

Electrochemical Generation of Ketyl Radicals and Their Applications

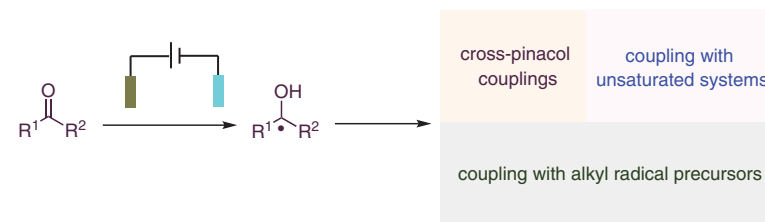
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Abstract Ketyl radicals display new reactivities beyond the intrinsic electrophilicity of carbonyls. Recent progress in organic electrosynthesis has fueled the generation and utilization of ketyl radicals under ‘greener’ conditions. This graphical review summarizes these electrochemical advancements into three major categories: cross-pinacol couplings, coupling of carbonyls with alkyl radical precursors, and coupling of carbonyls with unsaturated systems (alkenes, alkynes, cyanoarenes, and N-heterocycles).

Key words ketyl radicals, umpolung, electrosynthesis, electroreduction, carbonyl

Ketyl radicals have been widely used in modern organic synthesis to construct value-added alcohols from carbonyl compounds. In contrast to the intrinsic electrophilicity of carbonyls, the nucleophilic ketyl radicals display complementary reactivities with respect to the reaction

scope.¹ For this reason, the generation of ketyl radicals under mild conditions is of high synthetic value. Traditionally, the generation of ketyl radicals from carbonyl compounds has relied on the use of SmI₂ or active metals such as K, Sn, and Ti, but the requirement for stoichiometric quantities of metals or metal salts diminishes the synthetic utility of this approach. Recently, the rapid development of photoredox chemistry has stimulated a resurgence of interest in the chemistry of ketyl radicals since it represents a milder strategy for obtaining such radicals. However, due to the high reduction potential of carbonyls, the range of accessible photocatalysts that meet the redox properties that match with the corresponding carbonyls is limited. Organic electrosynthesis has emerged as a unique and irreplaceable tool for sustainable synthesis by employing electrons to circumvent the need for stoichiometric amounts of chemical redox agents.² Moreover, the direct electroreduction of carbonyls to the corresponding ketyl radicals obviates the use of expensive photocatalysts. As such, significant achievements toward the electrochemical generation of ketyl radicals have been made in the past decade. Since ketyl radicals are prone to homocoupling to afford pinacols, their employment in couplings with polarity-matched partners or other coupling partners in large molar excess are common strategies. In this graphical review, these electrochemical advancements are classified into three major categories: cross-pinacol couplings, coupling of carbonyls with alkyl radical precursors, and coupling of carbonyls with unsaturated systems (alkenes, alkynes, cyanoarenes, and heterocycles).

Biographical Sketches



Zhoumei Tan obtained her bachelor's degree from Nanyang Normal University in 2019. She is currently a

Ph.D. student at Beijing University of Technology under the guidance of Dr. Kun Xu. Her research interests focus

on alcohol transformations under electrophotochemical conditions.



Kun Xu completed his Ph.D. in 2014 via a collaborative program between the University of Science and Technology of China (USTC) and Rutgers University (RU), su-

pervised by Prof. Zhiyong Wang (USTC) and Prof. Xumu Zhang (RU). Currently, he is working at Beijing University of Technology as a professor of organic chemistry.

His research focuses on organic electrosynthesis and electrophotocatalysis.



Chengchu Zeng completed his Ph.D. training at the Institute of Chinese Academy of Sciences (ICCAS) with Prof. Zhi-tang Huang in 2001. He subsequently worked with Prof. J. Y. Becker as a post-doctoral researcher at

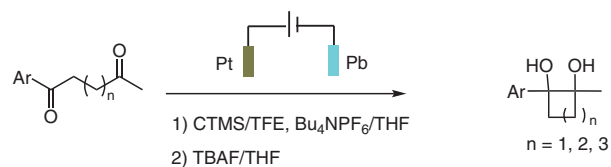
Ben-Gurion University in Israel. He began his independent career at Beijing University of Technology in August 2003 and was promoted to associate professor in 2003 and full professor in 2010. In 2011, he joined Prof.

R. D. Little's group at UC Santa Barbara (UCSB) as a visiting scholar. His research interests focus on the interface of organic chemistry and electrochemistry, and in particular on the electrosynthesis of fine chemicals.

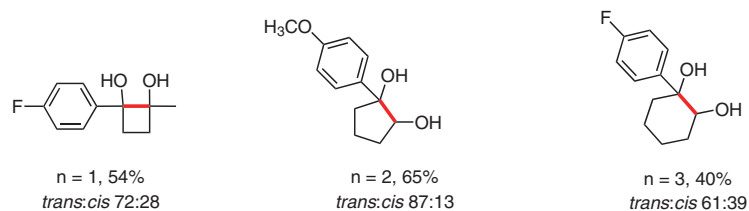
Notable Feature

- The electrogenerated ketyl radical undergoes further reduction to give a carbanion that attacks another carbonyl

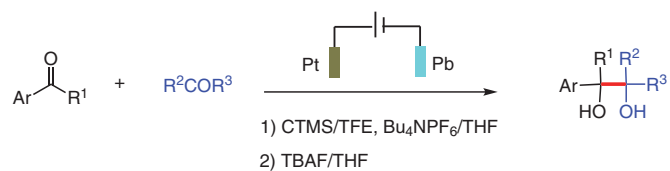
Intramolecular electroreductive cross-pinacol coupling



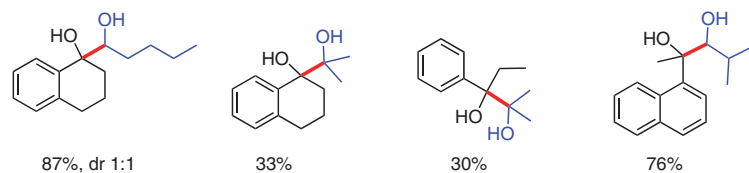
Selected scope



Intermolecular electroreductive cross-pinacol coupling of aromatic ketones with aliphatic aldehydes and ketones



Selected scope

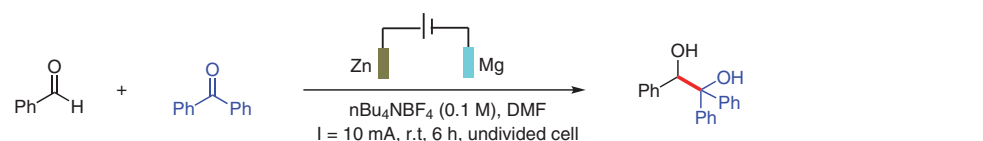


(3a) Kise, N. *Tetrahedron* **2007**, *63*, 5415.

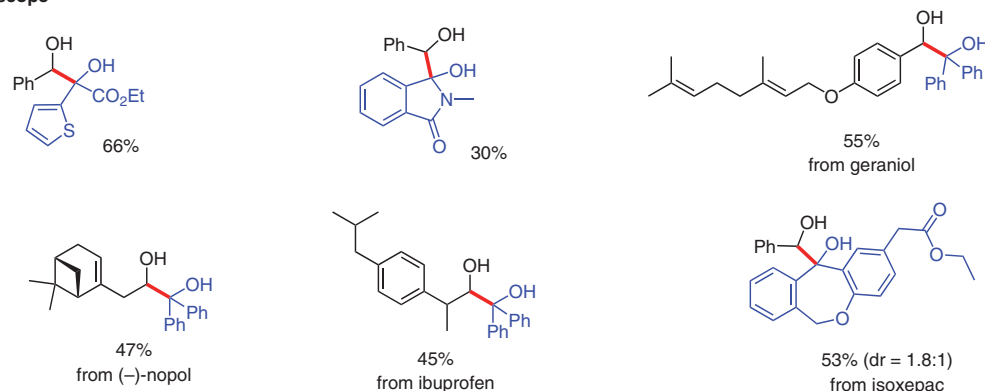
Notable Features

- Excellent functional group tolerance
- No external activating reagents

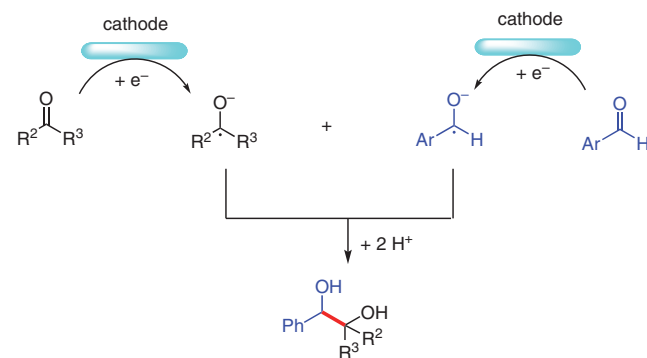
Intermolecular cross-pinacol couplings between aldehydes and ketones



Selected scope



Reaction mechanism:



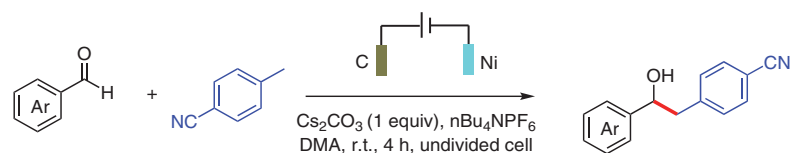
(3b) Zhang, B. *Green Chem.* **2022**, *24*, 8386.

Figure 1 Electrochemical cross-pinacol coupling^{3a,b}

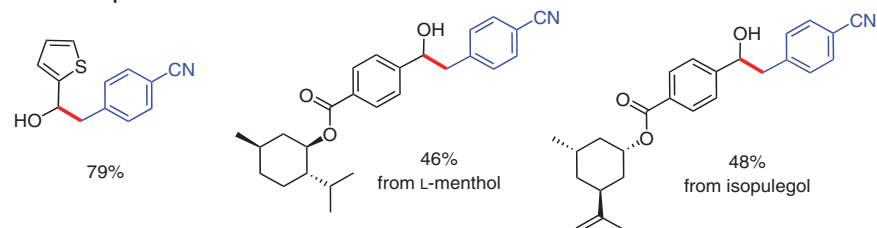
Notable Features

- Polarity-matched radical/radical cross-coupling
- The use of electron-deficient methylenes for radical coupling

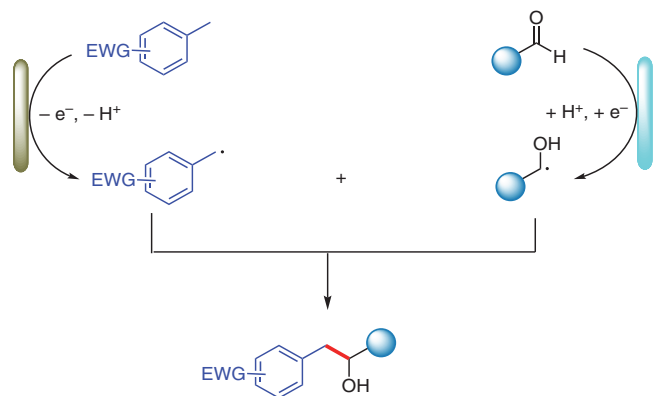
Radical cross-coupling between aldehydes and electron-deficient methylenes



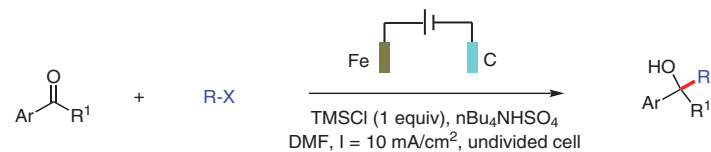
Selected scope



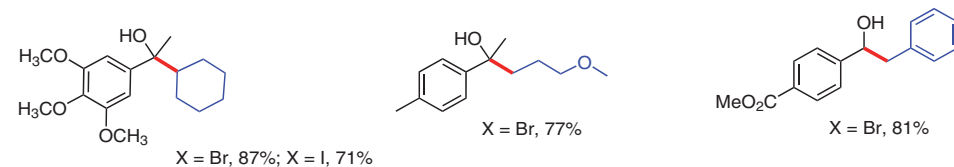
Reaction mechanism:

(4a) Xu, K. and Zeng, C.-C. *CCS Chem.* **2023**, *5*, 1973.

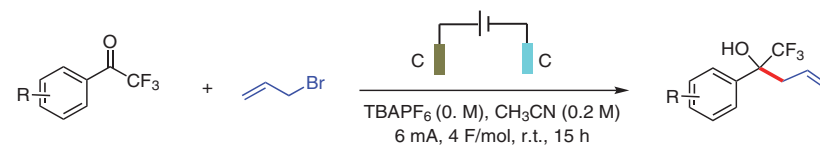
Electrocoupling between ketones and haloalkanes



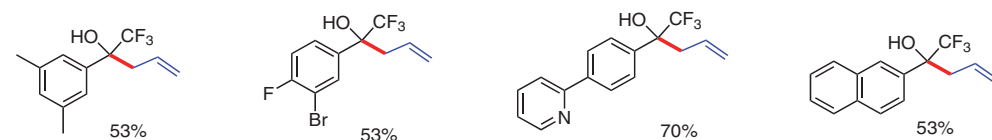
Selected scope

(4b) Huang, Y.-B. *Org. Lett.* **2022**, *24*, 9342.

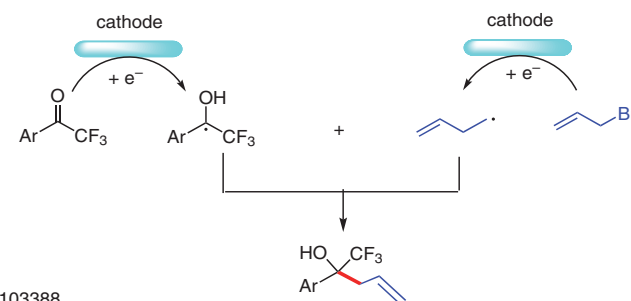
Electrocoupling between ketones and allyl bromide



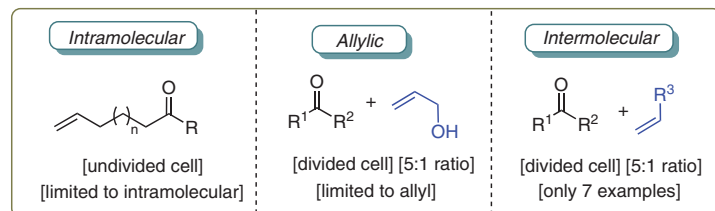
Selected scope



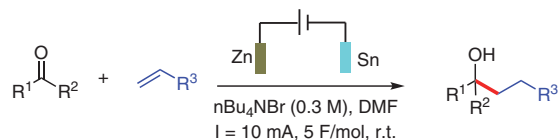
Reaction mechanism:

(4c) Cho, E. J. *iScience* **2021**, *24*, 103388.Figure 2 Electrochemical coupling of carbonyls with alkyl radical precursors^{4a-c}

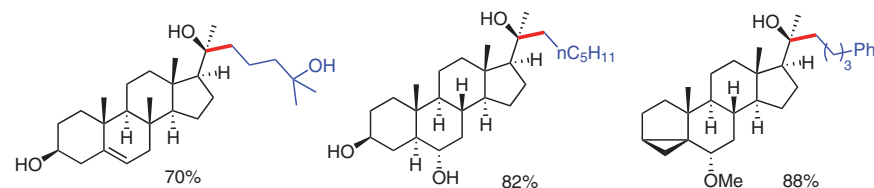
Seminal studies:

(5a) Mitani, M. *J. Am. Chem. Soc.* **1971**, *93*, 5284.(5b) Mitani, M. *J. Am. Chem. Soc.* **1978**, *100*, 545.(5c) Yamaguchi, Y. *J. Org. Chem.* **1989**, *54*, 6001.

Electroreductive olefin-ketone coupling



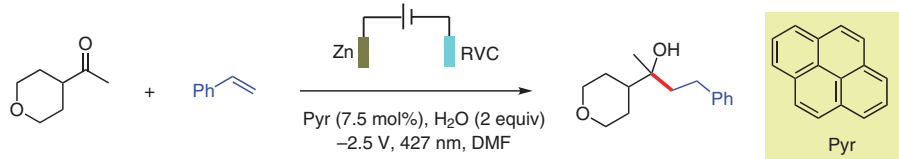
Selected scope

(5d) Baran, P. S. *J. Am. Chem. Soc.* **2020**, *142*, 20979.

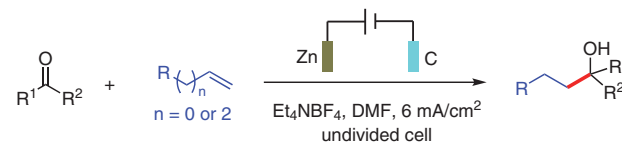
Notable Features

- Pyrene (Pyr) possesses a strong reducing ability upon electroreduction followed by light excitation

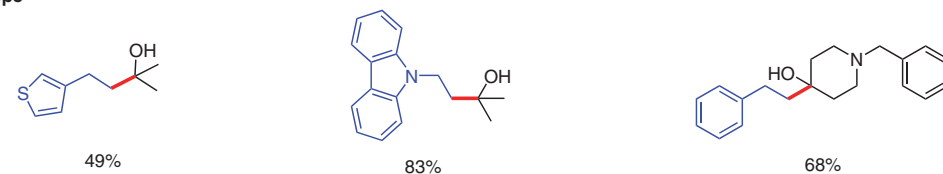
Electrophotochemical olefin-ketone coupling

(5e) Wickens, Z. K. *J. Am. Chem. Soc.* **2023**, *145*, 20169.

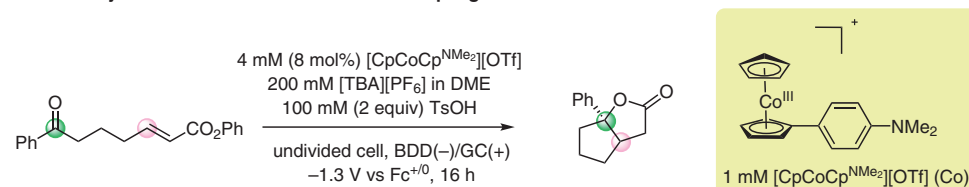
Electroreductive olefin-ketone coupling in the absence of a sacrificial anode



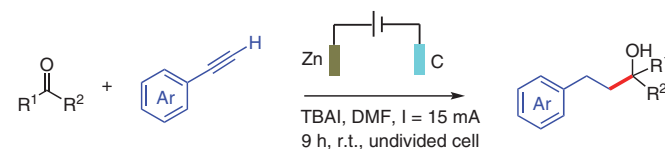
Selected scope

(5f) Huang, Y.-B. *Org. Lett.* **2022**, *24*, 1412.

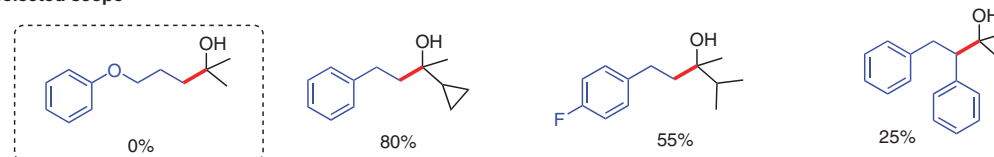
Cobalt-electrocatalyzed intramolecular olefin-ketone coupling

(5g) Peters, J. C. *Inorg. Chem.* **2022**, *61*, 6672.

Electroreductive alkyne-ketone coupling



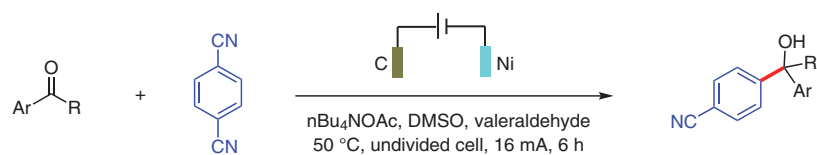
Selected scope

(5h) Satyanarayana, G. *Chem. Commun.* **2023**, *59*, 2915.Figure 3 Electrochemical coupling of ketones with alkenes and alkynes^{5a-h}

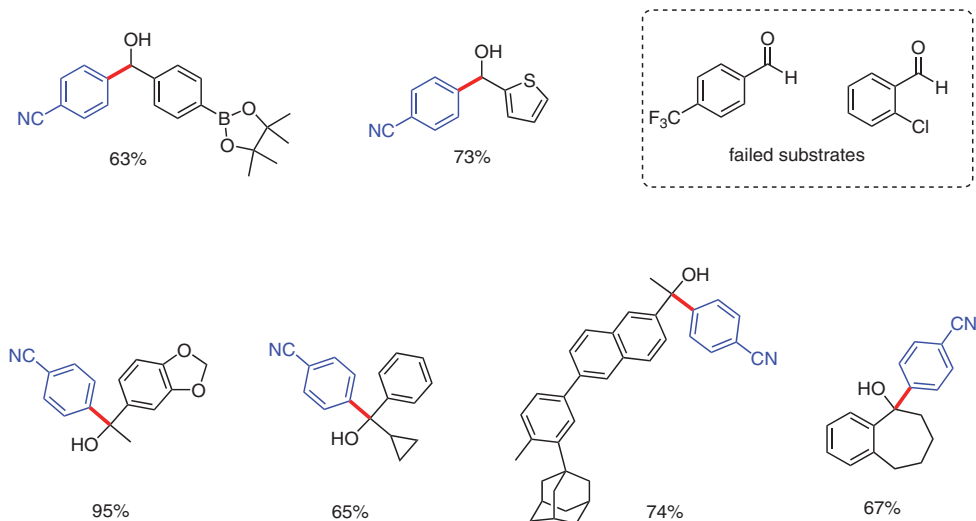
Notable Features

- The first example of electro-coupling of ketones with cyanoarenes
- Excellent functional group tolerance

Electrochemical coupling of aldehydes/ketones with cyanoarenes

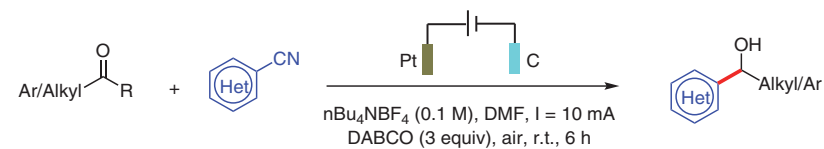


Selected scope

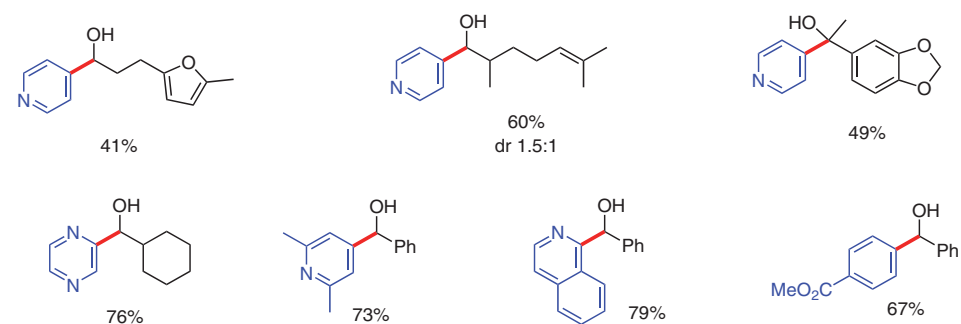


(6a) Zhang, S., Xu, K. and Findlater, M. *Angew. Chem. Int. Ed.* **2021**, *60*, 7275.

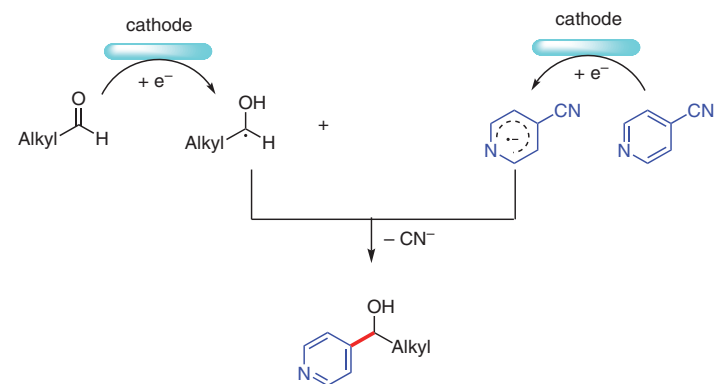
Electrochemical coupling of aldehydes with cyanoarenes



Selected scope



Reaction mechanism:



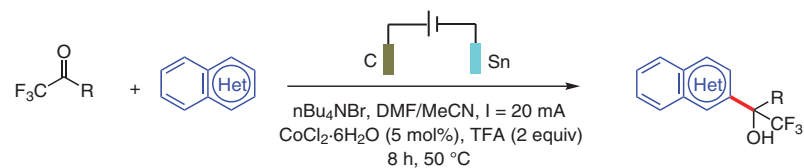
(6b) Xia, W.-J. *Org. Lett.* **2021**, *23*, 3472.

Figure 4 Electrochemical coupling of carbonyls with cyanoarenes^{6a,b}

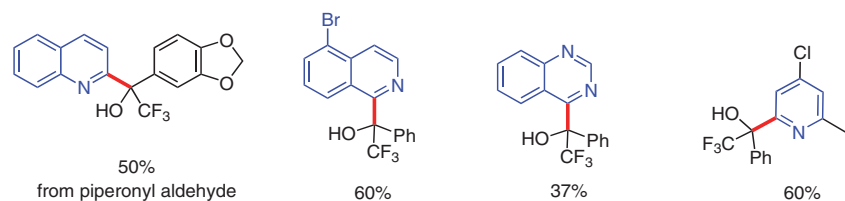
Notable Features

- The synergism of cobalt catalysis and bromide catalysis
- The first example of electrocoupling of N-heteroarenes with trifluoromethyl ketones

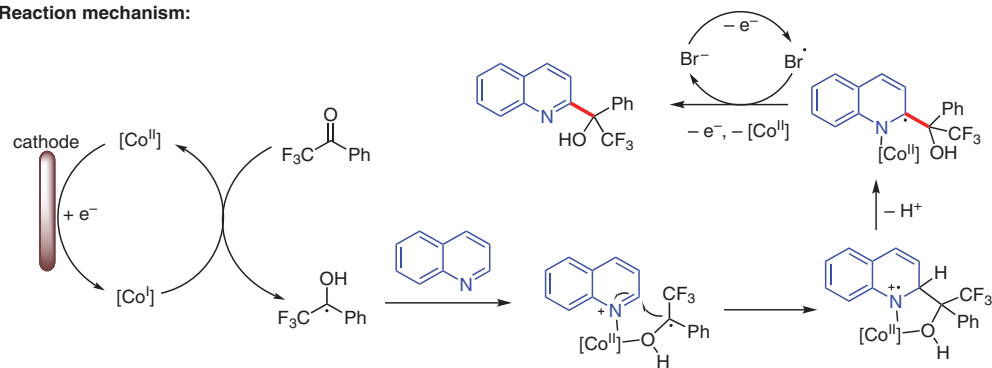
Cobalt-electrocatalytic coupling of N-heteroarenes with trifluoromethyl ketones



Selected scope

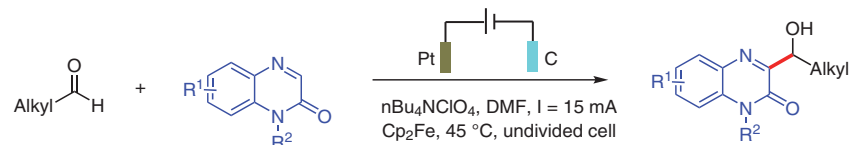


Reaction mechanism:

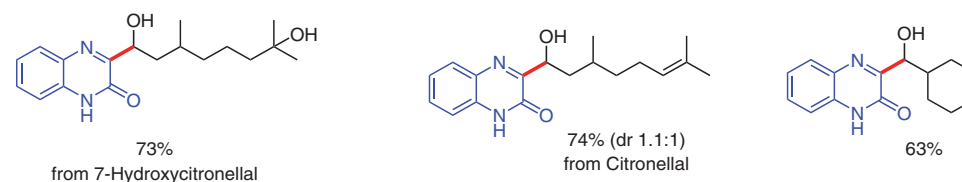


(7a) Huang, S.-L. *Chem. Sci.* **2023**, *14*, 143. Further reading: (7b) Xu, K. *Chin. J. Org. Chem.* **2023**, *43*, 789.

Electrocoupling of N-heteroarenes with aldehydes



Selected scope

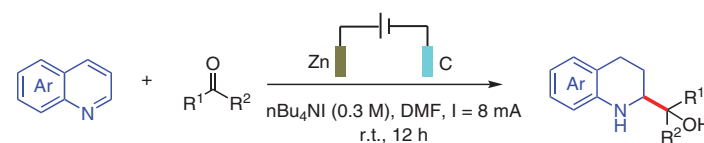


(7c) Tang, H.-T. *Org. Chem. Front.* **2022**, *9*, 5955.

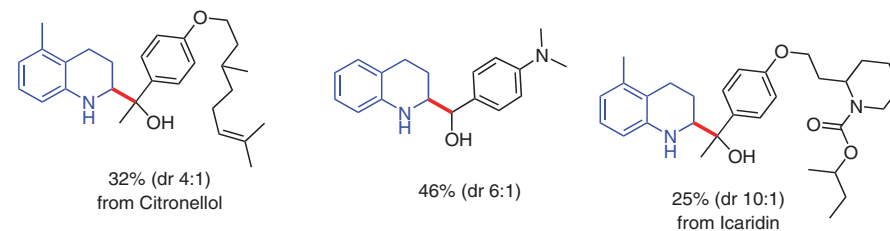
Notable Features

- The synergism of electroreduction and Lewis acid activation
- The facile synthesis of vicinal amino alcohols

Electroreductive cross-coupling of N-heteroarenes and carbonyls



Selected scope



(7d) Zhang, M. *J. Am. Chem. Soc.* **2023**, *145*, 10967.

Figure 5 Electrochemical coupling of carbonyls with N-heterocycles^{7a-d}

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

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- (6) (a) Zhang, S.; Li, L.-J.; Li, J.-J.; Shi, J.-X.; Xu, K.; Gao, W.-C.; Zong, L.-Y.; Li, G.-G.; Findlater, M. *Angew. Chem. Int. Ed.* **2021**, *60*, 7275. (b) Zhang, X.; Yang, C.; Gao, H.; Wang, L.; Guo, L.; Xia, W.-J. *Org. Lett.* **2021**, *23*, 3472.
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