A Journal of the Gesellschaft Deutscher Chemiker
Angewandte Chemie
International Edition
www.angewandte.org

Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202006016

Link to VoR: https://doi.org/10.1002/anie.202006016

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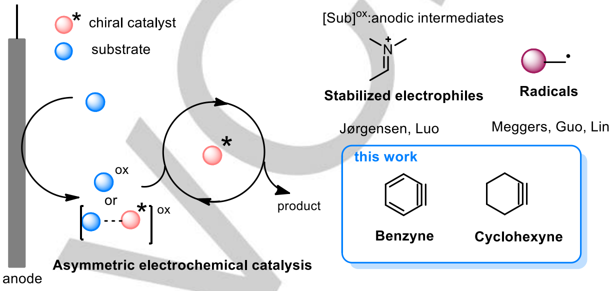
Catalytic Asymmetric Electrochemical α-Arylation of Cyclic β-Ketocarbonyls with Anodic Benzyne Intermediates

Longji Li,[b,+] Yao Li,[a,+] Niankai Fu,[b] Long Zhang[a] and Sanzhong Luo[a, b]*

Dedicated to Professor Youqi Tang on the occasion of his 100th Birthday

Abstract: Asymmetric catalysis with benzyne remains elusive due to the highly fleeting and non-polar nature of benzyne intermediates. We reported herein an electrochemical approach for the oxidative generation of benzynes and cyclohexyne and its successful merging with chiral primary aminocatalysis, formulating the first catalytic asymmetric enamine-benzyne (cyclohexyne) coupling reaction. Cobalt acetate was identified to stabilize the *in-situ* generated arynes and facilitate its coupling with enamine. This catalytic enamine-benzyne protocol provides a concise method for the construction of diverse α-aryl or cyclohexenyl quaternary carbon stereogenic centers with good stereoselectivities.

The first asymmetric electrochemical catalysis was reported in 1966, [1] almost the same time when modern asymmetric catalysis was born.[2] However, the development in this field has long been overshadowed by the tremendous successes of its thermal counterparts as well as the recent breakthroughs in photochemical reactions.[3] The main challenges may at least come from the preconceptions that stereocontrol may be disfavored in a highly ionic media that is essential in electrochemical reactions. In addition, electrode interfacial e/mass transfer, distinctive from the typical solution phase asymmetric catalysis, is usually obscure in asymmetric electrochemical catalysis, which may hinder its rational development.[4] Echoing the pursuit of sustainable transformations, there recently appears a renaissance of asymmetric electrochemical catalysis by merging asymmetric catalysis and electrochemical process (Scheme 1).[5] Anodic oxidation could be employed to *in-situ* generate stabilized electrophilic species such as imine or iminium ion intermediates in asymmetric aminocatalytic process by the groups of Jørgensen[6] and Luo[7], respectively. Recently, the groups of Meggers[8], Guo[9] and Lin[10] have also developed asymmetric catalysis with anodically generated free radical species. Despite of these advances, the potentials of asymmetric electrochemical catalysis remains largely unexplored. Herein, we report an anodic generation of benzyne or cyclohexyne intermediates and its participation in an asymmetric arylation reaction by chiral primary amine catalysis.



Scheme 1. Reactive Intermediates in asymmetric electrochemical catalysis

As a highly fleeting intermediate, benzyne is seldom utilized in stereogenic reactions as the quench of this neutral and highly reactive species occur spontaneously, in most cases exceeding any noticeable external control. In addition, the benzyne trapping is always accompanied by undesired bond formation and fragmentation, adding more complexity in stereocontrolling.[11] Hence, enantioselective reactions with benzynes are extremely rare, to achieve asymmetric catalysis with a benzyne intermediate remains elusive and has not been reported so far. Recently, Garg and Houk reported an enantioseletive coupling of preformed chiral enamine and benzynes (Scheme 2, **I**).[12] Building on this pioneering study, we tried to develop a catalytic enamine arylation of β-ketoesters with benzynes on the basis of our chiral primary amine catalyst.[13] It should be noted a general catalytic asymmetric arylation of β-ketoesters has not been achieved. The only catalytic version with high enantioselectivity was reported by Ma in the coupling of 2-methylacetoacetate with 2-iodotrifluoroacetanilides (Scheme 2, **I**).[14]

We initially examined the coupling of a cyclic ketoester **2a** with the typical Kobayashi benzyne precursor (2-(Trimethylsilyl)phenyl triflate) in the presence of our chiral primary amine catalyst. Though the reaction gave a promising 80% *ee*, further efforts in improving the productivity were in vain and the yield never exceeded 10% (Scheme 2, **II**). In this context, we pursued different benzyne precursors and 1-aminobenzotriazole, first developed by Campbell and Rees, appeared as a promising alternative requiring an oxidative condition for benzyne generation.[15] The common applied protocol utilized $Pb(OAc)_4$ as the oxidant, which is toxic and undesirable in terms of reaction-economy and sustainability and also causes issues on compatibility.[16] We then explore an electrochemical approach to address these issues, and such an electrochemical aryne generation, to the best of our knowledge, was unknown.

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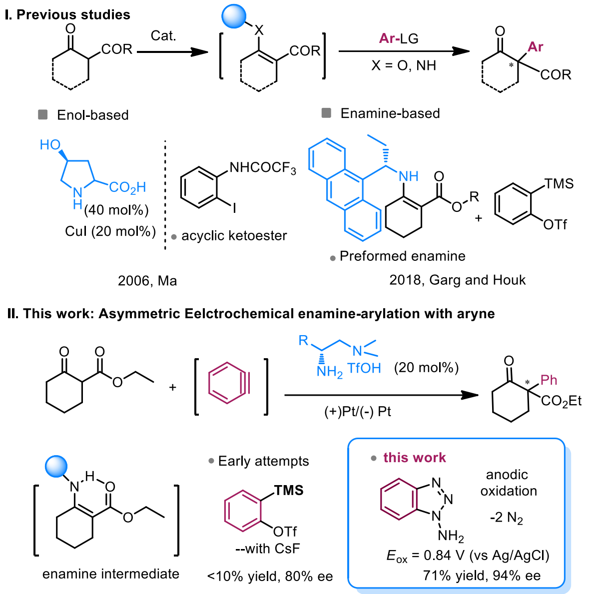
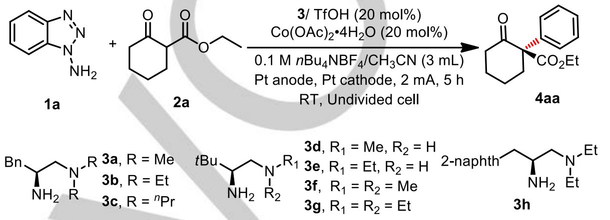


Scheme 2. Asymmetric electrochemical arylation of cyclic β-ketocarbonyls

We commenced the studies on catalytic asymmetric arylation by using 1-aminobenzotriazole (**1a**) with ethyl 2-oxocyclohexanecarboxylate (**2a**) as model substrates. Oxidative compatibility of the primary amine catalyst and enamine intermediate was the primary concern. By cyclic voltammetry (CV) analysis, it was found that 1-aminobenzotriazole **1a** (E_{ox} = 0.84 V) was much easier to be oxidized than the primary amine catalyst (e.g. **3a**, E_{ox} = 1.54 V) and the corresponding enamine intermediate (E_{ox} = 1.15 V). Beyond the issues on stereocontrol, another challenge is the selective capture of the benzyne by the catalytic enamine intermediate in preference to other reactive species such as aminocatalyst itself and uncontrolled enol species. Bearing these issues in mind, we first screened different aminocatalysts focusing our efforts exclusively in a simple electrochemical system consisting $Co(OAc)_2\cdot 4H_2O$ (20 mol%) as the additive and the platinum plates as the electrodes in an undivided cell. Gratifyingly, in the catalysis with our chiral primary amine catalyst **3a**/TfOH, the desired α-arylation product was obtained in 71% yield and 94% *ee* under the optimized conditions (Table 1, entry 1).

Critical to the successful coupling were the identification of primary amine catalyts **3a** as well as the use of $Co(OAc)_2\cdot 4H_2O$ as an additive. Other *L*-tert Leucine derived primary amine catalysts **3b**~**3c** and *L*-phenylalanine derived **3d**~**3g** showed inferior results in terms of both yield and enantioselectivity (Table 1, entries 2-8) for the model reaction. When the reaction was conducted in the absence of amine catalyst (**3a**/TfOH), no desired product was detected (Table 1, entry 9), indicating the essential role of aminocatalysis in facilitating the desired benzyne trapping. Among different metal additive screened, $Co(OAc)_2\cdot 4H_2O$ was found to significantly improve the productivity, and the reaction gave only 28% yield with 88% *ee* in its absence (Table 1, entry 13). Other metals such as $Zn(OAc)_2\cdot 2H_2O$ or $Ni(OAc)_2\cdot 4H_2O$ or other cobalt salts showed no improvement on yields (Table 1, entries 10-12). Mechansitically, the role of cobalt acetate may lie in its capability in binding the triple bond, resulting in the stabilization of benzyne intermediate to ensure a high propensity for enamine trapping (*vida infro* for detailed discussions). During optimization, it was verified that the use of MeCN as media was important for reaction efficiency as the use of either DCM (Table 1, entry 14) or MeOH (Table 1, entry 15) resulted in lower yields. Other anode material such as graphite (Table 1, entry 16) were found to be less efficient

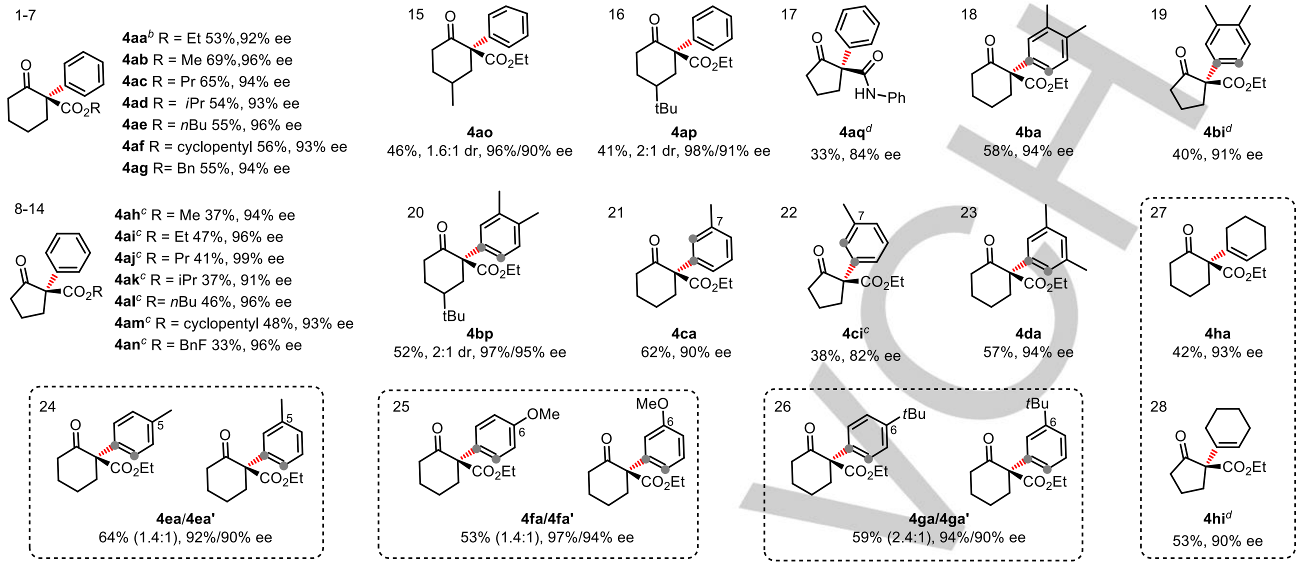
Table 1. Screening and optimization[a]



Entry	Variation from standard conditions	Yield [%][b]	*ee* [%][d]
1	None	71(67[c])	94
2	**3b**	36	78
3	**3c**	27	63
4	**3d**	14	74
5	**3e**	26	67
6	**3f**	41	90
7	**3g**	37	82
8	**3h**	47	84
9	No **3**	N. D	---
10	$Zn(OAc)_2\cdot 2H_2O$	40	89
11	$Ni(OAc)_2\cdot 4H_2O$	35	90
12	Other cobalt salts, e.g. $CoCl_2$, $CpCo(CO)_2$, Cp_2Co	trace-23	---
13	No additive	28	88
14	CH_2Cl_2	25	92
15	CH_3OH	trace	---
16	C (+) |Pt (-)	30	89
17	3 mA	57	93
18	1 mA	41	92

[a] General conditions: **1a** (0.20 mmol), **2a** (0.10 mmol), **3** (20 mol%) in a 0.1 M nBu_4NBF_4 solvent mixture (3.0 mL) at room temperature. [b]

Determined by GC-MS analysis with an internal standard. [c] Isolated by flash chromatography. [d] Determined by HPLC.



Scheme 3. Substrate scopes. Reaction conditions: [a] **1** (0.20 mmol), **2a** (0.10 mmol), **3a** (20 mol%), nBu$_4$NBF$_4$ (0.1 M), MeCN (3.0 mL), constant current = 2 mA, reaction time 4−5 h (see SI). [b] **1a** (0.80 mmol), **2a** (0.40 mmol), **3a** (20 mol%) in a 0.1 M nBu$_4$NBF$_4$ solvent mixture (12.0 mL) at room temperature was electrolyzed at constant current of 8 mA. [c] With **3f** as the amine catalyst and m-NO$_2$PhCOOH (50 mol %) as an additive. [d] With **3f** as the amine catalyst and m-NO$_2$PhCOOH (20 mol %) as an additive. Note: Grey dot denotes triazole carbons; the number indicates the position of substituents in the parent N-aminobenzotriazole (entries 21, 22 and 24-26).

than platinum. Further optimization showed a current of 2 mA was optimal, increasing the current to 3 mA or decreasing to 1 mA all led to reduction of productivity (Table 1, entries 17 and 18).

With the optimized conditions in hand, we then explored the the scopes of substrates for this asymmetric electrochemical catalysis. Different ester moieties in the cyclohexane β-ketoesters including methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, cyclopentyl and benzyl ester groups were tolerated to give the desired arylation adduct in good yields (up to 69%) with high enantioselectivity (93~96% *ee*) (Scheme 3, entries 2-7). Prochiral 4-substituted cyclohexanone could also be applied to furnish the expected desymmetric arylation adducts (Scheme 3, entries 15 and 16). Though the diastereoselectivity was low in these cases, both diasteroisomers were obtained with high enantioselectivity, indicating the arylation step is under strict catalytic control. The reaction worked well with cyclopentanone and in these cases chiral primary amine catalyst **3f** was found to give better enantioselectivity (Scheme 3, entries 8-14). A free ketoamide could also be accommodated to afford α-arylated adduct **4ar** (33% yield, 84% *ee*, entry 17). Acyclic β-ketoesters have also been attempted with unfortunately no desired adducts being observed.[17]

Subsequently, the effect of substituents on different position of 1-aminobenzotriazole was investigated. Symmetric dimethyl substituted benzyne such as *ortho*-dimethyl- (Scheme 3, entries 18-20) or *meta*-dimethyl- substituted (entry 23) ones gave the expected arylated adducts in good yields and high enantioselectivities. In the latter, a single regioisomer **4da** was isolated. For mono-substituted benzyne, the *ortho*-methyl substitution led to regioselectively single adducts with high enantioselectivity (Scheme 3, entries 21-22). On the other hand, two regioisomers were observed for *meta*-methyl substituted benzyne (or aryne) (Scheme 3, entry 24). Both regio-isomers were obtained with high enantioselectivity. Similar effect was also observed when replacing methyl group with methoxyl and t-butyl group (Scheme 3, entries 25 and 26). In the latter case, the bulkiness of t-butyl moiety enhanced the bias toward *para*-isomer **4ga**. The present electrochemical reaction could also be conducted on a 0.4 mmol scale, affording 53% yield and 92% ee (Scheme 3, entry 1).

We next challenged the current catalysis with non-aromatic, strained cyclic alkynes. For this end, a triazole precursor for cyclohexyne was synthesized[18] and tested in the reaction. Delightfully, the reaction worked smoothly to give cyclohexene products in good stereoselectivities (Scheme 3, entries 27-28).

To probe the *in-stiu* generated benzyne or cyclohexyne, we have added typical quenching reactant to the catalytic reactions. When two equivalents of tetraphenylcyclopentadienone was added, the corresponding quenching adducts (**4ar** and **4hr**) were obtained in 52% and 41% yield, respectively (Scheme 4, a), and only trace amount of enamine coupling products were detected. These results verified the electrochemical generation of reactive benzyne or cyclohexyne intermediates.

Experiments were conducted to reveal the role of the cobalt salts. By CV analysis, no obvious reaction current was observed with cobalt acetate in the current asymmetric electrochemical catalysis (Scheme S7, SI). The redox potential of Co(OAc)$_2$·4H$_2$O was determined to be E$_{ox}$ = 0.83 V, which is comparable to that of 1-aminobenzotriazole **1a** (E$_{ox}$ = 0.84 V). These observations suggest that cobalt acetate is unlikely a redox mediator for anodic generation of benzyne. The effect of cobalt acetate could be further verified in benzyne quenching with other reagents such as furan, cyclopentadienone and diphenyl diselenide. In the absence

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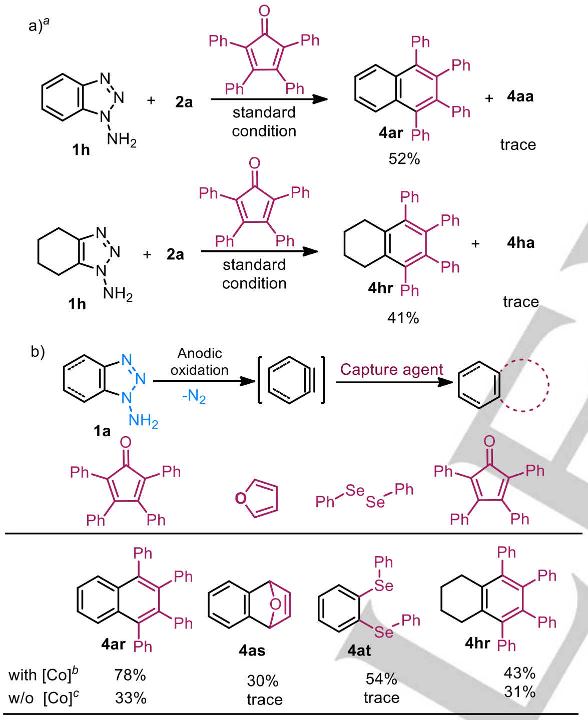
of cobalt acetate, only trace quenching adducts were detected under anodic conditions (Scheme 4, b) and the triazole precursor **1a** was completely consumed with unidentified brown tar deposited on anode. In contrast, the addition of cobalt acetate significantly facilitates the expected benzyne quenching with much less anode deposition. Provided the known catalytic capability of cobalt in activating and transforming alkynes[19] we proposed that the cobalt may bind with the triple bond of benzyne, hence stabilize this transient species and enhance its propensity in coupling with the enamine intermediate. Our density functional theory (DFT) calculation indicated that coordination with cobalt acetate could stabilizing benzyne by 18.6 kcal/mol (Figure 1 and Figure S8 for details).[19] In comparison, nickel acetate shows only 5.5 kcal/mol stabilization while zinc acetate is destabilizing by 1.1 kcal/mol. Considering that cobalt acetate only showed marginal effect on enantioselectivity (Table 1, entry 1 *vs* 13, 94% *ee vs* 88% *ee*), the effect of complexation on the stereocontrol in enamine trapping should be minor, if not neglectable. In this instance, the benzyne-Co complex may be regarded as reservoir of free benzyne for enamine trapping under anodic conditions.



Scheme 4. Benzyne or cyclohexyne-capture experiments.

DFT calculations were performed to elucidate the origins of enantioselectivity of α-arylation.[20] The calculated energies difference between **TS-R** and **TS-S**, 1.9 kcal/mol, is in good accordance with the experimental value of 2.1 kcal/mol (94% *ee*) favoring *R*-selectivity. The distortion/interaction model [21] could be invoked to explain the origin of the energy difference between **TS-R** and **TS-S**. Energy decomposition analysis showed that the disfavored **TS-S** has higher distortion energy in enamine (ΔE_{dist}(enamines) = 9.1 kcal/mol) than that in **TS-R** (ΔE_{dist}(enamines) = 6.1 kcal/mol). In both transition states, an intramolecular H-bonding between the enamine N-H and carbonyl was noted to restrict the conformational flexibility and distortion mainly came from the catalyst part (Figure 2).

In **TS-R**, the dihedral angle of the catalyst skeleton (relative to the planar enamine) as highlighted in green is -62.0°, slightly deviated from that of the starting enamine intermediate (-66.0°). In comparison, the disfavored **TS-S** has a dihedral angle of -84.5°, a large conformation distortion in order to minimize the steric effect for benzyne attacking. The preference of enamine *Re*-facial benzyne attack can also be accounted by considering the concerted C-C formation and H-transfer with either enamine N-H or protonated tertiary amine N-H, which is clearly favored in the *Re*-facial sphere.[22]

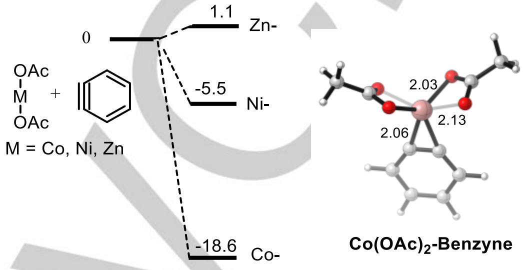


Figure 1. Calculated geometries and binding free energies of benzyne and acetate complex at B3LYP-D3BJ/Def2-TZVPP-SMD//B3LYP/6-31g(d)+SDD(M) (M = Co, Ni, Zn) level. Energies are given in kcal/mol. Interatomic distances are denoted in Å.

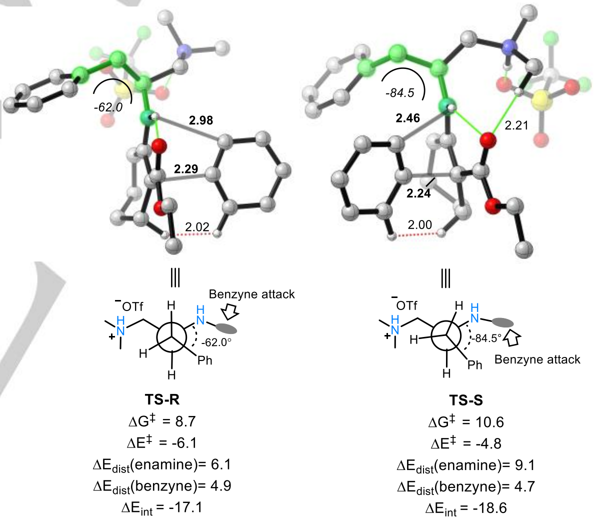


Figure 2. Calculated transition state structures for addition of benzyne and chiral enamine at B3LYP-D3BJ/Def2-TZVPP-SMD//B3LYP/6-31g(d) level. Energies are given in kcal/mol. Interatomic distances are denoted in Å. Noncritical hydrogen atoms are omitted for clarity.

In summary, we have developed an electrochemical method for the generation of benzyne and cyclohexyne. Catalytic asymmetric α-arylation or cyclohexenylation of cyclic β-ketocarbonyls with benzyne or cyclohexyne was realized by merging the anodic benzyne generation and chiral primary amine catalysis. The use of cobalt acetate as an additive was found to stabilize the benzyne intermediate and hence facilitate its coupling with chiral enamine intermediate. The enamine-aryne coupling could be applied to cyclic β-ketocarbonyls, such as five or six-membered ring β-keto esters and five-membered ring β-ketoamide, allowing the rapid construction of diverse optically active α-aryl or cyclohexenyl derivatives with good stereoselectivities.

Acknowledgements

We thank the Natural Science Foundation of China (21861132003, 21672217and 21521002) and Tsinghua University Initiative Scientific Research Program for financial support. S.L. is supported by the National Program of Top-notch Young Professionals.

Keywords: chiral primary amine • electrochemical catalysis• asymmetric arylation • benzyne • enamine

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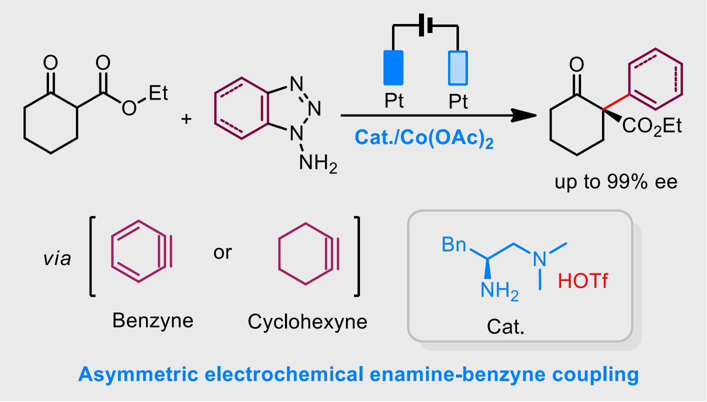
[22] We also tried to located the transition structures involving H-transfer with protonated tertiary amine N-H (without counterion), but no transition state could be identified for the major enantiomer and the reaction involving this process seems barrierless.

10.1002/anie.202006016

COMMUNICATION



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