

Copper-Catalyzed Alkyl–Alkyl Cross-Coupling Reactions Using Hydrocarbon Additives: Efficiency of Catalyst and Roles of Additives

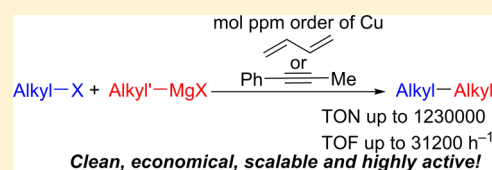
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S Supporting Information

ABSTRACT: Cross-coupling of alkyl halides with alkyl Grignard reagents proceeds with extremely high TONs of up to 1230000 using a Cu/unsaturated hydrocarbon catalytic system. Alkyl fluorides, chlorides, bromides, and tosylates are all suitable electrophiles, and a TOF as high as 31200 h^{−1} was attained using an alkyl iodide. Side reactions of this catalytic system, i.e., reduction, dehydrohalogenation (elimination), and the homocoupling of alkyl halides, occur in the absence of additives. It appears that the reaction involves the β -hydrogen elimination of alkylcopper intermediates, giving rise to olefins and Cu–H species, and that this process triggers both side reactions and the degradation of the Cu catalyst. The formed Cu–H promotes the reduction of alkyl halides to give alkanes and Cu–X or the generation of Cu(0), probably by disproportionation, which can oxidatively add to alkyl halides to yield olefins and, in some cases, homocoupling products. Unsaturated hydrocarbon additives such as 1,3-butadiene and phenylpropyne play important roles in achieving highly efficient cross-coupling by suppressing β -hydrogen elimination, which inhibits both the degradation of the Cu catalyst and undesirable side reactions.

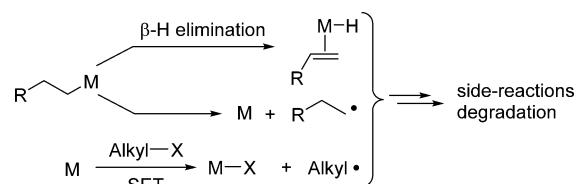


INTRODUCTION

Transition-metal-catalyzed cross-coupling reactions of organohalides with organometallic reagents are one of the most useful and reliable methods for constructing carbon skeletons.¹ A variety of catalytic systems have been developed and are widely employed in both the laboratory and in industrial processes as indispensable synthetic tools;² however, large amounts of expensive catalysts (1–10 mol % of Pd in many cases) and heteroatom ligands (such as phosphorus compounds) are often needed to achieve high product yields.^{2a,d} From both environmental and economic points of view, curtailing the amount of noble metal catalysts and costly toxic ligands that are used, or replacing them with lower cost metals and more readily available safer ligands, has attracted considerable interest in modern synthetic chemistry.³ A great deal of effort has been paid to improve the efficiency of the reactions,^{4,5} and for example, the turnover numbers (TONs) of Pd-catalyzed Suzuki–Miyaura coupling between two sp²-hybridized carbons have reached the range of 10⁶ to 10¹¹.⁴ Concerning cross-coupling between an sp²-carbon and an sp³-carbon, high TONs of 10³–10⁴ orders have been achieved.^{4h,6} However, for reactions employing sp³-carbon electrophiles, examples of high efficiencies are available only for the reactions of benzyl halides.⁶ Since alkyl groups are the most difficult coupling patterns to be manipulated in transition-metal-catalyzed reactions, especially in the cases of alkyl derivatives having a β -hydrogen(s), alkyl–alkyl cross-coupling is much less efficient⁷ and the highest TON of 970 was achieved when alkyl Grignard reagents were used.^{7a,b} This is mainly due to the facile β -

hydrogen elimination from alkylmetal intermediates that are generated in situ, which triggers isomerization,⁸ elimination,⁹ and/or reduction¹⁰ of the alkyl moieties. Difficulties may also arise from homolysis of alkylmetal intermediates and/or a single-electron transfer (SET) from a metal to alkyl halides to generate alkyl radical intermediates¹¹ as illustrated in Scheme 1 (vide infra).¹²

Scheme 1. Possible Pathways in Metal-Catalyzed Alkyl–Alkyl Cross-Coupling



We previously reported on alkyl–alkyl cross-coupling reactions of unactivated alkyl halides with Grignard reagents catalyzed by Ni, Pd, Cu, or Co using unsaturated hydrocarbons such as 1,3-butadiene and phenylpropyne as additives.^{7a–c,13,14} The high potential of these reactions as useful synthetic tools was demonstrated by their successful application to reagents with a low reactivity, such as alkyl chlorides and fluorides, as

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well as alkyl tosylates^{7a,b,14} and to the synthesis of biologically active compounds and natural products.¹⁵ Here we report on the use of a Cu/diene or alkyne catalytic system in the highly efficient catalysis of cross-coupling reactions of unactivated alkyl halides with Grignard reagents using as little as mol ppm (defined as 10^{-6} mole ratio = 10^{-4} mol %) orders of Cu. We also provide evidence to show that butadiene and alkyne ligands play important roles in suppressing both side reactions and the degradation of the Cu catalyst.¹⁶

RESULTS AND DISCUSSION

Highly Efficient Alkyl–alkyl Cross-Coupling Reaction.

In initial experiments, we tested the catalytic performance of Cu in the reaction of *n*-NonBr with *n*-BuMgCl in the presence of phenylpropyne^{14c} employing small amounts of the catalyst in the mol ppm (10^{-4} mol %) order.¹⁷ As shown in Table 1, *n*-

Table 1. Coupling Reaction of Alkyl (Pseudo)halides with *n*-BuMgCl Using Phenylpropyne as an Additive^a

$\text{R-X} + \text{n-Bu-MgCl} \xrightarrow[\text{THF, 25 } ^\circ\text{C, 24 h}]{\text{CuCl}_2 \text{ (cat.)}, \text{Ph-C}\equiv\text{C-Me (1 equiv)}} \text{R-n-Bu}$				
entry	RX	CuCl ₂ (mol ppm)	yield ^b (%)	TON
1	<i>n</i> -NonBr	100	95	9500
2	<i>n</i> -NonBr	50	81	16200
3 ^c	<i>n</i> -NonBr	1	40	400000
4 ^d	<i>n</i> -NonCl	5000	70	140
5	<i>n</i> -NonCl	25	nd	
6 ^e	<i>n</i> -NonI	100	52	5200
7	<i>n</i> -NonI	25	>99	>29600
8	<i>n</i> -OctOTs	1000	>99	>990
9	<i>n</i> -OctOTs	300	89	2967
10	<i>n</i> -OctOTs	100	49	4900
11	<i>n</i> -OctOTs	25	30	12000
12	<i>n</i> -OctF	3000	92	307
13	<i>n</i> -OctF	1000	44	440
14 ^f	<i>n</i> -OctF	1000	nd	
15	<i>n</i> -OctF	500	22	440
16 ^f	<i>n</i> -OctF	500	26	520

^aReaction conditions: RX (1 mmol), *n*-BuMgCl (1.67–1.80 M in THF, 1.3 mmol), CuCl₂, phenylpropyne (1 mmol), decane (internal standard) in THF at 25 °C for 24 h. ^bYield was determined by GC. ^c10 mol % alkyne, at 40 °C for 48 h. ^dUnder reflux conditions. ^e10 mol % alkyne, at 40 °C for 10 min. ^fWithout additive.

NonBr coupled with *n*-BuMgCl to give the desired product nearly qualitatively when only 100 mol ppm of catalyst was used (entry 1). When the catalyst was reduced to 50 mol ppm, the yield decreased to 81% (entry 2).¹⁸ A similar reaction using only 1 mol ppm of CuCl₂ at 40 °C afforded the product in 40% yield, indicating a high TON of 400000 (entry 3). Although *n*-NonCl reacted sluggishly at rt (entry 5),^{14c} it coupled with *n*-BuMgCl in refluxing THF using 5000 mol ppm (0.5 mol %) of catalyst to give the corresponding product in 70% yield in 24 h (entry 4). The coupling of *n*-NonI proceeded quantitatively in the presence of 25 mol ppm of Cu (entry 7). When the reaction was stopped at an early stage after stirring for 10 min, a 52% yield of product was found, with an unprecedentedly high turnover frequency (TOF) of 31200 h⁻¹ (entry 6). Reactions of alkyl tosylates and fluorides,^{14a,b} which are less reactive than the corresponding iodide but more reactive than a chloride, proceeded in nearly quantitative yields at rt with 1000 and

3000 mol ppm of Cu, respectively (entries 8 and 12). When the Cu was reduced from 3000 mol ppm to 1000 and 500 mol ppm in the reaction of *n*-OctF, the yield correspondingly decreased from 92% to 44% and 22%, respectively, as shown in entries 12, 13, and 15. Under the same conditions as entry 15 using 500 mol ppm of Cu, the reaction proceeded in the absence of phenylpropyne affording a similar yield of 26% (entry 16). However, interestingly, no cross-coupling product was detected when large amounts of Cu (1000 mol ppm or more) were used in the absence of phenylpropyne (entry 13 vs 14). The reaction mixture in the case of entry 13 using phenylpropyne was a clear brownish yellow solution, but in the absence of phenylpropyne, a black precipitate soon (in a few minutes) appeared after the addition of the Grignard reagent in entry 14. These results indicate the decomposition of Cu started rapidly and was accelerated at high concentrations in the absence of phenylpropyne, probably due to the autocatalytic decomposition observed earlier^{17a,19} and that phenylpropyne suppressed this aggregation of the copper catalyst, probably via the formation of Cu–alkyne complexes.²⁰

Additive effects of 1,3-butadiene in the coupling reactions of various alkyl halides with *n*-BuMgCl using different amounts of CuCl₂ were also examined, and the results are summarized in Table 2, which are practically quite similar to the results

Table 2. Coupling Reaction of Alkyl (Pseudo)halides with *n*-BuMgCl Using 1,3-Butadiene as an Additive^a

$\text{R-X} + \text{n-Bu-MgCl} \xrightarrow[\text{THF, 25 } ^\circ\text{C, 24 h}]{\text{CuCl}_2 \text{ (cat.)}, \text{1,3-butadiene (1 equiv)}} \text{R-n-Bu}$				
entry	RX	CuCl ₂ (mol ppm)	yield ^b (%)	TON
1	<i>n</i> -NonBr	100	96	9600
2	<i>n</i> -NonBr	50	71	14200
3	<i>n</i> -NonBr	25	52	20800
4	<i>n</i> -NonBr	10	49	49000
5	<i>n</i> -NonCl	25	nd	
6	<i>n</i> -NonI	25	86	34400
7	<i>n</i> -OctOTs	3000	>99	333
8	<i>n</i> -OctOTs	1000	97	970
9	<i>n</i> -OctOTs	500	86	1720
10	<i>n</i> -OctOTs	25	18	7200
11	<i>n</i> -OctF	10000	>99	>99
12	<i>n</i> -OctF	3000	84	280
13	<i>n</i> -OctF	1000	31	310
14 ^c	<i>n</i> -OctF	1000	nd	
15	<i>n</i> -OctF	500	18	360
16 ^c	<i>n</i> -OctF	500	26	520

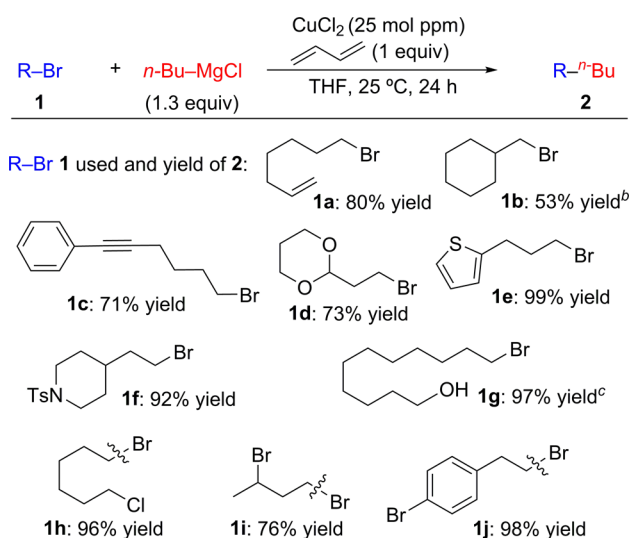
^aReaction conditions: A mixture of RX (1 mmol), *n*-BuMgCl (1.3 mmol), 1,3-butadiene (1 mmol), CuCl₂, and decane (internal standard) in THF was stirred at 25 °C for 24 h. ^bYield was determined by GC. ^cWithout additive.

obtained using phenylpropyne shown in Table 1. By using only 10 mol ppm (0.001 mol %) of CuCl₂ and 1 equiv of 1,3-butadiene, the reaction of *n*-NonBr with *n*-BuMgCl provided the corresponding product in 49% yield after stirring at room temperature for 24 h (entry 4). The yield of the product increased when the catalyst loading was increased, and a nearly quantitative yield (96%) was attained using 100 mol ppm of catalyst with the TON as high as 9600 (entry 1). A reaction of nonyl iodide was completed with only 25 mol ppm of CuCl₂ and afforded tridecane in 86% yield with a high TON of 34400

(entry 6), although alkyl fluoride and tosylate reacted more slowly and chloride was sluggish. Satisfactory results for alkyl tosylate and fluoride were obtained by the use of 1000 mol ppm and 10000 mol ppm of CuCl_2 , respectively (entries 8 and 11). In the latter case, an interesting additive effect similar to the case of phenylpropyne shown in Table 1 was observed. When catalyst loading was less than 500 mol ppm, 1,3-butadiene exerted almost no effect (entry 15 vs 16), but a remarkable effect of 1,3-butadiene was observed in the reaction with more than 1000 mol ppm catalyst loading (entry 13 vs 14), in which black precipitates were formed in the absence of 1,3-butadiene; however, a clear brownish yellow solution was kept during the reaction in the presence of 1,3-butadiene. Although 1,3-butadiene^{13h,14b} exerted additive effects similar to those for phenylpropyne, phenylpropyne afforded slightly better yields in coupling reactions of alkyl fluorides.

As shown in Scheme 2, the present Cu/butadiene system provided cross-coupling products containing alkene, alkyne,

Scheme 2. Coupling of Alkyl Bromides Catalyzed by the Cu/1,3-Butadiene System^a



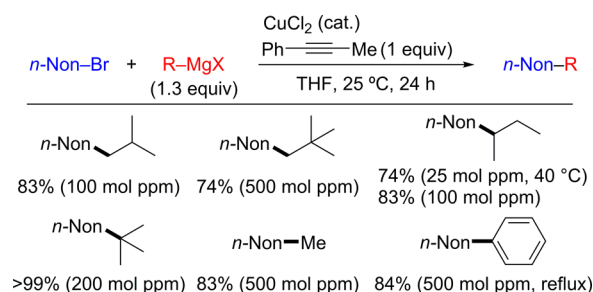
^aReaction conditions: RX (1 mmol), $n\text{-BuMgCl}$ (1.3 mmol), CuCl_2 (25 mol ppm), 1,3-butadiene (1 mmol), decane (internal standard) in THF at 25 °C for 24 h. Yield was determined by GC. ^b100 mol ppm of CuCl_2 was used. ^c2.3 equiv of $n\text{-BuMgCl}$ was used.

acetal, thiophene, and *N*-tosylamide functionalities in good to excellent yields with a Cu loading of only 25 mol ppm, with high TONs of approximately 40000. A reaction of *N,N*-diethyl-6-bromohexanamide with $n\text{-BuMgCl}$ in the presence of 25 mol ppm of CuCl_2 gave the corresponding coupling product in 60% yield with complete consumption of the amide employed. When the corresponding *tert*-butyl ester was subjected to the reaction using 100 mol ppm of CuCl_2 , the desired coupling product was obtained in a moderate yield (45%) in 6 h with recovery of the starting material only in 17%. Cyclohexylmethyl bromide (**1b**) also coupled with $n\text{-BuMgCl}$ to afford the corresponding coupling product somewhat less efficiently, probably due to steric reasons. It was possible to couple an alkyl bromide bearing a hydroxyl group **1g** using an in situ protection protocol^{18d} employing 2.3 equiv of Grignard reagent. When dihalogenated compounds **1h–j** were employed as substrates, chemoselective coupling took place at a terminal bromomethylene carbon. In these reactions, the corresponding

coupling products bearing alkyl chloride, internal alkyl bromide, and aryl bromide moieties were produced in 96%, 76%, and 98% yields, respectively.

Congested alkyl Grignard reagents also afforded satisfactory results, demonstrating the applicability of the present catalyst for the construction of branched carbon skeletons (Scheme 3).

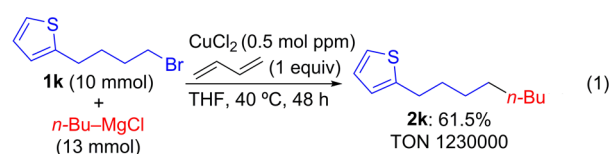
Scheme 3. Coupling Reaction of Various Grignard Reagents^a



^aReaction conditions: $n\text{-NonBr}$ (1 mmol), RMgX (1.3 mmol), CuCl_2 , phenylpropyne (1 mmol), decane or undecane (internal standard) in THF at 25 °C for 24 h. Yield was determined by GC.

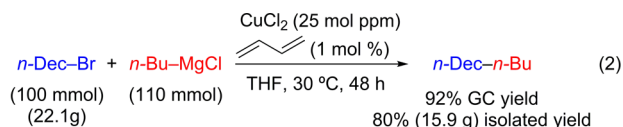
For example, β -branched Grignard reagents bearing isobutyl or neopentyl groups coupled with $n\text{-NonBr}$ at 25 °C in good yields using 100 and 500 mol ppm of catalyst, respectively. *s*- BuMgCl also underwent cross-coupling in the presence of 100 mol ppm of CuCl_2 giving a product in 83% yield under the same conditions. When the reaction was conducted at 40 °C, a 74% yield of product was obtained using only 25 mol ppm of catalyst. *t*- BuMgCl worked perfectly to construct a quaternary carbon center using 200 mol ppm of CuCl_2 , although it has been reported that the cross-coupling of tertiary alkyl Grignard reagents sometimes afford mixtures of products via isomerization.^{7a,b,14b,c,21} Liu et al. successfully developed a new Cu-catalyzed system for cross-coupling of congested secondary alkyl halides with secondary alkyl Grignard reagents to construct adjacent branched carbon centers by use of TMEDA and LiOMe as the additives.^{21e} Hu et al. reported that Cu catalyzes cross-coupling reaction of primary alkyl halides possessing various functional groups with secondary or tertiary alkyl Grignard reagents without any additives.^{21f} In these catalytic systems, Cu catalyst in 0.5–10 mol % loading was employed. It is noteworthy that Cu has potent catalytic activity to achieve the alkyl–alkyl coupling reaction with much lower levels of loadings. On the other hand, methyl and phenyl Grignard reagents were found to be less reactive and required 500 mol ppm of catalyst in refluxing THF to produce good yields.

The highest TON of 1230000 was achieved in the reaction of **1k** with $n\text{-BuMgCl}$ using 0.5 mol ppm of CuCl_2 and 1,3-butadiene as the additive, giving **2k** in 62% after 48 h at 40 °C (eq 1).²²



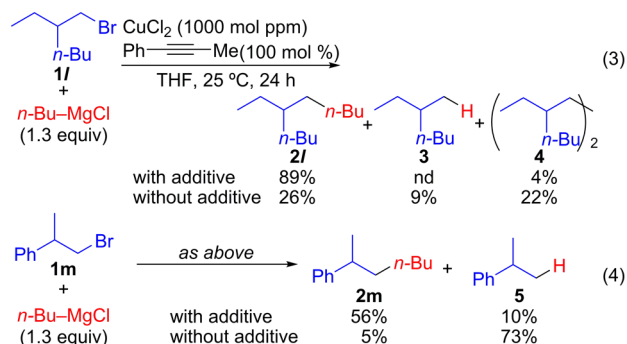
To demonstrate the synthetic usefulness of the present coupling reaction, we carried out a large-scale reaction. When

the reaction was carried out on a 0.1 mol scale with 25 mol ppm of CuCl_2 and 1 mol % of 1,3-butadiene (ca. 12 mM in the reaction mixture), the desired product was formed in 92% GC yield and isolated in 80% yield (15.9 g) after the usual workup and distillation (eq 2). It is noteworthy that the present catalyst



system can be used efficiently in large-scale production without the need for phosphine or amine ligands, which may cause difficulties in the workup process when used in large amounts. For example, the coupling product was obtained in an essentially pure form, 92% purity by GC analysis, after simple aqueous workup and removing volatiles.

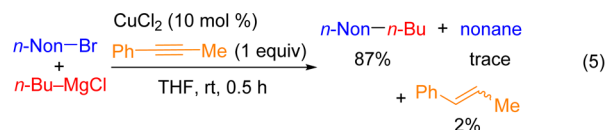
Effects of Unsaturated Hydrocarbon Additives. To shed light on the roles of unsaturated hydrocarbon additives,^{16,23} we examined the reaction of β -branched alkyl bromides **1l** with $n\text{-BuMgCl}$ in the presence of 1000 mol ppm of CuCl_2 in the absence of any additive. After 24 h, only 26% of the coupling product **2l** was obtained along with 9% of the reduced product **3** and a significant amount (22%) of the homocoupling product **4**, which was likely produced via the homocoupling of **1l** mediated by the reduced $\text{Cu}(0)$ species that was generated in situ.²⁴ In the presence of phenylpropyne, the yield of **2l** was improved to 89% and side reactions were suppressed, with **4** being formed in only 4% yield (eq 3). The



more remarkable effect of phenylpropyne is shown in eq 4. The reaction of **1m** with $n\text{-BuMgCl}$ in the absence of an additive yielded the undesired reduction product **5** as the major product and only 5% of the coupling product **2m**. In contrast to this unsatisfactory result, the addition of phenylpropyne suppressed the reduction of **1m**, resulting in the production of **2m** in 56% yield (eq 4). These results clearly indicate that the addition of unsaturated hydrocarbon additives suppresses not only catalyst degradation but also undesirable side reactions, such as reduction and homocoupling, thus improving both the selectivity and yield of the reaction.

Figure 1 shows the time-course for the cross-coupling reaction of an alkyl bromide with $n\text{-BuMgCl}$ using 500 and 25 mol ppm of catalyst with and without phenylpropyne. With a catalyst loading of 500 mol ppm, the addition of phenylpropyne not only improved product yields (\bullet vs \blacksquare) but also suppressed the reduction of halides (\circ vs \square) (Figure 1a). In the absence of phenylpropyne, the cross-coupling was terminated at an early stage (in ca. 10 h). In contrast, when the catalyst loading was reduced to 25 mol ppm, the formation of the coupling product continued and the yield increased regardless of whether phenylpropyne was present or not (Figure 1b, \bullet and \blacksquare). However, even in this case, undesirable reduction was again dramatically suppressed when the additive was present (\circ vs \square). Interestingly, the additive appeared to slow the cross-coupling slightly (vide infra).

We then examined the possibility of an alkyne or diene trapping Cu-H to form the corresponding vinyl- or allylcopper which can regenerate alkylcopper by transmetalation with an alkyl Grignard reagent. When $n\text{-NonBr}$ was reacted with $n\text{-BuMgCl}$ using 10 mol % of CuCl_2 without an additive, 20% of nonane (200% based on the Cu used) was formed along with the cross-coupling product and nonene in a roughly 1:2:1 ratio. However, as shown in eq 5, only 2% of reduced alkyne was



obtained when the same reaction was conducted using 1 equiv of phenylpropyne and quenched with 1 N HCl aq, indicating that Cu-H may, in part, be trapped by phenylpropyne but this

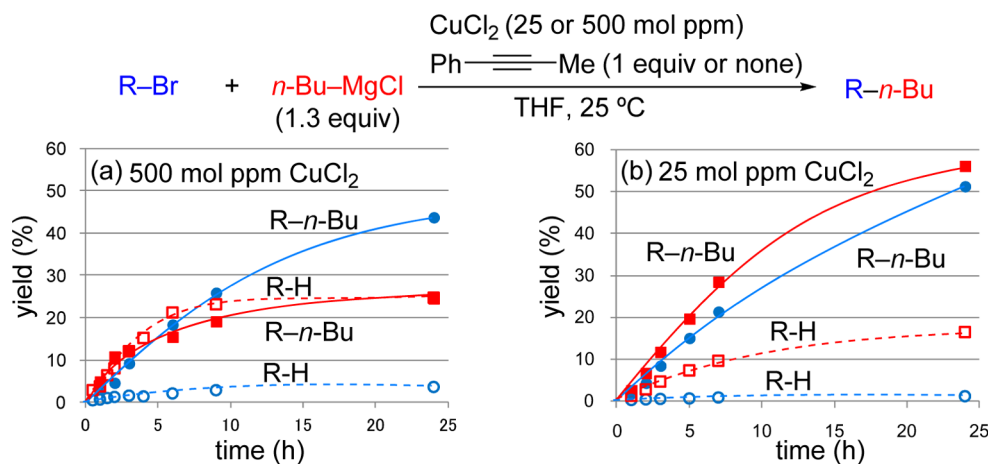


Figure 1. Time-course of reaction of RBr and $n\text{-BuMgCl}$ (a) with 500 mol ppm of CuCl_2 ($\text{R} = \text{PhCH(Me)CH}_2$: **1m**) and (b) 25 mol ppm of CuCl_2 ($\text{R} = n\text{-Non}$). With alkyne R-n-Bu : \bullet (solid line), R-H : \circ (dashed line), without alkyne R-n-Bu : \blacksquare (solid line), R-H : \square (dashed line).

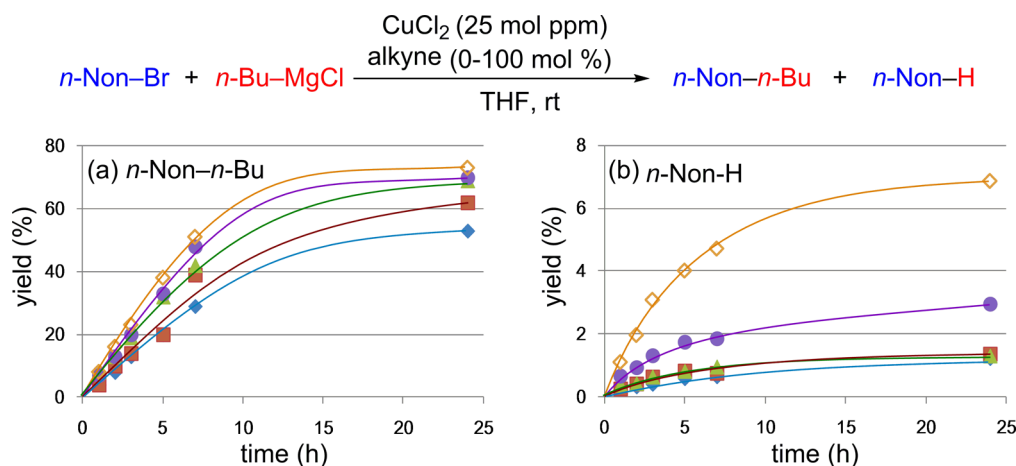


Figure 2. Time-courses of coupling product (a) and reduced product (b) in the reaction of *n*-NonBr with *n*-BuMgCl with 25 mol ppm of CuCl₂ and 100 mol % (◆), 50 mol % (■), 25 mol % (▲), 5 mol % (●), or 0 mol % (◇) of phenylpropyne.

is not the main route for additives to suppress the degradation of catalysts.

To gain insights into the active species, we then examined the effects of alkynes on reaction rates and selectivities. The coupling of *n*-NonBr with *n*-BuMgCl using 25 mol ppm of CuCl₂ was conducted in the presence of different amounts of phenylpropyne, and the time-course for the reactions is illustrated in Figures 2 and 3. Without the additive, the cross-

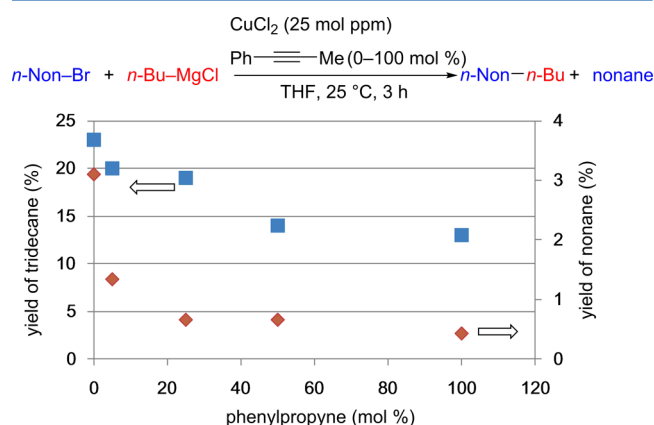


Figure 3. Plots of the yields of the cross-coupling product (■, left axis) and nonane (◆, right axis) against the amount of phenylpropyne used at 3 h reaction time.

coupling reaction was fast, and the yield reached 51% after 7 h (Figure 2a). In the presence of phenylpropyne, the coupling reaction gradually and continuously became slower as the amount of the additive was increased to 100 mol %. On the other hand, the formation of a side product, nonane, was suppressed drastically by only small amounts of phenylpropyne, and no further change was detected for phenylpropyne at concentrations higher than 25 mol % (Figure 2b). The relationships between the amounts of the phenylpropyne and the yields of the products are shown in Figure 3. These observations suggest that phenylpropyne at higher concentrations generates Cu complexes coordinated by two acetylene molecules as a resting state of the catalytic system.²⁵

Next, we conducted a similar experiment with less reactive substrates, alkyl chlorides. Since *n*-NonCl was much less reactive, the reaction was performed in refluxing THF, and the

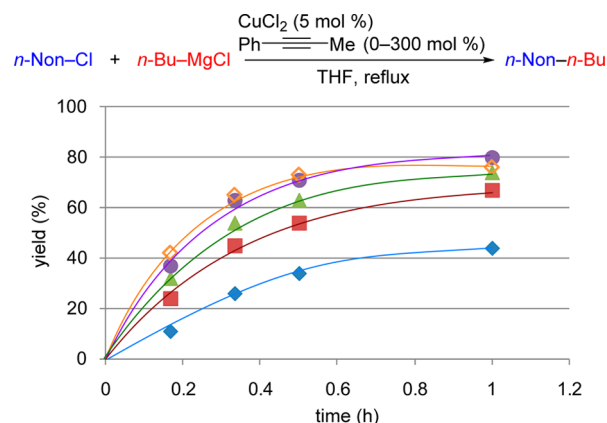


Figure 4. Time-courses of the cross coupling reaction of *n*-NonCl with *n*-BuMgCl with 5 mol % of CuCl₂ and 300 mol % (◆), 100 mol % (■), 50 mol % (▲), 10 mol % (●), or 5 mol % (◇) of phenylpropyne.

time-course of these reactions is shown in Figure 4. Although no reaction, neither cross-coupling nor reduction, took place without phenylpropyne due to the quick degradation of the Cu catalyst under the conditions employed, the yield of the coupling product reached 76% within 1 h in the presence of 5 mol % of phenylpropyne (1 equiv to Cu). The use of 2 equiv (10 mol %) of phenylpropyne showed similar results with a slightly improved yield of product. Addition of larger amounts of phenylpropyne led to depression of catalytic activity, but the yield of coupling product gradually increased to ca. 80% by prolonging the reaction time. Again, a stoichiometric amount of phenylpropyne exerted a remarkable effect to promote the coupling reaction efficiently but the rate was gradually retarded as the additive was increased up to 60 equiv based on Cu.

The time-course for the initial stage of the reaction of *n*-NonBr with *n*-BuMgCl catalyzed by 25 mol ppm of CuCl₂ using phenylpropyne, phenylbutyne, or phenylhexyne (PhC≡CR, R = Me, Et, *n*-Bu) is shown in Figure 5. In all cases, including the reaction without an additive, cross-coupling proceeded smoothly at rates decreasing in the order of phenylhexyne (R = *n*-Bu, ▲), phenylbutyne (R = Et, ■), and phenylpropyne (R = Me, ◆). Again, the addition of phenylpropyne slowed the reaction (◆) compared to the reaction without alkynes (●). In the case of phenylbutyne (R =

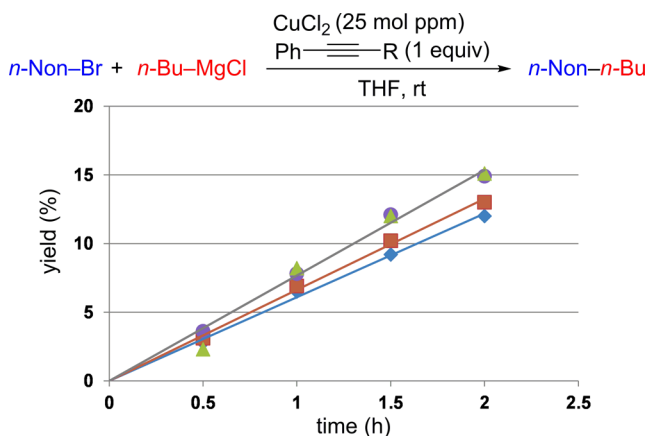
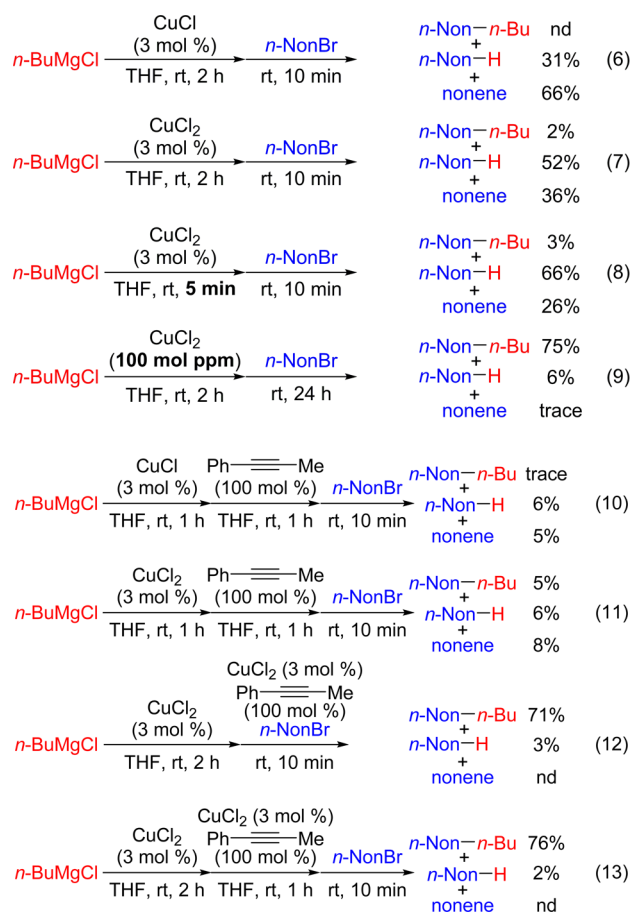


Figure 5. Time-courses for the coupling product in the reaction of *n*-NonBr with *n*-BuMgCl with 25 mol ppm of CuCl₂ and 100 mol % of 1-phenyl-1-propyne (R = Me, ◆), 1-phenyl-1-butyne (R = Et, ■), or 1-phenyl-1-hexyne (R = *n*-Bu, ▲). In the absence of additive (●).

Et), the initial rate of the reaction was slightly faster than the case of phenylpropyne (■ vs ◆). Phenylhexyne (R = *n*-Bu) did not retard the cross-coupling, and the reaction proceeded at the same rate as the reaction without an additive. This may be because the coordination of the second alkyne molecule to Cu is unfavorable due to the bulkiness of the *n*-Bu group. The reduction of *n*-NonBr did not occur in the presence of these additives, though the reduced product nonane was produced in 2% yield in the absence of the additive after completion of the reaction under these conditions.

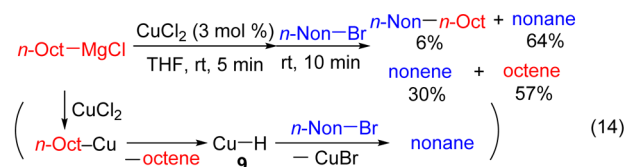
It is known that alkylcopper species (Cu-R) undergo β -hydrogen elimination²⁶ and react with Grignard reagents to form more stable cuprates^{27,28} which serve as the active catalytic species for cross-coupling reactions. Taking into account this body of evidence and the results shown above, it seems likely that alkyne or diene (L) coordinates to alkylcopper to form (L)Cu-R, which is stable to β -hydrogen elimination but still has a potent catalytic activity as the active key species for cross-coupling reactions. Under high concentrations of alkynes or dienes, (L)Cu-R reacts with another molecule of additive to form (L₂)Cu-R as a resting state especially in the case of less hindered additives.

Side Reactions and Catalyst Degradation. Detailed pathways of side reactions and degradation of the catalysts has not yet been discussed in the reports concerning alkyl–alkyl cross-coupling reactions.¹² Therefore, we carried out several control experiments employing various combinations of reagents and conditions (eqs 6–13).²⁸ When the CuCl and CuCl₂ were treated separately with *n*-BuMgCl for 2 h in the absence of an additive before the addition of *n*-NonBr to consciously generate decomposed Cu species, none or only a trace amount of the coupling product, tridecane C₁₃H₂₈, was produced, and as the side products, nonane C₉H₂₀ and nonene C₉H₁₈ were formed in nearly 1:2 and 2:1 ratios, respectively (eqs 6 and 7). When the pretreatment time of CuCl₂ was shortened to 5 min, similar results were obtained as shown in eq 8. These results indicate that the Cu catalyst quickly decomposed when treated with alkyl Grignard reagents in the absence of additives and promote the side reactions of the alkyl bromide to yield alkane and olefins, probably via reduction with Cu–H generated by the β -elimination of *n*-Bu–Cu formed from the reaction of CuCl₂ with *n*-BuMgCl¹⁹ and via an oxidative addition/ β -elimination sequence, respectively. The same



reaction as eq 7 but employing only 100 mol ppm of the Cu salt afforded a 75% yield of the coupling product along with 6% of nonane and a trace amount of nonene, even in the absence of an additive (eq 9). This difference between eqs 7 and 9 suggests that the decomposition of the catalytic active species largely depends on the concentration of Cu and is fast at higher concentrations, as has been observed previously.^{17a,19} When phenylpropyne was added after an 1 h pretreatment, the catalytic active species was not regenerated but side reactions were efficiently suppressed in either case of CuCl or CuCl₂ (eqs 10 and 11). When both phenylpropyne and a second portion of CuCl₂ were added after the decomposition of the initially added catalyst by the same pretreatment as eq 7, cross-coupling proceeded to give tridecane in 71% yield (eq 12). In addition, a similar result was obtained even when *n*-NonBr was added after stirring the reaction mixture for 1 h (eq 13). These results clearly indicate that phenylpropyne protects the catalyst from degradation, even in the presence of Cu metal species that can accelerate the deactivation of Cu catalysts.

In order to examine the degradation processes of Cu in the absence of additives, 1.0 mmol of *n*-NonBr was added to a mixture of *n*-OctMgCl (1.3 mmol) and 3 mol % of CuCl₂ in THF being stirred for 5 min at rt (eq 14). As expected from the



result of eq 8, the desired cross-coupling product was obtained only in 6% yield, and nonane was formed in 64% yield, along with octene in 57% and nonene in 30% yields. This result can be explained by the rapid β -hydrogen elimination of *n*-Oct-Cu generated in situ to form octene and Cu-H (9),²⁶ which then reacts with *n*-NonBr to give nonane and CuBr.

When the same reaction as shown in eq 7 was conducted employing *n*-OctMgCl instead of *n*-BuMgCl and the reaction was quenched with diphenyl disulfide (1.5 mmol), *n*-Oct-SPh was not formed and octene and octane were formed in nearly quantitative amounts as well as octene and nonane were formed in nearly equal amounts. This result indicates that *n*-OctMgCl was completely consumed within 10 min after the addition of *n*-Non-Br and may support the intermediacy of Cu-H (9) as a key species in the reduction of nonyl bromide (Scheme 4, first

Scheme 4. Effect of Alkyne on Side Reactions

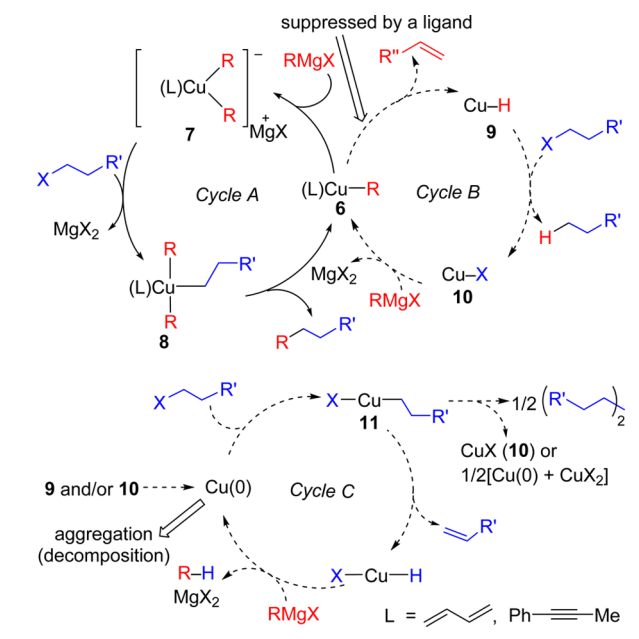
<i>n</i> -Oct-MgCl (1.3 mmol) + (Ph-C≡Me) (1.0 mmol)	CuCl ₂ (3 mol %)	<i>n</i> -Non-Br (1.0 mmol)	PhSSPh (1.5 mmol)	
	THF, rt, 2 h	rt, 10 min	rt, 10 min	
	GC yield (mmol)			
	<i>n</i> -Non- <i>n</i> -Oct	<i>n</i> -Non-H	Nonene	Octane ^a Octene ^a
without alkyne ^b	0.05	0.47	0.24	0.56 0.54
with alkyne	0.79	nd	nd	<0.01 <0.01

^aControl experiments proved that small amounts of octane and octene (16% and 4%, respectively) were present in the solution of the octyl Grignard reagent that was used or arose during handling, so their yields were corrected by subtracting these amounts. ^bAverage of four runs.

run). In sharp contrast, no significant amounts of side products arising from either *n*-NonBr or *n*-OctMgCl were detected in the presence of an alkyne additive (Scheme 4, second run) and cross-coupling proceeded exclusively.

Proposed Mechanisms for the Present Catalytic System. Based on the results shown above, proposed catalytic pathways, including side reactions, are illustrated in Scheme 5. First, an alkylcopper **6**, generated from the copper salt and the Grignard reagent,²⁸ reacts with the Grignard reagent to form dialkyl cuprate **7**, which undergoes nucleophilic substitution with alkyl halides²³ by an ionic mechanism to afford the desired coupling products through reductive elimination of *cis*-oriented two alkyl groups from the complex **8** (cycle A).^{13b,14,23} Because the alkylcopper is less thermally stable, it undergoes decomposition via β -hydrogen elimination to give alkenes and Cu-H **9**,²⁶ which then reacts with alkyl halides to yield the corresponding alkanes along with CuX **10** (cycle B). Degradation of the Cu catalyst would be triggered by the formation of Cu(0) from **9** and/or **10** via their disproportionation or related processes and the resulting Cu(0) promotes another side reaction via **11** to give alkenes from alkyl halides and alkanes from Grignard reagents (cycle C). When β -hydrogen elimination from **11** is relatively slow, homocoupling of the alkyl halides takes place via the disproportionation of **11** to give (RCH₂CH₂)₂Cu and CuX₂ or via the homolysis of its alkyl-copper bond, as shown in eq 3.²⁴ Aggregation of Cu(0) leads to the fatal deactivation of catalyst.^{17a,19} An alkyne or a diene coordinates to a Cu atom to suppress β -hydrogen elimination in cycle B by blocking this elimination process and possibly by accelerating the competing ate complex formation leading to **7**.

Scheme 5. Proposed Catalytic Cycles of Cross-Coupling (Solid Line) and Side Reactions (Dashed Line)



CONCLUSION

We disclosed herein that Cu catalyzes the cross-coupling of alkyl halides with alkyl Grignard reagents in the presence of an alkyne or a diene with very high TONs of up to the order of 10⁶ and TOFs higher than 10⁴ h⁻¹. Based on mechanistic studies regarding the Cu-catalyzed alkyl-alkyl coupling reaction, the following conclusions can be made: (i) the Cu catalyst is rapidly deactivated under conditions of high catalyst loading and catalyst degradation can be suppressed by lowering the catalyst loading, (ii) degradation of Cu catalyst is triggered by β -hydrogen elimination from Cu-R (**6**) to form Cu-H (**9**) which promotes the reduction of alkyl halides to give alkanes, (iii) the disproportionation or homolysis of Cu-H (**9**) and/or Cu-X (**10**) would form Cu(0) which results in lethal deactivation of the catalyst via aggregation, and (iv) the resulting Cu(0) species catalyzes the dehydrohalogenation and homocoupling of alkyl halides via oxidative addition. It was also found that when the reaction was run with a low loading of Cu, catalyst degradation was not a serious problem but it was not possible to improve selectivity. Although redundant coordination of the additive slows down the coupling reaction slightly and once the Cu catalyst is deactivated it could not be reactivated by additives, the additive suppresses side reactions, thus enhancing both selectivity and catalyst efficiency even in the presence of deactivated metals.

Since the predawn of history of the coupling reactions, copper retained its standing in the center of the mainstream in this field in both catalytic²⁹ and stoichiometric characteristics;^{23,30} however, the mechanistic details of these catalytic reactions are not clear in many cases, mainly due to the ease of one electron redox, aggregation, and the disproportionation of copper species. The present studies shed light on the mechanistic details of Cu-catalyzed alkyl-alkyl cross-coupling reactions including problematic side reactions and provide useful information in organometallic and synthetic organic chemistry for developing efficient Cu-mediated transformations and new applications.

■ EXPERIMENTAL SECTION

All experiments using air- and moisture-sensitive compounds were performed with standard Schlenk techniques under a nitrogen atmosphere. All glass reaction vessels and Teflon-coated magnetic stir bars were washed with concd HNO₃ and then with ultrapure water several times and dried in a dry oven before use. CuCl₂ was added as a THF solution, being prepared in a glass vessel equipped with a septum and stored under nitrogen atmosphere. The handling of CuCl₂ and Grignard solutions was carried out with plastic syringes equipped with a Teflon tube instead of metallic syringe needles. Liquid substrates were added by a micropipette. Dehydrated THF was purified by SPS prior to use.³¹ THF solutions of Grignard reagents were purchased and used after titration. All catalytic reactions were performed with highly pure CuCl₂ (99.999%). All other commercially available reagents were used as received unless otherwise stated.

Nuclear magnetic resonance (¹H NMR and ¹³C NMR) spectra were recorded at 400 MHz (¹H NMR) and 100 MHz (¹³C NMR) in 5 mm NMR tubes. All ¹H NMR chemical shifts were reported in ppm relative to tetramethylsilane at δ 0.00 as an internal reference. All ¹³C NMR chemical shifts were reported in ppm relative to carbon resonance in chloroform-*d*₁ at δ 77.00. Infrared spectra were recorded using ATR. GC analyses were performed on an instrument equipped with a flame ionization detector and a GL Sciences InertCap 5 capillary column (i.d. 0.25 mm, length 30 m, df 0.25 μ m). GC yields were determined using a hydrocarbon as an internal standard. HPLC separations were performed on a recycling preparative HPLC equipped with JAIGEL-1 and -2 columns or Shodex K2001 and 2002 columns (GPC) using CHCl₃ as an eluent. GC mass analyses (EI) were performed in the electron-impact mode (70 eV) equipped with an InertCap SMS/NP column (i.d. 0.25 mm, length 30 m, df 0.25 μ m). EI and CI conventional and high-resolution mass spectra were recorded with a double-focusing magnetic sector mass instrument.

Coupling products **2a,c,g–j,m** are commercially available, and their GC analysis was conducted using their authentic samples. Coupling products **2d³²** and **2e³³** are known compounds. The yields of these compounds were determined by GC analysis using an internal standard (decane).

Synthesis of Starting Materials. 2-(3-Bromopropyl)thiophene (1e). To a flame-dried flask containing thiophene (3.0 g, 36 mmol) and THF (15 mL) was added *n*-BuLi (1.6 M in hexane, 21.2 mL) at 0 °C. After the mixture was stirred at the same temperature for 1 h, 1,3-dibromopropane (6.84 mL, 33 mmol) was added, and the mixture was allowed to warm to ambient temperature slowly and stirred for 12 h. The resulting mixture was quenched by 20 mL of satd NH₄Cl aq, and the product was extracted with Et₂O several times. The combined organic layer was washed with brine, dried over MgSO₄, concentrated, and purified by distillation (bp = 103–107 °C/3 mmHg) to give the title compound (1.42 g, 21%): ¹H NMR (400 MHz, CDCl₃) δ 2.21 (quin, *J* = 7.2 Hz, 2H), 3.02 (t, *J* = 7.2 Hz, 2H), 3.43 (t, *J* = 6.4 Hz, 2H), 6.84 (dd, *J* = 3.3, 0.9 Hz, 1H), 6.93 (dd, *J* = 5.0, 3.3 Hz, 1H), 7.14 (dd, *J* = 5.0, 0.9 Hz, 1H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 28.0, 32.7, 34.3, 123.5, 124.9, 126.9, 143.0; IR (Zn/Se-ATR, neat) 2937, 1438, 1256, 959, 850, 822, 699 cm⁻¹; MS (EI) *m/z* (relative intensity) 206 ([M(⁸¹Br)]⁺, 17), 204 ([M(⁷⁹Br)]⁺, 16), 99 (5), 98 (11), 97 (100); HRMS (EI) *m/z* [M]⁺ calcd for C₇H₉⁷⁹BrS 203.9608, found 203.9608.

2-(4-Bromobutyl)thiophene (1k). The title compound was synthesized by a method similar to that for **1e** using 1,4-dibromobutane instead of 1,3-dibromopropane: ¹H NMR (400 MHz, CDCl₃) δ 1.72–1.89 (m, 4H), 2.79 (t, *J* = 7.2 Hz, 2H), 3.35 (t, *J* = 6.6 Hz, 2H), 6.71–6.73 (m, 1H), 6.84–6.86 (m, 1H), 7.04–7.06 (m, 1H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 28.9, 30.1, 31.2, 33.4, 123.1, 124.3, 126.7, 144.5; IR (Zn/Se-ATR, neat) 2936, 2856, 1439, 1249, 957, 849, 826, 699 cm⁻¹; MS (EI) *m/z* (relative intensity) 220 ([M(⁸¹Br)]⁺, 13), 218 ([M(⁷⁹Br)]⁺, 13), 97 (100), 99 (5); HRMS (EI) *m/z* [M]⁺ calcd for C₈H₁₁⁷⁹BrS 217.9765, found 217.9767.

4-(2-Bromoethyl)-1-tosylpiperidine (1f). To a CH₂Cl₂ solution (100 mL) of 4-(hydroxyethyl)piperidine (2.58 g, 20 mmol) and Et₃N (5 mL) cooled in an ice bath was added TsCl (4.20 g, 22 mmol), and

then the reaction mixture was stirred at rt for overnight. The resulting mixture was diluted with CH₂Cl₂ (ca. 300 mL) and washed with water, 1 N HCl aq, satd NaHCO₃ aq, and brine. The organic layer was dried over Na₂SO₄ and concentrated to give a crude tosylated compound, which was used in the next step without further purification. The crude product was dissolved in THF, and PPh₃ (6.56 g, 25 mmol) and CBr₄ (8.29 g, 25 mmol) were added at 0 °C. After being stirred at rt for overnight, the resulting mixture was diluted with Et₂O, passed through a short pad of silica gel, and concentrated. The residue was subjected to column chromatography (silica gel, hexane/EtOAc = 4/1 to 1/4) to give the title compound as a white solid (6.92 g, quantitative yield): mp = 112–113 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.25 (ddt, *J* = 24.4, 12.3, 4.0 Hz, 2H), 1.34–1.46 (m, 1H), 1.65–1.73 (m, 5H), 2.16 (dt, *J* = 11.0, 3.0 Hz, 2H), 2.37 (s, 3H), 3.33 (t, *J* = 6.7 Hz, 2H), 3.72 (d, *J* = 12.0 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 21.5, 30.7, 30.9, 33.3, 38.4, 46.3, 127.7, 129.6, 132.9, 143.4; IR (Zn/Se-ATR, neat) 2922, 2842, 1598, 1441, 1329, 1305, 1250, 1161, 1089, 1079, 938, 927, 903, 807, 725, 651, 595 cm⁻¹; MS (EI) *m/z* (relative intensity) 368 ([M(⁸¹Br)]⁺, 100), 346 ([M(⁷⁹Br)]⁺, 98), 302 (2), 268 (18), 270 (1); HRMS (CI) *m/z* [M + H]⁺ calcd for C₁₄H₂₁⁷⁹BrNO₂S 346.0473, found 346.0473.

5,8-Diethyldecane (4). An authentic sample of **4** was prepared according to the literature and compared by GC analysis:³⁴ ¹H NMR (400 MHz, CDCl₃) δ 0.83 (t, *J* = 7.6 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H), 1.18–1.29 (m, 11H); ¹³C NMR (100 MHz, CDCl₃) δ 10.9, 14.2, 23.2, 25.86, and 25.89 (2 isomers), 29.0, 29.9, 32.86, and 32.88 (2 isomers), 39.2; IR (Zn/Se-ATR, neat) 2957, 2923, 2858, 1461, 1379 cm⁻¹.

Typical Procedure for the Cross-Coupling of *n*-NonBr with *n*-BuMgCl Using Phenylpropyne. To a flame-dried Schlenk tube equipped with a septum and a stirring bar was added CuCl₂ solution (25 \times 10⁻⁶ M in THF, 1 mL, 25 \times 10⁻⁶ mmol) under an atmosphere of nitrogen. *n*-NonBr (190 μ L, 1 mmol), decane (49 μ L, 0.25 mmol) as an internal standard, and 1-phenyl-1-propyne (123 μ L, 1 mmol) were added at ambient temperature followed by addition of *n*-BuMgCl (1.73 M in THF, 0.75 mL, 1.3 mmol) at the same temperature. The reaction mixture was stirred in a water bath at 25 °C for 24 h. The reaction was quenched with 1 N HCl aq, and the products were extracted with Et₂O and analyzed by GC.

Typical Procedure for the Cross-Coupling of *n*-NonBr with *n*-BuMgCl Using 1,3-Butadiene. To a flame-dried Schlenk tube equipped with a septum and a stirring bar was added a CuCl₂ solution (25 \times 10⁻⁶ M in THF, 1 mL, 25 \times 10⁻⁶ mmol) under an atmosphere of nitrogen. *n*-NonBr (190 μ L, 1 mmol) and decane (49 μ L, 0.25 mmol) as an internal standard were added at ambient temperature. The reaction mixture was cooled in a dry ice–ethanol bath at –78 °C, *n*-BuMgCl (1.73 M in THF, 0.75 mL, 1.3 mmol) was added, and then 1,3-butadiene (22.4 mL as a gas, 1 mmol) was introduced into the reaction vessel kept at –78 °C via a syringe. The reaction mixture was stirred in a water bath at 25 °C for 24 h. The reaction was quenched by adding 1 N HCl aq, and the products were extracted with Et₂O and analyzed by GC.

Pentylcyclohexane (2b). According to the procedure using 1,3-butadiene mentioned above, 181 mg (1.0 mmol) of **1b** was reacted with *n*-BuMgCl (1.76 M in THF, 0.75 mL, 1.3 mmol) using 100 mol ppm of CuCl₂. After purification by GPC (with CHCl₃ as eluent), the title compound **2b** was obtained as a colorless oil (84 mg, 53%): ¹H NMR (400 MHz, CDCl₃) δ 0.74–0.83 (m, 5H), 1.04–1.25 (m, 12H), 1.55–1.63 (m, 5H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 14.1, 22.7, 26.5, 26.6, 26.6, 26.8, 32.2, 32.2, 33.5, 37.5, 37.7; IR (Zn/Se-ATR, neat) 2920, 2851, 1448, 960, 888 cm⁻¹; MS (EI) *m/z* (relative intensity) 154 ([M]⁺, 27), 97 (4), 83 (100); HRMS (EI) *m/z* [M]⁺ calcd for C₁₁H₂₂ 154.1722, found 154.1718.

4-Hexyl-1-tosylpiperidine (2f). According to the same procedure using 1,3-butadiene mentioned above, 363 mg (1.0 mmol) of **1f** was reacted with *n*-BuMgCl (1.76 M in THF, 0.75 mL, 1.3 mmol) in the presence of 25 mol ppm of Cu and 1,3-butadiene (1.0 mmol). After purification by GPC (with CHCl₃ as eluent), the title compound **2f** was obtained as a white solid (228 mg, 70%): mp = 64–65 °C; ¹H NMR (400 MHz, CDCl₃) δ 0.79 (t, *J* = 7.1 Hz, 3H), 1.14–1.23 (m, 13H), 1.63 (d, *J* = 13.0 Hz, 2H), 2.12 (dt, *J* = 12.6, 2.8 Hz, 2H), 2.36

(s, 3H), 3.68 (d, $J = 12.1$ Hz, 2H), 7.25 (d, $J = 7.8$ Hz, 2H), 7.57 (d, $J = 7.8$ Hz, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 14.1, 21.5, 22.6, 26.5, 29.3, 31.5, 31.8, 35.1, 36.0, 46.5, 127.7, 129.5, 133.1, 143.3; IR (Zn/Se-ATR, neat) 2922, 2846, 1598, 1465, 1336, 1249, 1165, 1090, 928, 813, 724, 652, 607 cm^{-1} ; MS (EI) m/z (relative intensity) 323 ($[\text{M}]^+$, 10), 308 (9), 184 (8), 169 (12), 168 (100); HRMS (EI) m/z $[\text{M}]^+$ calcd for $\text{C}_{18}\text{H}_{29}\text{NO}_2\text{S}$ 323.1919, found 323.1921.

2-Octylthiophene (2k). According to the procedure using 1,3-butadiene mentioned above, 2.19 g (10 mmol) of **1k** was reacted with $n\text{-BuMgCl}$ (1.76 M in THF, 7.4 mL, 13 mmol) using CuCl_2 (0.5 mol ppm, in 1 mL THF) and 1,3-butadiene (10 mmol, 224 mL at rt). GC yield (61.5%) was determined using decane as an internal standard. After silica gel column chromatography (hexane), pure title compound **2k** was obtained from selected fractions as a pale yellow oil along with a mixture of **2k** and inseparable byproducts from other fractions of chromatography. Therefore, an isolated yield is not given. Following spectral data were obtained for the isolated pure compound: ^1H NMR (400 MHz, CDCl_3) δ 1.00 (t, $J = 6.9$ Hz, 3H), 1.20–1.27 (m, 10H), 1.60 (quin, $J = 7.3$ Hz, 2H), 2.74 (t, $J = 7.7$ Hz, 2H), 6.69–6.70 (m, 1H), 6.82–6.84 (m, 1H), 7.01–7.03 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 14.1, 22.7, 29.1, 29.2, 29.3, 29.9, 31.8, 31.9, 122.7, 123.9, 126.6, 145.9; IR (Zn/Se-ATR, neat) 2924, 2854, 1463, 941, 850, 820, 691 cm^{-1} ; MS (EI) m/z (relative intensity) 196 ($[\text{M}]^+$, 26), 153 (3), 139 (3), 111 (9), 97 (100); HRMS (EI) m/z $[\text{M}]^+$ calcd for $\text{C}_{12}\text{H}_{20}\text{S}$ 196.1286, found 196.1285.

5-Ethyldecane (2l). According to the procedure using phenylpropyne mentioned above, 193 mg (1.0 mmol) of **1l** was reacted with $n\text{-BuMgCl}$ (1.76 M in THF, 0.75 mL, 1.3 mmol) using 1000 mol ppm of CuCl_2 and 1.0 mmol of phenylpropyne. After purification by GPC (with CHCl_3 as an eluent), the title compound **2l** was obtained as a colorless oil (151 mg, 89%): ^1H NMR (400 MHz, CDCl_3) δ 0.76 (t, $J = 7.4$ Hz, 3H), 0.80–0.84 (m, 6H), 1.08–1.29 (m, 17H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 10.9, 14.1, 14.2, 22.7, 23.2, 25.9, 26.4, 29.0, 32.4, 32.9, 33.2, 38.8; IR (Zn/Se-ATR, neat) 2958, 2924, 2857, 1461, 936, 726 cm^{-1} ; MS (EI) m/z (relative intensity) 170 ($[\text{M}]^+$, 4), 141 (18), 140 (23), 112 (13), 98 (16), 85 (28), 71 (52); HRMS (EI) m/z $[\text{M}]^+$ calcd for $\text{C}_{12}\text{H}_{26}$ 170.2035, found 170.2029.

■ ASSOCIATED CONTENT

● Supporting Information

NMR spectra of isolated compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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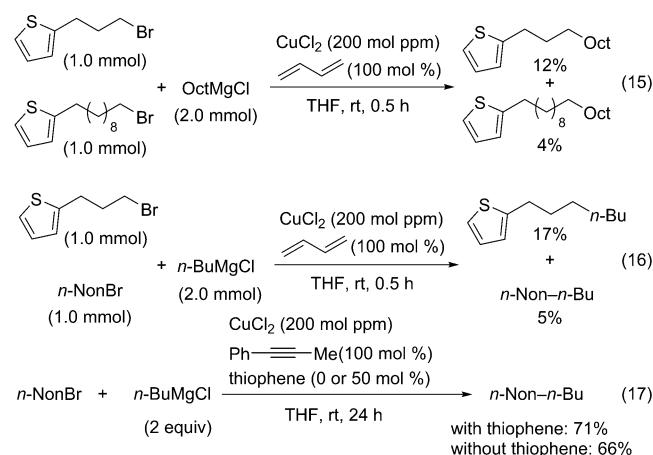
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