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Copper-Catalyzed Cross-Coupling of Nonactivated Secondary Alkyl Halides and Tosylates with Secondary Alkyl Grignard Reagents

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Supporting Information

ABSTRACT: Practical catalytic cross-coupling of secondary alkyl electrophiles with secondary alkyl nucleophiles under Cu catalysis has been realized. The use of TMEDA and LiOMe is critical for the success of the reaction. This cross-coupling reaction occurs via an S_N2 mechanism with inversion of configuration and therefore provides a general approach for the stereocontrolled formation of C−C bonds between two tertiary carbons from chiral secondary alcohols.

Since the pioneering studies of Kochi and Tamura,[1] Suzuki,[2] and Knochel,[3] transition-metal-catalyzed C−C cross-couplings of nonactivated alkyl electrophiles have emerged as an important category of reactions.[4] While many transition-metal catalysts can now promote the coupling of primary alkyl halides or pseudohalides, the number of examples involving coupling of nonactivated secondary alkyl electrophiles is much smaller.[5] To solve this problem, Ni catalysts have been intensively studied for the coupling of secondary alkyl electrophiles,[6] whereas some Pd,[7] Fe,[8] and Co[9] catalysts have also been examined for the same purpose. It is noteworthy that most of the reported coupling reactions of secondary alkyl electrophiles proceed by a radical mechanism.[5,10] This mechanism disfavors the use of secondary alkyl tosylates[11] (which can be readily made from inexpensive secondary alcohols), and therefore, alternative catalysts need to be explored. Furthermore, most of the nucleophiles in the previous coupling reactions of secondary alkyl electrophiles are either aromatic or primary alkyl organometallic reagents.[12] It remains challenging to develop *cross-coupling reactions of secondary alkyl electrophiles with secondary alkyl nucleophiles*. Such transformations are desirable because they would increase the flexibility in the synthesis of complex carbon skeletons.

Here we report the cross-coupling of nonactivated secondary alkyl halides and pseudohalides with secondary alkyl Grignard reagents under Cu catalysis. Our work was inspired by the recent advances[13−17] in Cu-catalyzed cross-coupling of alkyl electrophiles to replace the classical stoichiometric alkylation reactions of organocopper reagents. Previous studies by Burns,[13] Kambe,[14] Cahiez,[15] and others,[16] including us,[17] have shown that the coupling of primary alkyl halides can be effectively promoted by different Cu catalysts. However, only a special Cu catalyst (i.e., Burns' catalyst "CuBr/LiSPh/LiBr/THF") was found to be able to induce the cross-coupling of secondary alkyl sulfonates with primary Grignard reagents *but still not secondary or aromatic ones*.[13] Through NMR analysis it was proposed that the active species of Burns' catalyst consisted of Cu ligated with LiBr in aggregated forms.[13] This hypothesis prompted us to examine the effect of other Li additives, which led to the discovery of an easier-to-use yet more powerful catalyst, namely, CuI/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA)/LiOMe. This catalyst expands the synthetic toolbox for the construction of C−C bonds between two tertiary carbons through transition-metal-catalyzed cross-coupling. Moreover, because this Cu-catalyzed cross-coupling reaction proceeds by an S_N2 mechanism, it provides a general approach for the stereocontrolled formation of C−C bonds from chiral secondary alcohols.

Our study began with an examination of the cross-coupling of 4-phenylbutan-2-yl tosylate (**1a**) with cyclohexylmagnesium bromide (CyMgBr, **2a**). We initially used CuI as the catalyst and THF as the solvent. Hexamethylphosphoramide (HMPA) was used as a cosolvent according to the previous work.[13] We also employed TMEDA as the additive because it may suppress undesirable side reactions such as olefin formation via loss of hydrogen halide.[8,10] Unfortunately, the yield of the desired product under these conditions was very low (Table 1, entry 1). Addition of LiCl or LiBr did not significantly improve the reaction (entries 2 and 3), but we were delighted to find that LiI, LiO^tBu, and LiOMe provided modest yields (entries 4−6). Further optimization increased the yield to 85% at 0 °C (entry 7). Interestingly, HMPA is not essential for the reaction (entry 8), but the use of TMEDA is important (entry 9). Other additives besides TMEDA, including P^{n}Bu$_3$, *N*-methylpyrrolidone (NMP), and PhC≡CCH$_3$, could also promote the reaction but gave lower yields (entries 10−12). On the other hand, changing CuI to CuBr, Cu(I) thiophene-2-carboxylate (CuTc), or Cu(OTf)$_2$ dramatically reduced the yield (entries 13−15). A secondary alkyl bromide was also a good substrate (entry 16), but the present conditions were not effective for the coupling of an alkyl iodide, chloride, or mesylate (entries 17−19). Finally, the reaction did not occur in the absence of catalyst (entry 20). Pd and Ni salts did not promote the reaction (entries 21 and 22), ruling out the involvement of Pd or Ni contamination in the catalysis.

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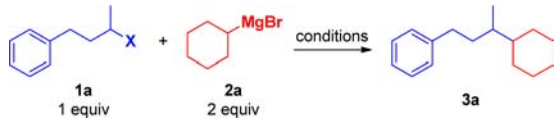
Table 1. Cross-Coupling between 1a and 2a[a]



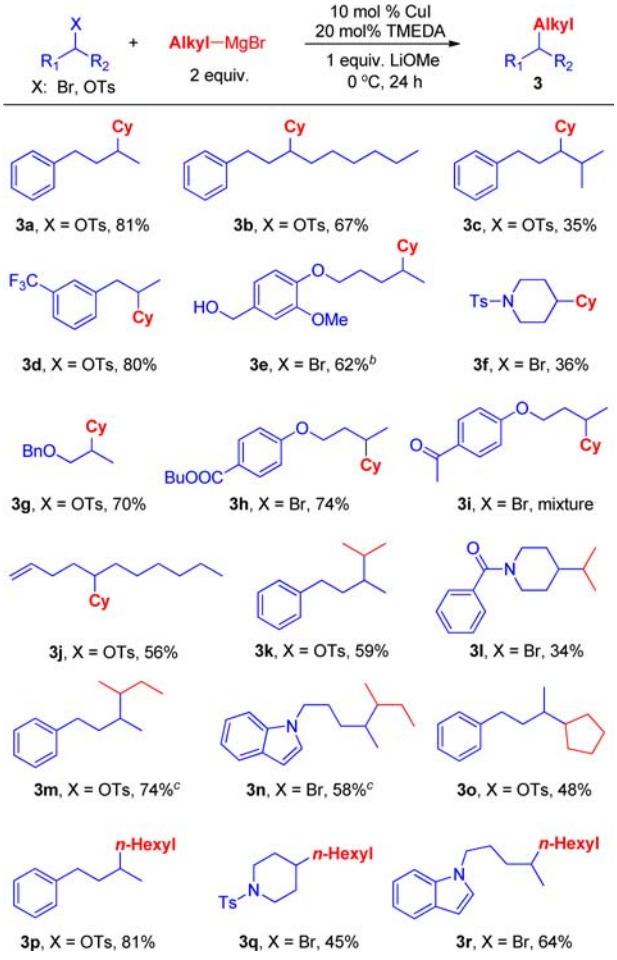
Entry	X	Catalyst (10 mol%)	Additive (20 mol %)	Li salt (1 equiv.)	Co-solvent	Temp. (°C)	Yield (%)[b]
1	OTs	CuI	TMEDA	-	HMPA	25	12
2	OTs	CuI	TMEDA	LiCl	HMPA	25	15
3	OTs	CuI	TMEDA	LiBr	HMPA	25	18
4	OTs	CuI	TMEDA	LiI	HMPA	25	43
5	OTs	CuI	TMEDA	LiO^{t}Bu	HMPA	25	46
6	OTs	CuI	TMEDA	LiOMe	HMPA	25	65
7	OTs	CuI	TMEDA	LiOMe	HMPA	0	85
8	**OTs**	**CuI**	**TMEDA**	**LiOMe**	**-**	**0**	**86(81[c])**
9	OTs	CuI	-	LiOMe	-	0	72
10	OTs	CuI	P^{n}Bu$_3$	LiOMe	-	0	76
11	OTs	CuI	NMP	LiOMe	-	0	75
12	OTs	CuI	PhC≡CCH$_3$	LiOMe	-	0	83
13	OTs	CuBr	TMEDA	LiOMe	-	0	54
14	OTs	CuTc	TMEDA	LiOMe	-	0	32
15	OTs	Cu(OTf)$_2$	TMEDA	LiOMe	-	0	56
16	Br	CuI	TMEDA	LiOMe	-	0	84
17	I	CuI	TMEDA	LiOMe	-	0	43
18	Cl	CuI	TMEDA	LiOMe	-	0	8
19	OMs	CuI	TMEDA	LiOMe	-	0	21
20	OTs	-	TMEDA	LiOMe	-	0	Trace
21	OTs	Pd(OAc)$_2$	TMEDA	LiOMe	-	0	Trace[d]
22	OTs	NiI$_2$	TMEDA	LiOMe	-	0	Trace[d]

[a]Conditions: R–X (0.5 mmol), CyMgBr (1 M in THF, 1 mL), catalyst (10 mol %), additive (20 mol %), Li salt (0.5 mmol), HMPA (50 μL). [b]GC yields after 24 h (averages of two runs). [c]Isolated yield. [d]2 mol % catalyst was added. NiI$_2$ was used in entry 22 because it is an anhydrous salt. NiCl$_2$ and NiBr$_2$ as hydrated salts gave the same negative results.

The above results show that CuI/TMEDA/LiOMe is a competent catalyst for the cross-coupling of secondary alkyl bromides and tosylates with secondary alkyl Grignard reagents. In regard to the scope of this method (Table 2), secondary alkyl electrophiles with different chain lengths and branching can participate in the reaction. Both cyclic (**3a–j**, **3o**) and acyclic (**3k–n**) Grignard reagents are good substrates. The same reaction conditions can also be used for coupling with primary alkyl Grignard reagents (**3p–r**). More importantly, a variety of synthetically useful functional groups, including CF$_3$ (**3d**), ether (**3e**, **3g**, **3h**), *N*-Ts (**3f**, **3q**), ester (**3h**), olefin (**3j**), amide (**3l**), heterocycle (**3n**, **3r**), and even an unprotected OH group (**3e**) can be tolerated in the transformation. It is interesting that an ester moiety (**3h**) can survive the reaction conditions (surprisingly, we did not observe ester exchange between LiOMe and the butyl ester in **3h**). However, the presence of a ketone group leads to a mixture of products (**3i**).

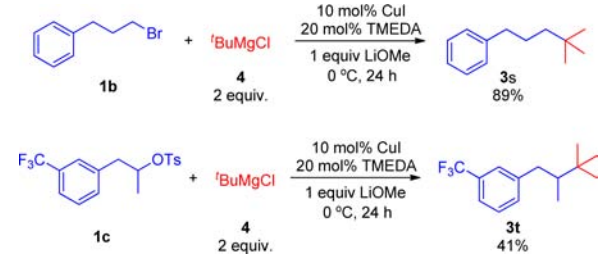
Further tests showed that the present catalyst may also be used for coupling with tertiary alkyl Grignard reagents (Scheme 1). Such reactions are synthetically useful, as they allow the attachment of a ^{t}Bu group to a primary or secondary carbon atom. The reaction between **1c** and **4** also represents the first example of catalytic cross-coupling between a tertiary carbon and a quaternary carbon from ordinary, nonactivated aliphatic substrates.[18] Moreover, although previous studies of Cu-catalyzed cross-couplings have not shown any examples of the arylation of a nonactivated secondary electrophile,[13−17] our experiments show that CuI/TMEDA/LiOMe is active enough to promote the cross-coupling of secondary alkyl iodides with aryl Grignard reagents (Scheme 2).

Table 2. Substrate Scope of the Coupling Reaction[a]

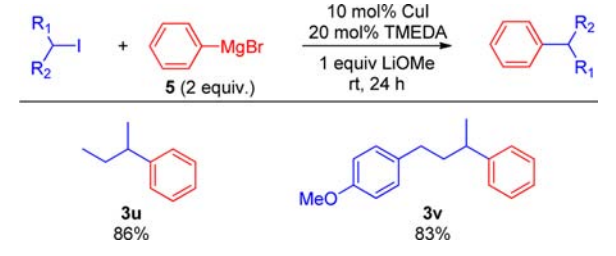


[a]Reactions were carried out at 0 °C for 24 h on a 0.5 mmol scale using 10 mol % CuI. For details, see the Supporting Information. Yields were determined through isolation of the desired products. [b]3 equiv of CyMgBr was used. [c]Diastereomeric mixture.

Scheme 1. Coupling with a Tertiary Grignard Reagent



Scheme 2. Coupling with an Aryl Grignard Reagent



In regard to the chemoselectivity of the reaction, we found that in the case of substrates with aryl and alkyl sites, the latter

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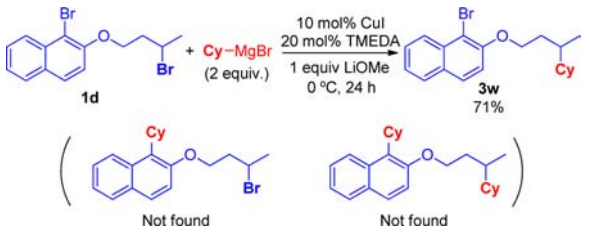
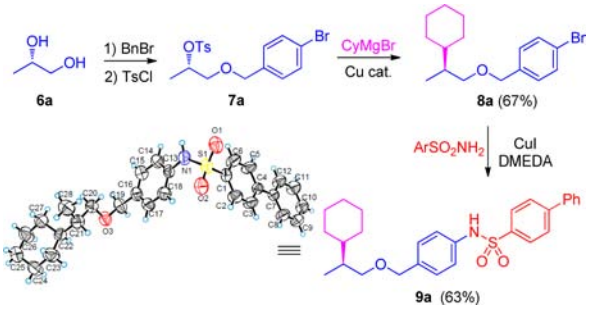
are much more reactive under the present conditions. Thus, when **1d** was treated with CyMgBr (Scheme 3), we observed

Scheme 3. Selectivity for Alkyl over Aryl Bromides



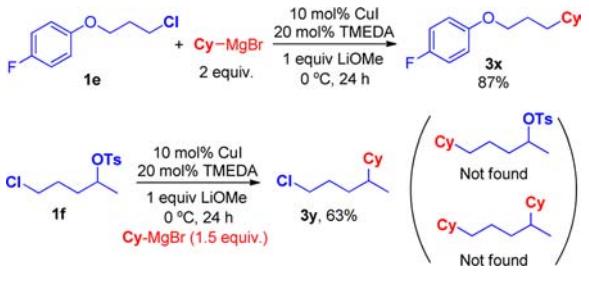
only the desired alkyl–alkyl cross-coupling at the alkyl–Br bond, whereas the aryl–alkyl cross-coupling at the aryl–Br bond did not take place. The same chemoselectivity was also observed for substrates with both alkyl–OTs and aryl–Br bonds (Scheme 4). The tolerance of an aryl–Br bond in the reaction allows for the design of sequential C–C and C–heteroatom[19] cross-couplings promoted by Cu catalysts.

Scheme 4. Site-Selective Sequential Cross-Couplings (DMEDA = *N,N′*-Dimethylethylenediamine)



Additionally, although the present catalyst cannot promote the cross-coupling of a secondary Grignard reagent with a secondary alkyl chloride (Table 1, entry 18), it is active enough to promote the alkyl–alkyl cross-coupling between a primary alkyl chloride and a secondary Grignard reagent (Scheme 5).

Scheme 5. Cross-Coupling with Primary Alkyl Chlorides



Similar Cu-catalyzed cross-coupling reactions of alkyl chlorides were accomplished previously by Kambe and co-workers, who used 1-phenylpropyne as an additive.[14] Interestingly, when a primary chloride and a secondary tosylate were both present in the substrate, only the tosylate underwent the cross-coupling. Thus, a secondary tosylate is more reactive than a primary chloride under the present reaction conditions. This observation is synthetically useful for the design of site-selective sequential cross-coupling reactions.

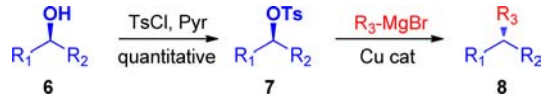
Kambe and co-workers previously showed that Cu-catalyzed cross-coupling of Grignard reagents with primary alkyl halides (with diastereometrically pure α,β-deuteriums) proceed via an S_N2 mechanism.[14] Here, the possibility of coupling with secondary alkyl halides allowed us to use chiral substrates to examine the stereochemistry of the reaction. As shown in Scheme 6, chiral tosylate **7b** can be readily prepared from the

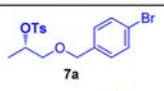
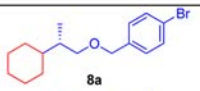
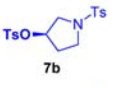
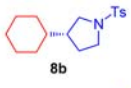
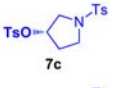
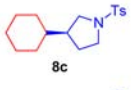
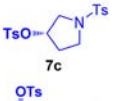
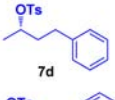
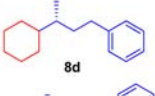
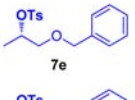
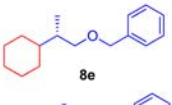
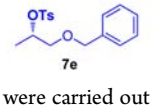
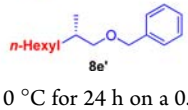
Scheme 6. Inversion of Configuration

corresponding chiral secondary alcohol. This tosylate undergoes catalytic cross-coupling with CyMgBr to produce **8b** in 70% yield. X-ray crystal analysis of **8b** revealed that the reaction occurs with inversion of configuration. This finding confirms that the present cross-coupling reactions for secondary alkyl halides also proceed by an S_N2 mechanism. It should be noted that the formation of **8b** involves a cyclic secondary alkyl tosylate. We also have evidence of inversion of configuration for an acyclic secondary alkyl tosylate (Scheme 4).

The importance of the above finding is that the present cross-coupling reaction provides a practical approach for the stereocontrolled formation of C–C bonds from chiral secondary alcohols. As shown in Table 3, both acyclic and cyclic chiral secondary alcohols can be easily converted to the

Table 3. Stereocontrolled Construction of C–C Bonds from Chiral Secondary Alcohols[a]



Entry	Alkyl-OTs	Product	Yield (%)[b]	ee (%)[c]
1			67	99
2			70	99
3			71	99
4			65	98
5			79	98
6			72	99
7			75	98

[a]Reactions were carried out at 0 °C for 24 h on a 0.5 mmol scale using 10 mol % CuI, 20 mol % TMEDA, 1 equiv of LiOMe, 0.5 mmol of R–OTs, and 1.0 mmol of R_3MgBr. For details, see the Supporting Information. [b]Isolated yields. [c]Determined by chiral HPLC analysis.

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corresponding chiral tosylates. Through the Cu-catalyzed cross-coupling reaction, the chiral tosylates can be alkylated with either primary or secondary alkyl Grignard reagents in good yields (65−79%). The enantioselectivities of these two-step transformations were measured to be as high as 98−99% ee. Because many methods are now available for the preparation of chiral secondary alcohols, the present method expands the toolbox for the construction of carbon skeletons with stereocontrol. Nonetheless, it is worth mentioning that all of the examples in Table 3 involved Grignard reagents possessing no chiral center. In a test experiment, we reacted *sec*-butylmagnesium bromide with chiral tosylate **7a**. ^{1}H NMR analysis of the product (obtained in 43% isolated yield) showed that this reaction produced two diastereoisomers in a 1:1 ratio (see the Supporting Information). Thus, the chiral center in the tosylate could not induce stereoselectivity at the chiral carbon in the Grignard reagent. It would be interesting to examine whether the use of chiral ligands can solve this problem.[20]

To summarize, we have developed a Cu-catalyzed cross-coupling reaction of nonactivated secondary alkyl bromides and tosylates with secondary alkyl Grignard reagents. This reaction represents a rare example of transition-metal-catalyzed cross-coupling between two tertiary alkyl carbons. The use of TMEDA and LiOMe as additives is crucial. The reaction tolerates a number of synthetically relevant functional groups, including esters, amides, and aryl halides, and aromatic and tertiary alkyl Grignard reagents are also good substrates. Furthermore, primary alkyl chlorides can be used in the reaction, but they are less reactive than secondary alkyl tosylates. Finally, X-ray crystal analysis of the products revealed that the reaction occurs via an S_N2 mechanism with inversion of configuration. Thus, the present cross-coupling reaction provides a general approach for the stereocontrolled formation of C−C bonds from chiral secondary alcohols.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectra, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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