Asymmetric Catalysis

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Enantioselective Synthesis of Tertiary and Quaternary Stereogenic Centers: Copper/Phosphoramidite-Catalyzed Allylic Alkylation with Organolithium Reagents**

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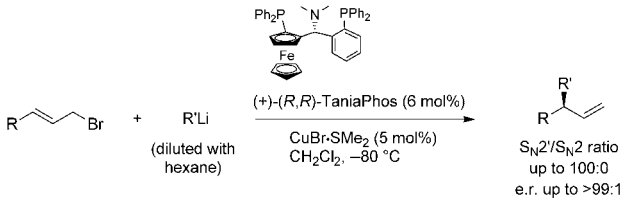
Copper-catalyzed asymmetric allylic alkylation (AAA) has become a very powerful tool for the enantioselective construction of optically active tertiary carbon stereocenters.[1] Recently, this C–C bond-forming reaction has also been successfully applied to the challenging enantioselective synthesis of all-carbon quaternary stereogenic centers in acyclic systems.[2] Organozinc,[3] aluminium,[4] and Grignard[5] reagents have been shown to be highly effective in the AAA reaction. However, the cheap and readily available organolithium reagents have not been successfully used in the catalytic asymmetric C–C bond formation of quaternary centers until now.

Organolithium reagents are among the most versatile and widely used reagents in organic synthesis.[6] However, the nature of these extremely reactive reagents has hampered its use in enantioselective catalytic C–C bond-formation processes, and successful applications pertain to the use of stoichiometric amounts of chiral ligands[7] or to catalytic asymmetric deprotonations[8] and additions to imines,[9] often with high catalyst loadings and modest enantioselectivities.

Recently, we reported for the first time a general and highly enantioselective catalytic method for the direct addition of organolithium reagents through a copper-catalyzed asymmetric allylic alkylation.[10] By using a catalyst comprising $CuBr{\cdot}SMe_2$ and TaniaPhos as a chiral ligand, and by selecting a proper combination of dichloromethane and *n*-hexane as solvent and co-solvent, we could tame the highly reactive alkyllithium reagents and apply these in a catalytic, highly regio- and enantioselective allylic alkylation of a large variety of allyl bromides (Scheme 1). A limitation found for the $CuBr{\cdot}SMe_2$/TaniaPhos system was that the use of simple allyl chlorides or secondary organolithium reagents in combination with this catalyst led to disappointing selectivities.[11] However, we showed in preliminary studies[10] that easily accessible phosphoramidites[12] might be suitable ligands for this transformation.



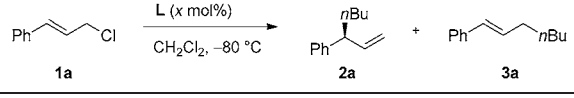
R = aryl, halogen-substituted aryl, alkyl, carbamate, ester, protected and free alcohols
R' = Me, Et, *n*Bu, *n*Hex

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

Herein, we report that the use of phosphoramidites as chiral ligands allows the use of both allyl chlorides or bromides in highly enantioselective allylic alkylations in combination with primary as well as secondary organolithium reagents. We also found that a phosphoramidite-based copper catalyst provides all-carbon quaternary stereogenic centers in an enantioselective manner.

We started our study by screening different copper salts, phosphoramidite ligands, and reaction conditions for the addition of *n*-butyllithium to cinnamyl chloride (**1a**) (Table 1). The use of copper(I) thiophene carboxylate (CuTC)[13] as the copper salt and the phosphoramidite ligand **L1** (Figure 1) in a 1:2 ratio gave rise to modest

Table 1: Screening of ligands and reaction conditions for the copper-catalyzed allylic substitution with *n*BuLi.[a]



1a **2a** **3a**

Entry	Cu salt	L	[Cu]/L	Addition time [h]	**2a**/**3a**[b]	e.r.[c] (**2a**)
1	CuTC	**L1**	1:2	2	58:42	67:33
2	CuTC	**L1**	1:1	2	71:29	86:14
3	$CuBr{\cdot}SMe_2$	**L1**	1:1	2	70:30	91:9
4	$CuBr{\cdot}SMe_2$	**L1**	1:1	5	91:9	98:2
5	$CuBr{\cdot}SMe_2$	**L2**	1:1	5	38:62	66:34
6	$CuBr{\cdot}SMe_2$	**L3**	1:1	5	49:51	86:14
7	$CuBr{\cdot}SMe_2$	**L4**	1:1	5	82:18	20:80

[a] Reactions performed on a 0.2 mmol scale. *n*BuLi was diluted with *n*-hexane and added dropwise. Full conversion was reached in all cases. [b] S_N2'/S_N2 ratio determined by GC and ^1H NMR analysis. [c] Determined by GC analysis using a chiral stationary phase.

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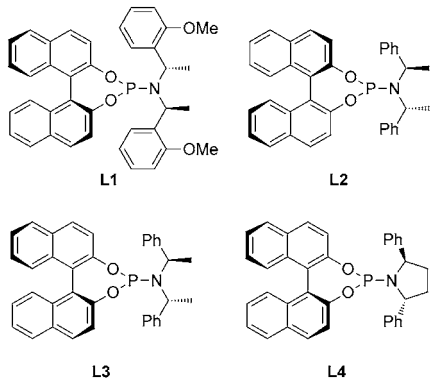
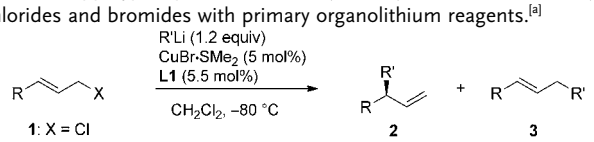


Figure 1. Phosphoramidite ligands.

selectivity (entry 1). A drastic improvement in the regio- and enantioselectivity was observed when a 1:1 copper/ligand ratio was used (entry 2). By changing the copper salt to $CuBr{\cdot}SMe_2$ we observed an enhancement of the enantioselectivity, thus obtaining **2a** with a 91:9 e.r. (entry 3). A longer addition time of 5 hours, using $CuBr{\cdot}SMe_2$ as the preferred copper salt, afforded the desired product **2a** with an excellent S_N2'/S_N2 ratio of 91:9 and 98:2 e.r. (entry 4). The use of different phosphoramidite ligands (Figure 1) did not improve these results (entries 5–7).

Once having established the optimized reaction conditions (Table 1, entry 4), we examined the scope of the copper/phosphoramidite-catalyzed addition of primary organolithium reagents to both allyl chlorides and bromides (Table 2). Excellent yields and enantiomeric ratios were obtained in nearly all cases.

Table 2: Copper/phosphoramidite-catalyzed allylic substitution of allyl chlorides and bromides with primary organolithium reagents.[a]



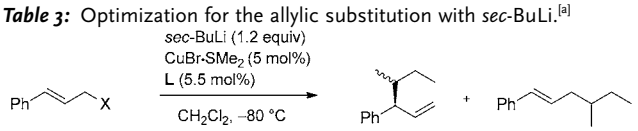
Entry	X	**1**/**4** (R)	R′	**2**/**3**[b]	Yield [%][c]	e.r.[d] (**2**)
1	Cl	**1a** (Ph)	*n*Bu	91:9	90	98:2 (**2a**)
2	Br	**4a** (Ph)	*n*Bu	87:13	92	96:4 (**2a**)
3	Cl	**1a** (Ph)	*n*Hex	80:20	90	98:2 (**2b**)
4	Br	**4a** (Ph)	*n*Hex	89:11	91	99:1 (**2b**)
5	Cl	**1a** (Ph)	Et[e]	85:15	90[f]	96:4 (**2c**)
6	Br	**4a** (Ph)	Et[e]	88:12	95[f]	95:5 (**2c**)
7	Cl	**1b** (1-naphthyl)	*n*Bu	50:50	93	96:4 (**2d**)
8	Br	**4b** (1-naphthyl)	*n*Bu	85:15	91	95:5 (**2d**)
9	Cl	**1c** (4-ClC_6H_4)	*n*Bu	90:10	89	98:2 (**2e**)
10	Br	**4c**, 4-Cl-C_6H_4	*n*Bu	85:15	88	97:3 (**2e**)
11	Cl	**1c** (4-ClC_6H_4)	Et[e]	89:11	72	98:2 (**2f**)
12	Cl	**1c** (4-ClC_6H_4)	*n*Hex	80:20	87	>99:1 (**2g**)
13	Cl	**1d** (Cy)	*n*Bu	90:10	91	88:12 (**2h**)
14	Br	**4d** (Me)	*n*Hex	90:10	99[f]	91:9 (**2i**)

[a] Reactions performed on a 0.2 mmol scale. The corresponding organolithium reagent was diluted with *n*-hexane and added over 5 h. [b] S_N2'/S_N2 ratios determined by GC and ^1H NMR analysis. [c] Yield of isolated product. [d] Determined by GC analysis using a chiral stationary phase. [e] EtLi was diluted with toluene. [f] Conversion.

The phosphoramidite/copper-catalyzed AAA proved to be also very efficient with allyl bromides, thus providing a complementary catalytic procedure for the earlier TaniaPhos-based method.[10] The addition of *n*BuLi to cinnamyl bromide (**4a**) afforded the product **2a** with comparable regio- and enantioselectivity as observed for **1a** (Table 2, entry 2). Different primary alkyl lithium reagents gave also very good enantioselectivities both with the chloride **1a** and bromide **4a** (entries 3–6). When the allyl chloride **1b** bearing the more sterically demanding 1-naphthyl substituent was used, the reaction still gave a good level of enantioselectivity but the S_N2'/S_N2 products were obtained in a 1:1 ratio (entry 7). However, when the analogous allyl bromide **4b** was used the corresponding product **2d** was obtained with high enantioselectivity and good regioselectivity (entry 8). Remarkably, the catalytic system also tolerates the presence of aromatic halides. Both *p*-chloro-substituted cinnamyl chloride (**1c**) and bromide (**4c**) could be used without any lithium–halogen exchange and with excellent enantioselectivity (97:3 to >99:1 e.r.; entries 9–12). Alkyl-substituted allyl halides could also be used for this transformation. Both substrates bearing cyclic (R = Cy; entry 13) and acyclic (R = Me; entry 14) aliphatic substituents afforded the corresponding products **2h** and **2i** with good selectivity but with slightly lower e.r. values.

The use of the optimal ligand **L1** for the addition of primary organolithium reagents in the reaction of a secondary organolithium reagent, such as *sec*-BuLi, to **1a** afforded the desired compound **5a** as a mixture of diastereoisomers with good regioselectivity (S_N2'/S_N2 91:9) but with disappointing enantioselectivity (Table 3, entry 1). The phosphoramidite **L3**

Table 3: Optimization for the allylic substitution with *sec*-BuLi.[a]



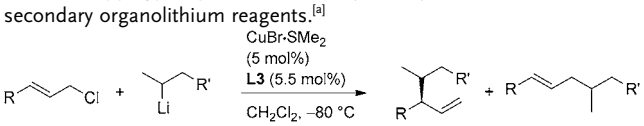
Entry	X	L	**5**/**6**[b,c]	e.r.[b] **5a**	**5a′**
1[d]	Cl	**L1**	91:9	60:40	66:34
2[e]	Cl	**L2**	90:10	28:72	26:74
3[f]	Cl	**L3**	97:3	91:9	91:9
4[g]	Br	**L3**	79:21	69:31	71:29

[a] Reaction conditions: see Table 2. Full conversion was reached in all cases. [b] Determined by GC analysis using a chiral stationary phase. [c] Compound **6a** was obtained as a racemic mixture in all cases. [d] d.r. = 1.5:1. [e] d.r. = 1.2:1. [f] d.r. = 1:1. [g] d.r. = 1.3:1.

was found to be the most effective ligand for the addition of *sec*-BuLi, thus affording the compound **5a** with a high S_N2'/S_N2 ratio (97:3) and 91:9 e.r. for both diastereoisomers (entry 3).[14] In this case, the use of the more reactive cinnamyl bromide (**4a**) led to a decrease in both regio- and enantioselectivity of the reaction (entry 4).

By using the optimized ligand **L3**, the addition of *sec*-BuLi to different allyl chlorides **1** provided the corresponding products **5** in high yields and with high regioselectivities and

Table 4: Copper/phosphoramidite-catalyzed allylic substitution with secondary organolithium reagents.[a]

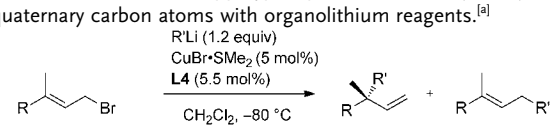


1 *sec*-BuLi (R' = Me)
*i*PrLi (R' = H)

Entry	**1** (R)	R′	**5**/**6** or **7**/**8**[b]	Yield [%][c]	e.r.[e] (**5**[d] or **7**)
1[d]	**1a** (Ph)	Me	97:3	80	91:9 (**5a**) 91:9 (**5a′**)
2[d]	**1b** (1-naphthyl)	Me	92:8	85	88:12 (**5b**) 88:12 (**5b′**)
3[d]	**1c** (4-ClC_6H_4)	Me	93:7	96	90:10 (**5c**) 88:12 (**5c′**)
4	**1a** (Ph)	H	90:10	77	96:4 (**7a**)
5	**1b** (1-naphthyl)	H	96:4	98	94:6 (**7b**)
6	**1c** (4-ClC_6H_4)	H	92:8	95	96:4 (**7c**)
7	**1d** (Cy)	H	89:11	83	91:9 (**7d**)

[a]–[c] See Table 2. Full conversion was reached in all cases. [d] d.r. = 1:1. [e] Determined by GC or HPLC analysis using a chiral stationary phase.

Table 5: Enantioselective copper/phosphoramidite-catalyzed synthesis of quaternary carbon atoms with organolithium reagents.[a]



9 **10** **11**

Entry	**9** (R)	R′	**10**/**11**[b]	Yield [%][c]	e.r.[d] (**10**)
1	**9a** (Ph)	*n*Bu	98:2	92	92:8 (**10a**)
2	**9a** (Ph)	*n*Hex	92:8	92	86:14 (**10b**)
3	**9b** (4-ClC_6H_4)	*n*Bu	97:3	72	90:10 (**10c**)
4	**9b** (4-ClC_6H_4)	*n*Hex	94:6	90	91:9 (**10d**)
5	**9c** (4-MeC_6H_4)	*n*Bu	94:6	91	88:12 (**10e**)
6	**9c** (4-MeC_6H_4)	*n*Hex	91:9	74	89:11 (**10f**)
7	**9d** (Cy)	*n*Bu	98:2	77	88:12 (**10g**)
8	**9e** (2-MeC_6H_4)	*n*Bu	92:8	92	53:47 (**10h**)
9	**9e** (2-MeC_6H_4)	*n*Hex	91:9	90	53:47 (**10i**)
10	**9f** (2-$MeOC_6H_4$)	*n*Bu	98:2	89	95:5 (**10j**)
11	**9f** (2-$MeOC_6H_4$)	*n*Hex	95:5	90	95:5 (**10k**)
12	**9g** (2-BrC_6H_4)	*n*Bu	>98:2	93	92:8 (**10l**)
13	**9g** (2-BrC_6H_4)	*n*Hex	>98:2	93	91:9 (**10m**)

[a]–[c] See Table 2. Addition time: 10 h. Full conversion was reached in all cases. [d] Determined by GC or HPLC analysis using a chiral stationary phase.

enantioselectivities (Table 4, entries 1–3). Although the e.r. values are only up to 91:9, it is important to note that these examples represent, to the best of our knowledge, the first catalytic asymmetric transfer of the *sec*-butyl moiety. Furthermore, the isopropyl moiety has been a challenging secondary alkyl group to transfer by the copper-catalyzed AAA, and generally only modest enantioselectivities are obtained with cinnamyl substrates and other organometallic reagents.[3b,15] Remarkably, by using *i*PrLi in combination with $CuBr{\cdot}SMe_2$ and **L3**, we could achieve 96:4 e.r. in the allylic alkylation of **1a** (entry 4). Similar to the addition of primary organolithium reagents, the addition of *i*PrLi to the more sterically demanding **1b** and the *p*-chloro-substituted **1c** gave rise to high enantioselectivities (entries 5 and 6). The cyclohexyl-substituted allyl chloride **1d** could also be used, but with slightly lower regio- and enantioselectivity were obtained (entry 7).

Notably, by using the same catalytic system ($CuBr{\cdot}SMe_2$/**L3**) phenyllithium could be used in the allylic substitution of *p*-chloro cinnamylbromide **4c**, thus providing the corresponding diaryl-substituted product with >99:1 e.r. but with low regioselectivity (S_N2'/S_N2 40:60).[10]

This protocol could also be extended to the first enantioselective synthesis of all-carbon quaternary stereogenic centers employing organolithium reagents. After extensive screening of different phosphoramidite ligands (see the Supporting Information for details), ligand **L4** (Figure 1) turned out to be the best ligand for the addition of *n*BuLi to *E*-trisubstituted allyl bromide **9a** (Table 5). When *n*BuLi was added over a 10 hour period to a solution of **9a** and the catalyst at −80 °C, the reaction gave rise to the product **10a** with 92:8 e.r. and with nearly perfect S_N2' selectivity (entry 1). The use of the trisubstituted allyl chloride analogue of **9a** did not result in any conversion. By using these optimized reaction conditions we examined the scope of this new method for the enantioselective synthesis of all-carbon quaternary centers (Table 5).

This new protocol was found to be very efficient with primary alkyl organolithium reagents, such as *n*BuLi and *n*-HexLi, which gave excellent regioselectivity and good enantioselectivities ranging from 86:14 to 92:8 e.r. when the phenyl derivative **9a** (entries 1 and 2) and *p*-chloro- and *p*-methyl-substituted allyl bromides **9b**,**c** were used (entries 3–6). An alkyl-substituted allyl bromide, such as the cyclohexyl derivative **9d**, could also be used in this transformation to afford the desired product **10g** with excellent regioselectivity and good enantioselectivity (entry 7). An intriguing and synthetically highly significant observation was made when *ortho*-substituted cinnamyl bromides were used. Reactions with the *o*-methyl-substituted bromide **9e** still showed very good regioselectivity but the corresponding products **10h**,**i** were obtained as a nearly racemic mixture (entries 8 and 9). In sharp contrast, when the *o*-methoxy-substituted bromide **9f** was used the desired products **10j**,**k** were obtained with excellent stereoselectivity (95:5 e.r.) and with almost total S_N2' selectivity (entries 10 and 11). A similar trend in the regio- and enantioselectivity was observed when another substrate bearing a coordinating functionality in the *ortho* position, such as *o*-bromo-substituted cinnamyl bromide (**9g**), was used (entries 12 and 13). These results suggest that a possible coordination between the methoxy or bromide substituent atom and the copper complex can be a key factor to afford high enantioselectivity when *ortho*-substituted cinnamyl bromides are used. It is also important to note, as described above for other aromatic halides, that there was no evidence of the common lithium–halogen exchange even in the case of *o*-bromo-substituted cinnamyl bromide **9g**.

In summary, we have developed efficient catalytic and highly enantioselective methodology for the asymmetric alkylation of both allyl chlorides and bromides with organolithium reagents using monodentate phosphoramidites as chiral ligands. These protocols include efficient asymmetric

addition of both primary and secondary organolithium reagents. Furthermore, for the first time, the enantioselective synthesis of quaternary carbon stereogenic centers using these extremely reactive organometallic reagents is presented.

Experimental Section

Typical procedure: A Schlenk tube equipped with septum and stirring bar was charged with CuBr·SMe_2 (0.01 mmol, 2.06 mg, 5 mol%) and the appropriate ligand (0.012 mmol, 6 mol%). Dry dichloromethane (2 mL) was added and the solution was stirred under nitrogen at room temperature for 15 min. Then, the allyl halide (0.2 mmol) was added and the resulting solution was cooled to −80 °C. In a separate Schlenk tube, the corresponding organolithium reagent (0.24 mmol, 1.2 equiv) was diluted with *n*-hexane (combined volume of 1 mL) under nitrogen and added dropwise to the reaction mixture over 5 h (over 10 h for quaternary centers) using a syringe pump. Once the addition was complete, the mixture was stirred for another 2 h at −80 °C. 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 reaction mixture was purified by flash chromatography on silica gel using different mixtures of *n*-pentane/Et_2O as the eluent.

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