Electrochemical Enantioselective Nickel-Catalyzed Cross-Coupling of Aldimines with Aryl Iodides

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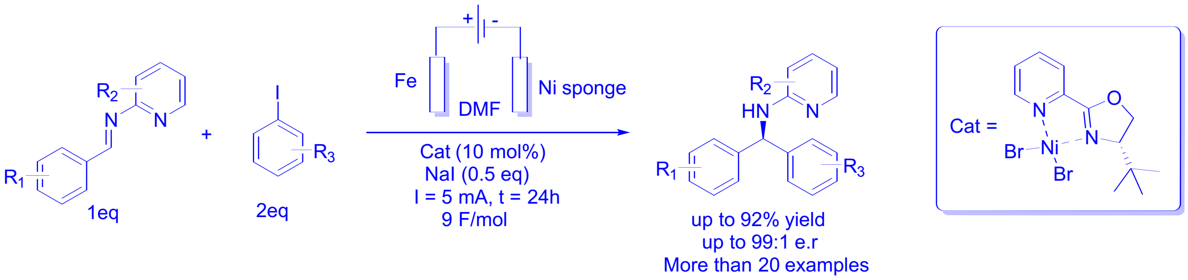
Benzylamines are key motifs in medicinal chemistry, modulating the physicochemical and pharmacological properties of bioactive molecules.[1] Conventional synthetic methods rely on the use of organometallic reagents or transition-metal-catalyzed (palladium, rhodium, and copper) processes, often requiring stoichiometric reducing agents.[2] Cobalt- or nickel-catalyzed reductive arylations have recently emerged as more sustainable alternatives.[3] For example, Zhou et al. developed a protocol using a chiral nickel complex and manganese as a co-reducing agent for the synthesis of chiral benzylamines.[3b] In 2022, Reisman's group described also a method using manganese as a co-reducing agent, as well as an electrochemical approach enabling the production of achiral benzylamines.[4] This strategy, which relies on the use of electrons as reducing agents, constitutes a sustainable approach, avoiding the use of stoichiometric metal reducing agents. However, the enantioselective synthesis of benzylamines via electrochemical processes remains largely unexplored.

In this context, we developed an enantioselective electrocatalytic coupling process of imines with halogenated derivatives, enabling the preparation of chiral benzylamines with good stereochemical control.



After optimizing the chemical and electrochemical parameters of the reaction, the electrochemical conditions developed enable the efficient synthesis of numerous highly enantioenriched benzylamines under mild conditions. This work ultimately opens up significant prospects for the development of more environmentally friendly synthetic methods, inline with sustainable development objectives.

References

[1] a) D. Ghislieri, N. J. Turner, *Top. Catal.* **2014**, *57*, 284-300 ; b) C. K. Prier, R. K. Zhang, A. R. Buller, S. Brinkmann-Chen, F. H. Arnold, *Nat. Chem.* **2017**, *9*, 629-634

[2] a) E. Le Gall, M. Troupel, J.-Y. Nédélec, *Tetrahedron* **2006,** *62,* 9953-9965 ; b) N. Tokunaga, Y. Otomaru, K. Okamoto, K. Ueyama, R. Shintani, T. Hayashi, *J. Am. Chem. Soc.* **2004**, *126*, 13584-13585 c) G.-N. Ma, T. Zhang, M. Shi, *Org. Lett.* **2009**, *11*, 875-878 ; d) C. Wu, X. Qin, A. M. P. Moeljadi, H. Hirao, J. S. Zhou, *Angew.Chem. Int.Ed.* **2019**, *131*, 2731-2735

[3] a) J. Xiao, M. Wang, X. Yin, S. Yang, P. Gu, X. Lv, Y. Zhao, Z. Shi, *Angew. Chem. Int. Ed.* **2023**, *62*, e202300743 ; b) L. Zhang, X. Wang, M. Pu, C. Chen, P. Yang, Y.-D. Wu, Y. R. Chi, J. S. Zhou, *J. Am. Chem. Soc.* **2023**, *145*, 8498-8509

[4] R. F. Turro, M. Brandstätter, S. E. Reisman, *Angew. Chem. Int. Ed.* **2022**, *61*, e202207597