Asymmetric Catalysis

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1,4-Dichloro- and 1,4-Dibromo-2-butenes as Substrates for Cu-Catalyzed Asymmetric Allylic Substitution**

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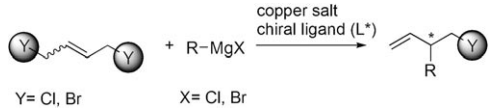
In recent years, the transition-metal-catalyzed asymmetric allylic alkylation (AAA) has become an effective method for the formation of enantiomerically enriched C–C bonds.[1,2] Complementary to the widely studied Pd-catalyzed version, investigations of the Cu-mediated reaction have shown that, with the use of hard nucleophiles such as organozinc[3] or organomagnesium reagents,[4] good to excellent control of chemo-, regio-, and enantioselectivity is achievable.[5]

Over the past years, our research group has developed the Cu-catalyzed addition of Grignard reagents promoted by phosphoramidite chiral ligands to allylic chlorides with excellent stereocontrol, both on disubstituted derivatives[6,7] and more recently on trisubstituted substrates.[7]



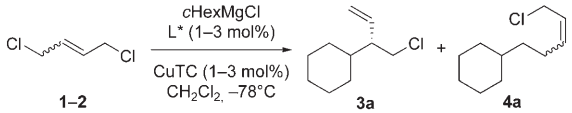
To broaden the scope of our methodology, we sought simple difunctionalized substrates that would offer the highest synthetic versatility. *Ideally, such a substrate should be commercially available at low cost and offer the possibility to use the resulting product both as an electrophile or as a potential nucleophile.*

We focus herein on difunctionalized allylic substrates, the 1,4-bishalo-2-butenes, which are small, simple, and commercially available. These allylic substrates are known to undergo clean S_N2' reactions to give racemic products using various cuprate reagents[8] and under the Cu-catalyzed addition of Grignard reagents.[9] We anticipated that the enantiomerically enriched products that result from the asymmetric Cu-catalyzed γ-substitution reaction would provide interesting chiral synthons because of their remaining tunable functionalities. Thus, besides the well-known transformations of the double bond (for example, oxidative cleavage, hydroboration, metathesis), the residual halide could undergo electrophilic or nucleophilic transformations and deliver new products with the preservation of the optical purity of the starting material.

We initially investigated the influence of the *cis* and *trans* geometry of the allylic substrate on the stereochemical outcome of the reaction. Other research groups have reported that a *cis* isomer yields a product with significant loss of enantioselectivity because of steric or other energetically competitive interactions between the catalyst and the substrate.[10] Two exceptions to this observation were reported by Okamoto and co-workers[11] in the addition of Grignard reagents to various allylic silylated ethers using chiral diaminocarbene catalysts,[12] and by Gennari and co-workers in the desymmetrization of *meso* cyclic allylic bisphosphates.[13]

Table 1 summarizes the comparative results for the asymmetric addition of cyclohexylmagnesium chloride to the *trans* and *cis* isomers of 1,4-dichloro-2-butene (**1** and **2**,

Table 1: Addition of cyclohexylmagnesium chloride to *trans* and *cis* 1,4-dichlorobutenes, **1** and **2**.



1–2
trans olefin (**1**)
cis olefin (**2**)

3a **4a**

Entry[a]	Substr.	L*	Conv. [%][b]	**3a**/**4a**[c]	*ee* [%][d]
1	**1**	**L1**	>99 (98)	100:0	75(*S*)
2	**2**		87	100:0	31(*S*)
3	**1**	**L2**	>99	100:0	52(*R*)
4	**2**		95	100:0	8(*R*)
5	**1**	**L3**	>99	100:0	54(*S*)
6	**2**		86	100:0	37(*S*)
7	**1**	**L4**	>99	100:0	38(*R*)
8	**2**		86	100:0	24(*S*)
9	**1**	**L5**	>99 (89)	100:0	74(*R*)
10[e]	**1**		>99	100:0	77(*R*)
11	**2**		92	100:0	44(*R*)
12	**1**	**L6**	>99	100:0	62(*R*)
13	**2**		91	100:0	39(*R*)
14	**1**	**L7**	>99	100:0	52(*R*)
15	**2**		93	100:0	49(*S*)

[a] Conditions: **1** or **2** (1 mmol), CuTC (1 mol%), **L*** (1.1 mol%) in CH_2Cl_2 (2 mL) at −78°C with addition of *c*HexMgCl in Et_2O (1.2 equiv) over 1 h. [b] Conversion determined by GC-MS (in parentheses: yield of isolated product after purification by column chromatography on silica gel). [c] Ratio determined by GC-MS and ^{1}H NMR spectroscopy. [d] Values of enantiomeric excess (and configuration in parentheses) of **3a** determined by GC on a chiral stationary phase. [e] 3 mol% of CuTC and 3.3 mol% of L*.

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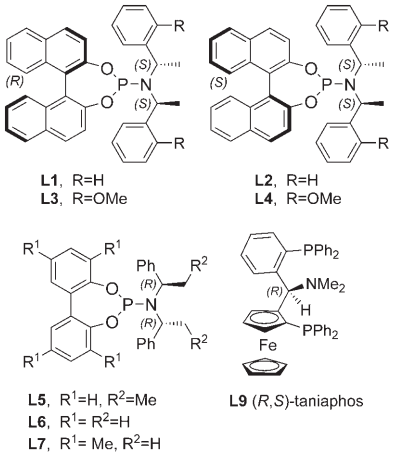
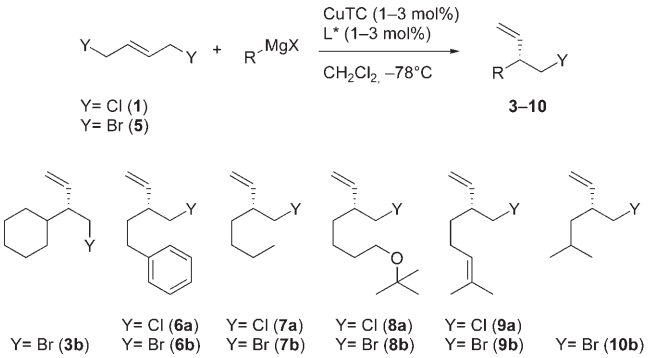
respectively), promoted by a small range of biphenol-[14] and binaphtol-based[6b,15] phosphoramidite ligands (Scheme 1).



Scheme 1. Chiral ligands used in the AAA reaction.

The best outcome for the allylic alkylation of *cis*-**2** was achieved using ligand **L7** (1 mol%), in which an *ee* value of 49% in product (*S*)-**3a** was attained (Table 1, entry 15). On the other hand, when the *trans*-**1** was treated by slow addition of cyclohexylmagnesium chloride (*c*HexMgCl, 1.1 equiv) in a reaction catalyzed by copper(I) thiophene carboxylate (CuTC, 1 mol%) and chiral ligand **L5** (1.1 mol%), the product (*R*)-**3a** was obtained in 89% yield and 74% *ee* (Table 1, entry 9). This was later improved to 77% *ee* by increasing the catalyst loading of CuTC/**L5** to 3 mol%, which was found to be optimal (Table 1, entry 10). The clear conclusions of these results are that higher enantioselectivities are achieved with the *trans* isomer than with the *cis*, and that there is complete regiocontrol towards the γ adduct in both cases (Scheme 2).[16]



Scheme 2. Enantioselective CuTC-catalyzed allylic alkylation of **1** and **5** with various Grignard reagents.

Next, to confirm these preliminary results, other Grignard reagents were added to the *trans* isomers of the difunctionalized allylic substrates, *trans*-1,4-dichloro-2-butene (**1**) and *trans*-1,4-dibromo-2-butene (**5**, Scheme 2), which afforded the γ adducts regiospecifically and providing compounds **3** to **10** in moderate to high enantioselectivity (Table 2 and 3). *It should be pointed out that we used the commercially available substrates **1** and **5** directly without prior purification.*

Table 2: Asymmetric CuTC-catalyzed allylic alkylation of **1** with RMgBr (Scheme 2, L* = **L1**–**L9**).

Entry	Product	L*	Conv [%][a]	γ/α[b]	*ee* [%][c]
1	**6a**	**L1**	>99 (98)	100:0	78(*R*)
2	**6a**	**L4**	>99	100:0	57(*S*)[18]
3[d]	**7a**	**L1**	>99 (55)	100:0	85(−)
4[d]	**7a**	ent-**L4**	>99	100:0	81(−)
5[d]	**7a**	**L9**	>99	100:0	10(+)
6	**8a**	**L1**	>99 (80)	100:0	85(−)
7	**8a**	ent-**L4**	>99	100:0	79(−)
8	**8a**	**L9**	35	100:0	32(+)
9	**9a**	**L1**	>99 (88)	100:0	85(−)
10	**9a**	ent-**L4**	>99	100:0	85(−)

[a] Conversion determined by GC-MS (in parentheses, yield of isolated product after purification by column chromatography on silica gel). [b] Ratio determined by GC-MS and ^{1}H NMR spectroscopy. [c] Values of enantiomeric excess (and configuration or optical rotation in parentheses) determined by GC on a chiral stationary phase. [d] 3 mol% of CuTC and 3.3 mol% of L*.

Good enantioselectivities of up to 85% *ee* were achieved in the allylic substitution of substrate **1** using saturated primary Grignard reagents and with both ligands **L1** and **L4**, to give products **7a**–**9a** (Table 2, entries 3, 6, 9, and 10). Another bidentate ferrocenyl-based ligand, taniaphos **L9**,[17] was also tested with allylic substrate **1** and only poor enantiomeric excesses of 10% and 32% for products **7a** and **8a**, respectively, were achieved (Table 2, entries 5 and 8). The bulkier phenethylmagnesium reagent gave adduct (*R*)-**6a** in the presence of the chiral ligand **L1** with 78% *ee* (Table 2, entry 1).

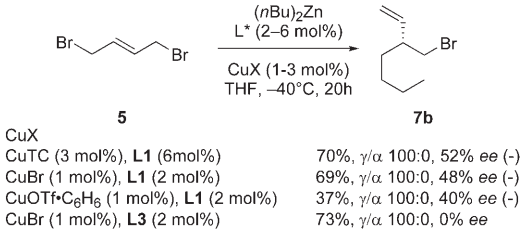
Likewise, allylic substitutions were performed on the corresponding commercially available *trans*-dibromo substrate **5**. According to previous results, addition of cyclohexylmagnesium chloride to the difunctionalized substrate **5** afforded a moderate asymmetric outcome of 63% *ee* for **3b** with **L2** (Table 3, entry 2).[19] We were delighted to observe that under similar conditions, using a catalyst loading as low as 1 mol% of CuTC and chiral ligand, chiral homoallylic bromide adducts with enantioselectivities as high as 92% *ee* could be achieved for the addition of the functionalized Grignard reagent, (4-*tert*-butoxybutyl)magnesium bromide, with ent-**L4** to provide compound (−)-**8b** (Table 3, entry 10). Again, ee values higher than 86% could not be reached using ligand **L9** (Table 3, entry 11). Moreover, the terpenic bromocitronellene (−)-**9b** was obtained with the best selectivity of this series in 94% *ee* using a CuTC/**L4** loading of 3 mol% (Table 3, entry 13). Overall, the dibromo substrates gave similar or better results in terms of their enantioselectivity than the dichloro derivatives when the two phosphoramidite ligands **L1** and **L4** were used.

For the sake of comparison, the AAA reaction was tested using traditional procedures for the diorganozinc reagents as shown in Scheme 3.[3,20] Although the reaction was found to

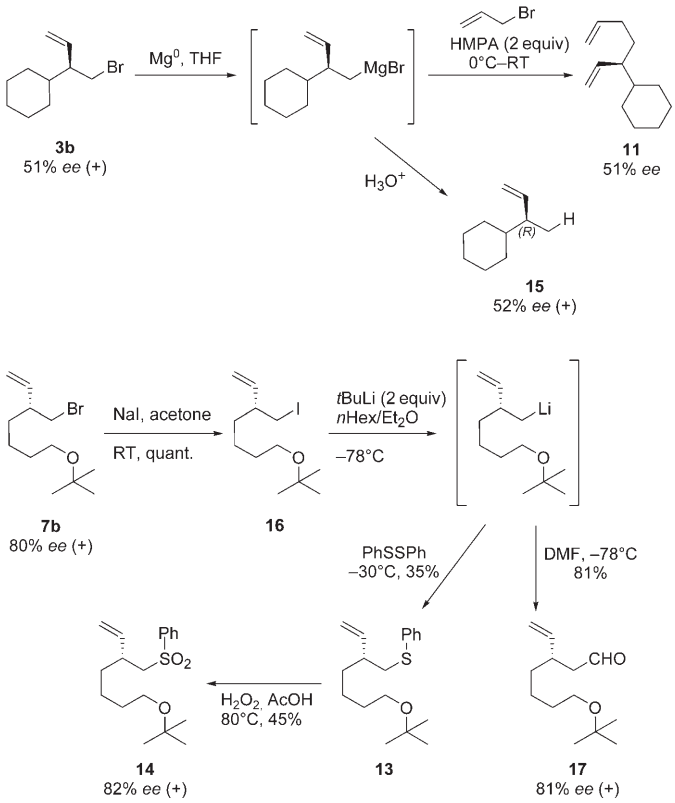
Table 3: Asymmetric CuTC-catalyzed allylic alkylation of **5** with RMgBr (Scheme 2, L* = **L1**–**L9**).

Entry	Product	L*	Conv. [%][a]	γ/α[b]	*ee* [%][c]
1	**3b**	**L1**	88	100:0	23(*S*)
2[d]	**3b**	**L2**	>99 (99)	100:0	63(*R*)
3	**3b**	ent-**L3**	>99 (83)	100:0	54(*R*)
4	**6b**	**L1**	>99 (94)	100:0	83(−)
5	**6b**	**L2**	>99	100:0	76(+)
6	**6b**	ent-**L4**	>99	100:0	67(−)
7	**7b**	**L1**	>99	100:0	86(−)
8	**7b**	ent-**L4**	>99 (80)	100:0	87(−)
9	**8b**	**L1**	>99	100:0	88(−)
10	**8b**	ent-**L4**	>99 (77)	100:0	92(−)
11	**8b**	**L9**	>99	100:0	86(+)
12[d]	**9b**	**L1**	75	100:0	89(−)
13[d]	**9b**	ent-**L4**	93 (70)	100:0	94(−)
14	**10b**	**L1**	>99 (79)	100:0	85(−)
15	**10b**	ent-**L4**	>99	100:0	84(−)

[a–d] See Table 2.



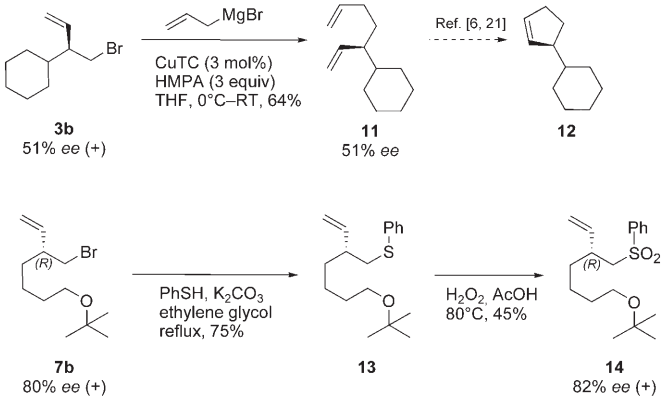
Scheme 3. Asymmetric allylic alkylation of **5** with a dibutylzinc reagent and a range of Cu catalysts. Tf = trifluoromethanesulfonyl.



Scheme 5. Electrophilic derivatization of chiral homoallylic bromides. DMF = *N*,*N*-dimethylformamide.

be regiospecific using these conditions, the reactivity was much lower, with incomplete conversions after one day, and the enantioselectivity was found to be much lower than when using Grignard reagents (Table 3, entries 7 and 8).

To illustrate the synthetic utility of this methodology, the chiral monohalides were easily derivatized through nucleophilic (Scheme 4) or electrophilic (Scheme 5) pathways. The brominated cyclohexyl adduct, 1-bromobut-3-en-2-ylcyclohexane ((+)-**3b**) with 51% *ee*, was transformed into the hepta-1,6-dien-3-ylcyclohexane (**11**) in 64% yield by addition



Scheme 4. Nucleophilic derivatization of chiral homoallylic bromides. HMPA = hexamethyl phosphoramide.

of allylmagnesium bromide with no loss of enantioselectivity (Scheme 4). Previous findings from our research group[6] showed that product **11** can undergo clean ring-closing metathesis with no loss in enantiomeric excess.[21] Conversely, adduct (+)-**7b** with 80% *ee* was derivatized through the addition of benzenethiolate with a good yield of 75% to afford compound **13**, which was further oxidized to give the chiral sulfone (+)-**14** to assess the optical purity of 82% *ee*.

Similar products were obtained through electrophilic means when the remaining halide moiety was transformed into an organometallic species (Scheme 5). The formation of a Grignard reagent from (+)-**3b** with 51% *ee* and subsequent addition of allyl bromide led to compound **11** with complete retention of the chiral information. A sample of the organomagnesium intermediate was hydrolyzed to give but-3-en-2-ylcyclohexane (**15**) and consequently we could assign the absolute stereochemistry by correlation with previous studies.[6a,20b,22] It should be mentioned that the racemic bromide **10b** has already been transformed into a Grignard reagent and used for the synthesis of analogues of keto-dipeptides.[9] An analogous organolithium reagent was prepared from the corresponding iodide **16** (from a Finkelstein reaction of the chiral bromide (+)-**7b**) by treatment with *tert*-butyllithium at −78 °C.[23] This reagent was later treated with diphenyldithiane to afford the sulfane **13**, and further chiral sulfone (+)-**14** in 82% *ee*. The similar treatment of bromide (+)-**7b** with *tert*-butyllithium followed by a dimethylformamide quench afforded the chiral aldehyde **17** with retention of the enantiomeric excess.[24]

In conclusion, we have succeeded in demonstrating the value of this allylic substitution methodology by forming highly tunable chiral synthons, starting from commercially available difunctionalized substrates, *trans*-1,4-bishalo-2-butenes. Both the dichloro and dibromo allylic substrates gave good enantioselectivities and excellent regioselectivities. Values for the enantiomeric excess of 85% and 94%, respectively for dichloro and dibromo substrates were obtained as exclusive γ adducts in both cases.

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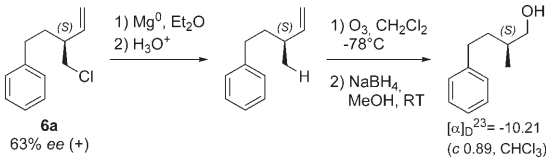

6a
63% *ee* (+)

$[\alpha]_D^{23}$= -10.21
(*c* 0.89, $CHCl_3$)

(Lit. $[\alpha]_D^{20} = -20$ ($c = 5.0$, $CHCl_3$) for 91% *ee*, R. W. Hoffmann et al., *Synthesis* **2002**, 207).

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[24] Chiral homoallylic chlorides also underwent transformations with retention of *ee* value, either through Grignard reaction or through prior formation of the iodide, although they were less reactive.

