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Synthesis of 2-Substituted Quinolines *via* Rhodium(III)-Catalyzed C–H Activation of Imidamides and Coupling with Cyclopropanols

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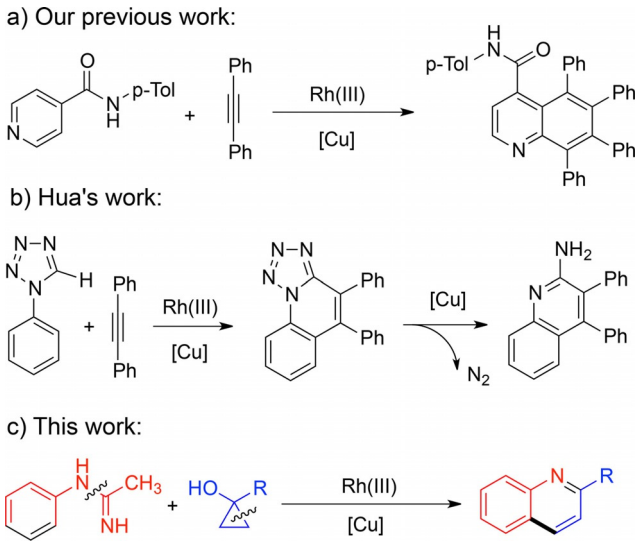
Abstract: An efficient synthesis of 2-substituted quinolines from readily available cyclopropanols and imidamides has been developed, where the cyclopropanol acts as a C_3 synthon. With the assistance of a bifunctional imidamide directing group, the reaction occurred *via* sequential C–H/C–C cleavage and C–C/C–N bond formation.

Keywords: C–H activation; C–N bond formation; cyclopropanols; imidamides; 2-substituted quinolines

N-Heterocyclic compounds are important motifs which are widely found in pharmaceuticals and natural products.[1] The high efficiency of transition metal-catalyzed C–H functionalization has opened valuable avenues in nitrogen-containing heterocycle synthesis, which obviates preactivation of the substrates and reduces the number of synthesis steps.[2] In this regard, Cp*Rh(III) catalysts have demonstrated to be very effective for the construction of heterocycles with high reactivity and good functional group compatibility.[3] Recently, the synthesis of six-membered heterocycles such as isoquinolines,[4] isoquinolones,[5] and pyridines,[6] *via* rhodium(III) catalysis has been widely reported. However, examples of quinoline synthesis *via* rhodium(III)-catalyzed C–H bond activation are still limited. In 2011, we reported the rhodium(III)-catalyzed two-fold C–H activation of functionalized pyridines and coupling with two alkyne molecules for the synthesis of polysubstituted quinolines (Scheme 1).[7] Hua reported a tandem C–H activation and denitrogenative annulation between 1-aryltetrazoles and internal alkynes for the synthesis of substituted 2-aminoquinolines.[8] Moreover, Miura,[9] Chen,[10] and You[11] have reported the synthesis of aza-fused polycyclic quinolines *via* Cp*Rh(III) catalysis. Very recently, Cp*Co(III) complexes have been applied to the redox-neutral couplings between amides and alkynes to generate multisubstituted quinolines.[12] All these methods employed an internal alkyne as a coupling partner. Thus, only mulitsubstituted quinolines were obtained. However, the preparation of 2-monosubstituted quinolines by way of rhodium(III)/cobalt(III) catalysis is still challenging. Given the prevalence of 2-substituted quinoline and the limitation of previous methods, further development of novel synthetic methods for 2-substituted quinolines from readily available starting materials would be of prime synthetic value.



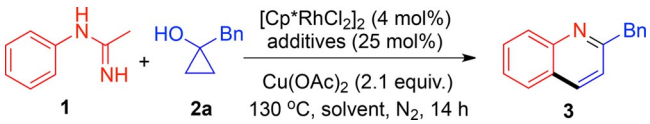
Scheme 1. The synthesis of quinolines *via* rhodium (III)-catalyzed C–H activation.

It has been reported that cyclopropanols can serve as a readily available C_3 synthon for the construction of cyclic compounds.[13] However, applications of cyclopropanols as a coupling partner in intermolecular C–H activation–annulation reactions have not been documented. We recently reported the *ortho* homoenolation of arenes using cyclopropanols *via* a rhodium(III)-catalyzed C–H activation pathway.[14] To further realize cyclization of the β-aryl ketone intermediate, a bifunctional nucleophilic directing group that attacks the resulting carbonyl group needs to be employed. We noted that amidines,[15] imidates,[16] benzamides,[17] and phenylhydrazine[18] bearing an NH group might serve this purpose. We now disclose a rhodium(III)-catalyzed annulative coupling between cyclopropanols and amidines for the synthesis of 2-substituted quinolines.

We initially selected *N*-phenylacetimidamide (**1a**) as a substrate for the coupling with 1-benzylcyclopropanol (**2a**) using $[Cp^*RhCl_2]_2$ (4 mol%) as a catalyst and CsOAc as a base in the presence of $Cu(OAc)_2$ oxidant. To our delight, 2-benzylquinoline (**3aa**) was obtained in 65% yield (Table 1, entry 1). Using $[Cp^*Rh(OAc)_2]$ as a catalyst also led to lower yield (entry 2). Switching to $[Cp^*CoCl_2]_2$ as a catalyst resulted in no desired product (entry 3). Effects of the solvent were then examined, and couplings in several other solvents all failed to give the desired product (entries 6–8). Screening of the additive revealed that NaOAc was slightly favored as a base (entry 9). Using a stronger base such as NaOMe decreased the yield (entry 10). Introduction of Mn(III) and Fe(III) salts further improved the yield (entries 11 and 12), which may facilitate electron-transfer during the oxidation process. Prolonging the reaction times further enhanced the yield (entry 13). A control experiment revealed that no desired product was generated when the rhodium catalyst was omitted. Our screening studies also showed that using other DGs such as an amide and a urea all failed to give any annulation product.

With the optimized conditions in hand, we first examined the scope and limitations of the imidamide substrate in the coupling with **2a** (Table 2). Imidamides bearing both electron-donating and electron-withdrawing *para*-substituents reacted smoothly to afford the quinolines in moderate to good yields (**3ba**–**3ha**), although introduction of an EWG tends to give an inferior yield (**3ga** and **3ha**). It is noteworthy that easily functionalized halogen groups are well tol-

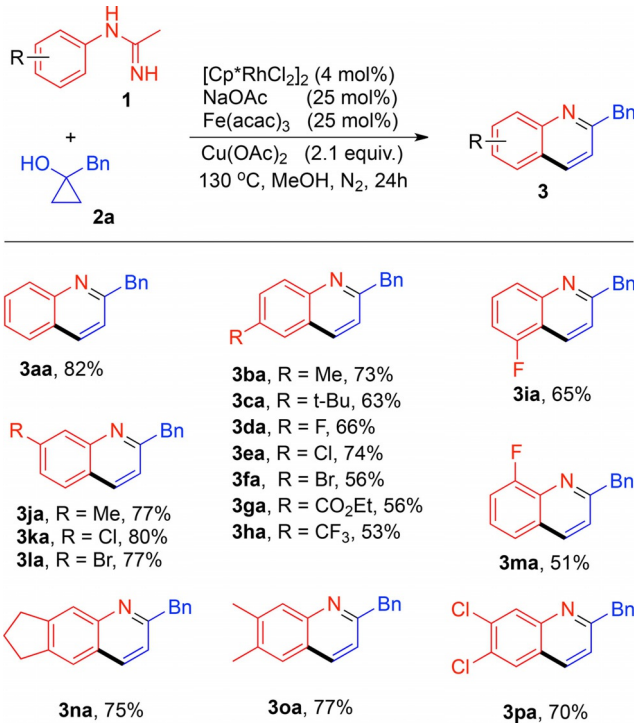
Table 1. Optimization studies.[a]



Entry	Solvent	Additives	Yield [%][b]
1	MeOH	CsOAc	65
2[c]	MeOH	CsOAc	58
3[d]	MeOH	CsOAc	NR
4[e]	MeOH	CsOAc	57
5[f]	MeOH	CsOAc	64
6	DMF	CsOAc	NR
7	DCE	CsOAc	NR
8	EtOH	CsOAc	NR
9	MeOH	NaOAc	67
10	MeOH	NaOMe	62
11[g]	MeOH	NaOAc, $Mn(OAc)_3$	76
12[h]	MeOH	NaOAc, $Fe(acac)_3$	77
13[i]	MeOH	NaOAc, $Fe(acac)_3$	82

[a] *Reaction conditions:* $[Cp^*RhCl_2]_2$ (4 mol%), additives (25 mol%), $Cu(OAc)_2$ (2.1 equiv.), **1a** (0.2 mmol), and **2a** (0.25 mmol) in a solvent (3 mL) at 130 °C under N_2 for 14 h.
[b] Isolated yield after column chromatography.
[c] $[Cp^*Rh(OAc)_2]$ (8 mol%) was used as a catalyst.
[d] $[Cp^*CoCl_2]_2$ (4 mol%) was used as a catalyst.
[e] At 140 °C.
[f] At 120 °C.
[g] NaOAc (25 mol%) and $Mn(OAc)_3$ (25 mol%) were used.
[h] NaOAc (25 mol%) and $Fe(acac)_3$ (25 mol%) were used.
[i] Reaction was performed for 24 h.

Table 2. Substrate scope of imidamides.[a,b]

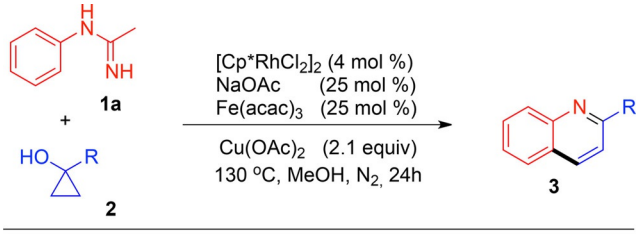


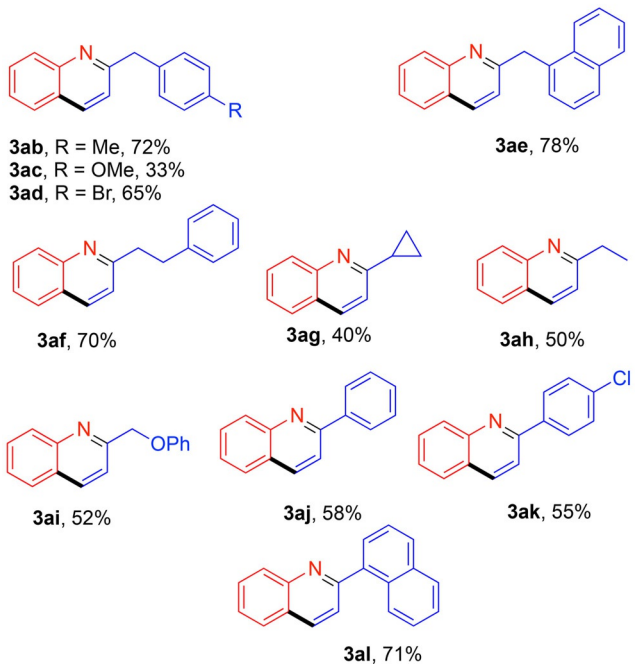
[a] Reactions were carried out using $[Cp^*RhCl_2]_2$ (4 mol%), NaOAc (25 mol%), $Fe(acac)_3$ (25 mol%), $Cu(OAc)_2$ (2.1 equiv.), **1** (0.2 mmol), and **2a** (0.25 mmol) in MeOH (3 mL) at 130 °C under N_2 for 24 h.
[b] Isolated yields.

erated (**3da–3fa**). Various *meta*-substituted imidamides coupled to give the desired quinoline in good yields at the less hindered *ortho* position (**3ja–3la**). In contrast, the coupling of a *meta*-F-substituted imidamide (**2i**) occurred exclusively at the more hindered position.[19] The imidamide with an *ortho*-F group also coupled to afford **3ma** in 51% yield. In addition, disubstituted imidamides were also viable for this transformation, affording the corresponding quinolines in 70–77% yields (**3na–3pa**).

To further define the scope of this system, the coupling of a range of cyclopropanols **2b–l** with imidamide **1a** was explored under the optimal conditions (Table 3). Introduction of different substituents to the phenyl group of 1-benzylcyclopropanol was well tolerated (**3ab–3ad**). When the phenyl group was replaced by a β-naphthyl, the reaction also proceeded smoothly and furnished the desired product in 78% yield (**3ae**). The substrate is not limited to a benzylcyclopropanol, elongation of the alkyl chain gave no obvious negative effect (**3af**). Other alkyl-, cyclopropyl-, phenoxymethyl- and arylcyclopropanols all coupled in good efficiency (**3ag–3al**).

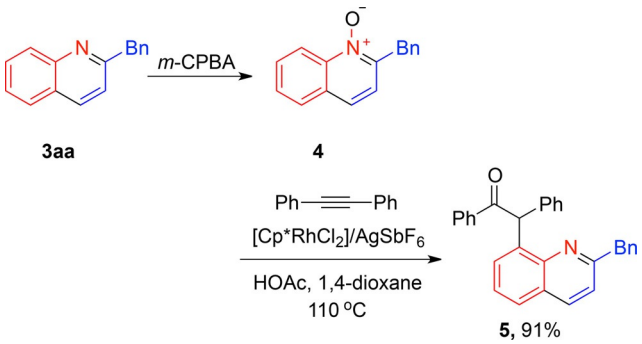
Table 3. Substrate scope of cyclopropanols.[a,b]





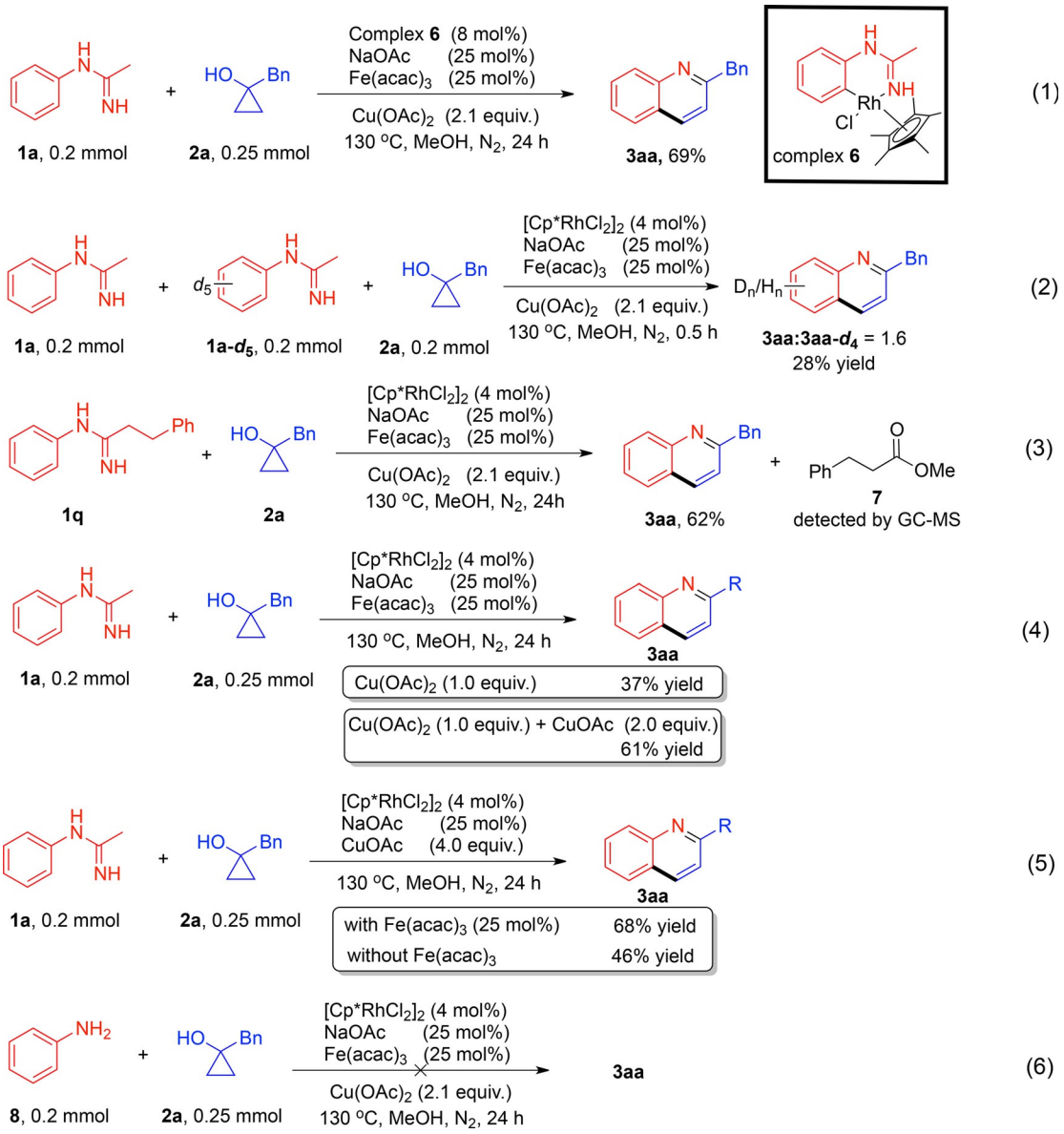
[a] See Table 2 for detailed conditions.
[b] Isolated yields.

A synthetic application of a quinoline product has been performed. Treatment of **3aa** with *m*-CPBA furnished the *N*-oxide (**4**) in nearly quantitative yield. Further functionalization *via* a combination of C–H activation with subsequent *O*-atom transfer was realized on the basis of our previous work (Scheme 2).[20]



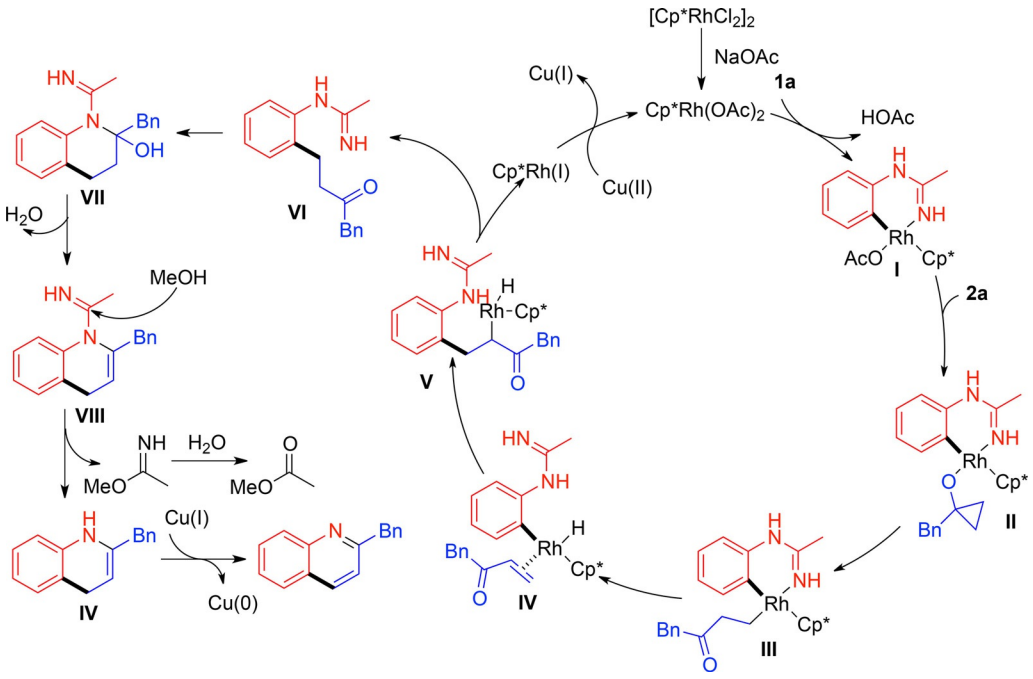
Scheme 2. Derivatization of 2-benzylquinoline.

We next carried out extensive mechanistic studies. A rhodacyclic complex (**6**) was prepared[15a] and was designated as a catalyst for the coupling of **1a** and **2a**. The fact that **3aa** was isolated in a comparably high yield 69% yield [Eq. (1)] suggested that C–H activation was involved. The kinetic isotope effect (KIE) of this reaction was then measured by intermolecular competition between **1a** and **1a**-d_5 at a low conversion. A relatively small value of $k_H/k_D = 1.6$ [Eq. (2)] seemed to suggest that C–H cleavage is probably not involved in the turnover-limiting step. Additional mechanistic experiments were performed to further probe the possible pathway of the reaction. Formation of an ester (**7**) was detected (GC-MS) as a co-product when **1q** was used as an arene substrate [Eq. (3)], indicating that that the reaction might include the nucleophilic attack of methanol to the imidamide carbon. Furthermore, control experiments were conducted to probe the role of Cu(I) species in this process. It was found that the yield of desired product decreased by half when only one equivalent of $Cu(OAc)_2$ was provided. However, further introduction of two equivalents of CuOAc increased the yield to 61% [Eq. (4)]. This seems to suggest that Cu(I) may act as an oxidant in the reaction. Indeed, switching to CuOAc (4 equiv.) as the sole oxidant in the presence or absence of $Fe(acac)_3$ afforded **3aa** in 68% and 46% yields, respectively [Eq. (5)]. Moreover, GC analysis of the head space of the reaction under the standard conditions revealed that essentially no H_2 was generated (see the Supporting Information). To probe the stage of C–N bond cleavage, simple aniline was allowed to couple with **2a** [Eq. (6)]. The absence of any desired product indicated the necessity of an imidamide directing group.



On the basis of our preliminary results and our previous studies,[14] a plausible catalytic cycle has been proposed (Scheme 3). Starting from [Cp*Rh(OAc)$_2$], cyclometallation of the imidamide gives a rhodacyclic intermediate **I**, ligand substitution of which generates an alkoxide species **II** that undergoes β-carbon elimination to yield a rhodium(III) homoenolate **III**. By following a sequence of β-hydride elimination and migratory insertion of the aryl group as we have recently extensively explored,[14] a rhodium(III) alkyl intermediate **V** was produced. Intramolecular nucleophilic addition of **VI** generates a hemiaminal, dehydration of which delivers an N-protected 1,4-dihydroquinoline **VIII**. Nucleophilic deprotection of **VIII** furnishes an NH-1,4-dihydroquinoline **IV**, which is readily oxidized[21] even by a Cu(I) species[22] to eventually furnish the product.

In summary, we have developed an efficient rhodium(III)-catalyzed annulative coupling between cyclopropanols and imidamides for the synthesis of 2-substituted quinolines. The reactions proceeded with broad substrate scope *via* sequential C–H/C–C activation and C–C/C–N bond formation. Of note, the cyclopropanol was introduced as a novel C_3 synthon in C–H activation chemistry. This efficient and facile protocol to approach synthetically important quinolines may find applications in the formation of complex structures.



Scheme 3. Proposed mechanism for the synthesis of quinolines.

Experimental Section

General Procedure: Imidamides Synthesis

A mixture of $AlCl_3$ (1.1 equiv.), aniline (1.1 equiv.) and carbonitrile (1 equiv.) was stirred at 130 °C under an inert atmosphere in a sealed tube overnight. The hot mixture was poured into a concentrated NaOH solution (40 mL) in a mixture of water and ice (100 mL) and stirred for about 15 minutes. Then the mixture was extracted with EtOAc (25 mL × 3). The combined organic layers were washed with brine (30 mL × 3), dried over anhydrous Na_2SO_4, and evaporated under vacuum. The residue was purified by column chromatography on silica gel.

General Procedure: Cyclopropanol Synthesis

Ethylmagnesium chloride (2 M solution in diethyl ether, 2.5 equiv.) was slowly added (within 20 min) to a solution of the ester (1 equiv.) and titanium(IV) isopropoxide (20 mol%) in THF at 0 °C. The black solution was stirred for 1 h, followed by addition of 1 M sulfuric acid (20 mL) at 0 °C to quench the reaction. The aqueous phase was extracted with Et_2O (3 × 50 mL), and the combined organic phases were dried over $MgSO_4$. Removal of solvent under vacuum afforded desired product.

General Procedure: Synthesis of Compounds 3

Imidamide (**1**, 0.2 mmol), cyclopropanol (**2**, 0.25 mmol), $[Cp^*RhCl_2]_2$ (4 mol%), NaOAc (25 mol%), $Fe(acac)_3$ (25 mol%), $Cu(OAc)_2$ (2.1 equiv.), and methanol (3.0 mL) were charged into a pressure tube. The reaction mixture was stirred at 130 °C for 24 h. After being cooled to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography using EA/PE to afford compound **3**.

Acknowledgements

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[22] At this stage, we cannot exclude the possibility of disproportionation of Cu(I) to Cu(0) and Cu(II), and that the Cu(II) acted as the real oxidant in this reaction.

