = 7.5, 1.9 Hz, 2H), 7.44-7.30 (m, 4H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 149.0, 136.1, 132.5, 131.0, 127.6, 118.3.

**HRMS (ESI)** Calcd for $C_{12}H_9Cl_2N_2$ ($M+H^+$): 251.0137. Found: 251.0130.

## II. 6. 3. General procedure for the synthesis of asymmetrical azo compounds

### II. 6. 3. 1. Stoichiometric conditions for asymmetrical azo compounds

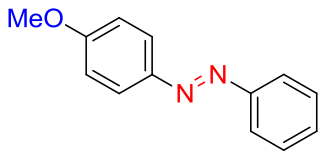
Under argon, reactions were carried out in a one compartment cell containing a magnetic stirring bar, samarium anode (20 $cm^2$ area), glassy carbon cathode (20 $cm^2$ area) and SCE as reference electrode. The cell is then charged with 50mL of electrolyte solution containing 0.04 M $n$Bu$_4$NPF$_6$ in degassed anhydrous THF, $n$Bu$_4$NI (8.0 mmol) as the source of iodide and 0.25 mmol and 0.75 mmol of two nitrobenzenes. The electrolysis was performed at i = 50 mA during 16200 seconds (time estimated for generating 4 mmol of $SmI_2$). During the electrolysis, the samarium rod act as anode and glassy carbon as cathode. The mixture was then diluted by $Et_2O$ (50 mL), quenched with $NaHCO_3$ (20 mL) and extracted witAh diethylether (3×20 mL). The combined extracts were washed with sodium thiosulfate and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel. The resulting compounds were identified by comparison of their physical and spectral data with those given in the literature.

## II. 6. 3. 2. Catalytic conditions for asymmetrical azo compounds

The reactions were carried out in an electrochemical cell containing a magnet, a samarium and a carbon electrode. $n$Bu$_4$NI (2.21g, 6.0 mmol) and $n$Bu$_4$NPF$_6$ (780 mg, 2.0 mmol, 0.04 mol/L) were added in the electrochemical cell, changed the air into argon and THF (50 ml) was added. The pre-electrolysis (samarium electrode as the anode) was performed at I= 50 mA during 400 seconds (time estimated for generating 0.1 mmol $SmI_2$). After the pre-electrolysis a dark blue solution was observed, two substrates (0.25 mmol and 0.75 mmol) and TMSCl (218 mg, 0.26 ml, 2.0 mmol) were added into the mixture sequentially. The polarity of electrodes was reversed that the samarium electrode as the cathode, then electrified which was performed at I= 50 mA at room temperature for 4.0 hours. The mixture was diluted by $Et_2O$ (50 ml), quenched by sat. $NaHCO_3$ (20 ml), extracted with $Et_2O$ (20 ml × 2), washed the organic phase by brine (20 ml), dried over $MgSO_4$, the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel to afford the pure products.

## II. 6. 3. 3. Characterization data of asymmetrical azo compounds

**(*E*)-1-(4-methoxyphenyl)-2-phenyldiazene (5a)**




**5a**

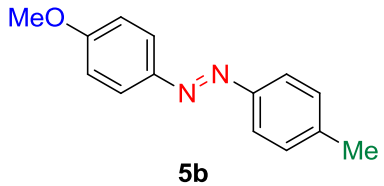
Purified directly by flash column chromatography (On silica gel, 99 / 1 pentane / ethyl acetate eluent) to give a yellow crystal (44 mg, 0.21 mmol, yield: 83%). The spectral data matched that reported in the literature.[78]

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.92 (d, $J$ = 9.0 Hz, 2H), 7.87 (d, $J$ = 7.6 Hz, 2H), 7.51-7.40 (m, 3H), 7.00 (d, $J$ = 9.0 Hz, 2H), 3.88 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 162.3, 153.0, 147.2, 130.6, 129.2, 124.9, 122.8, 114.4, 55.8.

**HRMS (ESI)** Calcd for $C_{13}H_{13}N_2O$ ($M+H^+$): 213.1022. Found: 213.1020.

**(*E*)-1-(4-methoxyphenyl)-2-(*p*-tolyl)diazene (5b)**




**5b**

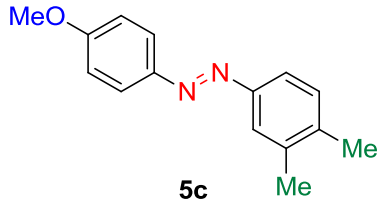
Purified directly by flash column chromatography (On silica gel, 98 / 2 pentane / ethyl acetate eluent) to give an orange crystal (45 mg, 0.20 mmol, yield: 80%). The spectral data matched that reported in the literature.[75]

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.89 (d, *J* = 9.0 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 6.99 (d, *J* = 9.0 Hz, 2H), 3.87 (s, 3H), 2.41 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 162.0, 151.0, 147.3, 141.0, 130.0, 124.8, 122.7, 114.4, 55.8, 21.6.

**HRMS (ESI)** Calcd for $C_{14}H_{15}N_2O$ ($M+H^+$): 227.1179. Found: 227.1175.

**(*E*)-1-(3,4-dimethylphenyl)-2-(4-methoxyphenyl)diazene (5c)**




**5c**

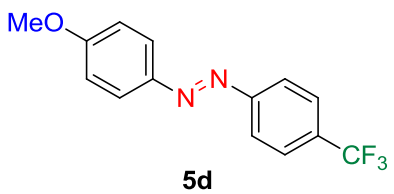
Purified directly by flash column chromatography (On silica gel, 98 / 2 pentane / ethyl acetate eluent) to give an orange crystal (49 mg, 0.20 mmol, yield: 81%). The spectral data matched that reported in the literature.[78]

**$^1$H NMR (300 MHz, $CDCl_3$)** δ 7.93 (d, *J* = 9.0 Hz, 2H), 7.69 (s, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.04 (d, *J* = 9.0 Hz, 2H), 3.91 (s, 3H), 2.38 (s, 3H), 2.36 (s, 3H).

**$^{13}$C NMR (75 MHz, $CDCl_3$)** δ 161.8, 151.2, 147.1, 139.6, 137.3, 130.2, 124.5, 123.2, 120.6, 114.2, 55.6, 19.9, 19.8.

**HRMS (ESI)** Calcd for $C_{15}H_{17}N_2O$ ($M+H^+$): 241.1335. Found: 241.1332.

**(*E*)-1-(4-methoxyphenyl)-2-(4-(trifluoromethyl)phenyl)diazene (5d)**




**5d**

Purified directly by flash column chromatography (On silica gel, 99 / 1 pentane / ethyl acetate eluent) to give an orange crystal (65 mg, 0.23 mmol, yield: 93%). The spectral data matched that reported in the literature.[86]

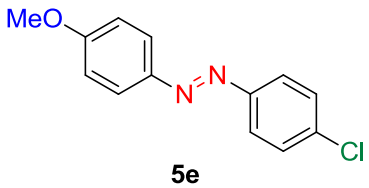
**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 7.96-7-90 (m, 4H), 7.73 (d, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 9.0 Hz, 2H), 3.88 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 162.7, 154.6, 146.9, 129.7, 126.2 (d, *J* = 3.6 Hz), 125.2, 123.5 (q, *J* = 180 Hz), 122.7, 114.3, 55.7.

**$^{19}$F NMR (235 MHz, $CDCl_3$)** δ = -62.4 (s).

**HRMS (ESI)** Calcd for $C_{14}H_{12}F_3N_2O$ ($M+H^+$): 281.0896. Found: 281.0893

**(*E*)-1-(4-chlorophenyl)-2-(4-methoxyphenyl)diazene (5e)**




**5e**

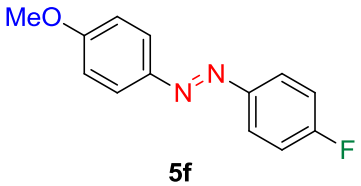
Purified directly by flash column chromatography (On silica gel, 99 / 1 pentane / ethyl acetate eluent) to give an orange crystal (57 mg, 0.23 mmol, yield: 92%). The spectral data matched that reported in the literature.[78]

**$^{1}$H NMR (250 MHz, $CDCl_3$)** δ 7.90 (d, *J* = 9.0 Hz, 2H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 9.0 Hz, 2H), 3.88 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 162.5, 151.3, 147.1, 136.4, 129.5, 125.1, 124.0, 114.5, 55.8.

**HRMS (ESI)** Calcd for $C_{13}H_{12}ClN_2O$ ($M+H^+$): 247.0633. Found: 247.0626.

**(*E*)-1-(4-fluorophenyl)-2-(4-methoxyphenyl)diazene (5f)**




**5f**

Purified directly by flash column chromatography (On silica gel, 99 / 1 pentane / ethyl acetate eluent) to give an orange crystal (55 mg, 0.24 mmol, yield: 95%). The spectral data matched that reported in the literature.[78]

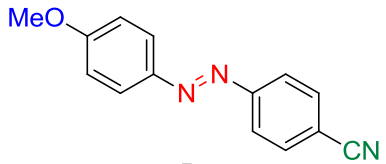
[86] Yang, Z.; Hou, S.; He, W.; Cheng, B.; Jiao, P.; Xu, J. *Tetrahedron* **2016**, *72*, 2186-2195.

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.89 (d, *J* = 9.0 Hz, 2H), 7.88 (t, *J* = 8.6 Hz, 2H), 7.16 (d, *J* = 8.6 Hz, 2H), 7.00 (d, *J* = 9.0 Hz, 2H), 3.88 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 164.2 (d, *J* = 250.7 Hz, C), 162.3, 149.5, 147.1, 124.9, 124.7 (d, *J* = 9.2 Hz, C), 116.1 (d, *J* = 22.3 Hz, C), 114.5, 55.8.

**HRMS (ESI)** Calcd for $C_{13}H_{12}FN_2O$ ($M+H^+$): 231.0928. Found: 231.0929.

**(*E*)-4-((4-methoxyphenyl)diazenyl)benzonitrile (5g)**




**5g**

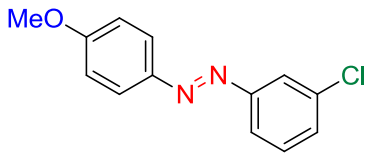
Purified directly by flash column chromatography (On silica gel, 99 / 1 pentane / ethyl acetate eluent) to give an orange crystal (101 mg, 0.43 mmol, yield: 85%). The spectral data matched that reported in the literature.[86]

**$^1$H NMR (300 MHz, $CDCl_3$)** δ 7.93 (d, *J* = 8.7 Hz, 2H), 7.92 (d, *J* = 8.7 Hz, 2H), 7.77 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 3.89 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 163.3, 155.0, 147.1, 133.4, 125.7, 123.3, 118.9, 114.6, 113.4, 55.9.

**HRMS (ESI)** Calcd for $C_{14}H_{12}N_3O$ ($M+H^+$): 238.0975. Found: 238.0974.

**(*E*)-1-(3-chlorophenyl)-2-(4-methoxyphenyl)diazene (5h)**




**5h**

Purified directly by flash column chromatography (On silica gel, 99 / 1 pentane / ethyl acetate eluent) to give an orange crystal (53 mg, 0.22 mmol, yield: 86%).

**Melting point**: 106- 108 °C

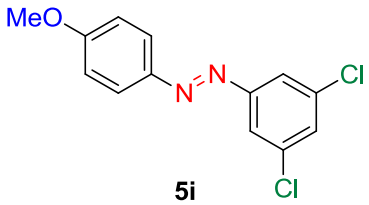
**IR (film) $\nu_{max}$:** 3068, 3005, 2960, 2929, 2837, 1600, 1584, 1502, 1458, 1254, 1180, 1142, 1030, 837 $cm^{-1}$.

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.90 (d, *J* = 9.0 Hz, 2H), 7.87 (t, *J* = 1.8 Hz, 1H), 7.79 (dt, *J* = 7.2, 1.8 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.41 (dt, *J* = 7.2, 1.8 Hz, 1H), 6.99 (d, *J* = 9.0 Hz, 2H), 3.87 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 162.7, 153.8, 147.0, 135.2, 130.2, 125.2, 122.3, 121.7, 114.5, 55.8.

**HRMS (ESI)** Calcd for $C_{13}H_{12}ClN_2O$ ($M+H^+$): 247.0633. Found: 247.0629.

**(*E*)-1-(3,5-dichlorophenyl)-2-(4-methoxyphenyl)diazene (5i)**




**5i**

Purified directly by flash column chromatography (On silica gel, 99 / 1 pentane / ethyl acetate eluent) to give an orange crystal (63 mg, 0.23 mmol, yield: 90%).

**Melting point**: 76-78 °C

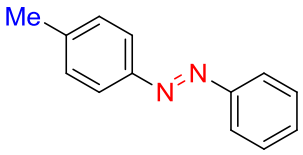
**IR (film) $\nu_{max}$:** 3083, 3003, 2965, 2946, 2929, 2839, 1601, 1583, 1502, 1462, 1409, 1297, 1254, 1144, 1033, 959, 854, 834, 802, 666 $cm^{-1}$.

**$^1$H NMR (300 MHz, $CDCl_3$)** δ 7.89 (d, $J$ = 9.0 Hz, 2H), 7.74 (d, $J$ = 1.8 Hz, 1H), 7.39 (t, $J$ = 1.8 Hz, 2H), 7.00 (d, $J$ = 9.0 Hz, 2H), 3.88 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 163.1, 154.2, 146.8, 135.7, 129.8, 125.5, 121.4, 114.6, 55.9.

**HRMS (ESI)** Calcd for $C_{13}H_{11}Cl_2N_2O$ ($M+H^+$): 281.0243. Found: 281.0242.

**(*E*)-1-phenyl-2-(*p*-tolyl)diazene (5j)**




**5j**

Purified directly by flash column chromatography (On silica gel, pentane eluent) to give a yellow crystal (43 mg, 0.22 mmol, yield: 88%). The spectral data matched that reported in the literature.[87]

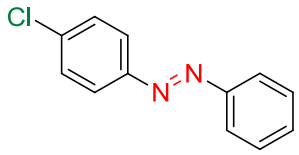
**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.93-7.86 (m, 2H), 7.82 (d, $J$ = 8.3 Hz, 2H), 7.53-7.39 (m, 3H), 7.30 (d, $J$ = 8.3 Hz, 2H), 2.42 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 153.0, 151.0, 141.8, 130.9, 130.0, 129.3, 123.1, 122.9, 21.7.

[87] Wang, L.; Ishida, A.; Hashidoko, Y.; Hashimoto, M. *Angew.Chem. Int. Ed*. **2017**, *56*, 870 –873.

**HRMS (ESI)** Calcd for $C_{13}H_{13}N_2$ ($M+H^+$): 197.1073. Found: 197.1077.

**(*E*)-1-(4-chlorophenyl)-2-phenyldiazene (5k)**



**5k**

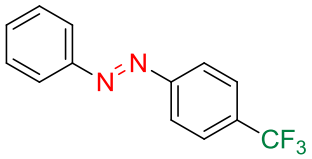
Purified directly by flash column chromatography (On silica gel, pentane eluent) to give a yellow crystal (42 mg, 0.19 mmol, yield: 77%). The spectral data matched that reported in the literature.[88]

**$^1$H NMR (250 MHz, $CDCl_3$)** δ 7.94-7.82 (m, 4H), 7.56-7.42 (m, 5H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 152.7, 151.2, 137.1, 131.5, 129.5, 129.3, 124.3, 123.1.

**HRMS (ESI)** Calcd for $C_{12}H_{10}ClN_2$ ($M+H^+$): 217.0527. Found: 217.0528.

**(*E*)-1-phenyl-2-(4-(trifluoromethyl)phenyl)diazene (5l)**



**5l**

Purified directly by flash column chromatography (On silica gel, pentane eluent) to give a yellow crystal (56 mg, 0.22 mmol, yield: 90%). The spectral data matched that reported in the literature.[89]

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.99 (d, $J$ = 8.6 Hz, 2H), 7.96-7.91 (m, 2H), 7.77 (d, $J$ = 8.6 Hz, 2H), 7.56-7.49 (m, 3H).

**$^{13}$C NMR (75 MHz, $CDCl_3$)** δ 154.4, 152.4, 131.8, 129.2, 126.3, 123.2, 123.0.

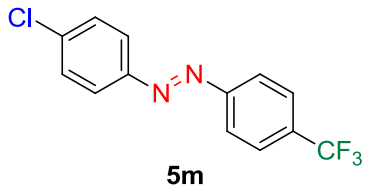
**$^{19}$F NMR (235 MHz, $CDCl_3$)** δ = -62.5 (s).

**HRMS (ESI)** Calcd for $C_{13}H_{10}F_3N_2$ ($M+H^+$): 251.0791. Found: 251.0797.

**(*E*)-1-(4-chlorophenyl)-2-(4-(trifluoromethyl)phenyl)diazene (5m)**

[88] Li, H.-Q.; Liu, X.; Zhang, Q.; Li, S.-S.; Liu, Y.-M.; He, H.-Y.; Cao, Y. *Chem. Commun.*, **2015**, *51*, 11217-11220.

[89] Dai, J. J.; Fang, C.; Xiao, B.; Yi, J.; Xu, J.; Liu, Z. J.; Lu, X.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135,* 8436−843.




**5m**

Purified directly by flash column chromatography (On silica gel, pentane eluent) to give a yellow crystal (57 mg, 0.20 mmol, yield: 80%).

**Melting point**: 113-115 °C

**IR (film) $\nu_{max}$:** 2929, 1938, 1608, 1585, 1480, 1407, 1328, 1142, 1103, 1065, 1009, 857, 605 $cm^{-1}$

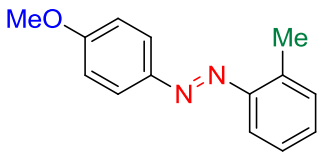
**$^1$H NMR (360 MHz, $CDCl_3$)** δ 8.02 (d, *J* = 8.2 Hz, 2H), 7.95 – 7.90 (m, 2H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.57 – 7.51 (m, 2H).

**$^{13}$C NMR (100 MHz, $CDCl_3$)** δ 154.2, 150.7, 137.9, 132.5 (q, *J* = 32.3 Hz), 129.5, 126.4 (d, *J* = 3.0 Hz), 124.4, 123.1

**$^{19}$F NMR (235 MHz, $CDCl_3$)** δ -62.6.

**HRMS (ESI)** Calcd for $C_{13}H_9ClF_3N_2$ ($M+H^+$): 285.0401. Found: 285.0406.

**(*E*)-1-(4-methoxyphenyl)-2-(*o*-tolyl)diazene (5n)**




**5n**

Purified directly by flash column chromatography (On silica gel, 98 / 2 pentane / ethyl acetate eluent) to give an orange crystal (45 mg, 0.20 mmol, yield: 80%).

**Melting point**: 55- 58 °C

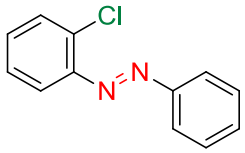
**IR (film) $\nu_{max}$:** 3061, 3004, 2959, 2927, 2837, 1601, 1584, 1502, 1455, 1415, 1295, 1252, 1144, 1032, 837, 763 $cm^{-1}$.

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.96 (d, *J* = 8.6 Hz, 2H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.40-7.25 (m, 3H), 7.04 (d, *J* = 8.6 Hz, 2H), 3.92 (s, 3H), 2.73 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 162.1, 151.0, 147.7, 137.7, 131.3, 130.5, 126.6, 125.0, 115.6, 114.4, 55.8, 17.7.

**HRMS (ESI)** Calcd for $C_{14}H_{15}N_2O$ ($M+H^+$): 227.1179. Found: 227.1181.

**(*E*)-1-(2-chlorophenyl)-2-phenyldiazene (5o)**




**5o**

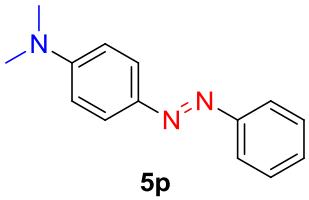
Purified directly by flash column chromatography (On silica gel, pentane eluent) to give a yellow crystal (43 mg, 0.20 mmol, yield: 88%). The spectral data matched that reported in the literature.[88]

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 8.00 (dd, *J* = 8.0, 1.7 Hz, 2H), 7.72 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.61 – 7.51 (m, 4H), 7.45 – 7.34 (m, 2H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 152.8, 148.7, 131.7, 131.6, 130.7, 129.2, 127.3, 123.4, 117.6.

**HRMS (ESI)** Calcd for $C_{12}H_{10}ClN_2$ ($M+H^+$): 217.0527. Found: 217.0526.

**(*E*)-*N*,*N*-dimethyl-4-(phenyldiazenyl)aniline (5p)**




**5p**

Purified directly by flash column chromatography (On silica gel, 80 / 20 pentane / ethyl acetate eluent) to give an orange crystal (96 mg, 0.43 mmol, yield: 85%). The spectral data matched that reported in the literature.[90]

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.91 (d, *J* = 9.0 Hz, 2H), 7.86 (d, *J* = 7.7 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 7.3 Hz, 1H), 6.79 (d, *J* = 9.1 Hz, 2H), 3.11 (s, 6H).

**$^{13}$C NMR (63 MHz, $CDCl_3$)** δ 153.2, 152.5, 143.7, 129.4, 128.9, 125.0, 122.2, 111.6, 40.4.

**HRMS (ESI)** Calcd for $C_{14}H_{16}N_3$ ($M+H^+$): 226.1339. Found: 226.1330.

[90] Chermahini, A. N.; Doukheh, M.; Hassan, Z. H.; Bostanian, M. *J. Ind. Eng. Chem.* **2012**, *18*, 826-833.

# Chapter III. The $Sm^{2+}$ electrocatalytic reduction of nitroarenes into amino aromatics

## III. 1. Introduction

In the previous chapter, we successfully established the $Sm^{II}$ electrocatalytic process for the selective reduction of nitrobenzenes to azobenzenes. During the optimization, we found that the amount of MeOH impacted dramatically the chemoselectivity (see Chapter II.2.1). Therefore, we decided to see if it is possible to convert directly and selectively the nitrobenzenes into anilines in catalytic manner.

The series of aromatic amines are basis in the modern industry. Especially, aniline and amino pyridine derivatives are indispensable building block which are widely used in the synthesis of dyes and pigments, pharmaceuticals, polymers, materials, biochemicals and agrochemicals.[91] Although a large number of methodologies was established, the reduction of nitroarenes is the most prominent. The current preparation methods which rely on hydrogenation of nitro aromatic compounds were based on the metal-catalyst with hydrogen gas, $NaBH_4$, silyl hydrides or other reductants.[91, 92]

Among the numerous available metals, the noble metals based catalysts such as Pt, Au, Ru and so on were widely used in the reduction of nitro aromatic into anilines.

## III. 2. 1. Catalytic reduction of nitroarenes into anilines by noble metals

In 2008, Motoyama and co-workers reported a catalytic system consisting of nanoplatinum particles dispersed on nanocarbon fiber support, Pt/CNF-P (3-10 atm $H_2$) (Scheme 3.1 (**1**)).[93] This system was used in the hydrogenation of nitroarenes to aromatic amines with other functional groups remaining intact. Later on, they improved

[91] (a) Downing,R. S.; Kunkeler, P. J.; Van Bekkum, H. *Catal. Today*, **1997**, *37*, 121–136; (b) Suchy,M.; Winternitz, P.; Zeller, M. World (WO) Patent 91/00278, 1991; (c) Ono, N. Alkylation, acylation and halogenation of nitro compounds. In *The Nitro Group in Organic Synthesis*; Terrier, F.: Wiley-VCH, New York, 2001; pp. 126–158.

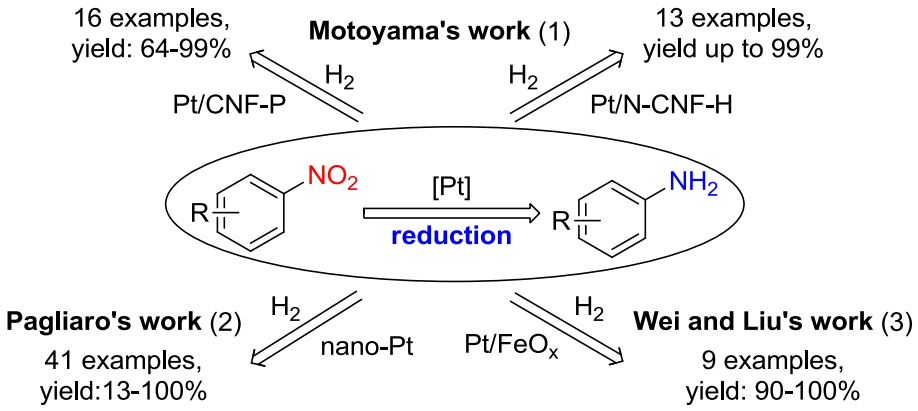
[92] Reviews: (a) Blaser, H. U.; Siegrist, U.; Steiner, H.; Studer, M. Catalystic hydrogenation and dehydrogenation. In *Fine Chemicals through Heterogeneous Catalysis*; Wiley-VCH: Weinheim, Germany, 2001; pp. 351-472) (b) Tafesh, A. M.; Weiguny, J. *Chem. Rev.*, **1996**, *96*, 2035-2052. (c) Downing, R. S.; Kunkeler, P. J.; van Bekkum, H. *Catal. Today* **1997**, *37*, 121-136. (e) Adams, J. P. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2586-2597.

[93] Takasaki, M.; Motoyama, Y.; Higashi, K.; Yoon, S.-H.; Mochida, I.; Nagashima, H.; *Org. Lett.* **2008,** *10,* 1601-1604.

platinum nanoparticles supported on nitrogen-doped (5 wt%) carbon nanofibers (N-CNF-H) with narrow size distributions (Scheme 3.1 (**1**)).[94] Pt/N-CNF-H compounds were found to act as efficient poisoning catalysts in the hydrogenation of nitroarenes, and the catalytic activity can be controlled by an appropriate choice of the platinum/nitrogen ratio. The hydrogenation of substituted nitroarenes over Pt (3 wt%)/N-CNF-H afforded the corresponding anilines in high yields with high functional groups tolerance.

At the same time, Pagliaro and co-workers developed a new series of nanostructured platinum catalysts to catalyze the selective reduction of nitroarenes by $H_2$ (Scheme 3.1 (**2**)).[95] The materials, made of organosilica physically doped with nanostructured platinum(0), are stable and efficient.

In 2014, Wei and Liu's group introduced highly active and chemoselective catalysts for hydrogenation of substituted nitroarenes by Pt/FeOx nanocrystallites under mild reaction conditions (40˚C, 3 bar $H_2$) (Scheme 3.1 (**3**)).[96] The anilines were afforded in high functional tolerance and excellent reusability of the heterogeneous catalyst.




**Scheme 3.1** The Pt catalyzed reduction of nitroarenes

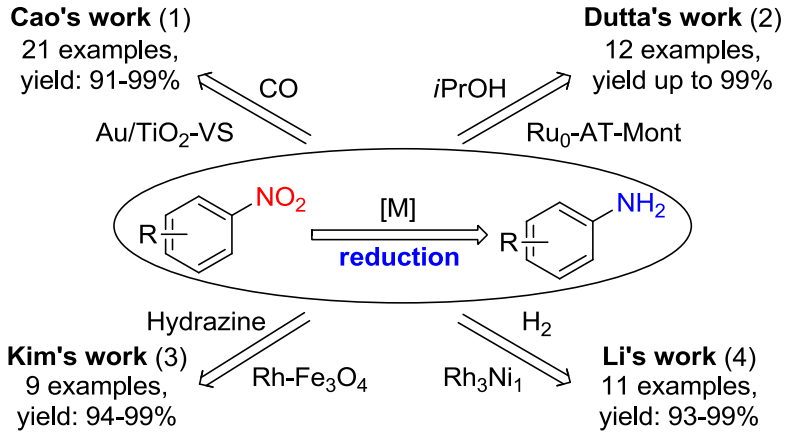
In 2009, gold could also be used as catalyst for the reduction of nitroarenes. In this context, Cao's group published an exceedingly efficient and highly chemoselective gold-catalyzed approach for the reduction of a wide range of organic nitro compounds to their corresponding amines with cheap and readily accessible CO (5 atm) and $H_2O$

[94] Motoyama, Y.; Lee, Y.; Tsuji, K.; Yoon, S.-H.; Mochida, I.; Nagashima, H.; *ChemCatChem* **2011,** *3,* 1578-1581.
[95] Pandarus, V.; Ciriminna, R.; Béland, F.; Pagliaro, M. *Adv. Synth. Catal*. **2011**, *353,* 1306-1316.
[96] Wei, H.; Liu, X.; Wang, A.; Zhang, L.; Qiao, B.; Yang, X.; Huang, Y.; Miao, S.; Liu, J.; Zhang, T. *Nat. Commun.* **2014,** *5,* 5634-5641.

as the hydrogen source (Scheme 3.2 (**1**)).[97] The room-temperature condition with the low operational pressure make this method readily adaptable to production at industrial scale.

In 2012, Dutta's group developed the 5 nm $Ru^0$-nanoparticles which are synthesized into the nanopores by impregnating $RuCl_3$ into the pores of the acid activated Mont (Montmorillonite) followed by polyol reduction. (Scheme 3.2 (**2**)).[98] The $Ru^0$-nanoparticles used as catalyst showed high activity and selectivity in the transfer hydrogen of substituted nitrobenzenes into the corresponding anilines. The heterogeneous catalyst is also found to remain active for several runs without significant loss in activity.

The facile synthesis of Rh-$Fe_3O_4$ heterodimer nanocrystals was reported by Kim and Hyeon *et al* (Scheme 3.2 (**3**)).[99] These heterodimer nanocrystals-catalyzed reduction of nitroarenes with good selectivity. The advantage of this method is the catalyst can be easily separated using a magnet and had good activity until 8 time's recycling. Besides, Li and co-workers demonstrated a series of novel bimetallic $Rh_xNi_y$ (x, y = 1, 2, 3) nanoparticles (Scheme 3.2 (**4**)).[100] Among that, $Rh_3Ni_1$ catalyst was highly active and selective for the hydrogenation of a scope of nitroarenes bearing various reducible groups.



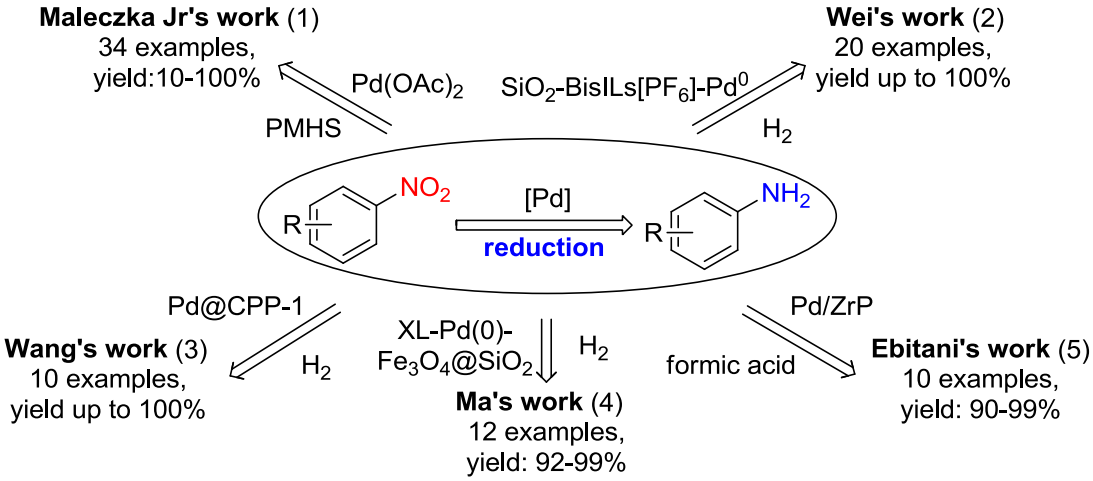

**Scheme 3.2** The other noble metals catalyzed reduction of nitroarenes

[97] He, L.; Wang, L.-C.; Sun, H.; Ni, J.; Cao, Y.; He, H.-Y.; Fan, K.-N. *Angew. Chem., Int. Ed.* **2009,** *48,* 9538-9541.
[98] Sarmah, P. P.; Dutta, D. K. *Green Chem.* **2012,** *14,* 1086-1093.
[99] Jang, Y.; Kim, S.; Jun, S. W.; Kim, B. H.; Hwang, S.; Song, I. K.; Kim, B. M.; Hyeon, T. *Chem. Commun.* **2011,** *47,* 3601-3603.
[100] Cai, S.; Duan, H.; Rong, H.; Wang, D.; Li, L.; He, W.; Li, Y. *ACS Catal.* **2013,** *3,* 608-612.

Pd catalysts are widely used in the reduction of organic functions. In 2005, Maleczka, Jr's group synthesized the nanoparticles from $Pd(OAc)_2$ and PMHS, in combination with aqueous KF, rapidly and mildly reduce nitro-substituted arenes and heteroarenes to corresponding amines in high yields (Scheme 3.3 (**1**)). [101] By substituting PMHS/KF with $Et_3SiH$, room-temperature reductions of aliphatic nitro groups are also viable. Both variations of the method exhibit good functional group compatibility. Recently, the Pd complexes ($SiO_2$-BisILs[$PF_6$]-$Pd^0$) exhibited benign reactivity on the nitroarenes. Wei's group developed an environmentally benign catalyst and procedure for the hydrogenation of nitro aromatics to arylamines by $H_2$ (Scheme 3.3 (**2**)).[102] This catalytic assembly combines the advantages of an ionic liquid, Pd nanoparticles, and a heterogeneous catalyst. Moreover, Wang's group developed the ultrafine palladium NPs with uniform distribution exhibit superior stability and recyclability (Scheme 3.3 (**3**)). [103] With the palladium NPs catalyst, the reaction presented a high reactivity in the hydrogenation of nitroarenes, and no obvious agglomeration and loss of catalytic activity were observed after recycling several times.

At the same time, Ma and co-workers described a methodology towards entangled Pd complexes over $Fe_3O_4@SiO_2$ (Scheme 3.3 (**4**)).[104] In this system, because of their surface "cross-linked" groups, the novel catalyst was successfully applied to hydrogenation of nitroarenes a high activity and durability. Furthermore, Ebitani's group published a highly efficient, base-free, heterogeneously Pd/ZrP catalyst for the synthesis of industrially important anilines by formic acid (Scheme 3.3 (**5**)).[105] The reaction illustrated the selective transfer hydrogenation of various functionalized nitroarenes to the corresponding anilines with excellent yields.

[101] Rahaim, R. J., Jr.; Maleczka, R. E., Jr. *Org. Lett.* **2005,** *7,* 5087-5090.
[102] Li, J.; Shi, X.-Y.; Bi, Y.-Y.; Wei, J.-F.; Chen, Z.-G. *ACS Catal.* **2011,** *1,* 657-664.
[103] Li, L.; Zhao, H.; Wang, J.; Wang, R. *ACS Nano* **2017,** *11,* 7572-7586.
[104] Wang, P.; Liu, H.; Niu, J.; Li, R.; Ma, J. *Catal. Sci. Technol.* **2014,** *4,* 1333-1339.
[105] Tuteja, J.; Nishimura, S.; Ebitani, K. *RSC Adv.* **2014,** *4,* 38241-38249.




**Scheme 3.3** The Pd catalyzed reduction of nitroarenes

Based on the noble metal heterogeneous catalysts, the reduction of nitroarenes presented high chemoselectivity and efficiency (up to 100% yield), which exhibited many advantages in this area. However, the drawbacks still existed. Normally, the catalysts were prepared by several steps and the high pressure or temperature were needed in this transformation.

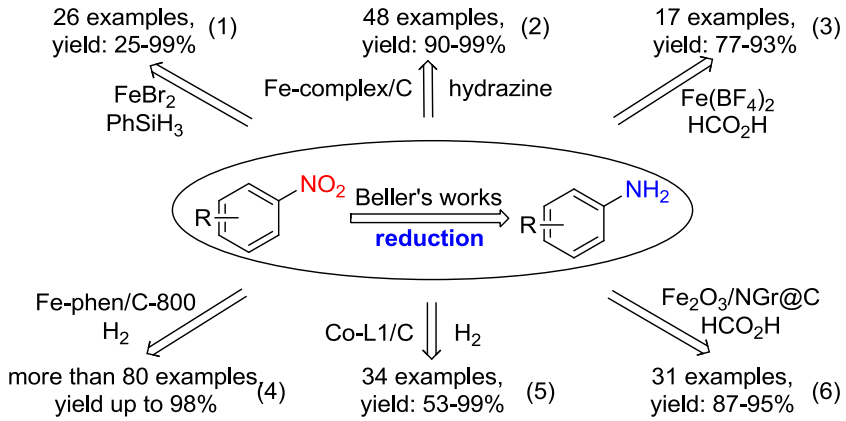
## III. 2. 2. Catalytic reduction of nitroarenes into anilines by base metals

Besides, the earth abundant metals (Fe, Co, Ni, Mo) were developed to catalyze this reduction of nitroarenes.

Since 2010, Beller's group has focused on the iron-catalyst and published several works on it. Firstly, they demonstrated the iron-based catalytic system consisting of $FeBr_2$-$Ph_3P$ for the reduction of nitroarenes with $PhSiH_3$ (Scheme 3.4 (**1**)).[106] The procedure is general and the selectivity of the catalyst has been demonstrated applying challenging substrates with C=O, C=N, C=C, and OH groups. One year later, they described an inexpensive and recyclable iron catalyst system is introduced for the efficient reduction of nitro compounds using hydrazine hydrate (Scheme 3.4 (**2**)).[107] In the same year, a novel transfer reduction of industrially important nitroarenes was

[106] Junge, K.; Wendt, B.; Shaikh, N.; Beller, M. *Chem. Commun.* **2010,** *46,* 1769-1771.
[107] Jagadeesh, R. V.; Wienhöfer, G.; Westerhaus, F. A.; Surkus, A.-E.; Pohl, M.-M.; Junge, H.; Junge, K.; Beller, M. *Chem. Commun.* **2011,** *47,* 10972-10974.

reported.[108] In the presence of well-defined iron complexes or the in situ combination of $Fe(BF_4)_2 \bullet 6H_2O$ and $P(CH_2CH_2PPh_2)_3$, selective transfer hydrogenation of various functionalized substrates to the corresponding anilines occurred in good to excellent yields at room temperature, and this catalytic process proceeds without any additional base (Scheme 3.4 (**3**)). Later, they introduced a convenient and stable iron oxide ($Fe_2O_3$)–based catalysts for this transformation by $H_2$ (50 bar, 120˚C).[109] Pyrolysis of iron-phenanthroline complexes on carbon furnishes a unique structure in which the active $Fe_2O_3$ particles are surrounded by a nitrogen-doped carbon layer. Highly selective hydrogenation of numerous structurally diverse nitroarenes (more than 80 examples) proceeded in good to excellent yield under industrially viable conditions (Scheme 3.4 (**4**)). Recently, the transfer hydrogen on functionalized and structurally diverse nitro arenes to anilines has been performed using durable and reusable iron oxide-based nanocatalysts (Scheme 3.4 (**6**)).[110] This $Fe_2O_3$/NGr@C catalyst shows a unique selectivity for the nitro group reduction in the presence of diverse functional groups. Instead of Fe, their group demonstrated a Co oxide catalyst system for the industrially important reduction of nitroarenes (Scheme 3.4 (**5**)).[111] It tolerates numerous other reducible functional groups and can be reused several times without loss of activity. Advantageously, during catalysis protective gas techniques or dry solvents are not necessary and reactions can be performed at an increased rate on water.




**Scheme 3.4** The Beller's works about the catalytic reduction of nitroarenes

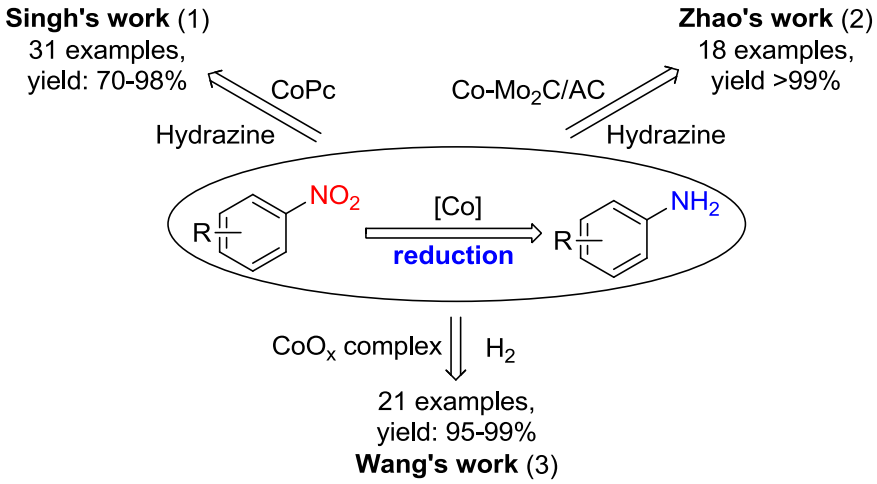
[108] Wienhöfer, G.; Sorribes, I.; Boddien, A.; Westerhaus, F.; Junge, K.; Junge, H.; Llusar, R.; Beller, M. *J. Am. Chem. Soc.* **2011,** *133,* 12875-12879.

[109] Jagadeesh, R. V.; Surkus, A.-E.; Junge, H.; Pohl, M.-M.; Radnik, J.; Rabeah, J.; Huan, H.; Schünemann, V.; Brückner, A.; Beller, M. *Science* **2013,** *342,* 1073-1076.

[110] Jagadeesh, R. V.; Natte, K.; Junge, H.; Beller, M. *ACS Catal.* **2015,** *5,* 1526-1529.

[111] Westerhaus, F. A.; Jagadeesh, R. V.; Wienhöfer, G.; Pohl, M.-M.; Radnik, J.; Surkus, A.-E.; Rabeah, J.; Junge, K.; Junge, H.; Nielsen, M.; Brückner, A.; Beller, M. *Nat. Chem.* **2013,** *5,* 537-543.

Besides, some other Co catalyst systems were also introduced. Indeed, in 2010, Singh's group published the cobalt phthalocyanines as catalysts for a very efficient regio- and chemoselective reduction of aromatic nitro compounds to generate the corresponding amines by the hydrazine (Scheme 3.5 (**1**)).[112] The present process is highly chemoselective and tolerant functional groups. Zhao's group presented a Co modified metal carbides for the chemoselective synthesis of various functionalized arylamines from corresponding nitroarenes by the hydrazine (Scheme 3.5 (**2**)).[113] Recently, Wang's group developed a scalable, environmentally benign, and straightforward strategy for the synthesis of $Co^0/Co_3O_4$@NCNTs (Scheme 3.5 (**3**)).[114] The hybrids display excellent catalytic performance for the hydrogenation of nitroarenes into the corresponding anilines.

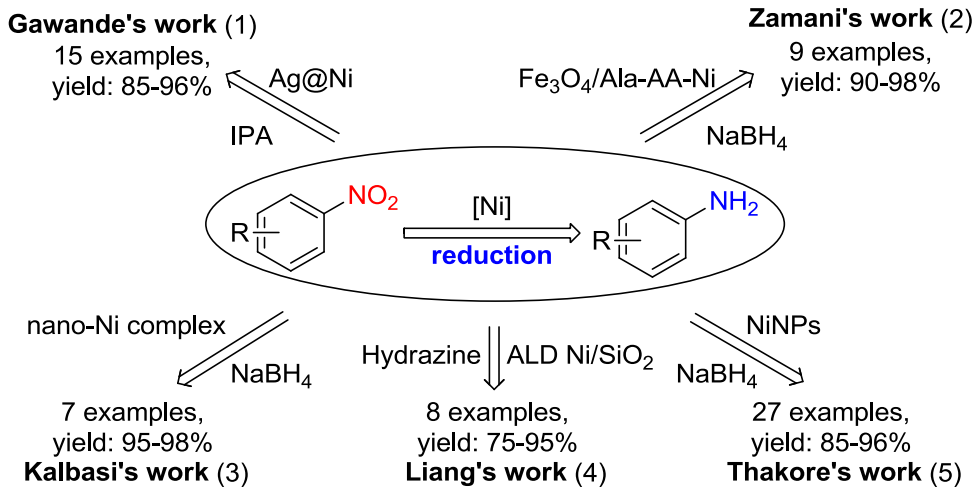



**Scheme 3.5** The Co catalyzed reduction of nitroarenes

As another ferrous element, Ni was also induced to this transformation. In 2013, Gawande and Peng *et al.* designed a magnetic core-shell Ag@Ni nanocatalyst for hydrogen transfer reactions (Scheme 3.6 (**1**)).[115] The reaction was broadly applicable as diverse aromatic nitro was converted to the corresponding amines in excellent yield (85–96%) and short reaction times. In 2014, Zamani's and Kalbasi's groups respectively reported the Ni nanocomposite catalysts in the reduction of various nitro

[112] Sharma, U.; Kumar, P.; Kumar, N.; Kumar, V.; Singha, B. *Adv. Synth. Catal.* **2010,** *352,* 1834-1840.
[113] Zhao, Z.; Yang, H.; Li, Y.; Guo, X. *Green Chem.* **2014,** *16,* 1274-1281.
[114] Wei, Z.; Wang, J.; Mao, S.; Su, D.; Jin, H.; Wang, Y.; Xu, F.; Li, H.; Wang, Y. *ACS Catal.* **2015,** *5,* 4783-4789.
[115] Gawande, M. B.; Guo, H.; Rathi, A. K.; Branco, P. S.; Chen, Y.; Varmad, R. S.; Peng, D.-L. *RSC Advances* **2013,** *3,* 1050-1054.

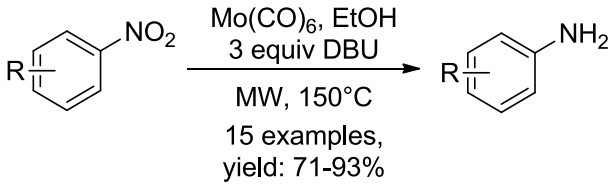
aromatic compounds by $NaBH_4$ in short reaction times and high yields (Scheme 3.6 (**2**) (**3**)).[116, 117] Later, Thakore and co-workers demonstrated the synthesis of IO@Ni core–shell MNPs and their application in reductive catalysis of nitrobenzenes (Scheme 3.6 (**5**)).[118] Notably, the reaction was performed in the environmentally friendly solvent water, moreover, broadly applicable as diverse aromatic nitro compounds were successively converted to the corresponding amines in excellent yield (85–96%). Furthermore, Liang's group described nickel nanoparticles deposited on both porous silica gel particles and 20−30 nm dense silica nanoparticles (Scheme 3.2 (**4**)).[119] The prepared Ni/silica gel catalysts can activate hydrazine hydrate as a reducing agent in the transfer hydrogenation of aryl nitro compounds into the corresponding amines with high selectivity and high yield.




**Scheme 3.6** The Ni catalyzed reduction of nitroarenes

Besides, Spencer's group developed an original $Mo(CO)_6$ catalyst under the microwave-mediated method for the synthesis of a series of anilines from their corresponding nitro precursors, which displays excellent chemoselectivity (Scheme 3.7).[120]

[116] Zamani, F.; Kianpour, S. *Catal. Commun.* **2014,** *45,* 1-6.
[117] Kalbasi, R. J.; Zamani, F. *RSC Adv.* **2014,** *4,* 7444-7453.
[118] Rathore, P. S.; Patidar, R.; Shripathic, T.; Thakore, S. *Catal. Sci. Technol.* **2015,** *5,* 286-295.
[119] Jiang, C.; Shang, Z.; Liang, X. *ACS Catal.* **2015,** *5,* 4814-4818.
[120] Spencer, J.; Anjum, N.; Patel, H.; Rathnam, R. P.; Verma, J. *Synlett.* **2007,** *16,* 2557-2558.



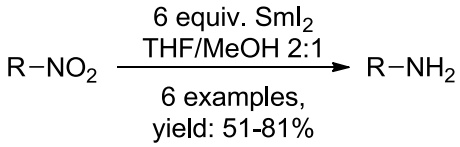

**Scheme 3.7** the Mo complex catalyzed reduction of nitroarenes

Although several catalyst systems were developed, poisonous excess reducing agents and drastic conditions such as high temperature and pressure were still the shortcoming. In addition, the vast majority of these methods weren't only lack of chemoselectivity over other functional groups such as halide, nitrile, ketone and protecting group, but also the metal-catalysts were facilely poisoned by heteroatoms (O, N, S, etc.). Hence, it's still urgently required an efficient and green method under a mild condition to realize the conversion from nitro to amine with a high chemoselectivity.

## III. 2. 3. The $SmI_2$ reduction of nitro compounds

In 1983, Kagan and co-workers published a reduction of nitroarenes by samarium diiodide. Even though only 3 examples with low yield, it opened a new aspect in this area.[121]

In 1991, Kende's group demonstrated that in the presence of MeOH as a proton source, using 6 molar equivalents of $SmI_2$ and by controlling the reaction time, a variety of nitroalkanes are reduced to amines in moderate to good yields.[122] (Scheme 3.3)

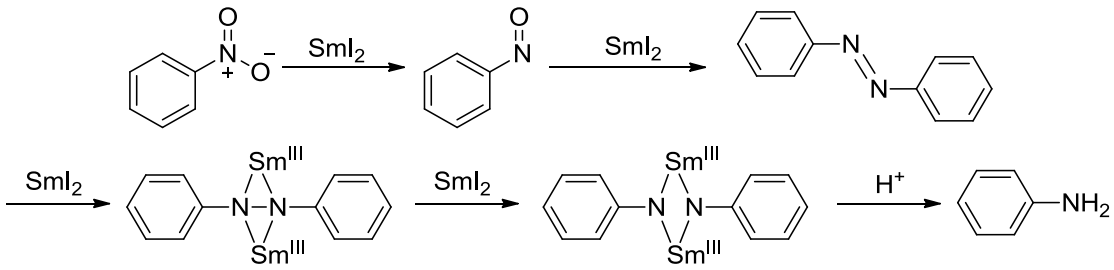



**Scheme 3.3** The $SmI_2$ reduction of nitroarenes into anilines in the THF/MeOH 2:1 solvent.

In 2002, Brady and Keogh *et al.* detected the mechanism by the intermediate crystal structure.[123] (Scheme 3.4) For the first time, both the organic and the inorganic

[121] Souppe, J.; Danon, L.; Namy, J. L.; Kagan, H. B. *J. Organomet. Chem.* **1983**, *250,* 227-236.
[122] Kende, A. S.; Mendoza, J. S. *Tetrahedron Lett.* **1991,** *32,* 1699-1702.
[123] Brady, E. D.; Clark, D. L.; Keogh, D. W.; Scott, B. L.; Watkin, J. G. *J. Am. Chem. Soc.* **2002,** *124,* 7007-7015.

intermediates involved in the reduction of nitroarenes by samarium(II) have been examined under rigorously anhydrous conditions. The reaction mechanism that has been deduced from this study clearly shows that 6 equiv. of $Sm^{II}$ are required to complete the transformation.




**Scheme 3.4** The mechanism of $SmI_2$ reduction of nitroarenes into anilines.

Due to the use of excess amount of $SmI_2$ and low selectivity in this reduction, we supposed to carry out this transformation under our $Sm^{II}$ electrocatalytic condition.

## III. 3. 1. Optimization of the reduction of nitroaroenes into anilines

At the beginning of this work, we referred to the established conditions and brought in the methanol as the proton donor. Using the *p*-methoxyl nitrobenzene as the test substrate, the reaction underwent in the catalysis conditions (5 mol% $SmCl_3$ and 2.0 equiv. TMSCl) in argon atmosphere. We demonstrated that it was possible to start the electrocatalysis by introducing $SmCl_3$ salts instead of electrogenerated $Sm^{II}$. From the entry **1-3**, it demonstrated that the larger amount of MeOH afforded the higher yield of amine product. However, even 100 equivalent MeOH added (Table 3.1, entry **3**), azo compound was still generated (trace are detected). Therefore, we evaluated the effect of TMSCl. As expected, with 8.0 equiv. TMSCl (Table 3.1, entry **4**), could afford a high yield of amine and avoided the azo compound generation. Then we also evaluated the electronic effect of the substituent by replacing the -OMe electron donating group into a strong electron withdrawing group $-CF_3$. Unfortunately, in this case we obtained the amine in only 80% yield with a large amount of azo compound (Table 3.1, entry **5)**. Even though 300 equiv. of MeOH, the reactivity was not improved too much. (Table 3.1, entry **6**)

Finally we decided to use the MeOH as the solvent which was never reported in the Sm(II) reaction. To our delight, with 8.0 equiv. TMSCl in methanol (the commercial anhydrous methanol without further treatment), it provided a quantitative *p*-$CF_3$ aniline without any precaution (without inert atmosphere) (Table 3.1, entry **7**).

In this last condition, we tried to decrease the amount of TMSCl, but the reaction would not be completed (Table 3.1, entry **8-11**). Consequently, 8.0 eq. TMSCl in the methanol seem to be the optimal condition. Finally, the *p*-MeO aniline was afforded in 98% yield. We have verified at this stage that without the current density, no reaction occurred (Table 3.1, entry **12, 13**).

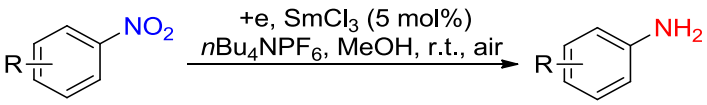
Compared to THF, the use of MeOH as the solvent brings three major advantages:

1. MeOH is one of the superior proton donners in the organic chemistry;

2. It's a good solvent to dissolve the ammonium salt and a large variety of substrates;

3. The methanol is also good solvent for electrochemistry, the current density could be higher than THF.

**Table 3.1** The optimization of reduction of nitro aromatic compounds



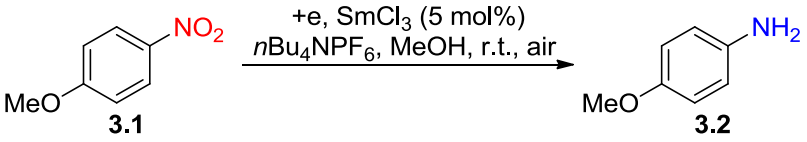

| Entry | R | TMSCl eq. | MeOH eq. | Conv. % | Yield %[e] |
|---|---|---|---|---|---|
| **1**[a] | *p*-MeO | 2.0 | 10 | >99 | trace[d] |
| **2**[a] | *p*-MeO | 2.0 | 50 | >99 | 27 |
| **3**[a] | *p*-MeO | 2.0 | 100 | >99 | 81 |
| **4**[a] | *p*-MeO | 8.0 | 100 | >99 | 98 |
| **5**[a] | *p*-$CF_3$ | 8.0 | 100 | >99 | 81 |
| **6**[a] | *p*-$CF_3$ | 8.0 | 300 | >99 | 83 |
| **7**[b] | *p*-$CF_3$ | 8.0 | solvent | >99 | 98 |
| **8**[b] | *p*-$CF_3$ | no | solvent | 27 | <5[d] |
| **9**[b] | *p*-$CF_3$ | 2.0 | solvent | 77 | 56 |
| **10**[b] | *p*-$CF_3$ | 4.0 | solvent | 91 | 80 |
| **11**[b] | *p*-$CF_3$ | 6.0 | solvent | >99 | 88 |
| **12**[b] | *p*-MeO | 8.0 | solvent | >99 | 98 |
| **13**[b,c] | *p*-MeO | 8.0 | solvent | <5 | trace[d] |

[a]reaction conditions: $ArNO_2$ (1.0 mmol), $SmCl_3$ (0.05 equiv.), MeOH (10-300 equiv.), $n$$Bu_4NPF_6$ (0.04 mol/L in THF) in THF (50 ml), Sm as the cathode, carbon as the anode, I= 0.05 A, r.t. in the air. [b] reaction conditions: $ArNO_2$ (1.0 mmol), $SmCl_3$ (0.05 equiv.), $n$$Bu_4NPF_6$ (0.01 mol/L in MeOH) in MeOH (50 ml), Sm as the cathode, carbon as the anode, I= 0.05 A, r.t. in the air. [c]Without electricity. [d]Analyzed by GC. [e]Isolated yields.

## III. 3. 2. The efficient of current density and concentration

Until now, in our electrochemical process we have always worked under a low current intensity implying long reaction time. Therefore, we investigated the possibility to improve the current intensity. Starting with 1.0 mmol *p*-methoxyl nitrobenzene, we changed the current intensity to survey the effect. Obviously, enhancing the current intensity could reduce the reaction time, however, in the meanwhile yield decrease according to the intensity. (Table 3.2, entry **1-4**). Finally, increasing the electrode surface, it is possible to reduce reaction time without losing in term of efficiency (Table 3.2, entry **5**).

**Table 3.2** The research of current [a]



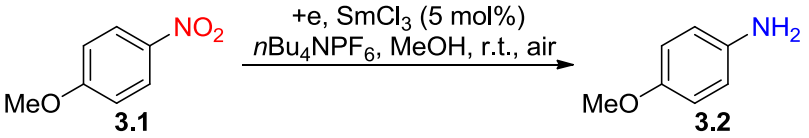

**3.1** **3.2**

| entry | Current (mA) | T h | Efficient % | Conv. | Yield %[b] |
|---|---|---|---|---|---|
| **1** | 50 | 5 | 86 | >99 | 98 |
| **2** | 100 | 3.5 | 61 | >99 | 94 |
| **3** | 200 | 2.5 | 43 | >99 | 92 |
| **4** | 400 | 2.0 | 27 | >99 | 87 |
| **5**[c] | 100 | 2.7 | 79 | >99 | 94 |

[a]reaction conditions: *p*-Nitroanisole (1.0 mmol), $SmCl_3$ (0.05 equiv.), $nBu_4NPF_6$ (0.01 mol/L) in MeOH (50 ml), Sm as the cathode, carbon as the anode, I= 0.05-0.4 A, r.t. in the air. [b]Isolated yields. [c]two electrode together (2 times superficial area)

The effect of substrate concentration in the electrolytic medium was then estimated. In this case, we observe that the increasing of the concentration results in decrease of the conversion (Table 3.3, entry **1-3**). With a higher current density, the conversion was improved (Table 3.3, entry **4**, **5**). The result illustrated this methodology could afford the aniline in gram scale in shorter reaction time.

**Table 3.3** The effect of concentration [a]



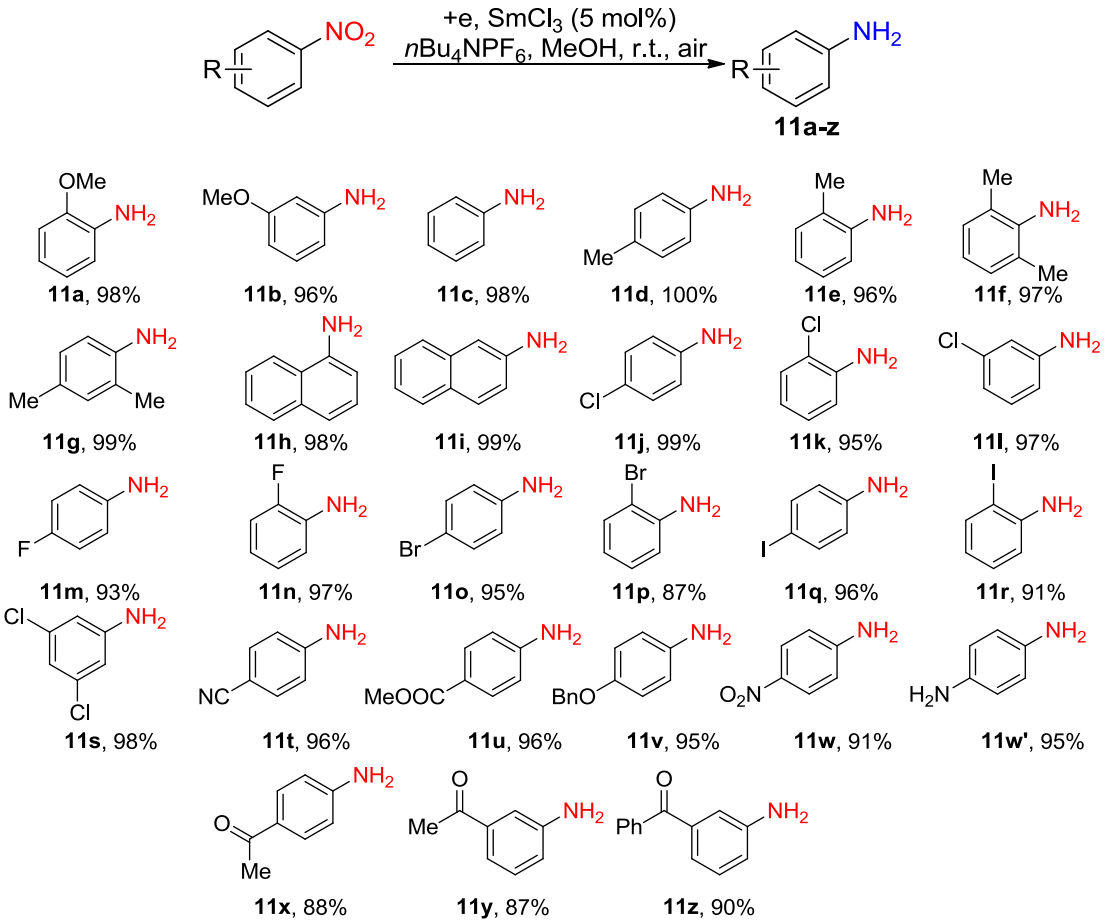

| entry | Amount (mmol) | I (mA) | T h | Conv. | Yield %[b] |
|---|---|---|---|---|---|
| **1** | 2.0 | 50 | 10 | >99 | 96 |
| **2** | 5.0 | 50 | 28 | 87 | 77 |
| **3** | 10.0 | 50 | 50 | 61 | 49 |
| **4** | 10.0 | 100 | 30 | 87 | 64 |
| **5**[c] | 10.0 | 100 | 30 | 91 | 76 |

[a]reaction conditions: *p*-Nitroanisole (2.0-10.0 mmol), $SmCl_3$ (0.05 equiv.), $nBu_4NPF_6$ (0.01 mol/L) in MeOH (50 ml), Sm as the cathode, carbon as the anode, I= 0.05-0.1 A, r.t. in the air. [b]Isolated yields. [c]two electrode together (2 times superficial area)

## III. 4. The scope of the reaction

With the optimized condition, we expended the method to *m*-, and *o*- methoxyl nitrobenzene to afford almost quantitative yields (Table 3.4, **11a**, **11b**). Then, the nitrobenzene, methyl and dimethyl substituted nitrobenzenes and nitronaphthalene were all obtained in great yields (more than 96% see Table 3.4, **11c-i**). Several halogenated nitrobenzene were also subjected to the electrocatalytic reduction. It is noteworthy that no dehalogenation occurred in any of these cases, all the halogenated nitroarenes can be selectively reduced to the corresponding anilines in excellent yields (Table 3.4, **11j-s**). Moreover, the other sensitive functional groups as CN-, MeOOC-, BnO-, PhCO- and $CH_3CO$- were reduced to the corresponding anilines in high chemoselectivity (Table 3.4, **11t-z**). Notably, the *p*-nitro nitrobenzene could be reduced sequentially (Table 3.4, **11w**, **11w'**). Similar to the reductive coupling of nitrobenzenes (Chapter II), it is worthy to note that our electrocatalytic approach proceeds with high functional group tolerance. For example, the nitro group is reduced prior to the ketone (Table 3.4, **11x-z**). As well-known, ketones are facile to produce the corresponding pinnacol or alcohol by using $Sm^{II}$, however, in our conditions these products are never observed.

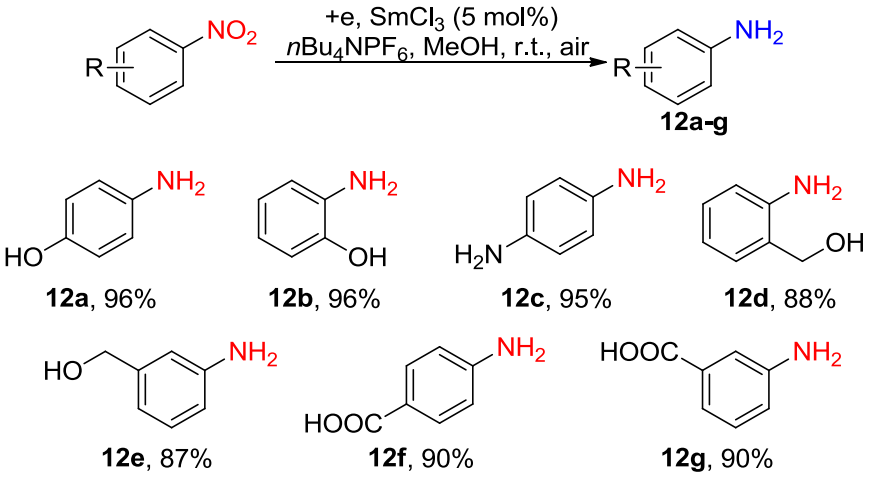
**Table 3.4** the Sm electrocatalytic reduction of nitroarenes into anilines[a]




[a]reaction conditions: substrates (1.0 mmol), $SmCl_3$ (0.05 equiv.), $n$Bu$_4$NPF$_6$ (0.01mol/L) in MeOH (50 ml), Sm as the cathode, carbon as the anode, I= 0.05 A, r.t. in the air. [b]Isolated yields.

We have also investigated the reduction of nitrobenzenes containing active hydrogen which is indeed a problem in the metal-catalyzed reduction. Active hydrogen groups could strongly coordinate the metal catalyst and finally poisoning this later. Initially, the reaction was attempted following the previously optimized conditions. However, after 4.5 h of electrolysis, there was still plenty of starting material. Even if the reaction time was extended, we observed the formation of some impurity mixed with the desired product. Fortunately, by increasing the quantity of catalyst from 5 to 10 mol. % the hydroxyl and amino substituted anilines were obtained in excellent yield (Table 3.5, **12a-e**). Normally, the carboxyl group poisoned the catalyst. However, it was also converted and isolated in 90% yield under this new condition (Table 3.5, **12f**, **12g**).

**Table 3.5** The Sm electrocatalytic reduction of nitroarenes with active hydrogen groups

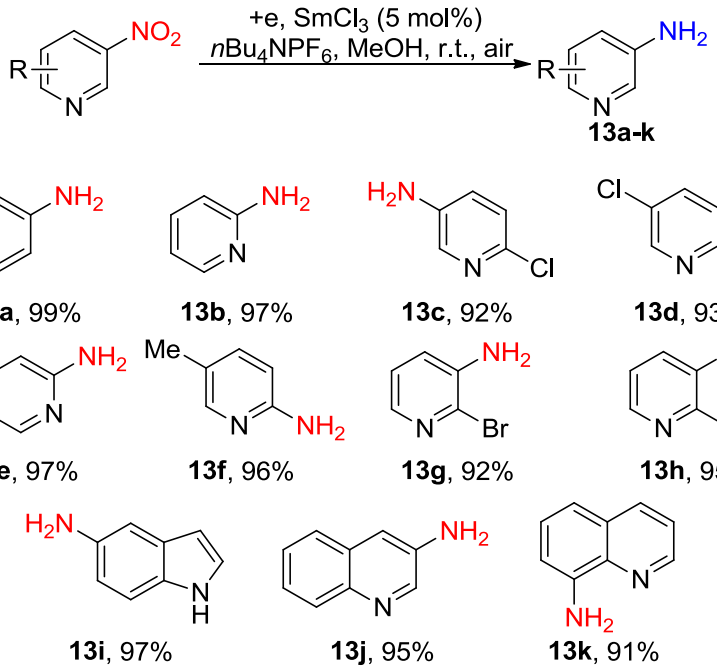



[a]reaction conditions: substrate (1.0 mmol), $SmCl_3$ (0.1 equiv.), $nBu_4NPF_6$ (0.01 mol/L) in MeOH (50 ml), Sm as the cathode, carbon as the anode, I= 0.05 A, r.t. in the air. [b]Isolated yields.

Amino pyridine derivation was a large family which was widely utilized in the pharmaceutical synthesis. The reduction of nitropyridines was a direct way to obtain the amino pyridines. However, a number of metal catalysts were also facilely poisoned by the nitrogen of pyridine which required a lot of catalyst to be used under high temperature and pressure to improve the reactivity.

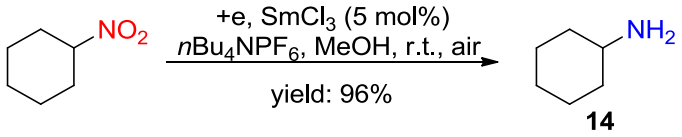
In this context, we used the 4-nitropyridine as the starting material. To our delight, with only 5 mol. % Sm, 4-aminopyridine was isolated in quantitative yield (Table 3.6, **13a**). In this case it was demonstrated that the pyridine has no effect on the $Sm^{II}$ catalyst regeneration. Then, we expanded to other nitropyridine substrates and isolated the corresponding amines in high yield and total chemoselectivity (Table 3.6, **13a-h**). Moreover, the nitroindole and nitroquinoline were reduced in excellent yields without the double bond hydrogenation which could occur in several hydrogenating conditions (Table 3.6, **13i-k**).

**Table 3.6** The Sm electrocatalytic reduction of nitro heteroaromatics




[a]reaction conditions: substrate (1.0 mmol), $SmCl_3$ (0.05 equiv.), $nBu_4NPF_6$ (0.01 mol/L) in MeOH (50 ml), Sm as the cathode, carbon as the anode, I= 0.05 A, r.t. in the air. [b]Isolated yields.

Besides the nitroaromatics, we tried the nitrocyclohexane. The 96% yield of cyclohexyl amine **14** illustrated the Sm electrocatalytic condition remained a powerful ability to reduce the alkyl nitrocompound.




**Scheme 3.31** The Sm electrocatalytic reduction of nitrocyclohexane into aminocyclohexane.

## III. 5. Conclusion

In summary, the Sm-electrocatalyzed reduction of functionalized and structurally diverse nitro arenes to anilines has been performed. For the first time, the Sm(II) reaction occurred in the methanol and without any protecting gas. This catalytic system showed a high chemoselectivity for the nitro group reduction in the presence of diverse functional groups. Especially, no matter the active hydrogen or *N*-substituted ring nitroaromatics afforded the corresponding products in high yield.

# III. 6. Experiment

## III. 6. 1. General Information

THF was distilled from sodium metal/benzophenone before use. All commercially available chemicals were used without purification. $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded on either a Bruker AM 360 (360 MHz), AM 300 (300 MHz), or AM 250 (250 MHz) instrument with samples dissolved in $CDCl_3$. $^{1}H$ NMR chemical shifts were referenced to the residual solvent signal; $^{13}C$ NMR chemical shifts were referenced to the deuterated solvent signal. Data are represented as follows: chemical shift δ (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (*J*) in Hz and integration. Mass spectra were recorded on a micrOTOF-q Brucker Daltonics spectrometer. Flash chromatography (FC) was performed on 40-63 µm silica gel with mixtures of ethyl acetate (EA) and pentane. TLC plates were visualized by exposure to UV (254 nm) and/or $KMnO_4$ stain. The gas chromatography (GC) were performed on a spectrometer Varian GC-430 (injection: split/splitless, FID detector, column VF1-MS: 15m x 0.25 mm x 0.25 microns, program: 1 min 50 °C, 10 °C/min to 250 °C, 250 °C 2 min, 23 min total). Infrared spectra were recorded on a FTIR spectrometer (Perkin-Elmer spectrum one, NaCl pellets or Bruker Vertex 70 ATR Pike Germanium) and are reported in $cm^{-1}$. Melting points were determined using a Büchi melting point apparatus. Electrolysis were performed with a AUTOLAB potentiostat/galvanostat (model: PGSTAT302N), in an undivided three-electrodes cell containing samarium rod working electrode, a standard glassy carbon counter electrode and a saturated calomel electrode (SCE) as reference. The samarium electrode used is based on a samarium rod of 12.7 mm (0.5 in) diameter and 5 cm length, directly connected to a copper wire to ensure current conductivity. This self-made electrode is stored under inert atmosphere when it is not used. All the samarium rods are purchased from Alfa Aesar (99.9 % metals basis excluding Ta).

## III. 6. 2. General condition for the electrocatalytic reduction of nitro aromatic compounds

Reactions were carried out in a one compartment cell containing a magnetic stirring bar, samarium cathode (20 $cm^2$ area), glassy carbon anode (20 $cm^2$ area) and

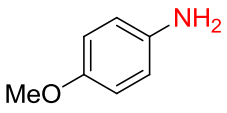
SCE as reference electrode. The cell is then charged with 50 mL of electrolyte solution containing 0.01 M $n$Bu$_4$NPF$_6$ in MeOH. After that, the corresponding nitrobenzene (1.0 mmol), $SmCl_3$ (0.05 mmol) and trimethylsilyl chloride (8.0 mmol) were then added in the mixture. The electrolysis was performed at i = 50 mA during 6 hours in the air. The mixture was then diluted by EtOAc (50 mL), quenched with $NaHCO_3$ (20 mL) and extracted with EtOAc (3×20 mL). The combined extracts were washed with sodium thiosulfate and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel. The resulting compounds were identified by comparison of their physical and spectral data with those given in the literature.

## III. 6. 3. General condition for the electrocatalytic reduction of nitro compounds with activate hydrogens

Reactions were carried out in a one compartment cell containing a magnetic stirring bar, samarium cathode (20 cm$^2$ area), glassy carbon anode (20 cm$^2$ area) and SCE as reference electrode. The cell is then charged with 50 mL of electrolyte solution containing 0.01 M $n$Bu$_4$NPF$_6$ in MeOH. After that, the corresponding nitrobenzene (1.0 mmol), $SmCl_3$ (0.1 mmol) and trimethylsilyl chloride (8.0 mmol) were then added in the mixture. The electrolysis was performed at i = 50 mA during 6 hours in the air. The mixture was then diluted by EtOAc (50 mL), quenched with $NaHCO_3$ (20 mL) and extracted with EtOAc (3×20 mL). The combined extracts were washed with 0.1 mol/L HCl, sodium thiosulfate and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel. The resulting compounds were identified by comparison of their physical and spectral data with those given in the literature.

## III. 6. 4. Characterization data of amino compounds

**4-methoxyaniline**



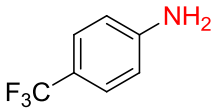
Column (Ethyl acetate: Pentane = 1: 1) to afford a colorless crystal (120 mg, yield: 98%);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 6.70-6.76 (m, 2H), 6.60-6.68 (m, 2H), 3.73 (s, 3H), 3.12 (brs, 2H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 153.0, 140.1, 116.6, 115.0, 55.9;

**HRMS (ESI)** Calcd for $C_7H_{10}NO$ ($M+H^+$): 124.0757. Found: 124.0762.

**4-(trifluoromethyl)aniline**



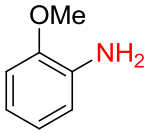

Column (Ethyl acetate: Pentane = 1: 5) to afford a colorless oil (158 mg, yield: 98%);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.35-7.42 (m, 2H), 6.61-6.67 (m, 2H), 3.87 (brs, 2H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 149.7, 126.7 (d, *J*= 4.0 Hz), 125.0 (q, *J*= 268.7 Hz), 119.9 (q, *J*= 32.4 Hz), 114.3;

**HRMS (ESI)** Calcd for $C_7H_7F_3N$ ($M+H^+$): 162. 0525. Found: 162.0526.

**2-methoxyaniline (11a)**




**11a**

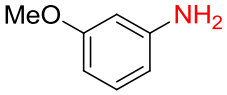
Column (Ethyl acetate: Pentane = 1: 3) to afford a yellow solid (121 mg, yield: 98%);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 6.70-6.76 (m, 2H), 6.79-6.99 (m, 4H), 3.94 (s, 3H), 3.88 (brs, 2H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 147.2, 136.2, 121.0, 118.3, 114.9, 110.4, 55.3;

**HRMS (ESI)** Calcd for $C_7H_{10}NO$ ($M+H^+$): 124.0757. Found: 124.0761.

**3-methoxyaniline (11b)**




**11b**

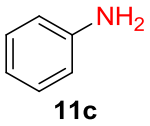
Column (Ethyl acetate: Pentane = 1: 3) to afford a brown solid (118 mg, yield: 96%);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.08-7.17 (m, 1H), 6.25-6.45 (m, 3H), 3.82 (s, 3H), 3.75 (brs, 2H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 160.7, 148.0, 130.1, 107.9, 103.9, 101.0, 55.1;

**HRMS (ESI)** Calcd for $C_7H_{10}NO$ ($M+H^+$): 124.0757. Found: 124.0763.

**aniline (11c)**




**11c**

Column (Ethyl acetate: Pentane = 1: 5) to afford a yellow oil (91 mg, yield: 98%);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.24-7.38 (m, 2H), 6.82-6.98 (m, 1H), 6.70-6.82 (m, 2H), 3.64 (brs, 2H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 146.7, 129.5, 118.6, 115.3;

**HRMS (ESI)** Calcd for $C_6H_8N$ ($M+H^+$): 94.0651. Found: 94.0648.

***p*-toluidine (11d)**


**11d**

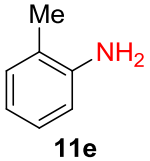
Column (Ethyl acetate: Pentane = 1: 2) to afford a colorless crystal (107 mg, yield: 100%);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 6.97 (d, *J*= 7.9 Hz, 2H), 6.61 (d, *J*= 7.9 Hz, 2H), 3.36 (brs, 2H), 2.24 (s, 3H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 144.0, 129.9, 128.0, 115.5, 20.6;

**HRMS (ESI)** Calcd for $C_7H_{10}N$ ($M+H^+$): 108.0808. Found: 108.0810.

***o*-toluidine (11e)**




**11e**

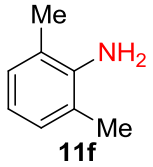
Column (Ethyl acetate: Pentane = 1: 2) to afford a yellow solid (103 mg, yield: 96%);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.11-7.21 (m, 2H), 6.80-6.90 (m, 1H), 6.73-6.80 (m, 1H), 3.61 (brs, 2H), 2.28 (s, 3H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 144.7, 130.5, 127.0, 122.4, 118.7, 115.0;

**HRMS (ESI)** Calcd for $C_7H_{10}N$ ($M+H^+$): 108.0808. Found: 108.0810.

**2,6-dimethylaniline (11f)**



**11f**

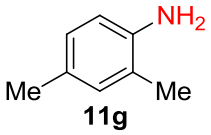
Column (Ethyl acetate: Pentane = 1: 5) to afford a brown solid (117 mg, yield: 97%);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 6.53 (s, 1H), 6.42 (s, 2H), 3.56 (brs, 2H), 2.34 (s, 6H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 146.5, 139.1, 120.5, 113.2, 21.4;

**HRMS (ESI)** Calcd for $C_8H_{12}N$ ($M+H^+$): 122.0964. Found: 112.0967.

**2,4-dimethylaniline (11g)**



**11g**

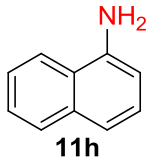
Column (Ethyl acetate: Pentane = 1: 2) to afford a yellow solid (120 mg, yield: 99%);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 7.17-7.25 (m, 2H), 6.88-6.96 (m, 1H), 3.73 (brs, 2H), 2.42 (s, 6H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 142.7, 128.2, 121.6, 117.9, 17.5;

**HRMS (ESI)** Calcd for $C_8H_{12}N$ ($M+H^+$): 122.0964. Found: 112.0967.

**naphthalen-1-amine (11h)**



**11h**

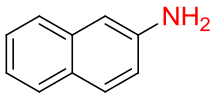
Column (Ethyl acetate: Pentane = 1: 2) to afford a brown solid (140 mg, yield: 98%);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 7.80-7.89 (m, 2H), 7.47-7.55 (m, 2H), 7.30-7.41 (m, 2H), 6.78-6.84 (m, 1H), 3.97 (brs, 2H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 142.2, 134.5, 128.7, 126.5, 126.0, 125.0, 123.8, 121.0, 119.1, 109.9;

**HRMS (ESI)** Calcd for $C_{10}H_{10}N$ ($M+H^+$): 144.0808. Found: 144.0807.

**naphthalen-2-amine (11i)**




**11i**

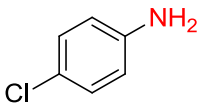
Column (Ethyl acetate: Pentane = 1: 2) to afford a yellow solid (141 mg, yield: 99%);

**$^{1}$H NMR (360 MHz, CDCl$_3$)** δ 7.60-7.80 (m, 3H), 7.37-7.48 (m, 1H), 7.23-7.31 (m, 1H), 6.94-7.05 (m, 2H), 3.81 (brs, 2H);

**$^{13}$C NMR (90 MHz, CDCl$_3$)** δ 144.3, 135.1, 129.4, 128.1, 127.9, 126.5, 126.0, 122.6, 118.4, 108.7;

**HRMS (ESI)** Calcd for $C_{10}H_{10}N$ ($M+H^+$): 144.0808. Found: 144.0810.

**4-chloroaniline (11j)**




**11j**

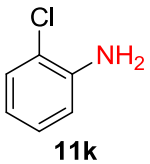
Column (Ethyl acetate: Pentane = 1: 2) to afford a yellow oil (126 mg, yield: 99%);

**$^{1}$H NMR (360 MHz, CDCl$_3$)** δ 7.10-7.20 (m, 2H), 6.58-6.68 (m, 2H), 3.62 (brs, 2H);

**$^{13}$C NMR (90 MHz, CDCl$_3$)** δ 145.1, 129.2, 123.1, 116.3;

**HRMS (ESI)** Calcd for $C_6H_7ClN$ ($M+H^+$): 128.0262. Found: 128.0266.

**2-chloroaniline (11k)**




**11k**

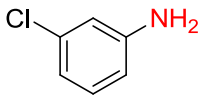
Column (Ethyl acetate: Pentane = 1: 2) to afford a brown oil (121 mg, yield: 95%);

**$^{1}$H NMR (360 MHz, CDCl$_3$)** δ 7.30-7.38 (m, 1H), 7.10-7.20 (m, 1H), 6.72-6.82 (m, 2H), 4.02 (brs, 2H);

**$^{13}$C NMR (90 MHz, CDCl$_3$)** δ 143.0, 129.5, 127.7, 119.3, 119.1, 116.0;

**HRMS (ESI)** Calcd for $C_6H_7ClN$ ($M+H^+$): 128.0262. Found: 128.0265.

**3-chloroaniline (11l)**




**11l**

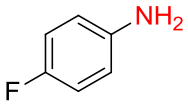
Column (Ethyl acetate: Pentane = 1: 2) to afford a yellow oil (123 mg, yield: 97%);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 7.00-7.10 (m, 1H), 6.69-6.78 (m, 1H), 6.65 (s, 1H), 6.47-6.56 (m, 1H), 3.62 (brs, 2H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 147.8, 134.9, 130.4, 118.5, 115.0, 113.3;

**HRMS (ESI)** Calcd for $C_6H_7ClN$ ($M+H^+$): 128.0262. Found: 128.0265.

**4-fluoroaniline (11m)**




**11m**

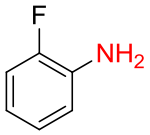
Column (Ethyl acetate: Pentane = 1: 3) to afford a yellow oil (103 mg, yield: 93%);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 6.85-6.96 (m, 2H), 6.60-6.70 (m, 2H), 3.48 (brs, 2H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 156.5 (*J*= 235.0 Hz), 142.6, 116.2 (*J*= 7.8 Hz), 115.7 (*J*= 22.3 Hz);

**HRMS (ESI)** Calcd for $C_6H_7FN$ ($M+H^+$): 112.0557. Found: 112.0562.

**2-fluoroaniline (11n)**




**11n**

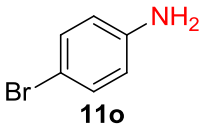
Column (Ethyl acetate: Pentane = 1: 2) to afford a yellow oil (108 mg, yield: 97%);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 6.98-7.15 (m, 2H), 6.74-6.90 (m, 2H), 3.76 (brs, 2H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 151.8 (*J*= 236.3 Hz), 134.6 (*J*= 13.1 Hz), 124.5 (*J*= 2.6 Hz), 118.6 (*J*= 7.8 Hz), 117.0 (*J*= 2.7 Hz), 115.3 (*J*= 18.4 Hz);

**HRMS (ESI)** Calcd for $C_6H_7FN$ ($M+H^+$): 112.0557. Found: 112.0559.

**4-bromoaniline (11o)**




**11o**

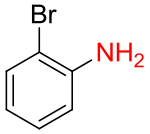
Column (Ethyl acetate: Pentane = 1: 3) to afford a yellow crystal (163 mg, yield: 95%);

**$^{1}$H NMR (360 MHz, CDCl$_3$)** δ 7.28 (d, *J*= 8.3 Hz, 2H), 6.58 (d, *J*= 8.3 Hz, 2H), 3.66 (brs, 2H);

**$^{13}$C NMR (90 MHz, CDCl$_3$)** δ 145.5, 132.0, 116.8, 110.1;

**HRMS (ESI)** Calcd for $C_6H_7BrN$ ($M+H^+$):171.9756 and 173.9736. Found: 171.9762 and 173.9742.

**2-bromoaniline (11p)**




**11p**

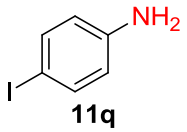
Column (Ethyl acetate: Pentane = 1: 3) to afford a red oil (149 mg, yield: 87%);

**$^{1}$H NMR (360 MHz, CDCl$_3$)** δ 7.35-7.42 (m, 1H), 7.05-7.18 (m, 1H), 6.70-6.80 (m, 1H), 6.53-6.63 (m, 1H), 3.95 (brs, 2H);

**$^{13}$C NMR (90 MHz, CDCl$_3$)** δ 144.2, 132.7, 128.5, 119.6, 115.9, 109.5;

**HRMS (ESI)** Calcd for $C_6H_7BrN$ ($M+H^+$):171.9756 and 173.9736. Found: 171.9756 and 173.9740.

**4-iodoaniline (11q)**




**11q**

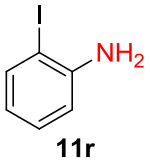
Column (Ethyl acetate: Pentane = 1: 2) to afford a colorless crystal (211 mg, yield: 96%);

**$^{1}$H NMR (360 MHz, CDCl$_3$)** δ 7.34-7.42 (m, 2H), 6.40-6.50 (m, 2H), 3.48 (brs, 2H);

**$^{13}$C NMR (90 MHz, CDCl$_3$)** δ 146.2, 138.0, 117.5, 79.5;

**HRMS (ESI)** Calcd for $C_6H_7IN$ ($M+H^+$): 219.09618. Found: 219.9618.

**2-iodoaniline (11r)**




**11r**

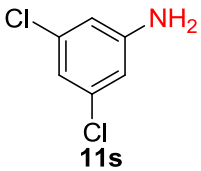
Column (Ethyl acetate: Pentane = 1: 3) to afford a brown solid (200 mg, yield: 91%);

**$^{1}$H NMR (360 MHz, CDCl$_3$)** δ 7.65-7.78 (m, 1H), 7.11-7.22 (m, 1H), 6.70-6.81 (m, 1H), 6.48-6.60 (m, 1H), 4.03 (brs, 2H);

**$^{13}$C NMR (90 MHz, CDCl$_3$)** δ 146.9, 139.1, 129.5, 120.2, 115.0, 84.4;

**HRMS (ESI)** Calcd for $C_6H_7IN$ ($M+H^+$): 219.09618. Found: 219.9617.

**3,5-dichloroaniline (11s)**




**11s**

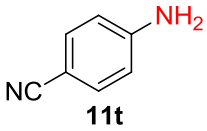
Column (Ethyl acetate: Pentane = 1: 5) to afford a grey solid (158 mg, yield: 98%);

**$^{1}$H NMR (360 MHz, CDCl$_3$)** δ 6.70 (s, 1H), 6.51 (s, 2H), 3.78 (brs, 2H);

**$^{13}$C NMR (90 MHz, CDCl$_3$)** δ 148.4, 135.5, 118.5, 113.4;

**HRMS (ESI)** Calcd for $C_6H_6Cl_2N$ ($M+H^+$): 161.9872. Found: 161.9877.

**4-aminobenzonitrile (11t)**




**11t**

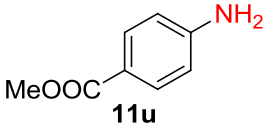
Column (Ethyl acetate: Pentane = 1: 2) to afford a yellow solid (113 mg, yield: 96%);

**$^{1}$H NMR (360 MHz, CDCl$_3$)** δ 7.31-7.40 (m, 2H), 6.58-6.69 (m, 2H), 4.23 (brs, 2H);

**$^{13}$C NMR (90 MHz, CDCl$_3$)** δ 150.8, 133.9, 120.4, 114.5, 99.8;

**HRMS (ESI)** Calcd for $C_7H_6N_2Na$ ($M+Na^+$): 141.0423. Found: 141.0421.

**methyl 4-aminobenzoate (11u)**




**11u**

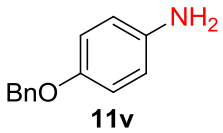
Column (Ethyl acetate: Pentane = 1: 3) to afford a yellow solid (143 mg, yield: 95%);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.87 (d, *J*= 8.6 Hz, 2H), 6.66 (d, *J*= 8.6 Hz, 2H), 4.16 (brs, 2H), 3.88 (s, 3H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.4, 151.1, 131.7, 113.9, 51.8;

**HRMS (ESI)** Calcd for $C_8H_{10}NO_2$ ($M+H^+$): 152.0706. Found: 152.0711.

**4-(benzyloxy)aniline (11v)**




**11v**

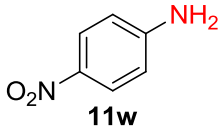
Column (Ethyl acetate: Pentane = 1: 1) to afford a red solid (189 mg, yield: 95%);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.35-7.58 (m, 5H), 6.85-6.92 (m, 2H), 6.65-6.72 (m, 2H), 5.05 (s, 2H), 3.41 (brs, 2H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 152.1, 140.4, 137.6, 128.6, 127.9, 127.6, 116.4, 116.1, 70.8;

**HRMS (ESI)** Calcd for $C_{13}H_{14}NO$ ($M+H^+$): 200.1070. Found: 200.1077.

**4-nitroaniline (11w)**




**11w**

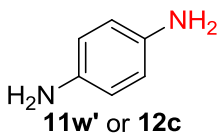
Column (Ethyl acetate: Pentane = 1: 3) to afford a colorless crystal (125 mg, yield: 91%);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 8.00-8.08 (m, 2H), 6.57-6.65 (m, 2H), 4.39 (brs, 2H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 152.7, 139.3, 126.6, 113.6;

**HRMS (ESI)** Calcd for $C_6H_7N_2O_2$ ($M+H^+$): 139.0502. Found: 139.0506.

**benzene-1,4-diamine (11w' or 12c)**




**11w'** or **12c**

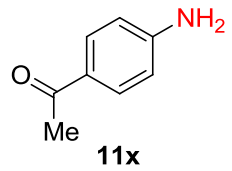
Column (Ethyl acetate: Methanol = 5: 1) to afford a red crystal (106 mg, yield: 98%);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 6.55 (s, 4H), 3.14 (brs, 4H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 138.8, 116.9;

**HRMS (ESI)** Calcd for $C_6H_9N_2$ ($M+H^+$): 109.0760. Found: 109.0763.

**1-(4-aminophenyl)ethanone (11x)**




**11x**

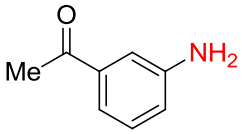
Column (Ethyl acetate: Pentane = 1: 3) to afford a yellow solid (119 mg, yield: 88%);

**$^1$H NMR (360 MHz, CDCl$_3$)** δ 7.70-7.82 (m, 2H), 6.52-6.66 (m, 2H), 4.20 (brs, 2H), 2.47 (s, 3H);

**$^{13}$C NMR (90 MHz, CDCl$_3$)** δ 196.8, 151.5, 130.9, 127.6, 113.8, 26.2;

**HRMS (ESI)** Calcd for $C_8H_9NNaO$ ($M+Na^+$): 158.0576. Found: 158.0576.

**1-(3-aminophenyl)ethanone (11y)**




**11y**

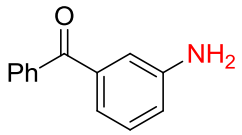
Column (Ethyl acetate: Pentane = 1: 1) to afford a red solid (118 mg, yield: 87%);

**$^1$H NMR (360 MHz, CDCl$_3$)** δ 7.15-7.35 (m, 3H), 6.80-6.88 (m, 1H), 3.96 (brs, 2H), 2.50 (s, 3H);

**$^{13}$C NMR (90 MHz, CDCl$_3$)** δ 198.7, 147.0, 138.0, 129.4, 119.6, 118.5, 113.9, 26.7;

**HRMS (ESI)** Calcd for $C_8H_{10}NO$ ($M+H^+$): 136.0757. Found: 136.0764.

**(2-aminophenyl)(phenyl)methanone (11z)**




**11z**

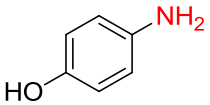
Column (Ethyl acetate: Pentane = 1: 3) to afford a grey solid (177 mg, yield: 90%);

**$^1$H NMR (360 MHz, CDCl$_3$)** δ 7.63- 7.72 (m, 2H), 7.44-7.58 (m, 4H), 7.26-7.36 (m, 1H), 6.70-6.79 (m, 1H), 6.59-6.66 (m, 1H), 6.16 (brs, 2H);

**$^{13}$C NMR (90 MHz, CDCl$_3$)** δ 199.2, 151.1, 140.2, 134.7, 134.4, 131.1, 129.2, 128.2, 118.2, 117.1, 115.6;

**HRMS (ESI)** Calcd for $C_{13}H_{11}NNaO$ ($M+Na^+$): 220.0733. Found: 220.0734.

**4-aminophenol (12a)**




**12a**

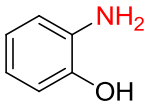
Column (Ethyl acetate: Methanol = 10: 1) to afford a colorless crystal (101 mg, yield: 93%);

**$^{1}$H NMR (250 MHz, DMSO-d$_6$)** δ 8.37 (brs, 1H), 6.35-6.53 (m, 4H), 4.40 (brs, 2H);

**$^{13}$C NMR (62.5 MHz, DMSO-d$_6$)** δ 148.2, 140.7, 115.6, 115.3;

**HRMS (ESI)** Calcd for $C_6H_8NO$ ($M+H^+$): 110.0600. Found: 110.0604.

**2-aminophenol (12b)**




**12b**

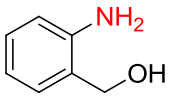
Column (Ethyl acetate: Pentane = 1: 2) to afford a colorless crystal (105 mg, yield: 96%);

**$^{1}$H NMR (250 MHz, DMSO-d$_6$)** δ 8.96 (brs, 1H), 6.32-6.70 (m, 4H), 4.48 (brs, 2H);

**$^{13}$C NMR (62.5 MHz, DMSO-d$_6$)** δ 144.0, 136.5, 119.5, 116.5, 114.4;

**HRMS (ESI)** Calcd for $C_6H_8NO$ ($M+H^+$): 110.0600. Found: 110.0603.

**(2-aminophenyl)methanol (12d)**




**12d**

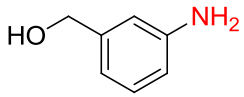
Column (Ethyl acetate: Pentane = 4: 1) to afford a white solid (113 mg, yield: 92%);

**$^{1}$H NMR (360 MHz, CDCl$_3$)** δ 7.08-7.15 (m, 1H), 6.96-7.05 (m, 1H), 6.62-6.74 (m, 2H), 4.59 (s, 2H), 3.45 (brs, 3H);

**$^{13}$C NMR (90 MHz, CDCl$_3$)** δ 146.1, 129.5, 129.4, 125.1, 118.4, 116.2, 64.4;

**HRMS (ESI)** Calcd for $C_7H_9NNaO$ ($M+Na^+$): 146.0576. Found: 146.0591.

**(3-aminophenyl)methanol (12e)**




**12e**

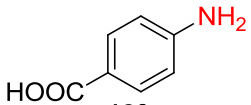
Column (Ethyl acetate: Pentane = 4: 1) to afford a white solid (115 mg, yield: 93%);

**$^{1}$H NMR (360 MHz, DMSO-d$_6$)** δ 6.92-7.00 (m, 1H), 6.58 (s, 1H), 6.41-6.50 (m, 2H), 5.00-5.07 (m, 1H), 4.98 (s, 2H), 4.33-4.41 (m, 2H);

**$^{13}$C NMR (90 MHz, DMSO-d$_6$)** δ 148.5, 143.2, 128.6, 114.2, 112.5, 112.2, 63.3;

**HRMS (ESI)** Calcd for $C_7H_{10}NO$ ($M+H^+$): 124.0757. Found: 124.0760.

**4-aminobenzoic acid (12f)**




**12f**

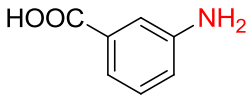
Column (Ethyl acetate: Pentane = 9: 1) to afford a brown solid (131 mg, yield: 96%);

**$^{1}$H NMR (360 MHz, DMSO-d$_6$)** δ 11.99 (brs, 1H), 7.63 (d, *J*= 7.9 Hz, 2H), 6.55 (d, *J*= 7.9 Hz, 2H), 5.88 (brs, 2H);

**$^{13}$C NMR (90 MHz, CDCl$_3$)** δ 167.6, 153.2, 131.3, 116.9, 112.7;

**HRMS (ESI)** Calcd for $C_7H_8NO_2$ ($M+H^+$): 138.0550. Found: 138.0552.

**3-aminobenzoic acid (12g)**




**12g**

Column (Ethyl acetate: Pentane = 8: 1) to afford a yellow solid (121 mg, yield: 88%);

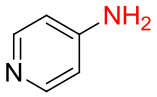
**$^{1}$H NMR (360 MHz, DMSO-d6)** δ 12.42 (brs, 1H), 7.12-7.21 (m, 1H), 7.02-7.10 (m, 2H), 6.73-6.81 (m, 1H), 5.37 (brs, 2H);

**$^{13}$C NMR (90 MHz, DMSO-d$_6$)** δ 167.9, 148.9, 131.3, 128.9, 118.0, 116.7, 114.5;

**HRMS (ESI)** Calcd for $C_7H_8NO_2$ ($M+H^+$): 138.0550. Found: 138.0552.

## III. 6. 5. Characterization data of aza amino aromatic compounds

**pyridin-4-amine (13a)**




**13a**

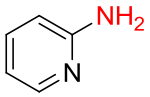
Column (Ethyl acetate: Pentane = 1: 1) to afford a colorless crystal (93 mg, yield: 99%);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 8.16-8.20 (m, 2H), 6.45-6.50 (m, 2H), 4.15 (brs, 2H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 152.9, 150.5, 109.8;

**HRMS (ESI)** Calcd for $C_5H_7N_2$ ($M+H^+$): 95.0604. Found: 95.0604.

**pyridin-2-amine (13b)**




**13b**

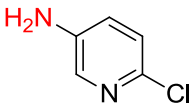
Column (Ethyl acetate: Pentane = 1: 1) to afford a yellow oil (91 mg, yield: 97%);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 8.00-8.04 (m, 1H), 7.33-7.40 (m, 1H), 6.56-6.62 (m, 1H), 6.42-6.47 (m, 1H), 4.47 (brs, 2H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 158.6, 148.2, 137.8, 114.0, 108.7;

**HRMS (ESI)** Calcd for $C_5H_7N_2$ ($M+H^+$): 95.0604. Found: 95.0604.

**6-chloropyridin-3-amine (13c)**




**13c**

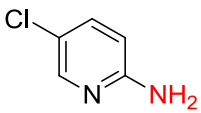
Column (Ethyl acetate: Pentane = 1: 1) to afford a yellow solid (118 mg, yield: 92%);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 7.77-7.81 (m, 1H), 6.90-7.07 (m, 2H), 3.54 (brs, 2H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 141.9, 140.2, 136.4, 125.0, 124.3;

**HRMS (ESI)** Calcd for $C_5H_6ClN_2$ ($M+H^+$): 129.0214. Found: 129.0213.

**5-chloropyridin-2-amine (13d)**




**13d**

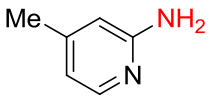
Column (Ethyl acetate: Pentane = 1: 1) to afford a grey crystal (119 mg, yield: 93%);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 8.00-8.04 (m, 1H), 7.37-7.42 (m, 1H), 6.45-6.49 (m, 1H), 4.44 (brs, 2H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 157.0, 146.6, 137.7, 121.1, 109.6;

**HRMS (ESI)** Calcd for $C_5H_6ClN_2$ ($M+H^+$): 129.0214. Found: 129.0212.

**4-methylpyridin-2-amine (13e)**




**13e**

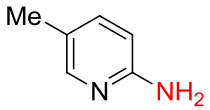
Column (Ethyl acetate: Pentane = 1: 1) to afford a yellow solid (105 mg, yield: 97%);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.85-7.89 (m, 1H), 6.40-6.44 (m, 1H), 6.25-6.27 (m, 1H), 4.41 (brs, 2H), 2.17 (s, 3H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 158.8, 148.8, 147.8, 155.5, 109.0, 21.1;

**HRMS (ESI)** Calcd for $C_6H_9N_2$ ($M+H^+$): 109.0760. Found: 109.0763.

**5-methylpyridin-2-amine (13f)**




**13f**

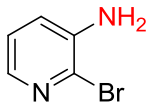
Column (Ethyl acetate: Pentane = 1: 1) to afford a yellow solid (104 mg, yield: 96%);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.81 (s, 1H), 7.13-7.17 (m, 1H), 6.32-6.37 (m, 1H), 4.41 (brs, 2H), 2.09 (s, 3H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 156.6, 147.6, 138.7, 122.7, 108.4, 17.4;

**HRMS (ESI)** Calcd for $C_6H_9N_2$ ($M+H^+$): 109.0760. Found: 109.0762.

**2-bromopyridin-3-amine (13g)**




**13g**

Column (Ethyl acetate: Pentane = 1: 1) to afford an orange crystal (159 mg, yield: 92%);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.67-7.70 (m, 1H), 6.92-6.99 (m, 2H), 4.13 (brs, 2H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 141.6, 139.1, 129.6, 123.8, 122.1;

**HRMS (ESI)** Calcd for $C_5H_6BrN_2$ ($M+H^+$): 172.9709. Found: 172.9707.

**2-chloropyridin-3-amine (13h)**


**13h**

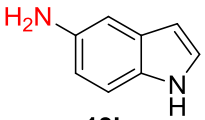
Column (Ethyl acetate: Pentane = 1: 1) to afford a yellow crystal (121 mg, yield: 95%);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 7.67-7.70 (m, 1H), 6.92-7.00 (m, 2H), 4.16 (brs, 2H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 139.9, 138.3, 136.8, 123.5, 122.6;

**HRMS (ESI)** Calcd for $C_5H_6ClN_2$ ($M+H^+$): 129.0214. Found: 129.0213.

**1*H*-indol-5-amine (13i)**




**13i**

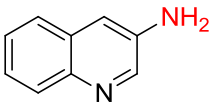
Column (Ethyl acetate: Pentane = 1: 1) to afford a grey solid (128 mg, yield: 97%);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 8.00 (brs, 1H), 7.08-7.20 (m, 2H), 6.92-6.95 (m, 1H), 6.61-6.68 (m, 2H), 6.34-6.37 (m, 1H), 3.32 (brs, 2H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 139.6, 130.9, 128.9, 124.9, 113.1, 111.7, 105.8, 101.7;

**HRMS (ESI)** Calcd for $C_8H_9N_2$ ($M+H^+$): 133.0760. Found: 133.0764.

**quinolin-3-amine (13j)**




**13j**

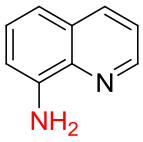
Column (Ethyl acetate: Pentane = 1: 1) to afford a red solid (137 mg, yield: 95%);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 8.40-8.57 (m, 1H), 7.90-8.05 (m, 1H), 7.50-7.61 (m, 1H), 7.32-7.50 (m, 2H), 7.10-7.22 (m, 1H), 4.01 (brs, 2H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 143.2, 142.7, 140.0, 129.3, 129.0, 127.0, 126.0, 125.6, 114.9;

**HRMS (ESI)** Calcd for $C_9H_9N_2$ ($M+H^+$): 145.0760. Found: 145.0764.

**quinolin-8-amine (13k)**




**13k**

Column (Ethyl acetate: Pentane = 1: 1) to afford a red solid (131 mg, yield: 91%);

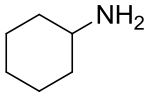
**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 8.72-8.85 (m, 1H), 7.97-8.11 (m, 1H), 7.28-7.42 (m, 2H), 7.08-7.13 (m, 1H), 6.86-7.00 (m, 1H), 5.06 (brs, 2H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 147.5, 144.1, 138.5, 136.1, 128.9, 127.5, 121.4, 116.1, 110.1;

**HRMS (ESI)** Calcd for $C_9H_9N_2$ ($M+H^+$): 145.0760. Found: 145.0768.

## III. 6. 6. Characterization data of alphatic amino compound

**cyclohexanamine (14)**




**14**

Column (Ethyl acetate: Pentane = 2: 1) to afford a brown oil (95 mg, yield: 96%);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 2.41-2.56 (m, 1H), 1.61-1.70 (m, 2H), 1.51-1.60 (m, 2H), 1.40-1.50 (m, 1H), 0.81-1.20 (m, 7H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 50.4, 36.8, 25.6, 25.1;

**HRMS (ESI)** Calcd for $C_6H_{14}N$ ($M+H^+$): 100.1121. Found: 100.1117.

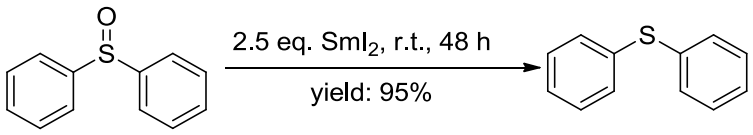
# Chapter IV. The Sm electrocatalytic reduction of sulfoxides

## IV. 1. Introduction

In the chapter II and III, we developed the $Sm^{II}$ electrocatalytic conditions to selectively reduce the nitrobenzenes into azobenzenes or anilines just by replacing THF with methanol as electrolytic solvent. As another hetero-O bond, the reduction of sulfones and sulfoxides are very important transformations in organic chemistry.

It is noteworthy that the deoxygenation of sulfoxides to the corresponding sulfides is a fundamental and significant process in both chemistry and biology.[124] In the past several years, chiral sulfoxides are introduced to the asymmetric synthesis as a chiral auxiliary. Subsequent to the asymmetric induction, the sulfinyl group is removed through deoxygenation followed by desulfidation.[125]

$SmI_2$ as a single electron transfer (SET) reagent was widely used in the reduction of organic chemistry. Kagan's report demonstrated the reduction of diphenyl sulfoxide by $SmI_2$.[126] With 2.5 equiv $SmI_2$, the reaction took 2 days to afford the sulfide in 95% yield (Scheme 4.1).




**Scheme 4.1** The reduction of sulfoxides into the sulfides by $SmI_2$.

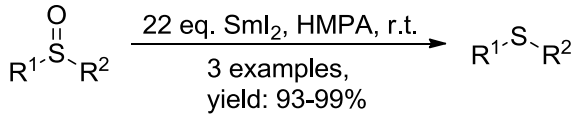
The HMPA is a harmful but significant additive to improve $SmI_2$ reactivity. In 1989, Inanaga's group reported a reduction of sulfoxides into the sulfides by $SmI_2$-HMPA

[124] M. Madesclaire, *Tetrahedron*, **1988**, *44*, 6537-6580. (b) Kukushkin, V. Y. *Coord. Chem. Rev.* **1995,** *139,* 375-407. (c) Espenson, J. H. *Coord. Chem. Rev.* **2005,** *249,* 329-341. (d) Sousa, S. C. A.; Fernandes, A. C. *Coord. Chem. Rev.* **2015,** *284,* 67-92.

[125] (a) Barbachyn, M. R.; Johnson, C. R. *In Asymmetric Synthesis;* Morrison, J. D., Scott, J. W., Eds.; Academic: Orlando, 1984; Vol. 4, pp 227-261. (b) Posner, G. H. *In The Chemistry of Sulfones and Sulfoxides;* Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; Wiley: New York, 1988; pp 823-849. (c) Solladie, G. *In Asymmetric Synthesis;* Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 2, pp 157-199. (d) M. C. Carreno, *Chem. Rev.* **1995,** *95,* 1717-1760. (e) Walker, A. J. *Tetrahedron: Asymmetry* **1992,** *3,* 961-998.

[126] Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980,** *102,* 2693-2698.

system.[127] Under 22 equiv. $SmI_2$ and the HMPA as the solvent, the products were provided in 1 day (Scheme 4.2).

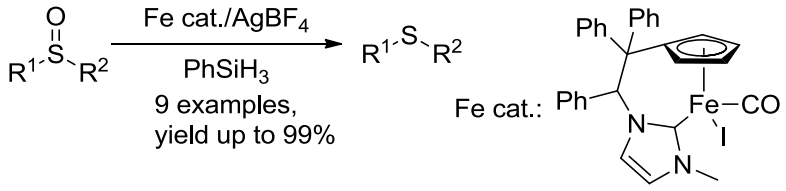



**Scheme 4.2** The reduction of sulfoxides into the sulfides by $SmI_2$-HMPA system.

Although the reduction by $SmI_2$ was performed, there were several drawbacks. The long time reaction or the use of harmful HMPA as the solvent limited the amount of substrates. The excess amount of $SmI_2$ lead to a number of by-products. The hazardous condition caused the low chemoselectivity and over reduction occurred.

## IV. 2. The catalytic reduction of sulfoxides into sulfides

Due to the significance of the transformation, many different catalytic methodologies were reported. In 2012, Royo's group synthesized Fe(II) complexes for the catalytic deoxygenation of sulfoxides into the sulfides.[128] The (Cp-NHC)Fe(CO)I/$AgBF_4$ catalytic system is demonstrated for both aliphatic and aromatic substrates by using $PhSiH_3$ as a reducing agent (Scheme 4.3).




**Scheme 4.3** The Fe complexes catalyzed reduction of sulfoxides with $PhSiH_3$.

In the same year, Fernandes's group developed an oxo-rhenium complexes catalyzed deoxygenation of aromatic and aliphatic sulfoxides to the corresponding sulfides.[129] The scope illustrated the $ReOCl_3(PPh_3)_2$ was an efficient catalyst for reduction without any reducing agents (Scheme 4.4).

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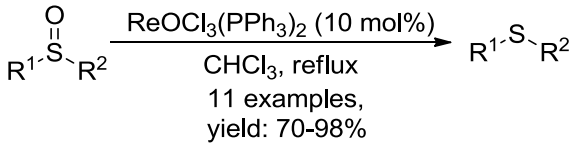
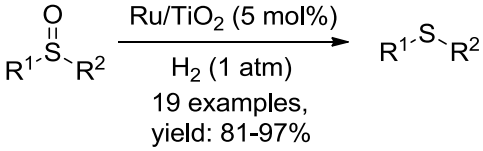
[127] Handa, Y.; Inanaga, J.; Yamaguchi, M. *J. Chem. Soc., Chem. Commun.* **1989,** 298-299.
[128] Cardoso, J. M. S.; Royo, B. *Chem. Commun.* **2012,** *48*, 4944-4946.
[129] Sousa, S. C. A.; Bernardo, J. R.; Romão, C. C.; Fernandes, A. C. *Tetrahedron* **2012,** *68*, 8194-8197.



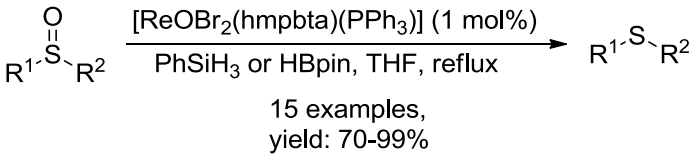

**Scheme 4.4** The Re complexes catalyzed reduction of sulfoxides into the sulfides.

Two years later, Kaneda's group demonstrated the Ru nanoparticles catalyzed hydrogenation of sulfoxides into the sulfides.[130] This hydrogenation extended to a wide range of sulfoxides under mild conditions. Moreover, the $Ru/TiO_2$ catalyst was readily recoverable (Scheme 4.5).



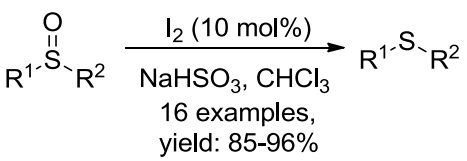

**Scheme 4.5** The Re nanoparticle catalyzed reduction of sulfoxides with $H_2$.

In 2014, Fernandes's group improved the $PhSiH_3$/[$ReOBr_2$(hmpbta)($PPh_3$)] and HBpin/[$ReOBr_2$(hmpbta) ($PPh_3$)] catalytic systems for the reduction of a large variety of sulfoxides with excellent yields and high chemoselectivity.[131] These systems allowed the reaction to be performed under air. (Scheme 4.6)




**Scheme 4.6** The $PhSiH_3$/[$ReOBr_2$(hmpbta)($PPh_3$)] system catalyzed reduction of sulfoxides into the sulfides.

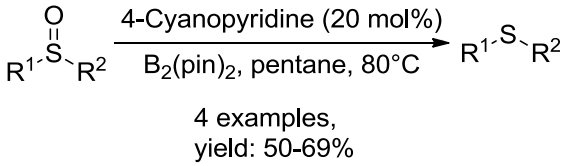
In 2015, Abbasi reported molecular iodine as a catalyst for the reduction of various sulfoxides using $NaHSO_3$.[132] This method presented in high yields under mild conditions, and the $I_2$ is an inexpensive commercially available reagent (Scheme 4.7).




[130] Mitsudome, T.; Takahashi, Y.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Angew. Chem. Int. Ed.* **2014,** *53,* 8348-8351.
[131] Sousa, S. C. A.; Bernardo, J. R.; Wolff, M.; Machura, B.; Fernandes, A. C. *Eur. J. Org. Chem.* **2014,** 1855-1859.
[132] Abbasi, M.; Mohammadizadeh, M. R.; Moradi, Z. *Tetrahedron Lett.* **2015,** *56,* 6610-6613.

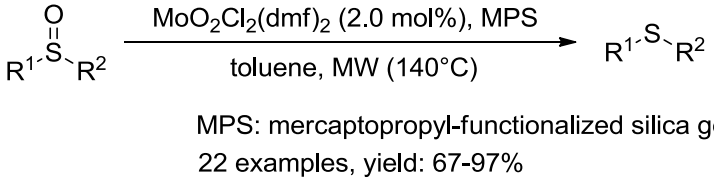
**Scheme 4.7** The $I_2$-catalyzed reduction of sulfoxides using $NaHSO_3$.

Recently, Zhu and Li *et al.* reported a B-B bond activation mode.[133] In this new mode, 4-cyanopyridine as the Lewis base formed a strong N-B bond with $B_2(pin)_2$ which catalyzed the deoxygenation of sulfoxides to sulfides (Scheme 4.8).



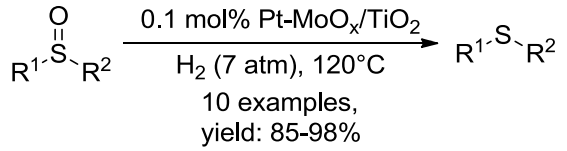

**Scheme 4.8** The boron/ cyanopyridine system catalyzed reduction of sulfoxides.

At the same time, Sanz's group developed the Mo-catalyzed sulfoxide deoxygenation using the mercaptopropyl-functionalized silica gel (MPS) as the reducing agent.[134] The purification was just a simple filtration. Moreover, the products were obtained in good to excellent yields with high functional group tolerance (Scheme 4.9).




**Scheme 4.9** The Mo complexes catalyzed reduction of sulfoxides under MW condition.

In the same year, Shimizu's group demonstrated the nanoparticle Pt–MoOx/ $TiO_2$ was an effective and reusable catalyst for the reduction of sulfoxides to sulfides without solvent.[135] Notably, the Pt–MoOx/$TiO_2$ catalyzed system represented the first example of catalytic conversion of a sulfone to a sulfide by $H_2$ (Scheme 4.10).




**Scheme 4.10** Pt–MoOx/ $TiO_2$ nanoparticle catalyzed reduction of sulfoxides with $H_2$.

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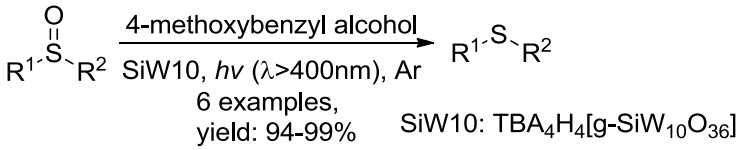
[133] Wang, G.; Zhang, H.; Zhao, J.; Li, W.; Cao, J.; Zhu, C.; Li, S. *Angew. Chem., Int. Ed.* **2016,** *55,* 5985-5989.

[134] García, N.; Fernández-Rodríguez, M. A.; García-García, P.; Pedrosa, M. R.; Arnáiza, F. J.; Sanz, R. *RSC Adv.* **2016,** *6,* 27083-27086.

[135] Touchy, A. S.; Siddiki, S. M. A. H.; Onodera, W.; Kona, K.; Shimizu, K. *Green Chem.* **2016,** *18,* 2554-2560.

Mizuno's group reported a photoredox system of $TBA_4H_4[g\text{-}SiW_{10}O_{36}]$, which could deoxygenate the sulfoxides into the corresponding sulfides with high efficiencies and selectivity.[136] In this process, the $TBA_4H_4[g\text{-}SiW_{10}O_{36}]$ transferred the electron from the alcohol to the sulfoxide (Scheme 4.11).




**Scheme 4.11** The $TBA_4H_4[g\text{-}SiW_{10}O_{36}]$ system photocatalyzed reduction of sulfoxides into the sulfides.

Even though several new catalytic methods have been developed to reduce sulfoxides into the sulfides, the limitation of side reactions, low selectivity, harsh reaction conditions still exists. These systems are generally based on the use of stoichiometric or excess amounts of reducing reagent such as dithiane,[137] phosphorous compound,[138] boron compounds,[139] low-valent metal compounds[140] and silanes.[141] The production of large quantities of waste is also the limitation for industrial development.

Inspired by the high chemoselective reduction of nitrobenzenes, therefore, we made a decision to investigate the selective reduction of sulfoxides under our electrocatalytic system.

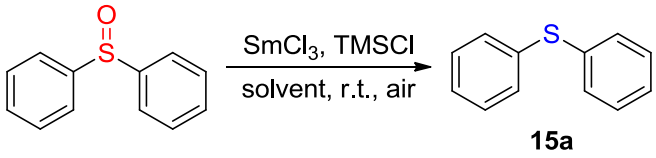
[136] Suzuki, K.; Jeong, J.; Yamaguchi, K.; Mizuno, N. *New J. Chem.* **2016,** *40,* 1014-1021.
[137] Iranpoor, N.; Firouzabadi, H.; Shaterian, H. R. *J. Org. Chem.* **2002,** *67*, 2826-2830.
[138] (a) Harpp, D. N.; Gleason, J. G.; Synder, J. P. *J. Am. Chem. Soc*. **1968,** *90*, 4181-4182.
[139] (a) Lappert, M. F.; Smith, J. K. *J. Chem. Soc.* **1961,** 3224-3230. (b) Brown, H. C.; Heim, P.; Yoon, N. M. *J. Am. Chem. Soc.* **1970,** *92*, 1637-1646. (c) Brown, H. C.; Nazer, B.; Cha, J. S.; Sikorski, A. *J. Org. Chem.* **1986,** *51*, 5264-5270.
[140] (a) Drabowicz, J.; Mikolajczyk, M. *Synthesis* **1976,** 527-528. (b) Fernandes, A. C.; Romão, C. C. *Tetrahedron* **2006,** *62*, 9650-9654.
[141] (a) Fernandes, A. C.; Romão, C. C. *Tetrahedron* **2006,** *62*, 9650-9654. (b) Thiel, K.; Zehbe, R.; Roeser, J.; Strauch, P.; Enthaler, S.; Thomas, A. *Polym. Chem.* **2013,** *4*, 1848-1856.

# IV. 3. Electrocatalytic reduction of sulfoxide into sulfides mediated by $SmI_2$

## IV. 3. 1. Optimization of electrochemical condition

At the beginning, we used the sulfinyl dibenzene as the starting material to demonstrate the reactivity under the Sm electrocatalytic systems in methanol or THF. The corresponding diphenyl sulfide was obtained in quantitative yield using 10 mol% $SmCl_3$ and 4.0 equiv. TMSCl in the methanol (Table 4.1, entry **1-4**). Surprisingly, when the electrolysis was performed in THF as the solvent, the product was obtained in excellent yield with only the 5 mol% $SmCl_3$ and 4.0 equiv. TMSCl (Table 4.1, entry **5-7**). Besides, we also tried the reduction in DMF, but the conversion was low (Table 4.1, entry **8**).

**Table 4.1** The optimization of the electrocatalytic reduction of diphenyl sulfoxide.[a]




**15a**

| entry | $SmCl_3$ eq. | TMSCl | solvent | Conv. %[b] | Yield %[c] |
|---|---|---|---|---|---|
| **1** | 0.1 | 8.0 | MeOH | >99 | 99 |
| **2** | 0.05 | 8.0 | MeOH | 78 | 77 |
| **3** | 0.1 | 4.0 | MeOH | >99 | 99 |
| **4** | 0.1 | 2.0 | MeOH | 61 | 60 |
| **5** | 0.1 | 4.0 | THF | >99 | 95 |
| **6** | 0.05 | 4.0 | THF | >99 | 97 |
| **7** | 0.05 | 2.0 | THF | 66 | 61 |
| **8** | 0.1 | 4.0 | DMF | 36 | 30 |

[a]standard conditions: diphenyl sulfoxide (1.0 mmol), $SmCl_3$ (0.05 or 0.1 equiv), TMSCl (2.0- 8.0 equiv.), $n$Bu$_4$NPF$_6$ (0.4 mmol in THF or 0.1 mmol in MeOH), Sm as the cathode, carbon as the anode, I= 0.05 A, r.t. in the air. [b]determined by NMR. [c]Isolated yields.

# IV. 4. The scope for reduction of sulfoxide into sulfides

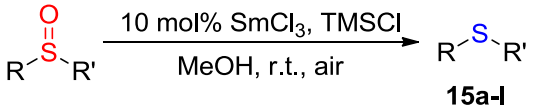
From the optimized conditions, we decided to evaluate the potential and the selectivity of the catalytic reduction of sulfoxides. Due to the difference in concentration of $n$Bu$_4$NPF$_6$ used as the electrolyte respectively 0.01 mol/L $n$Bu$_4$NPF$_6$

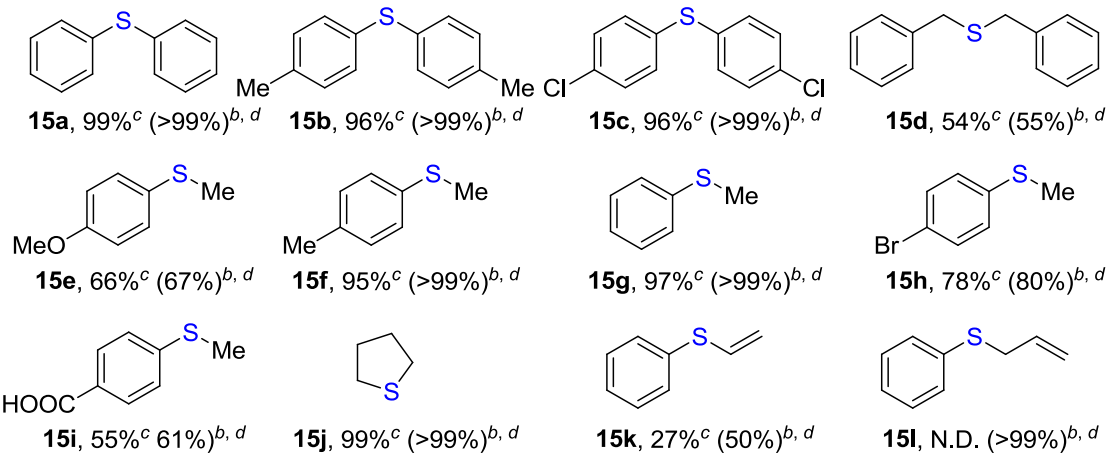
in methanol and 0.04 mol/L in THF, the methanol was firstly used to make the scope of the reaction.

## IV. 4. 1. Using MeOH as solvent

In this context, various diphenyl sulfoxides were reduced into the corresponding sulfides in high yield and total chemoselectivity (Table 4.2, **15a-c**), however, though the selectivity was good, the conversion of dibenzyl sulfoxide was only 55% and the resulting sulfide was recovered in only 54 % isolated yield (Table 4.2, **15d**). Several methyl-phenyl sulfoxides were also introduced in these electrochemical conditions such as **15e-I** (Table 4.2) in this case the conversion seems to be dependent on the electronic effect of the substituent on the phenyl. Indeed, the non-substituted one (**15g**) and the *p*-methyl (**15f**) were totally converted while *p*-OMe, *p*-Br and *p*-COOH were transformed with lower conversion. Moreover, to our disappointment, the substrates with a double bond (allyl and vinyl sulfoxides (Table 4.2, **15k, 15l**) ) were subjected to secondary reactions and lead to complicated mixtures. On the other hand, the aliphatic sulfoxide tetrahydrothiophene **15j** was totally converted and isolated in 99 % yield.

**Table 4.2** The scope of the electrocatalytic reduction of sulfoxides in MeOH.[a]



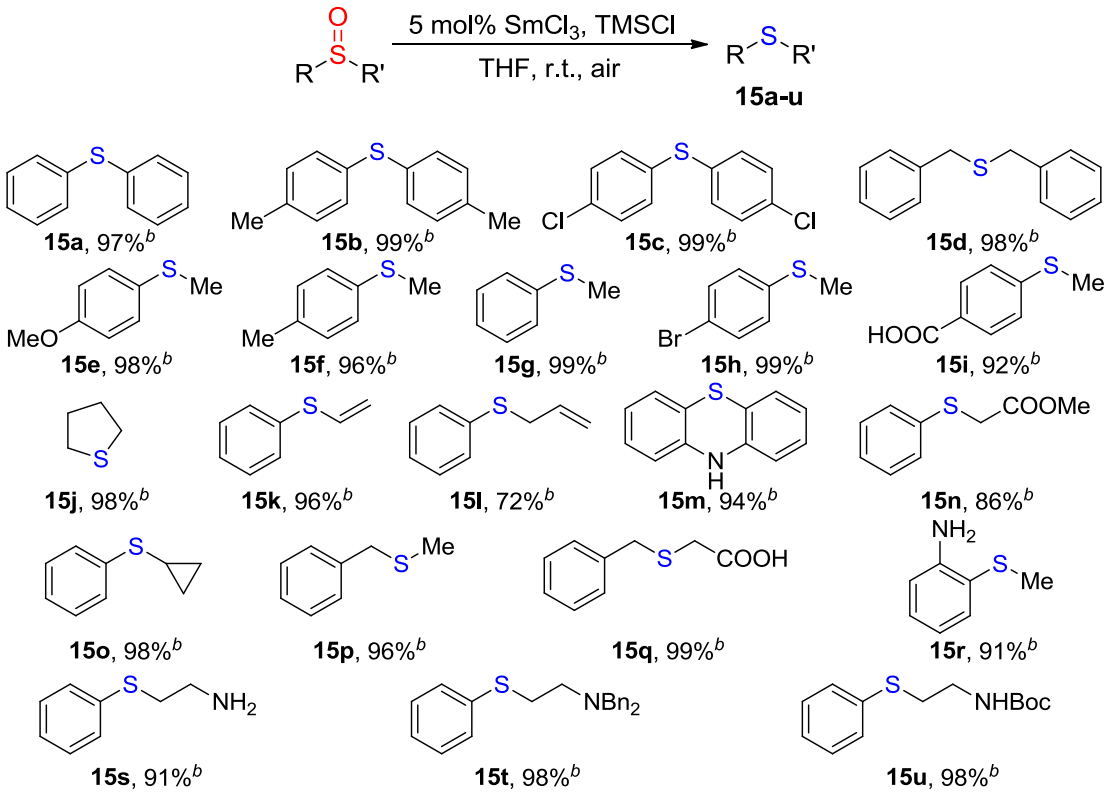

[a]standard conditions: substrates (1.0 mmol), $SmCl_3$ (0.05 equiv), TMSCl (4.0 equiv.), $n$Bu$_4$NPF$_6$ (0.1 mmol) in MeOH (50 ml), Sm as the cathode, carbon as the anode, I= 0.05 A, r.t. in the air. [b]determined by NMR. [c]Isolated yields. [d] conversion.

These results illustrated that the reactivity in the established electrochemical condition in the methanol is substrate dependent. According to our previous observation on the important effect of the solvent in nitrobenzene electrocatalytic reduction, we chose to perform the reduction of sulfoxides in THF instead of MeOH.

## IV. 4. 2. Using THF as solvent

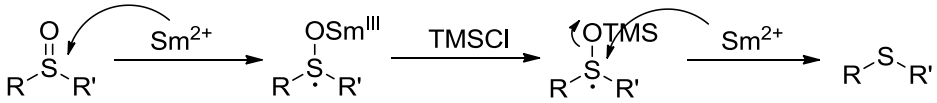
Since the result in methanol condition was unsatisfied, we demonstrated the Sm electrocatalytic system in THF. To our delight, under this condition, it exhibited high catalytic reactivity for the chemoselective reduction of various sulfoxides to sulfides (Table 4.3). The symmetric aromatic sulfoxides were reduced into the sulfides (Table 4.3, **15a-c**). Satisfyingly, benzylic sulfoxides were efficiently reduced to the corresponding sulfides completely in high yields (Table 4.3, **15d**). Moverover, this process presented a high chemoselectivity without affecting some sensitive functional groups such as double bond, cyclopropyl, ester and halogen and protecting group (Bn, Boc). (Table 4.3, **15c**, **15h**, **15k**, **15l**, **15n**, **15o**, **15t**, **15u**) Notably, the electrocatalytic condition was also applicable to the substrates with carboxyl or amino group, which were facile to poison the metal catalyst (Table 4.3, **15m**, **15q-s**).

**Table 4.3** The scope of the electrocatalytic reduction of sulfoxides in THF.[a]




[a]standard conditions: substrates (1.0 mmol), $SmCl_3$ (0.05 equiv), TMSCl (4.0 equiv.), $n$Bu$_4$NPF$_6$ (0.4 mmol) in THF (50 ml), Sm as the cathode, carbon as the anode, I= 0.05 A, r.t. in the air. [b]Isolated yields.

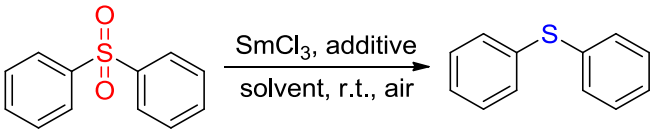
Concerning the reaction mechanism, to our best knowledge there is no report for the application of $SmI_2$ as reductant. We tried to follow the reaction by GC analysis. However, only starting material and the product were detected without any other plausible intermediates. Similar as the reduction of the nitrobenzenes in the THF, we assumed the plausible mechanism as followed according the fact that there is no proton in the electrolytic medium. At first, the sulfoxide received an electron to form a radical intermediate. Then, the trimethyl silyl group replaced the $Sm^{3+}$ and deoxygenated with second equivalent of electron to afford the sulfide. (Scheme 4.12)




Scheme **4.12** The plausible mechanism

The electrocatalytic deoxygenation of sulfoxides was established successfully using the THF as the solvent. The result illustrated that the transformation was in the

high chemoselectivity and efficiency. Therefore, we tried to perform the reduction of sulfones for which the reduction is more difficult. Indeed, 44 equiv. chemical $SmI_2$ and HMPA were needed to convert sulfonyl into sulfenyl group (Scheme 4.13).




Scheme **4.13** The reduction of sulfone by $SmI_2$

Due to the challenge for this transformation, we firstly used 10 mol % Sm source to attempt the reactivity. However, no reaction was happened neither in MeOH nor THF with 8.0 equivalent TMSCl. Even though the equivalent of Sm was improved to 100 mol%, the sulfone was stable in the electrocatalytic process. To our disappointment, changing the TMSCl into TMSOTf, $BF_3$•$Et_2O$, Ti(O*i*Pr)$_4$ or $Et_3N$-$H_2O$ , there was no effect on the sulfone reduction at all. Finally, we added HMPA which was a highly reactive condition, but no expected product was afforded.

## IV. 5. Conclusion

In conclusion, the efficient Sm electrocatalytic reduction of sulfoxides was established. With the reductive condition of nitrobenzenes, we demonstrated the different systems in methanol or THF to deoxygenate the sulfoxides. After the extension, the THF system was chosen to carry out this transformation. Notably, this process presented an efficient applicability to a wide range of sulfoxides. Avoiding the high temperature and pressure, the reaction occurred at room temperature in the air. Besides, the different solvent systems illustrated two possible Sm electrocatalytic processes which indicated other suitable reductions could be carried out in the future.

# IV. 6. Experiment

## IV. 6. 1. General Information

THF was distilled from sodium metal/benzophenone before use. All commercially available chemicals were used without purification. $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded on either a Bruker AM 360 (360 MHz), AM 300 (300 MHz), or AM 250 (250 MHz) instrument with samples dissolved in $CDCl_3$. $^{1}H$ NMR chemical shifts were referenced to the residual solvent signal; $^{13}C$ NMR chemical shifts were referenced to the deuterated solvent signal. Data are represented as follows: chemical shift δ (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (*J*) in Hz and integration. Mass spectra were recorded on a micrOTOF-q Brucker Daltonics spectrometer. Flash chromatography (FC) was performed on 40-63 µm silica gel with mixtures of ethyl acetate (EA) and pentane. TLC plates were visualized by exposure to UV (254 nm) and/or $KMnO_4$ stain. The gas chromatography (GC) were performed on a spectrometer Varian GC-430 (injection: split/splitless, FID detector, column VF1-MS: 15m x 0.25 mm x 0.25 microns, program: 1 min 50 °C, 10 °C/min to 250 °C, 250 °C 2 min, 23 min total). Infrared spectra were recorded on a FTIR spectrometer (Perkin-Elmer spectrum one, NaCl pellets or Bruker Vertex 70 ATR Pike Germanium) and are reported in $cm^{-1}$. Melting points were determined using a Büchi melting point apparatus. Electrolysis were performed with a AUTOLAB potentiostat/galvanostat (model: PGSTAT302N), in an undivided three-electrodes cell containing samarium rod working electrode, a standard glassy carbon counter electrode and a saturated calomel electrode (SCE) as reference. The samarium electrode used is based on a samarium rod of 12.7 mm (0.5 in) diameter and 5 cm length, directly connected to a copper wire to ensure current conductivity. This self-made electrode is stored under inert atmosphere when it is not used. All the samarium rods are purchased from Alfa Aesar (99.9 % metals basis excluding Ta).

## IV. 6. 2. General condition for the electrocatalytic reduction in MeOH

Reactions were carried out in a one compartment cell containing a magnetic stirring bar, samarium cathode (20 $cm^2$ area), glassy carbon anode (20 $cm^2$ area) and

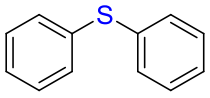
SCE as reference electrode. The cell is then charged with 50 mL of electrolyte solution containing 0.01 M $n$Bu$_4$NPF$_6$ in MeOH. After that, the corresponding sulfoxides (1.0 mmol), $SmCl_3$ (0.1 mmol) and trimethylsilyl chloride (4.0 mmol) were then added in the mixture. The electrolysis was performed at i = 50 mA during 4 hours in the air. The mixture was then diluted by $Et_2O$ (50 mL), quenched with 0.1 M HCl (20 mL) and extracted with $Et_2O$ (2×20 mL). The combined extracts were washed with sodium thiosulfate and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel. The resulting compounds were identified by comparison of their physical and spectral data with those given in the literature.

## IV. 6. 3. General condition for the electrocatalytic reduction in THF

Reactions were carried out in a one compartment cell containing a magnetic stirring bar, samarium cathode (20 cm$^2$ area), glassy carbon anode (20 cm$^2$ area) and SCE as reference electrode. The cell is then charged with 50 mL of electrolyte solution containing 0.04 M $n$Bu$_4$NPF$_6$ in THF. After that, the corresponding sulfoxides (1.0 mmol), $SmCl_3$ (0.05 mmol) and trimethylsilyl chloride (4.0 mmol) were then added in the mixture. The electrolysis was performed at i = 50 mA during 4 hours in the air. The mixture was then diluted by $Et_2O$ (50 mL), quenched with 0.1 M HCl (20 mL) and extracted with $Et_2O$ (2×20 mL). The combined extracts were washed with sodium thiosulfate and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel. The resulting compounds were identified by comparison of their physical and spectral data with those given in the literature.

## IV. 6. 4. Characterization data of sulfides

**Diphenylsulfane (15a)**




**15a**

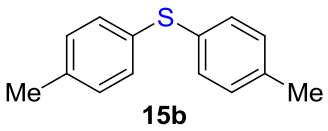
Column (Pentane) to afford a white solid (184 mg, yield: 99%);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 7.43 – 7.25 (m, 1H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 135.82, 131.08, 129.24, 127.09;

CAS registry No. [139-66-2]

**di-*p*-tolylsulfane (15b)**




**15b**

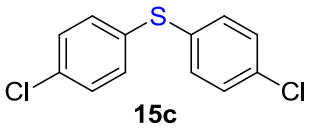
Column (Ethyl acetate: Pentane = 1: 100) to afford a white solid (212 mg, yield: 99%);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 7.37 – 7.23 (m, 4H), 7.14 (d, *J* = 8.0 Hz, 4H), 2.37 (s, 6H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 136.92, 132.68, 131.08, 129.94, 21.11;

CAS registry No. [620-94-0]

**bis(4-chlorophenyl)sulfane (15c)**




**15c**

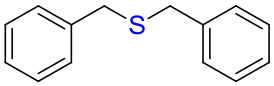
Column (Ethyl acetate: Pentane = 1: 100) to afford a white solid (254 mg, yield: 100%);

**$^{1}$H NMR (250 MHz, $CDCl_3$)** δ 7.36 – 7.25 (m, 8H).

**$^{13}$C NMR (63 MHz, $CDCl_3$)** δ 134.0, 133.5, 132.3, 129.5.

CAS registry No. [5181-10-2]

**Dibenzylsulfane (15d)**




**15d**

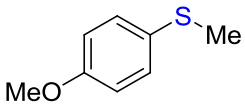
Column (Pentane) to afford a white solid (210 mg, yield: 98%);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 7.49 – 7.25 (m, 5H), 3.64 (s, 2H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 138.2, 129.0, 128.5, 127.0, 35.6.

CAS registry No. [538-74-9]

**(4-methoxyphenyl)(methyl)sulfane (15e)**




**15e**

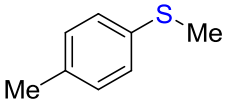
Column (Ethyl acetate: Pentane = 1: 100) to afford a colorless oil (151 mg, yield: 98%);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 7.30 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 3.81 (s, 3H), 2.47 (s, 3H).

**$^{13}$C NMR (91 MHz, $CDCl_3$)** δ 158.2, 130.2, 128.8, 114.6, 55.4, 18.1.

CAS registry No. [1879-16-9]

**methyl(*p*-tolyl)sulfane (15f)**




**15f**

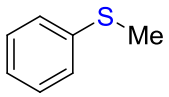
Column (Pentane) to afford a yellow oil (132 mg, yield: 96%);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 7.29 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 2.54 (s, 3H), 2.41 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 135.0, 134.9, 129.7, 127.3, 21.0, 16.5.

CAS registry No. [623-13-2]

**methyl(phenyl)sulfane (15g)**




**15g**

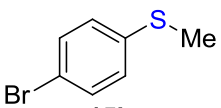
Column (Pentane) to afford a colorless oil (123 mg, yield: 99%);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 7.39 – 7.32 (m, 4H), 7.25 – 7.17 (m, 1H), 2.54 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 138.5, 128.9, 126.6, 125.1, 15.9.

CAS registry No. [100-68-5]

**(4-bromophenyl)(methyl)sulfane (15h)**




**15h**

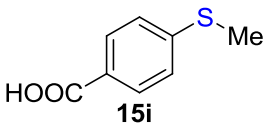
Column (Pentane) to afford a yellow solid (200 mg, yield: 99%);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.48 – 7.29 (m, 2H), 7.19 – 6.99 (m, 2H), 2.49 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 137.7, 131.8, 128.1, 118.6, 15.9.

CAS registry No. [104-95-0]

**4-(methylthio)benzoic acid (15i)**




**15i**

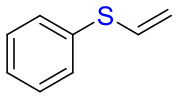
Column (Ethyl acetate: Pentane = 1: 1) to afford a yellow solid (155 mg, yield: 92%);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 8.03 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 2.55 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 171.6, 146.8, 130.5, 125.2, 124.8, 14.7.

CAS registry No. [13205-48-6]

**phenyl(vinyl)sulfane (15k)**




**15k**

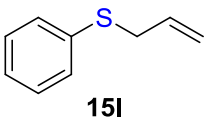
Column (Ethyl acetate: Pentane = 1: 100) to afford a colorless oil (131 mg, yield: 96%);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.46 – 7.32 (m, 5H), 6.71 – 6.54 (m, 1H), 5.45 – 5.43 (m, 1H), 5.42 – 5.39 (m, 1H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 134.3, 132.0, 130.6, 129.2, 127.2, 115.6.

CAS registry No. [1822-73-7]

**allyl(phenyl)sulfane (15l)**




**15l**

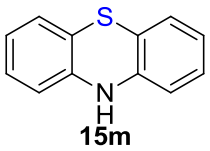
Column (Pentane) to afford a yellow oil (108 mg, yield: 72%);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.46 – 7.38 (m, 2H), 7.38 – 7.31 (m, 2H), 7.29 – 7.22 (m, 1H), 6.03 – 5.88 (m, 1H), 5.27 – 5.09 (m, 2H), 3.61 (dt, *J* = 7.2, 1.1 Hz, 2H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 136.0, 133.7, 129.8, 128.9, 126.3, 117.7, 37.2.

CAS registry No. [5296-64-0]

**10*H*-phenothiazine (15m)**




**15m**

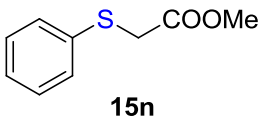
Column (Ethyl acetate: Pentane = 1: 5) to afford a yellow solid (187 mg, yield: 94%);

**$^{1}$H NMR (360 MHz, CDCl$_3$)** δ 7.12 – 6.97 (m, 4H), 6.86 (d, *J* = 7.0 Hz, 2H), 6.57 (d, *J* = 8.0 Hz, 2H), 5.82 (s, 1H).

**$^{13}$C NMR (90 MHz, CDCl$_3$)** δ 127.4, 126.9, 122.7, 114.5.

CAS registry No. [92-84-2]

**methyl 2-(phenylthio)acetate (15n)**




**15n**

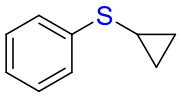
Column (Ethyl acetate: Pentane = 1: 5) to afford a white solid (157 mg, yield: 86%);

**$^{1}$H NMR (360 MHz, CDCl$_3$)** δ 7.45 – 7.38 (m, 2H), 7.35 – 7.27 (m, 2H), 7.27 – 7.19 (m, 1H), 3.71 (s, 3H), 3.66 (s, 2H).

**$^{13}$C NMR (90 MHz, CDCl$_3$)** δ 170.2, 135.0, 129.9, 129.1, 127.0, 52.6, 36.4.

CAS registry No. [17277-58-6]

**cyclopropyl(phenyl)sulfane (15o)**




**15o**

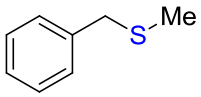
Column (Ethyl acetate: Pentane = 1: 100) to afford a white solid (147 mg, yield: 98%);

**$^{1}$H NMR (360 MHz, CDCl$_3$)** δ 7.44 (dt, *J* = 8.2, 1.5 Hz, 2H), 7.39 – 7.31 (m, 2H), 7.25 – 7.16 (m, 1H), 2.25 (tt, *J* = 7.4, 4.4 Hz, 1H), 1.12 (td, *J* = 6.6, 4.8 Hz, 2H), 0.80 – 0.71 (m, 2H).

**$^{13}$C NMR (90 MHz, CDCl$_3$)** δ 138.9, 128.8, 126.5, 125.0, 12.1, 8.6.

CAS registry No. [14633-54-6]

**benzyl(methyl)sulfane (15p)**




**15p**

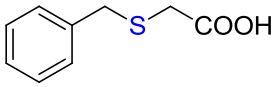
Column (Pentane) to afford a colorless oil (132 mg, yield: 96%);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 7.48 – 7.36 (m, 4H), 7.36 – 7.25 (m, 1H), 3.75 (s, 2H), 2.06 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 138.4, 129.0, 128.6, 127.0, 38.4, 15.0.

CAS registry No. [766-92-7]

**2-(benzylthio)acetic acid (15q)**




**15q**

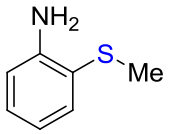
Column (Ethyl acetate: Pentane = 1: 3) to afford a white solid (171 mg, yield: 94%);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 11.35 (s, 1H), 7.47 – 7.26 (m, 5H), 3.89 (s, 2H), 3.13 (s, 2H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 177.3, 136.9, 129.3, 128.7, 127.5, 36.3, 32.0.

CAS registry No. [103-46-8]

**2-(methylthio)aniline (15r)**




**15r**

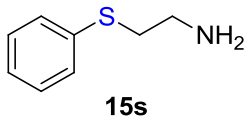
Column (Ethyl acetate: Pentane = 1: 5) to afford a yellow solid (126 mg, yield: 91%);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 7.42 (d, $J$ = 7.7 Hz, 1H), 7.19 – 7.11 (m, 1H), 6.77 (ddd, $J$ = 7.9, 6.2, 2.5 Hz, 2H), 4.27 (s, 2H), 2.41 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 147.2, 133.4, 129.0, 120.3, 118.8, 115.0, 17.8.

CAS registry No. [2987-53-3]

**2-(phenylthio)ethanamine (15s)**



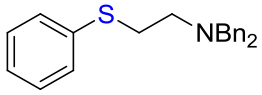
**15s**

Column (Ethyl acetate: Pentane = 1: 1) to afford a colorless oil (139 mg, yield: 91%);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.35 (d, *J* = 8.2 Hz, 2H), 7.26 (dd, *J* = 8.0, 7.3 Hz, 2H), 7.22 – 7.13 (m, 1H), 2.98 (t, *J* = 6.2 Hz, 2H), 2.98 (t, *J* = 6.2 Hz, 2H), 2.87 (t, *J* = 6.3 Hz, 2H), 1.56 (s, 2H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 135.7, 129.7, 129.0, 126.2, 40.9, 38.0.

***N,N*-dibenzyl-2-(phenylthio)ethanamine (15t)**



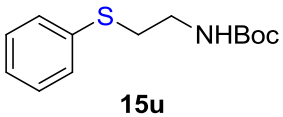
**15t**

Column (Ethyl acetate: Pentane = 1: 10) to afford a colorless oil (326 mg, yield: 98%);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.44 (dd, *J* = 5.2, 3.1 Hz, 4H), 7.40 – 7.34 (m, 4H), 7.34 – 7.26 (m, 2H), 7.26 – 7.11 (m, 4H), 3.68 (s, 4H), 3.14 – 3.02 (m, 2H), 2.85 – 2.75 (m, 2H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 139.4, 136.7, 128.9, 128.5, 128.3, 127.1, 125.6, 58.5, 52.7, 31.2.

***tert*-butyl (2-(phenylthio)ethyl)carbamate (15u)**



**15u**

Column (Ethyl acetate: Pentane = 1: 3) to afford a colorless oil (248 mg, yield: 98%);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.41 – 7.35 (m, 2H), 7.30 (ddd, *J* = 8.3, 4.5, 2.0 Hz, 2H), 7.24 – 7.18 (m, 1H), 4.98 (s, 1H), 3.34 (dd, *J* = 12.2, 6.0 Hz, 2H), 3.05 (t, *J* = 6.3 Hz, 2H), 1.45 (s, 9H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 155.7, 135.2, 129.8, 129.1, 126.4, 79.5, 39.6, 34.1, 28.4.

# Chapter V. The chemoselective Sm electrocatalytic reduction of phthalimides

## V. 1. Introduction

In the previous chapters, we developed the $Sm^{II}$ electrocatalyzed conditions to selectively reduce the nitro compounds and sulfoxides, which ameliorated the drawbacks of the chemical $SmI_2$ such as low chemoselectivity, large excess amounts of $SmI_2$, harmful additive and large volume of solvent. Next, we focused on the transformation of phthalimides which was never reported by $SmI_2$ chemistry.

Phthalimide is an important intermediate in the production of agricultural pesticides and wood preservatives, pigments and pharmaceuticals. As the starting material, the anthranilic acid and a large number of primary amines can be produced respectively by Hofmann degradation and the Gabriel synthesis.[142] Recent years, isoindolinones and derivatives have attracted great attention in pharmaceuticals and biochemicals.[143] Although several methods were developed for their synthesis, the reduction of phthalimide is still the most convenient and efficient pathway to these compounds.

The organometallic hydrides ($NaBH_4$[144] and $LiAlH_4$[145]) and Sn[146] or Zn[147] in a strong acid are the classical conditions to realize the translation, but the stoichiometric or excess amounts and harsh condition lead to a low functional group tolerance,

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[142] Lorz, P. M.; Towae, F. K.; Enke, W.; Jäckh, R.; Bhargava, N.; Hillesheim, W. Phthalic Acid and Derivatives; *Ullmann's Encyclopedia of Industrial Chemistry,* 2007; pp 131–180.

[143] (a) Romo, D.; Meyers, A. I. *Tetrahedron,* **1991,** *47,* 9503–9569. (b) Link, J. T.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995,** *117,* 552–553. (c) Yoon, U. C.; Jin, Y. X.; Oh, S. W.; Park, C. H.; Park, J. H.; Campana, C. F.; Cai, X.; Duesler, E. N.; Mariano, P. S. *J. Am. Chem. Soc.* **2003,** *125,* 10664–10671. (d) Othman, R. Ben; Affani, R.; Tranchant, M.-J.; Antoniotti, S.; Dalla, V.; Dunach, E. *Angew. Chem., Int. Ed.* **2010,** *49,* 776–780. (e) Xu, K.; Zhang, S.; Hu, Y.; Zha, Z.; Wang, *Z. Chem.–Eur. J.* **2013,** *19,* 3573– 3578. (f) Hamon, M.; Dickinson, N.; Devineau, A.; Bolien, D.; Tranchant, M.-J.; Taillier, C.; Jabin, I.; Harrowven, D. C.; Whitby, R. J.; Ganesan, A.; Dalla, V. *J. Org. Chem.* **2014,** *79,* 1900–1912.

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[145] (a) González, J. F.; Salazar, L.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **2005,** *61,* 7447–7455. (b) González, J. F.; de la Cuesta, E.; Avendaño, C. *Bioorg. Med. Chem.* **2007,** *15,* 112–118. (c) Conchon, E.; Anizon, F.; Aboab, B.; Prudhomme, M. *Synthesis* **2008,** *16,* 2569–2574.

[146] (a) Norman, M. H.; Minick, D. J.; Rigdon, G. C. *J. Med. Chem.* **1996,** *39,* 149-157. (b) Arizpe, A.; Sayago, F. J.; Jiménez, A. I.; Ordóñez. M.; Cativiela, C. *Eur. J. Org. Chem.* **2011,** 6732–6738.

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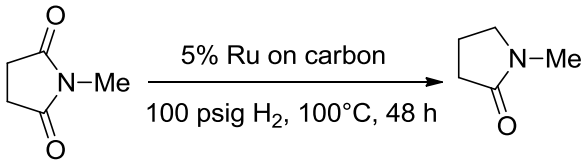
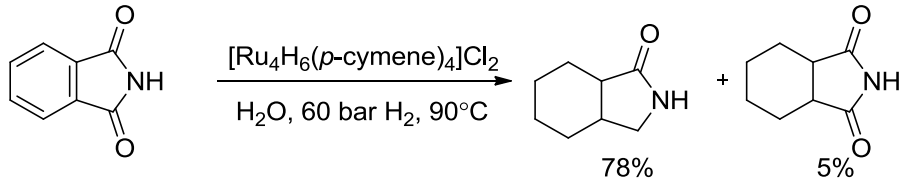
amounts of waste and even an overreduction. Since 1940, a Dupont patent described a use of Ni catalyst to reduce the phthalimide,[148] only a small number of organometallic complexes were used on it.

In 1993, Drago's group reported a ruthenium-catalyzed reduction of the *N*-methylsuccinimide into the *N*-methylpyrrolidinone, albeit with a harsh condition and only one example, that indicated the chemoselective catalytic reduction of lactims (Scheme 5.1).[149]




**Scheme 5.1** The Ru-catalyzed reduction of succinimide.

Recently, Bruneau's group reported a cyclic imides monoreduction with a concomitant hydrogenation of unsaturated bonds by a ruthenium catalyst (Scheme 5.2).[150] Using the phthalimide as the starting material, the aromatic ring was reduced at the same time.




**Scheme 5.2** The Ru complex catalyzed reduction of phthalimide with a concomitant hydrogenation of unsaturated bonds

Subsequently, Ikariya's and Bergens's group respectively used Cp*Ru(PN) catalytic system for hydrogenation of imides (Scheme 5.3).[151] This work presented the phthalimide (N-Bn or Ph) into amides and primary alcohols with chemoselectivity and stereoselectivity.

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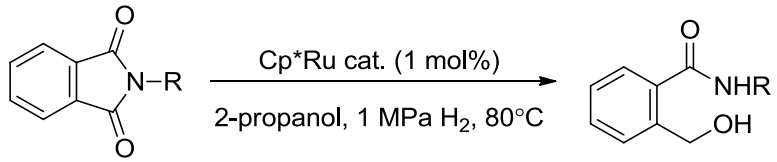
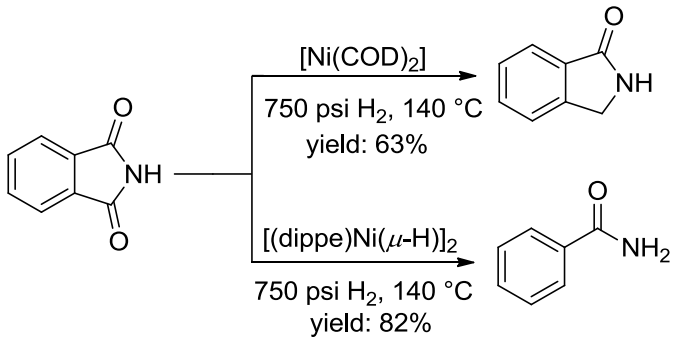
[148] Smith, A. M.; Whyman, R. *Chem. Rev.* **2014,** *114,* 5477−5510.
[149] Patton, D. E.; Drago, R. S. *J. Chem. Soc., Perkin Trans. 1* **1993,** 1611–1615.
[150] Aoun, R.; Renaud, J.-L.; Dixneuf, P. H.; Bruneau, C. *Angew. Chem., Int. Ed.* **2005,** *44,* 2021-2023.
[151] (a) Ito, M.; Sakaguchi, A.; Kobayashi, C.; Ikariya, T. *J. Am. Chem. Soc.* **2007,** *129,* 290–291. (b) Ito, M.; Kobayashi, C.; Himizu, A.; Ikariya, T. *J. Am. Chem. Soc.* **2010,** *132,* 11414–11415.




R= Bn, Ph
Cp*Ru cat.: Cp*RuCl(cod)+ligand+KO*t*-Bu (1:1:1)

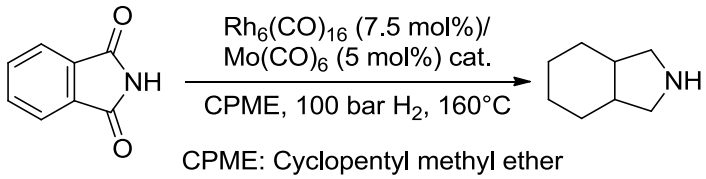
**Scheme 5.3** The Cp*Ru(PN) system catalyzed reduction of phthalimides into amides and primary alcohols.

In 2013, García and co-workers researched using the Ni complex catalyst to selectively reduce the phthalimide (Scheme 5.4).[152] The use of [Ni(COD)$_2$] allowed the phthalimide monoreduction to yield isoindolinone without any other byproducts, and benzamide was afforded instead by [(dippe)Ni($\mu$-H)]$_2$ catalyst under the same condition.




**Scheme 5.4** The Ni-catalyzed reduction of phthalimides into isoindolinones and benzamides respectively.

In 2014, Agbossou-Niedercorn's group presented a rhodium/molybdenum-catalyzed full reduction of *N*-unsubstituted cyclic imides (Scheme 5.5).[153]

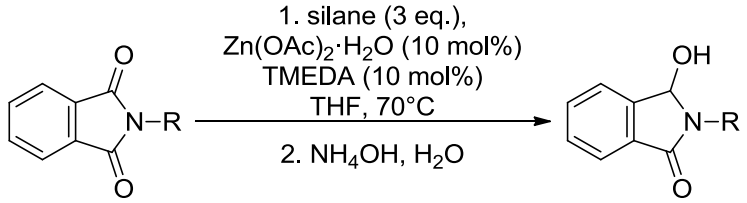



CPME: Cyclopentyl methyl ether

**Scheme 5.5** The Rh/Mo system catalyzed full reduction of phtalimides into cylic imides

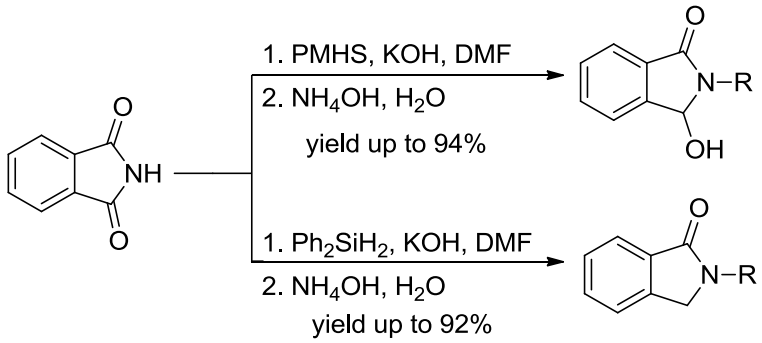
[152] Arévalo, A.; Ovando-Segovia, S.; Flores-Alamo, M.; García, J. J. *Organometallics* **2013,** *32,* 2939–2943.
[153] Maj, A. M.; Suisse, I.; Pinault, N.; Robert, N.; Agbossou- Niedercorn, F. *ChemCatChem* **2014,** *6,* 2621–2625.

Later on, Xie's group reported an efficient hydrosilylation of cyclic imides to ω-hydroxylactams by zinc catalysts with hydrosilanes (Scheme 5.6).[154a] Under the $Zn(OAc)_2$•$2H_2O$ and TMEDA catalyst system, the protocol showed good functional group tolerance as well as excellent regioselectivity for unsymmetrical imides bearing coordinating groups adjacent to the carbonyl.




**Scheme 5.6** The Zn-catalyzed reduction of phthalimides into hydroxylactams with hydrosilanes.

Then, they succeeded in chemoselectively reducing cyclic imides to the corresponding ω-hydroxylactams or lactams with a hydrosiloxane/KOH reduction system (Scheme 5.7).[154b]




**Scheme 5.7** The KOH-catalyzed reduction of phthalimides into aza-hemiacetals and isoindolinones respectively.

Most recently, Zhang's group published a tetradentate ruthenium complex directly catalyze amides to amines and alcohols (Scheme 5.8).[155]

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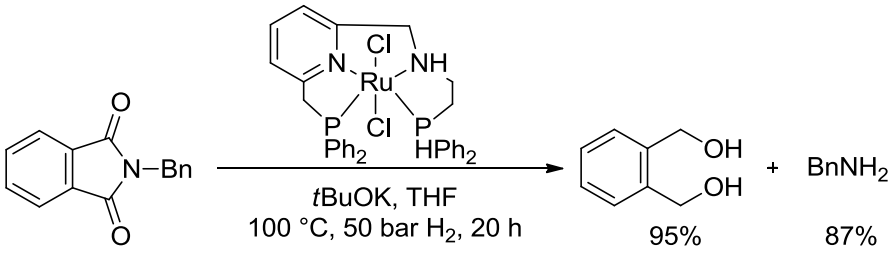
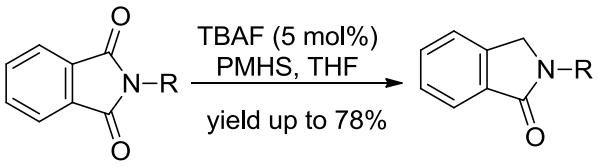
[154] (a) Ding, G.; Lu, B.; Li, Y.; Wan, J.; Zhang, Z.; Xie, X. *Adv. Synth. Catal.* **2015,** *357,* 1013–1021. (b) Ding, G.; Li, C.; Shen, Y.; Lu, B.; Zhang, Z.; Xie, X. *Adv. Synth. Catal.* **2016,** *358,* 1241–1250.

[155] Shi, L.; Tan, X.; Long, J.; Xiong, X.; Yang, S.; Xue, P.; Lv, H.; Zhang, X. *Chem.–Eur. J.* **2017,** *23,* 546–548.



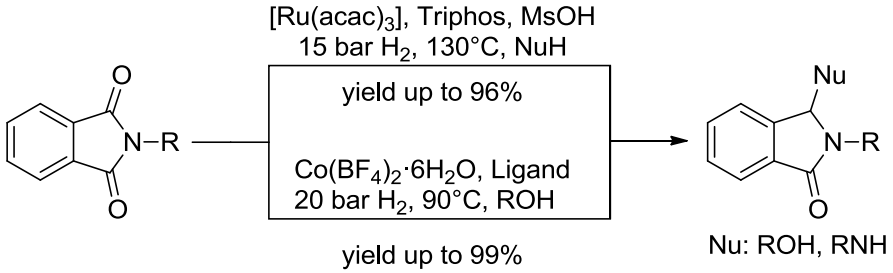

**Scheme 5.8** The Ru complex catalyzed reduction of phthalimides into amines and alcohols.

Notably, in 2011, Beller's group established a TBAF/PMHS system without metals to reduce phtalimides into isoindolinones with a high chemoselectivity (Scheme 5.9).[156a]




**Scheme 5.9** The TBAF-catalyzed reduction of phthalimides into isoindolinones.

Furthermore, they reported an efficient reductive alkoxylation and amination of phthalimide (Scheme 5.10).[156b,c] By using a [Ru/Triphos]-based catalyst system in combination with an organic acid, *N*-substituted phthalimides react with a wide range of alcohols and amines to afford the corresponding 2-substituted isoindolinones in good to excellent yields.[156b] Then, in the place of noble metal, they used the [Co/triphos] system accomplish the alkoxylation of phthalimide without any acid additive. [156c]



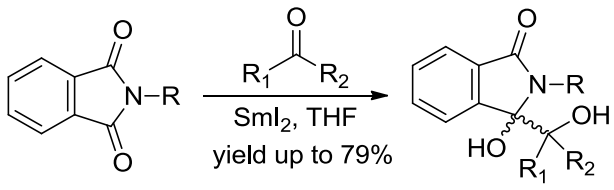

**Scheme 5.10** The Ru or Co complex catalyzed reduced alkoxylation of phthalimides.

[156] (a) Das, S.; Addis, D.; Knoepke, L. R.; Bentrup, U.; Junge, K.; Brueckner, A.; Beller, M. *Angew. Chem., Int. Ed.* **2011,** *50,* 9180–9184. (b) Cabrero-Antonino, J. R.; Sorribes, I.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2016,** *55,* 387–391. (C) Cabrero-Antonino, J. R.; Adam, R.; Papa, V.; Holsten, M.; Jungea, K.; Beller, M. ***Chem. Sci.*** **2017,** ***8,*** 5536-5546.

Although these procedures exhibit plenty of advancements, obviously the drawbacks still exist. The low yield and narrow scopes, using of precious catalysts and the employment of hydrosilanes or hydrogen under a high pressure and temperature as reducing reagents are all significant limitation. Especially, the desired isoindolinone derivatives can't be obtained due to the C-N bond cleavage and over reduction.

Since 1977 Kagan's group published the first article on $SmI_2$ in organic chemistry,[157] which has been one of the most important reducing agents available.[158] Even so, there is rare publication about phthalimide.

In 2000, Yoda's group reported a reduced coupling reaction between phthalimide and carbonyl compounds by $SmI_2$ (Scheme 5.11).[159] With 2-5 equiv. ketones or aldehydes, the phthalimide trapped the ketyl samarium radical intermediates.




**Scheme 5.11** The pinacol coupling between phthalimaide and carbonyl compounds by $SmI_2$.

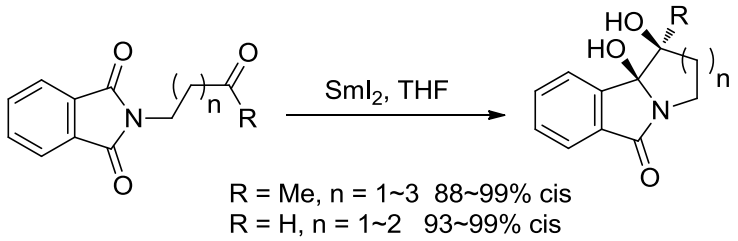
In 2010, Kise's group used the $SmI_2$ to realize the intramolecular coupling of *N*-(oxoalkyl)phthalimides (Scheme 5.12).[160] The procedure is similar as Yoda's report, but they contrasted the stereoselectivity of $SmI_2$ and electrical reduction.

[157] (a) Namy, J.L.; Girard, P.; Kagan, H. B. *Nouv. J. Chim.* **1977,** *1,* 5-9. (b) Girard, P.; Namy, J.L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980,** *102,* 2693-2698.

[158] For recent reviews on $SmI_2$, see: (a) Procter, D. J.; Flowers, R. A., II; Skrydstrup, T. *Organic Synthesis Using Samarium Diiodide: A Practical Guide*; RSC Publishing: Cambridge, 2009. (b) Szostak, M.; Spain, M.; Procter, D. J. *Chem. Soc. Rev.* **2013,** *42,* 9155-9183. (c) Szostak, M.; Fazakerley, N. J.; Parmar, D.; Procter, D. J. *Chem. Rev.* **2014,** *114,* 5959-6039. (d) JustBaringo, X.; Procter, D. J. *Acc. Chem. Res.* **2015,** *48,* 1263-1275.

[159] Yoda, H.; Matsuda, K.; Nomura, H.; Takabe, K. *Tetrahedron Lett.* **2000,** *41,* 1775–1779.

[160] Kise, N.; Sakurai, T. *Tetrahedron Lett.* **2010,** *51,* 70–74.




**Scheme 5.12** The intramolecular coupling of *N*-(oxoalkyl)phthalimides.

Finally, according to this both unique examples using of phthalimide as starting material in $SmI_2$ chemistry, the reactivity consist in the cross coupling of carbonyl group and never in reduction of phthalimides.

Recently, we developed that electrogenerating catalytically active $Sm^{2+}$ as a reducing agent could represent an elegant and cost-effective synthetic method for C-C and C-heteroatom bond forming transformations compared to all previous reported one.[161] The process performed a $Sm^{2+}$ regeneration to catalyze the reaction under the current intensity imposed. We also found that the electrochemical procedure significantly enhanced the reactivity of the $Sm^{II}$ species.[162] Inspiration of previous results, we desired to expand our system into more fields. Therefore, we decided to investigate the reactivity on phthalimides under our samarium electrocatalytic method in order to perform chemoselective reduction.

## V. 2. Sm electrocatalyzed alkoxylation of phthalimides

At the beginning, the *N*-methylphthalimide was chosen to explore the chemical reactivity. As we reported, under i = 50 mA and the $nBu_4NPF_6$ as the electrolyte, the reaction was conducted in THF with 10 mol % $SmCl_3$, 10.0 eq. MeOH and 4.0 eq. TMSCl. To our surprise, the methoxylation of one of the carbonyl groups product was afforded in spite of 66% conversion after 2 h. Inspired by the unprecedented reductive alkoxylation by $Sm^{2+}$, we optimized the different conditions to improve the chemoselectivity and yield.

[161] (a) Sun, L.; Sahloul, K.; Mellah, M. *ACS Catal.* **2013,** *3,* 2568-2573.
[162] (a) Sahloul, K.; Sun, L.; Requet, A.; Chahine, Y.; Mellah, M. *Chem. Eur. J.* **2012,** *18,* 11205-11209. (b) Sun, L.; Mellah, M. *Organometallics* **2014,** *33,* 4625-4628.

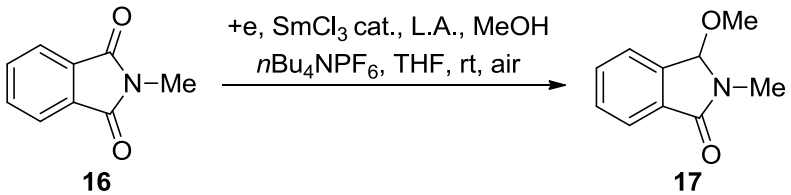
## V. 2. 1. Optimization of $Sm^{2+}$ reductive alkoxylation

Since, the selective methoxylation of the carbonyl groups product was afforded in around 66% conversion (Table 5.1. Entry **1**), we first evaluated the effect of the oxophile on the conversion. Regarding the Lewis acid, by replacing TMSCl with TMSOTf, the yield and conversion were decreased to 41% and 47% (Table 5.1, entry **2**). We tried also $Et_2O{\bullet}BF_3$ as a common additive in $SmI_2$ coupling reaction. However, reaction occurred in this case with very low conversion. Moreover, the use of $TiCl_4$ and $SnCl_4$ instead of TMSCl did not produce the desired methoxylated compound after complete conversion (Table 5.1, entry **3-5**).

At this point, the effect of concentration and amount of $SmCl_3$, TMSCl and methanol was explored intensively (Table 5.1, entry **6-17**). Firstly, under the 0.02 mol/L molarity, increasing the equivalent of TMSCl resulted a high conversion (Table 5.1, entry 1, **6-12**), nevertheless the yield of the alkoxylation product seems dependent on the amount of MeOH (Table 5.1, entry **7-9**). The loading of $SmCl_3$ even decreasing to 1% had only little effect (Table 5.1, entry **7**, **10-12**). For the intermolecular coupling reaction, the concentration is a crucial factor (Table 5.1, entry **14-17**). Gratifyingly, when the concentration increased to 0.1 mol/L, the yield was 97% with 2.5 equivalent TMSCl (Table 5.1, entry 16).

As controlled experiment, it was verified that without $SmCl_3$ initially introduced no reaction occurred (Table 5.1, entry **18**), also this was verified for TMSCl (Table 5.1, entry **19**). We have also confirmed no reaction occurred when no current intensity was imposed (Table 5.1, entry **20**).

**Table 5.1.** Optimization of reductive methoxylation of *N*-methyl phtalimide[a]




**16** **17**

| Entry | $SmCl_3$ eq. | Lewis acid eq. | MeOH eq. | *c* mol/L | t h | Conv. | yield[f] |
|---|---|---|---|---|---|---|---|
| **1**[b] | 10% | TMSCl 4.0 | 10 | 0.02 | 2.0 | 66% | 60% |
| **2**[b] | 10% | TMSOTf 4.0 | 10 | 0.02 | 2.0 | 47% | 41% |
| **3**[b] | 10% | $Et_2O{\bullet}BF_3$ 4.0 | 10 | 0.02 | 2.0 | <10% | Trace[e] |
| **4**[b] | 10% | $TiCl_4$ 4.0 | 10 | 0.02 | 2.0 | >99% | 0%[e] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **5** [b] | 10% | $SnCl_4$ 4.0 | 10 | 0.02 | 2.0 | >99% | 0%[e] |
| **6** [b] | 20% | TMSCl 4.0 | 10 | 0.02 | 2.0 | 65% | 60% |
| **7** [b] | 10% | TMSCl 8.0 | 10 | 0.02 | 2.0 | >99% | 89% |
| **8** [b] | 10% | TMSCl 8.0 | 5 | 0.02 | 2.0 | 45% | 41% |
| **9** [b] | 10% | TMSCl 8.0 | 20 | 0.02 | 2.0 | >99% | 79% |
| **10** [b] | 5% | TMSCl 8.0 | 10 | 0.02 | 2.5 | >99% | 96% |
| **11** [b] | 2% | TMSCl 8.0 | 10 | 0.02 | 2.5 | >99% | 97% |
| **12** [b] | 1% | TMSCl 8.0 | 10 | 0.02 | 2.5 | 91% | 88% |
| **13** [c] | 2% | TMSCl 1.0 | 10 | 0.1 | 4.0 | 10% | <5%[e] |
| **14** [c] | 2% | TMSCl 2.0 | 10 | 0.1 | 4.0 | 81% | 77% |
| **15** [c] | 2% | TMSCl 3.0 | 10 | 0.1 | 4.0 | >99% | 97% |
| **16** [c] | 2% | TMSCl 2.5 | 10 | 0.1 | 4.0 | >99% | 97% |
| **17** [c] | 1% | TMSCl 2.5 | 10 | 0.1 | 4.0 | >99% | 93% |
| **18** [c] | no | TMSCl 2.5 | 10 | 0.1 | 1 d | 0 | 0[e] |
| **19** [c] | 2% | no | 10 | 0.1 | 1 d | 0 | 0[e] |
| **20** [c,d] | 2% | TMSCl 2.5 | 10 | 0.1 | 1 d | 0 | 0[e] |

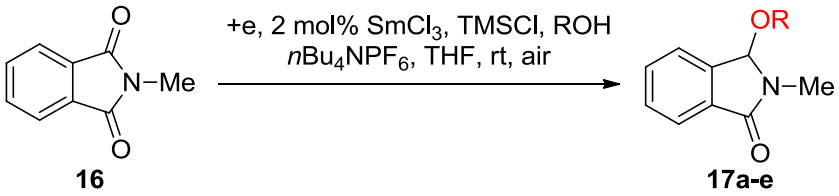
[a]standard conditions: **16** (1.0 mmol), $SmCl_3$ (0-0.1 equiv), MeOH (5-20 equiv), $n$Bu$_4$NPF$_6$ (0.04 mol/L in THF) in THF, Sm as the cathode, carbon as the anode, I= 0.05 A, r.t. in the air. [b]reaction in 50 ml THF. [c]reaction in 10 ml THF. [d]Without electricity. [e]Analyzed by GC. [f]Isolated yields.

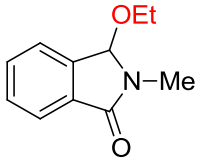
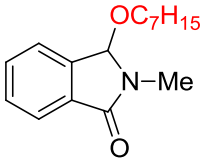
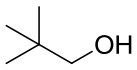
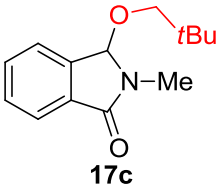
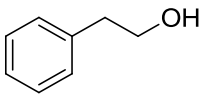
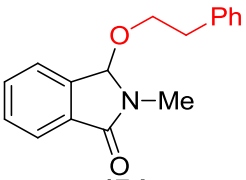
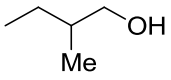
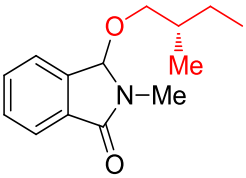
## V. 2. 2. Reductive alkoxylation of *N*-methyl phtalimide

With the optimal condition in hand, the scope of electrocatalytic reductive alkoxylation with different alcohols was probed. As we expected, all of the primary alkyl alcohols gave the corresponding 2-alkoxylated isoindolinones with excellent yields (**17a-f**).

Specifically, the less activated alcohol heptanol afforded the corresponding product **17b** in 91% yield (Table 5.2, entry **2**). Moreover, the hindered alcohols products **17c-e** were provided efficiently (Table 5.2, entry **3-5**).

**Table 5.2.** Scope of reductive alkoxylation of *N*-methyl phtalimides with the primary alcohols[a]



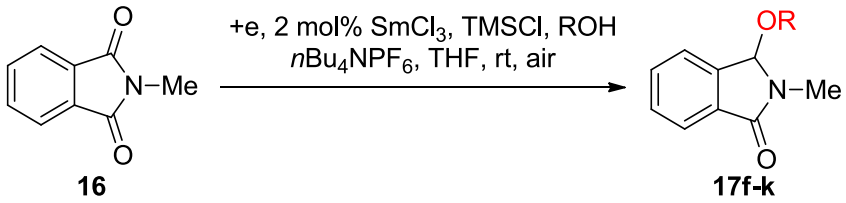

| entry | ROH | time h | Product | yield %[c] |
|---|---|---|---|---|
| **1** | EtOH | 4.0 |  **17a** | 94 |
| **2** | $nC_7H_{15}OH$ | 4.0 |  **17b** | 91 |
| **3** |  | 4.0 |  **17c** | 94 |
| **4** |  | 4.0 |  **17d** | 97 |
| **5** |  | 4.0 |  **17e** | 98 |

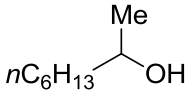
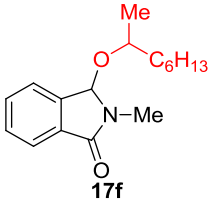
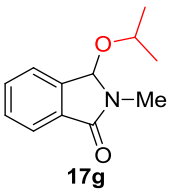
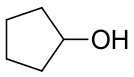
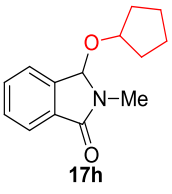
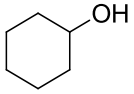
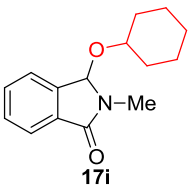
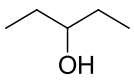
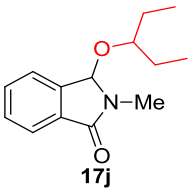
[a]standard conditions: **16** (1.0 mmol), $SmCl_3$ (0.02 equiv), ROH (10 equiv), $nBu_4NPF_6$ (0.4 mmol) in THF (10 ml), Sm as the cathode, carbon as the anode, I= 0.05 A, r.t. in the air. [b]determined by NMR. [c]Isolated yields.

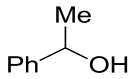
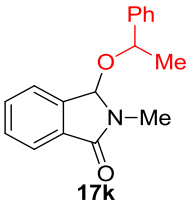
Due to the steric hindrance, the secondary alcohol alkoxylation is a challenge, especially the cycloalkyl alcohol which was never reported before. Satisfyingly, the octan-2-ol and isopropanol afforded the **17f** and **17g** in high yield but after 6 hours of electrolysis (Table 5.3, entry **1**, **2**), even the hindered pentan-3-ol still afforded a 61% yield (Table 5.3, entry **5**).

Under the same condition, the cyclopentanol and cyclohexanol were attempted. To our pleasure, both of the transformations performed in 73% yield (Table 5.3, entry **3**, **4**). It is important to note here that to our best knowledge it was the first example of this kind of alkoxylation. Notably, the diastereomeric selectivity of asymmetric 1-phenylethanol was 5:1 in a 81% yield (Table 5.3, entry **6**). Therefore, prolonging the reaction time, both linear and cycloalkyl alcohols afforded the alkoxylation products in good to excellent yields and high chemoselectivity.

**Table 5.3** Scope of reductive alkoxylation of *N*-methyl phtalimides with the secondary alcohols[a]



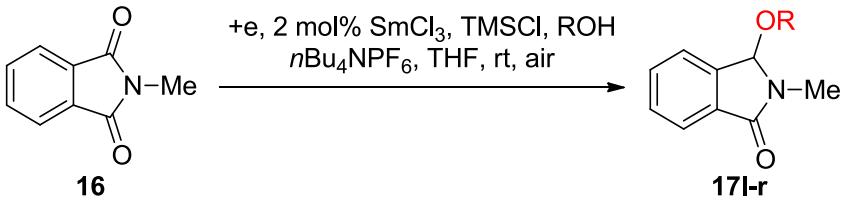

| entry | ROH | time h | Product | yield %[c] |
|---|---|---|---|---|
| **1** |  | 6.0 |  **17f** | 94 |
| **2** | *i*PrOH | 6.0 |  **17g** | 93 |
| **3** |  | 6.0 |  **17h** | 73 |
| **4** |  | 6.0 |  **17i** | 73 |
| **5** |  | 6.0 |  **17j** | 61 |

| | | | | |
|---|---|---|---|---|
| **6** |  | 6.0 |  **17k** | 81, d.r.= 5:1[b] |

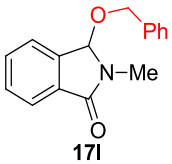
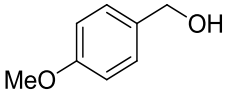
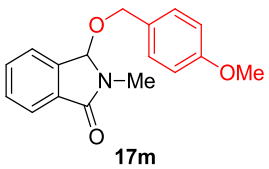
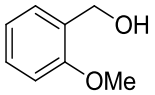
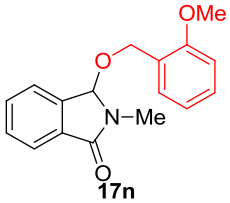
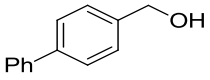
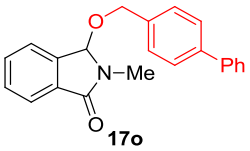
[a]standard conditions: **16** (1.0 mmol), $SmCl_3$ (0.02 equiv), ROH (10 equiv), $nBu_4NPF_6$ (0.4 mmol) in THF (10 ml), Sm as the cathode, carbon as the anode, I= 0.05 A, r.t. in the air. [b]determined by NMR. [c]Isolated yields.

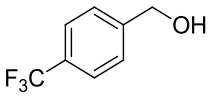
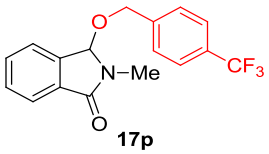
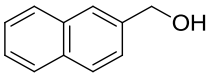
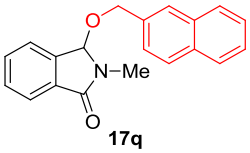
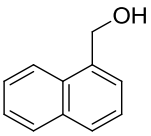
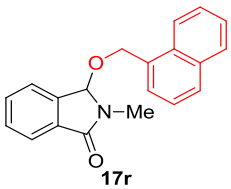
In addition, benzyl alcohol and derivatives also provided the corresponding benzyloxylation products in excellent yields without any hydrogenation of aromatic rings (Table 5.4). The results illustrated that either the electron donating or withdrawing substitutions on the benzene rings were no effect to this reaction (Table 5.4, entry **1-5**). Furthermore, as well as the benzyl alcohols, the naphthyl alcohols afforded the products in excellent yields (Table 5.4, entry **6**, **7**).

**Table 5.4** Scope of reductive alkoxylation of *N*-methyl phtalimides with the benzyl alcohols[a]




**16** **17l-r**

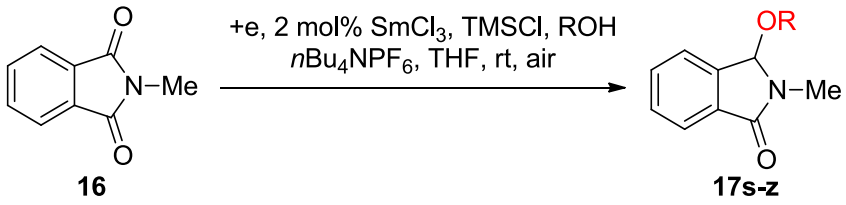
| entry | ROH | time h | Product | yield %[c] |
|---|---|---|---|---|
| **1** | BnOH | 4.0 |  **17l** | 94 |
| **2** |  | 4.0 |  **17m** | 95 |
| **3** |  | 4.0 |  **17n** | 92 |
| **4** |  | 4.0 |  **17o** | 96 |

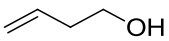
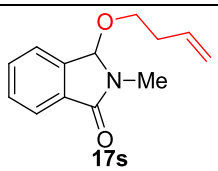
| | | | | |
|---|---|---|---|---|
| **5** |  | 4.0 |  **17p** | 87 |
| **6** |  | 4.0 |  **17q** | 93 |
| **7** |  | 4.0 |  **17r** | 92 |

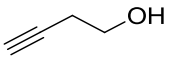
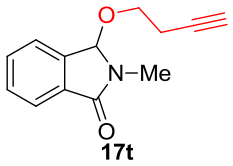
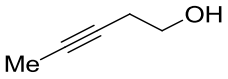
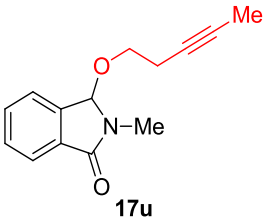
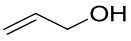
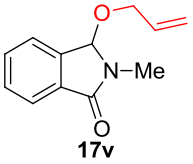
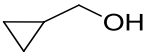
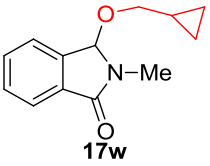
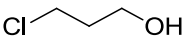
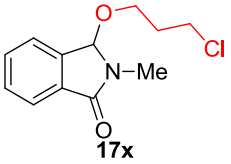
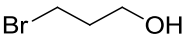
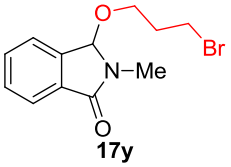
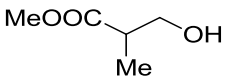
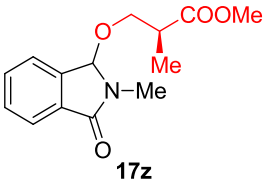
[a]standard conditions: **16** (1.0 mmol), $SmCl_3$ (0.02 equiv), ROH (10 equiv), $n$Bu$_4$NPF$_6$ (0.4 mmol) in THF (10 ml), Sm as the cathode, carbon as the anode, I= 0.05 A, r.t. in the air. [b]determined by NMR. [c]Isolated yields.

Due to the reductive conditions used in this alkoxylation, the functional group tolerance was one of the significant aspects. For this reason, we demonstrated some alcohols with various groups. Normally, the double or triple bond is sensitive in most carbonyl group reductive conditions. To our satisfaction, controlling the conduction time, the corresponding product were afforded without any effect on the unsaturated bond or cyclopropyl group (Table 5.5, entry **1-5**). Besides, no dehalogenation was occurred when the chloro and bromo substituted alcohols were used as the nucleophiles (Table 5.5, entry **6**, **7**) but also the ester group was stable under the condition (Table 5.5, entry **8**).

**Table 5.5** Scope of reductive alkoxylation of *N*-methyl phtalimides with the funcitonalized alcohols[a]




| entry | ROH | time h | Product | yield %[c] |
|---|---|---|---|---|
| **1** |  | 4.0 |  **17s** | 91 |

| | | | | |
|---|---|---|---|---|
| **2** |  | 4.0 |  **17t** | 93 |
| **3** |  | 4.0 |  **17u** | 91 |
| **4** |  | 4.0 |  **17v** | 93 |
| **5** |  | 4.0 |  **17w** | 96 |
| **6** |  | 4.0 |  **17x** | 91 |
| **7** |  | 4.0 |  **17y** | 88 |
| **8** |  | 4.0 |  **17z** | 95 |

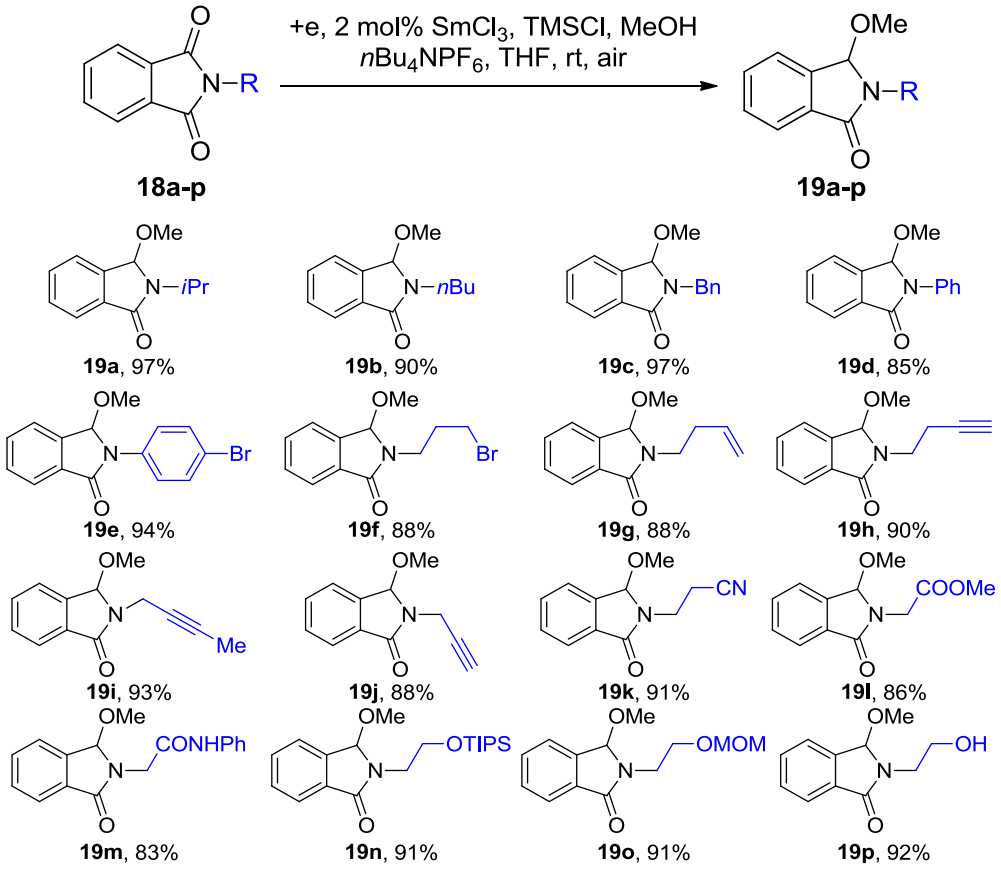
[a]standard conditions: **16** (1.0 mmol), $SmCl_3$ (0.02 equiv), ROH (10 equiv), $nBu_4NPF_6$ (0.4 mmol) in THF (10 ml), Sm as the cathode, carbon as the anode, I= 0.05 A, r.t. in the air. [b]determined by NMR. [c]Isolated yields.

## V. 2. 3. Reductive methoxylation of *N*-substituted phthalimides

Next, we investigated the reductive methoxylation of a variety of *N*-substituted phthalimides. As we expected, *N*-alkyl phthalimides (**18a-c**) afforded the products (**19a-c**) in high isolated yields. Although the *N*-aryl substrates (**18d**, **18e**) were less active than the *N*-alkyl substrates, prolonging two more hours they still presented the products 85% **19d** and 94% **19e**, respectively. Furthermore, the result illustrated that

the system widely tolerated diverse functional groups including bromide (**19f**), double and triple bond (**19g-j**), nitrile (**19k**), ester (**19l**) and amide (**19m**). Moreover, the sensitive MOM and TIPS as the hydroxyl protect group were inactive in the electrocatalytic condition (**19n**, **19o**). Interestingly, the phthalimide with the hydroxyl group presented an excellent yield, no methoxylation occurred as the previous report (**19p**).[156b]

**Table 5.6** Scope of reductive methoxylation of *N*-substituted phtalimides[a, b]

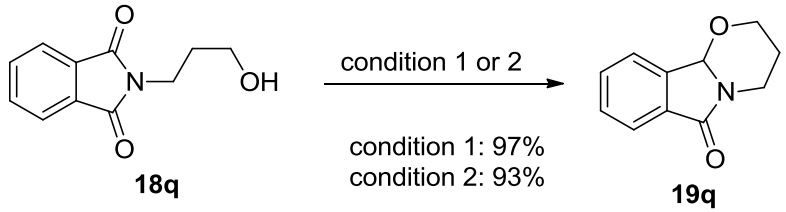



[a]standard conditions: **18** (1.0 mmol), $SmCl_3$ (0.02 equiv), MeOH (10 equiv), $nBu_4NPF_6$ (0.4 mmol) in THF (10 ml), Sm as the cathode, carbon as the anode, I= 0.05 A, r.t. in the air. [b]Isolated yields.

## V. 2. 4. Intramolecular reductive alkoxylation of *N*-substituted phtalimides

The intramolecular reductive alkoxylation gives a significant tricyclic building block in one step (Scheme 5.13). Using the *N*-(3-hydroxypropyl)phthalimide, the reaction was conducted in THF (*c*= 0.2 mol/L) for 6h to afford the product in 97% yield

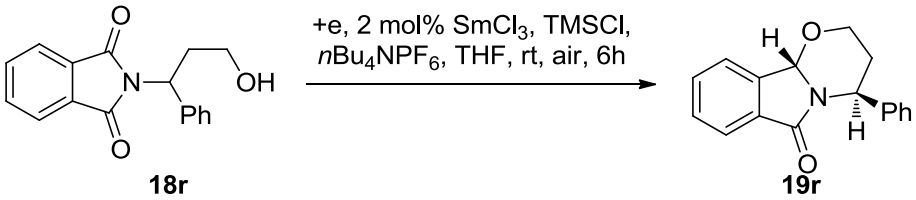
(*condition 1*). Interestingly, in the present of 10.0 equivalent MeOH, the tricyclic product was still the single product in 93% yield (*condition 2*).




*condition 1*: +e, 2 mol% $SmCl_3$, 2.5 eq. TMSCl, rt, air, 6h
*condition 2*: +e, 2 mol% $SmCl_3$, 10.0 eq. MeOH, 2.5 eq. TMSCl, rt, air, 6h

**Scheme 5.13** The intramolecular reductive alkoxylation of *N*-(3-hydroxypropyl)phthalimide.

To demonstrate the stereoselectivity, starting from the asymmetric *N*-(3-hydroxy-1-phenylpropyl)phthalimide **18r**, the reaction provided a 91% isolated yield (Scheme 5.14). To our surprise, the intramolecular cyclization afforded a single stereoselective tricyclic product **19r** and the structure was determined by noesy.

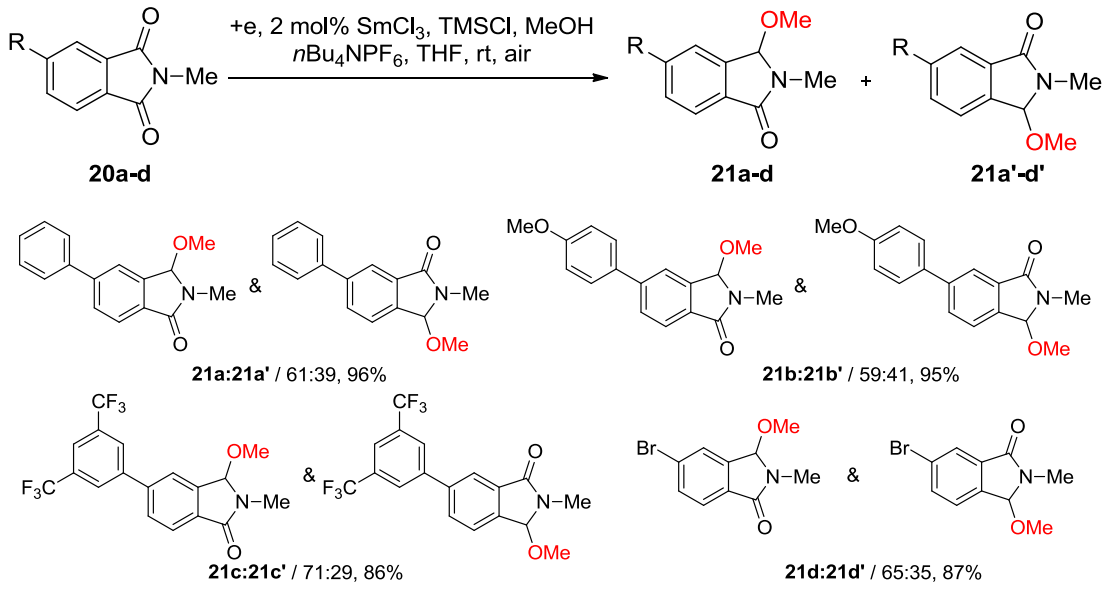



**Scheme 5.14** The stereoselective intramolecular reductive alkoxylation of *N*-(3-hydroxy-1-phenylpropyl)phthalimide

## V. 2. 5. Regioselective methoxylation of unsymmetrical aryl ring-substituted phthalimides

To our knowledge, the regioselectivity of non-symmetric aryl substituted phthalimides is a challenge owing to the similar reactivity of two carbonyl groups. Up to now, only Beller's group described the research on it.[15b, 15c] For all the examples, methoxylated products were successfully isolated in high yields as a mixture of regioisomers. With the 3,5 –ditrifluoro or 4-bromo phenyl C4-substituted, the regioselectivities are about 2:1 (Table 5.7).

**Table 5.7** Selective reductive methoxylation of different partially aryl-ring-substituted *N*-methylphtalimides.[a,b]



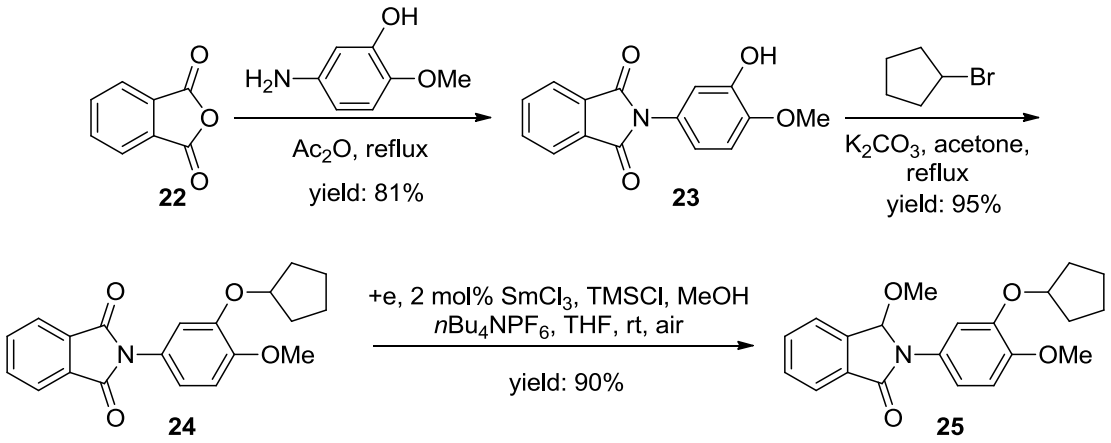

[a]standard conditions: **20** (1.0 mmol), $SmCl_3$ (0.02 equiv), MeOH (10 equiv), $n$Bu$_4$NPF$_6$ (0.4 mmol) in THF (10 ml), Sm as the cathode, carbon as the anode, I= 0.05 A, r.t. in the air. [b]Isolated yields.

## V. 2. 6. Application in the total synthesis

Tumor necrosis factor-α (TNF-α) is a key cytokine in the inflammatory cascade. Excessive TNF-α levels have been found to be associated with a number of inflammatory and autoimmune conditions including rheumatoid arthritis, Crohn's disease, aphthous ulcers, erythema nodosum leprosum in leprosy, septic, cachexia, graft versus host disease, asthma, ARDS and AIDS. Thus, control of TNF-α levels could be a key to the treatment of a wide range of diseases.

As an application in total synthesis, we used the electrocatalytic alkoxylation to synthesize 3-methoxy-2-(3-cyclopentyloxy-4-methoxyphenyl)-1-isoindolinone **25** as a TNF-α production in the gram-scale.[163] Refering to the literature,[164] *N*-substituted phthalimide **24** was obtained in 2 steps from the phthalic anhydride. Under the optimized condition (2 mol% $SmCl_3$, 2.5 eq. TMSCl, 10 eq. MeOH, in THF, r.t., air), the isoindolinone derivatives **25** was successfully afforded in 90% (1.59 g) isolated yield (Scheme 5.15).

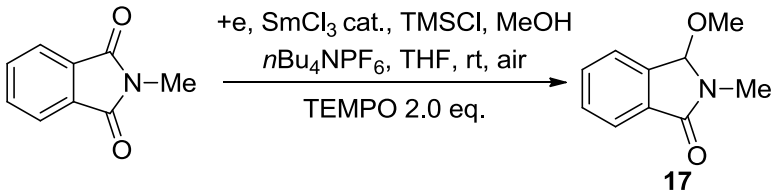
[163] Park, J. S.; Baik, K. U.; Cho, J. V.; Yoo, E. S.; Byun, Y. S.; Park, M. H. *Arch. Pharm. Res.* **2001**, *24,* 367-370.
[164] Wen, L.; Tang, F.; Ge, C.; Wang, X.; Han, Z.; Wu, J. *Synth. Commun.* **2002,** *42,* 3288-3295.




**Scheme 5.15** The total synthesis of isoindolinone derivative **25**.

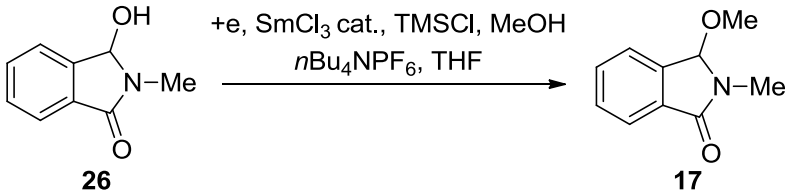
## V. 2. 7. Plausible mechanism of reduced alkoxylation

Finally, regarding to more details in this system, several reactions were performed. In the presence of 2.0 eq. TEMPO, the product **17** was afforded successfully, indicating that no radicals were generated (Scheme 5.16).




**Scheme 5.16** The reductive methoxylation with TEMPO

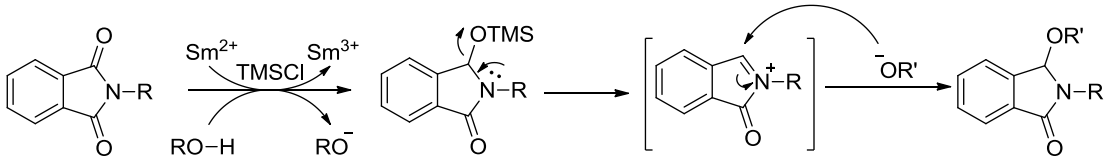
As an intermediate detected by GC, the 3-hydroxylactams **26** can be converted into compound **17** under the previous catalytic condition (Scheme 5.17).




**Scheme 5.17** The reductive methoxylation of the 3-hydroxylactams.

Based on all the results, a plausible mechanism is depicted in Scheme **5.18**. The phthalimide is reduced to the aza-hemiacetal in the first step. Then, with the aid of

TMSCl, an imine onium intermediate is generated. At last, the alkoxyl ion as a nucleophile attacked the onium to give the final product.




**Scheme 5.18** The plausible mechanism of reductive alkoxylation of phthalimides.

## V. 3. Sm electrocatalyzed reduction of phthalimides

After the establishment of the reductive alkoxylation of phthalimides, we continued demonstrating the transformation of phthalimides into the corresponding ω-hydroxylactams and isoindolinones.

ω-Hydroxylactams as important precursors to N-acyliminium ions are important structural motifs and versatile building blocks in natural products and pharmaceuticals.[165] Isoindolinones represent an attractive target for organic synthesis and a valuable scaffold for medicinal chemistry because of their widespread and diverse biological activities.[166] Both of them could be obtained by the selective reduction of phthalimides.

### V. 3. 1. Optimization of phthalimides reduction

Methanol and isopropanol as the normal proton donor in the chemical $SmI_2$ reaction (Chapter I) provided the alkoxylated products in our electrocatalytic process. For the purpose to reduce the phthlimides into the ω-Hydroxylactams, we used the water as the nucleophile in the beginning. Although the correct product **27a** was obtained, the TMSCl was useless in this transformation (Table 5.8, entry **1**). Next, we changed the water into *tert*-butanol or acetic acid, a mixture of **27a** and **28a** was afforded in low chemoselectivity (Table 5.8, entry **2**, **3**).

---

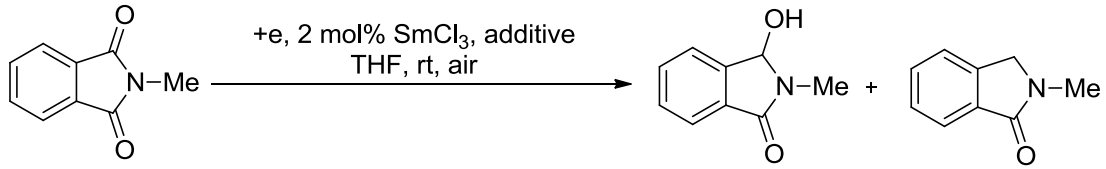
[165] (a) Corey, E. J.; Mehrotra, M. M. *Tetrahedron Lett.* **1988,** *29,* 57-60. (b) Chiyoda, K.; Shimokawa, J.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2012,** *51,* 2505-2508. (c) Owen, R. T. *Drugs Today* **2011,** *47,* 263-275.

[166] (a) Link, J. T.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995,** *117,* 552-553. b) Yoon, U. C.; Jin, Y. X.; Oh, S.W.; Park, C. H.; Park, J. H.; Campana, C. F.; Cai, X.; Duesler, E. N.; Mariano, P. S. *J. Am. Chem. Soc.* **2003,** *125,* 10664-10671.

With the knowledge of the $Sm^{II}$ electrocatalyzed system, we decided to add an acid instead of TMSCl for the $Sm^{2+}$ regeneration. Fortunately, under the 5.0 equivalent of methylsulfonic acid was an excellent choice to afford the ω-Hydroxylactams in high chemoselectivity and yield (Table 5.8, entry **4-7**). Interestingly, decreasing the amount of MsOH and adding *t*BuOH as the proton donor, the isoindolinone **28a** was provided in 18%. To our surprise, $NH_4Cl$ in the mixture of THF/$H_2O$ (2:1) as the acid could afford a mixture of 85% **27a** and 10% **28a**. This condition was less acid than the MsOH process, which was a potential method for some acidic sensitive substrates.

We then researched on the direct reduction of phthalimides into the isoindolinones. To our excitement, adding the TMSCl in the MsOH system, the isoindolinone **28a** as the single product was obtained (Table 5.8, entry **10-13**). With the optimization, the best condition for this was 2.5 equivalent TMSCl and 5 equivalent MsOH in 10 hours (Table 5.8, entry **11**).

**Table 5.8** The optimization of phthalimides reduction[a]




**16** **27a** **28a**

| entry | TMSCl eq. | Proton eq. | Time h | Conv. % | A %[b] | B %[b] |
|---|---|---|---|---|---|---|
| 1 | 2.5 | 10.0 $H_2O$ | 5 | >99 | 97 | 0 |
| 2 | 2.5 | 10.0 *t*BuOH | 5 | >99 | 30 | 68 |
| 3 | 2.5 | 10.0 AcOH | 5 | >99 | 35 | 64 |
| 4 | 0 | 10.0 AcOH | 5 | 0 | 0 | 0 |
| 5 | 0 | 10.0 $CF_3COOH$ | 5 | 0 | 0 | 0 |
| 6 | 0 | 10.0 MsOH | 2.5 | >99 | 99 | 0 |
| 7 | 0 | 5.0 MsOH | 2.5 | >99 | 99 | 0 |
| 8 | 0 | 2.0 MsOH<br>8.0 *t*BuOH | 2.5 | >99 | 77 | 18 |
| 9 | 0 | 10.0 $NH_4Cl$<br>($H_2O$/THF 1:2) | 5 | >99 | 85 | 10 |

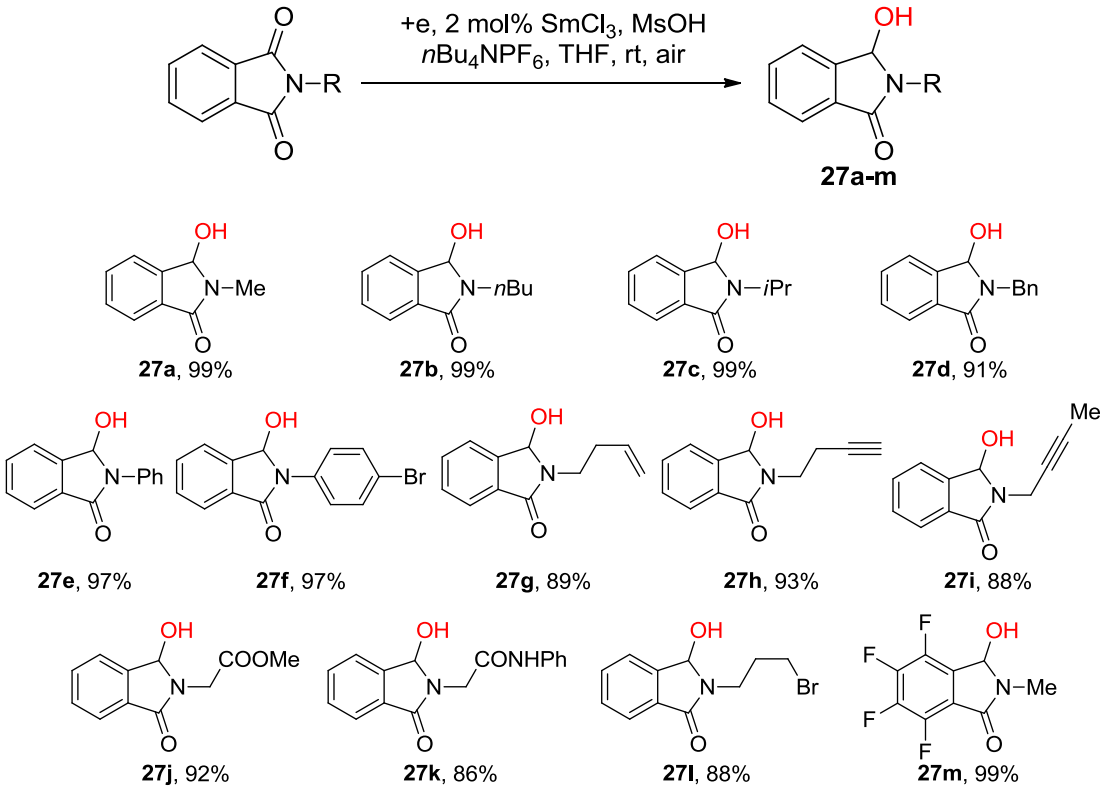
| | | | | | | |
|---|---|---|---|---|---|---|
| 10 | 2.5 | 10.0 MsOH | 5 | >99 | 0 | 91 |
| 11 | 2.5 | 5.0 MsOH | 10 | >99 | 0 | 93 |
| 12 | 2.5 | 2.0 MsOH | 10 | 35 | 0 | 33 |
| 13 | 1.5 | 5.0 MsOH | 10 | >99 | 66 | 30 |

[a]standard conditions: **16** (1.0 mmol), $SmCl_3$ (0.02 equiv), additives, $n$Bu$_4$NPF$_6$ (0.4 mmol) in THF (10 ml), Sm as the cathode, carbon as the anode, I= 0.05 A, r.t. in the air. [b]Isolated yields.

## V. 3. 2. The scope of the reduction of phthalimides into ω-hydroxylactams

With the optimized condition, we extended to other phthalimides. The butyl N-substituted substrate afforded the product in a quantitative yield (Table 5.9, **27a**). As well as the butyl phthalimide, the hindered isopropyl N-substituted also presented completely (Table 5.9, **27c**). The benzyl group on the nitrogen was facile removed under the reductive condition such as Pd/C, $H_2$. Under our eletrocatalytic condition, the benzyl was stable in the reductive process (Table 5.9, **27d**). The phenyl N-substituted substrates were converted efficiently (Table 5.9, **27e**, **27f**). The sensitive functional groups were always facile to be reduced accompanied with the hydrogenation of carbonyl group. To our satisfying, the ω-hydroxylactams containing the double or triple bond were obtained without any by-products (Table 5.9, **27g-i**). Notably, the carbonyl group of ester and amide could be reduced in the chemical $SmI_2$ reaction. Therefore, the reduction of phthalimides with these groups was valuable to investigate. Fortunately, the transformations were in high chemoselectivity and yield (Table 5.9, **27j**, **27k**). Dehalogenation was another side effect in this reductive process. The **27f** and **27l** illustrated that no dehalogenation occurred to neither the alkyl nor aryl bromide. Finally, the four fluro substituted phthalimide was also reduced in 99% yield (Table 5.9, **27m**). These results illustrated the acidic condition provided a high chemoselective and efficient process for this transformation.

**Table 5.9** The scope of the reduction of phthalimides into ω-Hydroxylactams[a, b]

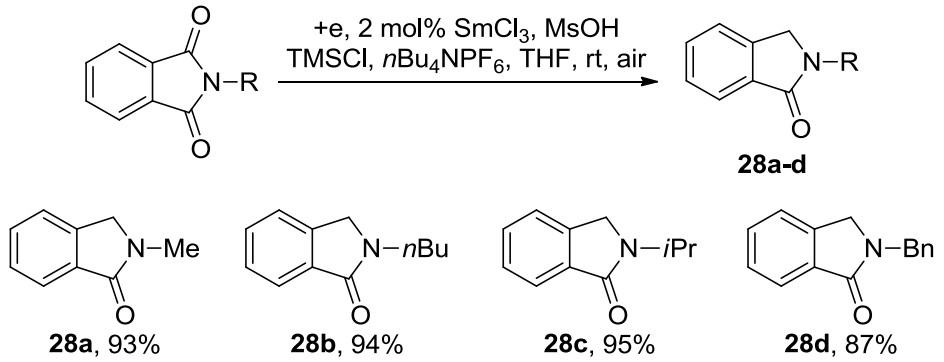



[a]standard conditions: **Substrate** (1.0 mmol), $SmCl_3$ (0.02 equiv), MsOH (5.0 equiv), $n$Bu$_4$NPF$_6$ (0.4 mmol) in THF (10 ml), Sm as the cathode, carbon as the anode, I= 0.05 A, r.t. in the air. [b]Isolated yields.

## V. 3. 3. Sm electrocatalyzed reduction of phthalimides into isoindolines

With the aid of TMSCl, the isoindolinones were obtained in the optimized condition. Therefore, we extended the substrates into other *N*-substituted phthalimides. Till now, only 4 examples were performed, but all of the transformations were in high chemoselectivity and efficiency (Table 5.10). Later on, we will attempt other substrates.

**Table 5.10** The scope of the reduction of phthalimides into isoindolinones[a, b]




[a]standard conditions: **substrate** (1.0 mmol), $SmCl_3$ (0.02 equiv), MsOH (5.0 equiv), TMSCl (2.5 equiv), $n$Bu$_4$NPF$_6$ (0.4 mmol) in THF (10 ml), Sm as the cathode, carbon as the anode, I= 0.05 A, r.t. in the air. [b]determined by NMR. [c]Isolated yields.

# V. 4. Conclusion

In conclusion, the electrocatalytic reduction of phthalimides was introduced chemoselectively into the alkoxylated products, ω-Hydroxylactams and isoindolinones.

To our delight, a mild, high functional group tolerance and efficient Sm ion electrocatalytic reductive alkoxylation of phthalimides was established for the first time. Thanks to the electrochemistry, the methodology successfully avoids the high temperature and pressure in the present of hydrogen, the harmful phosphorus ligands and inert gas protection in classic $Sm^{2+}$ reaction. As the scope showed, no matter the primary alcohols or secondary alcohols reacts with phtalimides affords the corresponding 2-substituted isoindolinones in good to excellent yields. Besides, there is no effect on the aromatic ring, unsaturated bond, nitrile, ester, amide or hydroxyl group. Notably, the intramolecular cyclization of compound **19r** performs a high yield and single stereoselectivity. In addition, the gram-scale synthesis exhibits a bright application prospect and the *N*-acyliminium ion intermediates were significant for other isoindolinone derivatives.

Besides, the selective reductions of phthalimides were also established under the Sm electrocatalytic conditions. Instead of TMSCl, MsOH was used to carry out the ω-hydroxylactams in excellent yield and high chemoselectivity. The functional group tolerance was a significant point in this type of transformation.

# General conclusion

Inspired by the previous work in our laboratory, we have investigated the potential of the electrocatalytic procedure based on Sm as reducing reagent. Especially for the reduction of different functional groups.

Starting from the nitrobenzenes, the Sm electrocatalyzed system selectively afforded either the azo aromatic compounds or amino aromatics in high chemoselectivity and functional group tolerance depending on the electrochemical conditions.

For the synthesis of azobenzenes, we have developed a facile, efficient and safe alternative process for a wide variety of azobenzene derivatives, including symmetrical and asymmetrical ones. The efficiency and the wide functional tolerance of this procedure provide a new tool in the arsenal to access azobenzenes. The use of electrochemistry to perform catalytic reactions in mild conditions employing $SmI_2$ as a reductant, the absence of precious metals, bases, and non-hazardous substances make our protocol a great alternative to current methods (*Publication just accepted in ACS catalysis 2017*).

For anilines, the Sm-electrocatalyzed reduction of functionalized and structurally diverse nitro arenes to anilines has been performed in the methanol and without inert atmospher for the first time. This catalytic system showed a high chemoselectivity for the nitro group reduction in the presence of diverse functional groups. Especially, no matter the active hydrogen or *N*-substituted ring nitroaromatics afforded the corresponding products in high yield.

For sulfoxides deoxygenation, the efficient Sm electrocatalytic reductive condition was established, with the different reductive condition in methanol or THF. After the extension, the THF that presented an efficient applicability to a wide range of sulfoxides was chosen to carry out this transformation avoiding the high temperature, pressure and without any additives as HMPA.

Finally, we developed a new catalytic $SmI_2$ reduction of phthalimides which was never reported before using $SmI_2$ as reducing reagent. By only changing the proton sources, three different products were provided in the electrocatalytic processes. Using the alcohols as nucleophiles, the unprecedented reductive alkoxylation of phthalimides by $Sm^{2+}$ was performed in high chemoselectivity and functional group tolerance. Using the MsOH, the corresponding aza-hemiacetals was provided in the efficient reductive

conditions of phthalimides. Furthermore, with the aid of TMSCl, the phthalimides could be directly converted into the corresponding isoindolinones.

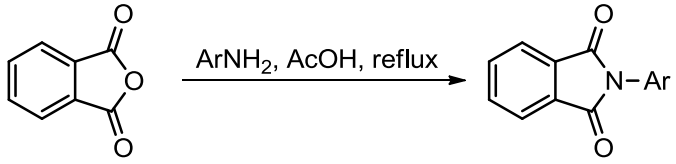
Compared with the classic $SmI_2$ reaction, the advantages such as the catalytic amount of Sm, less solvent and no protecting gas used, higher chemoselectivity and functional group tolerance illustrated the electrocatalytic process was a better choice.

# V. 5. Experiment

## V. 5. 1. General Information

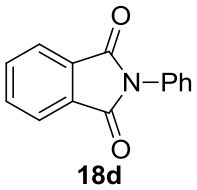
THF was distilled from sodium metal/benzophenone before use. All commercially available chemicals were used without purification. $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded on either a Bruker AM 360 (360 MHz), AM 300 (300 MHz), or AM 250 (250 MHz) instrument with samples dissolved in $CDCl_3$. $^{1}H$ NMR chemical shifts were referenced to the residual solvent signal; $^{13}C$ NMR chemical shifts were referenced to the deuterated solvent signal. Data are represented as follows: chemical shift δ (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (*J*) in Hz and integration. Mass spectra were recorded on a micrOTOF-q Brucker Daltonics spectrometer. Flash chromatography (FC) was performed on 40-63 μm silica gel with mixtures of ethyl acetate (EA) and pentane. TLC plates were visualized by exposure to UV (254 nm) and/or $KMnO_4$ stain. The gas chromatography (GC) were performed on a spectrometer Varian GC-430 (injection: split/splitless, FID detector, column VF1-MS: 15m x 0.25 mm x 0.25 microns, program: 1 min 50 °C, 10 °C/min to 250 °C, 250 °C 2 min, 23 min total). Infrared spectra were recorded on a FTIR spectrometer (Perkin-Elmer spectrum one, NaCl pellets or Bruker Vertex 70 ATR Pike Germanium) and are reported in $cm^{-1}$. Melting points were determined using a Büchi melting point apparatus. Electrolysis were performed with a AUTOLAB potentiostat/galvanostat (model: PGSTAT302N), in an undivided three-electrodes cell containing samarium rod working electrode, a standard glassy carbon counter electrode and a saturated calomel electrode (SCE) as reference. The samarium electrode used is based on a samarium rod of 12.7 mm (0.5 in) diameter and 5 cm length, directly connected to a copper wire to ensure current conductivity. This self-made electrode is stored under inert atmosphere when it is not used. All the samarium rods are purchased from Alfa Aesar (99.9 % metals basis excluding Ta).

## V. 5. 2. Preparation of the substrates




**General procedure for 18d, 18e:** a mixture of aniline (5.0 mmol) and Phthalic anhydride (740 mg, 5.0 mmol) in acetic acid (10 ml) was refluxed overnight with stirring. After cooling to the room temperature, diluted by water (20 ml) and extracted with ethyl acetate (2x10 ml). The oraganic phase was washed by saturated $NaHCO_3$ (5 ml) and brine (5 ml), dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel to afford the product.

**2-phenylisoindoline-1,3-dione (18d)**




**18d**

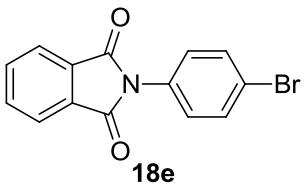
Following the general procedure, the product was obtained as a colorless solid (1.06 g, 95%). (eluent: ethyl acetate/pentane: 1:5);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 8.01 – 7.93 (m, 2H), 7.86 – 7.72 (m, 2H), 7.60 – 7.36 (m, 5H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.3, 134.4, 131.8, 131.7, 129.2, 128.1, 126.6, 123.8.

**HRMS (ESI)** calculated for $C_{14}H_9NNaO_2^+$ [M+Na]: 246.0525. Found: 246.0534.

**2-(4-bromophenyl)isoindoline-1,3-dione (18e)**




**18e**

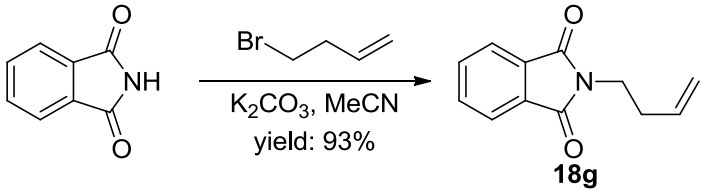
Following the general procedure, the product was obtained as a colorless solid (1.38 g, 92%). (eluent: ethyl acetate/pentane: 1:5);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.97 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.82 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.65 (d, *J* = 8.7 Hz, 2H), 7.37 (d, *J* = 8.7 Hz, 2H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 166.9, 134.6, 132.3, 131.6, 130.7, 128.0, 123.9, 121.8.

**HRMS (ESI)** calculated for $C_{14}H_8BrNNaO_2^+$ [M+Na]: 323.9631 and 325.9611. Found: 323.9621 and 325.9626.

**2-(but-3-en-1-yl)isoindoline-1,3-dione (18g)**



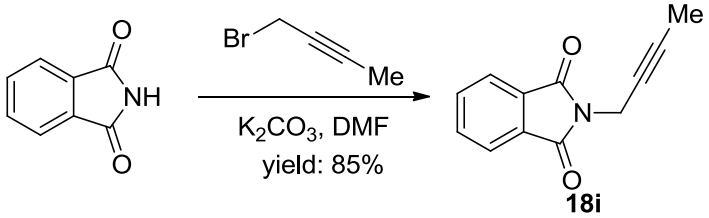

To a solution of $K_2CO_3$ (2.07 g, 15.0 mmol) and phthalimide (0.89 g, 6.0 mmol) in MeCN (15.0 ml), 4-bromobut-1-ene (0.61 g, 5.0 mmol, 0.43 ml) was added dropwise with stirring at room temperature. The resulting reaction was refluxed for 13 h. Then, cooled to room temperature and quenched by water (50 ml), extracted with ethyl acetate (2x15 ml). The oraganic phase was washed by 0.1 mol/L HCl (5 ml) and brine (5 ml), dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel (eluent: ethyl acetate/pentane: 1:5) to afford the product as a colorless solid (1.12g, 93%).

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.82 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.75 – 7.64 (m, 2H), 5.78 (ddt, *J* = 17.1, 10.1, 6.9 Hz, 1H), 5.04 (ddd, *J* = 14.8, 7.2, 5.9 Hz, 2H), 3.75 (t, *J* = 7.1 Hz, 2H), 2.43 (q, *J* = 7.0 Hz, 2H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 168.4, 134.5, 134.0, 132.1, 123.3, 117.6, 37.4, 32.9.

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{12}H_{11}NNaO_2^+$: 224.0682. Found: 224.0679.

**2-(but-2-yn-1-yl)isoindoline-1,3-dione (18i)**




To a solution of $K_2CO_3$ (1.73 g, 12.5 mmol) and phthalimide (0.74 g, 5.0 mmol) in DMF (5.0 ml), 1-bromobut-2-yne (1.06 g, 10.0 mmol, 0.70 ml) was added dropwise with stirring at room temperature overnight. Then, quenched by water (50 ml), extracted with ethyl acetate (2x15 ml). The oraganic phase was washed by 0.1 mol/L HCl (5 ml) and brine (5 ml), dried over $MgSO_4$, concentrated and purified by flash chromatography

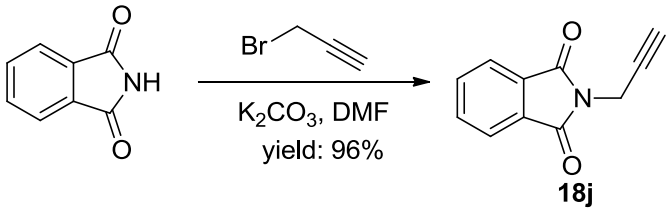
on silica gel (eluent: ethyl acetate/pentane: 1:5) to afford the product as a yellow solid (0.85g, 85%).

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.88 (dd, *J* = 5.3, 3.1 Hz, 1H), 7.74 (dd, *J* = 5.3, 3.0 Hz, 1H), 4.41 (d, *J* = 2.3 Hz, 1H), 1.78 (t, *J* = 2.1 Hz, 2H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.3, 134.1, 132.1, 123.5, 79.3, 72.6, 27.4, 3.5.

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{12}H_9NNaO_2^+$: 222.0525. Found: 222.0532.

**2-(prop-2-yn-1-yl)isoindoline-1,3-dione (18j)**




**18j**

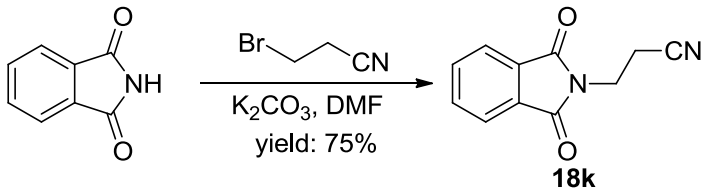
To a solution of $K_2CO_3$ (1.73 g, 12.5 mmol) and phthalimide (0.74 g, 5.0 mmol) in DMF (5.0 ml), 3-bromoprop-1-yne (1.19 g, 10.0 mmol, 0.86 ml) was added dropwise with stirring at room temperature overnight. Then, quenched by water (50 ml), extracted with ethyl acetate (2x15 ml). The oraganic phase was washed by 0.1 mol/L HCl (5 ml) and brine (5 ml), dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel (eluent: ethyl acetate/pentane: 1:5) to afford the product as a colorless solid (0.89g, 96%).

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.87 (dd, *J* = 5.4, 2.9 Hz, 2H), 7.74 (dd, *J* = 5.4, 2.9 Hz, 2H), 4.45 (d, *J* = 2.3 Hz, 2H), 2.24 (d, *J* = 2.4 Hz, 1H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.0, 134.2, 131.9, 123.6, 71.5, 27.0.

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{11}H_7NNaO_2^+$: 208.0369. Found: 208.0371.

**3-(1,3-dioxoisoindolin-2-yl)propanenitrile (18k)**




**18k**

To a solution of $K_2CO_3$ (2.07 g, 15.0 mmol) and phthalimide (0.74 g, 5.0 mmol) in DMF (10.0 ml), 3-bromopropanenitrile (0.80 g, 6.0 mmol, 0.50 ml) was added dropwise with stirring at room temperature overnight. Then, quenched by water (50 ml), extracted with ethyl acetate (2x15 ml). The oraganic phase was washed by 0.1 mol/L HCl (5 ml)

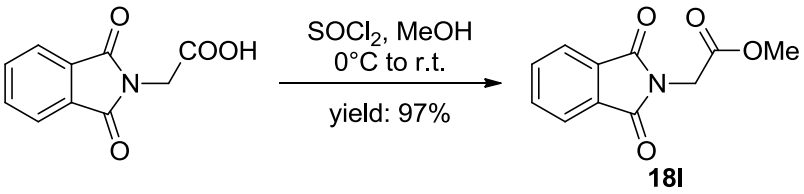
and brine (5 ml), dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel (eluent: ethyl acetate/pentane: 1:5) to afford the product as a yellow oil (0.75g, 75%).

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.87 (dd, *J* = 5.4, 3.0 Hz, 1H), 7.76 (dd, *J* = 5.5, 3.1 Hz, 1H), 4.01 (t, *J* = 6.9 Hz, 1H), 2.81 (t, *J* = 6.9 Hz, 1H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.6, 134.6, 131.7, 123.8, 117.0, 33.6, 17.3.

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{11}H_8N_2NaO_2^+$: 223.0478. Found: 223.0465.

**methyl 2-(1,3-dioxoisoindolin-2-yl)acetate (18l)**



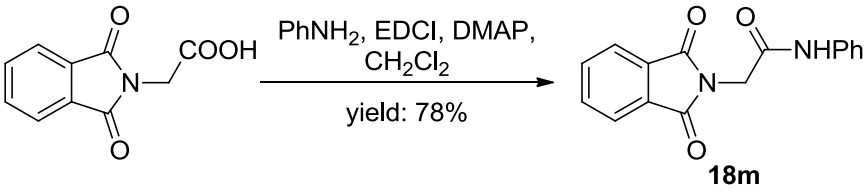

2-(1,3-dioxoisoindolin-2-yl)acetic acid (0.62 g, 3.0 mmol) was dissolved in MeOH (30 ml), then cooled to 0 ˚C. $SOCl_2$ (0.54 g, 4.5 mmol, 0.33 ml) was added into the mixture, warmed up to room temperature and stirred overnight. Quenched by saturated $NaHCO_3$ (10 ml), extracted with ethyl acetate (2x15 ml). The oraganic phase was washed by brine (5 ml), dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel (eluent: ethyl acetate/pentane: 1:2) to afford the product as a white solid (0.64 g, 97%).

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.87 (dd, *J* = 5.1, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.2, 3.1 Hz, 2H), 4.44 (s, 2H), 3.75 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.7, 167.4, 134.3, 132.0, 123.6, 52.7, 38.7.

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{11}H_9NNaO_4^+$: 242.0424. Found: 242.0421.

**2-(1,3-dioxoisoindolin-2-yl)-N-phenylacetamide (18m)**




To a solution of 2-(1,3-dioxoisoindolin-2-yl)acetic acid (1.03 g, 5.0 mmol) and aniline (0.47 g, 5.0 mmol, 0.46 ml) in $CH_2Cl_2$ (100 ml), DMAP (61 mg, 0.5 mmol) and EDCI (1.15 g, 6.0 mmol) were added with stirring at room temperature. After 20 hours,

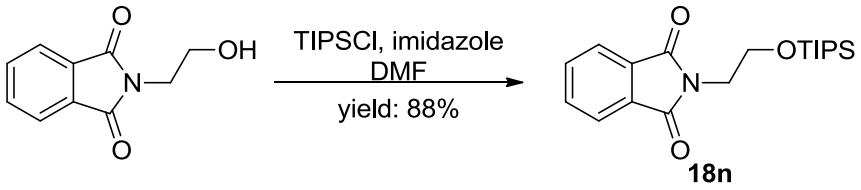
concentrated and purified by flash chromatography on silica gel (eluent: ethyl acetate/pentane: 1:1) to afford the product as a white solid (1.09 g, 78%).

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 7.95 (dd, *J* = 5.2, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.62 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.16 (d, *J* = 7.2 Hz, 1H), 4.55 (s, 2H).

**$^{13}$C NMR (63 MHz, $CDCl_3$)** δ 167.9, 138.9, 134.6, 131.8, 130.0, 129.7, 128.9, 128.8, 123.9, 61.7.

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{16}H_{12}N_2NaO_3^+$: 303.0740. Found: 303.0732.

**2-(2-((triisopropylsilyl)oxy)ethyl)isoindoline-1,3-dione (18n)**




**18n**

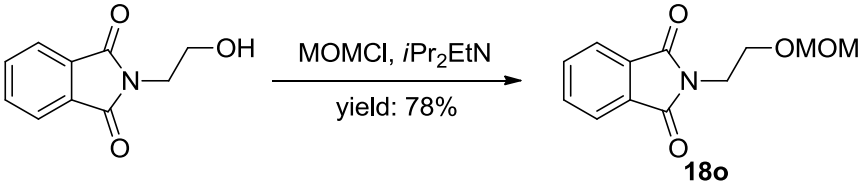
2-(2-hydroxyethyl)isoindoline-1,3-dione (0.96 g, 5.0 mmol) and imidazole (0.85g, 12.5 mmol) were added in DMF (10 ml), stirred at room temperature for 10 min, then TIPSCl (1.93 g, 10.0 mmol, 2.14 ml) was added dropwise into the mixture. After 15 h, the reaction was quenched by saturated $NH_4Cl$ (20 ml), extracted with ethyl acetate (2x15 ml). The oraganic phase was washed by brine (5 ml), dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel (eluent: ethyl acetate/pentane: 1:20) to afford the product as a colorless solid (1.53 g, 88%).

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 7.88 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.4, 3.0 Hz, 2H), 4.02 – 3.82 (m, 4H), 1.09 – 0.93 (m, 21H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 168.4, 133.9, 132.2, 123.2, 60.3, 40.2, 17.8, 11.9.

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{19}H_{29}NNaO_3Si^+$: 370.1809. Found: 370.1794.

**2-(2-(methoxymethoxy)ethyl)isoindoline-1,3-dione (18o)**




**18o**

2-(2-hydroxyethyl)isoindoline-1,3-dione (0.96 g, 5.0 mmol) and Chloromethyl methyl ether (0.81g, 10.0 mmol, 0.76 ml) were added in *i*$Pr_2$EtN (10 ml), stirred at room temperature overnight. Quenched by saturated $NaHCO_3$ (20 ml), extracted with ethyl

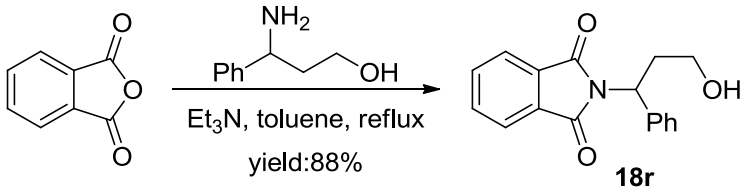
acetate (2x15 ml). The oraganic phase was washed by brine (5 ml), dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel (eluent: ethyl acetate/pentane: 1:5) to afford the product as a yellow solid (0.92 g, 78%).

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.94 – 7.79 (m, 2H), 7.79 – 7.60 (m, 2H), 4.61 (d, *J* = 1.7 Hz, 2H), 3.93 (td, *J* = 5.8, 1.2 Hz, 2H), 3.85 – 3.67 (m, 2H), 3.30 (d, *J* = 1.9 Hz, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 168.3, 134.0, 132.1, 123.3, 96.2, 64.3, 55.3, 37.7.

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{12}H_{13}NNaO_4^+$: 258.0737. Found: 258.0744.

**2-(3-hydroxy-1-phenylpropyl)isoindoline-1,3-dione (18r)**



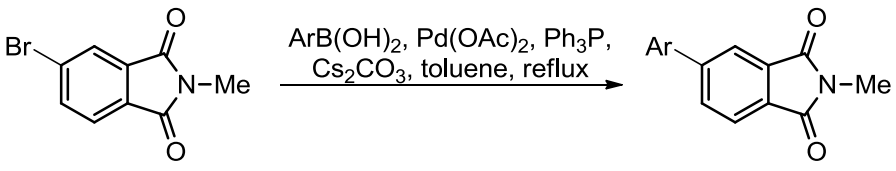

**18r**

A mixture of 3-amino-3-phenylpropan-1-ol (0.76 g, 5.0 mmol), Phthalic anhydride (0.74 g, 5.0 mmol), trimethylamine (51 mg, 0.5 mmol, 0.06 ml) and toluene (7.5 ml) in a flask fitted with a Dean-Stark tube was heated under reflux for 3 h. Cooled to room temperature, removed the solvent by evaporator. The residue was dissolved with ethyl actate (20 ml) and washed by 2N HCl (5 ml), sat. $NaHCO_3$ (5 ml) and brine (5 ml). The organic phase was dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel (eluent: ethyl acetate/pentane: 1:2) to afford the product as a yellow solid (1.24 g, 88%).

**$^1$H NMR (300 MHz, $CDCl_3$)** δ 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.73 – 7.62 (m, 2H), 7.62 – 7.51 (m, 2H), 7.37 – 7.21 (m, 3H), 5.62 (dd, *J* = 9.9, 6.2 Hz, 1H), 3.71 (dt, *J* = 7.4, 5.3 Hz, 2H), 2.95 – 2.72 (m, 1H), 2.63 – 2.46 (m, 1H), 2.25 (s, 1H).

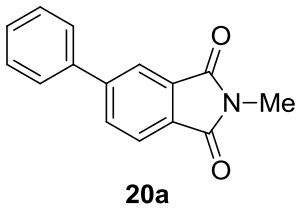
**$^{13}$C NMR (75 MHz, $CDCl_3$)** δ 168. 6, 139.2, 134.0, 131.8, 128.6, 128.2, 127.9, 123.3, 59.7, 51.5, 33.6.

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{17}H_{15}NNaO_3^+$: 304.0944. Found: 304.0947.



**General procedure for 20a, 20b and 20c:** To a solution of 4-bromo-*N*-methylphthalimide (0.48 g, 2.0 mmol), organoborane (1.5 eq, 3.0 mmol), $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), $PPh_3$ (105.2 mg, 0.4 mmol) and $Cs_2CO_3$ (1.3 g, 4.0 mmol) in toluene (10 mL), changed the air into argon, the mixture was refluxed overnight. When the reaction was complete, cooled to room temperature, diluted by distillated water (10 ml) and extracted with $CH_2Cl_2$ (3x 5 ml). The combined organic layers were washed by brine, dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel column chromatography to afford the corresponding ring-substituted *N*-methylphthalimide derivative.

**2-methyl-5-phenylisoindoline-1,3-dione (20a)**




**20a**

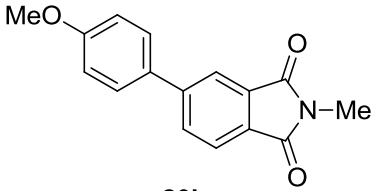
Following the general procedure, the product was obtained as a colorless solid (418 mg, 88%). (eluent: ethyl acetate/pentane: 1:3);

**$^1$H NMR (250 MHz, $CDCl_3$)** δ 8.06 (s, 1H), 7.91 (s, 2H), 7.71 – 7.57 (m, 2H), 7.49 (dd, *J* = 8.3, 6.9 Hz, 3H), 3.22 (s, 3H).

**$^{13}$C NMR (63 MHz, $CDCl_3$)** δ 168.4 (2xC), 147.3, 139.1, 133.1, 132.4, 130.7, 129.2, 128.8, 127.3, 123.6, 121.8, 24.0.

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{15}H_{11}NNaO_2^+$: 260.0682. Found: 260.0677.

**5-(4-methoxyphenyl)-2-methylisoindoline-1,3-dione (20b)**




**20b**

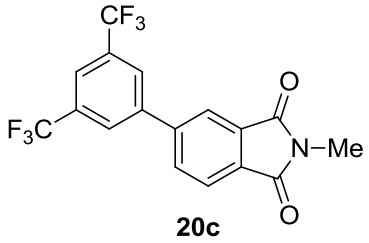
Following the general procedure, the product was obtained as a colorless solid (284 mg, 53%). (eluent: ethyl acetate/pentane: 1:3);

**$^1$H NMR (250 MHz, $CDCl_3$)** δ 7.98 (s, 1H), 7.84 (d, *J* = 1.0 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H), 3.19 (s, 3H).

**$^{13}$C NMR (63 MHz, $CDCl_3$)** δ 168.5, 168.4, 160.3, 146.8, 133.1, 131.6, 131.3, 129.9, 128.4, 123.6, 121.1, 114.6, 55.4, 23.9.

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{16}H_{13}NNaO_3^+$: 290.0788. Found: 290.0784.

**5-(3,5-bis(trifluoromethyl)phenyl)-2-methylisoindoline-1,3-dione (20c)**




**20c**

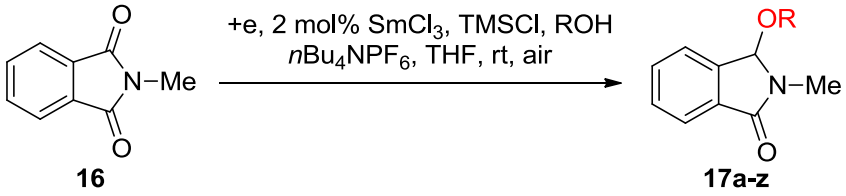
Following the general procedure, the product was obtained as a colorless solid (618 mg, 83%). (eluent: ethyl acetate/pentane: 1:5);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 8.12–8.06 (m, 3H), 8.02 – 7.94 (m, 3H), 3.25 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.8 (2C), 144.0, 141.2, 133.5, 132.8, 132.7 (q, *J*= 33.3 Hz), 132.1, 127.5 (d, *J*= 2.7 Hz), 124.1, 122.5 (quint, *J*= 3.6 Hz), 121.9, 121.6, 24.2.

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{17}H_9F_6NNaO_2^+$: 396.0430. Found: 396.0412.

## V. 5. 3. Characterization data of reductive alkoxylation of methyl phthalimide

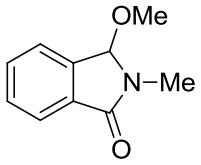



**16** **17a-z**

**General procedure for the reductive alkoxylation of methyl phthalimide:** Reactions were carried out in a three necked cell containing a magnetic stirring bar, samarium cathode (20 $cm^2$ area), glassy carbon anode (20 $cm^2$ area) and SCE as reference electrode. $nBu_4NPF_6$ (156 mg, 0.4 mmol, 0.04 mol/L in THF) as the electrolyte, methyl phthalimide (161 mg, 1.0 mmol), alcohol (10 equivalent, 10 mmol) and $SmCl_3$ (5.0 mg, 0.02 mmol) were added in anhydrous THF (10 ml), TMSCl (272 mg, 2.5 mmol, 0.32 ml) was added dropwise with stirring, then electrolysis was performed at i = 50 mA during 4 hours. After the reaction was complete, the mixture was quenched by 0.1 mol/L HCl (10 ml), extracted with ethyl acetate (2×20 mL). The

combined oraganic layer was washed by 10% $Na_2S_2O_3$ (10 ml) and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel.

**3-methoxy-2-methylisoindolin-1-one (17)**




**17**

Following the general procedure, the product was obtained as a colorless oil (172 mg, 97%). (eluent: ethyl acetate/pentane: 1:3);

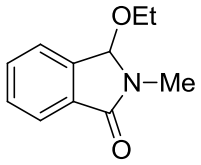
**IR (film)** $\nu_{max}$: 3082, 3054, 2993, 2933, 2831, 1704, 1617, 1599, 1470, 1431, 1395, 1261, 1204, 1192, 1103, 1076, 1033, 746, 695 $cm^{-1}$;

**$^1$H NMR (300 MHz, $CDCl_3$)** δ 7.79 (dd, *J* = 6.3, 1.6 Hz, 1H), 7.60-7.43 (m, 3H), 5.73 (s, 1H), 3.05 (s, 3H,), 2.87 (s, 3H).

**$^{13}$C NMR (75 MHz, $CDCl_3$)** δ 167.8 (C=O), 140.3 (C), 133.2 (C), 132.0 (CH), 130.00 (CH), 123.4 (2xCH), 88.0 (O-CH-N), 49.2 (O-$CH_3$), 26.5 (N-$CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{10}H_{11}NNaO_2^+$: 200.0682. Found: 200.0689.

**3-ethoxy-2-methylisoindolin-1-one (17a)**




**17a**

Following the general procedure, the product was obtained as a colorless oil (180 mg, 94%). (eluent: ethyl acetate/pentane: 1:3);

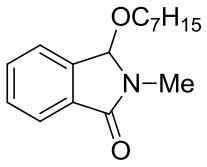
**IR (film)** $\nu_{max}$: 2975, 2925, 2879, 1705, 1617, 1471, 1431, 1394, 1260, 1204, 1181, 1104, 1073, 1032 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.73 (d, *J* = 7.6 Hz, 1H), 7.55-7.39 (m, 3H), 5.68 (s, 1H), 3.02 (s, 3H,), 3.18-2.89 (m, 2H), 1.08 (t, *J* = 7.2 Hz, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.5 (C=O), 141.0 (C), 133.0 (C), 131.9 (CH), 129.8 (CH), 123.2 (2xCH), 87.7 (O-CH-N), 57.8 (O-$CH_2$), 26.5 (N-$CH_3$), 15.1 ($CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{11}H_{13}NNaO_2^+$: 214.0838. Found: 214.0843.

**3-(heptyloxy)-2-methylisoindolin-1-one (17b)**




**17b**

Following the general procedure, the product was obtained as a colorless oil (238 mg, 91%). (eluent: ethyl acetate/pentane: 1:3);

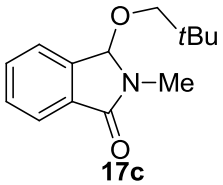
**IR (film)** $\nu_{max}$: 2925, 2855, 1711, 1617, 1600, 1469, 1430, 1394, 1262, 1203, 1181, 1104, 1078, 1034, 745, 698 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.83 (d, *J* = 7.6 Hz, 1H), 7.62-7.49 (m, 3H), 5.78 (s, 1H), 3.16-3.06 (m, 1H), 3.11 (s, 3H,), 2.99-2.89 (m, 1H), 1.19-1.55 (m, 10H), 0.88 (t, *J* = 7.2 Hz, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.6 (C=O), 141.0 (C), 133.1 (C), 131.9 (CH), 129.8 (CH), 123.3 (2xCH), 87.8 (O-CH-N), 62.2 (O-$CH_2$), 31.8 ($CH_2$), 29.6 ($CH_2$), 29.1 ($CH_2$), 26.6 ($CH_3$), 26.2 ($CH_2$), 22.6 ($CH_2$), 14.1($CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{16}H_{23}NNaO_2^+$: 284.1621. Found: 284.1616.

**2-methyl-3-(neopentyloxy)isoindolin-1-one (17c)**




**17c**

Following the general procedure, the product was obtained as a colorless oil (219 mg, 94%). (eluent: ethyl acetate/pentane: 1:3);

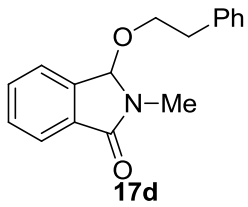
**IR (film)** $\nu_{max}$: 2956, 2868, 1711, 1470, 1428, 1393, 1261, 1204, 1181, 1104, 1075, 1030, 746 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.78 (m, 1H), 7.57-7.42 (m, 3H), 5.75 (s, 1H), 3.05 (s, 3H), 2.71 (d, *J* = 10.1 Hz, 1H), 2.53 (d, *J* = 10.1 Hz, 1H), 0.85 (s, 9H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.7 (C=O), 141.1 (C), 133.1 (C), 131.9 (CH), 129.8 (CH), 123.4 (CH), 123.3 (CH), 87.8 (O-CH-N), 72.0 (O-$CH_2$), 31.5 (CH), 26.8 (3x$CH_3$), 26.7 (N-$CH_3$).

**HRMS (ESI)** [M+Na$^+$] calculated for $C_{14}H_{19}NNaO_2^+$: 256.1308. Found: 256.1307.

**2-methyl-3-phenethoxyisoindolin-1-one (17d)**



**17d**

Following the general procedure, the product was obtained as a colorless oil (259 mg, 97%). (eluent: ethyl acetate/pentane: 1:4);

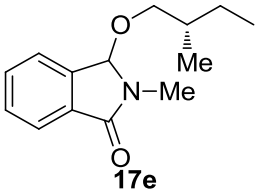
**IR (film)** $\nu_{max}$: 3085, 3058, 3027, 2922, 2873, 1707, 1616, 1602, 1469, 1453, 1428, 1394, 1261, 1204, 1180, 1105, 1072, 1031, 746, 697 cm$^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.80 (dd, *J* = 6.3, 1.8 Hz, 1H), 7.55-7.45 (m, 2H), 7.35 (dd, *J* = 6.3, 1.8 Hz, 1H), 7.31-7.18 (m, 3H), 7.17-7.11 (m, 2H), 5.72 (s, 1H), 3.30 (dt, *J* = 9.4, 6.8 Hz, 1H), 3.17 (dt, *J* = 9.4, 6.8 Hz, 1H), 2.92 (s, 3H), 2.81 (t, *J* = 6.8 Hz, 2H).

**$^{13}$C NMR (63 MHz, $CDCl_3$)** δ 167.6 (C=O), 140.7 (C), 138.7 (C), 133.0 (C), 131.9 (CH), 129.9 (CH), 129.0 (2xCH), 128.4 (2xCH), 126.4 (CH), 123.3 (2xCH), 87.8 (O-CH-N), 63.0 (O-$CH_2$), 36.2 ($CH_2$), 26.7 (N-$CH_3$).

**HRMS (ESI)** [M+Na$^+$] calculated for $C_{17}H_{17}NNaO_2^+$: 290.1151. Found: 290.1154.

**2-methyl-3-((S)-2-methylbutoxy)isoindolin-1-one (17e)**



**17e**

Following the general procedure, the product was obtained as a colorless oil (the mixture of two epimers: 228 mg, 98%). (eluent: ethyl acetate/pentane: 1:5);

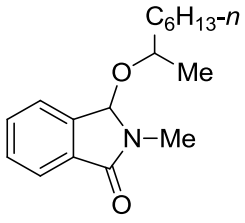
**IR (film)** $\nu_{max}$: 3055, 2960, 2925, 2873, 1702, 1617, 1600, 1466, 1430, 1395, 1262, 1203, 1182, 1105, 1070, 1034, 971, 798, 745, 699 cm$^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.79 (d, *J* = 7.6 Hz, 1H), 7.62 – 7.41 (m, 3H), 5.75 (s, 1H), 3.07 (s, 3H), 2.90 (ddd, *J* = 24.8, 8.8, 6.1 Hz, 1H), 2.72 (ddd, *J* = 21.4, 8.8, 6.2 Hz, 1H), 1.62 – 1.47 (m, 1H), 1.38 (dt, *J* = 12.9, 6.2 Hz, 1H), 1.15 – 0.98 (m, 1H), 0.94 – 0.74 (m, 6H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.6 (C=O), 140.9 (C), 133.0 (C), 131.8 (CH), 129.7 (CH), 123.2 (2xCH), 87.7 (O-CH-N), 66.9 (O-$CH_2$), 66.8 (O-$CH_2$), 34.9 ($CH_2$), 34.8 ($CH_2$), 26.5 (N-$CH_3$), 26.1 ($CH_2$), 26.0 ($CH_2$), 16.6 ($CH_2$), 16.6 ($CH_2$), 11.3 ($CH_3$), 11.2 ($CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{14}H_{19}NNaO_2^+$: 256.1308. Found: 256.1312.

**2-methyl-3-(octan-2-yloxy)isoindolin-1-one (17f)**




**17f**

Following the general procedure, the product was obtained as a colorless oil (the mixture of two epimers: 258 mg, 94%). (eluent: ethyl acetate/pentane: 1:3);

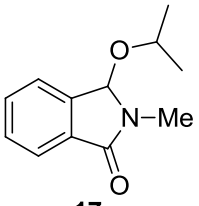
**IR (film)** $\nu_{max}$: 2960, 2925, 2856, 1703, 1617, 1468, 1430, 1395, 1261, 1203, 1180, 1104, 1061, 1035, 746, 693 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.79 (d, *J* = 7.4 Hz, 1H), 7.60 – 7.46 (m, 3H), 5.72 – 5.66 (m, 1H), 3.64 – 3.48 (m, 1H), 3.14 – 3.07 (m, 3H), 1.38 – 1.14 (m, 12H), 1.12 – 1.06 (m, 1H), 0.92 – 0.82 (m, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.6 (C=O), 167.4 (C=O), 142.4 (C), 141.9 (C), 132.6 (C), 132.5 (C), 131.7 (CH), 129.7 (CH), 123.4 (CH), 123.3 (CH), 123.2 (CH), 88.1 (O-CH-N), 87.9 (O-CH-N), 72.7 (O-$CH_2$), 72.6 (O-$CH_2$), 37.6 ($CH_2$), 31.8 ($CH_2$), 31.7 ($CH_2$), 29.4 ($CH_2$), 29.2 ($CH_2$), 27.0 (N-$CH_3$), 25.4 ($CH_2$), 25.2 ($CH_2$), 22.6 ($CH_2$), 21.5 ($CH_3$), 20.9 ($CH_3$), 14.1 ($CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{17}H_{25}NNaO_2^+$: 298.1777. Found: 298.1773.

**3-isopropoxy-2-methylisoindolin-1-one (17g)**




**17g**

Following the general procedure, the product was obtained as a colorless oil (191 mg, 93%). (eluent: ethyl acetate/pentane: 1:3);

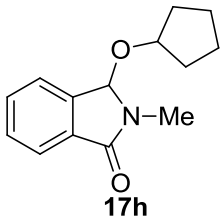
**IR (film)** $\nu_{max}$: 2969, 2919, 2851, 1681, 1436, 1397, 1258, 1205, 1104, 1063 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.79 (d, *J* = 7.2 Hz, 1H), 7.60-7.45 (m, 3H), 5.69 (s, 1H), 3.65 (hept, *J* = 6.1 Hz, 1H), 3.11 (s, 3H,), 1.19 (d, *J* = 6.1 Hz, 3H), 1.09 (d, *J* = 6.1 Hz, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.6 (C=O), 142.1 (C), 132.8 (C), 131.9 (CH), 129.9 (CH), 123.5 (CH), 123.4 (CH), 88.1 (O-CH-N), 68.3 (O-CH), 27.1 (N-$CH_3$), 23.9 (2x$CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{12}H_{15}NNaO_2^+$: 228.0995. Found: 228.0994.

**3-(cyclopentyloxy)-2-methylisoindolin-1-one (17h)**




**17h**

Following the general procedure, under 6 hours electrolysis, the product was obtained as a colorless oil (168 mg, 73%). (eluent: ethyl acetate/pentane: 1:4);

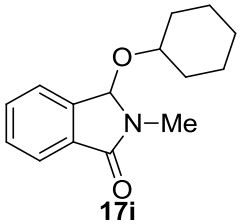
**IR (film)** $\nu_{max}$: 2958, 2873, 1701, 1617, 1600, 1472, 1433, 1396, 1331, 1258, 1204, 1179, 1104, 1064, 1034, 746, 695 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.76 (d, *J* = 7.2 Hz, 1H), 7.60-7.43 (m, 3H), 5.67 (s, 1H), 3.78 (quint, *J* = 6.0 Hz, 1H), 3.06 (s, 3H), 1.76-1.56 (m, 4H), 1.55-1.30 (m, 4H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.7 (C=O), 142.1 (C), 132.8 (C), 131.8 (CH), 129.8 (CH), 123.6 (CH), 123.3 (CH), 88.0 (O-CH-N), 76.7 (O-$CH_2$), 33.7(2x$CH_2$), 26.9 (N-$CH_3$), 23.4 ($CH_2$), 23.2 ($CH_2$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{14}H_{17}NNaO_2^+$: 254.1151. Found: 254.1154.

**3-(cyclohexyloxy)-2-methylisoindolin-1-one (17i)**




**17i**

Following the general procedure, under 6 hours electrolysis, the product was obtained as a colorless oil (178 mg, 73%). (eluent: ethyl acetate/pentane: 1:4);

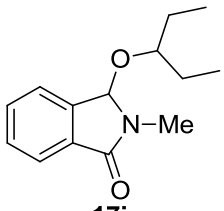
**IR (film)** $\nu_{max}$: 2932, 2856, 1708, 1617, 1469, 1430, 1395, 1258, 1204, 1180, 1154, 1102, 1068, 1034, 748, 696 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.81 (d, *J* = 7.2 Hz, 1H), 7.60-7.43 (m, 3H), 5.73 (s, 1H), 3.32 (quint, *J* = 3.6 Hz, 1H), 3.12 (s, 3H), 1.90-1.58 (m, 4H), 1.54-1.04 (m, 6H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.7 (C=O), 142.4 (C), 132.8 (C), 131.9 (CH), 129.8 (CH), 123.5 (CH), 123.4 (CH), 88.1 (O-CH-N), 74.3 (O-$CH_2$), 34.0 ($CH_2$), 33.8 ($CH_2$), 27.1 (N-$CH_3$), 25.5 ($CH_2$), 24.3 (2x$CH_2$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{15}H_{19}NNaO_2^+$: 268.1308. Found: 268.1310.

**2-methyl-3-(pentan-3-yloxy)isoindolin-1-one (17j)**




**17j**

Following the general procedure, under 6 hours electrolysis, the product was obtained as a colorless oil (142 mg, 61%). (eluent: ethyl acetate/pentane: 1:4);

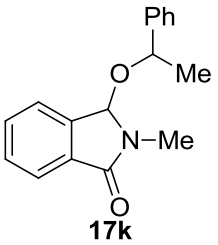
**IR (film)** $\nu_{max}$: 2962, 2926, 2877, 2852, 1701, 1615, 1467, 1431, 1396, 1258, 1204, 1102, 1062, 1033, 747, 694 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.81 (d, *J* = 7.3 Hz, 1H), 7.61 – 7.47 (m, 3H), 5.71 (s, 1H), 3.47 (p, *J* = 5.7 Hz, 1H), 3.14 (s, 3H), 1.72 – 1.59 (m, 4H), 0.95 – 0.89 (m, 6H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.5 (C=O), 142.3 (C), 132.5 (C), 131.7 (CH), 129.6 (CH), 123.3 (2xCH), 88.2 (O-CH-N), 79.1 (O-CH), 27.2 (N-$CH_3$), 26.7 ($CH_2$), 26.1 ($CH_2$), 9.4 ($CH_3$), 9.0 ($CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{14}H_{19}NNaO_2^+$: 256.1308. Found: 256.1306.

**2-methyl-3-(1-phenylethoxy)isoindolin-1-one (17k)**



**17k**

Following the general procedure, under 6 hours electrolysis, the product was obtained as a colorless oil (the mixture of two epimers: 216 mg, 81%). (eluent: ethyl acetate/pentane: 1:3);

**IR (film)** $\nu_{max}$: 2977, 2925, 1694, 1647, 1472, 1430, 1395, 1052, 1034, 947, 797, 745, 701 $cm^{-1}$;

Major product: **$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.82 (dd, *J* = 6.3, 1.6 Hz, 1H), 7.54 (pd, *J* = 7.5, 1.3 Hz, 2H), 7.43 – 7.28 (m, 6H), 5.73 (s, 1H), 4.37 (q, *J* = 6.5 Hz, 1H), 2.72 (s, 3H), 1.43 (d, *J* = 6.5 Hz, 3H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.5 (C=O), 143.4 (C), 141.5 (C), 132.7 (C), 131.9 (CH), 129.8 (CH), 128.6 (2xCH), 127.9 (CH), 126.4 (2xCH), 123.2 (2xCH), 88.2 (O-CH-N), 74.4 (O-CH), 27.0 (N-$CH_3$), 24.3($CH_3$);

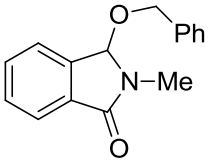
**HRMS (ESI)** [M+$Na^+$] calculated for $C_{17}H_{17}NNaO_2^+$: 290.1151. Found: 290.1151.

Minor product: **$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.77 (d, *J* = 7.6 Hz, 1H), 7.42 – 7.20 (m, 6H), 7.12 – 7.04 (m, 2H), 5.74 (s, 1H), 4.42 (q, *J* = 7.2 Hz, 1H), 3.10 (s, 3H), 1.47 (d, *J* = 6.5 Hz, 3H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.4 (C=O), 143.8 (C), 141.4 (C), 132.3 (C), 132.0 (CH), 129.6 (CH), 128.5 (2xCH), 127.6 (CH), 126.1 (2xCH), 123.0 (2xCH), 87.5 (O-CH-N), 72.8 (O-CH), 26.9 (N-$CH_3$), 24.5 ($CH_3$);

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{17}H_{17}NNaO_2^+$: 290.1151. Found: 290.1151.

**3-(benzyloxy)-2-methylisoindolin-1-one (17l)**



**17l**

Following the general procedure, the product was obtained as a colorless oil (238 mg, 94%). (eluent: ethyl acetate/pentane: 1:3);

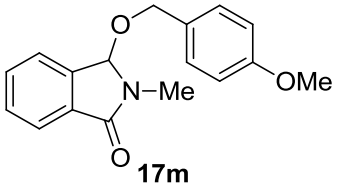
**IR (film)** $\nu_{max}$: 3061, 3032, 2913, 1705, 1616, 1601, 1497, 1470, 1454, 1429, 1394, 1261, 1204, 1180, 1102, 1063, 1029, 749, 699 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.85 (d, *J* = 7.2 Hz, 1H), 7.60-7.49 (m, 3H), 7.35-7.21 (m, 5H), 5.87 (s, 1H), 4.12 (d, *J* = 10.8 Hz, 1H), 4.00 (d, *J* = 10.8 Hz, 1H), 3.10 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.6 (C=O), 140.6 (C), 137.2 (C), 133.0 (C), 132.0 (CH), 130.0 (CH), 128.5 (2xCH), 127.9 (CH), 127.8 (2xCH), 123.4 (2xCH), 87.8 (O-CH-N), 64.4 (O-$CH_2$), 26.7 (N-$CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{16}H_{15}NNaO_2^+$: 276.0995. Found: 276.1002.

**3-((4-methoxybenzyl)oxy)-2-methylisoindolin-1-one (17m)**




**17m**

Following the general procedure, the product was obtained as a white solid (268 mg, 95%). (eluent: ethyl acetate/pentane: 1:4);

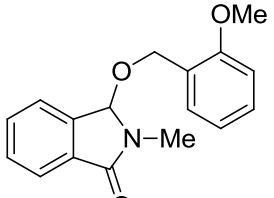
**IR (film)** $\nu_{max}$: 3038, 3000, 2953, 2933, 2913, 2871, 2836, 1704, 1613, 1586, 1514, 1470, 1428, 1393, 1302, 1250, 1204, 1177, 1102, 1063, 1032, 821, 747, 695 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.82 (d, *J* = 7.2 Hz, 1H), 7.60-7.47 (m, 3H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 5.82 (s, 1H), 4.04 (d, *J* = 10.6 Hz, 1H), 3.93 (d, *J* = 10.6 Hz, 1H), 3.76 (s, 3H), 3.08 (s, 3H).

**$^{13}$C NMR (63 MHz, $CDCl_3$)** δ 167.6 (C=O), 159.4(C), 140.8 (C), 133.0 (C), 132.0 (CH), 129.9 (CH), 129.5 (2xCH), 129.3 (C), 123.4 (CH), 123.4 (CH), 113.9 (2xCH), 87.8 (O-CH-N), 64.3 (O-$CH_2$), 55.3 ($OCH_3$), 26.7 (N-$CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{17}H_{17}NNaO_3^+$: 306.1101. Found: 306.1108.

**3-((2-methoxybenzyl)oxy)-2-methylisoindolin-1-one (17n)**




**17n**

Following the general procedure, the product was obtained as a colorless oil (259 mg, 92%). (eluent: ethyl acetate/pentane: 1:4);

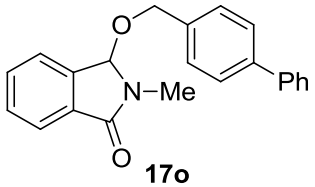
**IR (KBr)** $\nu_{max}$: 3082, 3047, 3033, 3007, 2948, 2938, 2923, 2902, 2884, 2832, 2347, 1698, 1604, 1494, 1467, 1430, 1393, 1342, 1289, 1249, 1201, 1177, 1122, 1101, 1059, 1033, 753, 697 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.85 (d, *J* = 7.2 Hz, 1H), 7.59-7.48 (m, 3H), 7.33-7.22 (m, 2H), 6.96-6.89 (m, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 5.88 (s, 1H), 4.25 (d, *J* = 11.3 Hz, 1H), 4.05 (d, *J* = 11.3 Hz, 1H), 3.76 (s, 3H), 3.10 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.7 (C=O), 157.2(C), 140.9 (C), 133.1 (C), 131.9 (CH), 129.9 (CH), 129.6 (CH), 129.3 (CH), 125.6 (C), 123.5 (CH), 123.3 (CH), 120.5 (CH), 110.2 (CH), 88.0 (O-CH-N), 59.9 (O-$CH_2$), 55.2 ($OCH_3$), 26.6 (N-$CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{17}H_{17}NNaO_3^+$: 306.1101. Found: 306.1105.

**3-([1,1'-biphenyl]-4-ylmethoxy)-2-methylisoindolin-1-one (17o)**




**17o**

Following the general procedure, the product was obtained as a white solid (303 mg, 96%). (eluent: ethyl acetate/pentane: 1:3);

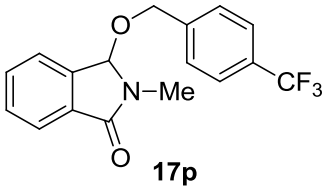
**IR (KBr)** $\nu_{max}$: 3052, 3030, 2914, 2894, 2872, 2860, 1703, 1470, 1426, 1393, 1201, 1103, 1075, 1035, 825, 755, 694 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.91 (d, *J* = 7.2 Hz, 1H), 7.65-7.52 (m, 7H), 7.50-7.42 (m, 2H), 7.40-7.31 (m, 3H), 5.94 (s, 1H), 4.20 (d, *J* = 11.3 Hz, 1H), 4.07 (d, *J* = 11.3 Hz, 1H), 3.17 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.8 (C=O), 141.0 (C), 140.8 (C), 140.7 (C), 136.3 (C), 133.1 (C), 132.2 (CH), 130.2 (CH), 128.9 (2xCH), 128.4 (2xCH), 127.5 (CH), 127.3 (2xCH), 127.2 (2xCH), 123.5 (2xCH), 88.0 (O-CH-N), 64.2 (O-$CH_2$), 26.8 (N-$CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{22}H_{19}NNaO_2^+$: 352.1308. Found: 352.1300.

**2-methyl-3-((4-(trifluoromethyl)benzyl)oxy)isoindolin-1-one (17p)**




**17p**

Following the general procedure, the product was obtained as a colorless oil (268 mg, 87%). (eluent: ethyl acetate/pentane: 1:4);

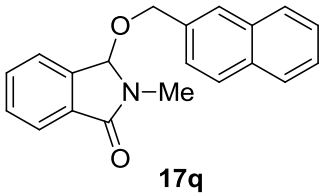
**IR (film)** $\nu_{max}$: 3053, 2923, 2868, 1709, 1619, 1471, 1427, 1395, 1325, 1263, 1204, 1164, 1123, 1066, 1034, 1018, 824, 747, 698 $cm^{-1}$;

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 7.89-7.84 (m, 1H), 7.62-7.51 (m, 3H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 7.6 Hz, 2H), 5.93 (s, 1H), 4.19 (d, *J* = 12.1 Hz, 1H), 4.04 (d, *J* = 12.1 Hz, 1H), 3.11 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.7 (C=O), 141.4 (C), 140.2 (C), 132.9 (C), 132.2 (CH), 130.2 (CH), 129.9 (q, *J*= 32.4 Hz) (C), 127.6 (2xCH), 125.3 (q, *J*= 4.5 Hz) (2xCH), 124.1 (q, *J*= 270.0 Hz) ($CF_3$), 123.4 (d, *J*= 9.0 Hz) (2xCH), 87.8 (O-CH-N), 63.2 (O-$CH_2$), 26.7 (N-$CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{17}H_{14}F_3NNaO_2^+$: 344.0869. Found: 344.0868.

**2-methyl-3-(naphthalen-2-ylmethoxy)isoindolin-1-one (17q)**




**17q**

Following the general procedure, the product was obtained as a white solid (283 mg, 93%). (eluent: ethyl acetate/pentane: 1:4);

**IR (film)** $\nu_{max}$: 3053, 2921, 2857, 1706, 1617, 1601, 1508, 1469, 1428, 1393, 1262, 1203, 1179, 1102, 1066, 1033, 894, 854, 819, 746, 694 $cm^{-1}$;

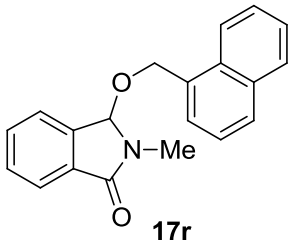
**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 7.94-7.88 (m, 1H), 7.88-7.79 (m, 3H), 7.72 (s, 1H), 7.64-7.45 (m, 5H), 7.42-7.35 (m, 1H), 5.96 (s, 1H), 4.32 (d, *J* = 11.3 Hz, 1H), 4.19 (d, *J* = 11.3 Hz, 1H), 3.17 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.9 (C=O), 140.8 (C), 134.8 (C), 133.4 (C), 133.2 (C), 133.1(C), 132.2 (CH), 130.2 (CH), 128.4 (CH), 128.0 (CH), 127.9 (CH), 126.7

(C), 126.4 (CH), 126.2 (CH), 125.8 (CH), 123.6 (2xCH), 88.1 (O-CH-N), 64.7 (O-$CH_2$), 26.9 (N-$CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{20}H_{17}NNaO_2^+$: 326.1151. Found: 326.1161.

**2-methyl-3-(naphthalen-1-ylmethoxy)isoindolin-1-one (17r)**




**17r**

Following the general procedure, the product was obtained as a white solid (278 mg, 92%). (eluent: ethyl acetate/pentane: 1:4);

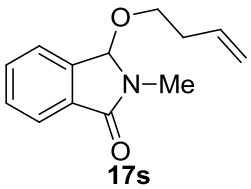
**IR (film)** $\nu_{max}$: 3051, 2920, 2885, 1946, 1704, 1617, 1598, 1511, 1471, 1428, 1394, 1354, 1263, 1203, 1179, 1102, 1032, 800, 778, 747, 695 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.98 (d, *J* = 8.3 Hz, 1H), 7.96-7.77 (m, 3H), 7.66-7.47 (m, 5H), 7.46-7.32 (m, 2H), 5.93 (s, 1H), 4.60 (d, *J* = 11.2 Hz, 1H), 4.54 (d, *J* = 11.2 Hz, 1H), 3.10 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.8 (C=O), 140.8 (C), 133.8 (C), 133.1 (C), 133.0 (C), 132.1 (CH), 131.6 (C), 130.2 (CH), 128.9 (CH), 128.8 (CH), 126.6 (C), 126.5 (CH), 126.0 (CH), 125.4 (CH), 123.7 (CH), 123.6 (CH), 123.5 (CH), 88.0 (O-CH-N), 63.0 (O-$CH_2$), 26.9 (N-$CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{20}H_{17}NNaO_2^+$: 326.1151. Found: 326.1152.

**3-(but-3-en-1-yloxy)-2-methylisoindolin-1-one (17s)**




**17s**

Following the general procedure, the product was obtained as a colorless oil (198 mg, 91%). (eluent: ethyl acetate/pentane: 1:4);

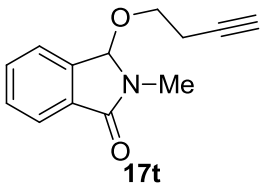
**IR (film)** $\nu_{max}$: 3077, 2920, 2873, 1708, 1641, 1617, 1469, 1430, 1394, 1261, 1204, 1181, 1103, 1074, 1032, 746 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.82 (d, *J* = 7.2 Hz, 1H), 7.62-7.48 (m, 3H), 5.79 (s, 1H), 5.75 (ddt, *J* = 17.3, 10.4, 6.8 Hz, 1H), 5.07 (dd, *J* = 17.3, 1.4 Hz, 1H), 5.05 (dd, *J* = 10.4, 1.4 Hz, 1H), 3.15 (dt, *J* = 9.0, 6.7 Hz, 1H), 3.10 (s, 3H), 3.00 (dt, *J* = 9.0, 6.7 Hz, 1H), 2.27 (t, *J* = 6.8 Hz, 2H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.8 (C=O), 140.9 (C), 135.0 (=CH), 133.1 (C), 132.1 (CH), 130.1 (CH), 123.51 (CH), 123.48 (CH), 117.0 ($=CH_2$), 87.9 (O-CH-N), 61.4 ($O-CH_2$), 34.1 ($CH_2$), 26.7 ($N-CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{13}H_{15}NNaO_2^+$: 240.0995. Found: 240.1005.

**3-(but-3-yn-1-yloxy)-2-methylisoindolin-1-one (17t)**




**17t**

Following the general procedure, the product was obtained as a colorless oil (201 mg, 93%). (eluent: ethyl acetate/pentane: 1:3);

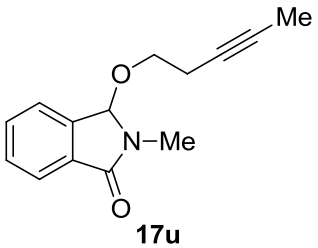
**IR (film)** $\nu_{max}$: 3054, 2926, 2883, 2119, 1704, 1694, 1682, 1617, 1600, 1471, 1434, 1395, 1261, 1204, 1181, 1107, 1063, 1033, 1015, 746, 696 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.80 (d, *J* = 7.2 Hz, 1H), 7.60-7.46 (m, 3H), 5.80 (s, 1H), 3.23-3.00 (m, 2H), 3.10 (s, 3H), 2.42-2.34 (m, 2H), 2.01-1.97 (m, 1H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.6 (C=O), 140.4 (C), 133.0 (C), 132.1 (CH), 130.1 (CH), 123.4 (2xCH), 87.7 (O-CH-N), 81.1 (C≡), 69.7 (HC≡), 60.3 ($O-CH_2$), 26.7 ($N-CH_3$), 19.8 ($CH_2$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{13}H_{13}NNaO_2^+$: 238.0838. Found: 238.0840.

**2-methyl-3-(pent-3-yn-1-yloxy)isoindolin-1-one (17u)**




**17u**

Following the general procedure, the product was obtained as a colorless oil (208 mg, 91%). (eluent: ethyl acetate/pentane: 1:5);

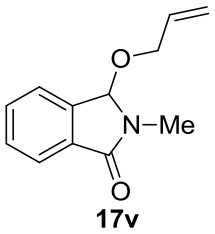
**IR (film)** $\nu_{max}$: 2920, 2885, 2851, 1706, 1616, 1470, 1432, 1395, 1261, 1204, 1181, 1107, 1076, 1032, 845, 807, 746 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.80 (d, *J* = 7.2 Hz, 1H), 7.63-7.43 (m, 3H), 5.80 (s, 1H), 3.15 (dt, *J* = 8.6, 6.8 Hz, 1H), 3.10 (s, 3H), 3.01 (dt, *J* = 8.6, 6.8 Hz, 1H), 2.41-2.24 (m, 2H), 1.75 (t, *J* = 2.3 Hz, 1H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.7 (C=O), 140.7 (C), 133.1 (C), 132.1 (CH), 130.1 (CH), 123.5 (2xCH), 87.8 (O-CH-N), 77.1 (C≡), 75.7 (C≡), 61.0 (O-$CH_2$), 26.7 (N-$CH_3$), 20.2 ($CH_2$), 3.60 ($CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{14}H_{15}NNaO_2^+$: 252.0995. Found: 252.1001.

**3-(allyloxy)-2-methylisoindolin-1-one (17v)**




**17v**

Following the general procedure, the product was obtained as a colorless oil (188 mg, 93%). (eluent: ethyl acetate/pentane: 1:3);

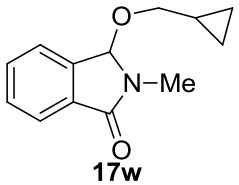
**IR (film)** $\nu_{max}$: 3081, 3055, 3021, 2918, 2867, 1711, 1647, 1617, 1600, 1470, 1428, 1394, 1262, 1204, 1181, 1104, 1064, 1034, 1014, 747, 698 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.80 (d, *J* = 7.2 Hz, 1H), 7.60-7.46 (m, 3H), 5.88-5.72 (m, 1H), 5.80 (s, 1H), 5.21 (dd, *J* = 17.3, 1.4 Hz, 1H), 5.12 (dd, *J* = 10.4, 1.4 Hz, 1H), 3.61 (dd, *J* = 12.2, 5.4 Hz, 1H), 3.49 (d, *J* = 12.2, 5.4 Hz, 1H), 3.08 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.7 (C=O), 140.7 (C), 133.8 (=CH), 133.1 (C), 132.1 (CH), 130.1 (CH), 123.5 (CH), 123.4 (CH), 117.3 (=$CH_2$), 87.8 (O-CH-N), 63.4 (O-$CH_2$), 26.7 (N-$CH_3$).

**HRMS (ESI**) [M+$Na^+$] calculated for $C_{12}H_{13}NNaO_2^+$: 226.0838. Found: 226.0839.

**3-(cyclopropylmethoxy)-2-methylisoindolin-1-one (17w)**




**17w**

Following the general procedure, the product was obtained as a colorless oil (208 mg, 96%). (eluent: ethyl acetate/pentane: 1:3);

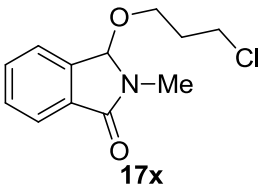
**IR (film)** $\nu_{max}$: 2923, 1682, 1618, 1600, 1472, 1437, 1397, 1312, 1257, 1205, 1179, 1104, 1062, 1036, 746, 695 $cm^{-1}$;

**$^{1}$H NMR (300 MHz, $CDCl_3$)** δ 7.77 (d, *J* = 6.9 Hz, 1H), 7.57-7.43 (m, 3H), 5.76 (s, 1H), 3.07 (s, 3H), 2.88 (dd, *J* = 10.2, 7.2 Hz, 1H), 2.78 (dd, *J* = 10.2, 7.2 Hz, 1H), 1.02-0.87 (m, 1H), 0.54-0.41 (m, 1H), 0.11-0.00 (m, 1H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.6 (C=O), 141.0 (C), 133.0 (C), 132.0 (CH), 129.9 (CH), 123.4 (CH), 123.3 (CH), 87.7 (O-CH-N), 67.2 (O-$CH_2$), 26.6 (N-$CH_3$), 10.6 (CH), 3.3 ($CH_2$), 3.1 ($CH_2$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{13}H_{15}NNaO_2^+$: 240.0995. Found: 240.0999.

**3-(3-chloropropoxy)-2-methylisoindolin-1-one (17x)**




**17x**

Following the general procedure, the product was obtained as a colorless oil (218 mg, 91%). (eluent: ethyl acetate/pentane: 1:3);

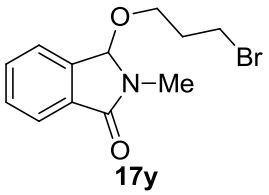
**IR (film)** $\nu_{max}$: 3054, 2960, 2927, 2882, 1705, 1617, 1470, 1429, 1394, 1299, 1262, 1204, 1181, 1107, 1070, 1032, 745 $cm^{-1}$;

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 7.80 (d, *J* = 7.2 Hz, 1H), 7.60-7.46 (m, 3H), 5.75 (s, 1H), 3.63 (t, *J* = 6.5 Hz, 1H), 3.26 (dt, *J* = 9.4, 5.8 Hz, 1H), 3.08 (s, 3H), 3.06 (dt, *J* = 9.4, 5.8 Hz, 1H), 1.94 (quint, *J* = 6.1 Hz, 2H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.7 (C=O), 140.6 (C), 133.0 (C), 132.1 (CH), 130.1 (CH), 123.5 (CH), 123.4 (CH), 87.8 (O-CH-N), 58.3 (O-$CH_2$), 41.6 ($CH_2Cl$), 32.3($CH_2$), 26.7 (N-$CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{12}H_{14}ClNNaO_2^+$: 262.0605. Found: 262.0605.

**3-(3-bromopropoxy)-2-methylisoindolin-1-one (17y)**



**17y**

Following the general procedure, the product was obtained as a colorless oil (248 mg, 88%). (eluent: ethyl acetate/pentane: 1:2);

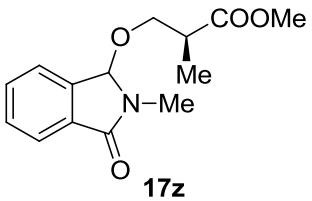
**IR (film)** $\nu_{max}$: 3081, 3055, 3026, 2926, 2876, 1707, 1616, 1596, 1469, 1429, 1394, 1261, 1204, 1180, 1105, 1069, 1031, 743, 697 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.82 (dd, *J* = 7.2, 1.0 Hz, 1H), 7.60 – 7.51 (m, 3H), 5.77 (s, 1H), 3.51 (td, *J* = 6.5, 1.3 Hz, 2H), 3.30 – 3.23 (m, 1H), 3.11 (s, 3H), 3.07 – 3.05 (m, 1H), 2.08 – 1.99 (m, 2H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.6 (C=O), 140.5 (C), 132.9 (C), 132.0 (CH), 130.0 (CH), 123.4 (CH), 123.3 (CH), 87.7 (O-CH-N), 59.2 (O-$CH_2$), 32.3 (Br-$CH_2$), 30.1 ($CH_2$), 26.6 (N-$CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{12}H_{14}BrNNaO_2^+$: 306.0100 and 308.0081. Found: 306.0098 and 308.0078.

**(2S)-methyl 2-methyl-3-((2-methyl-3-oxoisoindolin-1-yl)oxy)propanoate (17z)**



**17z**

Following the general procedure, the product was obtained as a colorless oil (251 mg, 95%). (eluent: ethyl acetate/pentane: 1:2);

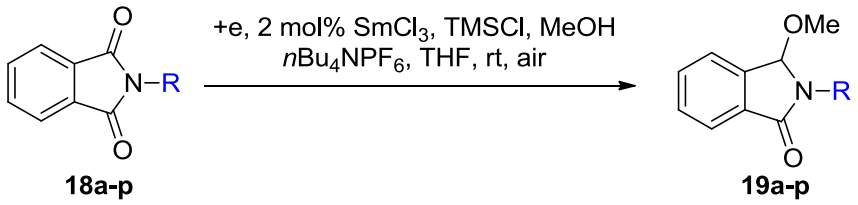
**IR (film)** $\nu_{max}$: 2976, 2950, 2881, 1701, 1617, 1601, 1471, 1436, 1394, 1261, 1207, 1181, 1155, 1103, 1067, 1032, 749, 697 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.80 – 7.73 (m, 1H), 7.58 – 7.44 (m, 3H), 5.73 (s, 1H), 3.66 (s, 3H), 3.29 – 2.88 (m, 2H), 3.04 (s, 3H). 2.72 – 2.57 (m, 1H), 1.07 (m, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 174.8 (C=O), 174.7 (C=O), 167.6 (C=O), 167.5 (C=O), 140.3 (C), 132.9 (C), 132.8 (C), 132.0 (CH), 131.9 (CH), 123.0 (CH), 123.4 (CH), 123.3 (2xCH), 87.6 (O-CH-N), 87.5 (O-CH-N), 63.7 (O-$CH_2$), 63.6 (O-$CH_2$), 51.8 (O-$CH_3$), 39.7 (CH), 39.7 (CH), 26.5 (N-$CH_3$), 13.9 ($CH_3$).

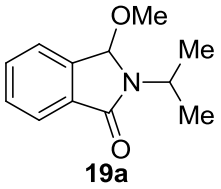
**HRMS (ESI)** [M+Na$^+$] calculated for $C_{14}H_{17}NNaO_4^+$: 286.1050. Found: 286.1051.

## V. 5. 4. Characterization data of reductive methoxylation of *N*-substituted phthalimides




**General procedure for the reductive methoxylation of *N*-substituted phthalimides:** Reactions were carried out in a three necked cell containing a magnetic stirring bar, samarium cathode (20 cm$^2$ area), glassy carbon anode (20 cm$^2$ area) and SCE as reference electrode. $nBu_4NPF_6$ (156 mg, 0.4 mmol, 0.04 mol/L in THF) as the electrolyte, N-substituted phthalimide (1.0 mmol), methanol (320 mg, 10 mmol, 0.4 ml) and $SmCl_3$ (5.0 mg, 0.02 mmol) were added in anhydrous THF (10 ml), TMSCl (272 mg, 2.5 mmol, 0.32 ml) was added dropwise with stirring, then electrolysis was performed at i = 50 mA during 4 hours. After the reaction was complete, the mixture was quenched by 0.1 mol/L HCl (10 ml), extracted with ethyl acetate (2×20 mL). The combined oraganic layer was washed by 10% $Na_2S_2O_3$ (10 ml) and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel.

**2-isopropyl-3-methoxyisoindolin-1-one (19a)**




Following the general procedure, the product was obtained as a colorless oil (199 mg, 97%). (eluent: ethyl acetate/pentane: 1:3);

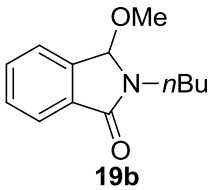
**IR (film)** $\nu_{max}$: 2977, 2934, 2829, 1692, 1615, 1467, 1403, 1365, 1225, 1191, 1076, 750, 697 cm$^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** $\delta$ 7.79 (dd, *J* = 4.5, 3.7 Hz, 1H), 7.59 – 7.44 (m, 3H), 5.99 (s, 1H), 4.40 (hept, *J* = 6.9 Hz, 1H), 2.89 (s, 3H), 1.39 (dd, *J* = 9.0, 6.9 Hz, 6H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.6 (C=O), 140.4 (C), 133.3 (C), 131.9 (CH), 129.8 (CH), 123.3 (CH), 123.2 (CH), 85.6 (O-CH-N), 48.8 (O-$CH_3$), 43.8 (N-CH), 21.0 ($CH_3$), 20.1 ($CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{12}H_{15}NNaO_2^+$: 228.0995. Found: 228.1002.

**2-butyl-3-methoxyisoindolin-1-one (19b)**




**19b**

Following the general procedure, the product was obtained as a colorless oil (198 mg, 90%). (eluent: ethyl acetate/pentane: 1:5);

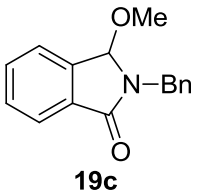
**IR (film)** $\nu_{max}$: 3056, 2959, 2933, 2872, 2828, 1709, 1616, 1602, 1467, 1412, 1375, 1323, 1206, 1190, 1103, 1067, 937, 749, 696 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.82 – 7.68 (m, 1H), 7.58 – 7.38 (m, 3H), 5.81 (s, 1H), 3.73 (dt, *J* = 13.8, 7.8 Hz, 1H), 3.15 (ddd, *J* = 13.9, 7.9, 6.3 Hz, 1H), 2.80 (s, 3H), 1.68 – 1.49 (m, 2H), 1.31 (dd, *J* = 14.9, 7.5 Hz, 2H), 0.88 (t, *J* = 7.3 Hz, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.5 (C=O), 140.3 (C), 133.2 (C), 131.8 (CH), 129.8 (CH), 123.3 (2xCH), 86.1 (O-CH-N), 49.0 (O-$CH_3$), 39.1 ($CH_2$), 30.1 ($CH_2$), 20.2 ($CH_2$), 13.7 ($CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{13}H_{17}NNaO_2^+$: 242.1151. Found: 242.1147.

**2-benzyl-3-methoxyisoindolin-1-one (19c)**




**19c**

Following the general procedure, the product was obtained as a colorless oil (245 mg, 97%). (eluent: ethyl acetate/pentane: 1:5);

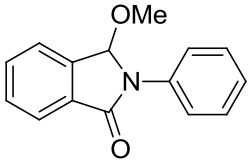
**IR (KBr)** $\nu_{max}$: 2924, 2829, 1703, 1647, 1616, 1493, 1465, 1406, 1356, 1200, 1102, 1068 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.89 (dd, *J* = 6.5, 1.1 Hz, 1H), 7.64 – 7.46 (m, 3H), 7.41 – 7.25 (m, 5H), 5.73 (s, 1H), 5.21 (d, *J* = 14.7 Hz, 1H), 4.22 (d, *J* = 14.7 Hz, 1H), 2.90 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.5 (C=O), 140.4 (C), 136.8 (C), 133.0 (C), 132.1 (CH), 130.0 (CH), 128.7 (2xCH), 128.6 (2xCH), 127.7 (CH), 123.7 (CH), 123.5 (CH), 85.6 (O-CH-N), 49.3 (O-$CH_3$), 43.1 ($CH_2$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{16}H_{15}NNaO_2^+$: 276.0995. Found: 276.0996.

**3-methoxy-2-phenylisoindolin-1-one (19d)**




**19d**

Following the general procedure, the product was obtained as a colorless oil (203 mg, 85%). (eluent: ethyl acetate/pentane: 1:5);

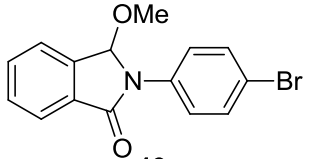
**IR (KBr)** $\nu_{max}$: 3079, 3059, 3043, 3024, 2950, 2929, 1686, 1596, 1500, 1390, 1306, 1152, 751, 732 $cm^{-1}$;

**$^1$H NMR (300 MHz, $CDCl_3$)** δ 7.95 (d, *J* = 7.4 Hz, 1H), 7.88 – 7.76 (m, 2H), 7.72 – 7.57 (m, 3H), 7.47 (ddd, *J* = 10.1, 4.5, 2.0 Hz, 2H), 7.29 – 7.22 (m, 1H), 6.50 (s, 1H), 2.94 (s, 3H).

**$^{13}$C NMR (75 MHz, $CDCl_3$)** δ 166.7 (C=O), 139.7 (C), 137.3(C), 132.9 (C), 132.8 (CH), 130.3 (CH), 129.1 (2xCH), 125.3 (CH), 123.9 (CH), 123.4 (CH), 121.7 (2xCH), 87.3 (O-CH-N), 49.1 (O-$CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{15}H_{13}NNaO_2^+$: 262.0838. Found: 262.0847.

**2-(4-bromophenyl)-3-methoxyisoindolin-1-one (19e)**




**19e**

Following the general procedure, the product was obtained as a colorless oil (298 mg, 94%). (eluent: ethyl acetate/pentane: 1:5);

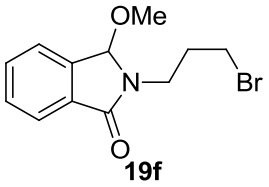
**IR (KBr)** $\nu_{max}$: 3061, 2997, 2954, 2931, 2854, 2829, 1783, 1714, 1589, 1493, 1467, 1413, 1376, 1296, 1218, 1129, 1109, 1075, 1058 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.94 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.83 – 7.78 (m, 2H), 7.73 – 7.68 (m, 1H), 7.65 – 7.60 (m, 2H), 7.59 – 7.54 (m, 2H), 6.46 (s, 1H), 2.91 (s, 3H).

**$^{13}$C NMR (63 MHz, $CDCl_3$)** δ 166.6 (C=O), 139.5 (C), 136.6 (C), 133.0 (CH), 132.7 (C), 132.1 (2xCH), 130.5 (CH), 124.0 (CH), 123.5 (CH), 122.7 (2xCH), 118.2 (C), 87.2 (O-CH-N), 49.0 (O-$CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{15}H_{12}BrNNaO_2^+$: 339.9944 and 341.9924. Found: 339.9941 and 341.9920.

**2-(3-bromopropyl)-3-methoxyisoindolin-1-one (19f)**



**19f**

Following the general procedure, the product was obtained as a colorless oil (249 mg, 88%). (eluent: ethyl acetate/pentane: 1:4);

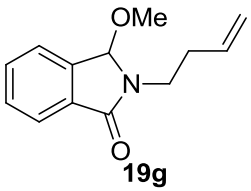
**IR (film)** $\nu_{max}$: 2929, 2857, 2313, 1672, 1641, 1468, 1418, 1107, 1051 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.89 – 7.77 (m, 1H), 7.65 – 7.47 (m, 3H), 5.90 (s, 1H), 3.94 – 3.73 (m, 1H), 3.58 – 3.37 (m, 3H), 2.92 (s, 3H), 2.43 – 2.13 (m, 2H).

**$^{13}$C NMR (63 MHz, $CDCl_3$)** δ 167.9 (C=O), 140.4 (C), 132.8 (C), 132.2 (CH), 130.0 (CH), 123.5 (2xCH), 86.8 (O-CH-N), 49.5 (O-$CH_3$), 38.5 (N-$CH_2$), 31.3 (Br-$CH_2$), 30.4 ($CH_2$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{12}H_{14}BrNNaO_2^+$: 306.0100 and 308.0081. Found: 306.0091 and 308.0074.

**2-(but-3-en-1-yl)-3-methoxyisoindolin-1-one (19g)**



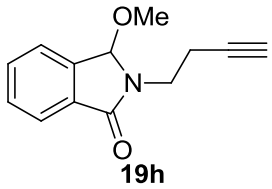
**19g**

Following the general procedure, the product was obtained as a colorless oil (191 mg, 88%). (eluent: ethyl acetate/pentane: 1:2);

**IR (film)** $\nu_{max}$: 3078, 2933, 2829, 1698, 1642, 1617, 1601, 1469, 1439, 1412, 1366, 1331, 1296, 1206, 1103, 1070, 918, 747, 697 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.87 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.59 (qdd, *J* = 8.4, 6.9, 1.2 Hz, 3H), 5.95 (s, 1H), 5.94 – 5.81 (m, 1H), 5.27 – 4.95 (m, 2H), 3.94 (dt, *J* = 14.1, 7.5 Hz, 1H), 3.34 (ddd, *J* = 13.8, 7.7, 6.3 Hz, 1H), 2.91 (s, 3H), 2.58 – 2.40 (m, 2H).
**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.7 (C=O), 140.3 (C), 135.2 (=CH), 133.1 (C), 132.0 (CH), 129.9 (CH), 123.4 (CH), 123.4 (CH), 117.1 (=$CH_2$), 86.3 (O-CH-N), 49.1 (O-$CH_3$), 38.7 (N-$CH_2$), 32.6 ($CH_2$).
**HRMS (ESI)** [M+$Na^+$] calculated for $C_{13}H_{15}NNaO_2^+$: 240.0995. Found: 240.0997.

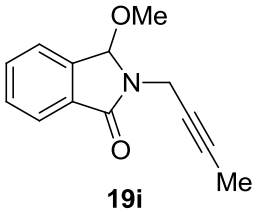
**2-(but-3-yn-1-yl)-3-methoxyisoindolin-1-one (19h)**



**19h**

Following the general procedure, the product was obtained as a colorless oil (193 mg, 90%). (eluent: ethyl acetate/pentane: 1:3);
**IR (film)** $\nu_{max}$: 3083, 3056, 2934, 2829, 2118, 1701, 1616, 1601, 1470, 1412, 1367, 1333, 1297, 1207, 1130, 1104, 1076, 1025, 962, 802, 745, 697 $cm^{-1}$;
**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.88 – 7.74 (m, 1H), 7.64 – 7.42 (m, 3H), 6.06 (s, 1H), 3.92 (ddd, *J* = 13.4, 7.2, 5.9 Hz, 1H), 3.56 – 3.38 (m, 1H), 2.87 (s, 3H), 2.71 – 2.48 (m, 2H), 1.98 (s, 1H).
**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.7 (C=O), 140.4 (C), 132.8 (C), 132.1 (CH), 123.0 (CH), 123.5 (CH), 123.5 (CH), 86.8 (O-CH-N), 81.4 (C≡), 70.1 (HC≡), 49.3 (O-$CH_3$), 38.2 (N-$CH_2$), 18.2 ($CH_2$).
**HRMS (ESI)** [M+$Na^+$] calculated for $C_{13}H_{13}NNaO_2^+$: 238.0838. Found: 238.0840.

**2-(but-2-yn-1-yl)-3-methoxyisoindolin-1-one (19i)**



**19i**

Following the general procedure, the product was obtained as a colorless oil (200 mg, 93%). (eluent: ethyl acetate/pentane: 1:5);

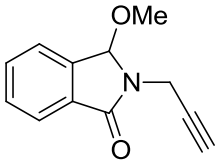
**IR (film)** $\nu_{max}$: 3024, 2956, 2926, 2858, 2829, 1771, 1708, 1616, 1468, 1407, 1353, 1293, 1204, 1190, 1152, 1103, 1072, 945, 747 $cm^{-1}$;

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.88 – 7.82 (m, 1H), 7.65 – 7.51 (m, 3H), 6.06 (s, 1H), 4.69 (dd, *J* = 17.2, 2.5 Hz, 1H), 3.96 – 3.84 (m, 1H), 2.98 (s, 3H), 1.82 (dd, *J* = 3.1, 1.8 Hz, 3H).

**$^{13}$C NMR (100 MHz, $CDCl_3$)** δ 166.9 (C=O), 140.5 (C), 132.8 (C), 132.2 (CH), 129.9 (CH), 123.7 (CH), 123.5 (CH), 85.9 (O-CH-N), 79.7 (C≡), 73.2 (C≡), 49.8 (O-$CH_3$), 29.4 ($CH_2$), 3.5 ($CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{13}H_{15}NNaO_2^+$: 240.0995. Found: 240.0998.

**3-methoxy-2-(prop-2-yn-1-yl)isoindolin-1-one (19j)**




**19j**

Following the general procedure, the product was obtained as a colorless oil (177 mg, 88%). (eluent: ethyl acetate/pentane: 1:4);

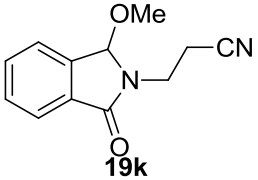
**IR (film)** $\nu_{max}$: 2929, 2829, 2117, 1697, 1683, 1613, 1465, 1420, 1401, 1351, 1289, 1202, 1135, 1104, 1076, 1065, 934, 797, 752 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.84 (d, *J* = 7.2 Hz, 1H), 7.57 (ddd, *J* = 10.5, 7.2, 5.3 Hz, 3H), 6.04 (s, 1H), 4.70 (dd, *J* = 17.5, 2.5 Hz, 1H), 3.97 (dd, *J* = 17.5, 2.4 Hz, 1H), 2.97 (s, 3H), 2.26 (s, 1H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 166. 9 (C=O), 140.5 (C), 132.4 (CH), 130.1 (CH), 123.8 (CH), 123.6 (CH), 86.0 (O-CH-N), 77.9 (C≡), 72.0 (C≡), 49.9 (O-$CH_3$), 29.0 ($CH_2$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{12}H_{11}NNaO_2^+$: 224.0682. Found: 224.0681.

**3-(1-methoxy-3-oxoisoindolin-2-yl)propanenitrile (19k)**




**19k**

Following the general procedure, the product was obtained as a colorless oil (197 mg, 91%). (eluent: ethyl acetate/pentane: 1:2);

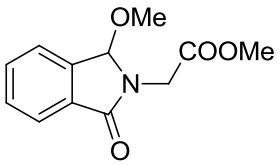
**IR (film)** $\nu_{max}$: 2934, 2835, 2248, 1702, 1616, 1470, 1412, 1368, 1333, 1207, 1133, 1104, 1076, 749, 697 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.92 – 7.82 (m, 1H), 7.71 – 7.52 (m, 3H), 6.07 (s, 1H), 3.98 (ddd, *J* = 13.9, 6.9, 5.5 Hz, 1H), 3.72 (ddd, *J* = 14.2, 8.0, 6.6 Hz, 1H), 2.96 (s, 3H), 2.94 – 2.84 (m, 1H), 2.76 (ddd, *J* = 16.8, 6.4, 5.5 Hz, 1H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 168.0 (C=O), 140.3 (C), 132.7 (CH), 132.2 (C), 130.3 (CH), 123.8 (CH), 123.7 (CH), 117.9 (CN), 87.0 (O-CH-N), 49.8 (O-$CH_3$), 35.9 (N-$CH_2$), 17.1 ($CH_2$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{12}H_{12}N_2NaO_2^+$: 239.0791. Found: 239.0790.

**methyl 2-(1-methoxy-3-oxoisoindolin-2-yl)acetate (19l)**



**19l**

Following the general procedure, the product was obtained as a yellow oil (202 mg, 86%). (eluent: ethyl acetate/pentane: 1:2);

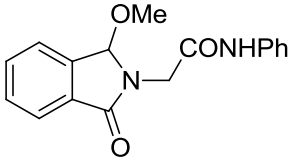
**IR (film)** $\nu_{max}$: 2954, 2849, 1749, 1713, 1617, 1469, 1422, 1210, 1078, 946, 750 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.85 (dd, *J* = 7.3, 1.0 Hz, 1H), 7.64 – 7.49 (m, 3H), 6.02 (s, 1H), 4.62 (d, *J* = 17.7 Hz, 1H), 3.95 (d, *J* = 17.7 Hz, 1H), 3.74 (s, 3H), 2.91 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 169.3 (C=O), 167.8 (C=O), 140.6 (C), 132.4 (CH), 132.3 (C), 130.0 (CH), 123.8 (CH), 123.6 (CH), 86.7 (O-CH-N), 52.3 (O-$CH_3$), 49.6 (O-$CH_3$), 40.5 ($CH_2$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{12}H_{13}NNaO_4^+$: 258.0737. Found: 258.0746.

**2-(1-methoxy-3-oxoisoindolin-2-yl)-*N*-phenylacetamide (19m)**



**19m**

Following the general procedure, the product was obtained as a colorless oil (246 mg, 83%). (eluent: ethyl acetate/pentane: 1:1);

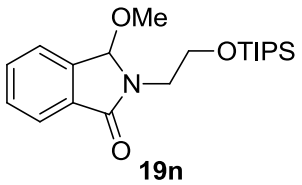
**IR (film)** $\nu_{max}$: 2920, 2885, 2851, 2341, 1706, 1616, 1552, 1469, 1300, 1253, 1194, 946, 750 $cm^{-1}$;

**$^1$H NMR (250 MHz, $CDCl_3$)** δ 8.89 (s, 1H), 7.94 – 7.76 (m, 1H), 7.58 (ddd, *J* = 17.3, 11.4, 6.7 Hz, 5H), 7.24 (t, *J* = 7.8 Hz, 2H), 7.05 (t, *J* = 7.4 Hz, 1H), 6.10 (s, 1H), 4.60 (d, *J* = 16.1 Hz, 1H), 4.20 (d, *J* = 16.1 Hz, 1H), 3.01 (s, 3H);

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 168.7 (C=O), 166.5 (C), 141.0 (C), 137.7 (C), 132.7 (CH), 131.9 (C), 130.2 (CH), 128.9 (2xCH), 124.3 (CH), 123.7 (2xCH), 119.9 (2xCH), 87.9 (O-CH-N), 50.6 (O-$CH_3$), 44.5 (N-$CH_2$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{17}H_{16}N_2NaO_3^+$: 319.1053. Found: 319.1053.

**3-methoxy-2-(2-((triisopropylsilyl)oxy)ethyl)isoindolin-1-one (19n)**




**19n**

Following the general procedure, the product was obtained as a colorless oil (338 mg, 93%). (eluent: ethyl acetate/pentane: 1:5);

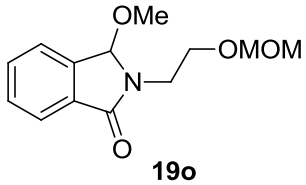
**IR (film)** $\nu_{max}$: 2935, 2862, 2722, 1706, 1616, 1465, 1404, 1311, 1202, 1104, 1071, 995, 923, 881, 744 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.87 – 7.76 (m, 1H), 7.61 – 7.43 (m, 3H), 6.08 (s, 1H), 3.99 (td, *J* = 8.6, 3.8 Hz, 1H), 3.95 – 3.85 (m, 2H), 3.46 – 3.29 (m, 1H), 2.87 (s, 3H), 1.15 – 0.92 (m, 21H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.7 (C=O), 140.8 (C), 133.1 (C), 131.9 (CH), 129.8 (CH), 123.3 (2xCH), 87.6 (O-CH-N), 61.7 (SiO-$CH_2$), 49.2 (O-$CH_3$), 41.7 (N-$CH_2$), 17.9 (6x$CH_3$), 11.8 (3xCH).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{20}H_{33}NNaO_3Si^+$: 386.2122. Found: 386.2124.

**3-methoxy-2-(2-(methoxymethoxy)ethyl)isoindolin-1-one (19o)**




**19o**

Following the general procedure, the product was obtained as a colorless oil (228 mg, 91%). (eluent: ethyl acetate/pentane: 1:1);

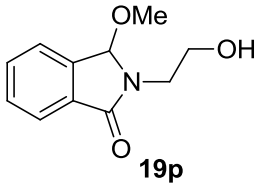
**IR (film)** $\nu_{max}$: 2935, 2885, 2823, 2773, 1703, 1613, 1465, 1409, 1144, 1110, 1071, 917, 749 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.80 (dd, *J* = 7.3, 0.9 Hz, 1H), 7.60 – 7.44 (m, 3H), 6.02 (s, 1H), 4.58 (s, 2H), 3.99 (dt, *J* = 14.3, 4.8 Hz, 1H), 3.76 (dd, *J* = 6.0, 5.0 Hz, 2H), 3.42 (dt, *J* = 14.3, 6.1 Hz, 1H), 3.27 (s, 3H), 2.86 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.7 (C=O), 140.6 (C), 132.9 (C), 132.0 (CH), 129.9 (CH), 123.4 (2xCH), 96.3 ($OCH_2O$), 87.1 (O-CH-N), 65.6 (O-$CH_2$), 55.3 (OMO-$CH_3$), 49.2 (O-$CH_3$), 39.1 (N-$CH_2$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{13}H_{17}NNaO_4^+$: 274.1050. Found: 274.1051.

**2-(2-hydroxyethyl)-3-methoxyisoindolin-1-one (19p)**




**19p**

Following the general procedure, the product was obtained as a colorless oil (190 mg, 92%). (eluent: ethyl acetate/methanol: 5:1);

**IR (film)** $\nu_{max}$: 3419, 2936, 2832, 2120, 1682, 1617, 1601, 1470, 1416, 1365, 1206, 1105, 1076, 748, 697 $cm^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.88 – 7.78 (m, 1H), 7.65 – 7.48 (m, 3H), 5.95 (s, 1H), 3.90 (dd, *J* = 5.4, 4.0 Hz, 2H), 3.84 – 3.72 (m, 1H), 3.65 (ddd, *J* = 14.5, 5.8, 4.1 Hz, 1H), 3.41 (brs, 1H), 2.95 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 169.0 (C=O), 140.4 (C), 132.6 (C), 132.3 (CH), 130.1 (CH), 123.6 (CH), 123.5 (CH), 87.7 (O-CH-N), 61.7(HO-$CH_2$), 49.6 (O-$CH_3$), 43.6 (N-$CH_2$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{11}H_{13}NNaO_3^+$: 230.0788. Found: 230.0790.

**3,4-dihydro-2*H*-[1,3]oxazino[2,3-*a*]isoindol-6(10b*H*)-one (19q)**

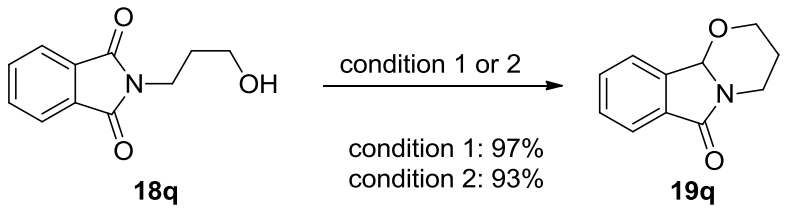
Reaction was carried out in a three necked cell containing a magnetic stirring bar, samarium cathode (20 $cm^2$ area), glassy carbon anode (20 $cm^2$ area) and SCE as reference electrode;

Condition 1: *n*$Bu_4NPF_6$ (156 mg, 0.4 mmol, 0.04 mol/L in THF) as the electrolyte, 2-(3-hydroxypropyl)isoindoline-1,3-dione (205 mg, 1.0 mmol) and $SmCl_3$ (5.0 mg, 0.02

mmol) were added in anhydrous THF (10 ml), TMSCl (272 mg, 2.5 mmol, 0.32 ml) was added dropwise with stirring, then electrolysis was performed at i = 50 mA during 6 hours.

Condition 2: $n$Bu$_4$NPF$_6$ (156 mg, 0.4 mmol, 0.04 mol/L in THF) as the electrolyte, 2-(3-hydroxypropyl)isoindoline-1,3-dione (205 mg, 1.0 mmol), methanol (320 mg, 10 mmol, 0.4 ml) and $SmCl_3$ (5.0 mg, 0.02 mmol) were added in anhydrous THF (10 ml), TMSCl (272 mg, 2.5 mmol, 0.32 ml) was added dropwise with stirring, then electrolysis was performed at i = 50 mA during 6 hours.

After the reaction was complete, the mixture was quenched by 0.1 mol/L HCl (10 ml), extracted with ethyl acetate (2×20 mL). The combined oraganic layer was washed by 10% $Na_2S_2O_3$ (10 ml) and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel.




Following the condition 1, the product was obtained as a colorless oil (183 mg, 97%); Following the condition 2, the product was obtained as a colorless oil (176 mg, 93%). (eluent: ethyl acetate/pentane: 1:1);

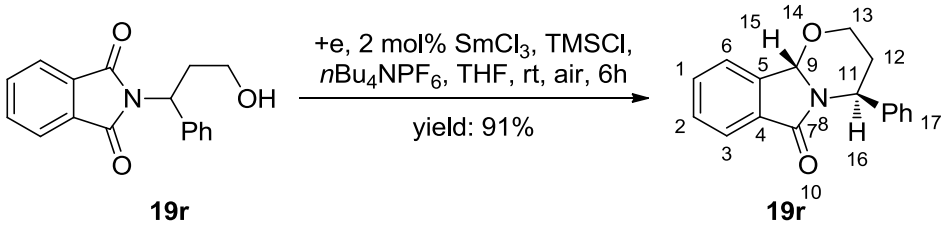
**IR (film)** $\nu_{max}$: 2957, 2862, 1703, 1426, 1281, 1057 cm$^{-1}$;

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.84 (dd, $J$ = 7.0, 1.1 Hz, 1H), 7.60 – 7.50 (m, 3H), 5.57 (s, 1H), 4.59 – 4.35 (m, 1H), 4.31 – 4.09 (m, 1H), 3.96 (td, $J$ = 12.2, 2.1 Hz, 1H), 3.37 – 3.17 (m, 1H), 1.94 – 1.81 (m, 1H), 1.66 (dtd, $J$ = 13.6, 3.6, 1.7 Hz, 1H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 165.9 (C=O), 141.2 (C), 132.8 (C), 131.9 (CH), 123.0 (CH), 123.6 (CH), 123.1 (CH), 85.1 (O-CH-N), 67.3 (O-$CH_3$), 37.8 (N-$CH_2$), 24.6 ($CH_2$).

**HRMS (ESI)** [M+Na$^+$] calculated for $C_{11}H_{11}NNaO_2^+$: 212.0682. Found: 212.0683.

**4-phenyl-3,4-dihydro-2H-[1,3]oxazino[2,3-a]isoindol-6(10bH)-one (19r)**

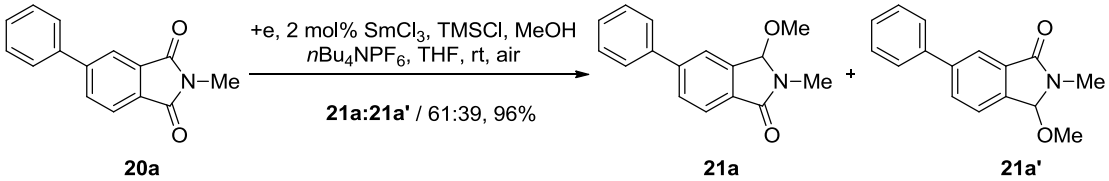



$nBu_4NPF_6$ (156 mg, 0.4 mmol, 0.04 mol/L in THF) as the electrolyte, 2-(3-hydroxy-1-phenylpropyl)isoindoline-1,3-dione (281 mg, 1.0 mmol) and $SmCl_3$ (5.0 mg, 0.02 mmol) were added in anhydrous THF (10 ml), TMSCl (272 mg, 2.5 mmol, 0.32 ml) was added dropwise with stirring, then electrolysis was performed at i = 50 mA during 6 hours. After the reaction was complete, the mixture was quenched by 0.1 mol/L HCl (10 ml), extracted with ethyl acetate (2×20 mL). The combined oraganic layer was washed by 10% $Na_2S_2O_3$ (10 ml) and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluent: ethyl acetate/pentane: 1:3) to afford the product as a colorless oil (241 mg, 91%). The relative stereochemistry of H15 and H16 was determined by NOESY experiment.

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.93 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.62 – 7.54 (m, 3H), 7.41 – 7.35 (m, 2H), 7.34 – 7.29 (m, 3H), 5.81 (d, *J* = 4.4 Hz, 1H), 5.72 (s, 1H), 4.13 (ddd, *J* = 6.6, 3.7, 2.3 Hz, 1H), 4.00 (ddd, *J* = 11.3, 7.0, 3.8 Hz, 1H), 2.38 – 2.26 (m, 2H).

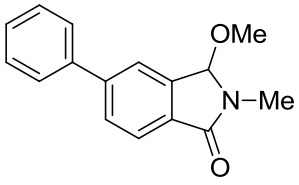
**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 166.9 (C=O), 141.5 (C), 138.9 (C), 132.3 (C), 132.2 (CH), 130.1 (CH), 128.9 (2xCH), 127.3 (CH), 126.7 (2xCH), 123.9 (CH), 123.4 (CH), 82.7 (O-CH-N), 64.0 (O-$CH_2$), 48.6 (N-CH), 28.1 ($CH_2$).

## V. 5. 5. Regioselectivity of reductive methoxylation of aryl-ring-substituted *N*-methylphtalimides



Following the general procedure, the mixture of 5.6a and 5.6a' was obtained in 96% yield (243 mg). (eluent: ethyl acetate/petane: 1:4).

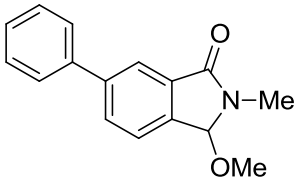
**3-methoxy-2-methyl-5-phenylisoindolin-1-one (21a)**




**21a**

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.87 (d, *J* = 8.2 Hz, 1H), 7.75-7.71 (m, 1H), 7.65-7.55 (m, 3H), 7.51-7.35 (m, 3H), 5.80 (s, 1H), 3.10 (s, 3H), 2.94 (s, 3H).

**3-methoxy-2-methyl-6-phenylisoindolin-1-one (21a')**

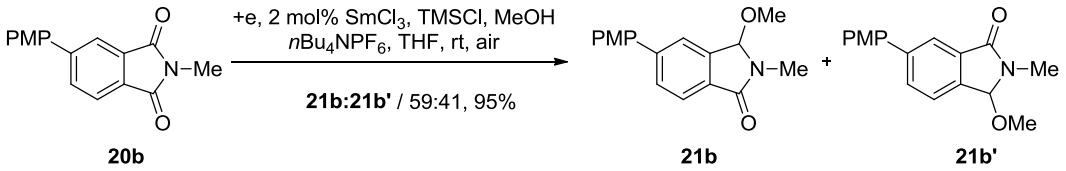



**21a'**

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 8.04 (d, *J* = 1.5 Hz, 1H), 7.80 (dd, *J* = 7.8, 1.6 Hz 1H), 7.65-7.55 (m, 3H), 7.51-7.35 (m, 3H), 5.80 (s, 1H), 3.10 (s, 3H), 2.94 (s, 3H).

21a and 21a': **$^{13}$C NMR (90 MHz, $CDCl_3$)** δ167.8, 167.7, 145.4, 143.4, 141.1, 140.1, 140.0, 139.1, 134.0, 132.1, 130.9, 129.1, 128.3, 128.1, 127.5, 127.3, 123.8, 122.0, 121.9, 88.1, 88.0, 49.4, 26.6

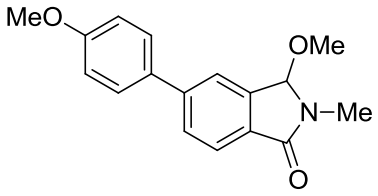
**HRMS (ESI)** [M+$Na^+$] calculated for $C_{16}H_{15}NNaO_2^+$: 276.0995. Found: 276.0997.




**20b** **21b** **21b'**

Following the general procedure, the mixture of 5.6b and 5.6b' was obtained in 95% yield (269 mg). (eluent: ethyl acetate/petane: 1:4).

**3-methoxy-5-(4-methoxyphenyl)-2-methylisoindolin-1-one (21b)**




**21b**

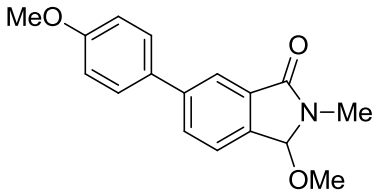
White solid. **IR (film)** $\nu_{max}$: 3039, 2996, 2934, 2835, 2532, 2043, 1703, 1607, 1520, 1448, 1361, 1254, 1185, 1120, 1080, 1037, 960, 825, 779, $cm^{-1}$;

**$^{1}$H NMR (250 MHz, $CDCl_3$)** δ 7.85 (d, *J* = 8.3 Hz, 1H), 7.77 – 7.64 (m, 2H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 5.80 (s, 1H), 3.87 (s, 3H), 3.10 (s, 3H), 2.94 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.8 (C=O), 159.9 (C), 144.9 (C), 141.1 (C), 132.4 (C), 131.4 (CH), 128.5 (2xCH), 123.7 (CH), 121.4 (CH), 114.5 (2xCH), 88.0 (O-CH-N), 55.4 (ArO-$CH_3$), 49.2 (O-$CH_3$), 26.5 (N-$CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{17}H_{17}NNaO_3^+$: 306.1101. Found: 306.1111.

**3-methoxy-6-(4-methoxyphenyl)-2-methylisoindolin-1-one (21b')**



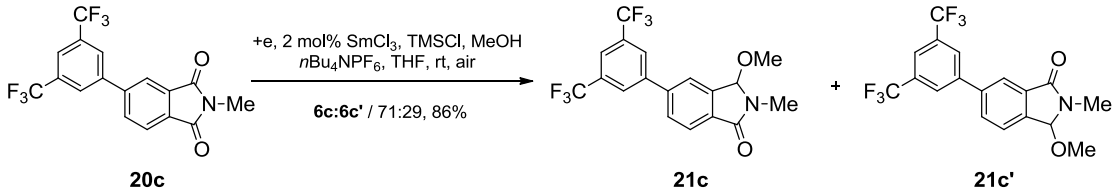

**21b'**

White solid. **IR (film)** $\nu_{max}$: 3039, 2996, 2934, 2835, 2532, 2043, 1703, 1607, 1520, 1448, 1359, 1255, 1183, 1122, 1079, 1035, 959, 825, 779, 700 $cm^{-1}$;

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 8.02 (d, *J* = 1.5 Hz, 1H), 7.78 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.63 – 7.54 (m, 3H), 7.07 – 6.98 (m, 2H), 5.82 (s, 1H), 3.88 (s, 3H), 3.12 (s, 3H), 2.96 (s, 3H).

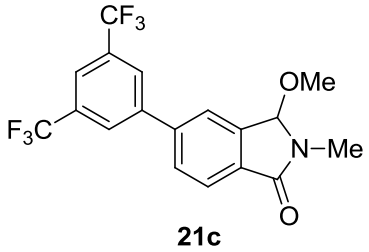
**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.8 (C=O), 159.7 (C), 142.9 (C), 138.3 (C), 133.9 (C), 132.3 (C), 130.4 (CH), 128.3 (2xCH), 123.7 (CH), 121.3 (CH), 114.4 (2xCH), 87.9 (O-CH-N), 55.4 (ArO-$CH_3$), 49.2 (O-$CH_3$), 26.5 (N-$CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{17}H_{17}NNaO_3^+$: 306.1101. Found: 306.1111.




Following the general procedure, the mixture of 5.6c and 5.6c' was obtained in 86% yield (335 mg). (eluent: ethyl acetate/petane: 1:4).

**5-(3,5-bis(trifluoromethyl)phenyl)-3-methoxy-2-methylisoindolin-1-one (21c)**



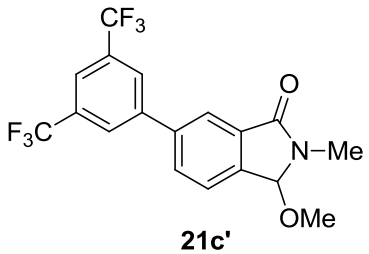

**21c**

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 8.09 (s, 2H), 8.03 – 7.93 (m, 2H), 7.85 – 7.77 (m, 2H), 5.89 (s, 1H), 3.17 (s, 3H), 3.01 (s, 3H).

**$^{13}$C NMR (75 MHz, $CDCl_3$)** δ 167.0 (C=O), 142.2 (C), 142.1 (C), 141.6 (C), 133.5 (C), 132.5 (q, *J* = 33.0 Hz, C), 129.3 (CH), 127.5 (CH), 124.3 (CH), 123.2 (q, *J* = 270.8 Hz, C), 122.2 (CH), 121.8 (cinq, *J* = 3.8 Hz, CH), 87.9 (O-CH-N), 49.5 (O-$CH_3$), 26.6 (N-$CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{18}H_{13}F_6NNaO_2^+$: 412.0743. Found: 412.0715.

**6-(3,5-bis(trifluoromethyl)phenyl)-3-methoxy-2-methylisoindolin-1-one (21c')**

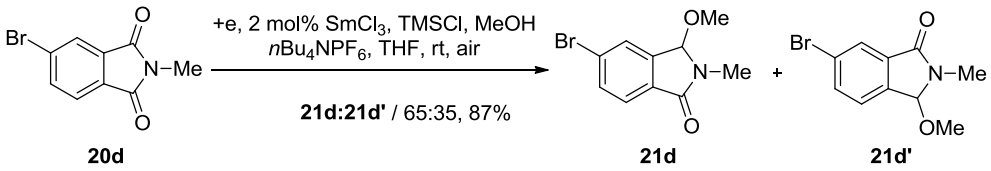



**21c'**

**$^{1}$H NMR (250 MHz, $CDCl_3$)** δ 8.10 (s, 3H), 7.94 (s, 1H), 7.87 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 5.88 (s, 1H), 3.16 (s, 3H), 2.99 (s, 3H).

**$^{13}$C NMR (75 MHz, $CDCl_3$)** δ 167.0 (C=O), 142.0 (C), 140.7 (C), 140.3 (C), 134.5 (C), 132.5 (q, *J* = 33.0 Hz, C) , 130.9 (CH), 127.4 (CH), 124.3 (CH), 123.2 (q, *J* = 270.8 Hz, C), 122.1 (CH), 121.7 (cinq, *J* = 3.8 Hz, CH), 87.9 (O-CH-N), 49.4(O-$CH_3$), 26.6 (N-$CH_3$).

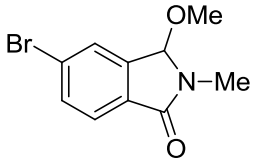
**HRMS (ESI)** [M+Na$^+$] calculated for $C_{18}H_{13}F_6NNaO_2^+$: 412.0743. Found: 412.0715.



20d 21d 21d'

Following the general procedure, the mixture of 5.6d and 5.6d' was obtained in 87% yield (222 mg). (eluent: ethyl acetate/petane: 1:4).

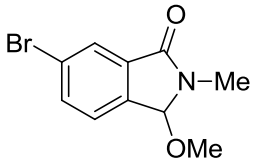
**5-bromo-3-methoxy-2-methylisoindolin-1-one (21d)**



**21d**

**$^1$H NMR (360 MHz, CDCl$_3$)** δ 7.67-7.62 (m, 3H), 5.71 (s, 1H), 3.04 (s, 3H), 2.90 (s, 3H).

**6-bromo-3-methoxy-2-methylisoindolin-1-one (21d')**



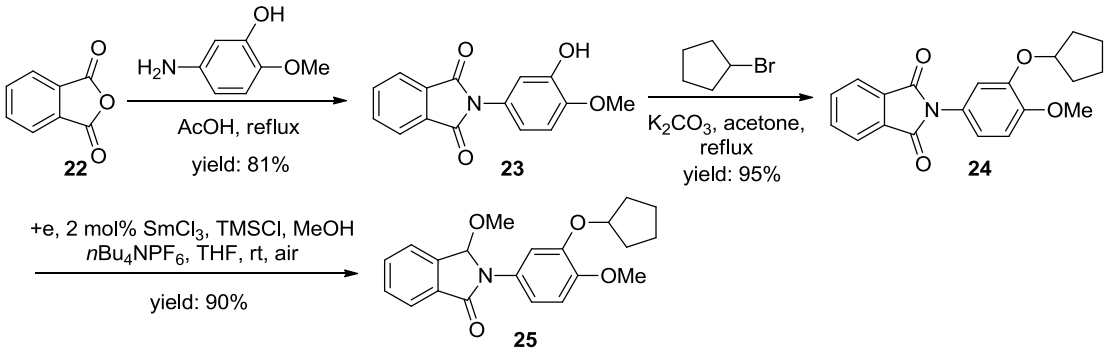
**21d'**

**$^1$H NMR (360 MHz, CDCl$_3$)** δ 7.92 (d, *J* = 1.8, 1H), 7.70-7.66 (m, 1H), 7.38 (d, *J* = 8.0, 1H), 5.71 (s, 1H), 3.05 (s, 3H), 2.88 (s, 3H).

21d and 21d': **$^{13}$C NMR (90 MHz, CDCl$_3$)** δ 166.8, 166.3, 142.3, 139.0, 135.2, 135.0, 133.4, 132.1, 126.9, 126.8, 126.7, 125.0, 124.9, 124.3, 87.7, 87.5, 49.53 (O-CH3, **2o'** ), 49.3, 26.6, 26.6.

**HRMS (ESI)** [M+Na$^+$] calculated for $C_{10}H_{10}BrNNaO_2^+$: 277.9787. Found: 277.9781.

# V. 5. 6. Total synthesis of 3-methoxy-2-(3-cyclopentyloxy-4-methoxyphenyl)-1-isoindolinone (25)




**2-(3-hydroxy-4-methoxyphenyl)isoindoline-1,3-dione (23)**

a mixture of 5-amino-2-methoxyphenol (1.39 g, 10.0 mmol) and Phthalic anhydride (1.48 g, 10.0 mmol) in acetic acid (20 ml) was refluxed overnight with stirring. After cooling to the room temperature, diluted by water (20 ml) and extracted with ethyl acetate (2x10 ml). The oraganic phase was washed by saturated $NaHCO_3$ (5 ml) and brine (5 ml), dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel (eluent: ethyl acetate/pentane: 2:1) to afford the product as a white solid (2.18 g, 81%).

**$^1$H NMR (300 MHz, $CDCl_3$)** δ 7.96 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.1 Hz, 2H), 6.96 (ddd, *J* = 10.8, 7.4, 2.3 Hz, 3H), 5.77 (s, 1H), 3.96 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.5 (C=O), 146.5 (C), 146.0 (C), 134.3 (2xCH), 131.8 (CH), 124.8 (C), 123.7 (2xCH), 118.7 (CH), 113.5 (CH), 110.7 (CH), 56.1 (O-$CH_3$).

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{15}H_{11}NNaO_4^+$: 292.0580. Found: 292.0579.

**2-(3-(cyclopentyloxy)-4-methoxyphenyl)isoindoline-1,3-dione (24)**

To a mixture of **5.8** (2.15 g, 8.0 mmol) and $K_2CO_3$ (5.52 g, 40 mmol) in acetone (40 ml),bromocyclopentane (5.92 g, 4.3 ml, 40 mmol) was added with stirring, then refluxed overnight. Cooled to room temperature, diluted by ethyl acetate (50 ml), filtered the turbid liquid to remove the salt, concentrated and purified by flash chromatography on silica gel (eluent: ethyl acetate/pentane: 1:1) to afford the product as a white solid (2.56 g, 95%).

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.91 (s, 2H), 7.76 (s, 2H), 6.95 (s, 3H), 4.76 (s, 1H), 3.87 (s, 3H), 1.97 – 1.46 (m, 8H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.6 (C=O), 149.7 (C), 147.9 (C), 134.3 (2xCH), 131.8 (CH), 124.2 (C), 123.6 (2xCH), 118.8 (CH), 113.3 (CH), 111.7 (CH), 80.6 (O-CH), 56.2 (O-$CH_3$), 32.7 (2x$CH_2$), 24.0 (2x$CH_2$).

**HRMS (ESI)** [M+$H^+$] calculated for $C_{20}H_{19}NNaO_4^+$: 360.1206. Found: 360.1199.

**3-methoxy-2-(3-cyclopentyloxy-4-methoxyphenyl)-1-isoindolinone (25)**

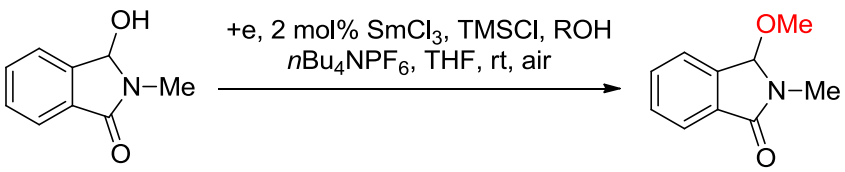
Reactions were carried out in a three necked cell containing a magnetic stirring bar, samarium cathode (20 $cm^2$ area), glassy carbon anode (20 $cm^2$ area) and SCE as reference electrode. n$Bu_4NPF_6$ (312 mg, 0.8 mmol, 0.04 mol/L in THF) as the electrolyte, **24** (1.69 g, 5.0 mmol), methanol (1.60 g, 50 mmol, 2.0 ml) and $SmCl_3$ (25.0 mg, 0.1 mmol) were added in anhydrous THF (20 ml), TMSCl (1.36 g, 12.5 mmol, 1.6 ml) was added dropwise with stirring, then electrolysis was performed at i = 50 mA during 30 hours. After the reaction was complete, the mixture was quenched by 0.1 mol/L HCl (50 ml), extracted with ethyl acetate (3×20 mL). The combined oraganic layer was washed by 10% $Na_2S_2O_3$ (20 ml) and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluent: ethyl acetate/pentane: 1:3) to afford the product as a colorless oil (1.59 g, 90%).

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.91 – 7.84 (m, 1H), 7.58 (ddd, *J* = 21.1, 10.1, 4.2 Hz, 4H), 7.20 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 6.36 (s, 1H), 4.82 (dt, *J* = 9.6, 3.2 Hz, 1H), 3.85 (s, 3H), 2.93 (s, 3H), 1.99 – 1.80 (m, 6H), 1.64 – 1.54 (m, 2H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 166.7 (C=O), 147.8 (C), 147.6 (C), 139.7 (C), 133.0 (C), 132.6 (CH), 130.5 (C), 130.3 (CH), 123.7 (CH), 123.4 (CH), 113.9 (CH), 112.0 (CH), 109.7 (CH), 87.8 (O-CH-N), 80.5 (O-CH), 56.2 (O-$CH_3$), 49.3 (O-$CH_3$), 32.8 (2x$CH_2$), 24.1 (2x$CH_2$).

**HRMS (ESI)** [M+$H^+$] calculated for $C_{20}H_{19}NNaO_4^+$: 360.1206. Found: 360.1199.

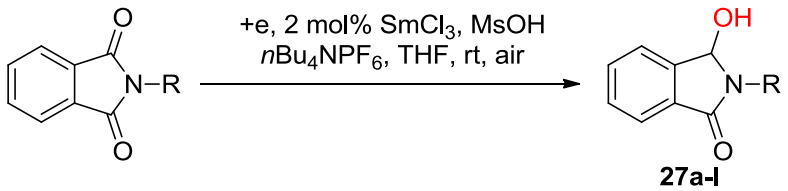
**The reductive methoxylation of 3-hydroxy-2-methylisoindolin-1-one**




Reactions were carried out in a three necked cell containing a magnetic stirring bar, samarium cathode (20 $cm^2$ area), glassy carbon anode (20 $cm^2$ area) and SCE as

reference electrode. $n$Bu$_4$NPF$_6$ (156 mg, 0.4 mmol, 0.04 mol/L in THF) as the electrolyte, 3-hydroxy-2-methylisoindolin-1-one (163 mg, 1.0 mmol), alcohol (10 equivalent, 10 mmol) and $SmCl_3$ (5.0 mg, 0.02 mmol) were added in anhydrous THF (10 ml), TMSCl (272 mg, 2.5 mmol, 0.32 ml) was added dropwise with stirring, then electrolysis was performed at i = 50 mA during 3 hours. After the reaction was complete, the mixture was quenched by 0.1 mol/L HCl (10 ml), extracted with ethyl acetate (2×20 mL). The combined oraganic layer was washed by 10% $Na_2S_2O_3$ (10 ml) and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel. The product was obtained as a colorless oil (161 mg, 91%). (eluent: ethyl acetate/pentane: 1:3)

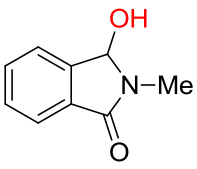
## V. 5. 7. Characterization data of ω-hydroxylactams




**27a-l**

**General procedure for the reduction of phthalimides into the ω-hydroxylactams:** Reactions were carried out in a three necked cell containing a magnetic stirring bar, samarium cathode (20 $cm^2$ area), glassy carbon anode (20 $cm^2$ area) and SCE as reference electrode. $n$Bu$_4$NPF$_6$ (156 mg, 0.4 mmol, 0.04 mol/L in THF) as the electrolyte, phthalimides (1.0 mmol) and $SmCl_3$ (5.0 mg, 0.02 mmol) were added in anhydrous THF (10 ml), MsOH (480 mg, 5.0 mmol, 0.32 ml) was added dropwise with stirring, then electrolysis was performed at i = 50 mA during 2.5 hours. After the reaction was complete, the mixture was quenched by water (10 ml), extracted with ethyl acetate (2×20 mL). The combined oraganic layer was washed by 10% $Na_2S_2O_3$ (10 ml) and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel.

**3-hydroxy-2-methylisoindolin-1-one (27a)**




**27a**

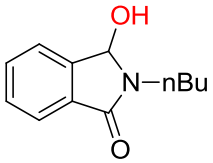
Following the general procedure, the product was obtained as a white solid (161 mg, 99%). (eluent: ethyl acetate/pentane: 1:1);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.48 (ddd, *J* = 10.0, 8.8, 4.3 Hz, 2H), 7.42 – 7.24 (m, 2H), 5.51 (s, 1H), 4.60 (s, 1H), 2.80 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.7, 143.9, 132.1, 131.2, 129.4, 123.2, 122.8, 83.4, 26.0.

**HRMS (ESI)** [M+$Na^+$] calculated for $C_9H_9NNaO_2^+$: 186.0525. Found: 186.0531.

**2-butyl-3-hydroxyisoindolin-1-one (27b)**




**27b**

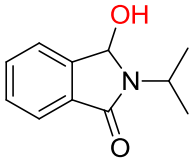
Following the general procedure, the product was obtained as a white solid (203 mg, 99%). (eluent: ethyl acetate/pentane: 1:2);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.58 (dt, *J* = 15.2, 7.4 Hz, 2H), 7.48 (d, *J* = 7.4 Hz, 1H), 7.41 (d, *J* = 7.3 Hz, 1H), 5.72 (s, 1H), 4.44 (s, 1H), 3.37 (dt, *J* = 14.1, 7.9 Hz, 1H), 3.18 (ddd, *J* = 13.8, 8.2, 5.8 Hz, 1H), 1.55 (tt, *J* = 14.4, 7.4 Hz, 2H), 1.29 (dt, *J* = 14.9, 7.4 Hz, 2H), 0.91 (t, *J* = 7.3 Hz, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.6, 144.0, 132.1, 131.4, 129.5, 123.3, 123.0, 81.5, 38.6, 30.2, 20.1, 13.7.

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{12}H_{15}NNaO_2^+$: 228.0995. Found: 228.1001.

**3-hydroxy-2-isopropylisoindolin-1-one (27c)**




**27c**

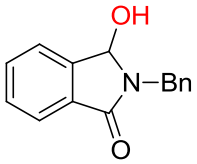
Following the general procedure, the product was obtained as a white solid (189 mg, 99%). (eluent: ethyl acetate/pentane: 1:2);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.49 – 7.37 (m, 3H), 7.35 – 7.25 (m, 1H), 5.76 (s, 1H), 5.24 (s, 1H), 4.15 (hept, *J* = 6.8 Hz, 1H), 1.30 (dd, *J* = 9.0, 6.9 Hz, 6H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.1, 144.1, 131.8, 131.7, 129.3, 122.9, 122.8, 81.2, 43.8, 21.8, 20.0.

**HRMS (ESI)** [M+Na$^+$] calculated for $C_{11}H_{13}NNaO_2^+$: 214.0838. Found: 214.0846.

**2-benzyl-3-hydroxyisoindolin-1-one (27d)**




**27d**

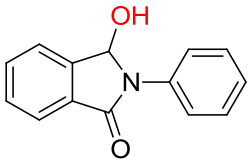
Following the general procedure, the product was obtained as a white solid (217 mg, 91%). (eluent: ethyl acetate/pentane: 1:2);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.67 – 7.50 (m, 3H), 7.52 – 7.39 (m, 1H), 7.39 – 7.22 (m, 5H), 5.59 (s, 1H), 4.77 (d, *J* = 14.8 Hz, 1H), 4.51 (s, 1H), 4.20 (d, *J* = 14.8 Hz, 1H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.5, 144.1, 136.7, 132.4, 131.2, 129.7, 128.8, 128.5, 127.7, 123.5, 123.3, 81.0, 42.5.

**HRMS (ESI)** [M+Na$^+$] calculated for $C_{15}H_{13}NNaO_2^+$: 262.0838. Found: 262.0843.

**3-hydroxy-2-phenylisoindolin-1-one (27e)**




**27e**

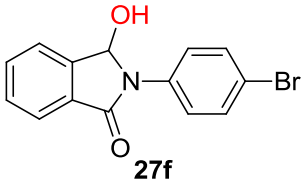
Following the general procedure, the product was obtained as a white solid (218 mg, 97%). (eluent: ethyl acetate/pentane: 1:1);

**$^1$H NMR (300 MHz, $CDCl_3$)** δ 7.78 – 7.54 (m, 5H), 7.43 (ddd, *J* = 15.9, 10.6, 4.7 Hz, 3H), 7.22 (t, *J* = 7.4 Hz, 1H), 6.37 (s, 1H), 3.62 (s, 1H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 166.5, 142.8, 137.0, 132.9, 131.4, 130.2, 129.1, 125.4, 123.9, 123.3, 121.9, 82.9.

**HRMS (ESI)** [M+Na$^+$] calculated for $C_{14}H_{11}NNaO_2^+$: 248.0682. Found: 248.0689.

**2-(4-bromophenyl)-3-hydroxyisoindolin-1-one (27f)**




**27f**

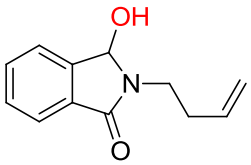
Following the general procedure, the product was obtained as a white solid (294 mg, 97%). (eluent: ethyl acetate/pentane: 1:1);

**$^1$H NMR (360 MHz, MeOD)** δ 7.83 (d, *J* = 7.5 Hz, 1H), 7.76 – 7.66 (m, 4H), 7.65 – 7.53 (m, 3H), 6.47 (s, 1H).

**$^{13}$C NMR (90 MHz, MeOD)** δ 168.4, 145.5, 137.7, 134.4, 133.0, 132.4, 131.1, 126.0, 124.7, 124.4, 119.6, 84.0.

**HRMS (ESI)** [M+Na$^+$] calculated for $C_{14}H_{10}BrNNaO_2^+$: 325.9787 and 327.9768. Found: 325.9773 and 327.9802.

**2-(but-3-en-1-yl)-3-hydroxyisoindolin-1-one (27g)**




**27g**

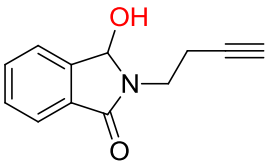
Following the general procedure, the product was obtained as a white solid (181 mg, 89%). (eluent: ethyl acetate/pentane: 1:2);

**$^1$H NMR (360 MHz, CDCl$_3$)** δ 7.55 (dt, *J* = 14.5, 7.4 Hz, 2H), 7.47 (d, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.3 Hz, 1H), 5.86 – 5.62 (m, 2H), 5.00 (t, *J* = 12.9 Hz, 2H), 4.53 (s, 1H), 3.44 (dt, *J* = 14.6, 7.5 Hz, 1H), 3.26 (dt, *J* = 13.8, 6.8 Hz, 1H), 2.32 (dd, *J* = 14.9, 7.6 Hz, 2H).

**$^{13}$C NMR (90 MHz, CDCl$_3$)** δ 167.6, 144.0, 135.1, 132.2, 131.2, 129.6, 123.3, 123.0, 117.1, 81.7, 38.2, 32.6.

**HRMS (ESI)** [M+Na$^+$] calculated for $C_{12}H_{13}NNaO_2^+$: 226.0838. Found: 226.0841.

**2-(but-3-yn-1-yl)-3-hydroxyisoindolin-1-one (27h)**




**27h**

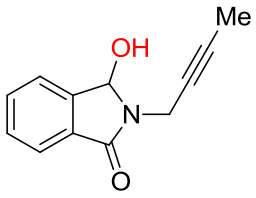
Following the general procedure, the product was obtained as a white solid (187 mg, 93%). (eluent: ethyl acetate/pentane: 1:2);

**$^1$H NMR (360 MHz, CDCl$_3$)** δ 7.60 – 7.43 (m, 3H), 7.45 – 7.31 (m, 1H), 5.88 (s, 1H), 5.00 (s, 1H), 3.58 – 3.32 (m, 2H), 2.45 (dd, *J* = 9.2, 4.4 Hz, 2H), 1.96 (t, *J* = 2.5 Hz, 1H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 167.7, 144.1, 132.4, 131.0, 129.6, 123.4, 123.1, 82.1, 81.5, 70.2, 37.9, 18.3.

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{12}H_{11}NNaO_2^+$: 224.0682. Found: 224.0688.

**2-(but-2-yn-1-yl)-3-hydroxyisoindolin-1-one (27i)**




**27i**

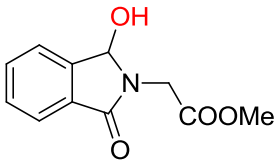
Following the general procedure, the product was obtained as a white solid (177 mg, 88%). (eluent: ethyl acetate/pentane: 2:1);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.67 – 7.51 (m, 3H), 7.46 (t, *J* = 7.3 Hz, 1H), 5.94 (d, *J* = 9.9 Hz, 1H), 4.25 (dd, *J* = 17.3, 2.3 Hz, 1H), 3.82 (dd, *J* = 17.3, 2.3 Hz, 1H), 1.77 (t, *J* = 2.3 Hz, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 166.8, 143.9, 132.5, 131.1, 129.7, 123.5, 123.3, 81.1, 79.8, 73.2, 28.8, 3.5.

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{12}H_{11}NNaO_2^+$: 224.0682. Found: 224.0689.

**methyl 2-(1-hydroxy-3-oxoisoindolin-2-yl)acetate (27j)**




**27j**

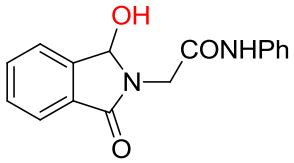
Following the general procedure, the product was obtained as a white solid (203 mg, 92%). (eluent: ethyl acetate/pentane: 2:1);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.58 (d, *J* = 7.6 Hz, 4H), 7.55 – 7.50 (m, 8H), 7.43 – 7.37 (m, 5H), 5.82 (s, 4H), 4.94 (s, 4H), 4.18 (d, *J* = 17.8 Hz, 4H), 4.02 (d, *J* = 17.8 Hz, 6H), 3.64 (s, 12H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 169.8, 167.8, 144.3, 132.6, 130.6, 129.6, 123.5, 123.3, 82.2, 52.3, 40.4.

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{11}H_{11}NNaO_4^+$: 244.0580. Found: 244.0583.

**2-(1-hydroxy-3-oxoisoindolin-2-yl)-*N*-phenylacetamide (27k)**




**27k**

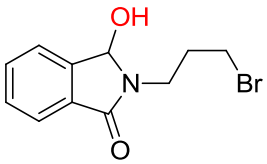
Following the general procedure, the product was obtained as a white solid (242 mg, 86%). (eluent: ethyl acetate/pentane: 3:1);

**$^{1}$H NMR (360 MHz, MeOD)** δ 7.80 (d, *J* = 7.5 Hz, 1H), 7.69 (dd, *J* = 6.2, 1.0 Hz, 2H), 7.58 (ddd, *J* = 9.6, 8.1, 4.4 Hz, 3H), 7.36 – 7.26 (m, 2H), 7.11 (dd, *J* = 10.6, 4.2 Hz, 1H), 6.01 (s, 1H), 4.61 (d, *J* = 16.9 Hz, 1H), 4.26 (d, *J* = 17.0 Hz, 1H).

**$^{13}$C NMR (91 MHz, MeOD)** δ 170.0, 168.9, 146.4, 139.4, 133.9, 132.3, 130.9, 129.9, 125.5, 124.7, 124.1, 121.3, 83.6, 43.5.

**HRMS (ESI)** [M+Na$^{+}$] calculated for $C_{16}H_{14}N_2NaO_3^{+}$: 305.0897. Found: 305.0899.

**2-(3-bromopropyl)-3-hydroxyisoindolin-1-one (27l)**




**27l**

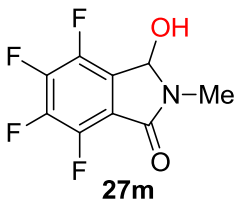
Following the general procedure, the product was obtained as a white solid (237 mg, 88%). (eluent: ethyl acetate/pentane: 2:1);

**$^{1}$H NMR (360 MHz, CDCl$_3$)** δ 7.81 (dd, *J* = 7.0, 1.1 Hz, 1H), 7.63 – 7.45 (m, 3H), 5.55 (s, 1H), 4.46 (ddd, *J* = 6.7, 4.7, 1.4 Hz, 1H), 4.22 (ddd, *J* = 7.4, 4.1, 2.0 Hz, 1H), 3.94 (td, *J* = 12.2, 2.1 Hz, 1H), 3.25 (td, *J* = 12.9, 4.0 Hz, 1H), 1.96 – 1.74 (m, 1H), 1.63 (dtd, *J* = 13.6, 3.6, 1.7 Hz, 1H).

**$^{13}$C NMR (90 MHz, CDCl$_3$)** δ 165.9, 141.2, 132.7, 131.9, 123.0, 123.6, 123.1, 85.1, 67.3, 37.8, 24.6.

**HRMS (ESI)** [M+Na$^{+}$] calculated for $C_{11}H_{12}BrNNaO_2^{+}$: 291.9944 and 293.9924. Found: 291.9949 and 293.9921.

**4,5,6,7-tetrafluoro-3-hydroxy-2-methylisoindolin-1-one (27m)**



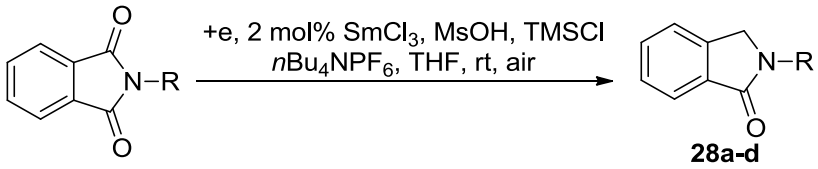

**27m**

Following the general procedure, the product was obtained as a white solid (233 mg, 99%). (eluent: ethyl acetate/pentane: 2:1);

**$^1$H NMR (360 MHz, MeOD)** δ 5.95 (s, 1H), 3.04 (s, 3H).

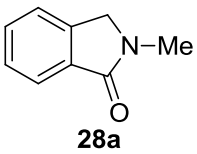
**HRMS (ESI)** [M+Na$^+$] calculated for $C_9H_5F_4NNaO_3^+$: 258.0149. Found: 258.0147.

## V. 5. 8. Characterization data of isoindolinones




**General procedure for the reduction of phthalimides into the isoindolinones:** Reactions were carried out in a three necked cell containing a magnetic stirring bar, samarium cathode (20 cm$^2$ area), glassy carbon anode (20 cm$^2$ area) and SCE as reference electrode. *n*$Bu_4NPF_6$ (156 mg, 0.4 mmol, 0.04 mol/L in THF) as the electrolyte, phthalimides (1.0 mmol) and $SmCl_3$ (5.0 mg, 0.02 mmol) were added in anhydrous THF (10 ml), TMSCl (272 mg, 2.5 mmol, 0.32 ml) and MsOH (480 mg, 5.0 mmol, 0.32 ml) were added dropwise with stirring, then electrolysis was performed at i = 50 mA during 10 hours. After the reaction was complete, the mixture was quenched by water (10 ml), extracted with ethyl acetate (2×20 mL). The combined oraganic layer was washed by 10% $Na_2S_2O_3$ (10 ml) and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel.

**2-methylisoindolin-1-one (28a)**



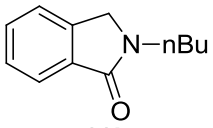

Following the general procedure, the product was obtained as a white solid (137 mg, 93%). (eluent: ethyl acetate/pentane: 2:1);

**$^1$H NMR (360 MHz, $CDCl_3$)** δ 7.86 (d, *J* = 7.4 Hz, 1H), 7.60 – 7.40 (m, 3H), 4.40 (s, 2H), 3.23 (s, 3H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 168. 7, 141.0, 132.9, 131.2, 128.0, 123.6, 122.6, 52.0, 29.5.

**HRMS (ESI)** [M+Na$^+$] calculated for $C_9H_9NNaO^+$: 170.0576. Found: 170.0577.

**2-butylisoindolin-1-one (28b)**




**28b**

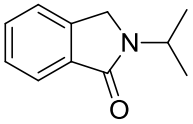
Following the general procedure, the product was obtained as a white solid (177 mg, 94%). (eluent: ethyl acetate/pentane: 2:1);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 7.92 – 7.78 (m, 6H), 7.58 – 7.40 (m, 18H), 4.39 (s, 13H), 3.63 (t, *J* = 7.3 Hz, 14H), 1.66 (dq, *J* = 12.7, 7.5 Hz, 16H), 1.39 (dq, *J* = 14.7, 7.3 Hz, 14H), 0.97 (t, *J* = 7.3 Hz, 20H).

**$^{13}$C NMR (90 MHz, $CDCl_3$)** δ 168.5, 141.1, 133.1, 131.1, 128.0, 123.2, 122.6, 49.9, 42.1, 30.5, 20.1, 13.8.

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{12}H_{15}NNaO^+$: 212.1046. Found: 212.1049.

**2-isopropylisoindolin-1-one (28c)**




**28c**

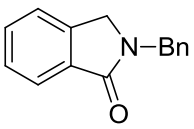
Following the general procedure, the product was obtained as a white solid (166 mg, 95%). (eluent: ethyl acetate/pentane: 2:1);

**$^{1}$H NMR (300 MHz, $CDCl_3$)** δ 7.88 – 7.77 (m, 1H), 7.56 – 7.36 (m, 3H), 4.67 (dt, *J* = 13.6, 6.8 Hz, 1H), 4.33 (s, 2H), 1.28 (d, *J* = 6.8 Hz, 6H).

**$^{13}$C NMR (75 MHz, $CDCl_3$)** δ 167.8, 141.2, 133.3, 131.0, 127.9, 123.5, 122.8, 45.0, 42.6, 20.8.

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{11}H_{13}NNaO^+$: 198.0889. Found: 198.0888.

**2-benzylisoindolin-1-one (28d)**




**28d**

Following the general procedure, the product was obtained as a white solid (194 mg, 87%). (eluent: ethyl acetate/pentane: 2:1);

**$^{1}$H NMR (360 MHz, $CDCl_3$)** δ 7.95 – 7.86 (m, 1H), 7.56 – 7.42 (m, 2H), 7.42 – 7.25 (m, 6H), 4.81 (s, 2H), 4.25 (s, 2H).

**$^{13}$C NMR (63 MHz, $CDCl_3$)** δ 168.5, 141.3, 137.1, 132.6, 131.4, 128.8, 128.2, 128.0, 127.7, 123.8, 122.8, 49.4, 46.4.

**HRMS (ESI)** [M+$Na^+$] calculated for $C_{15}H_{13}NNaO^+$: 246.0889. Found: 246.0887.