Organic LETTERS

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Efficient and General Aerobic Oxidative Cross-Coupling of THIQs with Organozinc Reagents Catalyzed by $CuCl_2$: Proof of a Radical Intermediate

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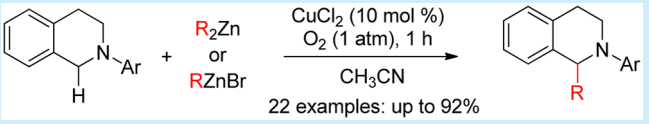
Supporting Information

ABSTRACT: A general new method for the highly concise synthesis of C-1-alkylated tetrahydroisoquinolines (THIQ) is reported. The $CuCl_2$-catalyzed procedure is based on a coupling of nonfunctionalized THIQs with organozinc reagents under aerobic conditions. It proceeds in high yields and is broadly applicable to a wide range of substrates. It relies on a regioselective sp^3 C−H bond activation allowing for an sp^3−sp^3 bond union under mild reaction conditions in a rapid and effective manner. Mechanistically it involves an iminium ion intermediate that is formed via an organic radical involving a single-electron-transfer process. For the first time for this type of reaction a radical intermediate has been proven by EPR spectroscopy.



C−C bond formation via C−H bond activation is one of the most challenging reactions in organic synthesis and has attracted great interest.[1] It not only breaks limitations of the traditional cross-coupling reaction but also enables direct access to C−C bonds quickly and effectively. However, this kind of reaction usually requires harsh conditions such as higher temperature, pressure, and acidic and oxidative conditions[2] and poses additional challenges of regioselectivity.[3] Within this context, the selective functionalization of reactive sp^3 C−H bonds adjacent to a nitrogen atom hold a special place as they may be effectively activated under oxidative conditions and the resulting iminium ion intermediates may react with various nucleophiles. Various metals such as copper,[4] ruthenium,[5] iron,[6] rhodium,[7] vanadium,[8] and platinum[9] have been developed for the activation of such positions, and several of these metal-catalyzed methods have been applied for activation of *N*-benzylic positions and used for C-1 derivatizations of tetrahydroisoquinolines (THIQs).[4b−l,5a,b,d−f,8,9] Alternatively, metal-free variants using DDQ,[10] hypervalent iodine,[11] or DEAD[12] were reported to oxidize THIQ structures.

Inspired by analogue studies in our group[13] and a hit in a screening program[14] in combination with certain limitations of existing methods in particular with respect to modularity and substrate scope, we desired a very general method for the synthesis of various C-1-substituted tetrahydroisoquinolines (THIQ) that would be based on a direct C−H activation.[15]

Herein, we report the design, development, and scope of a broadly applicable aerobic oxidative cross-coupling of THIQs (**2**, Figure 1) with organozinc reagents catalyzed by $CuCl_2$ to access diversely substituted derivatives **1** in an effective and broadly applicable manner. Furthermore, we report for the first time the detection and structural information on a radical intermediate in these oxidative amine activations by EPR spectroscopy. The reported procedure presents the first general extension of this

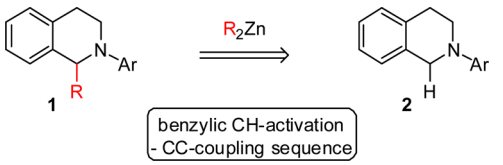


Figure 1. Proposed sp^3-CH-activation cross-coupling strategy of THIQs with organometallic reagents.

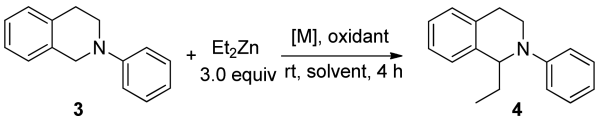
type of oxidative THIQ functionalization to organozinc reagents[5d] and is characterized by an extremely broad substrate scope that compares favorably to all existing methods.[4−12]

To test our notion for a modular approach to C-1-substituted tetrahydroisoquinolines by means of a copper-catalyzed coupling with various organozinc reagents, we evaluated the reaction of substrate **3** with diethylzinc under various reaction conditions, as shown in Table 1. Starting with $CuCl_2$ as catalyst, the reaction was carried out under various conditions with different solvents (entries 1−7). Best results were obtained in acetonitrile (0.1 M) with $CuCl_2$ (10 mol %) and O_2 as oxidant. After 4 h at room temperature, the desired ethyl derivative **4** was obtained in high yields (92%, entry 7). Only poor degrees of conversions were obtained with other solvents like THF, acetone, toluene, DMF, dichloromethane (DCM), and MeOH (entries 1−6), demonstrating a pronounced effect of the solvent on the outcome of the reaction. Among the oxidants evaluated (entries 7−10), oxygen (1 atm) was found to be optimal. Lower degrees of conversion were obtained with TBHP (entry 8), MnO_2 (entry 9), and ^{t}BuOO^{t}Bu (entry 10). Also other copper metals like CuCl, $CuBr_2$, CuBr, CuI, $Cu(OTf)_2$, and anhydrous Cu_2SO_4 (entries

Received: June 26, 2015

DOI: 10.1021/acs.orglett.5b01845
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Development and Optimization of Reaction Conditions[a]



entry	catalyst	oxidant	solvent[b]	conversion[c] (%)
1	$CuCl_2$	O_2	THF	10
2	$CuCl_2$	O_2	acetone	20
3	$CuCl_2$	O_2	toluene	<5
4	$CuCl_2$	O_2	DMF	35[d]
5	$CuCl_2$	O_2	DCM	<5
6	$CuCl_2$	O_2	MeOH	10
7	$CuCl_2$	O_2	CH_3CN	92[d]
8	$CuCl_2$	TBHP[e]	CH_3CN	64[d]
9[f]	$CuCl_2$	MnO_2	CH_3CN	30
10[f]	$CuCl_2$	$^tBuOO^tBu$	CH_3CN	35
11	CuCl	O_2	CH_3CN	7
12	$CuBr_2$	O_2	CH_3CN	28
13	CuBr	O_2	CH_3CN	15
14	CuI	O_2	CH_3CN	8
15	$Cu(OTf)_2$	O_2	CH_3CN	55[d]
16	Cu_2SO_4	O_2	CH_3CN	9
17	$FeCl_3$	O_2	CH_3CN	13
18	$RuCl_3 \cdot xH_2O$	O_2	CH_3CN	10
19	V_5O_2	O_2	CH_3CN	0

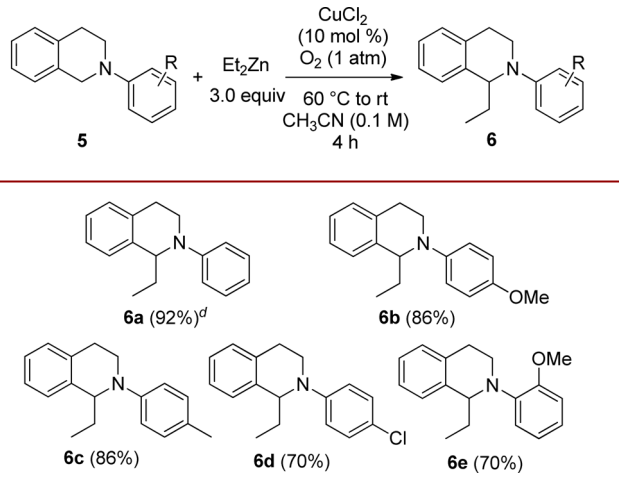
[a]Reaction was performed with **3** (0.20 mmol), Et_2Zn (3.0 equiv), [catalyst] (10 mol %), and the indicated oxidant in the given solvent (0.1 M) for 4 h under the room temperature. [b]All solvents were dried by molecular sieves. [c]Conversion was determined by ^1H NMR. [d]Isolated yield. [e]TBHP solution (5.0–6.0 M) in decane. [f]Reaction temperature, 60 °C, and time, 14 h.

11–16) and other metallic oxidants like $FeCl_3$, $RuCl_3$, and V_5O_2 (entries 17–19) resulted in all cases in lower degrees of conversion.

Having established optimal conditions for the coupling of **3** with Et_2Zn, we evaluated the generality of this C–H alkylation sequence. As shown in Scheme 1, the coupling of THIQs with various nitrogen bearing aryl substituents (**5**) was studied. It became apparent that variations of the electronic nature of these substituents had a strong effect on the conversion of the reaction. Therefore, after careful consideration, higher temperatures were employed to promote the reaction. After 1 h of oxidation at 60 °C, the reaction was cooled to room temperature, and subsequently, diethylzinc was added (Scheme 1). Substrates with strong electron-donating groups like a methoxy group (**6b**), with weak electron-donating groups like a methyl group (**6c**,**e**) all gave high yields. In addition, useful yields were obtained for substrates with halogen atoms such as Cl (**6d**). In contrast, no reaction with substrates that lack an *N*-aryl substituent or bear an alternative substitutent (e.g., a BOC group) was observed (not shown), demonstrating again that the *N*-aryl substituent is very important for reactivity, in full agreement with previous work.[4−12]

Importantly, aryl substituents with an *o*- or a *p*-methoxy group (i.e., compounds **6c** and **6e**) serve as suitable surrogates for the phenyl group, giving the products in similar yields as compared to the phenyl-protected amines. This is important, as removal of the *N*-aryl substituent may be required. While an *N*-aryl substituent was initially desired within this study,[14] removal of this substituent may be important to to expand the full value of

Scheme 1. Reaction Scope with Diethylzinc Reagent[a−d]

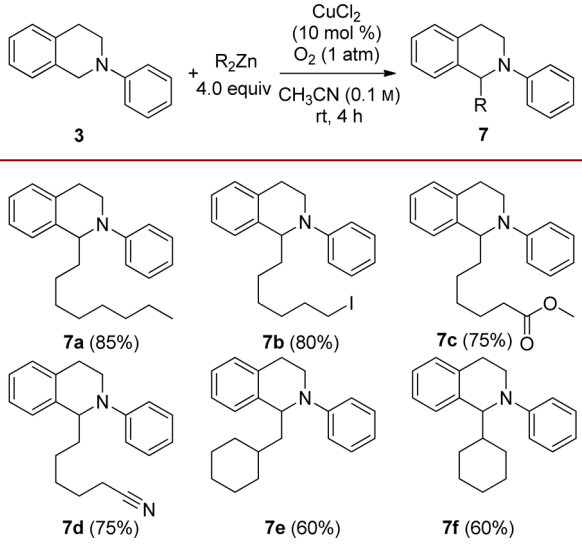


[a]Reaction was performed with **5** (0.20 mmol), Et_2Zn (3.0 equiv), $CuCl_2$ (10 mol %), and O_2 (1 atm) in CH_3CN (0.1 M) for 4 h under 60 °C to room temperature. [b]All solvents were dried by molecular sieves. [c]Isolated yield. [d]Reaction temperature: rt.

this method. Importantly, the groups of Stephensen[5f] and Tomioka[16] have reported on closely related C-1-alkylated THIQs with 2-methoxy-bearing and 4-methoxy-bearing aryl substituents that these aryl substitutents may be removed in high yields with CAN in the presence of stoichiometric amounts of $[Fe(bpy)_3]^{3+}$[5f] (*o*-methoxy group) or without a catalyst (*p*-methoxy group).[20] Indeed, the PMP group of **6b** could be readily removed with CAN.[17] This opens the valuable option of accessing the free secondary amines if a suitable protective group strategy is implemented.

As shown in Scheme 2, the reaction could also be readily expanded to other dialkylzinc reagents demonstrating the generality of this process. All dialkylzinc reagents may be readily prepared in situ by a method involving borane–diethylzinc

Scheme 2. Reaction Scope with Different Dialkylzinc Reagents[a,b]



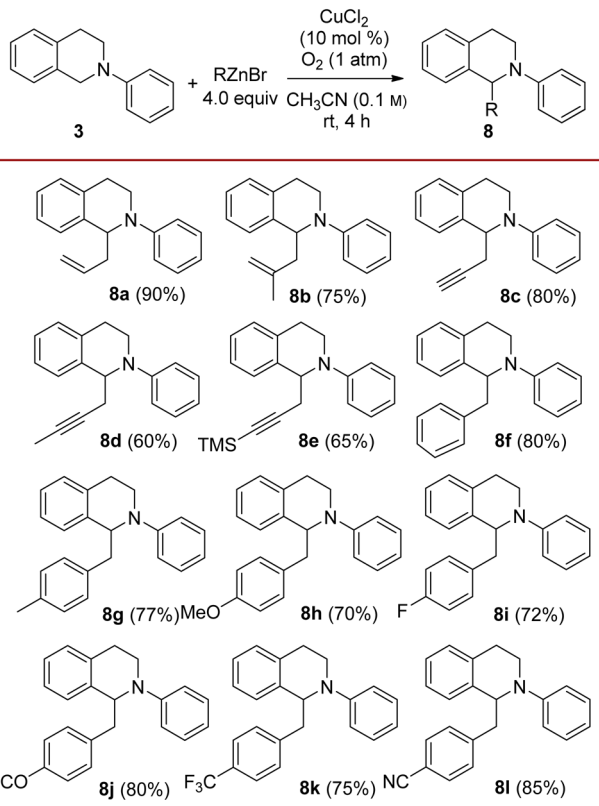
[a]Reaction was performed with **3** (0.20 mmol), Et_2Zn (4.0 equiv), $CuCl_2$ (10 mol %), and O_2 (1 atm) in CH_3CN (0.1 M, dried by molecular sieves) for 4 h at room temperature. [b]Isolated yield.

DOI: 10.1021/acs.orglett.5b01845
Org. Lett. XXXX, XXX, XXX–XXX

exchange[18,19] and includes reagents with valuable functionalities like an iodide (**7b**), an ester (**7c**), or a cyanide (**7d**). In all cases, good yields were obtained in the C−C coupling. However, steric hindrance at the α (see **7f**) or the β position (see **7e**) may result in a slight decrease of the reaction yield under the same conditions.

We then turned our attention to organozinc bromide reagents. The respective allylzinc, propargylzinc, and benzylzinc bromide derivatives were prepared by insertion from the corresponding bromide using activated zinc.[20] As shown in Scheme 3, good

Scheme 3. Reaction Scope Different Alkylzinc Bromide Reagents[a,b]

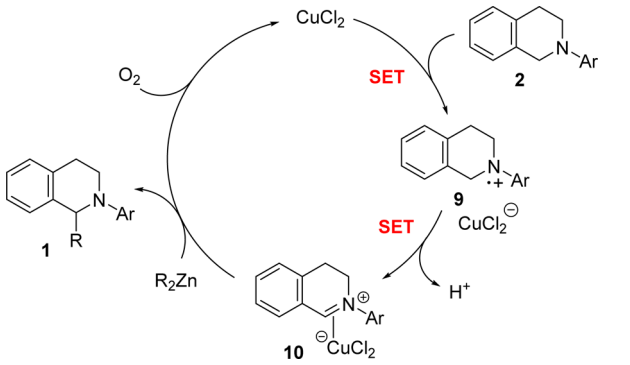


[a]Reaction was performed with **3** (0.20 mmol), Et_2Zn (4.0 equiv), $CuCl_2$ (10 mol %), and O_2 (1 atm) in CH_3CN (0.1 M, dried by molecular sieves) for 4 h at room temperature. [b]Isolated yield.

yields were obtained with terminal allyl bromide reagents (viz. **8a**, **8b**). In addition, all propargylzinc bromides studied gave rise to the desired products (**8c**, **8d**, and **8e**) with highest yields being obtained for simple propargylzinc bromide (**8c**, 80%). Due to partial alkyne to allene rearrangements, the other two propargylzinc bromide derivatives (**8d** and **8e**) gave slightly lower yields (60%, 65%). Benzyl bromide reagents were likewise added with useful yields (**8f–l**). A tendency of benzyl bromides with strong a electron-donating group such as methoxy (**8h**) toward dimerization during zinc insertion was observed, resulting in decreased yields for these substrates (**8h**: 70%). Benzyl bromide derivatives with weak electron-donating group or electron-withdrawing groups such as methyl, fluoride, or trifluoromethoxy groups or trifluoromethyl and cyanide groups reacted smoothly (**8f,g,i–l**: 75−85%).

As shown in Scheme 4, this reaction is expected to proceed via an iminium ion intermediate of type **10**, in agreement with mechanistic studies of Klussmann on copper-catalyzed oxidative

Scheme 4. Proposed Mechanism of the Cu-Catalyzed Aerobic Oxidative Cross-Coupling of THIQs with Organozinc Reagents



addition reactions of phenyltetrahydroisoquinolines with various nucleophiles,[4i,j] as well as calculations by the group of Zhang, Wiest, and Wu[21] and an additional mechanistic proposal.[22] This electrophilic intermediate should then react with the nucleophilic zinc reagent. Presumably, the copper catalyst has a direct influence on this coupling as alternative methods for oxidative generation of the iminium ion intermediate in the absence of a copper catalyst did not result in similar degrees of CC bond formation (see Table 1). Two main pathways have been postulated for generation of this iminium ion intermediate in these types of copper-catalyzed oxidative addition reactions. These involve either a single-electron-transfer process or a process in which O_2 is directly involved.[4a,i,j,21] In order to shine some light on this aspect of the coupling reaction we measured an EPR spectrum of THIQ and $CuCl_2$ in dry acetonitrile. We were able to detect a radical with a g value of 2.014 and a peak to peak line width of approximately 66 G. This is consistent with an organic radical that supports a reaction mechanism that involves a radical intermediate, presumably of type **9**. This should be formed by a single electron transfer (SET). The g value of 2.014 is much larger than the g value of the free electron (2.0023), which indicates that the radical is predominantly centered at the nitrogen, since carbon-centered radicals usually exhibit a g value near the value for a free electron.[23] Therefore, the radical intermediate is most likely not a benzylic radical. In principle, this may also be possibly due to the low pK_a associated with the α C−H bond of radical cations, particularly benzylic ones. Another SET and deprotonation should then give iminium ion **10**.

In conclusion, we have developed a new and broadly applicable alkylation of THIQ derivatives by an aerobic cross-coupling with diorganozinc reagents or organozinc bromide reagents under $CuCl_2$ catalyst in good yields. THIQ derivatives were oxidized to an intermediate iminium ion, which subsequently underwent a cross-coupling of organocuprate reagents. Furthermore, we have shown that this reaction proceeds via a nitrogen-centered radical that is produced by a single-electron-transfer reaction. This method could introduce a broad range of alkyl groups, allyl groups, propargyl groups, and benzyl groups efficiently. In addition, *ortho*- and *para*-susbstituted *N*-phenyl substrates react with similar efficiency, which opens the valuable option to also access the secondary amines. It is expected that this reaction will find useful applications in synthetic chemistry and pharmaceutics due to the attractive skeleton of the products and the broad applicability and generality of the process. The present studies are directed toward shedding further light on the mechanism of this reaction, to expand this type of cross-coupling also to other

DOI: 10.1021/acs.orglett.5b01845
Org. Lett. XXXX, XXX, XXX−XXX

radical-mediated processes, and to apply it in directed SAR studies.[13,14]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01845.

Experimental details, spectral data, and copies of NMR spectra for all new compounds (PDF)

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Author Contributions

[§]T.W. performed the synthetic work. M.S. performed the PMP deprotection.

Author Contributions

[‖]A.B. performed the EPR measurements.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Generous financial support by the Deutsche Forschungsgemeinschaft (SFB 813) and the Chinese Scholarship Council (stipend to T.W.) is gratefully acknowledged.

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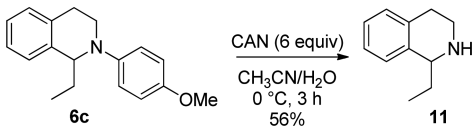
(17) For details on the removal of the PMP group of **6c**, see the Supporting Information.



6c **11**

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(19) While Et_2Zn is commercially available, all other alkylzinc reagents were prepared. For practical purposes, 4 equiv of these reagents were used in the coupling reaction. However, similar yields may also be obtained with only 3 equiv of the R_2Zn or RZnBr reagent. Full experimental details are found in the Supporting Information.

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DOI: 10.1021/acs.orglett.5b01845
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