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Communication

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Copper-Catalyzed Electrochemical Selective B-H Oxygenation of *o*-Carboranes at Room Temperature

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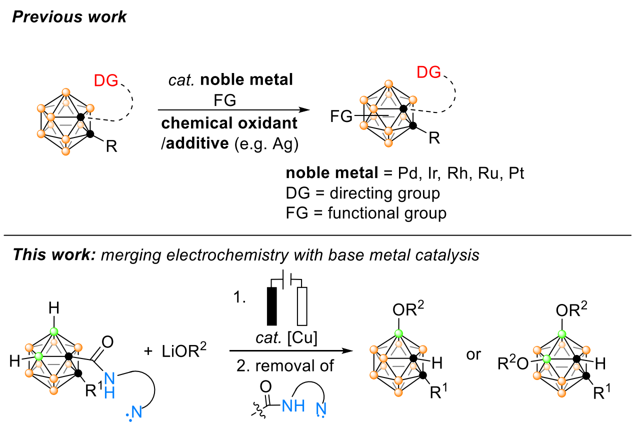
ABSTRACT: Copper-catalyzed electrochemical selective cage B-H oxygenation of *o*-carboranes has been achieved for the first time. Under constant electric current (4.0 mA) at room temperature, copper-catalyzed cross-coupling of carboranyl amides with lithium phenolates results in the formation of B(4,5)-diphenolated-*o*-carboranes via direct B-H activation, whereas the use of lithium *tert*-butoxide affords B(4)-monooxygenated products. This reaction does not require any additional chemical oxidants and generates H_2 and lithium salt as by-products. The control experiments indicate that a high valent Cu(III) species is likely involved in the reaction process.

Carboranes, polyhedral boron-carbon molecular clusters, possess unique properties including icosahedron geometry, three-dimensional aromaticity conjugated by σ-bonds, and inherent robustness.[1] These endowments enable carboranes as valuable building blocks for applications ranging from functional materials to pharmaceuticals.[2] Moreover, recent research indicates that the functionalization of bioactive molecules with carboranes will bring in strengthened potencies and new properties.[3] However, the progress of this research realm is encumbered by the shortage of efficient synthetic methods for carborane-functionalized molecules. For example, although phenol and its derivatives exist extensively in pharmaceutical drugs, the syntheses of *o*-carborane-functionalized phenol derivatives remain challenging, because of alcohol-induced deboronation of *o*-carboranes under basic conditions.[4] Attributing to the recent development in transition metal catalyzed cage B-H activation, vertex-specific functionalization of carboranes has been realized at different BH vertices.[5] In spite of this, most of the established protocols require noble transition metal catalysts[6] and an excess amount of chemical oxidants (e.g. silver salts),[7] which compromises the atom-economy and generality. In this connection, the exploration of synthetic methodologies with great consideration of atom-economy, sustainability and environmentally friendliness is eagerly desired for the functionalization of carboranes.

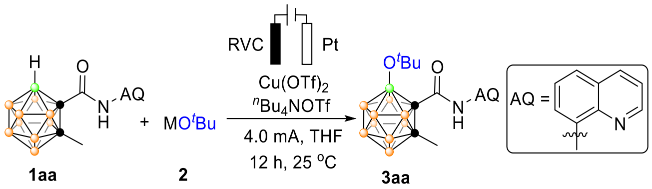
The past several years have witnessed a renaissance of electrochemistry in organic synthesis.[8] Due to the merits of stability, storability and readily availability, electricity is an important alternative form of energy to facilitate chemical transformations. Furthermore, in comparison with thermal energy and solar energy, electricity can serve as infinite electron pool and electron hole, and thus enable redox reactions without any external oxidants or reductants. Taking these points into consideration and on the basis of our previous study on Cu-promoted cage B-H activation of carboranes,[9] we initiated a proof-of-principle study using a combination of base metal catalysis and electrochemistry[10,11] for the functionalization of carboranes. We disclose herein the first example of copper-catalyzed electrochemical regioselective cage B-H oxygenation of *o*-carboranes with alkoxide or phenoxide (Scheme 1). The key features of current strategy include (a) replacement of chemical oxidants (e.g. silver salts) with electricity, (b) employment of earth abundant copper salt as catalyst, (c) room-temperature B-H oxygenation, and (d) use of removable directing group.

Scheme 1. Transition Metal Catalyzed B-H Functionalization of *o*-Carborane



To evaluate the feasibility of the strategy of electrochemical copper catalysis, carboranyl amide **1aa** was chosen as the model compound. Under constant electric current (4.0 mA), treatment of **1aa** with LiO^{t}Bu in the presence of 30 mol% Cu(OTf)$_2$ at room temperature for 12 h afforded the target cage B(4)-oxygenated product **3aa** in 60% isolated yield (entry 1, Table 1). To our delight, switching the cell membrane from AMI-7001 to P4 sintered glass led to a dramatically increased yield of 86% for **3aa** (entry 2, Table 1). Reducing the loading of copper catalyst resulted in decreased yields for **3aa** (entries 2-4, Table 1). Only trace amount of target product was observed, when Pt electrode was used as the anode instead of RVC one (RVC = reticulated vitreous carbon) (entry 6, Table 1). Other coupling partners such as NaO^{t}Bu and KO^{t}Bu gave no desired products, as they induced the deboronation,[4] suggestive of the crucial role of Li$^+$ ion (entries 7 and 8, Table 1). In addition, both copper catalyst and electricity were proved to be essential for this cross-coupling (entries 9 and 10, Table 1). In view of the yield of **3aa** and the reaction efficiency, entry 3 in Table 1 was chosen as the optimal reaction conditions (see Table S1 in the SI for more screening tests).

Table 1. Optimization of reaction conditions[a]

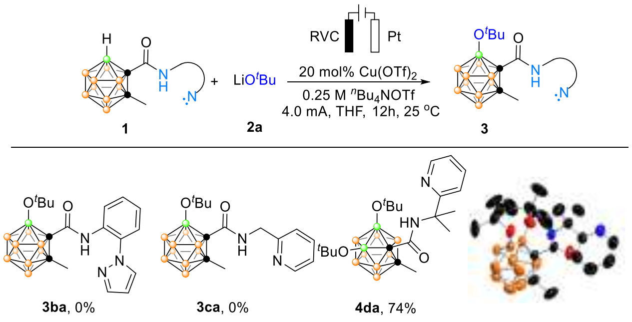


entry	*cat.* (mol %)	MO^{t}Bu (equiv)	**3aa**^{b} (%)
1^c	30	LiO^{t}Bu (5)	60
2	30	LiO^{t}Bu (5)	86
3	20	LiO^{t}Bu (5)	84
4	10	LiO^{t}Bu (5)	68
5	20	LiO^{t}Bu (3)	18
6^d	20	LiO^{t}Bu (5)	<5
7	20	NaO^{t}Bu (5)	N.R.
8	20	KO^{t}Bu (5)	N.R.
9	-	LiO^{t}Bu (5)	N.R.
10^e	20	LiO^{t}Bu (5)	8

[a] Reactions were conducted at 0.2 mmol scale in divided cell separated by P4 sintered glass membrane, **1** and **2** in anode cell, 2 mL of THF and 0.5 mmol ^{n}Bu$_4$NOTf in each cell. [b] Isolated yield. [c] AMI-7001 membrane was employed to separate anode and cathode. [d] Pt anode was employed. [e] No electric current.

With the optimized conditions in hand, other bidentate directing groups were examined for such electrochemical copper-catalyzed B-H oxygenation (Scheme 2). Interestingly, the use of (pyridin-2-yl)isopropyl (PIP) amide auxiliary produced B(4,5)-dioxygenated carboranes (**4da**) in 74% isolated yield (Scheme 2), which may be ascribed to the Thorpe-Ingold effect of PIP.[12] This result illustrates an important role of the directing groups in mono-/di-selectivity of the reaction.

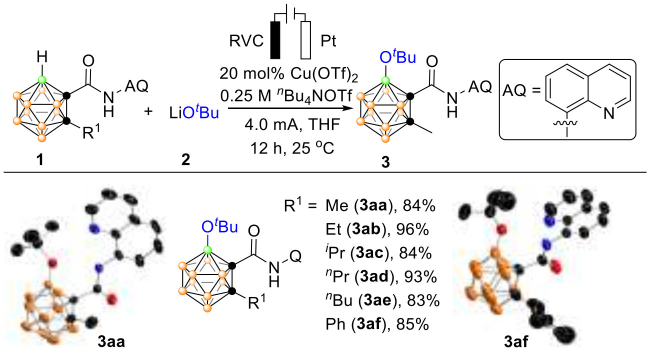
Scheme 2. Evaluation of Bidentate Directing Groups



[a] Reactions were conducted in divided cell separated by P4 sintered glass membrane with a RVC anode and a Pt cathode at 25 °C and 4.0 mA for 12 h. Anode: **1** (0.2 mmol), **2a** (5.0 equiv, 1.0 mmol), Cu(OTf)$_2$ (20 mol%, 0.04 mmol), ^{n}Bu$_4$NOTf (0.5 mmol, 2.5 equiv) and THF (2 mL). Cathode: ^{n}Bu$_4$NOTf (0.5 mmol, 2.5 equiv) and THF (2 mL).

The substrate scope was subsequently explored under the optimal reaction conditions using 8-aminoquinoline (AQ) as the directing group. A variety of substituents on cage C(2) including alkyls and phenyl worked well to afford the desired products **3** in 83%-96% isolated yields (Table 2). Sterically bulky group such as ^{i}Pr also gave the corresponding product **3ac** in 84% yield. It was noted that primary and secondary alkoxides were not compatible with this reaction because of deboronation of the cage.[4]

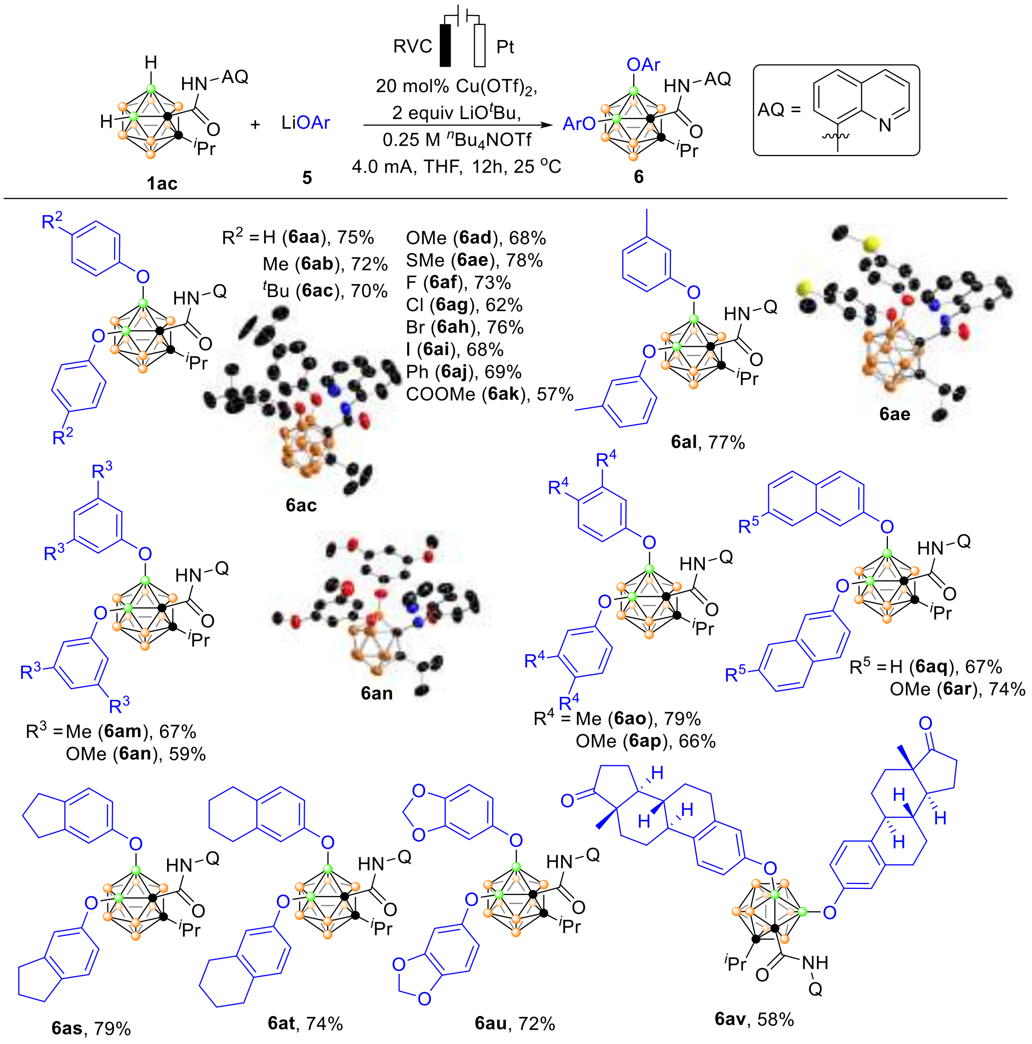
Table 2. Electrochemical Cage B-H Oxygenation with Lithium *tert*-Butoxide[a]



[a] Reactions were conducted in divided cell separated by P4 sintered glass membrane with a RVC anode and a Pt cathode at 25 °C and 4.0 mA for 12 h. Anode: **1** (0.2 mmol), **2** (5.0 equiv, 1.0 mmol), Cu(OTf)$_2$ (20 mol%, 0.04 mmol), ^{n}Bu$_4$NOTf (0.5 mmol, 2.5 equiv) and THF (2 mL). Cathode: ^{n}Bu$_4$NOTf (0.5 mmol, 2.5 equiv) and THF (2 mL).

Under the same reaction conditions aforementioned, treatment of carboranyl amide **1aa** with lithium phenolate gave, however, a mixture of mono- and di-phenolated products. After extensive screening (see Table S2 in the SI for detail), the optimal reaction conditions were able to be identified (Table 3). Accordingly, a new class of B(4,5)-diphenolated o-carboranes **6** were synthesized, and the results were compiled in Table 3. No obvious electronic effects were observed. Lithium phenolates with either electron-donating or electron-withdrawing substitutes served as competent coupling partners, giving **6** in 57%-79% isolated yields (**6aa** to **6ap**, Table 3). It was noteworthy that this cross-coupling was tolerant of many functional groups including –F, –Cl, –Br, –I, –SMe, –OMe and –COOMe. Substrates bearing naphthalene, tetrahydronaphtnelene, indane and benzodioxole rings performed well to deliver the corresponding **6aq** to **6au** in very good isolated yields. Estrone, one of three major endogenous estrogens, was also compatible with this reaction to give its carborane derivative **6av** in 58% yield, further illustrating the generality of this protocol. The reason why the reaction stopped at di-substitution may be attributable to steric reasons. The planar structure of AQ could accommodate two phenoxy units, but only one O^{t}Bu.

Table 3. Electrochemical Cage B-H Oxygenation with Lithium Phenoxides [a]

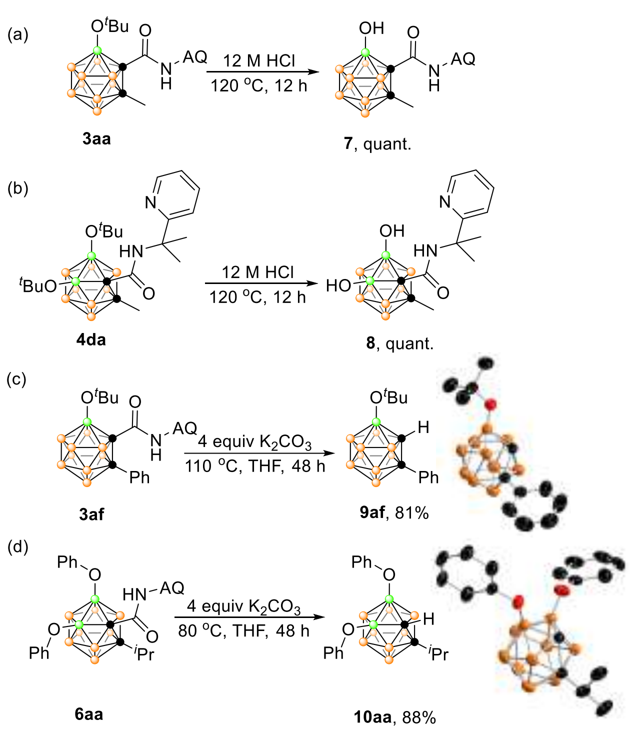


[a] Reactions were conducted in divided cell separated by P4 sintered glass membrane with a RVC anode and a Pt cathode at 25 °C and 4.0 mA for 12 h. Anode: **1ac** (0.20 mmol), **5** (8.0 equiv, 1.6 mmol), LiO^{t}Bu (2 equiv, 0.4 mmol), Cu(OTf)$_2$ (50 mol%, 0.1 mmol), ^{n}Bu$_4$NOTf (0.75 mmol, 3.75 equiv) and THF (2 mL). Cathode: ^{n}Bu$_4$NOTf (0.75 mmol,3.75 equiv) and THF (2 mL).

The transformations of the products (**3aa**, **4da**, **3af** and **6aa**) were also studied. Treatment of **3aa** or **4da** with HCl (conc.) at 120 °C for 12 h gave the B(4)-hydroxylated o-carborane **7** or B(4,5)-dihydroxylated o-carborane **8** in quantitative yields (Scheme 3a,b). Furthermore, the 8-aminoquinoline (AQ) bidentate directing group was easily removed by heating **3af** or **6aa** with K$_2$CO$_3$ in THF, generating **9af** or **10aa** in 81% or 88% isolated yield (Scheme 3c,d).[12c] In this regard, -CONH-AQ can serve as a traceless directing group for the functionalization of o-carboranes.

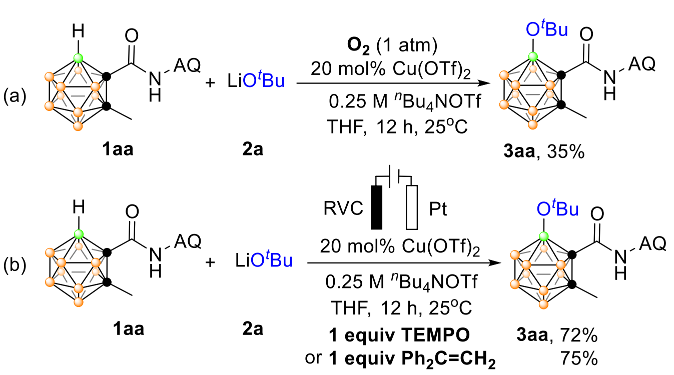
Compounds **3**, **4**, **6**, **7**, **8**, **9** and **10** were fully characterized by ^{1}H, ^{13}C, and ^{11}B NMR spectroscopy as well as high-resolution mass spectrometry (see the Supporting Information for detail). The molecular structures of **3aa**, **3af**, **4da**, **6ac**, **6ae**, **6an**, **9af** and **10aa** were further confirmed by single-crystal X-ray analyses.

Scheme 3. Transformations of 3aa,4da, 3af and 6aa

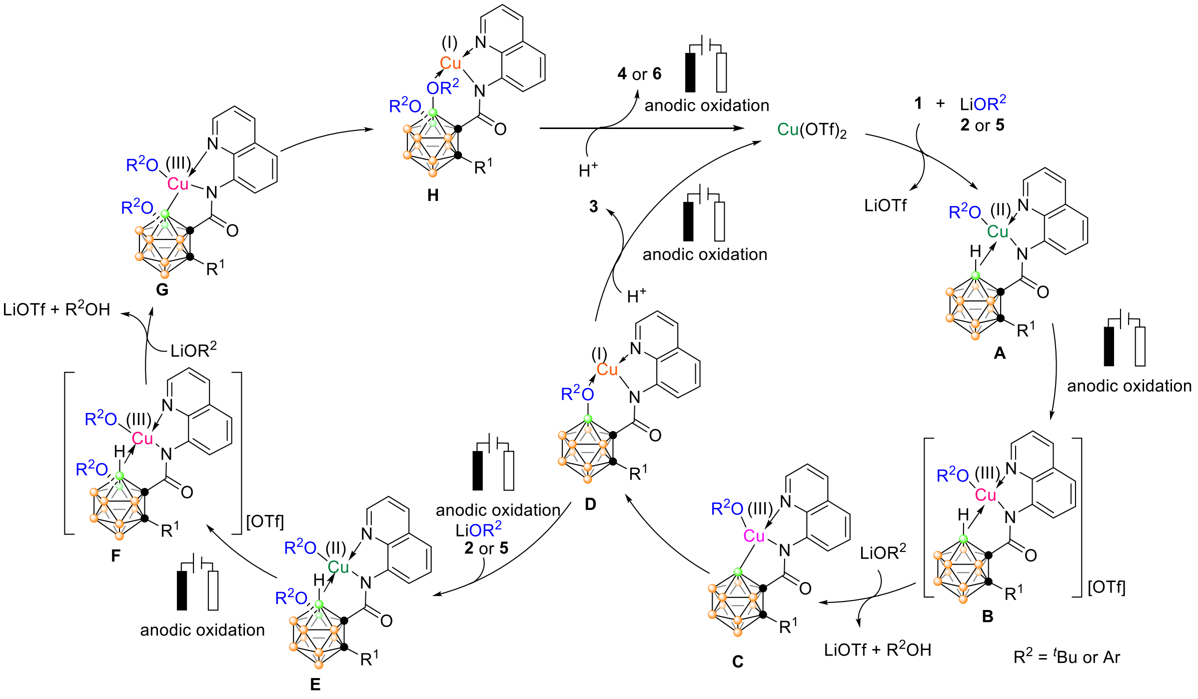


To gain some insights into the reaction mechanism, several control experiments were performed. In the absence of electric current, the employment of O_2 as the oxidant offered a yield of 35% for **3aa** (Scheme 4a). Without electric current and O_2, 20% $Cu(OTf)_2$ led to the formation of **3aa** in 8% yield (entry 10, Table 1). These results indicated that a high valent Cu(III) species, generated by the oxidation of O_2 or via disproportionation of copper(II) salt, [2Cu(II) → Cu(I) + Cu(III)],[13] may be involved in the reaction. On the other hand, the addition of radical scavengers such as TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) or $Ph_2C=CH_2$ to the reaction mixture brought in negligible influences on the formation of the product (Scheme 4b), suggesting that the radical process might not be involved in the reaction pathway.

Scheme 4. Control Experiments



Scheme 5. Plausible Reaction Mechanism



On the basis of the aforementioned experimental results and literature reports,[9,13] a plausible reaction mechanism is proposed in Scheme 5. Bidentate chelation of **1** with $Cu(OTf)_2$ followed by salt metathesis reaction gives an intermediate **A**.[9] Anodic oxidation occurs to generate an active Cu(III) species **B**.[13] Electrophilic attack of the Cu(III) center at the relatively electron rich B(4)-H affords the intermediate **C**, which undergoes reductive elimination and protonation to give the B(4)-monooxygenated product **3**. Anodic oxidation of Cu(I) in **D** to Cu(II) finishes the catalytic cycle. Such a cycle repeats to generate the B(4,5)-dioxygenated product **4** or **6**. It is noted that steric factor plays a considerable role in mono-/di-selectivity.

In summary, the first example of Cu-catalyzed electrochemical selective B-H oxygenation of *o*-carboranes has been realized under constant electric current at room temperature, resulting in the facile synthesis of a series of B(4)-monooxygenated and B(4,5)-diphenolated carborane derivatives in an economy, sustainable and green manner. The strategy of merging base metal catalysis with electrochemistry in this research opens up new avenues to the synthetic chemistry of carboranes and other boron clusters. This work will also provide useful references for electrochemical base metal catalysis in organic synthesis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization of the products (PDF)

Crystal structures (CIF)

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Notes

The authors declare no competing financial interests.

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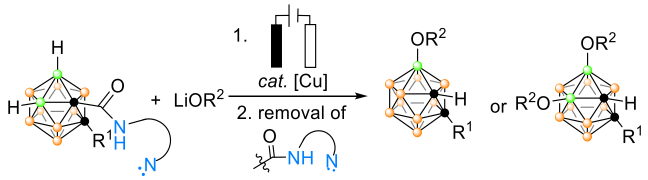

***Copper** catalysis*
*Promoted by **electricity***
No need of chemical oxidant

H_2 as by-product
***Controllable** mono-/di-selectivity*
*Mild condition **R.T.***