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Cross-Coupling

Copper-Catalyzed Cross-Coupling of Functionalized Alkyl Halides and Tosylates with Secondary and Tertiary Alkyl Grignard Reagents**

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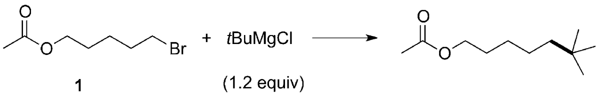
Efficient alkyl–alkyl cross-coupling reactions had been difficult to achieve because of the reluctance of alkyl electrophiles to undergo oxidative addition, and the propensity of metal alkyl intermediates for β-H elimination.[1] Recent work shows that these problems can be circumvented by the judicious choice of catalyst, ligand, and reaction conditions.[2–6] However, the coupling of non-activated alkyl electrophiles with secondary and tertiary alkyl nucleophiles is still challenging because of the difficulty in achieving transmetalation from sterically encumbered nucleophiles, and because the isomerization of metal alkyl species is often facile and would lead to undesired products.[7,8] As a result, these potentially valuable coupling reactions have not been systematically investigated and only a few examples have been reported.[3–5,7,9,10] Cahiez et al. and Kambe et al. showed that non-activated alkyl halides could be coupled to secondary and tertiary alkyl Grignard reagents in high yields in the presence of a copper salt, with or without a diene or alkyne ligand.[4,5,9] Together these studies provide an important proof of concept. However, only simple alkyl halides, such as octyl and decyl halides, were used as the substrates. These reactions demonstrated limited synthetic utility, because of the high reactivity of alkyl Grignard reagents towards functional groups. Following our earlier work on the functional-group-tolerant Kumada coupling of non-activated alkyl halides,[6,11] we decided to study the copper-catalyzed coupling reactions of functionalized alkyl electrophiles.[12] Herein, we describe a copper-based method that is efficient for the coupling of secondary and tertiary Grignard reagents with alkyl halides and tosylates containing important and sensitive functional groups. The high activity, broad substrate scope, and high functional-group tolerance of the copper catalysis demonstrate its value in preparative and synthetic useful reactions.

The coupling of ester-containing alkyl bromide **1** with *t*BuMgCl was used as the test reaction (Scheme 1). In the absence of a catalyst, no coupling product was formed. In the presence of a simple copper salt, such as CuCl, the coupling proceeded smoothly at room temperature. The yields were over 90 % for reactions in THF, toluene, and ether, but lower for reactions in *N*,*N*′-dimethylformamide (DMF) and *N*-methylpyrrolidone (NMP).[13] A catalyst loading of 0.5 mol % was sufficient to give a yield of 94 %. The coupling reaction could be catalyzed by a soluble copper(I) complex, such as $[(^{Me}N_2N)Cu(PPh_3)]$,[14] $[\{Cu(PPh_3)Cl\}_4]$, and $[Cu(Phen)(PPh_3)_2]NO_3$, to give the product in a similar yield.[13] $CuCl_2$ and $CuCl_2{\cdot}2\,H_2O$ were also suitable precatalysts.[13] Additional information on the influence of solvent, temperature, (pre)catalyst, and the (pre)catalyst loading can be found in Table S1 in the Supporting Information. It appears that Cu-catalyzed cross-coupling of **1** with *t*BuMgCl is highly efficient under mild reaction conditions, such as a small amount of CuCl, room temperature, in THF, and without additive.



(1)

1

(1.2 equiv)

Standard reaction conditions:
THF, RT, 1 h
CuCl (*n* mol%)

Yield: 0% (*n* = 0)
94% (*n* = 0.5)
94% (*n* = 3)

Scheme 1. Cross-coupling of **1** with *t*BuMgCl (yields determined by GC analysis).

Having demonstrated that copper catalysis could be applied for the coupling of a functionalized alkyl halide and a tertiary alkyl Grignard reagent, we decided to explore the scope of this catalysis. For the convenience of experimental manipulation, the reactions were carried out in THF, at room temperature, and with 3 mol % of CuCl as catalyst. A large number of functionalized alkyl electrophiles could be coupled to secondary and tertiary alkyl Grignard reagents to give the products in high yields upon isolation (Table 1). The coupling was generally completed within 1 hour.

Ester and amide groups were readily tolerated (Table 1, entries 1–4). A substrate containing a carboxylic acid group was successfully coupled when more than two equivalents of a Grignard reagent was used (Table 1, entry 5). Presumably one equivalent of the Grignard reagent first deprotonated the carboxylic acid group to form a carboxylate group, which did not interfere with the cross-coupling. Likewise, a substrate containing an alcohol group was coupled in a high yield under similar reaction conditions (Table 1, entry 6). As expected, the more robust ether and thioether groups were tolerated (Table 1, entries 7–10). Nitrile-containing substrates were coupled as well (Table 1, entries 11 and 12). An acetal group was tolerated, which is notable as upon transformation of this group useful aldehyde-containing compounds can be obtained (Table 1, entry 13). Gratifyingly, substrates containing important heterocyclic groups, such as indole, furan,

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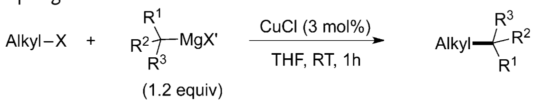
Table 1: Scope of Cu-catalyzed alkyl–alkyl coupling.[a]



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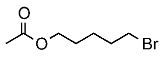
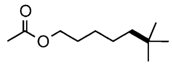
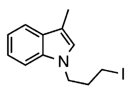
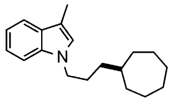
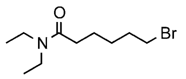
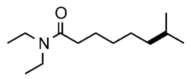
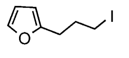
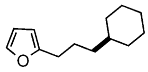
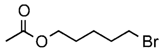
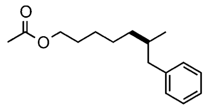
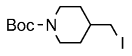
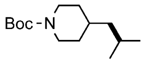
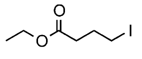
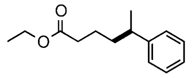
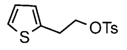
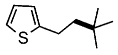
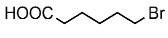
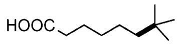
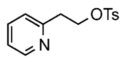
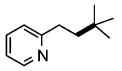
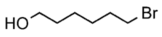
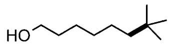
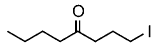
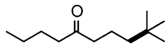
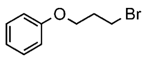
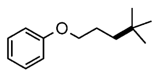
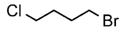
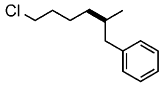
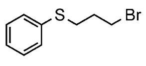
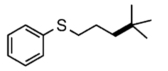
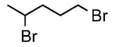
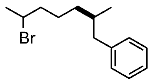
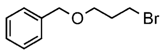
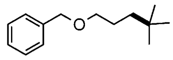
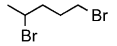
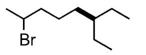
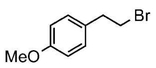
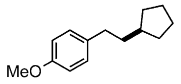
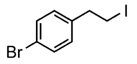
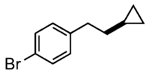
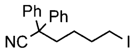
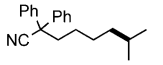
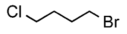
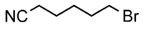
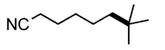
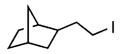
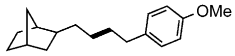
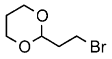
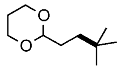
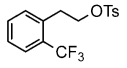
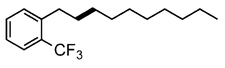
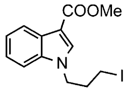
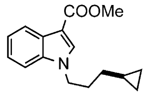
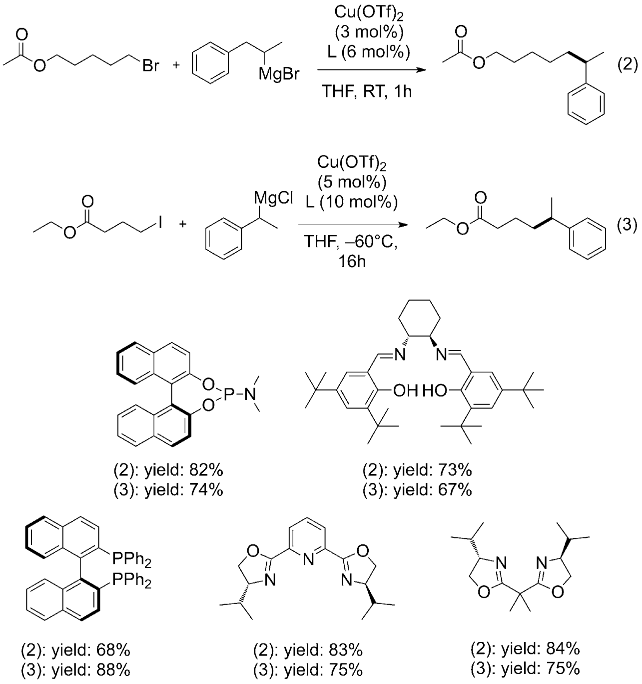
1			82	15			84
2			77	16			84
3			75	17			83
4			73	18			87
5			76[c]	19			74
6			91[c]	20			75[d]
7			81	21			93
8			82	22			85
9			90	23			76
10			80	24			94
11			82	25			90
12			75	26			93
13			86	27			78
14			82				

[a] See the Supporting Information for experimental details. [b] Yield of the isolated product. [c] 2.2 equiv of Grignard reagent was used. [d] 4 equiv of NMP was used as additive.

piperidine, thiophene, and pyridine groups, were coupled in high yields (Table 1, entries 14–19). The coupling of ketone-containing substrates was more challenging. Under the standard reaction conditions, the yields were about 30–50%.[13] However, it was found that NMP promoted the coupling of ketone-containing substrates. For example, with four equivalents of NMP as additive, the yield of a substrate containing an aliphatic ketone moiety was increased from 51% to 75% (Table 1, entry 20). The limit of the group tolerance of the coupling method was also probed, and these investigations indicated that aldehyde, nitro, and succinimide groups were not compatible with this method (see the Supporting Information, Table S2).[13]

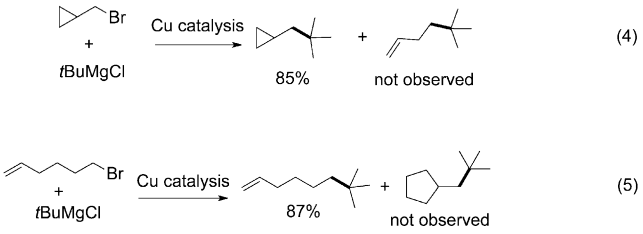
Not only alkyl iodides and bromides, but also alkyl tosylates could be coupled (Table 1, entries 18 and 19). Because tosylates are often easily prepared from the corresponding alcohols, this success significantly increases the synthetic utility of the present coupling method. Alkyl chlorides could not be coupled. Thus, for a molecule containing both a bromide and a chloride, selective coupling of the alkyl bromide was achieved (Table 1, entry 21). Likewise, because secondary alkyl halides could not be coupled, selective coupling of a primary alkyl bromide was accomplished for a molecule that also contained a secondary alkyl bromide (Table 1, entries 22–23). The coupling of an alkyl electrophile is selective in the presence of an aryl bromide moiety, which is on the same molecule (Table 1, entry 24). This feature could be useful for the sequential and selective functionalization of alkyl and aryl electrophiles. The nucleophilic coupling partners are not limited to *i*PrMgCl or *t*BuMgCl. Various acyclic and cyclic Grignard reagents could be used. Although the present work focuses on the coupling of secondary and tertiary alkyl Grignard regents, the same method can be used for the coupling of primary alkyl Grignard regents with high yields (Table 1, entries 25–27).

We attempted to develop enantioselective coupling reactions of a primary alkyl halide with a secondary alkyl Grignard reagent using a chiral copper catalyst. Two test reactions were investigated [Scheme 2, Eq. (2) and (3)]. Five chiral ligands commonly used for copper catalysis were applied in conjunction with a soluble copper salt—Cu(OTf)$_2$. As shown in Scheme 2, the yields of the coupling reactions were high regardless of the ligands employed. However, none of the five ligands gave rise to enantioselectivity, even at −60 °C. It is possible that the copper complexes containing these ligands cannot differentiate the two substituents of the secondary alkyl Grignard reagents. It is also possible that the active catalyst is an organocopper species without a chiral ligand attached. Further work is warranted to probe the origin of the lack of enantioselectivity, and to eventually develop an enantioselective coupling method.



Scheme 2. Cross-coupling reactions employing chiral ligands (yields determined by GC analysis).

A few experiments were conducted to probe the mechanism of the coupling reactions. The Cu-catalyzed coupling of **1** with *t*BuMgCl had the same yields in the absence and presence of an excess (100 equiv) amount of Hg.[13] This result suggests that a homogeneous copper species rather than heterogeneous copper particles is the active catalyst. The coupling of cyclopropylmethyl bromide with *t*BuMgCl yielded only neopentylcyclopropane, but not 5,5-dimethylhex-1-ene [Scheme 3, Eq. (4)]. The coupling of 6-bromo-1-hexene with *t*BuMgCl yielded only 7,7-dimethyloct-1-ene, but not neopentylcyclopentane [Scheme 3, Eq. (5)]. These results indicate that the activation of alkyl electrophile does not occur through a radical mechanism. Given that alkyl tosylates can be coupled in high yields, an S$_N$2 mechanism is more likely; this finding is consistent with the work of Kambe et al. on similar reactions.[4]



Scheme 3. Cross-coupling reactions to probe the reaction mechanism (yields determined by GC analysis).

In conclusion, we have developed a highly efficient method for the cross-coupling of non-activated and functionalized alkyl halides and tosylates with secondary and tertiary alkyl Grignard reagents.[15] The copper-based method is remarkably practical and general. The wide scope, and especially the tolerance to a large number of important yet sensitive functional groups, make this method attractive for the streamlined synthesis of functional molecules.[16]

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