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Investigating the Oxidation Step in the $CuCl_2$-Catalyzed Aerobic Oxidative Coupling Reaction of *N*-Aryl Tetrahydroisoquinolines

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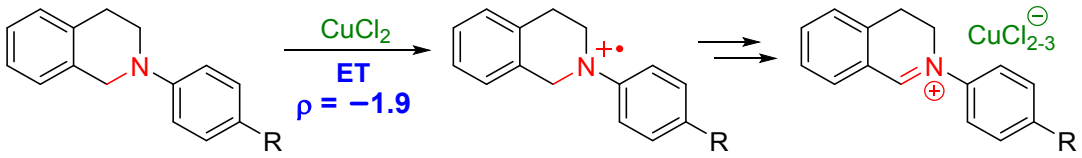
ABSTRACT



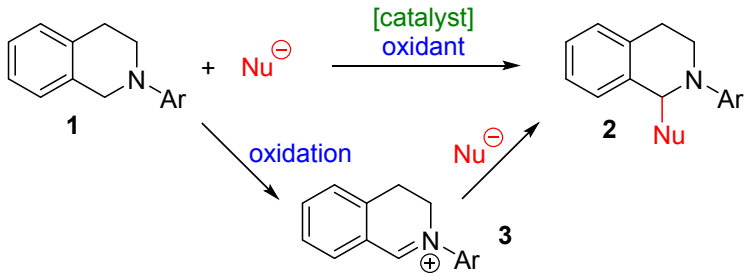
The oxidative coupling of *N*-aryl tetrahydroisoquinolines with nucleophiles has inspired the development of novel C-H functionalization reactions as well as mechanistic studies. Here, we investigate the oxidation step that forms iminium ions as key intermediates in the method using $CuCl_2$ as catalyst and oxygen as terminal oxidant. A strong electronic effect of substituents in the N-aryl ring was found by synthetic studies and a Hammett plot analysis, supporting initial electron transfer from the amine to Cu(II). The importance of the mechanism of oxidation on the substrate scope with differently substituted tetrahydroisoquinolines is discussed.

INTRODUCTION

The oxidative coupling of *N*-aryl tetrahydroisoquinolines **1** with various nucleophiles is a reaction that has attracted a lot of attention from organic chemists (Scheme 1).[1] Following pioneering reports from various groups,[2] especially from 2004 onwards by the group of C.-J. Li,[3] numerous methods comprising different catalysts, oxidants and nucleophiles have been reported. The majority of those methods is limited to tertiary *N*-aryl amines, most substrates besides **1** and *N*,*N*-dimethylanilines fail.

While the tetrahydroisoquinoline core is pharmaceutically interesting,[4] the *N*-aryl group is rarely desired and difficult to remove.[5] Nevertheless, this type of reaction serves as a model and inspiration for the development of novel oxidative C-H functionalization reactions.[6] By now, several methods have overcome these limitations and succeed with *N*-alkyl, *N*-acyl or secondary tetrahydroisoquinolines.[6-7]

Scheme 1. Oxidative coupling reactions of *N*-aryl tetrahydroisoquinolines 1 with nucleophiles via intermediate iminium ions

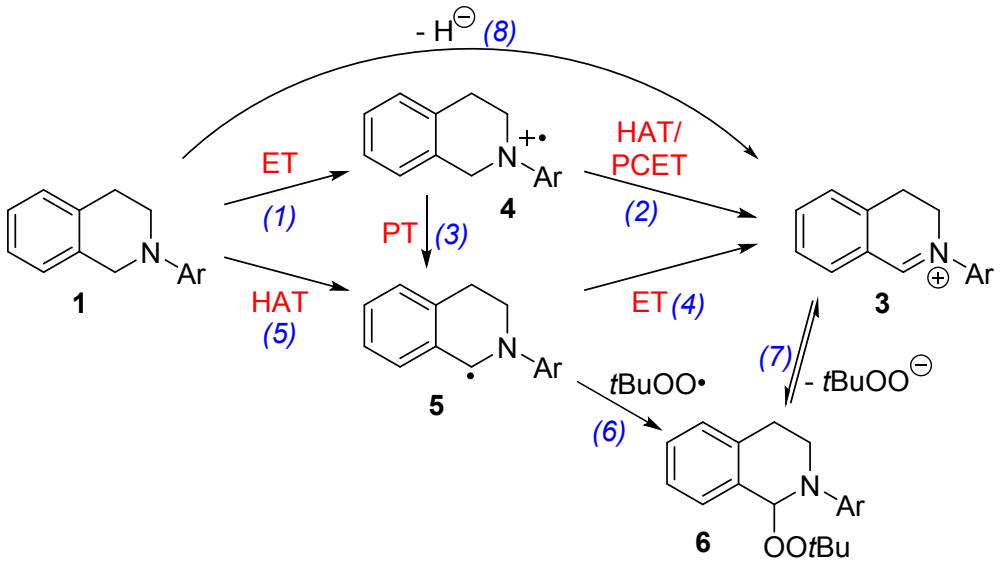


In recent years, a number of detailed experimental and theoretical studies have uncovered many aspects of the reaction mechanisms with *N*-aryl tetrahydroisoquinolines **1**, depending on the catalyst and oxidant used. Well-investigated systems are the combination of $CuCl_2$ as catalyst with oxygen,[8] CuBr as catalyst with *tert*-butylhydroperoxide (*t*BuOOH),[8b,8e,9] Rh_2cap_4 with *t*BuOOH (albeit using *N*,*N*-dimethylanilines, not **1**),[10] a binuclear Cu-catalyst with oxygen,[11] photocatalytic reactions with and without photocatalyst,[12] as well as the use of the oxidant DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) without catalyst.[13]

All of these reactions are suggested to share a common key intermediate, the iminium ion **3**, which is formed by oxidation and reacts with nucleophiles of sufficient reactivity to the final products **2** (Scheme 1). The iminium ion has been observed and characterized in several cases,[14] including reactions using $CuCl_2/O_2$,[8a,8f] CuBr/*t*BuOOH in the presence of acid,[8b] DDQ,[13b] as well as under irradiation with light.[12]

The actual mechanism of the oxidation is more complex. A key step suggested for the combination of catalytic $CuCl_2$ and O_2 is electron transfer (ET) from the amine to the catalyst (Scheme 2, step (*1*)), forming an ammoniumyl radical cation intermediate **4**. This was based on the observation that oxidation with $CuCl_2$ in the absence of oxygen forms an iminium **3** with a Cu(I) counterion.[8b] The radical cation **4**, formed from **1** by reaction with $CuCl_2$, has actually been observed recently by mass spectrometry.[8f] The iminium ion could be formed from **4** either by direct hydrogen atom transfer (HAT, step (*2*), supported by a computational study from Morgante et al.[8d]) or by sequential proton transfer (PT, step (*3*)) and ET (*4*) via C-radical **5**.[8b,8c] Alternatively, the conversion could take place in a concerted proton-coupled electron transfer (PCET), as suggested by Cheng et al. in a computational study.[8e] Initial ET has also been suggested to occur under photocatalyzed conditions,[12a] and when using DDQ as oxidant without additional catalyst.[13a]

Scheme 2. Overview of suggested pathways of oxidation to the iminium ion 3. Abbreviations: ET: electron transfer, HAT: hydrogen atom transfer, PT: proton transfer



In contrast, direct formation of **5** by HAT (*5*) to oxyl and peroxyl radicals formed in situ has been suggested for reactions with CuBr and *t*BuOOH.[8b,9] Under these conditions, **5** would couple with a peroxyl radical to the observable peroxide intermediate **6** (step *6*), which is a precursor to the iminium ion **3** via heterolytic C-O bond cleavage (*7*). The system of Rh_2cap_4 with *t*BuOOH has been

suggested to follow an ET-mechanism (steps (*1*)-(*3*)-(*4*)-(*7*)), with peroxyl radicals acting as electron acceptors,[10] while this has more recently been questioned, arguing in favour of a HAT-mechanism (steps (*5*)-(*6*)-(*7*)).[9] However, *N*,*N*-dimethylanilines instead of **1** were used in the Rh-catalyzed reactions. A third type of mechanism via hydride transfer, directly furnishing the iminium ion **3** in a single step (*8*), has been proposed for a reaction with an *ortho*-quinone as oxidant.[15]

We have recently investigated the CuBr/*t*BuOOH system with respect to the formation of peroxide **6**, relying to a large degree on Hammett plot analyses with **1** bearing different substituents on the *N*-aryl ring.[9] A small slope ($\rho = -0.55$ vs. σ and $\rho = -0.41$ vs. σ^+) was found, i.e. a weak substituent effect on the oxidation step, supporting HAT (*5*) via an uncharged intermediate **5**. For a mechanism via initial ET, a larger slope would be expected, due to the generation of positive charge on the nitrogen atom in **4**. However, ρ values from reactions with amines **1** that were suggested to run via an ET-mechanism were not available at the time for comparison.

Several studies with substituted *N*,*N*-dimethylanilines as substrates and a variety of catalysts, oxidants and reaction conditions are known, though. Four cases using oxygen as oxidant have been proposed to proceed via initial ET, reporting a large span of negative slopes ($\rho = -3.35$ vs. σ,[16] $\rho = -2.2$ vs. σ^+,[17] $\rho = -1.9$ vs. σ^+,[18,19] and $\rho = -0.61$ vs. σ[20]). While they are mostly rather large, the latter is not and very close to the value we had obtained previously for the CuBr/*t*BuOOH-system. Reactions suggested to proceed via initial ET but using other oxidants also span a large range of negative slopes ($\rho = -3.8$ vs. σ^+,[21] $\rho = -2.5$ vs. σ^+,[22] $\rho = -1.09$ vs. σ[23] and $\rho = -0.88$ vs. σ^+[24]). And while slopes for reactions suggested to proceed via initial HAT would be expected to be rather low, very different values have been reported ($\rho = -3.26$ vs. σ[2c] and $\rho = -0.42$ vs. σ[25]). A slope for a proposed hydride transfer has also been reported ($\rho = -3.15$ vs. σ[26]), and recently, Tsang et al. have actually reported a slope from an oxidative coupling reaction with *N*-aryl tetrahydroisoquinolines **1** and DDQ as oxidant ($\rho = -2.1$ vs. σ[13a]). Due to this large variety in the reported slopes, substrates, catalysts and oxidants, we decided to analyze a reaction with **1** ourselves, using conditions that would likely favour a mechanism via initial ET.

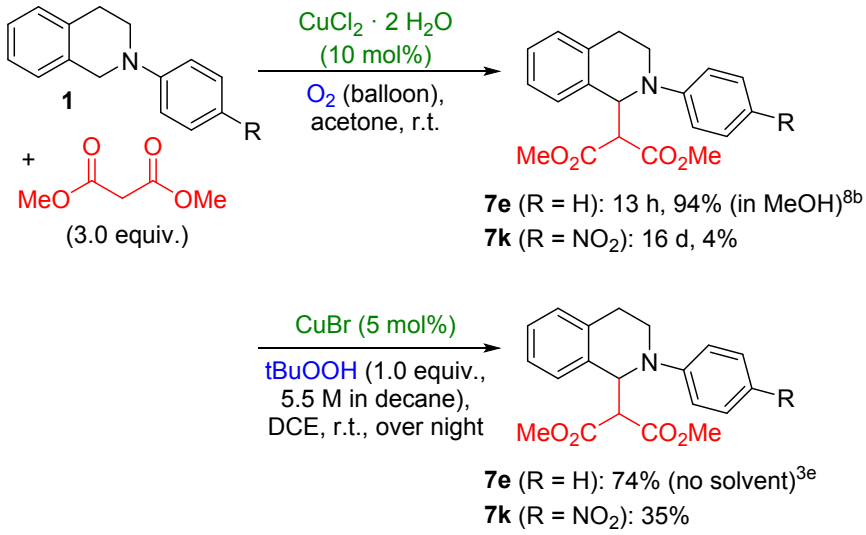
Here, we present a Hammett plot study of the oxidation step in the oxidative coupling of *N*-aryl tetrahydroisoquinolines, catalyzed by $CuCl_2$ dihydrate and using O_2 as terminal oxidant. We use reaction conditions as developed previously by our group, which we had suggested to proceed via initial ET from the amine based on several mechanistic studies.[8a-c,27] Also included is the aerobic preparation of several iminium ions **3** from substituted *N*-aryl tetrahydroisoquinolines, many of which could be characterized by X-ray crystallography.

RESULTS AND DISCUSSION

Initially, we tested in situ IR and UV-VIS spectroscopy to monitor the known[8a] oxidation of amines **1** to the iminium ions **3** with stoichiometric amounts of $CuCl_2$ dihydrate. However, these attempts failed to give reliable data in our hands.[28] We then looked at the oxidative coupling reaction as shown in Scheme 1, searching for a highly reactive nucleophile that would make the addition step zero order, so the oxidation step become rate controlling. We found trimethylsilyl cyanide to react significantly faster than several other nucleophiles tested before[8a-c] (see the Supporting Information, chapter 1). However, the reaction rate was very sensitive to the amount of water in the system, the NMR-spectra were often too broadened for reliable analysis, and reproducing the reactions turned out to be problematic.

During these experiments, it appeared that the very electron-poor *para*-nitrophenyl-substituted amine **1k** was unreactive, regardless of the nucleophile employed. This is in contrast to results obtained with the CuBr/*t*BuOOH system, with which we had observed significant conversion of **1k**.[9] Investigating this case more carefully in the oxidative coupling with dimethylmalonate as a representative nucleophile in acetone, a preferred solvent for reactive nucleophiles,[8a] we found that **1k** does in fact form the desired product, but only exceedingly slow (Scheme 3).

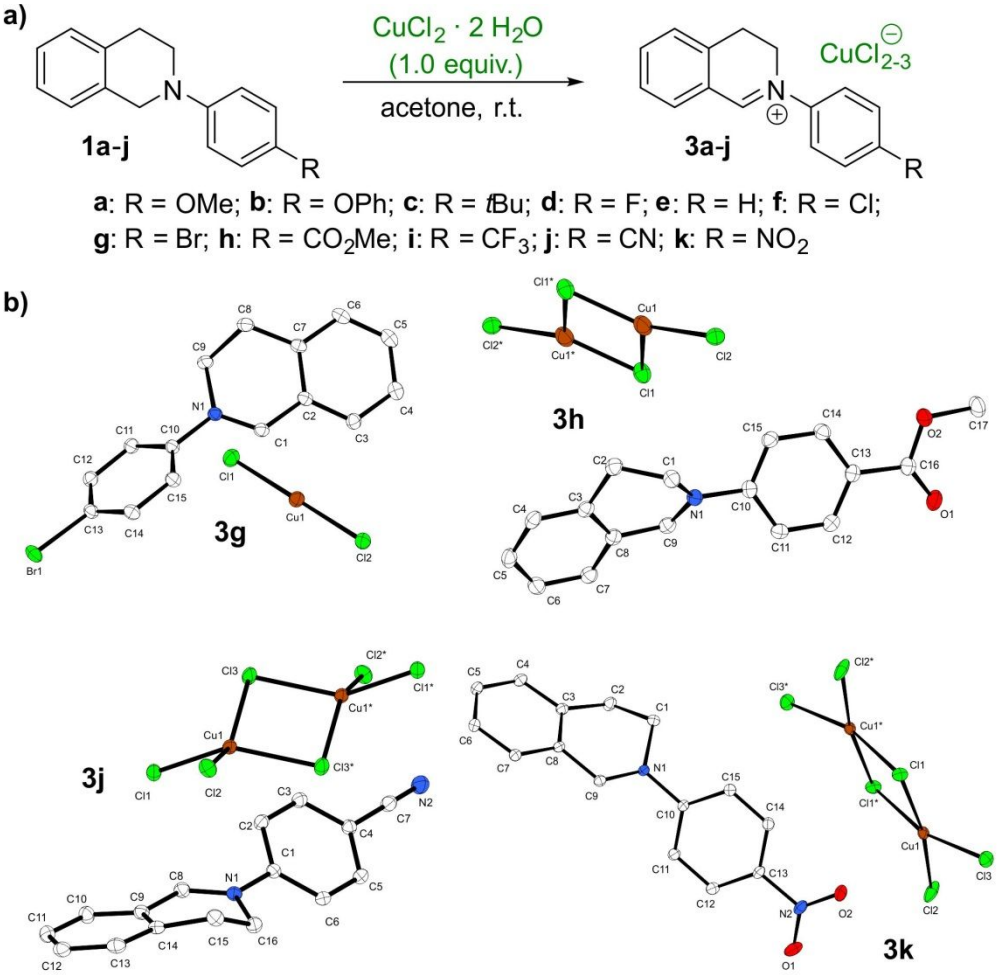
Scheme 3. Comparison of *N*-phenyl and *N*-(*p*-nitrophenyl) tetrahydroisoquinoline in the oxidative coupling with dimethylmalonate, using the currently investigated method ($CuCl_2$ / O_2) and the method developed by the Li group[3d] (CuBr / *t*BuOOH)



After 8 days, about 2% of the product **7k** could be observed by ^{1}H-NMR spectroscopy, and about 4% after 16 days. In contrast, the coupling product of the phenyl-substituted **1e** with dimethylmalonate, **7e**, was reported to form in 94% after less than a day.[8b] Using the CuBr/*t*BuOOH system for comparison, **7e** was reported to give 74% yield after reaction overnight,[3d] and we received an isolated yield of 35% of the *p*-nitro substituted product **7k** with the same method in 1,2-dichloroethane (DCE), a solvent we had found to give very good results[9] (Scheme 3). While this is a rather low yield from a synthetic perspective, it clearly shows that the strongly electron-withdrawing nitro group lowers the performance of the CuBr/*t*BuOOH method only slightly, but the $CuCl_2/O_2$ method nearly fails. These reactions were also performed in switched solvents without a remarkable change ($CuCl_2/O_2$ in DCE: 5% after 8 d; CuBr/*t*BuOOH in acetone: 24 h, 39%), confirming that the different reactivities are not merely due to solvent effects.

In order to investigate the electronic effect of substituents in the *N*-aryl group more quantitatively, we turned our attention again to the oxidation step in the absence of any nucleophile. We discovered that we could monitor the Cu(II)-mediated formation of the iminium ions **3** by ^{1}H-NMR under diluted conditions. This way, the evaluation of the NMR spectra was generally not hampered by line-broadening due to paramagnetic Cu-species. We synthesized the *para*-substituted iminium ions **3a**-**k** by reaction with stoichiometric amounts of $CuCl_2$ dihydrate, in order to later use them as references in competition experiments (Scheme 4a).

Scheme 4. Oxidation of substituted *N*-aryl tetrahydroisoquinolines to the iminium ions 3 with Cu(II), a) synthesis of reference compounds; b) selected ORTEP structures of iminium salts; displacement ellipsoids are drawn at the 50% probability level.

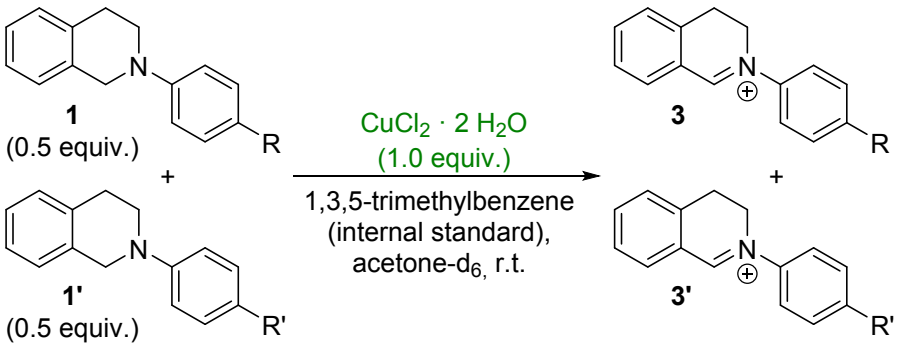


We also managed to grow crystals suitable for X-ray structure analysis from most products, including the *p*-nitro-substituted iminium **3k** (selected ones are shown in Scheme 4b, see the Supporting Information, chapter 5, for all structures). Interestingly, while the counterions were in most cases of dichlorocuprate(I) or dimeric bis-dichlorocuprate(I) type (e.g. **3g** and **3h**, Scheme 4b), as seen before,[8a] we also obtained three crystal structures with Cu(II) counterions (e.g. **3j** and **3k**, Scheme 4b).

In order to obtain a Hammett plot for this oxidation step, we performed competition experiments between the differently substitued *N*-aryl tetrahydroisoquinolines (except for **1k**, which was too

slow) (Scheme 5). This way, relative rates of iminium ion formation were measured. A reliable determination of absolute rates by separate kinetic measurement of each substituted amine by NMR spectroscopy was considered as impossible, as the more electron-rich amines **1a**-**1e** react too fast, giving full conversion after a few minutes. Competition experiments can be used in these cases even at high conversion, provided some of each starting material is left unreacted by the time of measurement, by calculating the relative rates from the conversion of each amine with the Ingold-Shaw equation[29] (see the Supporting Information, chapter 2.3). Note that relative rates from competition experiments reflect not necessarily the rate-controlling step but the product- or selectivity-controlling step. The reactions were performed with stoichiometric amounts of Cu(II) in order to achieve high conversions without the necessity for aerobic reoxidation of Cu(I), which might otherwise perturb the measurement of relative rates of amine oxidation.

Scheme 5. Competition experiments, conducted to measure relative rates of oxidation.



a: R = OMe; **b**: R = OPh; **c**: R = *t*Bu; **d**: R = F; **e**: R = H; **f**: R = Cl;
g: R = Br; **h**: R = CO_2Me; **i**: R = CF_3; **j**: R = CN

The relative rates thus measured are reported in Table 1. The rate for **1a** can only be estimated since it was fully converted already in the first measurement (see the Supporting Information, chapter 2.4). Also shown are the relative rates obtained previously for the oxidation of amines **1** to the peroxides **6** using CuBr and *t*BuOOH, where available for the given substituents.[9] It is obvious from this qualitative comparison, that the oxidation with Cu(II) is subject to a much stronger substituent effect than the oxidation with *t*BuOOH. While the *para*-methoxy substituted amine is reacting

approximately 600 times faster than the *para*-cyano substituted one, it is only 3-4 times faster in the CuBr/*t*BuOOH-case (compare Table 1, entries 1 and 9).

Table 1. Relative rates of differently substituted amines 1 in the oxidation with Cu(II) and *t*BuOOH, respectively[a]

entry	Amine	R	r_{rel} ($CuCl_2$)	r_{rel} (*t*BuOOH)[b]
1	**1a**	OMe	ca. 600	3.7
2	**1b**	OPh	229	
3	**1c**	*t*Bu	119	
4	**1d**	F	39	
5	**1e**	H	36	2.1
6	**1f**	Cl	18	1.8
7	**1g**	Br	14	
8	**1h**	CO_2Me	2.9±0.2	
9	**1i**	CF_3	2.4	1.3
10	**1j**	CN	1.0	1.0

[a]Relative rates in the oxidation of substituted amines **1**, as shown in Scheme 5; [b]relative rate of oxidation to the peroxide **6** using the CuBr/tBuOOH-system for comparison, reported previously;[9] [c]standard deviation given for measurements from competition experiments with different reference compounds.

The decadic logarithm of the relative rates was found to correlate very well with Hammett sigma parameters, with the best linear fit versus σ^+ (Figure 1. Amine **1a** was left out, judging the data as not reliable enough. For alternative plots, see the Supporting Information, chapter 2.7). The slope was

determined as ρ = −2.0 against σ⁺ and ρ = −2.6 against σ. This is a significantly larger slope than the one obtained from the CuBr/*t*BuOOH-system (ρ = −0.41 against σ⁺),[9] supporting a different mechanism, namely ET from the amine's lone pair, resulting in a positive charge on the nitrogen bound to the substituted arene. This fits very well with the slope of ρ = −2.1 against σ, as measured for the reaction with DDQ that was suggested to start with ET,[13a] and also with the generally steep slopes of related reactions via ET, that were discussed above.

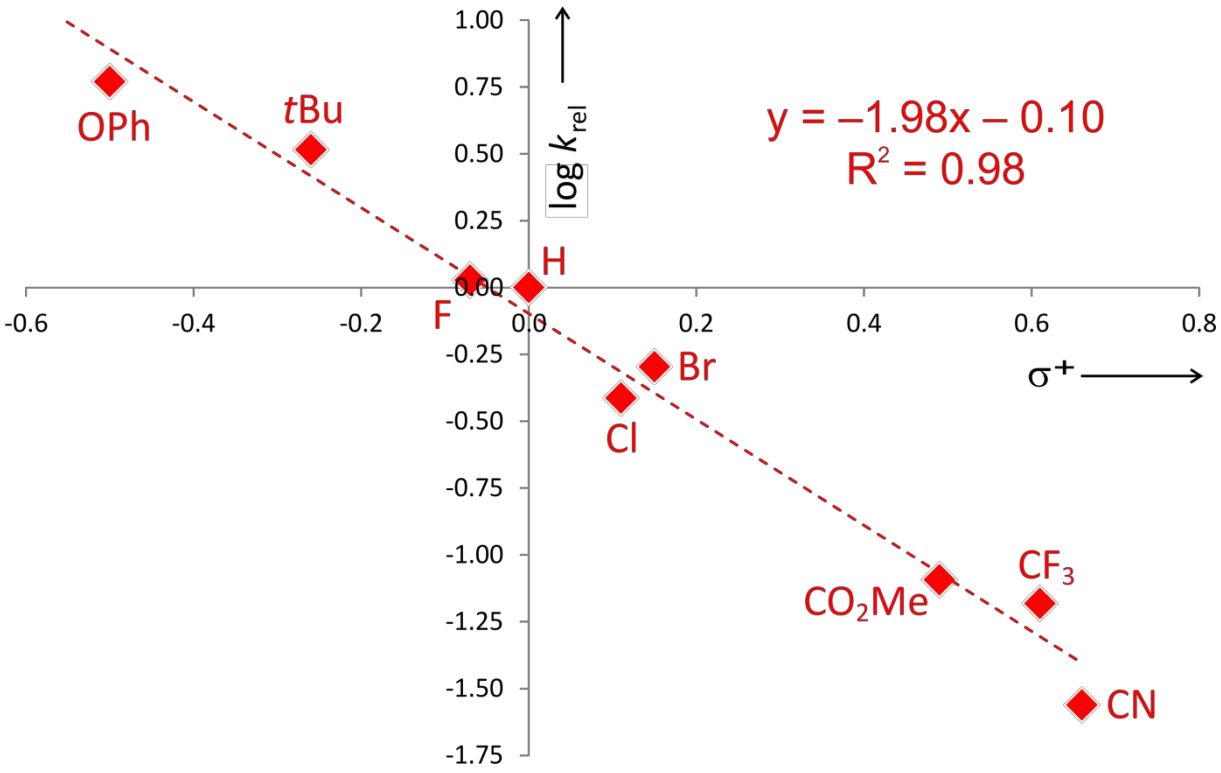


Figure 1: Hammett plot of the oxidation of amines **1** by Cu(II), determined from competition experiments as shown in Scheme 5.

The suggested mechanism of oxidation by multiple steps as shown in Scheme 2 above raises the question whether the product-controlling step responsible for the relative rates is actually the initial ET (step (*1*)) and not a subsequent one. We think this is the case, for the following reasons:

One could imagine that coordination of the amine's lone pair to Cu(II) is preceding the actual ET step, and that the relative rates mirror this equilibrium involving Cu(II) and two different amines. However, we often observed strong line broadening of the ^{1}H-NMR signals of unreacted amine starting

material during the competition experiments, while all other peaks remained sharp (see Supplementary Figure 5-1). This indicates binding of paramagnetic Cu(II) to the amines prior to any further step, and that these complexes apparently are a resting state of the reaction. Thus, complexation is fast and one can rule out that this is the product-controlling step. After the presumed ET (step (*1*)), two pathways from the ammoniumyl radical cation **4** to the observed iminium ion **3** appear possible (Scheme 2): via two steps by proton transfer (PT, forming C-radical **5**) and ET (steps (*3*) and (*4*)), or via one step by HAT (step (*2*)). If the PT step were product-controlling, the radical cations **4** with the most electron-withdrawing substituents should be most acidic, resulting in faster rates and thus a positive slope of the Hammett plot. This is obviously not the case. If the second ET (step *4*) were product-controlling, the Hammett plot would have a negative slope, as is observed. However, if this were the case, the resting state of the reaction would be C-radical **5**. Especially in the case of very slowly reacting amines like the *p*-NO_2-substituted **1k**, this species would easily react in alternative ways, for example with oxygen, forming a hydroperoxide or amide as major products. This is not the case, discounting the second ET step as product-controlling. Conversion of **4** to **3** by HAT (step (*2*)) would not change the charge of the molecule, so the slope of the Hammett plot would be expected to be less steep, as in the case we had measured previously for the CuBr/*t*BuOOH-system ($\rho = -0.41$ against σ^+).[9] Additionally, we had previously measured a low intermolecular kinetic isotope effect of 1.3, which indicated that C-H bond cleavage (by whichever mechanism) is not product-controlling.[8c] A concerted proton-coupled electron transfer (PCET) would most likely be subject to opposing electronic effects, as outlined above for sequential PT and ET, and thus exhibit a rather insignificant slope. Thus, we consider it most likely that the Hammett plot in Figure 1 actually reflects the initial ET step as suggested in Scheme 2.

From the separate oxidative coupling and oxidation reactions, resp., shown above in Schemes 3 and 4, we could estimate a few absolute rate constants. The Hammett plot slopes thus obtained are certainly less reliable, but nevertheless correlate very well with the one obtained from competition experiments (see the Supporting Information, chapter 3, for details). This indicates that the product-

controlling step is actually also the rate-controlling step in reactions with a single amine substrate. We also measured one competition experiment of amines **1g** and **1i** under argon instead of under air, which was slower but gave the same relative rate as measured before (see the Supporting Information, chapter 2.8, for details). This supports the notion that the oxidation of the amines takes place by reaction with Cu(II) and that oxygen is only involved in the reoxidation of Cu(I). Finally, we also measured kinetic isotope effects for the oxidation of the parent amine **1e**. Due to line-broadening of leftover starting material by the presence of paramagnetic Cu-species, the values could not be determined with satisfactory precision. Nevertheless, the estimated values fully support the conclusion of this study, that the reaction proceeds via a rate-controlling ET pathway (see the Supporting Information, chapter 4, for details).

This does not provide any information by which pathway the proposed ammoniumyl radical cation **4** actually reacts to the iminium ion. We had previously observed that the parent amine **1e** can be oxidized to the iminium **3e** in the absence of oxygen by stoichiometric $CuCl_2$ dihydrate, thus proposing that Cu(II) would be involved in the further conversion of **4e**, which might make sequential PT-ET or PCET most likely.[8b] A recent computational study, however, favoured formation of **3e** from radical cation **4e** by direct HAT to oxygen or a hydroperoxyl radical, provided that oxygen is present.[8d]

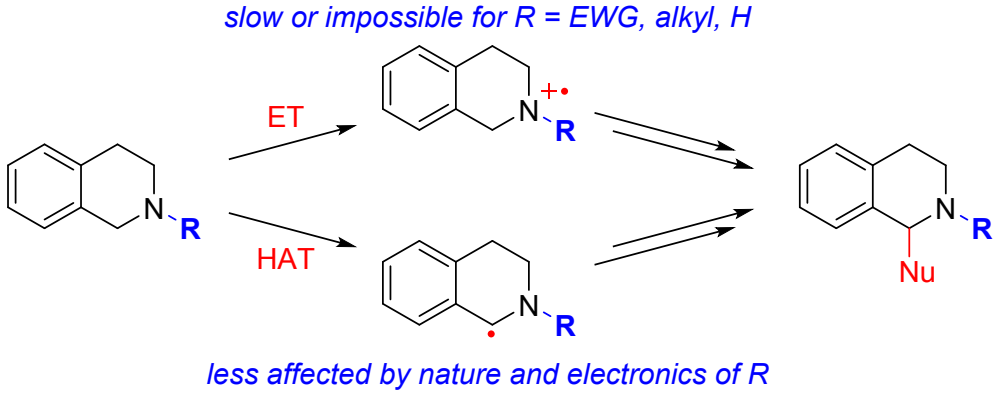
CONCLUSIONS

Hammett plots, together with KIE-experiments, are decisive mechanistic probes to distinguish between ET-PT and HAT mechanisms in the oxidation of amines. As has been discussed above, the slope values ρ found in the literature span a relatively broad range for each case. While some conclusions from the discussed publications may be wrong, it also underlines that the Hammett plot slopes are dependent on the catalysts and substrates employed. Here, we present a Hammett plot study with *N*-aryl tetrahydroisoquinolines as substrates, a very common amine in oxidative coupling (or CDC) reactions with nucleophiles. We investigated the method using $CuCl_2$ dihydrate as catalyst and oxygen as oxidant, in order to compare the results with those previously reported for the

method using CuBr as catalyst and *t*BuOOH as oxidant. In both systems, the same substrate type was investigated and we looked at the oxidation step only, leaving out any potential influence of the bond formation to the nucleophile. Together, these values for very similar reactions and catalyst give a clear distinction: the significantly larger ρ-value found here (ρ = −2.0 against σ^+) supports the previous assignment of a reaction mechanism via electron transfer (ET).

Does it matter very much whether these synthetic methods proceed via initial ET or HAT? It does indeed, because the mechanism affects the product scope. ET reactions are more susceptible to electronic changes of the substrate, so amines with strongly electron-withdrawing substituents may easily fail or give very poor yields. This was shown here for the case of the *para*-NO_2-substituted amine **1k**, which only gave traces of product even after extended reaction times. Possibly related to a lack of stabilization of the intermediate ammoniumyl radical cation is the often observed failure of secondary or *N*-alkyl substituted tetrahydroisoquinolines. For such substrates, one should utilize synthetic methods that proceed via HAT, which is much less affected by changes of the *N*-substituent (Scheme 6). For example, employing peroxides appears suitable, which easily generate intermediate oxyl radicals that are well-known HAT-acceptors.[30]

Scheme 6. Effect of the mechanism on the product scope in oxidative coupling reactions with tetrahydroisoquinolines



For the substrate **1k** or the closely related *p*-nitro-*N*,*N*-dimethylaniline, six successful methods using *t*BuOOH as oxidant are reported,[9,26,31] but also three methods using oxygen.[32] The latter may work

better than our $CuCl_2/O_2$-method due to higher oxidation potentials of the catalyst or higher reaction temperatures. However, tetrahydroisoquinolines bearing *N*-acyl or carbamate groups – providing even less stabilization of an ammoniumyl radical cation formed by ET[13a] – no aerobic method is known but only those using synthetic oxidants like *t*BuOOH.[7a,7c,33]

EXPERIMENTAL SECTION

General Information. Unless otherwise indicated, all reagents and solvents were purchased from commercial distributors and used as received. Solvents (ethyl acetate, pentane) used for column chromatography were of technical grade and used after distillation in a rotary evaporator. TLC was used to check the reactions for full conversion and was performed on Macherey-Nagel Polygram Sil G/UV254 thin layer plates. TLC spots were visualized by UV-light irradiation and staining with KMnO4. Flash column chromatography was carried out using Merck Silica Gel 60 (40-63 µm). Yields refer to pure isolated compounds. ^{1}H and ^{13}C NMR spectra were measured with Bruker AV 400, AV 500 and AV 600 spectrometers. All ^{13}C NMR spectra are broadband ^{1}H decoupled. All chemical shifts are given in ppm downfield relative to TMS and were referenced to the solvent residual peaks.[34] ^{1}H-NMR chemical shifts are designated using the following abbreviations as well as their combinations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal. High resolution mass spectra were recorded with a Bruker APEX III FTICR-MS or a Finnigan SSQ 7000 quadrupole MS or a Finnigan MAT 95 double focusing sector field MS instrument. Melting points were determined in open capillary tubes on a EZ-Melt Automated Melting Point Apparatus and are uncorrected. For details of X-ray structure analysis, see the corresponding CIF-files. The substituted *N*-aryl tetrahydroisoquinolines **1a** (OMe),[35] **1c** (*t*Bu),[8a] **1d** (F),[36] **1e** (H),[35] **1f** (Cl),[37] **1g** (Br),[38] **1i** (CF_3)[37] **1j** (CN)[36] and **1k** (NO_2)[39] were synthesized according to previously published methods. Amine **1k** was also synthesized by a different method (see below), which gave significantly higher yields. The iminium ion **3e** has been synthesized as described before.[8a]

General procedure for the synthesis of *N*-aryl tetrahydroisoquinolines 1b, 1h and 1k. This general method was previously published,[40] but had not been used to isolate the amines listed below. A solution of 1-(2-iodoethyl)-2-(iodomethyl)benzene (1 g, 2.69 mmol), a substituted aniline (2.69 mmol, 1.0 equiv.), $NaHCO_3$ (451.7 mg, 5.38 mmol) and sodium dodecylsulphate (ca. 9 mg) in 10.8 mL of water was stirred under reflux for 3 h. The reaction solution was cooled to room temperature and extracted with ethyl acetate. The combined ethyl acetate phases were washed with water and dried over magnesium sulfate. The solvent was removed by rotary evaporation and the residue was purified by column chromatography.

*2-(4-Phenoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**1b**)*. Purification was performed by chromatography on silica gel using 5% EtOAc /pentane as the eluents. Yield: 720 mg, 88.9%, white solid, mp 84.1 °C. ^{1}H NMR (500 MHz, DMSO-d6): δ 7.36-7.30 (m, 2H), 7.23-7.15 (m, 4H), 7.08-7.02(m,3H), 6.99-6.92 (m,2H), 6.93-6.88 (m, 2H), 4.35 (s, 2H), 3,50 (t, J = 5.90 Hz, 2H), 2.92 (t, J = 5.90 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d6): δ 158.3, 147.8, 147.0, 134.5, 134.4, 129.8, 128.4, 126.6, 126.2, 125.8, 122.3, 120.5, 117.1, 116.4, 50.5, 46.4, 28.2; HRMS-(ESIpos) (*m/z*): M^+ + H calcd for $C_{21}H_{20}N_1O_1$: 302.1539; found 302.1545.

*Methyl 4-(3,4-dihydroisoquinolin-2(1H)-yl)benzoate (**1h**)*. Purification was performed by chromatography on silica gel using 10% EtOAc /pentane as the eluents. Yield: 1.583 g, 88.1%, white solid, mp 102.2 °C. ^{1}H NMR (500 MHz, DMSO-d6): δ 7.84-7.79 (m, 2H), 7.27-7.16 (m, 4H), 7.02-6.96 (m, 2H), 4.52 (s, 2H), 3.77 (s, 3H), 3.63 (t, J = 5.94 Hz, 2H), 2.92 (t, J = 5.94 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d6): δ 166.2, 152.8, 134.9, 134.0, 130.8, 128.1, 126.5, 126.5, 126.1, 117.0, 112.2, 51.4, 48.2, 44.2, 28.1; HRMS m/z: calcd for $C_{17}H_{17}N_1O_2Na_1$ [M^++Na]: 290.1152; found: 290.1153.

2-(4-Nitrophenyl)-1,2,3,4-tetrahydroisoquinoline (**1k**). Purification was performed by chromatography on silica gel using 10% EtOAc /pentane as the eluents. Yield: 1.279 g, 62.4%, orange solid, mp 141.3 °C. ^{1}H NMR (500 MHz, DMSO-d6): δ 8.12-8.06 (m, 2H), 7.29-7.18 (m, 4H), 7.05-6.98 (m, 2H), 4.62 (s, 2H), 3.69 (t, J = 5.87 Hz, 2H), 2.95 (t, J = 5.87 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-

d6): δ 153.8, 136.2, 135.0, 133.6, 127.9, 126.8, 126.5, 126.3, 125.8, 111.6, 48.0, 44.3, 28.0; HRMS-(EI) (m/z): M^+ calcd for $C_{15}H_{14}N_2O_2$: 254.1055, found: 254.1054.

General procedure for the synthesis of iminium ions 3. The amine (0.4 mmol, 1.0 equiv.) and $CuCl_2$•2 H_2O (0.8 mmol, 2.0 equiv.) are dissolved in sufficient ethanol, methanol or acetonitrile to give a homogeneous solution (3-12 ml). A layer of pentane or hexane may be added to enhance crystallization. After standing overnight, the crystals formed are collected by filtration and washed with a small amount of solvent.

*2-(4-Methoxyphenyl)-3,4-dihydroisoquinolin-2-ium dichlorocuprate(I) (**3a**)*. Synthesized in ethanol, yield: 128.9 mg, 82.9%; yellow solid, mp 135.2 °C; ^{1}H NMR (500 MHz, DMSO-d6): *δ* 9.54 (s, 1H), 8.02-7.98(m, 1H), 7.90-7.80 (m, 3H), 7.64-7.58 (m,2H), 7.25-7.20 (m, 2H), 4.56 (t, *J* = 7.94 Hz, 2H), 3.87 (s, 3H), 3.41 (t, *J* = 7.94 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d6): *δ* 165.4, 160.7, 137.9, 136.6, 135.7, 134.3, 128.1, 128.1, 125.5, 124.1, 114.8, 55.8, 50.7, 24.8; HRMS m/z: calculated for $C_{16}H_{16}N_1O_1$ [M^+]: 238.1226, found: 238.1224 (M-$CuCl_2^-$). The nature of the inorganic counterion was determined by X-ray crystallography (see the Supporting Information).

*2-(4-Phenoxyphenyl)-3,4-dihydroisoquinolin-2-ium di- or trichlorocuprate (**3b**)*. Synthesized in THF, yield: 62 mg, 43.0%; black solid, mp 88.7 °C (decomp.); ^{1}H NMR (500 MHz, DMSO-d6): *δ* 9.58 /brs, 1H), 8.10-6.99 (brm, 13H), 4.58 (brs, 2H, 3.43 (brs, 2H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d6): *δ* 165.7, 157.8, 154.5, 137.5, 136.9, 136.0, 133.9, 129.6, 127.5, 124.7, 124.0, 123.8, 118.7, 118.0, 50.2, 24.3; HRMS-(ESI pos) (*m/z*): calcd for $C_{21}H_{18}N_1O_1$,300.1383; found 300.1378 (M^+ - $CuCl_{2-3}$). The crystals were received as fine needles and structure determination by X-ray crystallography was not successful. The exact nature of the counterion could therefore not be determined. However, the significant line broadening observed in the NMR spectra indicates a paramagnetic Cu(II) counterion ($CuCl_3^-$), as observed in the case of **3c**, **3j** and **3k**.

*2-(4-(tert-Butyl)phenyl)-3,4-dihydroisoquinolin-2-ium di- or trichlorocuprate (**3c**)*. Synthesized in ethanol, yield: 104.6 mg, 69.9%; yellow solid, mp 186-188 °C, ^{1}H NMR (500 MHz, DMSO-d6): *δ* 9.59

(s, 1H), 8.07-7.55 (m, 8H), 4.59 (s, 2H), 3.42 (s, 2H), 1.32 (s, 9H); $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d6): δ 166.0, 153.1, 139.7, 137.7, 136.3, 134.1, 127.7, 126.2, 124.9, 121.8, 50.1, 34.1, 30.3, 24.4; HRMS m/z: calculated for $C_{19}H_{22}N_1$ [M^+]: 264.1747, found: 264.1741 (M-$CuCl_2^-$). The nature of the inorganic counterion was determined by X-ray crystallography (see the Supporting Information).

*2-(4-Fluorophenyl)-3,4-dihydroisoquinolin-2-ium dichlorocuprate(I) (**3d**)*. Synthesized in ethanol, yield: 134.4 mg, 84.9%; yellow solid, mp 149.5-150.5 °C; ^{1}H NMR (500 MHz, DMSO-d6): δ 9.62 (s, 1H), 8.06-7.87(m, 4H), 7.67-7.55 (m, 4H), 4.58 (t, J = 7.90 Hz, 2H), 3.43 (t, J = 7.90 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d6): δ 167.3, 162.7 (d, J = 248.8 Hz), 139.3, 139.2, 138.4, 136.9, 134.7, 128.2, 128.2, 125.4, 125.4, 125.3, 116.8 (d, J = 24.04 Hz), 50.9, 24.8; HRMS m/z: calculated for $C_{15}H_{13}F_1N_1$ [M^+]: 226.1026, found226.1022 (M-$CuCl_2^-$). The nature of the inorganic counterion was determined by X-ray crystallography (see the Supporting Information).

*2-(4-Chlorophenyl)-3,4-dihydroisoquinolin-2-ium dichlorocuprate(I) (**3f**)*. Synthesized in methanol, yield: 109.8 mg, 70.9%; yellow solid, mp 150-151 °C; ^{1}H NMR (500 MHz, DMSO-d6): δ 9.64 (s, 1H), 8.04-8.00(m, 1H), 7.94-7.88 (m, 3H), 7.83-7.78 (m, 2H), 7.66-7.59 (m, 2H), 4.58 (t, J = 7.95 Hz, 2H), 3.43 (t, J = 7.95 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d6): δ 167.5, 141.6, 138.5, 137.1, 135.3, 134.9, 129.9, 128.3, 128.3, 125.4, 124.7, 50.7, 24.8; HRMS m/z: calculated for $C_{15}H_{13}Cl_1N_1$ [M^+]: 242.0731, found: 242.0722 (M-$CuCl_2^-$). The nature of the inorganic counterion was determined by X-ray crystallography (see the Supporting Information).

*2-(4-Bromophenyl)-3,4-dihydroisoquinolin-2-ium dichlorocuprate(I) (**3g**)*. Synthesized in methanol, yield: 113.7 mg, 77.7%; yellow solid, mp 148-149 °C; ^{1}H NMR (500 MHz, DMSO-d6): δ 9.64 (s, 1H), 8.04-7.79(m, 6H), 7.66-7.58 (m, 2H), 4.58 (t, J = 7.90 Hz, 2H), 3.42 (t, J = 7.90 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d6): δ 167.4, 141.9, 138.5, 137.0, 134.8, 132.7, 128.2, 128.2, 125.3, 124.8, 123.9, 50.5, 24.7; HRMS m/z: calculated for $C_{15}H_{13}N_1Br_1$ [M^+]: 286.0226, found: 286.0227 (M-$CuCl_2^-$). The nature of the inorganic counterion was determined by X-ray crystallography (see the Supporting Information).

*2-(4-(Methoxycarbonyl)phenyl)-3,4-dihydroisoquinolin-2-ium dichlorocuprate(I) (**3h**)*. Synthesized in methanol, yield: 112.3 mg, 74.9%; yellow solid, mp 150-155 °C; ^{1}H NMR (500 MHz, DMSO-d6): δ 9.74 (s, 1H), 8.27-8.22(m, 2H), 8.07-8.00 (m, 3H), 7.95-7.90 (m,1H), 7.67-7.60 (m, 2H), 4.63 (t, *J* = 7.91 Hz, 2H), 3.92 (s, 3H), 3.45 (t, *J* = 7.91 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d6): δ 168.1, 165.0, 146.1, 138.8, 137.3, 135.1, 131.3, 130.7, 128.3, 128.3, 125.4, 123.2, 52.6, 50.5, 24.8; HRMS m/z: calculated for $C_{17}H_{16}N_1O_2$ [M^+]: 266.1176, found: 266.1173 (M-$CuCl_2^-$). The nature of the inorganic counterion was determined by X-ray crystallography (see the Supporting Information).

*2-(4-(Trifluoromethyl)phenyl)-3,4-dihydroisoquinolin-2-ium di- or trichlorocuprate (**3i**)*. Synthesized in ethanol, yield: 72 mg, 44.8%; orange solid, mp 124.5 °C; ^{1}H NMR (500 MHz, DMSO-d6): δ 9.72 (brs, 1H), 8.31-7.97 (brm, 5H), 7.91 (brs, 1H), 7.63 (brs, 2H), 4.64 (brs, 2H), 3.47 (brs, 2H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d6): δ 168.0, 144.9, 138.2, 136.5, 134.6, 129.7 (q, J_{CF}=32.2 Hz), 127.7, 126.6, 124.6, 123.9 (q, J_{CF}=272.6 Hz), 123.8, 123.2, 121.6, 50.2, 24.4; HRMS-(ESI pos) (*m/z*): calcd for $C_{16}H_{13}F_3N_1$, 276.0995; found 276.0990 (M^+ - $CuCl_{2\text{-}3}$). The crystals were received as fine needles and structure determination by X-ray crystallography was not successful. The exact nature of the counterion could therefore not be determined. However, the significant line broadening observed in the NMR spectra indicates a paramagnetic Cu(II) counterion ($CuCl_3^-$), as observed in the case of **3c**, **3j** and **3k**.

*2-(4-Cyanophenyl)-3,4-dihydroisoquinolin-2-ium trichlorocuprate (**3j**)*. Synthesized in acetonitrile, yield: 68 mg, 39.5%; orange solid, mp 193.7 °C; ^{1}H NMR (500 MHz, DMSO-d6): δ 9.69 (brs, 1H), 8.37-7.49 (m,8H), 4.63 (brs, 2H), 3.47 (brs, 2H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d6): δ 167.6, 144.4, 137.9, 135.9, 134.2, 133.0, 127.2, 124.0, 122.6, 116.1, 111.6, 49.7, 24.0; HRMS-(ESI pos) (*m/z*): calcd for $C_{16}H_{13}N_2$, 233.1073; found 233.1073 (M^+ - $CuCl_3$). The nature of the inorganic counterion was determined by X-ray crystallography (see the Supporting Information).

2-(4-Nitrophenyl)-3,4-dihydroisoquinolin-2-ium trichlorocuprate (**3k**). Synthesized in acetonitrile, yield: 79 mg, 61,4%; dark green solid, mp 206 °C; ^{1}H NMR (500 MHz, DMSO-d6): δ 9.74 (brs, 1H), 8.68-7.45 (m, 8H), 4.65 (brs, 2H), 3.48 (brs, 2H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d6): δ 168.1, 146.8,

145.9, 138.1, 136.2, 134.5, 127.4, 124.4, 123.2, 50.0, 24.2; HRMS-(ESI pos) (*m/z*): calcd for $C_{15}H_{13}N_2O_2$, 253.0972; found 253.0971 (M^+ - $CuCl_3$). The nature of the inorganic counterion was determined by X-ray crystallography (see the Supporting Information).

*Dimethyl 2-(2-(4-nitrophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)malonate (**7k**)*. Using the CuBr/tBuOOH method: to a mixture of CuBr (2.58 mg, 0,018mmol), dimethyl malonate (0.123 ml; 1.08 mmol, 3.0 equiv,) and **1k** (91.54 mg; 0.36 mmol, 1.0 equiv.) in 1,2-dichloroethane (1 mL) was added *tert*-butyl hydroperoxide (65.5 µL; ca. 5.5M solution in decane; 0.36 mmol, 1.0 equiv.). The resulting mixture was stirred at room temperature over night. Purification was performed by preparative thin layer chromatography on silica gel using 0.7% isopropanol in CH_2Cl_2 as the eluent. Yield: 48.3 mg, 34.9%; yellow oil, ^{1}H NMR (500 MHz, DMSO-d6): δ 8.12-8.06 (m, 2H), 7.28-7.23 (m,2H), 7.22-7.15 (m, 2H), 7.11-7.05 (m, 2H), 5,83 (d, J = 9.75 Hz, 1H), 4,18 (d, J = 9.75 Hz, 1H), 3.79-3.67 (m, 2H), 3.62 (s, 3H), 3,44 (s, 3H), 3.14-3.02 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d6): δ 167.3, 166.8, 152.9, 137.0, 134.7, 134.7, 128.7, 128.1, 126.9, 126.1, 125.6, 112.3, 57.1, 56.5, 52.6, 52.6, 42.2, 25.9; HRMS-(ESI pos) (*m/z*): M^+ + H calcd for $C_{20}H_{21}N_2O_6$, 385.1394; found 385.1390. Using the same method in acetone instead of 1,2-dichloroethane, 39.0% were isolated.

Using the $CuCl_2/O_2$ method: to a solution of **1k** (0.36 mmol, 91.54 mg) in acetone (1.5 mL), dimethyl malonate (1.08 mmol, 0.123 mL) and $CuCl_2 \bullet H_2O$ (0.036 mmol, 6 mg) are added and the mixture is stirred under an atmosphere of oxygen (1 atm) at room temperature. At regular time intervals, aliquots of 50 µl were taken from the reaction mixture, diluted to 0.4 ml with DMSO-d6 and measured by ^{1}H-NMR immediately. The yield was determined by the ratio of starting material and product (3 d: 1.2%, 8 d: 1.8%, 16 d: 3.7%, 29 d: 8.3%). The reaction was stopped after 29 days, no attempt was made to isolate the product due to the low yield. Using the same method in 1,2-dichloroethane instead of acetone, a yield of 4.8% was determined after 8 d.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental details including NMR spectra and kinetic experiments, X-ray crystallographic data and CIF files.

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Notes

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REFERENCES

(1) (a) Cheng, M.-X.; Yang, S.-D. Recent Advances in the Enantioselective Oxidative α-C–H Functionalization of Amines. *Synlett* **2017**, *28*, 159-174; (b) Szatmári, I.; Sas, J.; Fülöp, F. C-3 Functionalization of Indole Derivatives with Isoquinolines. *Curr. Org. Chem.* **2016**, *20*, 2038-2054; (c) Qin, Y.; Lv, J.; Luo, S. Catalytic asymmetric α-C(sp3)–H functionalization of amines. *Tetrahedron Lett.* **2014**, *55*, 551-558; (d) Shi, L.; Xia, W. Photoredox functionalization of C–H bonds adjacent to a nitrogen atom. *Chem. Soc. Rev.* **2012**, *41*, 7687-7697; (e) Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. W. Direct α-Functionalization of Saturated Cyclic Amines. *Chem. Eur. J.* **2012**, *18*, 10092-10142; (f) Jones, K. M.; Klussmann, M. Oxidative Coupling of Tertiary Amines: Scope, Mechanism and Challenges. *Synlett* **2012**, *23*, 159-162.

(2) For seminal cases, see: (a) Santamaria, J.; Herlem, D.; Khuong-Huu, F. Oxydation photochimique d'amines tertiaires et d'alcaloïdes--VIII: Oxydation photochimique d'alcaloïdes indolinoindolizidiniques, vincadifformine, tabersonine, N(a)-acétyl dihydro-2,16 vincadifformine et N(a)-acétyl dihydro-2,16 tabersonine. *Tetrahedron* **1977**, *33*, 2389-2392; (b) Chiba, T.; Takata, Y. Anodic cyanation of tertiary aliphatic and heterocyclic amines. *J. Org. Chem.* **1977**, *42*, 2973-2977; (c) Murahashi, S.; Naota, T.; Miyaguchi, N.; Nakato, T. Ruthenium-catalyzed oxidation of tertiary amines with hydrogen peroxide in the presence of methanol. *Tetrahedron Lett.* **1992**, *33*, 6991-6994.

(3) (a) Li, Z.; Li, C.-J. CuBr-Catalyzed efficient alkynylation of sp3 C-H bonds adjacent to a nitrogen atom. *J. Am. Chem. Soc.* **2004**, *126*, 11810-11811; (b) Li, Z.; Li, C.-J. Catalytic Enantioselective Alkynylation of Prochiral sp3 C-H Bonds Adjacent to a Nitrogen Atom. *Org. Lett.* **2004**, *6*, 4997-4999; (c) Li, Z.; Li, C.-J. Highly efficient copper-catalyzed nitro-Mannich type reaction: Cross-dehydrogenative-coupling between sp3 C-H bond and sp3 C-H bond. *J. Am. Chem. Soc.* **2005**, *127*, 3672-3673; (d) Li, Z.; Li, C.-J. Highly efficient CuBr-catalyzed cross-dehydrogenative coupling (CDC) between tetrahydroisoquinolines and activated methylene compounds. *Eur. J. Org. Chem.* **2005**, 3173-3176.

(4) (a) Le, V. H.; Inai, M.; Williams, R. M.; Kan, T. Ecteinascidins. A review of the chemistry, biology and clinical utility of potent tetrahydroisoquinoline antitumor antibiotics. *Nat. Prod. Rep.* **2015**, *32*, 328-347; (b) Bentley, K. W. b-Phenylethylamines and the isoquinoline alkaloids. *Nat. Prod. Rep.* **2006**, *23*, 444-463; (c) Scott, J. D.; Williams, R. M. Chemistry and Biology of the Tetrahydroisoquinoline Antitumor Antibiotics. *Chem. Rev.* **2002**, *102*, 1669-1730.

(5) (a) Tsang, A. S. K.; Ingram, K.; Keiser, J.; Hibbert, D. B.; Todd, M. H. Enhancing the usefulness of cross dehydrogenative coupling reactions with a removable protecting group. *Org. Biomol. Chem.* **2013**, *11*, 4921-4924; (b) Renaud, J.; Bischoff, S. F.; Buhl, T.; Floersheim, P.; Fournier, B.; Halleux, C.; Kallen, J.; Keller, H.; Schlaeppi, J.-M.; Stark, W. Estrogen Receptor Modulators: Identification and Structure−Activity Relationships of Potent ERα-Selective Tetrahydroisoquinoline Ligands. *J. Med. Chem.* **2003**, *46*, 2945-2957.

(6) (a) Arun, V.; Mahanty, K.; De Sarkar, S. Nickel-Catalyzed Dehydrogenative Couplings. *ChemCatChem* **2019**, *11*, 2243-2259; (b) Trammell, R.; Rajabimoghadam, K.; Garcia-Bosch, I. Copper-Promoted Functionalization of Organic Molecules: from Biologically Relevant Cu/O2 Model Systems to Organometallic Transformations. *Chem. Rev.* **2019**, *119*, 2954-3031; (c) Qin, Y.; Zhu, L.; Luo, S. Organocatalysis in Inert C–H Bond Functionalization. *Chem. Rev.* **2017**, *117*, 9433-9520; (d) Lv, L.; Li, Z. J. T. i. C. C. Fe-Catalyzed Cross-Dehydrogenative Coupling Reactions. *Top. Curr. Chem.* **2016**, *374*, 38; (e) Stockerl, S.; Mancheño, O. G. Non-covalent organocatalysis in asymmetric oxidative C(sp3)–H bond functionalization – broadening C–H bond coupling reactions. *Org. Chem. Front.* **2016**, *3*, 277-280; (f) Zheng, C.; You, S.-L. Recent development of direct asymmetric functionalization of inert C-H bonds. *RSC Adv.* **2014**, *4*, 6173-6214.

(7) For representative cases, see: (a) Ghobrial, M.; Schnürch, M.; Mihovilovic, M. D. Direct Functionalization of (Un)protected Tetrahydroisoquinoline and Isochroman under Iron and Copper Catalysis: Two Metals, Two Mechanisms. *J. Org. Chem.* **2011**, *76*, 8781-8793; (b) Richers, M. T.; Breugst, M.; Platonova, A. Y.; Ullrich, A.; Dieckmann, A.; Houk, K. N.; Seidel, D. Redox-Neutral α-

Oxygenation of Amines: Reaction Development and Elucidation of the Mechanism. *J. Am. Chem. Soc.* **2014**, *136*, 6123-6135; (c) Liu, X.; Sun, S.; Meng, Z.; Lou, H.; Liu, L. Organocatalytic Asymmetric C–H Vinylation and Arylation of N-Acyl Tetrahydroisoquinolines. *Org. Lett.* **2015**, *17*, 2396-2399.

(8) (a) Boess, E.; Sureshkumar, D.; Sud, A.; Wirtz, C.; Farès, C.; Klussmann, M. Mechanistic Studies on a Cu-Catalyzed Aerobic Oxidative Coupling Reaction with N-Phenyl Tetrahydroisoquinoline: Structure of Intermediates and the Role of Methanol as a Solvent. *J. Am. Chem. Soc.* **2011**, *133*, 8106-8109; (b) Boess, E.; Schmitz, C.; Klussmann, M. A Comparative Mechanistic Study of Cu-Catalyzed Oxidative Coupling Reactions with N-Phenyl Tetrahydroisoquinoline. *J. Am. Chem. Soc.* **2012**, *134*, 5317-5325; (c) Scott, M.; Sud, A.; Boess, E.; Klussmann, M. Reaction Progress Kinetic Analysis of a Copper-Catalyzed Aerobic Oxidative Coupling Reaction with N-Phenyl Tetrahydroisoquinoline. *J. Org. Chem.* **2014**, *79*, 12033-12040; (d) Morgante, P.; Dughera, S.; Ghigo, G. Aerobic CuCl2-Catalyzed Dehydrogenative Cross-Coupling of Tertiary Amines. A Combined Computational and Experimental Study. *J. Phys. Chem. A* **2019**, *123*, 2796-2814; (e) Cheng, G.-J.; Song, L.-J.; Yang, Y.-F.; Zhang, X.; Wiest, O.; Wu, Y.-D. Computational Studies on the Mechanism of the Copper-Catalyzed sp3-C-H Cross-Dehydrogenative Coupling Reaction. *ChemPlusChem* **2013**, *78*, 943–951; (f) Willms, J. A.; Gleich, H.; Schrempp, M.; Menche, D.; Engeser, M. Investigations of the Copper-Catalyzed Oxidative Cross-Coupling of Tetrahydroisoquinolines with Diethylzinc by a Combination of Mass Spectrometric and Electrochemical Methods. *Chem. Eur. J.* **2018**, *24*, 2663-2668.

(9) Boess, E.; Wolf, L. M.; Malakar, S.; Salamone, M.; Bietti, M.; Thiel, W.; Klussmann, M. Competitive Hydrogen Atom Transfer to Oxyl- and Peroxyl Radicals in the Cu-Catalyzed Oxidative Coupling of N-Aryl Tetrahydroisoquinolines Using tert-Butyl Hydroperoxide. *ACS Catal.* **2016**, *6*, 3253-3261.

(10) Ratnikov, M. O.; Doyle, M. P. Mechanistic Investigation of Oxidative Mannich Reaction with tert-Butyl Hydroperoxide. The Role of Transition Metal Salt. *J. Am. Chem. Soc.* **2013**, *135*, 1549-1557.

(11) (a) Liu, Y.; Wang, C.; Xue, D.; Xiao, M.; Li, C.; Xiao, J. Reactions Catalysed by a Binuclear Copper Complex: Aerobic Cross Dehydrogenative Coupling of N-Aryl Tetrahydroisoquinolines. *Chem. Eur. J.*

2017, *23*, 3051-3061; (b) Liu, Y.; Wang, C.; Xue, D.; Xiao, M.; Liu, J.; Li, C.; Xiao, J. Reactions Catalysed by a Binuclear Copper Complex: Relay Aerobic Oxidation of N-Aryl Tetrahydroisoquinolines to Dihydroisoquinolones with a Vitamin B1 Analogue. *Chem. Eur. J.* **2017**, *23*, 3062-3066.

(12) (a) Bartling, H.; Eisenhofer, A.; König, B.; Gschwind, R. M. The Photocatalyzed Aza-Henry Reaction of N-Aryltetrahydroisoquinolines: Comprehensive Mechanism, H•- versus H+-Abstraction, and Background Reactions. *J. Am. Chem. Soc.* **2016**, *138*, 11860-11871; (b) Franz, J. F.; Kraus, W. B.; Zeitler, K. No photocatalyst required - versatile, visible light mediated transformations with polyhalomethanes. *Chem. Commun.* **2015**, *51*, 8280-8283.

(13) (a) Tsang, A. S. K.; Hashmi, A. S. K.; Comba, P.; Kerscher, M.; Chan, B.; Todd, M. N-Aryl Groups are Ubiquitous in Cross Dehydrogenative Couplings Because They Stabilize Reactive Intermediates. *Chem. Eur. J.* **2017**, *23*, 9313-9318; (b) Tsang, A. S.-K.; Jensen, P.; Hook, J. M.; Hashmi, A. S. K.; Todd, M. H. An oxidative carbon–carbon bond-forming reaction proceeds via an isolable iminium ion. *Pure Appl. Chem.* **2011**, *83*, 655-665.

(14) (a) Dhineshkumar, J.; Lamani, M.; Alagiri, K.; Prabhu, K. R. A Versatile C–H Functionalization of Tetrahydroisoquinolines Catalyzed by Iodine at Aerobic Conditions. *Org. Lett.* **2013**, *15*, 1092-1095; (b) Freeman, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. Functionally Diverse Nucleophilic Trapping of Iminium Intermediates Generated Utilizing Visible Light. *Org. Lett.* **2012**, *14*, 94-97.

(15) Zhang, R.; Qin, Y.; Zhang, L.; Luo, S. Mechanistic Studies on Bioinspired Aerobic C–H Oxidation of Amines with an ortho-Quinone Catalyst. *J. Org. Chem.* **2019**, *84*, 2542-2555.

(16) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. Aerobic Ruthenium-Catalyzed Oxidative Cyanation of Tertiary Amines with Sodium Cyanide. *J. Am. Chem. Soc.* **2003**, *125*, 15312-15313.

(17) Yamaguchi, K.; Wang, Y.; Mizuno, N. A Widely Applicable Regioselective Aerobic α-Cyanation of Tertiary Amines Heterogeneously Catalyzed by Manganese Oxides. *ChemCatChem* **2013**, *5*, 2835-2838.

(18) Re-calculated slope, using the sigma-parameter values as used in this study.

(19) Shearer, J.; Zhang, C. X.; Hatcher, L. Q.; Karlin, K. D. Distinguishing Rate-Limiting Electron versus H-Atom Transfers in Cu2(O2)-Mediated Oxidative N-Dealkylations: Application of Inter- versus Intramolecular Kinetic Isotope Effects. *J. Am. Chem. Soc.* **2003**, *125*, 12670-12671.

(20) Burka, L. T.; Guengerich, F. P.; Willard, R. J.; Macdonald, T. L. Mechanism of cytochrome P-450 catalysis. Mechanism of N-dealkylation and amine oxide deoxygenation. *J. Am. Chem. Soc.* **1985**, *107*, 2549-2551.

(21) Baciocchi, E.; Bietti, M.; Lanzalunga, O.; Lapi, A.; Raponi, D. N-Demethylation of N,N-Dimethylanilines by the Benzotriazole N-Oxyl Radical: Evidence for a Two-Step Electron Transfer−Proton Transfer Mechanism. *J. Org. Chem.* **2010**, *75*, 1378-1385.

(22) Baciocchi, E.; Bietti, M.; Gerini, M. F.; Lanzalunga, O. Electron-Transfer Mechanism in the N-Demethylation of N,N-Dimethylanilines by the Phthalimide-N-oxyl Radical. *J. Org. Chem.* **2005**, *70*, 5144-5149.

(23) Wang, M.-Z.; Zhou, C.-Y.; Wong, M.-K.; Che, C.-M. Ruthenium-Catalyzed Alkylation of Indoles with Tertiary Amines by Oxidation of a sp3 C-H Bond and Lewis Acid Catalysis. *Chem. Eur. J.* **2010**, *16*, 5723-5735.

(24) Baciocchi, E.; Lanzalunga, O.; Lapi, A.; Manduchi, L. Kinetic Deuterium Isotope Effect Profiles and Substituent Effects in the Oxidative N-Demethylation of N,N-Dimethylanilines Catalyzed by Tetrakis(pentafluorophenyl)porphyrin Iron(III) Chloride. *J. Am. Chem. Soc.* **1998**, *120*, 5783-5787.

(25) Uneyama, K.; Namba, H.; Oae, S. Hydrogen Abstraction Reaction of α-Heteroatom Substituted Compounds by t-Butoxy Radical. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1928-1937.

(26) Singhal, S.; Jain, S. L.; Sain, B. Heterogeneously Catalyzed Oxidative Cyanation of Tertiary Amines with Sodium Cyanide/Hydrogen Peroxide using Polymer-Supported Iron(II) Phthalocyanines as Catalyst. *Adv. Synth. Catal.* **2010**, *352*, 1338-1344.

(27) Sureshkumar, D.; Sud, A.; Klussmann, M. Thieme Chemistry Journal Awardees - Where Are They Now? Aerobic Oxidative Coupling of Tertiary Amines with Silyl Enolates and Ketene Acetals. *Synlett* **2009**, 1558-1561.

(28) A succesful observation of iminium ion formation from x1x by IR-spectroscopy has been reported in ref. 12b

(29) (a) Ingold, C. K.; Shaw, F. R. The nature of the alternating effect in carbon chains. Part XXII. An attempt further to define the probable mechanism of orientation in aromatic substitution. *J. Chem. Soc.* **1927**, 2918-2926; (b) Brown, H. C.; Wang, K. K.; Scouten, C. G. Hydroboration kinetics: Unusual kinetics for the reaction of 9-borabicyclo[3.3.1]nonane with representative alkenes. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 698-702.

(30) Salamone, M.; Bietti, M. Tuning Reactivity and Selectivity in Hydrogen Atom Transfer from Aliphatic C–H Bonds to Alkoxyl Radicals: Role of Structural and Medium Effects. *Acc. Chem. Res.* **2015**, *48*, 2895-2903.

(31) (a) Gu, K.; Zhang, Z.; Bao, Z.; Xing, H.; Yang, Q.; Ren, Q. Thiourea-Catalyzed Cross-Dehydrogenative Coupling of C(sp3)–H with Diethyl Phosphite. *Eur. J. Org. Chem.* **2016**, *2016*, 3939-3942; (b) Ullah, B.; Zhou, Y.; Chen, J.; Bao, Z.; Yang, Y.; Yang, Q.; Ren, Q.; Zhang, Z. New catalytic effect of thiourea on the oxidative cyanation of N-aryltetrahydroisoquinolines. *Tetrahedron Lett.* **2019**, *60*, 348-351; (c) Han, W.; Ofial, A. R. Iron catalyzed oxidative cyanation of tertiary amines. *Chem. Commun.* **2009**, 5024-5026; (d) Sakai, N.; Mutsuro, A.; Ikeda, R.; Konakahara, T. Cobalt–Catalyzed Oxidative α-Cyanation of Tertiary Aromatic Amines with Trimethylsilyl Cyanide and tert-Butyl Hydroperoxide. *Synlett* **2013**, *24*, 1283-1285.

(32) (a) Jiang, J.-X.; Li, Y.; Wu, X.; Xiao, J.; Adams, D. J.; Cooper, A. I. Conjugated Microporous Polymers with Rose Bengal Dye for Highly Efficient Heterogeneous Organo-Photocatalysis. *Macromolecules* **2013**, *46*, 8779-8783; (b) Yang, W.; Wei, L.; Yan, T.; Cai, M. Highly efficient heterogeneous aerobic oxidative C-C coupling from Csp3-H bonds by a magnetic nanoparticle-immobilized bipy-gold(iii) catalyst. *Catal. Sci. Technol.* **2017**, *7*, 1744-1755; (c) Dutta, B.; Sharma, V.; Sassu, N.; Dang, Y.; Weerakkody, C.; Macharia, J.; Miao, R.; Howell, A. R.; Suib, S. L. Cross dehydrogenative coupling of N-aryltetrahydroisoquinolines (sp3 C-H) with indoles (sp2 C-H) using a heterogeneous mesoporous manganese oxide catalyst. *Green Chem.* **2017**, *19*, 5350-5355.

(33) (a) Wanner, K. T.; Praschak, I.; Nagel, U. Asymmetric Electrophilic α-Amidoalkylation, VII: Generation, Crystal Structure, and Trapping Reactions of a Chiral 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline Derived N-Acyliminium Ion. *Arch. Pharm.* **1990**, *323*, 335-350; (b) Dubs, C.; Hamashima, Y.; Sasamoto, N.; Seidel, T. M.; Suzuki, S.; Hashizume, D.; Sodeoka, M. Mechanistic Studies on the Catalytic Asymmetric Mannich-Type Reaction with Dihydroisoquinolines and Development of Oxidative Mannich-Type Reactions Starting from Tetrahydroisoquinolines. *J. Org. Chem.* **2008**, *73*, 5859-5871; (c) Richter, H.; García Mancheño, O. Dehydrogenative Functionalization of C-H Bonds Adjacent to a Heteroatom Mediated by Oxoammonium Salts. *Eur. J. Org. Chem.* **2010**, 4460-4467; (d) Liu, X.; Sun, B.; Xie, Z.; Qin, X.; Liu, L.; Lou, H. Manganese Dioxide–Methanesulfonic Acid Promoted Direct Dehydrogenative Alkylation of sp3 C–H Bonds Adjacent to a Heteroatom. *J. Org. Chem.* **2013**, *78*, 3104-3112; (e) Schweitzer-Chaput, B.; Klussmann, M. Brønsted acid-catalyzed C-H Functionalisation of N-Protected Tetrahydroisoquinolines via Intermediate Peroxides. *Eur. J. Org. Chem.* **2013**, 666-671.

(34) Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. NMR Chemical Shifts of Trace Impurities: Common Laboratory Solvents, Organics, and Gases in Deuterated Solvents Relevant to the Organometallic Chemist. *Organometallics* **2010**, *29*, 2176-2179.

(35) Li, Z.; Li, C.-J. CuBr-catalyzed direct indolation of tetrahydroisoquinolines via cross-dehydrogenative coupling between sp3 C-H and sp2 C-H bonds. *J. Am. Chem. Soc.* **2005**, *127*, 6968-6969.

(36) Xie, W.; Liu, N.; Gong, B.; Ning, S.; Che, X.; Cui, L.; Xiang, J. Electrochemical Cross-Dehydrogenative Coupling of N-Aryl-tetrahydroisoquinolines with Phosphites and Indole. *Eur. J. Org. Chem.* **2019**, *2019*, 2498-2501.

(37) Nauth, A. M.; Otto, N.; Opatz, T. α-Cyanation of Aromatic Tertiary Amines using Ferricyanide as a Non-Toxic Cyanide Source. *Adv. Synth. Catal.* **2015**, *357*, 3424-3428.

(38) Shu, X.-Z.; Xia, X.-F.; Yang, Y.-F.; Ji, K.-G.; Liu, X.-Y.; Liang, Y.-M. Selective Functionalization of sp3 C−H Bonds Adjacent to Nitrogen Using (Diacetoxyiodo)benzene (DIB). *J. Org. Chem.* **2009**, *74*, 7464-7469.

(39) Toma, G.; Yamaguchi, R. Cobalt-Catalyzed C–N Bond-Forming Reaction between Chloronitrobenzenes and Secondary Amines. *Eur. J. Org. Chem.* **2010**, *2010*, 6404-6408.

(40) Ma, Y.-N.; Yang, X.-J.; Pan, L.; Hou, Z.; Geng, H.-L.; Song, X.-P.; Zhou, L.; Miao, F. Synthesis of 2-Aryl-3,4-dihydroisoquinolin-2-ium Bromides and Their in Vitro Acaricidal Activity against Psoroptes cuniculi. *Chem. Pharm. Bull.* **2013**, *61*, 204-211.