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Enantioselective Synthesis of All-Carbon Quaternary Stereogenic Centers via Copper-Catalyzed Asymmetric Allylic Alkylation of (*Z*)-Allyl Bromides with Organolithium Reagents

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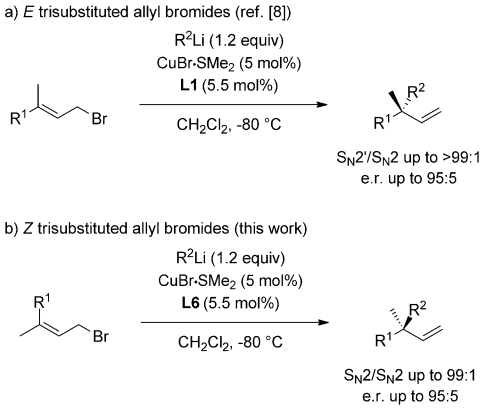
Abstract: A copper/phosphoramidite catalyzed asymmetric allylic alkylation of *Z* trisubstituted allyl bromides with organolithium reagents is reported. The reaction affords all-carbon quaternary stereogenic centers in high yields and very good regio- and enantioselectivity. This systematic study illustrates the crucial role of the olefin geometry of the allyl substrate on the outcome of the reaction and provides a viable alternative to access these important structural motifs.



Scheme 1. Copper-catalyzed AAA of trisubstituted allyl bromides with organolithium reagents.

The development of catalytic enantioselective methods for the construction of all-carbon quaternary stereogenic centers, that is, carbon atoms bearing four different carbon substituents, is an important challenge in the field of organic synthesis.[1] Copper-catalyzed asymmetric allylic alkylation (AAA) with organometallic reagents[2] of trisubstituted allyl substrates represents a powerful alternative for the synthesis of these highly congested structural moieties in acyclic systems. Stereoselective procedures using chiral allyl substrates have been developed.[3] Alternatively, the use of different chiral copper catalysts in combination with organozinc,[4] organoaluminium,[5] organomagnesium[6] and organoboron[7] reagents has been shown to be highly effective in the AAA of prochiral trisubstituted allyl compounds. Recently, we reported, for the first time, the use of organolithium reagents for the copper-catalyzed allylic alkylation of *E* trisubstituted allyl bromides.[8,9] By using a catalyst comprising $CuBr{\cdot}SMe_2$ and a chiral phosphoramidite as ligand, and by selecting a proper combination of dichloromethane and hexane as solvent and co-solvent, we could tame the highly reactive alkyllithium reagents and use them for the regio- and enantioselective synthesis of a range of all-carbon stereogenic centers, avoiding side reactions such as lithium–halogen exchange or homocoupling reactions (Scheme 1 a).

Chiral (*Z*)-allyl substrates have been commonly used in stereoselective copper-catalyzed AAA reactions in order to obtain the opposite enantiomer (with similar enantioselectivity) than the one obtained from the (*E*)-allyl substrates as a function of olefin geometry control.[3] However, the use of prochiral *Z* trisubstituted allyl substrates in combination with a chiral copper catalyst has been much less explored and only single examples have been reported by Hoveyda,[4d,5a] Ohmiya and Sawamura[7d] and our group.[6b] In these cases the enantioselectivity of the process is controlled by the chiral catalyst and the product is obtained either as the antipode of the enantiomer product derived from the *E* isomer with lower enantioselectivity[4d,5a,7d] or as the same enantiomer with similar enantioselectivity,[6b] depending on the catalytic system used. As the olefin geometry of the allyl substrate is an important selectivity parameter, and lacking comprehensive information on the copper-catalyzed AAA of *Z* trisubstituted allyl compounds,[10] we decided to investigate this reaction using organolithium reagents as part of our research program based on the development of direct catalytic cross-coupling reactions of these highly reactive compounds.[8,9,11] Herein, we report a catalytic methodology that allows for the copper-catalyzed AAA of *Z* trisubstituted allyl bromides (Scheme 1 b). The reaction affords all-carbon quaternary stereogenic centers in high yields and very good regio- and enantioselectivity, representing a viable alternative to the previously reported copper-catalyzed AAA of the *E* trisubstituted allyl derivatives.[8]

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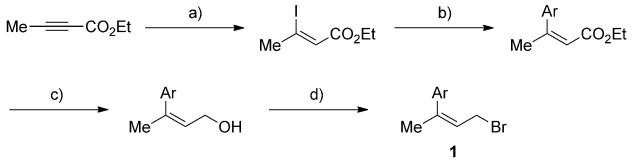
(*Z*)-Allyl bromides **1** required for this study were synthesized in a straightforward manner according to the synthetic route depicted in Scheme 2. Reaction of commercially available ethyl but-2-ynoate with NaI in acetic acid afforded ethyl (*Z*)-3-iodo-but-2-enoate with complete *Z* selectivity.[12] Suzuki coupling,[13] followed by reduction of the ester moiety and final bromination of the resulting alcohol gave rise to the desired (*Z*)-allyl bromides in good overall yield. The bromination step turned out to be sensitive to double-bond isomerization and specific conditions—depending on each substrate—had to be used in order to minimize this isomerization (see the Supporting information for further details).



1a, Ar = Ph (*Z*/*E* 96:4)
1b, Ar = 3-Cl-C_6H_4 (*Z*/*E* >99:1)
1c, Ar = 3-F-C_6H_4 (*Z*/*E* 99:1)
1d, Ar = 4-Cl-C_6H_4 (*Z*/*E* 97:3)
1e, Ar = 4-Me-C_6H_4 (*Z*/*E* 60:40)
1f, Ar = 2-OMe-C_6H_4 (*Z*/*E* 92:8)
1g, Ar = 2-Br-C_6H_4 (*Z*/*E* >99:1)
1h, Ar = 2-Me-C_6H_4 (*Z*/*E* 96:4)
1i, Ar = 1-naphthyl (*Z*/*E* 96:4)

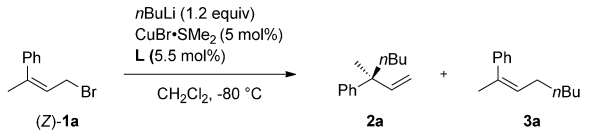
Scheme 2. Synthesis of (*Z*)-allyl bromides **1**. Conditions: a) NaI (1.6 equiv), AcOH (6.4 equiv), 115 °C, 1.5 h, 92%; b) $ArB(OH)_2$ (1.5 equiv), $Pd(OAc)_2$ (5 mol%), $AsPh_3$ (10 mol%), K_3PO_4 (3.0 equiv), toluene, 90 °C, 21 h, 67–88%; c) DIBAL-H (3.0 equiv), CH_2Cl_2, −78 °C, 1 h, 71–97%; d) NBS/PPh_3 or PBr_3 (see the Supporting Information).

We started our study on the copper-catalyzed AAA of (*Z*)-allyl bromides by performing the reaction between (*Z*)-**1a** (86:14 *Z*/*E* mixture) and *n*BuLi using the conditions previously reported for the copper-catalyzed AAA of (*E*)-allyl bromides ($CuBr{\cdot}SMe_2$/**L1**).[8] Interestingly, the use of the (*Z*)-allyl bromide gave rise to the same product enantiomer than the one obtained from the *E* isomer although with lower enantiomeric ratio (Table 1, entries 1 and 2).

After screening different phosphoramidite ligands[14] (entries 2–7), **L6** (Figure 1) turned out to be the most effective for the addition of *n*BuLi to (*Z*)-allyl bromide **1a** (entry 7). It is important to note that ligand **L6** is more effective for the AAA of (*Z*)-**1a** than for the corresponding *E* isomer (entries 7 and 8). These results point at a clear matched/mismatched effect between the geometry of the olefin and the chiral ligand.

Accordingly, the use of a more *Z* enriched mixture of **1a** (*Z*/*E* = 96:4) gave rise to an increase of the enantioselectivity affording product **2a** as the *S* enantiomer with a very good 6:94 e.r. (entry 9). Finally, a longer addition time of *n*BuLi led to a slight enhancement of both the regio- and enantioselectivity, thus obtaining **2a** with an excellent S_N2'/S_N2 ratio of 95:5 and 5:95 e.r. (entry 10). The fact that the opposite enantiomer of **2a** is obtained depending on the absolute configuration of the binol moiety regardless of the alkene geometry (see for example, **L1** vs. **L2**) indicates that binol configuration largely dictates the π-face selectivity and the absolute configuration of the all-carbon quaternary center.

Table 1. Screening of phosphoramidite ligands and reaction conditions.



Entry[a]	**1a** (*Z*/*E*)	L	**2a**/**3a**[b]	e.r.[c,d]
1[e]	0:100	**L1**	98:2	92:8 (*R*)
2	86:14	**L1**	94:6	67:33 (*R*)
3[f]	86:14	**L2**	n.a.[h]	n.a.[h]
4	86:14	**L3**	90:10	73:27 (*R*)
5	86:14	**L4**	95:5	33:67 (*S*)
6[g]	86:14	**L5**	98:2	78:22 (*R*)
7	86:14	**L6**	94:6	9:91 (*S*)
8	0:100	**L6**	90:10	19:81 (*S*)
9	96:4	**L6**	90:10	6:94 (*S*)
10[e]	96:4	**L6**	95:5	5:95 (*S*)

[a] Reactions were performed on a 0.2 mmol scale. *n*BuLi was diluted with hexane and added dropwise. Full conversion was reached in all cases unless otherwise noted. [b] S_N2'/S_N2 ratio determined by GC and ^1H NMR analysis. [c] Determined by chiral HPLC analysis. [d] Absolute configuration shown in brackets. [e] *n*BuLi added over 10 h; [f] < 10% conversion; only homocoupling products formed; [g] 85% conversion. [h] Not applicable.

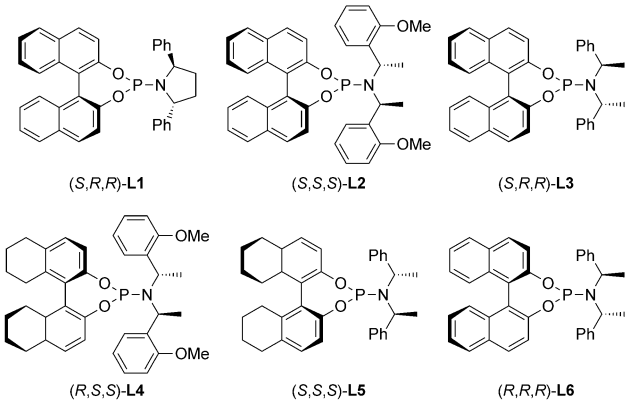
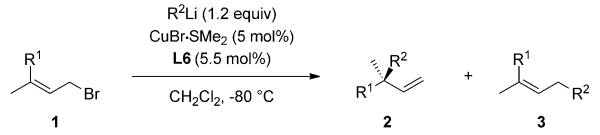


Figure 1. Chiral phosphoramidite ligands used in this study.

Remarkably, monodentate phosphoramidite ligand **L6** promotes the formation of the same enantiomer for the addition of *n*BuLi to either the *Z* or *E* trisubstuted allyl bromide (Table 1, entries 7–9). This suggests that the alkylcopper/phosphoramidite complex recognizes the γ center and not the leaving group of the substrate at the stage of the π-copper(I)/olefin complex formation.[10] This is in sharp contrast with the results obtained by the groups of Hoveyda[5a] and Sawamura[7d] in which they showed that the use of bidentate ligands for the copper-catalyzed AAA of a *Z* trisubstituted allyl substrate gave rise to the opposite enantiomer than the product derived from the *E* isomer, most probably arising from a recognition of the leaving group of the substrate.

Having established the optimized conditions (Table 1, entry 10), we set out to investigate the scope of the copper-catalyzed AAA of *Z* trisubstituted allyl bromides with organolithium reagents (Table 2).

Table 2. Copper-catalyzed AAA of (*Z*)-allyl bromides **1** with organolithium reagents.



Entry[a]	**1** (R^1)	R^2	**2**/**3**[b]	Yield [%][c]	e.r.[d] (**2**)
1	**1a** (Ph)	*n*Bu	95:5	80	95:5 (**2a**)
2	**1a** (Ph)	Et	84:16	42[e]	90:10 (**2b**)
3	**1a** (Ph)	*n*Hex	90:10	74	95:5 (**2c**)
4	**1b** (3-Cl-C_6H_4)	*n*Hex	94:6	47[f]	91:9 (**2d**)
5	**1c** (3-F-C_6H_4)	*n*Hex	98:2	46[g]	92:8 (**2e**)
6	**1d** (4-Cl-C_6H_4)	*n*Bu	92:8	86	94:6 (**2f**)
7	**1d** (4-Cl-C_6H_4)	*n*Hex	94:6	85	94:6 (**2g**)
8	**1e** (4-Me-C_6H_4)	*n*Bu	85:15	78	88:12 (**2h**)
9	**1f** (2-OMe-C_6H_4)	Et	99:1	74	84:16 (**2i**)
10	**1f** (2-OMe-C_6H_4)	*n*Bu	90:10	77	88:12 (**2j**)
11	**1f** (2-OMe-C_6H_4)	*n*Hex	96:4	80	90:10 (**2k**)
12[h]	**1g** (2-Br-C_6H_4)	*n*Bu	–	–	–
13[h]	**1h** (2-Me-C_6H_4)	*n*Bu	–	–	–
14[h]	**1i** (1-naphthyl)	*n*Bu	–	–	–

[a] Conditions: see Table 1. Full conversion obtained unless otherwise noted. [b] S_N2'/S_N2 ratio determined by GC and ^1H NMR analysis. [c] Yield of isolated product. [d] Determined by chiral HPLC analysis; [e] 60% conversion; [f] 65% conversion; [g] 64% conversion. [h] No conversion.

This protocol was found to be efficient with organolithium reagents such as EtLi, *n*BuLi and *n*HexLi. All-carbon quaternary centers **2a–c** and **2f,g** were obtained with very good regioselectivity and enantiomeric ratios ranging from 90:10 to 95:5 when the phenyl derivative **1a** (entries 1–3) and *p*-chloro-substituted substrate **1e** (entries 6 and 7) were used. Although less reactive, *m*-chloro- and *m*-fluoro-substituted allyl bromides **1b** and **1c** (entries 4 and 5) were also effective substrates and gave rise to the corresponding all-carbon quaternary centers **2d** and **2e**, respectively, with excellent regio- and enantioselectivity. It is important to note that in these cases, in which a substrate bearing an aromatic halide (**1b**–**1d**) is used, no traces of side products derived from lithium–halogen exchange or nucleophilic aromatic substitution were found, showing the halide tolerability of this catalytic system. Interestingly, the copper-catalyzed AAA of *p*-methyl-substituted substrate **1e**, which was obtained as a 60:40 *Z*/*E* mixture, still afforded the corresponding product **2h** with a good enantioselectivity (entry 8), comparable with the one obtained from the pure (*E*)-allyl bromide by our previously reported procedure (Table 3).

An intriguing observation was made when *ortho*-substituted (*Z*)-allyl bromides were used. While the copper-catalyzed AAA of *o*-methoxy-substituted substrate **1f** afforded the corresponding products **2i–k** with full conversion and good regio- and enantioselectivity (entries 9–11), the use of other *ortho*-substituted (*Z*)-allyl bromides **1g–i** did not result in any conversion. ^1H NMR analysis (see the Supporting Information) shows that the protons of the CH_2Br group of *ortho*-substituted (*Z*)-allyl bromides **1g–i** are diastereotopic while these

Table 3. Comparison of the copper-catalyzed AAA with organolithium reagents of (*Z*)-allyl bromides versus (*E*)-allyl bromides (results given for the addition of *n*HexLi).

Entry	Ar	*Z* (**L6**)		*E* (**L1**)	
		2/**3**	e.r.	**2**/**3**	e.r.
1	Ph	95:5	95:5	92:8	86:14
2	4-Cl-C_6H_4	94:6	94:6	94:6	91:9
3[a]	4-Me-C_6H_4	85:15[b]	88:12[b]	94:6	88:12
4	2-OMe-C_6H_4	96:4	90:10	95:5	95:5
5	2-Br-C_6H_4	–[c]	–[c]	> 99:1	91:9

[a] *n*BuLi was used. [b] Reaction performed on a 60:40 *Z*/*E* mixture. [c] No conversion.

protons are equivalent in *o*-methoxy-substituted substrate **1f** (Figure 2). This diastereotopicity suggests that in substrates **1g–i** hindered rotation between the aryl group and the double bond exists leading to a loss of co-planarity. This might obstruct the coordination of the alkylcopper complex to these substrates, thus prohibiting the reaction.

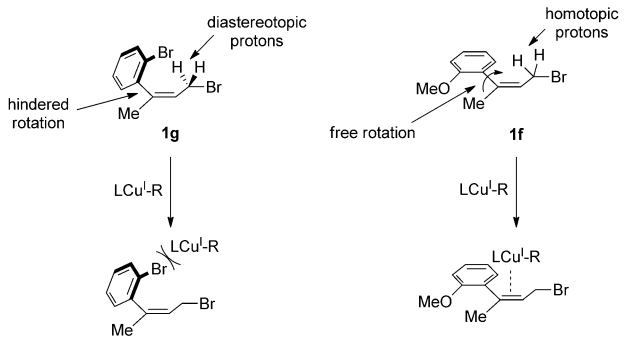


Figure 2. Effect of *ortho*-substituents on the geometry of the (*Z*)-allyl bromides **1**.

An interesting feature of the copper-catalyzed AAA of (*Z*)-allyl bromides is its complementarity with the AAA of the corresponding *E* isomers (Table 3). While the catalytic system for the (*Z*)-allyl bromides gives rise to higher enantiomeric ratios when phenyl and *para*-substituted substrates are used (entries 1–3), our previously reported catalytic system for the copper-catalyzed AAA of (*E*)-allyl bromides affords excellent enantioselectivity when *ortho*-substituted substrates are used, also in the case of *o*-bromo-substituted substrates (entries 4 and 5).

In summary, we have developed a catalytic methodology for the asymmetric allylic alkylation of *Z* trisubstituted allyl bromides with organolithium reagents. All-carbon quaternary stereogenic centers are obtained in high yields with very good regio- and enantioselectivity. In some cases, the reaction affords selectivity values higher than the ones obtained through our previously described asymmetric alkylation of (*E*)-allyl bromides. The addition of organolithium reagents to (*Z*)-allyl bromides provides a versatile and complementary method for the synthesis of all-carbon quaternary centers.

Experimental Section

Typical procedure for the copper-catalyzed AAA of *Z* trisubstituted allyl bromides with organolithium reagents

A Schlenk tube equipped with septum and stirring bar was charged with CuBr·SMe_2 (5 mol%) and the ligand **L6** (5.5 mol%). Dry CH_2Cl_2 (1 mL) was added and the solution was stirred under nitrogen at room temperature for 30 min. Then, allyl bromide **1** (0.2 mmol) was dissolved in dry CH_2Cl_2 (1 mL) and was added to the solution which was cooled to −80 °C. In a separate Schlenk tube, the organolithium reagent (0.24 mmol) was diluted with *n*-hexane (0.8 mL, combined volume of 1 mL) under nitrogen and added dropwise to the reaction mixture over 5 h using a syringe pump. Once the addition was complete, the mixture was stirred at −80 °C for 10 h. The reaction was quenched with a saturated aqueous NH_4Cl solution (2 mL) and the mixture was warmed to room temperature. The aqueous layer was extracted with CH_2Cl_2 (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 reaction mixture was purified by flash chromatography on silica gel using *n*-pentane as eluent.

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Keywords: allylic compounds · asymmetric catalysis · copper · phosphoramidites · organolithium reagents

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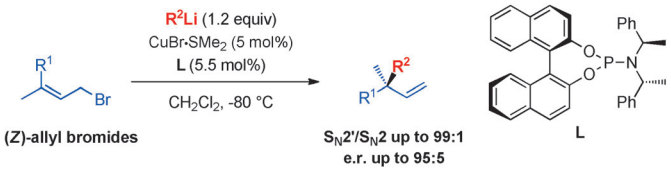

Origin of asymmetry: The copper-catalyzed asymmetric allylic alkylation of *Z* trisubstituted allyl bromides with organolithium reagents was investigated. A catalytic system comprising $CuBr{\cdot}SMe_2$ and chiral phosphoramidite ligand **L** (see scheme) was found to enable the formation of all-carbon quaternary centers in high yields with very good regio- and enantioselectivity.

Asymmetric Catalysis

M. Fañanás-Mastral, R. Vitale, M. Pérez, B. L. Feringa**

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Enantioselective Synthesis of All-Carbon Quaternary Stereogenic Centers via Copper-Catalyzed Asymmetric Allylic Alkylation of (*Z*)-Allyl Bromides with Organolithium Reagents