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Asymmetric Allylic Alkylation of Acyclic Allylic Ethers with Organolithium Reagents

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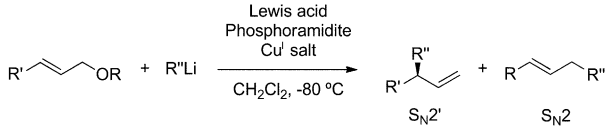
Asymmetric allylic substitution is one of the most powerful synthetic transformations with numerous applications in the total synthesis of biologically active compounds and natural products.[1] The use of metal complexes such as Pd,[2] Mo[3], or Ir[4] in combination with mainly allylic carbonates or acetates represents an excellent methodology for the use of stabilized nucleophiles in this transformation. On the other hand, Cu-catalyzed asymmetric allylic alkylation (AAA)[5–7] is characterized by the formation of C–C bonds with organometallic reagents. Allylic substrates with good leaving groups, such as allylic halides[6] and allylic phosphates,[7] are typically used in these transformations. A major challenge is to accomplish similar catalytic AAA by using allylic substrates with robust protecting groups. In synthesis it might also offer new opportunities if otherwise inert stable protecting groups can be used as leaving groups in later stages of synthetic schemes to perform enantioselective C–C bond formation through asymmetric allylic substitution. A possible strategy will be to apply asymmetric allylic alkylation of quite stable alkyl/aryl protected allylic ethers. Nevertheless their low reactivity is a major limitation towards their use in allylic alkylation.[8–11] A few non-enantioselective examples of allylic alkylation were described by using allylic ethers including -OMe, -OPh, -OPy in combination with metals such as Cu,[8] Ni,[9] Zr,[10] Co[11] and Rh.[11] As far as we know, the only examples of AAA of allylic ethers were reported by Okamoto et al.[8b] using pyridyl-ethers (Cu), and Consiglio et al.[9a] with phenyl-ethers (Ni), both in combination with Grignard reagents and with moderate enantiomeric ratios (e.r.). Oxabicyclic alkenes, studied by Lautens[12a–c] and others,[12d–g] containing a strained bridgehead ether linkage, represent a special case and their particular structural properties were found to be the driving force for their unusual reactivity. Despite the excellent results achieved, their application seems limited to specific cyclic substrates.[12] Therefore, it remains to be established if the satisfactory implementation of asymmetric catalysis to simple acyclic allylic ethers, in which the stable protecting groups is transformed into a leaving group and a stereogenic center is generated, can be accomplished, .

Recently, we reported the first example on the application of organolithium reagents in a highly enantioselective catalytic asymmetric allylic alkylation of allylic halides.[13] We have anticipated that the use of organolithium reagents in combination with Lewis acids will be the key to address very low reactivity of acyclic allylic ethers in asymmetric allylic alkylations.[8a,12g]

Herein, we report for the first time that organolithium reagents in combination with a Lewis acid and copper/phosphoramidite catalysis allow to use stable allylic ethers (-OMe, -OBn) in asymmetric allylic alkylation and affords S_N2' products with excellent regio- and enantioselectivity (Scheme 1).



Scheme 1. Asymmetric allylic alkylation of acyclic allylic ethers.

We started our investigation by testing various allylic groups (-OR) in combination with a Lewis acid under the conditions of the copper-catalyzed allylic alkylation (in this case using $CuBr{\cdot}SMe_2$ in combination with phosphoramidite **L1**[14]) and *n*-butyllithium (Table 1). We chose $BF_3{\cdot}OEt_2$ as the Lewis acid because it is compatible with organolithium and organocopper reagents.[8a,12g]

Allylic esters (-OBz and -OAc) led to low conversions, and a mixture of the ester and corresponding allyl alcohol was recovered from the reaction. The use of allylic ethers, such as -OPh, -OTHP, -OMOM, -O*i*Pr, or -OTBS gave poor results, both in terms of reactivity and regioselectivity (see the Supporting Information, Table S1). However, promising results were observed when -OMe (**1a**) and -OBn (**2a**) ethers were used. In these cases complete conversion, regioselectivities around 50%, and encouraging enantiomeric ratios (84:16 and 91:9) were obtained (Table 1, entries 1 and 2).

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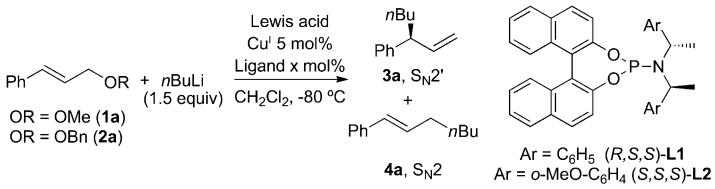
Table 1. Screening of reaction conditions and Lewis acids.[a]



Ph–OR + nBuLi (1.5 equiv)
OR = OMe (**1a**)
OR = OBn (**2a**)

Entry	OR	Cu/L[b]	Lewis acid [(equiv)][c]	Conv. [%][d]	**3a**/**4a**[e]	e.r. **3a** [f]
1	OMe	**C1**/**L1** (1:1)	**A** (1.5)	100	55:45	84:16
2	OBn	**C1**/**L1** (1:1)	**A** (1.5)	100	37:63	91:9
3	OMe	**C1**/**L1** (1:2)	**A** (1.5)	100	63:37	90:10
4	OMe	**C1**/**L1** (1:2)	**A** (1.5) **B** (3.0)	100	75:25	93:7
5	OMe	**C1**/**L2** (1:2)	**A** (1.5) **B** (3.0)	100 (72)	87:13	97:3
6	OMe	**C2**/**L2** (1:2)	**A** (2.0) **B** (4.0)	100 (80)	91:9	98:2
7	OMe	**C2**/**L2** (1:2)	**A** (2.0) **B** (6.0)	100 (80)	91:9	99:1
8	OBn	**C2**/**L2** (1:2)	**A** (2.0) **B** (6.0)	100 (86)	95:5	99:1

[a] Conditions: 0.2 mmol of allylic ether (0.1 M in CH_2Cl_2), *n*BuLi (1.5 equiv) diluted in hexane, 2 h addition time. [b] **C1** = CuBr·SMe$_2$; **C2** = CuTC. [c] **A** = BF_3·OEt_2; **B** = TMSOTf. The mixtures of Lewis acids were prepared in CH_2Cl_2 (0.5 mL) at −80 °C. [d] Isolated product yield in brackets. [e] S_N2'/S_N2 ratios were determined by GC analysis. [f] Determined by chiral GC analysis.

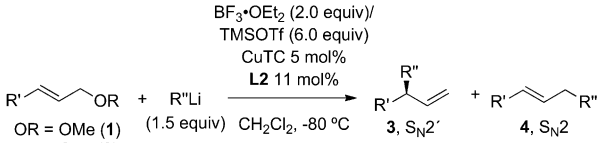
Notably, use of a Lewis acid in combination with a copper catalyst was essential for the successful execution of this C–C bond formation. The reaction does not proceed in the absence of either the copper catalyst or the Lewis acid, leading to a complete recovery of the starting material (see the Supporting Information, Table S2). These results show that the addition of a Lewis acid has a dramatic effect on the reactivity of the allylic ether. In particular, the absence of a Lewis acid in this system allows the allylic ether to act as a robust protecting group, if desired.

We next investigated the effect of different conditions, ligands and Lewis acids by using methyl ether **1a** (Table 1, entries 3–7). By increasing the copper/ligand ratio from 1:1 to 1:2 the regioselectivity significantly improved (Table 1, entry 3). Different boron-based Lewis acids were tested, but the desired product was not obtained in those cases.[15] We next tested the synergistic effect of combining BF_3·OEt_2 and TMSOTf, as reported by Aggarwal et al.,[16] forming the new Lewis acid "BF_2OTf" in situ. TMSOTf was completely inert in our system, however, when used in combination with BF_3·OEt_2 (2:1 ratio), the regio- and enantioselectivity increased again significantly (Table 1, entry 4). Further ligand screening (see the Supporting Information, Table S3) revealed that **L2**[6a] is the preferred ligand in this asymmetric transformation. The use of this ligand in combination with a 2:1 mixture of TMSOTf and BF_3·OEt_2 gave an improved regioselectivity of 87:13 (**3a**:**4a**), and an e.r. of 97:3 (Table 1, entry 5). By using CuTC as Cu^{I} salt instead of CuBr·SMe$_2$ (see the Supporting Information, Table S4), both regio- and enantioselectivity were further enhanced (Table 1, entry 6). In addition, when the TMSOTf/BF_3·OEt_2 ratio was increased, excellent regio- and enantioselectivities were obtained; this outcome is comparable to our recent results with allylic halides (Table 1, entry 7).[13] Remarkably, applying these optimized conditions to the allylic benzyl ether **2a** afforded a significant increase in regioselectivity (95:5) and a near perfect enantiomeric ratio (99:1 e.r.) (Table 1, entry 8).

With these optimized conditions, we studied the scope of the reaction and for this purpose a number of -OMe (**1**) and -OBn (**2**) allylic ethers were tested with various organolithium reagents (Table 2).[17]

Allylic ethers **1a** and **2a** underwent a facile reaction with *n*BuLi and *n*HexLi displaying excellent regio- (S_N2'/S_N2 up to 96:4) and enantioselectivity (up to 99:1), (Table 2, entries 1–4). The more sterically hindered 1-naphthyl-substituted substrates gave different results for both ethers, with exceptional regioselectivity for substrate **2b** (>98:2) and a slight decrease for substrate **1b**; a similar trend was observed for the e.r. values (Table 2, entries 5–8). The transformation is also compatible with aromatic chlorides (Table 2, entries 9–12). Linear aliphatic substrates can also be used, but in this case the methyl ethers **1d** and **1e** are less suitable due to problems arising from their volatility and lower re-

Table 2. Copper-catalyzed AAA of allylic ethers with organolithium reagents.[a]

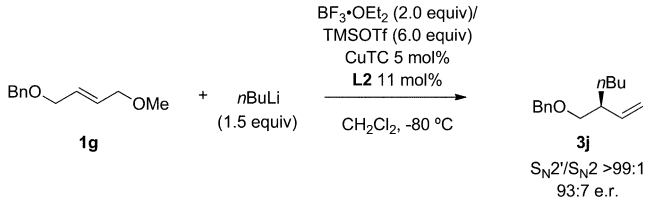


OR = OMe (**1**)
OBn (**2**)

Entry	R′	R″	Yield [%][b]	**3**/**4**[d]	**3**, e.r.[e]
1	**1a**, Ph	*n*Bu	80	91:9	**3a**, 99:1
2	**1a**, Ph	*n*Hex	80	91:9	**3b**, >99:1
3	**2a**, Ph	*n*Bu	86	95:5	**3a**, 99:1
4	**2a**, Ph	*n*Hex	92	96:4	**3b**, >99:1
5	**1b**, 1-Np	*n*Bu	80	84:16	**3c**, 96:4
6	**1b**, 1-Np	*n*Hex	80	82:18	**3d**, 95:5
7	**2b**, 1-Np	*n*Bu	84	>98:2	**3c**, 99:1
8	**2b**, 1-Np	*n*Hex	80	>98:2	**3d**, 98:2
9	**1c**, 4-ClPh	*n*Bu	70	80:20	**3e**, 97:3
10	**1c**, 4-ClPh	*n*Hex	88[c]	91:9	**3f**, 98:2
11	**2c**, 4-ClPh	*n*Bu	81	97:3	**3e**, 99:1
12	**2c**, 4-ClPh	*n*Hex	79	90:10	**3f**, 99:1
13	**1d**, C_3H_7	*n*Hex	50[c]	70:30	**3g**, n.d.[f]
14	**1e**, C_8H_{17}	*n*Bu	11[c]	90:10	**3h**, n.d.[f]
15	**2f**, CH_3	*n*Hex	100[c]	97:3	**3i**, 95:5
16	**2d**, C_3H_7	*n*Hex	100[c]	95:5	**3g**, >99:1
17	**1g**, CH_2OBn	*n*Bu	60[c]	>99:1	**3j**, 93:7
18	**2g**, CH_2OBn	*n*Hex	55[c]	>99:1	**3k**, 98:2

[a] Conditions: 0.2 mmol of allylic ether (0.1 M in CH_2Cl_2), organolithium reagent (1.5 equiv) diluted in hexane and added over 2 h to a solution of substrate, catalyst, and Lewis acids in dichloromethane at −80 °C. [b] Isolated product yield. [c] Conversion determined by GC analysis. [d] S_N2'/S_N2 ratios were determined by GC analysis. [e] Determined by chiral GC or HPLC analysis. [f] n.d. = Not determined.

activity. However, the corresponding benzyl ethers **2f** and **2d** gave excellent S_N2' selectivity (>95:5) and e.r. (>95:5) (Table 2, entries 15 and 16). The presence of a methyl substituent in the allylic ether **2f**, allows for the preparation of a range of synthons with a methyl group at the stereocenter; an important structural moiety that is present in many natural compounds.[18] The compatibility of two ether moieties in the same molecule was demonstrated by the use of allyl substrate **1g**, which bears both an allylic-OMe and -OBn ether, and **2g**, which contains two allylic -OBn moieties (Table 2, entries 17 and 18). Although the conversion was lower in both cases in comparison with the previous results, the S_N2' selectivity observed was complete, with excellent enantiomeric ratios. Surprisingly, in the case of **1g**, with internal competition between -OMe and -OBn moieties as leaving group, we observed that substitution occurred towards the -OMe group instead of the -OBn group (Scheme 2). Despite



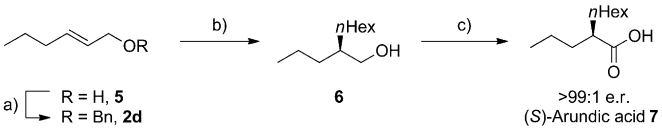
Scheme 2. Compatibility and selectivity with two distinct ether functionalities.

the fact that allylic -OBn ethers proved to be more reactive substrates in previous cases (see for example, Table 2, entries 13–16), we envision that a possible interaction between the aromatic ring of the benzyl group and the copper complex could control the regioselectivity of the reaction.[19]

The application of this new concept is illustrated by the shortest enantioselective synthesis of (*S*)-Arundic acid **7**.[20] Arundic acid **7** is a small but important molecule with outstanding pharmacological properties that is currently undergoing phase II trials for the treatment of acute ischemic stroke as well as clinical development for Alzheimer's and Parkinson's disease.[21]

The synthesis starts with the treatment of commercially available alcohol **5** with BnBr and NaH in THF. Alcohol **6** was obtained by asymmetric allylic alkylation of **2d** followed by direct reductive ozonolysis of the alkene **3g** in MeOH/CH_2Cl_2. The resulting alcohol **6** was oxidized to afford Arundic acid **7** in three steps from alcohol **5** with >99:1 e.r. and in 61% overall yield (Scheme 3).

In summary, the first example of the highly enantioselective asymmetric allylic alkylation of inert allylic ethers with organolithium reagents is presented. The Lewis acid compatibility with organolithium reagents, under copper/phosphoramidite-catalyzed conditions, is essential to allow this novel highly enantioselective transformation to occur. Excellent results reported for allylic methyl ethers (-OMe), with similar selectivities than those recently reported for allylic halides, were even improved for allylic benzyl ethers



Scheme 3. Synthesis of Arundic acid. Conditions: a) BnBr, NaH (60%), THF, 0°C to RT, 90%; b) i) BF_3•OEt_2 (2.0 equiv)/TMSOTf (6.0 equiv), **L2** (11 mol%), CuTC (5 mol%), *n*-HexLi (sol. in hexane), CH_2Cl_2, −80°C, ii) O_3, MeOH, −80°C. iii) $NaBH_4$, MeOH, −80°C to RT, 72% for two steps; c) TEMPO (cat.), IBD, CH_3CN/H_2O (1:1), 94%, >99:1 e.r. (61% overall yield).

(-OBn). The potential for application in organic synthesis is demonstrated by a three-step synthesis of pharmaceutically important (*S*)-Arundic acid. Mechanistic studies on the exact nature of this highly selective transformation based on the combination of Lewis acids and organolithium reagents are ongoing.

Experimental Section

Typical procedure: A Schlenk tube equipped with septum and stirring bar was charged with CuTC (0.01 mmol, 1.90 mg, 5 mol%) and the ligand **L2** (0.022 mmol, 11 mol%). Dry dichloromethane (0.5 mL) was added and the solution was stirred under nitrogen at room temperature for 15 min. In another Schlenk tube BF_3•OEt_2 (0.4 mmol, 50 μL, 2.0 equiv) was added to a solution of TMSOTf (1.2 mmol, 215 μL, 6.0 equiv) in dichloromethane (0.5 mL) at −80°C, and the resulting "BF_2OTf" solution was stirred for 15 min. Then, the corresponding allyl ether **1–2** (0.2 mmol) in CH_2Cl_2 (1 mL) was added at −80°C to the copper/ligand solution prepared earlier and subsequently a solution of "BF_2OTf" in dichloromethane (0.4 mmol, 600 μL, 2.0 equiv) was added. In a separate Schlenk tube, the corresponding organolithium reagent (0.30 mmol, 1.5 equiv) was diluted with hexane (combined volume of 1 mL) under nitrogen and added dropwise to the reaction mixture over 2 h using a syringe pump. The reaction was quenched with a saturated aqueous NH_4Cl solution (2 mL) and the mixture was warmed up to room temperature, diluted with dichloromethane and the layers were separated. The aqueous layer was extracted with dichloromethane (3×5 mL) and the combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography on silica gel using different mixtures of *n*-pentane/Et_2O as the eluent.

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Keywords: allylic alkylation · allylic ethers · copper · Lewis acids · organolithium reagents

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[15] BCl_3 and BBr_3 proved to be too harsh on the system, and converted the substrate to the corresponding allylic halide. Other boron derivates, such as trialkyl boranes or trialkyl borates, were not reactive enough, leading to recovery of starting material in both cases (see the Supporting Information). Curiously, the effect of different coordinating solvents in the BF_3 complex was also important. For instance, when the BF_3•*t*BuOMe complex was tested in our system the starting material remained unaltered.

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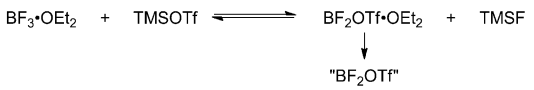

[17] Other commercially available lithium reagents such as MeLi (1.6 M in Et_2O) and PhLi (1.8 M in Bu_2O) were used, but the reaction is highly dependent on the nature of the organolithium solution and in both cases the substrate was recovered unaltered. Experiments with *n*BuLi (1.6 M in hexane) diluted in Et_2O confirmed these results (see the Supporting Information). Grignard reagents such as *n*HexMgBr were also tested. Despite the fact that the reaction proceeded, the selectivity (S_N2'/S_N2) and conversion were both lower than the results obtained with organolithium reagents (see the Supporting Information).

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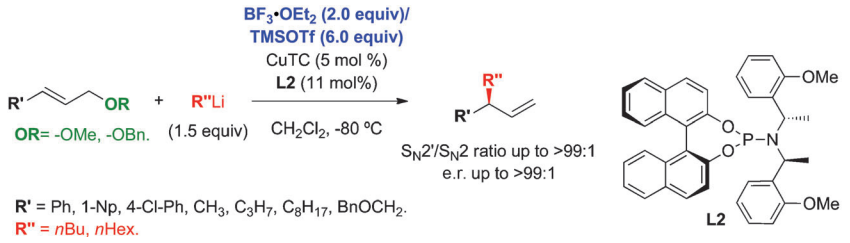

A highly efficient, regio- and enantioselective Cu^{I}/phosphoramidite-catalyzed asymmetric allylic alkylation of allyl ethers with organolithium reagents is reported (see scheme). The use of organolithium reagents is essential for this catalytic C–C bond formation due to their compatibility with different Lewis acids. The versatility of allylic ethers under the copper-catalyzed reaction conditions with organolithium reagents is demonstrated in the shortest synthesis of (*S*)-Arundic acid.

Asymmetric Catalysis

M. Pérez, M. Fañanás-Mastral, V. Hornillos, A. Rudolph, P. H. Bos, S. R. Harutyunyan, B. L. Feringa** ..... ▮▮▮▮–▮▮▮▮

Asymmetric Allylic Alkylation of Acyclic Allylic Ethers with Organolithium Reagents

