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Controllable, Sequential, and Stereoselective C−H Allylic Alkylation of Alkenes

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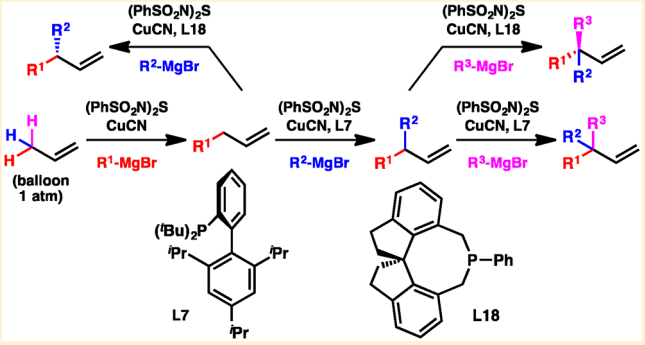
Supporting Information

ABSTRACT: The direct conversion of C−H bonds into new C−C bonds represents a powerful approach to generate complex molecules from simple starting materials. However, a general and controllable method for the sequential conversion of a methyl group into a fully substituted carbon center remains a challenge. We report a new method for the selective and sequential replacement of three C−H bonds at the allylic position of propylene and other simple terminal alkenes with different carbon groups derived from Grignard reagents. A copper catalyst and electron-rich biaryl phosphine ligand facilitate the formation of allylic alkylation products in high branch selectivity. We also present conditions for the generation of enantioenriched allylic alkylation products in the presence of catalytic copper and a chiral phosphine ligand. With this approach, diverse and complex products with substituted carbon centers can be generated from simple and abundant feedstock chemicals.



INTRODUCTION

The functionalization of C−H bonds has emerged as a powerful and versatile strategy for the conversion of inexpensive and abundant starting materials into products of greater value.[1] In particular, the conversion of C−H bonds into new C−C bonds enables the rapid generation of complex molecules from simple substrates.[2] Despite major advances in the field of selective C−H alkylation,[3] there are no general methods for the sequential conversion of a methyl group with three C−H bonds into a fully substituted carbon center with three new C−C bonds from three distinct carbon-based reagents (Figure 1A). The selective conversion of methyl groups into substituted carbon centers via controllable and sequential C−H functionalization would enable the efficient synthesis of a broad range of products from simple starting materials.

Based on our group's research in selective C−H allylic functionalization,[4] we became interested in addressing the unsolved problem of sequential C−H functionalization in the context of converting an allylic methyl group into a fully substituted allylic carbon center through three consecutive C−H allylic alkylations with three different carbon-based reagents (Figure 1B). The major challenges in achieving this goal are threefold. First, a mode of activation must be identified that is *reactive* enough to undergo multiple C−H functionalizations to generate a fully substituted carbon center. Second, each C−H allylic alkylation must be *selective* for the formation of the branched product over the linear product, which becomes more sterically challenging over subsequent steps. Third, to generate C−C bonds with three distinct carbon groups, the mode of activation must be *controllable* to avoid undesired over-functionalization of C−H bonds in any step of the process. Elegant methods have been reported for the generation of fully substituted carbon centers via C−H functionalization[5] and for branch-selective C−H allylic alkylation.[6] However, these strategies are not amenable to the conversion of simple alkenes

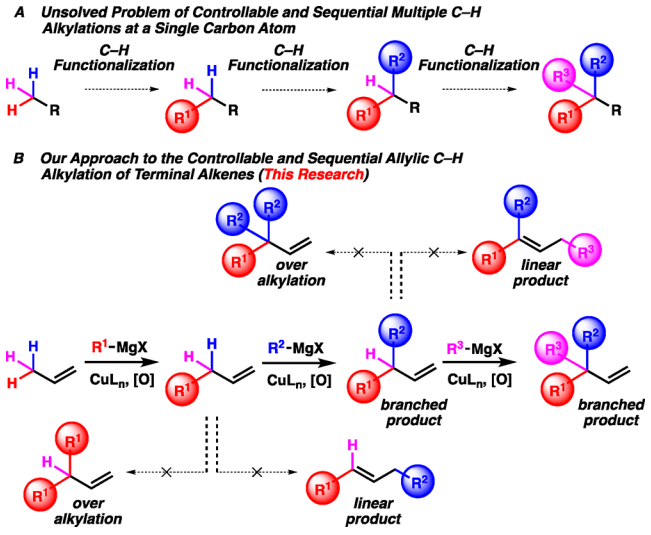


Figure 1. Controllable and sequential C−H alkylation.

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such as propylene into products with substituted allylic carbon centers via sequential C−H allylic alkylation. While these reported strategies have overcome the challenges of reactivity and selectivity for the formation of fully substituted carbons, traditional C−H functionalization and allylic alkylation approaches have not addressed the challenge of controllably forming distinct C−C bonds.

Herein, we report the first general method to create a fully substituted carbon center at the allylic position of simple alkenes such as propylene. Our approach uniquely enables the selective and sequential replacement of three C−H bonds with different carbon groups in a controllable fashion. The highly substituted terminal alkenes generated by this method are synthetically versatile precursors for many functional groups, including amines, alcohols, acids, epoxides, aldehydes, and internal alkenes. Therefore, we anticipate our method will provide a new strategy for converting simple alkenes into complex molecules with fully substituted carbons.

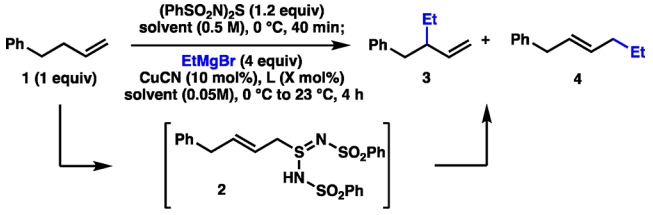
RESULTS AND DISCUSSION

Catalyst-Controlled Regioselectivity of Allylic Alkylation. A core feature of our controllable and sequential allylic alkylation strategy is the use of sulfur diimide reagent $PhSO_2N{=}S{=}NSO_2Ph$ (Table 1),[7] which we hypothesized could serve the dual role of an electrophilic oxidant for the activation of alkenes (**1** to **2**) and a controllable leaving group in the subsequent copper-catalyzed alkylation with Grignard reagents.

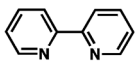
We first examined the selective conversion of alkene **1** to branched allylic alkylation product **3** with a tertiary allylic carbon. To develop a branch-selective, controllable, and sequential allylic alkylation of alkene **1**, we had to overcome the inherent preference of allylic sulfinamides such as **2** to undergo alkylation with Grignard reagents to selectively form linear products such as **4**.[4b] Initially, we observed predominantly linear selectivity with various copper catalysts (entries 1−3).[8] To our delight, CuCN reversed the regioselectivity of the reaction, and the desired branched product **3** was obtained as the major product with moderate 2.5:1 selectivity (entry 4). We observed an important solvent effect on the branch selectivity (entries 4−6). The use of CH_2Cl_2 as the primary solvent for allylic alkylations was beneficial for the branch selectivity of the reaction (entry 6). Based on detailed NMR studies by Gschwind and co-workers,[9] we surmise that CH_2Cl_2 facilitates the formation of soluble monoalkyl cyanocuprates (RCuCNMg) that favor the formation of branched allylic alkylation products, rather than insoluble copper-rich complexes or higher-order cuprates that would favor the formation of linear allylic alkylation products. As a practical advantage, solutions of Grignard reagents in Et_2O were tolerated by the reaction without negatively impacting the yield or branch selectivity of the process, as long as CH_2Cl_2 remained the predominant solvent.

To further improve the regioselectivity of the allylic alkylation, we introduced various ligands for the copper catalyst (entries 7−13). Bipyridine **L1** resulted in slightly higher regioselectivity of 10:1 (entry 7), while the more effective σ-donor triphenylphosphine **L2** provided a 14:1 ratio (entry 8). Furthermore, the more electron-rich phosphine **L3** improved regioselectivity (entry 9), whereas the more electron-poor phosphine **L4** diminished regioselectivity (entry 10). Based on this trend in selectivity, we examined electron-rich biaryl phosphine ligands.[10] CyJohnPhos **L5** provided a regioselectivity of 13:1 in favor of branched

Table 1. Optimization of Ligand-Controlled Branch-Selective Allylic Alkylation of Terminal Alkenes[g]



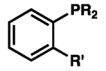
entry	ligand[a]	Cu source	solvent	3:4[b]	yield[c]
1	–	$Cu(OTf)_2$	Et_2O	1 : 1.5	27 %
2	–	CuTc	Et_2O	1 : 2.2	25 %
3	–	$CuBr{\cdot}SMe_2$	Et_2O	1 : 2.4	23 %
4	–	CuCN	Et_2O	2.5 : 1	33 %
5	–	CuCN	PhMe	5.7 : 1	44 %
6	–	CuCN	CH_2Cl_2	8.7 : 1	64 %
7	L1	CuCN	CH_2Cl_2	10 : 1	63 %
8	L2	CuCN	CH_2Cl_2	14 : 1	58 %
9	L3	CuCN	CH_2Cl_2	15 : 1	58 %
10	L4	CuCN	CH_2Cl_2	10 : 1	70 %
11	L5	CuCN	CH_2Cl_2	13 : 1	51 %
12	L6	CuCN	CH_2Cl_2	18 : 1	60 %
13	L7	CuCN	CH_2Cl_2	>20 : 1	66 %
14[d]	L7	CuCN	CH_2Cl_2	15 : 1	50 %
15[e]	L7	CuCN	CH_2Cl_2	>20 : 1	60 % (57 %)[f]



L1

PAr_3

L2: Ar = Ph
L3: Ar = *p*-MeO-C_6H_4
L4: Ar = C_6F_5



L5: R = Cy, R' = Ph
L6: R = Cy, R' = 2,4,6-*i*-Pr_3-C_6H_2
L7: R = *t*-Bu, R' = 2,4,6-*i*-Pr_3-C_6H_2

[a]24 mol % of monodentate ligand, 12 mol % of bidentate ligand. [b]Determined by ^1H NMR analysis. [c]NMR yield with 1,3-dimethoxybenzene as an internal standard. [d]5 mol % CuCN and 6 mol % ligand. [e]10 mol % CuCN and 12 mol % ligand. [f]Isolated yield in parentheses. [g]Reaction conditions: **1** (0.25 mmol, 1 equiv), $(PhSO_2N)_2S$ (0.30 mmol, 1.2 equiv), solvent (0.5 mL, 0.5 M), 0 °C, 40 min; then solvent (0.05 M by dilution), Cu source (10 mol %), ligand (12 or 24 mol %), EtMgBr (3 M in Et_2O, 4 equiv), 0 to 23 °C, 4 h.

product **3** (entry 11), which was similar to triphenylphosphine **L2**. Sterically hindered ligand **L6** enhanced regioselectivity to 18:1 (entry 12). Ultimately, the bulkier *t*-BuXPhos **L7** was identified as the optimal ligand, furnishing branched allylic product **3** in >20:1 regioselectivity (entry 13). This class of ligands has found broad utility in controlling product selectivity of palladium-catalyzed reactions. Guided by these studies, we hypothesize that the electron-rich and bulky phosphine ligand **L7** enhances the selectivity for the branched allylic alkylation by altering the relative rates of oxidative addition and reductive elimination en route to the desired product **3** (*vide infra*). Lowering the copper catalyst and ligand loading had a deleterious effect on the yield and regioselectivity (entry 14). Finally, we obtained the desired product **3** in 57% isolated yield and >20:1 regioselectivity with 10 mol % CuCN and 12 mol % ligand **L7** (entry 15).

Other organometallic reagents were assayed in the allylic alkylation of 4-phenyl-1-butene (Figure 2). Under unoptimized conditions, we were pleased to observe that organolithium, organozinc, and organoaluminum reagents were compatible coupling partners for the C−H allylic alkylation of terminal alkenes, with high selectivity for the branched product. Allylic sulfinamide intermediate **2** is presumably initially activated by nucleophilic Grignard reagent prior to oxidative addition with

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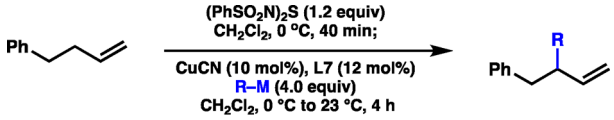


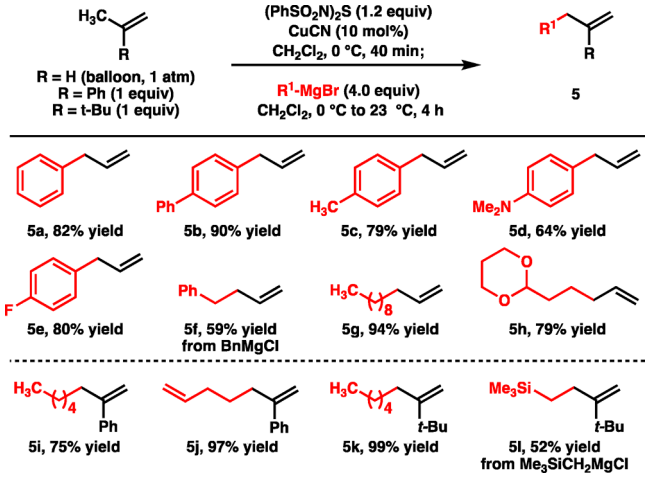
R–M	yield	B : L
n-BuLi	11% yield	>20 : 1
Et_2Zn	12% yield	>20 : 1
Et_3Al	20% yield	>20 : 1

Figure 2. Branch-selective C−H allylic alkylation of 4-phenyl-1-butene with other organometallic reagents.

the copper catalyst (*vide infra*). Therefore, these alternative organometallic reagents may require further optimization to generate the desired product in synthetically useful yields.

Allylic Alkylation of Propylene. We implemented our strategy for controllable and sequential construction of substituted carbon centers from simple alkenes by performing C−H allylic alkylation of propylene, the simplest terminal alkene with available allylic C−H bonds (Table 2). Since regioselectivity was not an issue in this allylic alkylation step, ligand **L7** was not required. Diverse Grignard reagents, including aromatic (**5a**−**e**), benzylic (**5f**), alkyl (**5g**), and heteroatom-containing (**5h**, **5l**) reagents, provided high yields of allylic alkylation products. A methyl group (**5c**), electron-donating dimethylamino group (**5d**), and electron-withdrawing fluorine group (**5e**) were also well tolerated. Alkenes with hindered internal substituents, such as phenyl (**5i**−**j**) and *tert*-butyl groups (**5k**−**l**), furnished the desired product in high yield. Bromide Grignard reagents provided the product in higher yields than chloride Grignard reagents, presumably due to an undesirable Schlenk equilibrium with the latter reagents.[11]

Table 2. Allylic Monofunctionalization of Propylene and Other 2-Substituted Alkenes[a]

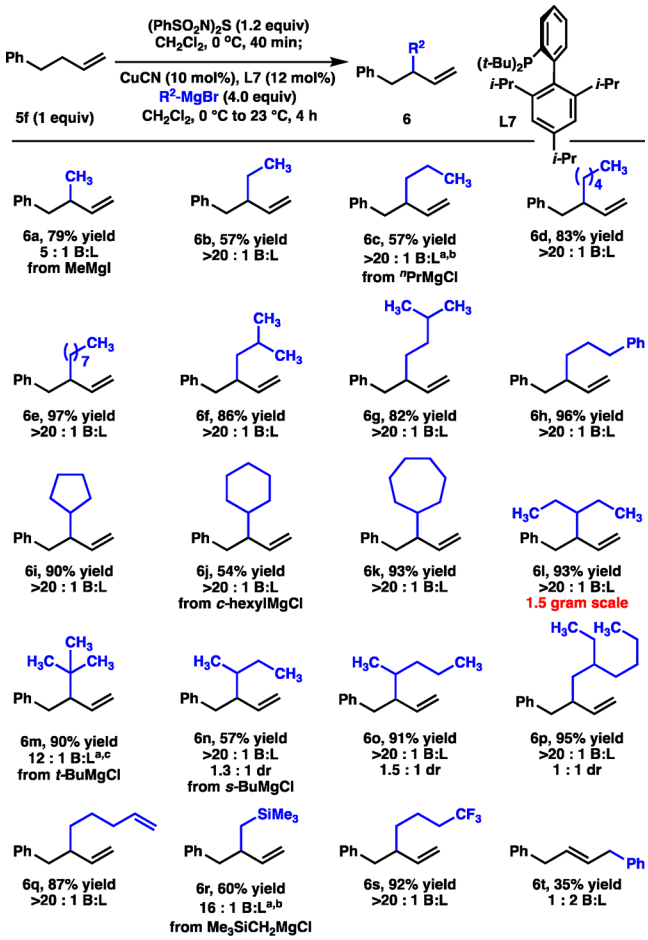


[a]Reaction conditions: Terminal alkene (R = H: 1 atm balloon; R = Ph, *t*-Bu: 0.25 mmol, 1 equiv), $(PhSO_2N)_2S$ (0.30 mmol, 1.2 equiv), CH_2Cl_2 (0.5 mL, 0.5 M), 0 °C, 40 min; then CH_2Cl_2 (0.05 M by dilution), CuCN (10 mol %), R^1 MgBr (4 equiv), 0 to 23 °C, 4 h.

Allylic Alkylation of Terminal Alkenes to Products with Allylic Tertiary Carbons. Once we established the efficient conversion of propylene to a variety of alkenes, we explored the conversion of these products to terminal alkenes with allylic tertiary carbons. Commercially available 4-phenyl-1-butene was coupled with several Grignard reagents (Table 3). In the presence of **L7**, primary (**6a**−**h**, **6p**), secondary cyclic (**6i**−**k**), acyclic (**6l**, **6n**, **6o**), and tertiary (**6m**) Grignard reagents provided excellent yields and high regioselectivities for the desired branched products **6**. Grignard reagents with functional groups were also compatible with the reaction conditions, which allowed for the incorporation of an unsaturated chain (**6q**), silyl group (**6r**), and trifluoromethyl group (**6s**) into the products. Reaction with phenylmagnesium bromide resulted in the linear constitutional isomer **6t** as the major product in poor regioselectivity (1:2 B:L), suggesting a modified reactivity of aryl-substituted allylcopper intermediates (*vide infra*). Organomagnesium chlorides, bromides, and iodides were tolerated. The branch-selective allylic alkylation could be performed on a gram scale without affecting the efficiency and regioselectivity of the reaction (**6l**).

We also explored branch-selective allylic alkylation starting from a diverse range of terminal alkene substrates (Table 4). Benzylic (**6u**), aromatic (**6v**−**x**), cyclic (**6y**), and acyclic (**6z**) alkyl substitution in the starting material were tolerated,

Table 3. Scope of Grignard Reagents for the Branch-Selective Allylic Alkylation[d]



[a]Two-pot procedure. [b]24 mol % **L7**. [c]No **L7**. [d]Reaction conditions: **5f** (0.25 mmol, 1 equiv), $(PhSO_2N)_2S$ (0.30 mmol, 1.2 equiv), CH_2Cl_2 (0.5 mL, 0.5 M), 0 °C, 40 min; then CH_2Cl_2 (0.05 M by dilution), CuCN (10 mol %), **L7** (12 mol %), R^2 MgBr (4 equiv), 0 to 23 °C, 4 h. B:L is branched:linear allylic alkylation products.

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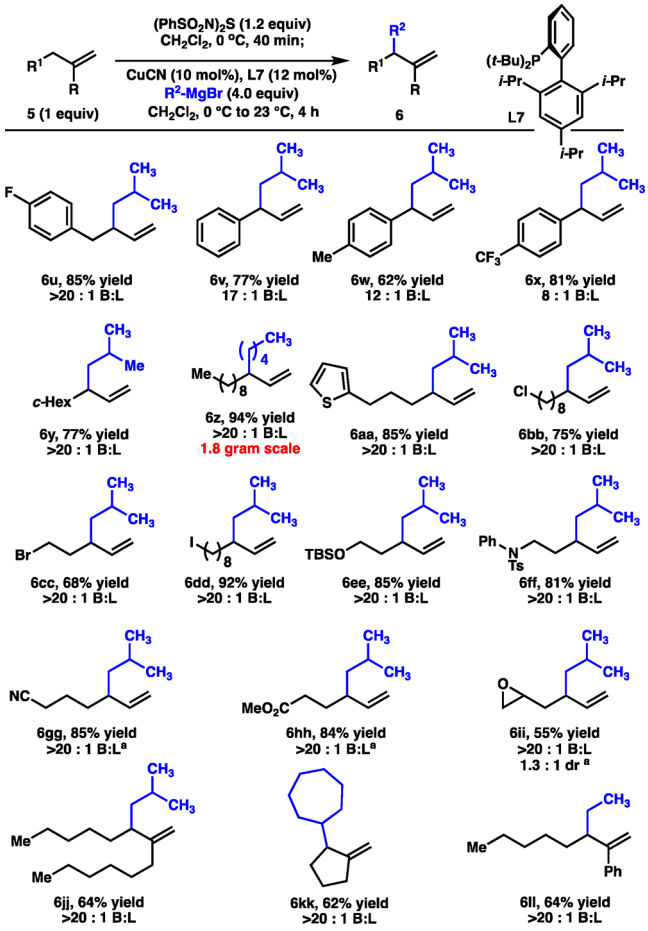
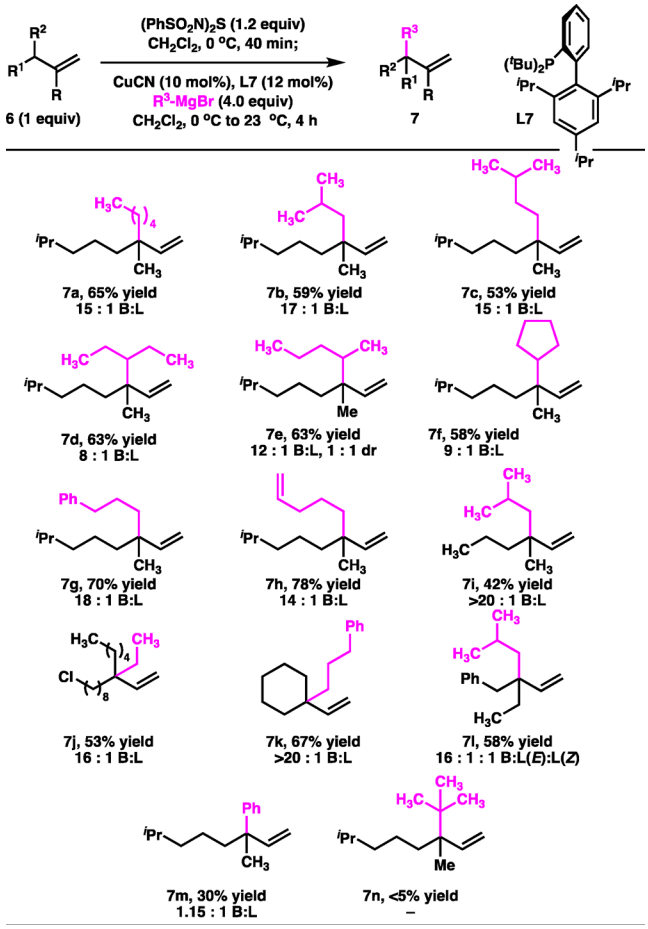
Table 4. Scope of Functionalized Alkenes for the Branch-Selective Allylic Alkylation[b]



[a]Reaction conducted at −78 to −20 °C for 48 h. [b]Reaction conditions: **5** (0.25 mmol, 1 equiv), $(PhSO_2N)_2S$ (0.30 mmol, 1.2 equiv), CH_2Cl_2 (0.5 mL, 0.5 M), 0 °C, 40 min; then CH_2Cl_2 (0.05 M by dilution), CuCN (10 mol %), **L7** (12 mol %), R^2MgBr (4 equiv), 0 to 23 °C, 4 h. B:L is branched:linear allylic alkylation products.

Table 5. Synthesis of Fully Substituted Allylic Carbon Centers from Tertiary Allylic Alkenes[a]



[a]Reaction conditions: **6** (0.25 mmol, 1 equiv), $(PhSO_2N)_2S$ (0.30 mmol, 1.2 equiv), CH_2Cl_2 (0.5 mL, 0.5 M), 0 °C, 40 min; then CH_2Cl_2 (0.05 M by dilution), CuCN (10 mol %), **L7** (12 mol %), R^3 MgBr (4 equiv), 0 to 23 °C, 4 h. B:L is branched:linear allylic alkylation products.

providing good yields and satisfying regioselectivities of products **6**. Electronically diverse phenyl rings (**6v**–**x**) did not impact the efficiency of the reaction. A variety of functional groups were tolerated, including halides (**6bb**, **6cc**, **6dd**), protected alcohol (**6ee**), protected amine (**6ff**), thiophene (**6aa**), and Grignard-sensitive functional groups such as nitrile (**6gg**), ester (**6hh**), and epoxide (**6ii**). Interestingly, 1,1-disubstitued alkenes formed the desired branched product in moderate yields and excellent regioselectivities (**6jj**, **6kk**, **6ll**). Under the reaction conditions, internal alkenes such as *trans*-5-decene did not yield any C−H allylic alkylation product. Since we observed significant amounts of the ene-adduct of this internal alkene at 0 °C, we conclude that the initial ene reaction with the sulfur diimide oxidant proceeded, but the subsequent reaction between the branched allylic sulfinamide and the Grignard reagent did not occur.

Allylic Alkylation of Terminal Alkenes to Products with Allylic Quaternary Carbons. Next, we examined the conversion of already generated branched terminal alkenes **6** into products with fully substituted allylic carbon centers (**7**, Table 5). With 3,7-dimethyl-1-octene as the standard substrate, reactions of primary (**7a**–**c**, **7g**,**h**) and secondary (**7d**–**f**) Grignard reagents furnished the desired products. Despite the inherent difficulty of constructing congested fully substituted carbon centers via an allylic C−H alkylation reaction, we obtained branched allylic alkylation products **7** in synthetically useful yields and regioselectivities with both primary and secondary Grignard reagents. Moreover, other 3,3-disubstituted alkenes, including a cyclic structure (**7k**) and a substrate with a primary chloride (**7j**), provided the desired product with high regioselectivity. The use of phenylmagnesium bromide resulted in diminished selectivity for the branched allylic arylation product **7m**. The inability to generate a product with two vicinal fully substituted carbon centers represents a current limitation to this chemistry (**7n**).

Controllable and Sequential Allylic Alkylation of Propylene. To demonstrate the utility of this controllable and sequential strategy in assembling fully substituted carbon centers, we prepared several products by iterative introduction of three different carbon-based substituents at the allylic position of propylene (Table 6). Generally, excellent regioselectivity was maintained for the three-step sequence. Different functional groups could be introduced in each step, including an acetal (**7p**), thiophene (**7q**), and alkenyl group (**7s**). We anticipate this chemistry will provide a new approach to a broad

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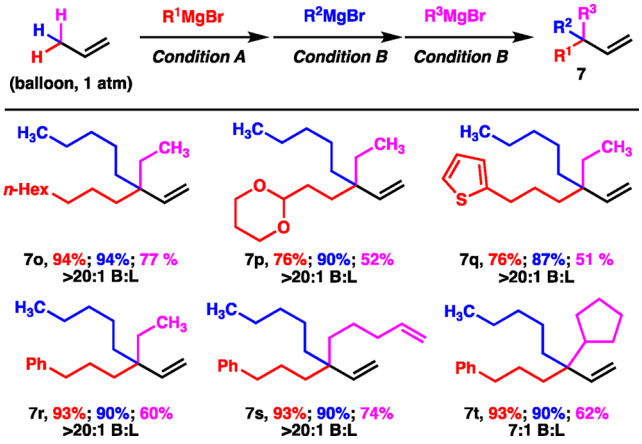
Table 6. Controllable and Sequential Allylic Alkylation of Propylene[a]



[a]Condition A: propylene (balloon, 1 atm), $(PhSO_2N)_2S$ (1 equiv), CuCN (10 mol %), CH_2Cl_2, 0 °C, 40 min; RMgBr (4 equiv), CH_2Cl_2, 0 to 23 °C, 4 h. Condition B: alkene (1 equiv), $(PhSO_2N)_2S$ (1.2 equiv), CuCN (10 mol %), **L7** (12 mol %), CH_2Cl_2, 0 °C, 40 min; RMgBr (4 equiv), CH_2Cl_2, 0 to 23 °C, 4 h. B:L ratios refer to the overall branched:linear allylic alkylation product ratios after the third alkylation step.

diversity and complexity of products with fully substituted carbon centers that can be generated from simple, abundant feedstock chemicals such as propylene.

Proposed Mechanism. We propose a mechanism that accounts for the high regioselectivity in the formation of the branched products in the allylic alkylation step (Figure 3). Initial oxidation of the alkene substrate yields ene adduct **9**, which is activated by the Grignard reagent to furnish allylic sulfimine **10**. For heterocuprates such as $[R^3Cu^ICNL_7]MgBr$, oxidative addition of the Cu^I complex to the allylic substrate dictates the regioselectivity of the allylic substitution.[12,13] Therefore, either allylic sulfimine **10** forms Cu^{III}-allyl complex **12** via transition state **11**, with ligand **L7** on the C1 side of the allyl system, to yield product **7**, or allylic sulfimine **10** forms Cu^{III}-allyl complex **14** via transition state **13**, with ligand **L7** on the C3 side, to give product **8**. We propose a preference for transition state **11** with improved FMO interactions between the HOMO of the organocuprate and the LUMO of allylic sulfimine **10**. Transition state **11** leads to conformationally stable enyl[$\sigma+\pi$]-allylcopper(III) complex **12**, in which the copper atom is σ-bonded to C3. Subsequent reductive elimination furnishes branched product **7**. To account for the enhanced regioselectivity and preference for transition state **11** in the presence of ligand **L7**, we propose that the electron-rich phosphine stabilizes transition state **11** for oxidative addition. In addition, the bulky *tert*-butyl groups on phosphorus and isopropyl substituents on the aromatic ring of ligand **L7** promote reductive elimination of enyl[$\sigma+\pi$]-allylcopper(III) complex **12** before isomerization can occur to the enyl[$\sigma+\pi$]-allylcopper(III) complex **14**, which would lead to the undesired linear product **8**. We surmise that excess Grignard reagent is required to obtain synthetically useful yields of product because of multiple roles for the Grignard reagent in the transformation. One equivalent of Grignard is consumed in the conversion of allylic sulfinamide **9** to allylic sulfimine **10**, and another equivalent is ultimately transferred to the product in the allylic alkylation step. Additional Grignard reagent may be required in the decomposition of the sulfur-containing leaving group into a thioether.[4b,14]

Enantioselective Allylic Alkylation. Given the importance of achiral phosphine **L7** for branch selectivity in the C−H allylic alkylation process, we hypothesized that the proper choice of a chiral phosphine ligand could facilitate the formation of enantioenriched terminal alkenes with allylic stereogenic centers (Table 7). Allylic sulfinamide **2** was generated from 4-phenylbutene, isolated, and then treated with catalytic CuCN and chiral ligands in CH_2Cl_2 at −78 °C. Upon addition of *i*-BuMgBr, the reaction mixture was warmed to 0 °C and stirred. We initially examined a broad range of chiral ligands, including bidentate phosphines **L8**−**L12** (entries 1−5). Although

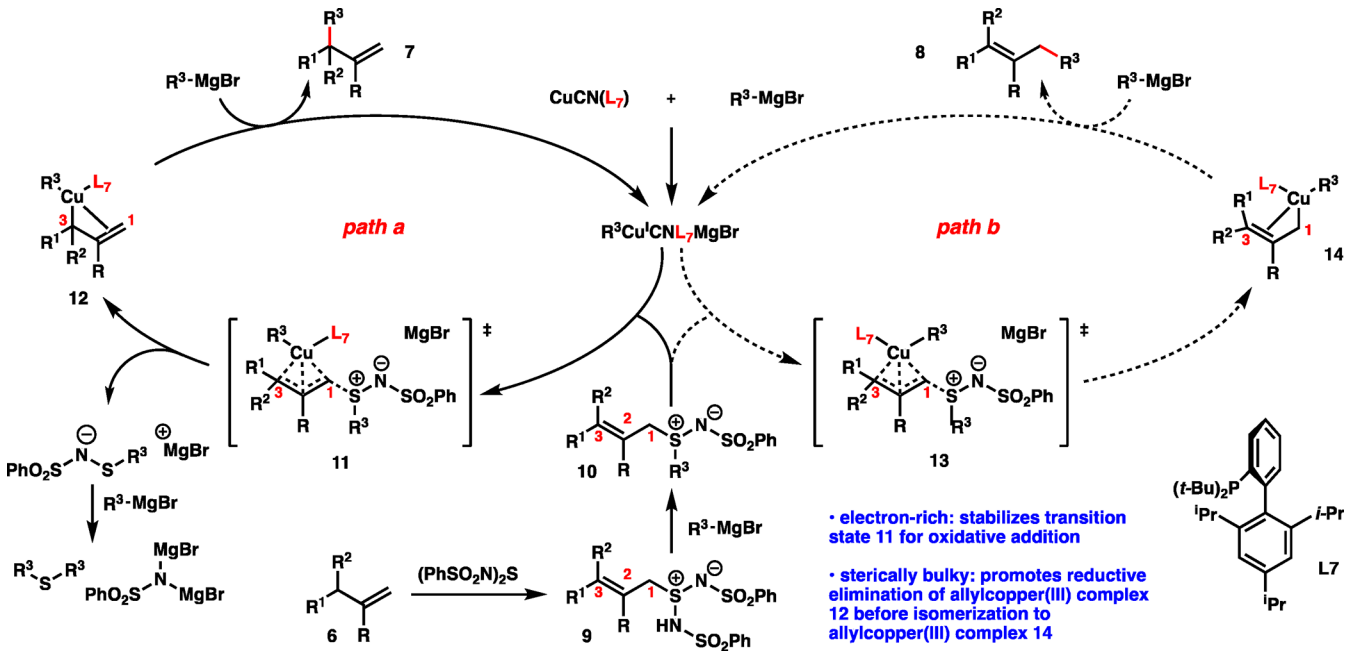


Figure 3. Proposed mechanism of ligand-controlled branch-selective allylic alkylation of terminal alkenes.

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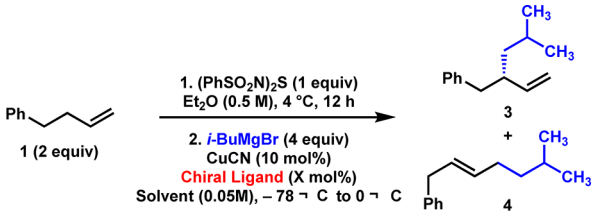
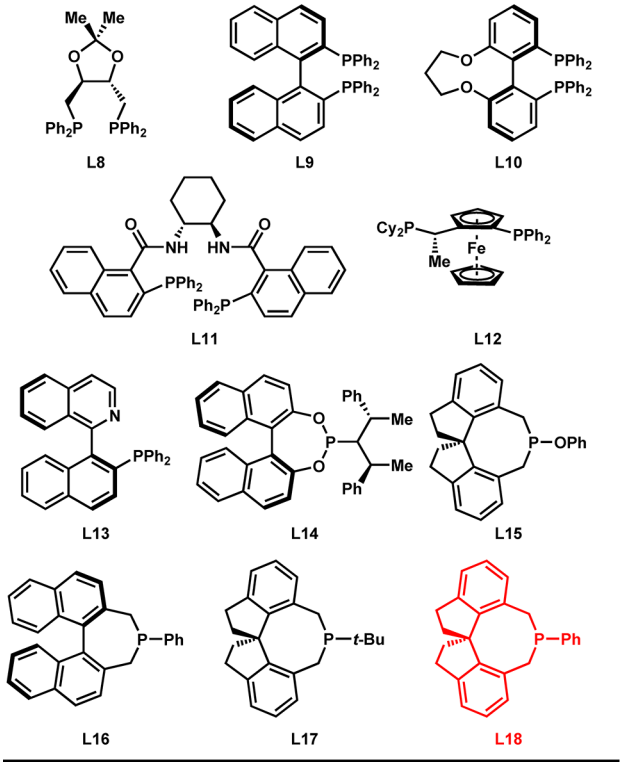
Table 7. Optimization of Catalytic Enantioselective Branch-Selective Allylic Alkylation[f]



entry	chiral ligand[a]	solvent	yield[b]	3:4[c]	er[d]
1	L8	CH_2Cl_2	47%	18 : 1	50.5 : 49.5
2	L9	CH_2Cl_2	63%	>20 : 1	51.5 : 48.5
3	L10	CH_2Cl_2	25%	>20 : 1	50.5 : 49.5
4	L11	CH_2Cl_2	64%	>20 : 1	50 : 50
5	L12	CH_2Cl_2	39%	8 : 1	51.5 : 48.5
6	L13	CH_2Cl_2	58%	>20 : 1	49 : 51
7	L14	CH_2Cl_2	69%	>20 : 1	48.5 : 51.5
8	L15	CH_2Cl_2	58%	>20 : 1	51 : 49
9	L16	CH_2Cl_2	86%	4 : 1	53.5 : 46.5
10	L17	CH_2Cl_2	41%	>20 : 1	49.5 : 50.5
11	L18	CH_2Cl_2	82%	>20 : 1	78 : 22
12	L18	*t*-BuOMe	48%	15 : 1	64 : 36
13	L18	PhMe	91%	>20 : 1	84 : 16
14[e]	L18	PhMe	86%	>20 : 1	94 : 6

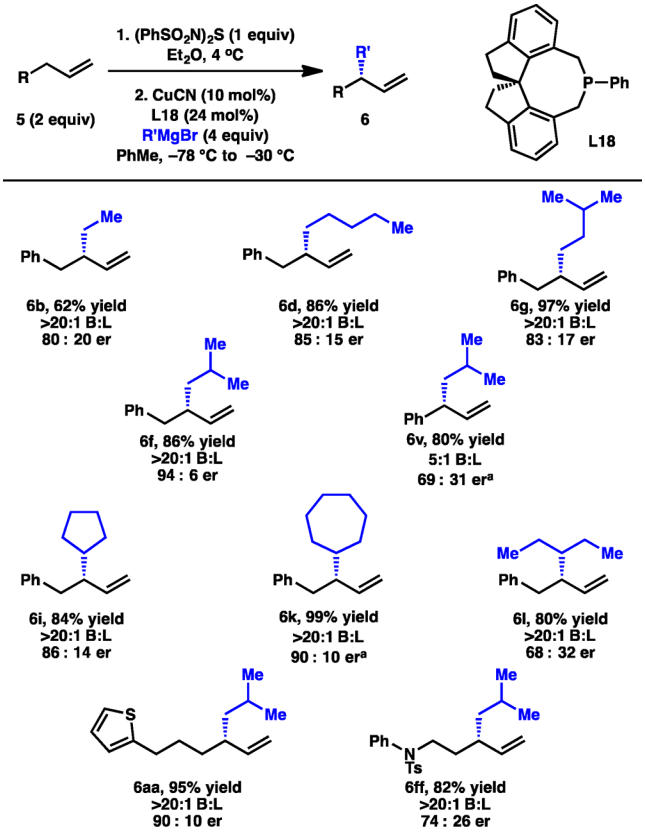


[a]24 mol % of monodentate ligand, 12 mol % of bidentate ligand. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis. [d]Determined by chiral HPLC analysis of derivative. [e]Reaction performed at −78 to −30 °C. [f]Reaction conditions for 1st step: $(PhSO_2N)_2S$ (2 mmol, 1 equiv), **1** (2 equiv), Et_2O (0.5 M), 4 °C, 12 h. Reaction conditions for 2nd step: **2** (0.1 mmol, 1 equiv), solvent (0.05 M by dilution), CuCN (10 mol %), chiral ligand (12 or 24 mol %), *i*-BuMgBr (2 M in Et_2O, 4 equiv), −78 to 0 °C.

selectivity for the branched product **3** was maintained across this diverse set of ligands, the allylic alkylation product was consistently generated with low levels of enantioselectivity. *P,N* ligand **L13**, phosphite **L14**, and phosphinite **L15** all furnished product **3** as essentially a racemate (entries 6−8). Finally, we examined a series of chiral monodentate phosphines. Whereas ligands **L16** and **L17** provided the allylic alkylation product in negligible levels of enantioselectivity (entries 9, 10), phosphine **L18** yielded product **3** in 82% yield, >20:1 regioselectivity, and 78:22 er (entry 11). Given the high selectivity for the branched product with ligand **L18**, we surmised that a broad range of reaction media would retain the high regioselectivity with the potential to improve the enantioselectivity. In ethereal solvent, product **3** was formed in reasonable regioselectivity but with diminished yield and enantioselectivity (entry 12). Aromatic solvents, such as toluene, furnished the desired product in high yield and regioselectivity with an improved enantiomeric ratio of 84:16 (entry 13). Gratifyingly, by initiating the reaction at −78 °C and warming it up to −30 °C, we obtained the branched allylic alkylation product **3** in 86% isolated yield, >20:1 regioselectivity, and 94:6 er (entry 14).

With the identification of optimal conditions for the catalytic enantioselective branch-selective allylic alkylation, we examined the scope of this transformation with other terminal alkenes and Grignard reagents (Table 8). 4-Phenylbutene coupled with primary Grignard reagents (**6b**, **6d**, **6g**, **6f**, **6v**) as well as

Table 8. Scope of Catalytic Enantioselective Branch-Selective Allylic Alkylation[b]



[a]$PhCF_3$ as a solvent, reaction performed at −78 to 0 °C. [b]Reaction conditions for 1st step: $(PhSO_2N)_2S$ (2 mmol, 1 equiv), **5** (2 equiv), Et_2O (0.5 M), 4 °C, 12 h. Reaction conditions for 2nd step: *ene adduct* (0.1 mmol, 1 equiv), PhMe (0.05 M by dilution), CuCN (10 mol %), **L18** (24 mol %), R′MgBr (4 equiv), −78 to −30 °C. B:L is branched:linear allylic alkylation products.

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secondary cyclic and acyclic Grignard reagents (**6i**, **6k**, **6l**). Other functionalized terminal alkenes were also compatible with the reaction, including a substrate with a remote heteroaromatic ring (**6aa**) and an unsaturated sulfonamide (**6ff**).

Preliminary studies with chiral ligands for the copper-catalyzed branch-selective allylic alkylation suggest that our method affords us the opportunity to transform simple terminal alkenes into enantioenriched alkenes (Figure 4). Conversion of

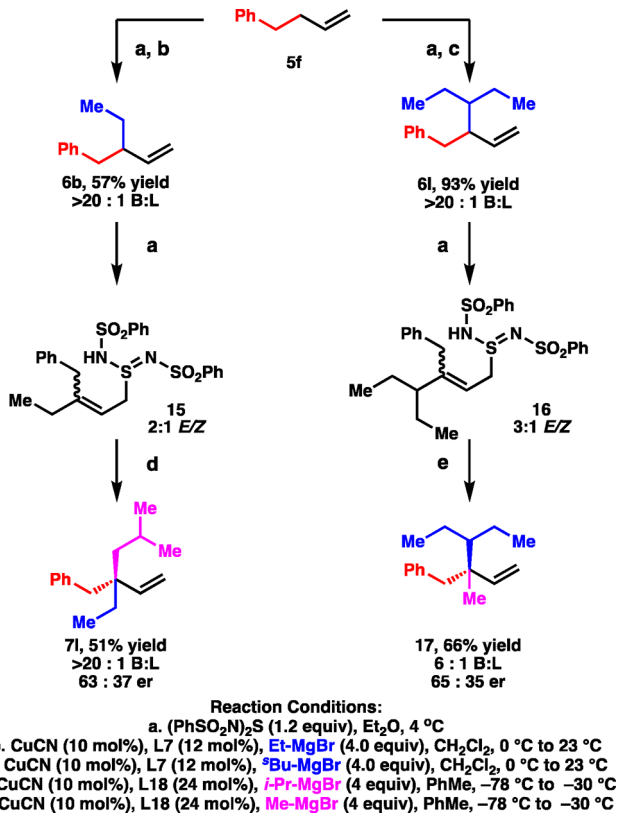

Figure 4. Synthesis of enantioenriched alkenes with either tertiary or quaternary allylic stereogenic centers. B:L is branched:linear allylic alkylation products.

4-phenylbutene to allylic sulfinamide **2** followed by subjection to the CuCN/**L7** conditions for branch-selective allylic alkylation furnished racemic products **6b** and **6l**. These two unsaturated hydrocarbons were then treated with the sulfur diimide oxidant to yield allylic sulfinamides **15** and **16**. Treatment with the CuCN/**L18** reaction conditions furnished enantioenriched alkenes **7l** and **17** with fully substituted allylic stereogenic centers. The lower enantioselectivity in forming the products with quaternary stereogenic centers compared to tertiary stereogenic centers may be due to the formation of trisubstituted allylic sulfinamides **15** and **16** as mixtures of *E*/*Z* isomers. We are currently examining catalyst-controlled methods for generating trisubstituted allylic sulfinamides in high selectivity for the *E*-alkene isomer.

CONCLUSION

In conclusion, we have developed a general method for converting multiple C−H bonds to C−C bonds via a ligand-controlled copper-catalyzed controllable and sequential allylic alkylation of alkenes. We demonstrated the formation of substituted carbon centers at the allylic position of simple terminal alkenes, including propylene, which provides efficient and flexible access to a diverse range of products. We proposed a mechanism that accounts for the catalyst and ligand control of branch selectivity in product formation. We also discovered conditions to generate enantioenriched allylic alkylation products in the presence of catalytic copper and chiral phosphine **L18**.

Our method represents a new chemical strategy for converting simple terminal alkene substrates into complex unsaturated products in synthetically useful yields, regioselectivities, and enantioselectivities. Importantly, the products generated by this method may also be accessed in theory with high regioselectivity and enantioselectivity through the catalytic allylic substitution of prefunctionalized allyl electrophiles with organometallic reagents.[15] Our approach and the traditional allylic substitution of allyl electrophiles have complementary strengths and weaknesses.[15] In some cases, we anticipate that the allylic substitution of prefunctionalized allyl halides, acetates, carbonates, or phosphates will be preferential. For example, while both strategies are compatible with organomagnesium, organolithium, organozinc, and organoaluminum reagents, in some cases the allylic substitution of preformed allylic electrophiles can be performed with organoborane reagents, including alkynyl boron reagents. In addition, currently the branched allylic arylation product with aryl nucleophiles cannot be accessed with our method. In other instances, we anticipate that our controllable and sequential strategy for allylic alkylation will be preferential. For some classes of substrates the selective synthesis of the prefunctionalized allyl electrophile may be challenging, whereas the unfunctionalized terminal alkene substrate will be readily accessible. Moreover, a sequential allylic alkylation with the traditional approach with two or three carbon-based nucleophiles would require multiple intermediary steps to generate the desired allylic electrophile for each round of alkylation, whereas our approach enables the sequential addition of carbon substituents in one pot for each step. Ultimately, the existence of two complementary strategies for regioselective and enantioselective allylic alkylation will be beneficial to the synthetic community.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b08801.

Experimental procedures and characterization data (PDF)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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