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High Diversity on Simple Substrates: 1,4-Dihalo-2-butenes and Other Difunctionalized Allylic Halides for Copper-Catalyzed S_N2' Reactions

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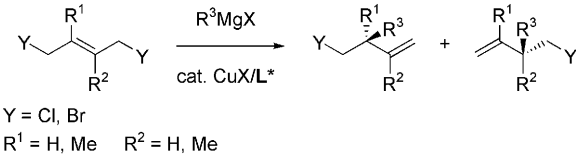
Abstract: Enantioselective allylic alkylation with an organomagnesium reagent catalyzed by copper thiophene carboxylate (CuTC) was carried out on difunctionalized substrates, such as commercially available 1,4-dichloro-2-butene and 1,4-dibromo-2-butene, and on similar compounds of higher substitution pattern of the olefin for the formation of all-carbon chiral quaternary centers. The high regioselectivity obtained throughout the reactions favored good regiocontrol for the addition of phenyl Grignard reagents. Other difunctionalized substrates (allylic ethers and allylic alcohols) also underwent asymmetric S_N2' substitution.

Keywords: allylic compounds · arylation · asymmetric catalysis · copper · nucleophilic substitution

Introduction

There is a growing industrial and pharmaceutical need for clean and efficient asymmetric methodologies to access optically and biologically active compounds. In this context, the well-documented allylic alkylation is a very useful reaction. It can be catalyzed by many transition metals with either soft or hard nucleophiles.[1] Copper usually favors regioselective S_N2' *anti* displacements of leaving group with hard nucleophiles, such as organometallic reagents (magnesium,[2] zinc,[3] or aluminum[4] reagents). Over the past decade, the literature has flourished with examples of efficient copper-catalytic S_N2' procedures, which afford nearly perfect enantioselectivities[5] on different types of substrates.

Versatility in the resulting chiral compounds is a key issue that has already been addressed by our group in an earlier report concerning difunctionalized bishalo substrates (Scheme 1).[6] These are small, simple, commercially available in both olefinic geometries, cheap, and can be used without further purification. More importantly, the resulting chiral synthons offer high versatility for subsequent derivatization, by nucleophilic or electrophilic pathways upon the remaining monohalide.



Y = Cl, Br
R^1 = H, Me R^2 = H, Me

Scheme 1. Asymmetric allylic alkylation of bisfunctionalized 1,4-dihalo-type substrates.[6]

In this context, we wish to report here our full results with further studies on higher substituted 1,4-dihalo substrates, with tri- and tetrasubstituted olefins. However, some important issues remain and have been poorly covered by the recent literature. The poor regioselectivity of allylic arylation has rarely been overcome, with very recent exceptions. By taking advantage of the excellent regioselectivity on such 1,4-dihalo substrates, we also investigated an arylation protocol.

However, we were initially interested in studying whether the double-bond geometry of the allylic electrophile had an influence on the reactivity and the stereochemical outcome of the reaction. Initially, we considered that the double-bond geometry would not control the facial approach of the soft organocopper nucleophile, thus that *E*- or *Z*-configured substrates would afford mirror-image products (Scheme 2).

Results and Discussion

Influence of the double-bond geometry in asymmetric allylic alkylation of 1,4-dihalo-2-butene: Literature precedents cov-

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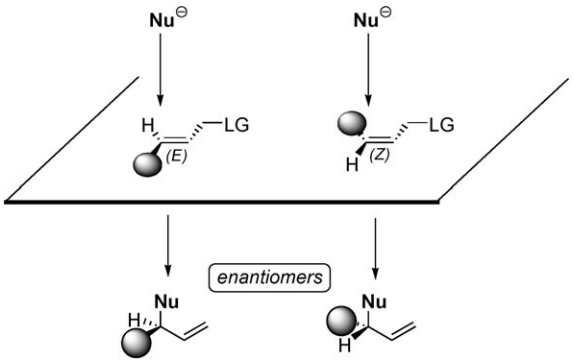
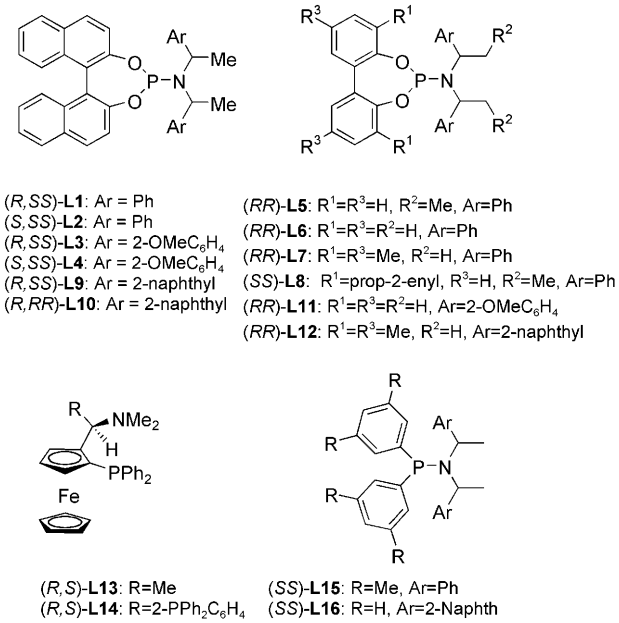
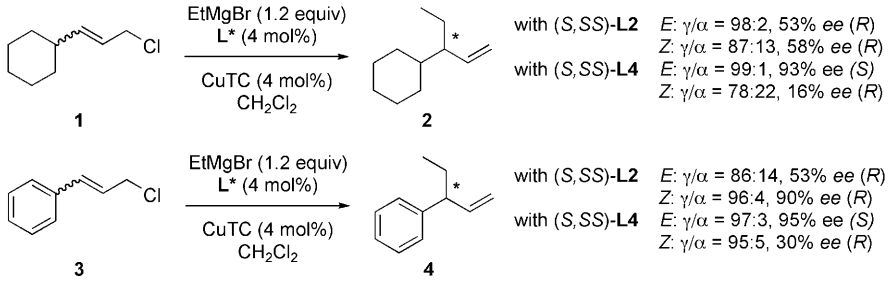


Scheme 2. Nucleophilic S_N2' approach to *E* and *Z* olefins (LG = leaving group).

ering the subject are scarce. Some examples were produced by Hoveyda and co-workers, who showed that the reactivity and enantioselectivities obtained are lower on the *cis* isomers of aromatic allylic phosphate using either chiral peptidic Schiff bases or diaminocarbene catalysts.[7] Diastereoselective procedures also suffer from the *cis* configuration of the substrate as was reported by Breit and Breuninger with the use of their chiral-directing *ortho*-diphenylphosphanylferrocene carboxylate (*o*-DPPF) unit.[8] However, some rare exceptions to these observations were reported. In an early case, Caló and co-workers published a diastereoselective procedure that used high excesses of copper bromide with a slow addition of a Grignard reagent (4:1 Cu/Grignard reagent) in THF.[9] Under these drastic conditions, they observed complete regio- and stereocontrol over the allylic substitution on either *Z* or *E* chiral heterocyclic sulfides. One of the more recent exceptions was reported by Okamoto and co-workers in the addition of Grignard reagents to various allylic silylated ethers using chiral diaminocarbene catalysts,[10] which promoted a better asymmetric outcome on the (*Z*)-allylic substrate. The desymmetrization of *meso*-cyclic allylic bisphosphates is the second example described by Gennari and co-workers, which proceeds with good enantiomeric excess of up to 98% *ee* on *cis*-type substrates.[11]

Thus far, these rare instances have not permitted conclusions on the influence of the double-bond geometry on the behavior of the copper-catalyzed asymmetric allylic substitution reaction to be drawn. Consequently, we decided to investigate the parameters that govern the chiral outcome for easily accessible substrates. Prior to our study, previous examples had been recorded by our group[12c] for the comparative allylic substitution of *cis*- and *trans*-cinnamyl chlorides (**3**) and their cyclohexyl analogue (**1**) under the set of typical conditions used by our group (Scheme 3).[12] The *cis*-configured substrates afforded generally lower enantioselectivities than their *trans* counterparts with the small library of ligands tested (**L1**–**L16**). An exception was noted with

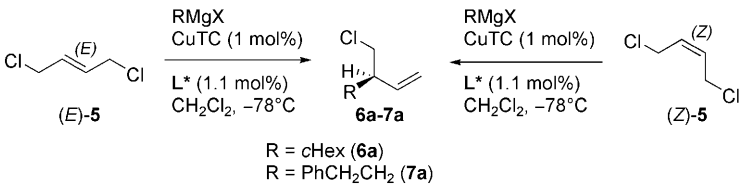




Scheme 3. CuTC-catalyzed asymmetric allylic substitution of (*E*)- and (*Z*)-allylic chlorides **1** and **3**.

ligand **L2**, which promoted up to 90% *ee* for the addition of ethylmagnesium bromide to (*Z*)-**3**. More importantly though, the better ligand, **L4**, for the substitution of (*E*)-**1** and (*E*)-**3** induced only very poor enantioselectivities on the *Z*-configured equivalents (values as high as 30% *ee*). Moreover, depending on the ligands used, the alkylcopper reagent would either recognize the leaving group or the γ substituent. These latter observations inferred that the ligand dictated the behavior of the copper reagent, forcing the copper cluster to recognize the *cis* and *trans* substrate differently.

To further comprehend the different behavior of isomers *E* and *Z*, and scope the field of difunctionalized allylic electrophiles, we directed our attention towards a readily accessible substrate: the commercially available 1,4-dichloro-2-butene (**5**), which is marketed in both geometrical configurations of the double bond (Scheme 4).



Scheme 4. Comparative Cu-catalyzed addition of RMgX to (*E*)- versus (*Z*)-1,4-dichloro-2-butene (**5**).

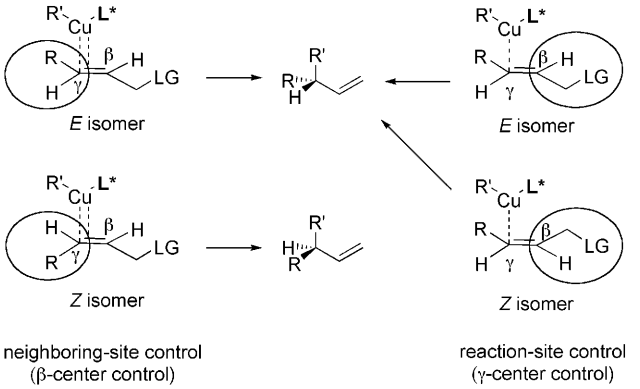
For substrate **5**, We first considered the addition of cyclohexylmagnesium chloride catalyzed by copper thiophene carboxylate (CuTC) (Table 1). The *Z* isomer invariably afforded **6a** with lower levels of asymmetric control over the allylic substitution (up to 49% *ee* with **L7**; Table 1, entry 14). Pleasingly, the totally regiocontrolled allylic displacement of the chloride was observed in every instance of Table 1. On the other hand, when *trans*-**5** was treated with slow addition of cyclohexylmagnesium chloride (1.1 equiv) in a reaction catalyzed by CuTC (1 mol%) and chiral ligand **L5** (1.1 mol%), the product (*R*)-**6a** was obtained in 89% yield and 74% *ee* (Table 1, entry 9). Furthermore, ligands **L1** and **L5** afforded the highest asymmetric induction on (*E*)-**5** with 75 and 74% *ee*, respectively (Table 1, entries 1 and 9).

Table 1. Comparative CuTC-catalyzed (1 mol%) addition of cyclohexylmagnesium chloride on (*E*)- and (*Z*)-**5** with chiral phosphoramidite ligands (1 mol%) (**L*** = **L1**–**L8**; Scheme 4).

Entry[a]	Geometry[b]	Ligand	R	Conv. [%][c]	S_N2'/S_N2[d]	*ee* [%][e]
1	*E*	**L1** (*R*,*SS*)	**6a**	100	100:0	75 (*S*)
2	*Z*		**6a**	87	100:0	31 (*S*)
3	*E*	**L2** (*S*,*SS*)	**6a**	100	100:0	52 (*R*)
4	*Z*		**6a**	95	100:0	8 (*R*)
5	*E*	**L3** (*R*,*SS*)	**6a**	100	100:0	54 (*S*)
6	*Z*		**6a**	86	100:0	37 (*S*)
7	*E*	**L4** (*S*,*SS*)	**6a**	100	100:0	38 (*R*)
8	*Z*		**6a**	86	100:0	24 (*S*)
9	*E*	**L5** (*RR*)	**6a**	100	100:0	74 (*R*)
10	*Z*		**6a**	92	100:0	44 (*R*)
11	*E*	**L6** (*RR*)	**6a**	100	100:0	62 (*R*)
12	*Z*		**6a**	91	100:0	39 (*R*)
13	*E*	**L7** (*RR*)	**6a**	100	100:0	52 (*R*)
14	*Z*		**6a**	93	100:0	49 (*S*)
15	*E*	**L8** (*SS*)	**6a**	100	100:0	73 (*S*)
16	*Z*		**6a**	71	100:0	25 (*S*)

[a] Conditions: **5** (1 mmol), CuTC (1 mol%), and **L*** (1.1 mol%) in CH_2Cl_2 (2 mL) at −78°C with addition of RMgX in Et_2O (1.1 equiv) over 1 h. [b] Geometry of the double bond. [c] Conversion (Conv.) determined by GC–MS and ^1H NMR spectroscopy. [d] Ratio determined by GC–MS and ^1H NMR spectroscopy. [e] Enantiomeric excess determined by chiral GC.

The relative configuration of the products resulting from the addition of the cyclohexylcopper nucleophile is random and strongly depends on the structural features of the ligand, although a major trend favors products of identical mirror image. The major occurrences suggest that, with a more sterically demanding nucleophile (i.e., a secondary Grignard reagent), we are able to control the γ-position reacting site, according to the Duhamel postulate (the latent trigonal center concept, Scheme 5).[13] Indeed, owing to dissimilar electronic and steric properties of the substituents on the sp^2 reacting sites, two types of competing control from the prostereogenic centers can be characterized, as was postulated by Duhamel and Plaquevent following their observations for the enantioselective protonation of prochiral enolates. By applying Duhamel's concept to the copper-catalyzed allylic substitution (Scheme 5), asymmetric reactions taking place at the C=C double bond can behave according to two distinct pathways. In the first, the *E* olefin will afford mirror-image products of those formed by the *Z*-configured substrate: the face selection of the reacting organocopper cluster is controlled by the orientation of the β center, namely neighboring-site control. The substituents on the reacting carbon center (γ) are seen as one big latent group and their positioning does not count in the facial approach of the organocopper nucleophile. However, the nature of the resulting enantiomer does not necessarily translate from the geometry of the double bond. Indeed, in some instances, the same enantiomer will arise from either *E* or *Z* configurations in the substrate, and is thus named reaction-site control.



Scheme 5. Duhamel's latent trigonal center concept applied to Cu-catalyzed asymmetric allylic alkylation (AAA).

The initial comparative study was undertaken with a secondary Grignard reagent, which is more sterically demanding to the reaction system. With a view to completing this comparative study, we looked into asymmetric S_N2' substitution with the aliphatic primary magnesium reagent, $PhCH_2CH_2MgBr$ (Table 2). The *Z* and *E* substrates of **5** behaved as in the previous cases with a net preferred asymmetric control over the *trans* isomer. Ligand **L1** afforded on both isomers of **5** a unique S_N2' adduct with enantioselectivities up to 78% *ee* for (*E*)-**5** and 39% *ee* for (*Z*)-**5** (Table 2, entries 1 and 2).

Interestingly, the different structural motif of the intermediate copper reagent changes the configurational outcome of the reaction. Instead of reaction-site control, mostly occurring for the cyclohexyl allylic substitution, the primary

Table 2. Comparative CuTC-catalyzed (1 mol%) addition of phenethylmagnesium bromide on (*E*)- and (*Z*)-**5** with chiral phosphoramidite ligands (1 mol%) (**L*** = **L1**–**L6**; Scheme 4).

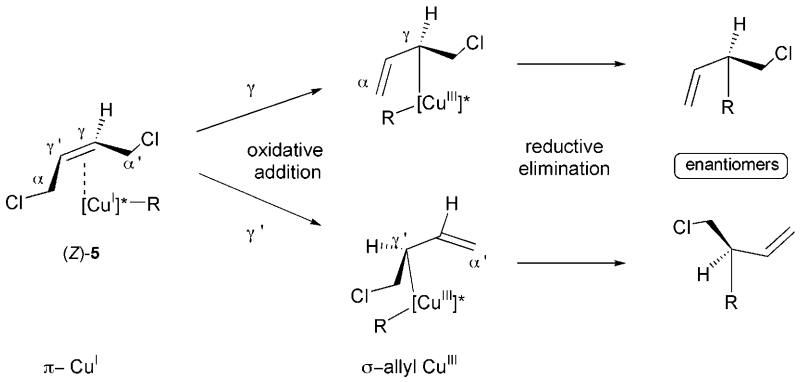
Entry[a]	Geometry[b]	Ligand	R	Conv. [%][c]	S_N2'/S_N2[d]	*ee* [%][e]
1	*E*	**L1** (*R*,*SS*)	**7a**	100	100:0	78 (*R*)
2	*Z*		**7a**	100	100:0	39 (*S*)
3	*E*	**L2** (*S*,*SS*)	**7a**	100	100:0	29 (*S*)
4	*Z*		**7a**	100	100:0	38 (*R*)
5	*E*	**L3** (*R*,*SS*)	**7a**	100	100:0	3 (*R*)
6	*Z*		**7a**	100	100:0	5 (*S*)
7	*E*	**L4** (*S*,*SS*)	**7a**	100	100:0	57 (*S*)
8	*Z*		**7a**	100	100:0	36 (*R*)
9	*E*	**L5** (*RR*)	**7a**	100	100:0	60 (*S*)
10	*Z*		**7a**	100	100:0	27 (*R*)
11	*E*	**L6** (*RR*)	**7a**	100	100:0	63 (*S*)
12	*Z*		**7a**	100	100:0	21 (*R*)

[a] Conditions: same as those for Table 1. [b] Geometry of the double bond. [c] Conversion (Conv.) determined by GC–MS and ^{1}H NMR spectroscopy. [d] Ratio determined by GC–MS and ^{1}H NMR spectroscopy. [e] Enantiomeric excess determined by chiral GC.

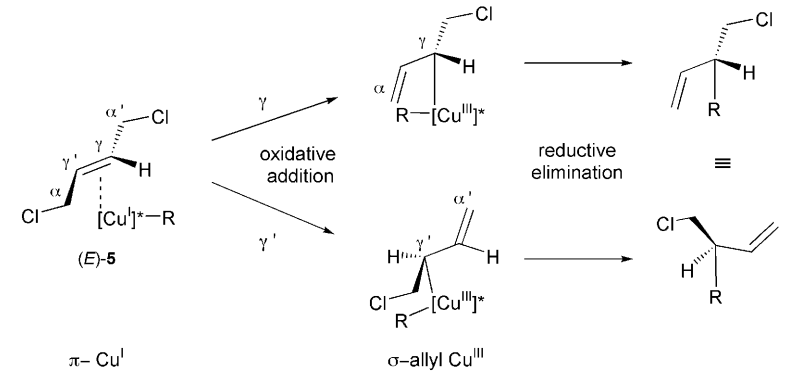
phenethyl behaves in a radically different mode, affording opposite enantiomers for the S_N2'-allylic displacement of *cis*- versus *trans*-prochiral electrophiles, no matter which chiral ligand is used. This implies that, with a linear alkyl reagent, the incoming organocopper reagent instead targets the leaving group and its surrounding geometry, thus neighboring-site control. From this line of screening, the tendency of the enantioselectivity implies that *cis* and *trans* substrates have opposite affinities for the chiral ligands. Indeed, it is most obvious when going from **L4** to **L6**, for which increasing *ee* values for (*E*)-**5** match decreasing *ee* values for (*Z*)-**5** (Table 2, entries 7–12).

The obvious conclusion for such results is that higher enantioselectivities are achieved with the *trans* isomer in each case, rather than with the *cis*, and that the regiocontrol towards the γ adduct is not affected in either case. Nevertheless, a plausible source of poor enantiomeric control could stem from isomerization of the double bond by the metal catalyst or by the reaction media. We therefore monitored the *Z*/*E* ratio (before and during the reaction) and the evolution of the enantioselectivity during the slow addition of cyclohexylmagnesium chloride (*c*HexMgCl) to the *cis*-**5** substrate. To our delight, we observed that the *Z* substrate was stable in our copper-catalytic system, even at room temperature over a period of one hour. As the organomagnesium reagent was slowly added, there were no significant changes in either stereoselective parameters to suggest a destabilization of the substrate in the reaction media and, thus, that any isomerization from *cis* to *trans* was taking place in the course of the reaction.

According to the comparative results obtained in the copper-mediated allylic substitution of the *E*- and *Z*-configured substrates, lower enantioselectivities occurring on the *cis*-allylic halides can be attributed to possible negative interactions, which result in spatial obstructions of the two reacting partners, the chiral organocopper nucleophile and the *cis*-prochiral substrate. Schemes 6 and 7 illustrate the two different stereochemical outcomes for the identical facial approach of a copper catalyst upon the difunctionalized substrates (*Z*)-**5** or (*E*)-**5**, respectively. For the reaction of substrate (*Z*)-**5**, one observes that, at the early stage of π–copper(I) complex formation, there is no facial differentiation hitherto, and that the allylic displacements can give rise to two enantiomers in the reductive elimination process. Indeed, due to its inherent symmetry, the crucial asymmetric differentiation step for the allylic alkylation of the *cis*-bishalide (**5**) occurs at a later stage, and relies on the σ-allyl species formed during the oxidative addition of the metal to either the γ or γ′ centers (Scheme 6).



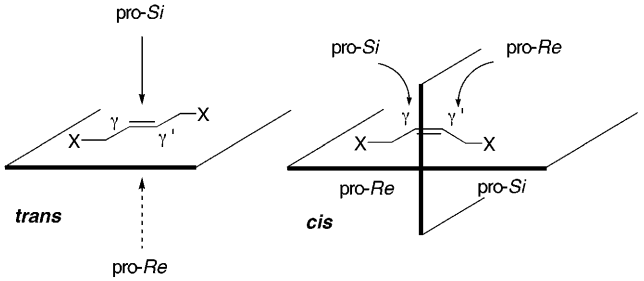
Scheme 6. Cu-catalyzed alkylation of (*Z*)-**5**.



Scheme 7. Cu-catalyzed alkylation of (*E*)-**5**.

Conversely, the stereoselectivity of the S_N2' displacement reaction on the *E* isomer of **5** is intimately correlated with the facial approach of the copper(I) cluster, thus to its subsequent d–π* bond formation. Both of the γ and γ′ oxidative adducts produce the same enantiomers in the final reductive elimination step (Scheme 7).

In short, both (*E*)- and (*Z*)-1,4-dichloro-2-butene belong to different symmetry point groups (C_{2v} and C_{2h}, respectively). This implies that, as pictured in Scheme 8, due to the additional mirror plane cutting the *cis* substrate at the epicenter of the double bond, the γ and γ′ prochiral centers become mirror images of one another, thus producing enantiomorphic adducts. In conclusion, the oxidative addition of the copper locks the fate of the enantiomeric outcome of the reaction.



Scheme 8. Different enantiotopic faces for *trans*- and *cis*-1,4-dihalo-2-butene.

***trans*-1,4-Dichloro- and *trans*-1,4-dibromo-2-butene—highly potent, commercially available substrates**: As noted in the above-mentioned study conducted on *cis* versus *trans* substrates, the double activation of 1,4-dichloro-2-butene (**5**), induced by the two allylic reacting sites, awarded regiospecificity to the S_N2'-allylic displacement reaction. These allylic substrates are known to undergo clean S_N2' reactions in a racemic fashion for various cuprates[14] and under copper-catalyzed addition of Grignard reagents.[15] To confirm the preliminary results, other Grignard reagents were added to the *trans* isomer of the commercially available difunctionalized allylic substrates, *trans*-1,4-dichloro-2-butene (**5**) and *trans*-1,4-dibromo-2-butene (**8**; Scheme 9). Both substrates afforded γ adducts regiospecifically and provided compounds **6**–**12** with moderate-to-high enantioselectivities (Tables 3 and 4).

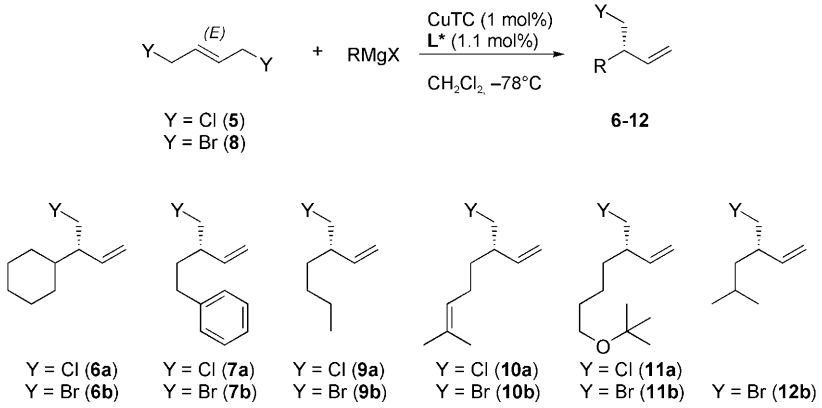
As we proceeded with an optimization of the reaction conditions for the addition of cyclohexylmagnesium chloride, a slight increase of the catalyst loading to 2 mol% resulted in an improvement of the enantioselectivity from 74 to 77% *ee* (Table 3, entries 2 and 4). Additionally, the copper source could be changed to copper bromide, which catalyzed the allylic substitution with comparable enantioselectivity (Table 3, entry 3). Generally, good enantioselectivities of up to 85% *ee* were obtained for the different additions of primary saturated Grignard reagents to **5** with biphenol-based ligand **L1** (Table 3, entries 7, 11, and 14). As the ferrocenyl-based bidentate ligand taniaphos **L14** has been used with some success on other types of substrates,[16] it was tested on the allylic compound **5** but reached only poor enantioselectivities of 10 and 32% *ee* for products **9a** and **11a**, respectively (Table 3, entries 10 and 13).

For comparison, the reactions were carried out on the *trans*-1,4-dibromo derivative **8** with the same set of organomagnesium reagents, as displayed in Table 4. Although we

Table 3. Asymmetric allylic alkylation of **5** catalyzed by CuTC in CH_2Cl_2 at −78°C (Scheme 9).

Entry	R	Product	Ligand	Conv. [%][a]	γ/α[b]	*ee* [%][c]
1	*c*Hex	**6a**	**L1**	>99 (98)	100:0	75 (*S*)
2	*c*Hex	**6a**	**L5**	>99 (89)	100:0	74 (*R*)
3[e]	*c*Hex	**6a**	**L5**	>99	100:0	75 (*R*)
4[f]	*c*Hex	**6a**	**L5**	>99	100:0	77 (*R*)
5	$PhCH_2CH_2$	**7a**	**L1**	>99 (98)	100:0	78 (*R*)
6	*n*Bu	**9a**	**L1**	>99	100:0	84 (−)
7[d]	*n*Bu	**9a**	**L1**	>99 (55)	100:0	85 (−)
8[d]	*n*Bu	**9a**	*ent*-**L4**	>99	100:0	81 (−)
9	*n*Bu	**9a**	**L5**	>99	100:0	81 (+)
10[d]	*n*Bu	**9a**	**L14**	>99	100:0	10 (+)
11	$tBuOCH_2(CH_2)_2CH_2$	**11a**	**L1**	>99 (80)	100:0	85 (−)
12	$tBuOCH_2(CH_2)_2CH_2$	**11a**	*ent*-**L4**	>99	100:0	79 (−)
13	$tBuOCH_2(CH_2)_2CH_2$	**11a**	**L14**	35	100:0	32 (+)
14	$(CH_3)_2C{=}CH(CH_2)_2$	**10a**	**L1**	>99 (88)	100:0	85 (−)
15	$(CH_3)_2C{=}CH(CH_2)_2$	**10a**	*ent*-**L4**	>99	100:0	85 (−)

[a] Conversion (Conv.) determined by GC–MS and ^{1}H NMR spectroscopy (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] Enantiomeric excess (and configuration or optical rotation in parenthesis) determined by GC on chiral stationary phase. [d] 3 mol% of CuTC and 3.3 mol% of **L***. [e] CuBr used in place of CuTC. [f] 2 mol% of CuTC and 2.2 mol% of **L***.



Scheme 9. Asymmetric allylic alkylation on *trans*-1,4-dichloro- (**5**) and *trans*-1,4-dibromo-2-butene (**8**).

Table 4. CuTC-catalyzed asymmetric allylic alkylation of **8** with RMgX (Scheme 9).

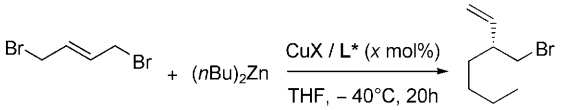
Entry	R	Product	Ligand	Conv. [%][a]	γ/α[b]	*ee* [%][c]
1	*c*Hex	**6b**	**L1**	88	100:0	23 (*S*)
2[d]	*c*Hex	**6b**	**L2**	>99 (99)	100:0	63 (*R*)
3	*c*Hex	**6b**	*ent*-**L3**	>99 (83)	100:0	54 (*R*)
4	$PhCH_2CH_2$	**7b**	**L1**	>99 (94)	100:0	83 (−)
5	$PhCH_2CH_2$	**7b**	**L2**	>99	100:0	76 (+)
6	$PhCH_2CH_2$	**7b**	*ent*-**L4**	>99	100:0	67 (−)
7	*n*Bu	**9b**	**L1**	>99	100:0	86 (−)
8	*n*Bu	**9b**	*ent*-**L4**	91 (80)	100:0	87 (−)
9	$tBuOCH_2(CH_2)_2CH_2$	**11b**	**L1**	>99	100:0	88 (−)
10	$tBuOCH_2(CH_2)_2CH_2$	**11b**	*ent*-**L4**	>99 (77)	100:0	92 (−)
11	$tBuOCH_2(CH_2)_2CH_2$	**11b**	**L14**	>99	100:0	86 (+)
12[d]	$(CH_3)_2C{=}CH(CH_2)_2$	**10b**	**L1**	75	100:0	89 (−)
13[d]	$(CH_3)_2C{=}CH(CH_2)_2$	**10b**	*ent*-**L4**	93 (70)	100:0	94 (−)
14	*i*Bu	**12b**	**L1**	>99 (79)	100:0	85 (−)
15	*i*Bu	**12b**	*ent*-**L4**	>99	100:0	84 (−)

[a]–[d] See Table 3 footnotes.

could not reach higher than 63% *ee* for the addition of the cyclohexyl moiety with ligand **L2** (entry 2), we were pleased to observe that for all other linear Grignard reagents the dibromo substrate **8** afforded higher enantioselectivities than its dichloro counterpart with either ligands **L1** or *ent*-**L4**, again with all reactions undergoing regiospecific γ substitution. When subjecting substrate (*E*)-**8** to a linear Grignard reagent, such as *n*-butylmagnesium chloride, the asymmetric induction was in line with the stereoselectivities obtained with 1,4-dichloro-2-butene (**5**). With catalyst loading as low as 1 mol%, both ligands **L1** and *ent*-**L4** promoted the asymmetric substitution reaction with good selectivity ranging from 86 to 87% *ee* (Table 4, entries 7 and 8). We were pleased to see that under similar conditions, chiral homoallylic bromide adducts with enantioselectivities as high as 92% *ee* could be achieved with the addition of the functionalized Grignard reagent (4-*tert*-butoxybutyl)magnesium bromide with *ent*-**L4** to provide compound (−)-**11b** (Table 4, entry 10). Again, *ee* values higher than 86% could not be reached using the taniaphos-family ligand **L14** (Table 4, entry 11). Moreover, the terpenic bromocitronellene (−)-**10b** was obtained with the best selectivity of this series in 94% *ee* using a CuTC/*ent*-**L4** loading of 3 mol% (Table 4, entry 13). Conversely, ligand **L1** and *ent*-**L4** induced lower values of 85% *ee* with the slightly hindered isobutyl copper reagent **12b** (Table 4, entries 14 and 15). Overall, the dibromo substrates **8** gave (similar or) better results in terms of enantioselectivity than the dichloro derivatives **5** when the two phosphoramidite ligands **L1** and *ent*-**L4** were used.

To compare the use of different Grignard reagents with our procedure, we investigated a corresponding commercially available zinc reagent (*n*-dibutylzinc), which was tested with a set of different copper salts, in THF at −40°C. This methodology was less reactive (maximum 73% conversion) and did not afford as high enantioselectivities (up to 52% *ee* with CuTC/**L1**) (Table 5, entry 1). Nevertheless, this procedure was again exclusively γ selective.

Table 5. Copper-catalyzed asymmetric allylic alkylation of **8** with *n*-dibutylzinc.

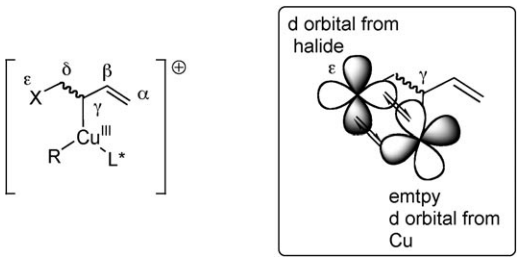


8 **9b**

Entry	CuX/*x* [mol%]	**L***/*x* [mol%]	Conv. [%][a]	γ/α[b]	*ee* [%][c]
1	CuTC/3	**L1**/6	70	100:0	52 (−)
2	CuBr/1	**L1**/2	69	100:0	48 (−)
3	CuBr/1	**L3**/2	73	100:0	0
4	$CuOTf{\cdot}C_6H_6$/1	**L1**/2	37	100:0	40 (−)

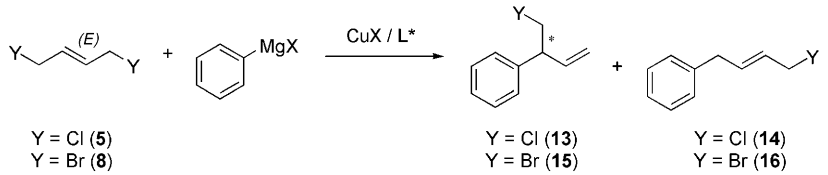
[a]–[c] See Table 3 footnotes.

The impressive regioselectivity observed throughout these examples can be explained by a stabilization of the intermediate Cu^{III} species formed after the oxidative addition of the reagent to the allylic substrate. If one refers to the accepted mechanism for the Cu-catalyzed S_N2' reaction described by Bäckvall et al.,[17] the imperative for a regiospecific branched product formation is a rapid reductive elimination to prevent any isomerization through a transitory π–allyl Cu^{III} species that would support formation of a thermodynamic rearrangement product, the linear S_N2 product. In the presence of a halide in the ε position, one can suppose that this halide gives some electronic density to the empty d orbitals of the electron-poor metal through π bonding. This tethered intermediate would prevent loss of regioselectivity (Scheme 10).



Scheme 10. Internal stabilization of the transient copper(III) species by the adjacent halide.

S_N2' arylation: Throughout the chemical literature the addition of aryl moieties has been a challenging target in asymmetric synthetic allylation.[18] Bäckvall et al. showed that regioselectivity was a key issue for the Cu-catalyzed addition of phenylmagnesium bromide on allylic acetates and chlorides, obtaining the nonregioselective α substituent in higher yields with clean *anti* displacement of the leaving group.[19] To counter the preference of the aryl Grignard towards the α product, addition time of the organomagnesium reagent and catalyst loading had to be increased dramatically to obtain a slightly favored regioselective S_N2' adduct. Only recently, Hoveyda and co-workers have reported one of the rare examples of highly regio- and enantioselective arylation on very specific vinylsilane substrates.[20]



Scheme 11. Asymmetric allylic arylation of difunctionalized substrates **5** and **8**.

In view of our regioselective successes mentioned above, we reasoned that the highly regiocontrolling substrates, namely 1,4-dihalo-2-butenes **5** and **8**, may control a preferential γ insertion of the aryl moiety under copper catalysis (Scheme 11).

Our first results under racemic conditions (Table 6, entries 1 and 2) were very promising and showed in the case of 1,4-dibromo-2-butene (**8**), a clean and complete regiospecific

Table 6. CuTC-catalyzed allylic arylation of 1,4-dihalo-2-butenes **5** and **8** (Scheme 11).[a]

Entry	Substrate	CuX/*x* [mol%]	**L***/*x* [mol%]	*T* [°C]	Conv. [%][b]	S_N2'/ S_N2[c]	*ee* [%][d]
1	**5**, Cl	CuTC	–	−78	>99	80:20[e]	–
2	**8**, Br	CuTC	–	−78	>99	100:0	–
3	**8**, Br	CuTC/1	**L1**/1	−65	>99	100:0	0
4	**8**, Br	CuTC/1	**L2**/1	−65	>99	100:0	0
5	**8**, Br	CuTC/3	*ent*-**L3**/3	−35	97	75:25	2 (−)
6	**8**, Br	CuTC/3	*ent*-**L4**/3	−35	93	78:22	15 (+)
7	**8**, Br	CuTC/3	**L6**/3	−35	97	80:20	22 (−)
8	**8**, Br	CuTC/5	**L11**/5	−35	86	76:24	9 (+)
9	**8**, Br	CuTC/3	**L13**/3	−35	97	36:64	13 (−)
10	**8**, Br	CuTC/3	**L14**/3	−35	98	90:10	3 (+)
11	**8**, Br	CuTC/5	*ent*-**L6**/5	−50	90	90:10	30 (+)
12	**8**, Br	CuTC/3	**L6**/3	−78	>99	99:1	20 (−)
13	**8**, Br	CuTC/5	**L11**/5	−50	90	90:10	25 (+)

[a] Conditions: **5** or **8** (1 mmol), CuTC (*x* mol%), and **L*** (*x* mol%) in CH_2Cl_2 (2 mL) at −78°C with addition of RMgX in Et_2O (1.1 equiv) over 1 h. [b] Conversion (Conv.) determined by GC–MS and ^{1}H NMR spectroscopy. [c] Ratio determined by GC–MS and ^{1}H NMR spectroscopy. [d] Enantiomeric excess determined by chiral GC. [e] Linear S_N2 product of arylation isolated was bromide (*E*)-**16**.

S_N2' arylation into **15**. However, higher substitution patterns were observed as minor byproducts formed in these reactions, that is, 1,2-diphenylbut-3-ene and (*E*)-1,4-diphenylbut-2-ene. These likely result from a second allylic arylation of the preformed linear product **16**, when an excess phenylmagnesium reagent is present. Our first attempts to induce enantioselectivity, using our traditional S_N2' methodology (CuTC, addition of ArMgX over 1 h) with chiral ligands **L1** and **L2** (Table 6, entries 3 and 4), produced exclusively the branched aryl adduct **15** as a racemic mixture. After screening a variety of chiral phosphorous ligands and N-heterocyclic carbenes (NHCs),[21] the biphenol-based ligand **L6** produced the chiral aryl adduct **15** with 22% *ee* at −35°C (Table 6, entry 7). From that point, we investigated different temperatures (Table 6) and copper salts (Table 7). When lowering the temperature to −50°C in the presence of **L6** (Table 6, entry 11), the enantiomeric excess was increased to 30% for the branched adduct **15**, parallel to an increase of the γ selectivity to 90%. Further decrease in the temperature of the reaction to −78°C impaired the enantioselective outcome, while affording a nearly regiospecific S_N2' displacement (Table 6, entry 12). Completing our study by the screening of copper salts (at −50°C and in the presence of ligand *ent*-**L6**) showed that CuTC and $Cu(OAc)_2$ were the most efficient, the latter affording up to 35% *ee* and 95% γ selectivity (Table 7, entry 8).

Table 7. Copper salt screening for the asymmetric allylic arylation of **8** (Scheme 11).[a]

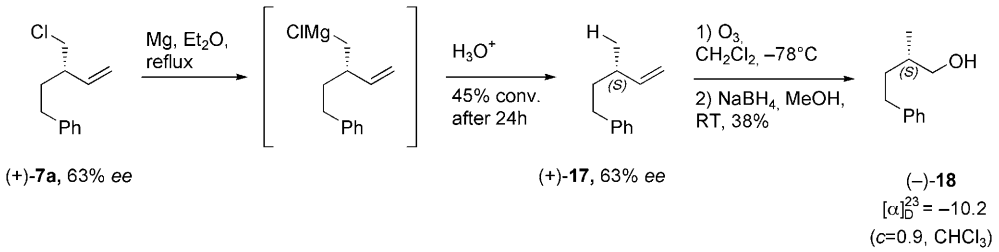
Entry	Cu salt	Ligand	*T* [°C]	Conv. [%][b]	**15**/**16**[c]	*ee* [%][d]
1	CuTC	*ent*-**L6**	−50	90	90:10	30 (+)
2	CuBr	*ent*-**L6**	−50	94	87:13	26 (+)
3	$CuBr{\cdot}SMe_2$	*ent*-**L6**	−50	91	78:22	30 (+)
4	$Cu(OTf)_2$	*ent*-**L6**	−50	86	88:12	9 (+)
5	CuCN	*ent*-**L6**	−50	95	97:3	3 (+)
6	$CuBr_2$	*ent*-**L6**	−50	94	94:6	12 (+)
7	CuCl	*ent*-**L6**	−50	91	92:8	28 (+)
8	$Cu(OAc)_2$	*ent*-**L6**	−50	74	95:5	35 (+)
9	$Cu(OAc)_2{\cdot}2H_2O$	*ent*-**L6**	−50	91	92:8	25 (+)

[a]–[d] See Table 6 footnotes.

Other attempts of arylation on the 1,4-dichloro derivative **5** or using other aryl sources (such as solutions of 4-methoxyphenyl or 4-chlorophenyl Grignard reagents in diethyl ether, or in situ generated zinc-based organocuprates from zinc bromide and aryl Grignard reagents) furnished good-to-high branched-to-linear ratios (up to 94% γ selectivity), without reaching higher than <10% *ee*. Nevertheless, the difunctionalized substrate **8** is a promising substrate for a regioselective allylic arylation and further studies should be undertaken.

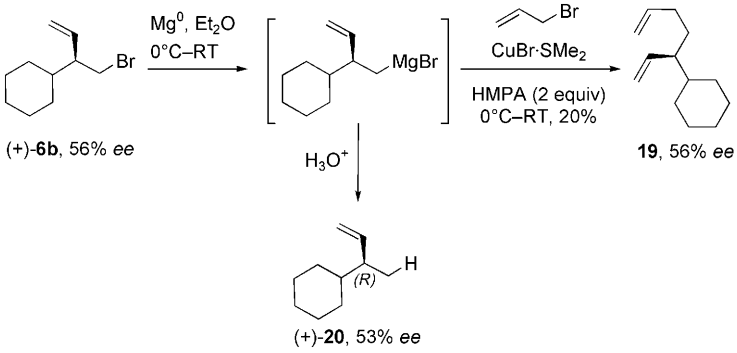
Derivatization of homoallylic chiral halides: The chiral synthons, obtained through the catalyzed asymmetric allylation of 1,4-dichloro- (**5**) and 1,4-dibromo-2-butene (**8**), bear remaining tunable functionalities. To further illustrate the synthetic utility of this methodology, we derivatized the chiral monohalides through electrophilic and nucleophilic pathways.

The remaining halides could be derivatized by electrophilic means through transformation into an organometallic species. To establish the absolute configuration of our chiral adducts, we attempted the reduction of chloride (+)-**7a** (63% *ee*) into (+)-**17** by several means. The Grignard procedure worked best, although conversion was not complete after 24 h (Scheme 12). Nevertheless, following hydrolysis of the organomagnesium reagent, compound (+)-**17** was obtained with complete retention of its chiroptical information. Further ozonolysis and reduction afforded (*S*)-2-methyl-4-



Scheme 12. Reduction of chiral homoallylic chloride (+)-**7a**.

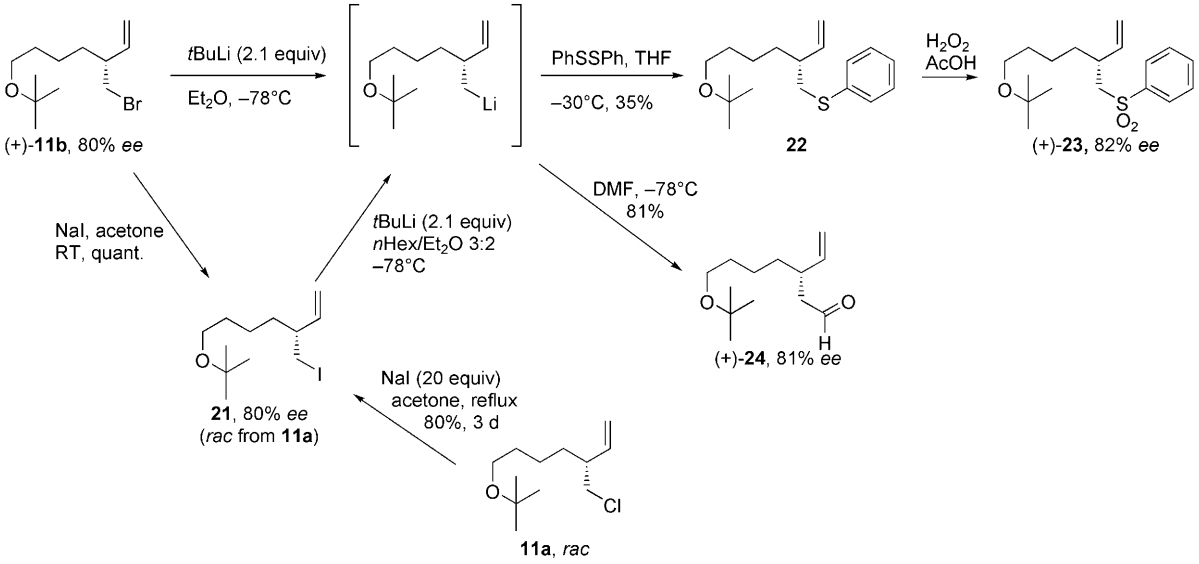
phenylbutan-1-ol (**18**) with 38% yield, which allowed us to determine its absolute stereochemistry by optical rotation. However, a poor reactivity of the chloride can be avoided through transformation into the corresponding iodide (from a Finkelstein reaction of the chiral chloride, see Scheme 14 below). Chiral bromides underwent similar treatments. The formation of a Grignard reagent from the chiral cyclohexyl adduct (+)-**6b** with 56% *ee* and subsequent addition of allyl bromide led to compound **19** with complete retention of the chiral information (Scheme 13).[22] Hydrolysis of a sample of the organomagnesium reagent produced but-3-en-2-ylcyclohexane (**20**) with 53% *ee*. Consequently, by correlation with previous studies, we could assign its absolute configuration.[23] It should be mentioned that the racemic bromide **12b** had already been transformed into a Grignard reagent and used by Jennings-White and Almquist for the synthesis of analogues of keto-dipeptides.[15]



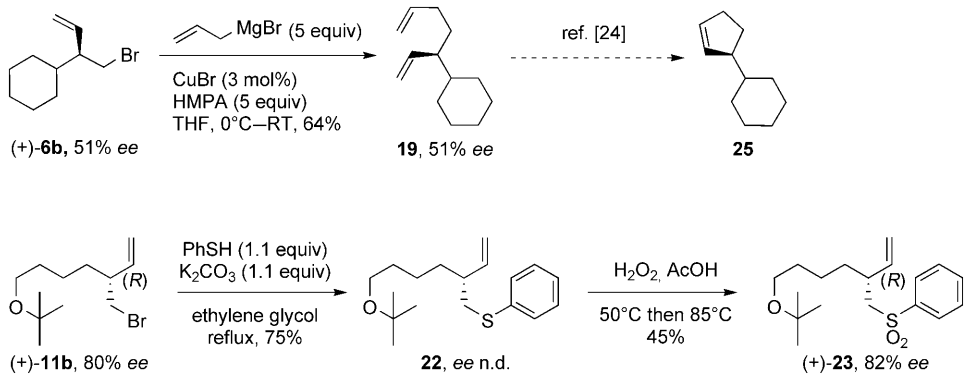
Scheme 13. Electrophilic derivatization of chiral homoallylic bromides **6b** by using a Grignard reagent.

In parallel, organolithium reagents were prepared by treatment of the chiral homoallylic bromide (+)-**11b**, or, better, its iodide counterpart (+)-**21**, with *tert*-butyllithium at −78°C (Scheme 14). Subsequent treatment with diphenyldisulfide afforded **22**, which was further oxidized with hydrogen peroxide into the chiral sulfone (+)-**23** with complete stereoretention. Chiral aldehyde (+)-**24** was obtained by a dimethylformamide (DMF) quench of the organolithium intermediate, and once more we did not observe any loss in the enantiomeric excess (81% *ee*).

Similar derivatization products could be assessed through more straightforward nucleophilic procedures. Indeed, the brominated cyclohexyl adduct, 1-bromobut-3-en-2-ylcyclohexane ((+)-**6b**) with 51% *ee*, was transformed into the hepta-1,6-dien-3-ylcyclohexane (**19**) in 64% yield with no loss of enantioselectivity by adding allylmagnesium bromide (Scheme 15). Previous findings from our research group showed that product **19** can undergo clean ring-closing



Scheme 14. Transformation of chiral homoallylic bromide (+)-**11b** by using an organolithium reagent.

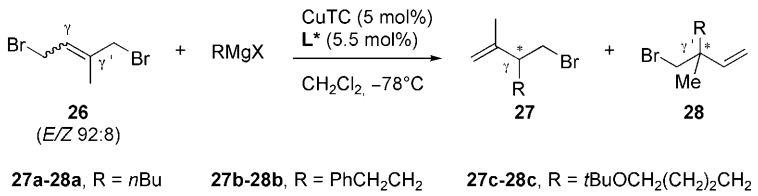


Scheme 15. Nucleophilic derivatization of chiral homoallylic bromides **6b** and **11b**.

metathesis with retention of enantiomeric excess.[24] Conversely, adduct (+)-**11b** with 80% *ee* was derivatized through the addition of benzenethiolate in a good yield of 75% to afford compound **22**, which was further oxidized to give the chiral sulfone (+)-**23** with an optical purity of 82% *ee* (Scheme 15).

Tri- and tetrasubstituted olefins—formation of chiral quaternary centers: As we have achieved good enantioselectivities on the simple β,γ-monosubstituted 1,4-dibromo-2-butene (**8**), we were interested in testing our methodology on more-substituted olefinic patterns. Indeed, our group was the first to disclose a highly regio- and enantioselective methodology for the allylic substitution of a broad range of β-disubstituted allylic electrophiles.[8,25] In such cases and with as low as 3 mol% CuTC in combination with binaphthol-based phosphoramidite ligand (*S*,*SS*)-**L2**, remarkable *ee* values as high as >99% were reached.

We combined both aspects into a single allylic electrophile, the trisubstituted and unsymmetrical (*E*)-1,4-dibromo-2-methylbut-2-ene (**26**; Scheme 16), which was prepared from isoprene by using referenced procedures and was used without further purification.[26] Interestingly, products arising from the γ or γ′ substitution of this challenging unsymmetrical dibromide **26** (i.e., primary versus secondary sites) would evidently afford different products, whilst producing in the latter case an all-carbon quaternary center. We anticipated that such an allylic electrophile would react regioselectively towards the incoming nucleophile depending on the selected ligand. Copper-catalyzed reactions were carried out with an array of aliphatic and functionalized Grignard reagents: *n*-butyl (**a**), phenethyl (**b**), and *tert*-butoxybutyl (**c**) magnesium bromides. The results are summarized in Table 8. As expected, when adding the *n*-butyl Grignard reagent to **26** in the presence of ligand **L2**, product **27a** was formed preferentially (tertiary-to-quaternary ratio 96:4) with 86% *ee* (Table 8, entry 2). The minor quaternary product **28a** (4%) was obtained with 26% *ee*. Similar behaviors were noted with **L2** for the other Grignard reagents. Chiral compounds **27b** and **27c** were obtained with equally good regio- and enantioselectivities (Table 8, entries 7 and 10), with tertiary selectivities of 94 and 98%, respectively, and *ee* values of 87% for both adducts. Under such conditions, the reagent evidently recognizes the substrate as a β-disubstituted allylic electrophile. However, when using the chiral bis-orthomethoxy phosphoramidite ligand *ent*-**L4**, approximately 20% of the chiral adduct **28a** was formed with up to 69% *ee* (Table 8, entry 3). Although this result was noted for the minor product of this reaction, it is one of the highest recorded enantioselectivities for a Cu-catalyzed AAA with a Grignard reagent. Close asymmetric results were obtained for adducts **28b** and **28c** with **L1** or *ent*-**L4**, affording 62 and 67% *ee*, respectively (Table 8, entries 6 and 11). It is worth noting that,



Scheme 16. Unsymmetrical substrate **26** used in Cu-catalyzed AAA.

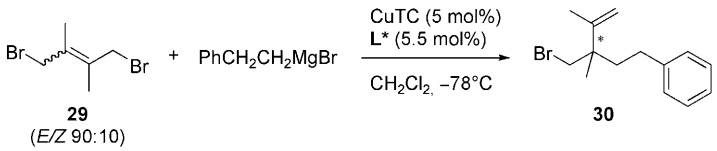
Table 8. Allylic substitution of **26** catalyzed by CuTC (5 mol%) and **L*** (5.5 mol%) in CH_2Cl_2 at −78°C (Scheme 16).

Entry	R	Ligand	Conv. [%][a]	**27**/**28**[a]	*ee* [%] in **27**	*ee* [%][a] in **28**
1	*n*Bu (**a**)	**L1**	100	69:31	4	56
2	*n*Bu (**a**)	**L2**	100	96:04	86	26
3	*n*Bu (**a**)	*ent*-**L4**	100	82:18	50	69
4	*n*Bu (**a**)	**L9**	100	68:32	2	61
5	*n*Bu (**a**)	**L10**	100	94:06	82	47
6	$PhCH_2CH_2$ (**b**)	**L1**	100	75:25	29	62
7	$PhCH_2CH_2$ (**b**)	**L2**	100	94:06	87	6
8	$PhCH_2CH_2$ (**b**)	*ent*-**L4**	100	94:06	54	32
9	$tBuOCH_2(CH_2)_2CH_2$ (**c**)	**L1**	84	72:28	8	59
10	$tBuOCH_2(CH_2)_2CH_2$ (**c**)	**L2**	100	98:02	87	32
11	$tBuOCH_2(CH_2)_2CH_2$ (**c**)	*ent*-**L4**	80	84:16	56	67

[a] Conversion, product ratio, and enantiomeric excess values of S_N2' adducts were determined by chiral GC analysis.

as observed for the monosubstituted dibromide **8**, the reaction was once more highly S_N2'-specific and clean.[27]

To further challenge our system, we attempted the first reported asymmetric Cu-catalyzed alkylation of a difunctionalized tetrasubstituted allylic electrophile, namely, (*E*)-1,4-dibromo-2,3-dimethylbut-2-ene (**29**) (Scheme 17). The latter



29 (*E*/*Z* 90:10) **30**

Scheme 17. Formation of chiral quaternary centers from **29**.

was prepared from 2,3-dimethylbuta-1,3-diene and collected after pentane precipitation as a 90:10 *E*/*Z* mixture without further purification. As illustrated in Table 9, CuTC-catalyzed S_N2' reaction on **29** with a slow addition of the phenethylmagnesium reagent (1.1 equiv) over an hour afforded clean γ-substitution product **30** (γ/α 100:0). However, enantiomeric excess values for the latter were disappointing, with the better ligand (*R*,*SS*)-**L1** affording at the most 30% *ee* (Table 9, entry 1).

Table 9. Allylic substitution of **29** catalyzed by CuTC and chiral phosphoramidite ligands **L*** in CH_2Cl_2 at −78°C (**L*** = **L1**–**L33**; Scheme 17).

Entry	Product	Ligand	Conv. [%][a]	S_N2'/S_N2[a]	*ee* [%][a]
1	**30**	**L1**	100 (60)	100:0	30 (−)
2	**30**	**L2**	100	100:0	24 (+)
3	**30**	*ent*-**L3**	100	100:0	20 (+)
4	**30**	*ent*-**L4**	100	100:0	10 (−)
5	**30**	**L12**	100	100:0[b]	12 (+)
6	**30**	**L19**	100	100:0	27 (−)
7	**30**	**L16**	96	100:0	20 (+)
8	**30**	**L15**	94	100:0	5 (+)

[a] Conversion, product ratio, and enantiomeric excess values of S_N2' adducts were determined by chiral GC analysis (in parentheses, yield of the isolated product after purification by flash chromatography over silica gel). [b] 49% of double-substitution byproducts were observed with a γ/α ratio of 64:36.

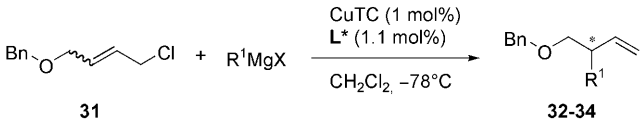
Other difunctionalized substrates—formation of chiral homoallylic alcohol derivatives: Bifunctional allylic substrates, in the form of protected allylic alcohols, silyl ethers,[10,28] or benzyl[16a,28] ethers, have previously been used in copper-catalyzed S_N2' substitution. Our trials to alkylate regio- and enantioselectively the benzyl ether **31** are summarized in Scheme 18. Confirming our prior results on *cis*-type substrates, the allylic alkylation of (*Z*)-**31** with cyclohexylmagnesium reagent proved less stereoselective with up to 43% *ee* with **L3**, in comparison to the reaction carried out on the (*E*)-**31** isomer, which afforded a clean branched adduct **32** (γ/α 100:0) with 82% *ee*. In comparison, addition of the smaller ethyl- and methylmagnesium bromide to **31** produced (−)-**33** and (+)-**34** with 87 and 70% *ee*, respectively. In these last cases, the regioselectivity decreases slightly to 88 and 77% γ selectivity for the ethyl and methyl adducts, respectively.

Another interesting, small, and readily available difunctionalized substrate was thought of. Indeed, an old procedure developed by Colonge and Poilane yields diverse allylic alcohols by the treatment of unprotected (*Z*)-4-chlorobut-2-en-1-ol (**35**) with organomagnesium reagents.[29] Inspired by this study, we investigated a similar reaction under the copper-catalytic S_N2' conditions (Scheme 19).

More than two equivalents of the magnesium reagent were necessary to obtain a complete conversion of **35** (Table 10, entries 1 and 2), the first leading to deprotonation and thus in situ protection of the free alcohol. Analogous S_N2' reactions of **35** were carried out enantioselectively by the slow addition of excess phenethylmagnesium bromide, catalyzed by CuTC (3 mol%) and chiral ligands **L1**–**L4** (3.3 mol%). The moderate optical purities of the newly formed chiral alcohol **36** (44% *ee* at the most with *ent*-**L4**, Table 10, entry 5) are consistent with the poor results obtained previously on the *cis*-difunctionalized substrates (see above). Moreover, the reaction does not proceed with high regiocontrol, affording at the most 71% γ selectivity (Table 10, entry 4).

Conclusion

Difunctionalized allylic substrates are excellent starting materials for the elaboration of more-complex chiral synthons. From these studies it is clear that *E*-configured substrates afford higher enantioselectivites than their *Z* counterparts. Of particular interest is (*E*)-1,4-dibromo-2-butene, because it is an inexpensive commercially available compound (even less expensive than the chloro substrate in the Aldrich catalog), and it affords high enantioselectivities. In addition, the resulting adducts can be further used as electrophilic or nucleophilic reagents.

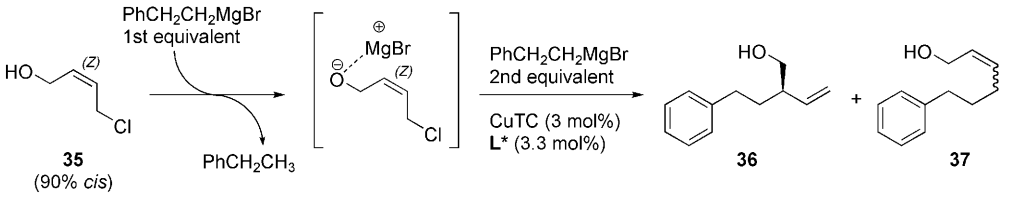


31 **32-34**

on (*Z*)-**31** with (*R*,*SS*)-**L3** R^1 = *c*Hex (**32**), 100% conv., γ/α=100:0, 43% *ee* (−)

on (*E*)-**31** with (*S*,*SS*)-**L2** R^1 = *c*Hex (**32**), 100% conv., γ/α=100:0, 82% *ee* (+)
with (*R*,*RR*)-**L4** R^1 = Et (**33**), 97% conv., 54% yield, γ/α=88:12, 87% *ee* (−)
with (*R*,*RR*)-**L4** R^1 = Me (**34**), 56% conv., 30% yield, γ/α=77:23, 70% *ee* (+)

Scheme 18. Cu-catalyzed AAA on (*E*)- and (*Z*)-**31**.



Scheme 19. Asymmetric copper-catalyzed S_N2' reaction on unprotected allylic alcohol (*Z*)-**35**.

Table 10. CuTC-catalyzed allylic alkylation on (*Z*)-4-chlorobut-2-enol (**35**) with phenethylmagnesium bromide (Scheme 19).

Entry	Equiv. RMgX	Ligand	Conv. [%][a]	**36**/**37**[a]	*ee* [%][b]
1[c]	1.2	*rac*-**L6**	<50	n.d.[d]	–
2[c]	2.5	*rac*-**L6**	100 (14)	53:47	–
3	2.5	**L1**	100 (32)	57:43	34
4	2.5	**L2**	100 (31)	71:29	26
5	2.5	*ent*-**L4**	100 (15)	65:35	44

[a] Conversion and product ratios determined by ^{1}H NMR spectroscopy (in parentheses, yield of isolated product after purification by flash chromatography on silica gel). [b] Enantiomeric excess of branched adduct determined by chiral GC analysis. [c] The racemic equivalent of phosphoramidite ligand **L6** was used. [d] Not determined.

Experimental Section

General remarks: ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker 400F NMR spectrometer in $CDCl_3$ unless otherwise stated, and chemical shifts (δ) are given in ppm relative to residual $CHCl_3$. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), and dt (doublet of triplet). IR spectra were recorded on a Perkin-Elmer FTIR spectrometer. The evolution of reaction was followed by means of TLC and GC–MS (EI mode) on an HP6890 instrument. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter at 20 °C in a 10 cm cell in the stated solvent; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1} (concentration *c* is given as g/100 mL). Enantiomeric excesses were determined by means of chiral GC measurements either on a HP6890 (H_2 as vector gas) or HP6850 (H_2 or He as vector gas) instrument with the stated column. Temperature programs are described as follows: initial temperature [°C]—initial time [min]—temperature gradient [°C min^{-1}]—final temperature [°C]; retention times (t_R) are given in min. In some cases, enantiomeric excess values were determined by means of chiral supercritical fluid chromatography (SFC) measurements on a Berger SFC with the stated column. Gradient programs are described as follows: initial methanol concentration [%]—initial time [min]—percentage gradient of methanol [% min^{-1}]—final methanol concentration [%]. Flash chromatography was performed by using silica gel 32–63 μm, 60 Å. THF, diethyl ether, and dichloromethane were dried by filtration over alumina (activated at 350 °C under a nitrogen atmosphere for 12 h). Copper(I) thiophenecarboxylate (CuTC) was purchased from Frontier Scientific.

Typical procedure for the enantioselective copper-catalyzed allylic substitution with Grignard reagents: CuTC (1 mol %) and chiral ligand (1.1 mol %) were charged in a dried Schlenk tube, under an inert gas, and suspended in dichloromethane (2 mL). The mixture was stirred at room temperature for 30 min, followed by the addition of the allylic halide (1 mmol) at room temperature before cooling the mixture to −78 °C in an ethanol/dry ice bath. The Grignard (3 M in diethyl ether, 1.2 equiv) diluted in CH_2Cl_2 (0.6 mL) was added over 60 min by using a syringe pump. Upon completion of the addition, the reaction mixture was left a further 4 h at −78 °C. The reaction was quenched by addition of aqueous HCl (1 N, 2 mL) and then Et_2O (10 mL). The aqueous phase was separated and further extracted with Et_2O (3×3 mL). The combined organic fractions were washed with brine (5 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The oily residue was purified by means of flash column chromatography. Gas chromatography on a chiral stationary phase showed the enantiomeric excess of the S_N2' product.

(*S*)-(1-Chlorobut-3-en-2-yl)benzene (13): R_f = 0.88 (silica gel, pentane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.32 (m, 2H), 7.29–7.23 (m, 3H), 6.02 (ddd, ^1J = 7.3 Hz, ^2J = 10.4 Hz, ^3J = 17.4 Hz, 1H), 5.23 (d, ^2J = 10.3 Hz, 1H), 5.17 (d, ^3J = 17.2 Hz, 1H), 3.79 (d, J = 2.0 Hz, 1H), 3.77 (s, 1H), 3.70–3.65 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.8, 138.1, 128.8, 128.8, 127.9, 127.9, 127.3, 117.2, 52.0, 47.9 ppm; the enantiomeric excess was measured by chiral GC with a Hydrodex B6-TBDM, hydrogen flow (program: 70–0–1–170); t_R = 38.30 (−), 40.98 (+).

(+)-(1-Bromobut-3-en-2-yl)benzene (15): R_f = 0.79 (silica gel, pentane); $[\alpha]_D^{22}$ = +12.0 (c = 0.28, $CHCl_3$) for 35 % *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.34 (m, 2H), 7.30–7.29 (m, 1H), 7.28–7.22 (m, 2H), 6.03 (ddd, ^1J = 10.4 Hz, ^2J = 7.3 Hz, ^3J = 17.4 Hz, 1H), 5.22 (dd, ^1J = 10.4 Hz, ^4J = 1.0 Hz, 1H), 5.17 (dd, ^3J = 17.2 Hz, ^4J = 1.3 Hz, 1H), 3.71 (m, 1H), 3.65 (s, 1H), 3.63 ppm (d, J = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.3, 138.6, 128.9, 128.9, 127.8, 127.8, 127.4, 117.2, 51.9, 36.5 ppm; IR (neat): $\tilde{\nu}$ = 3063 (w), 2959 (w), 2923 (w), 1873 (w), 1640 (w), 1601 (w), 1493 (m), 1453 (m), 1416 (w), 1258 (w), 1220 (m), 1074 (w), 989 (m), 920 (s), 762 (m), 748 (m), 698 (s), 650 cm^{-1} (m); MS (EI mode): m/z (%): 212 (21), 210 (21), 154 (17), 131 (22), 118 (20), 117 (100), 116 (14), 115 (42), 91 (30), 77 (16), 51 (19); HRMS (EI mode): m/z calcd for $C_{10}H_{10}Br$: 210.0044; found: 210.0044; the enantiomeric excess was measured by chiral GC with a Chirasil-Dex CB, helium flow (program: 70–0–1–170); t_R = 47.55 (−), 48.33 (+).

(+)-(*S*)-(3-Methylpent-4-enyl)benzene (17): $[\alpha]_D^{22}$ = +1.4 (c = 0.9 in $CHCl_3$) for 63 % *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 5H), 5.77 (ddd, ^1J = 7.6 Hz, ^2J = 10.1 Hz, ^3J = 17.4 Hz, 1H), 5.03 (d, J = 17.2 Hz, 1H), 5.00 (d, J = 7.3 Hz, 1H), 2.71–2.57 (m, 2H), 2.24–2.17 (m, 1H), 1.68–1.62 (m, 1H), 1.06 ppm (d, J = 6.56 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.6, 142.9, 128.5, 128.4, 125.8, 113.1, 38.6, 37.6, 33.7, 20.4 ppm; MS (EI mode): m/z (%): 160 (14), 145 (19), 131 (9), 117 (11), 104 (100), 91 (96), 77 (13), 65 (14), 55 (7); the enantiomeric excess was measured by chiral GC with a Hydrodex-B-3P column, hydrogen flow (program: 70–0–1–170); t_R = 23.48 (+), 24.28 (−).

(−)-(*S*)-2-Methyl-4-phenylbutan-1-ol (18): A solution of olefin (+)-**13** (0.86 mmol) in dry CH_2Cl_2 (30 mL) was cooled to −78 °C, and ozone was passed through until a persisting blue color appeared (≈10 min). After completion of the reaction, the excess ozone was removed by purging with O_2 and N_2. After cooling the system with an ice bath, sodium borohydride (1.72 mmol) and methanol (5 mL) were added to the reaction. The resulting mixture was permitted to warm to RT and was stirred overnight. More $NaBH_4$ (1.72 mmol) was added at 0 °C, while allowing the temperature to rise to RT, to decompose the ozonide. After 7 d, the reaction was hydrolyzed with H_2O (15 mL), extracted with Et_2O, and dried over Na_2SO_4. The crude product was then subjected to column chromatography on silica gel (pentane/Et_2O 75:25). The alcohol was obtained as a slightly yellow oil (0.33 mmol, 38 % yield). $[\alpha]_D^{22}$ = −10.2 (c = 0.9 in $CHCl_3$) for 63 % *ee*; (ref. [30]: $[\alpha]_D^{22}$ = +20.0 (c = 1.5 in $CHCl_3$) for 99 % *ee* (*R*)); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.26 (m, 2H), 7.20–7.16 (m, 3H), 3.51 (dd, ^1J = 38.1 Hz, ^2J = 5.8 Hz, 1H), 3.51 (dd, ^2J = 5.8 Hz, ^3J = 17.2 Hz, 1H), 2.75–2.56 (m, 2H), 1.81–1.63 (m, 2H), 1.49–1.38 (m, 2H), 0.99 ppm (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 128.5, 125.9, 68.3, 35.5, 35.1, 33.4, 16.6 ppm.

(−)-[3-(Bromomethyl)-4-methylpent-4-enyl]benzene (27b): R_f = 0.95 (silica gel, pentane); $[\alpha]_D^{22}$ = −10.3 (c = 1.1 in $CHCl_3$) for 62 % *ee* (contain-

ing 3% of **28b** with 7% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.27 (m, 2H), 7.21–7.17 (m, 3H), 4.99 (d, J = 1.3 Hz, 1H), 4.86 (s, 1H), 3.40 (d, J = 6.6 Hz, 2H), 2.67–2.43 (m, 3H), 1.96–1.87 (m, 1H), 1.72 (m, 1H), 1.72 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.3, 142.0, 128.5, 128.5, 126.0, 114.3, 48.9, 36.6, 33.5, 33.4, 18.9 ppm; MS (EI mode): *m*/*z* (%): 210 (2), 174 (2), 117 (7), 105 (42), 104 (100), 92 (10), 91 (58), 77 (8), 69 (17), 67 (6), 65 (10); the enantiomeric excess was measured by chiral GC with a Hydrodex B6-TBDM column, hydrogen flow (program: 100–0–1–170); t_R = 46.89 (+), 47.4 (−) [for **28b**: the enantiomeric excess was measured by chiral GC with a Chirasil Dex CB, helium flow (program: 100–0–1–170); t_R = 51.98 (major), 52.3 (minor)].

(−)-3-(Bromomethyl)-7-*tert*-butoxy-2-methylhept-1-ene (27c): R_f = 0.46 (silica gel, pentane/Et_2O 97.5:2.5); $[\alpha]_D^{22} = -8.0$ (c = 1.13 in $CHCl_3$) for 87% *ee* (containing 2% of **28c** with 37% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.89 (s, 1H), 4.78 (s, 1H), 3.38 (d, J = 1.3 Hz, 1H), 3.36 (d, J = 2.3 Hz, 1H), 3.32 (t, J = 6.6 Hz, 2H), 2.45–2.38 (m, 1H), 1.66 (s, 3H), 1.58–1.22 (m, 6H), 1.17 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.8, 113.6, 72.6, 61.4, 49.4, 36.8, 31.6, 30.6, 27.7, 24.0, 18.9 ppm; MS (EI mode): *m*/*z* (%): 263 (5), 261 (5), 141 (6), 123 (29), 96 (10), 81 (15), 69 (26), 67 (12), 59 (22), 57 (100), 55 (15); the enantiomeric excess was measured by chiral GC with a Hydrodex B6-TBDM column, hydrogen flow (program: 100–0–1–170); t_R = 37.29 (+), 37.64 (−) [for **28c**: the enantiomeric excess was measured by chiral GC with a Hydrodex B3P, hydrogen flow (program: 100–60–1–110–30–20–170); t_R = 90.00 (major), 90.86 (minor)].

(−)-[3-(Bromomethyl)-3,4-dimethylpent-4-enyl]benzene (30): $[\alpha]_D^{22} = -3.0$ (c = 1.03 in $CHCl_3$) for 30% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.26 (m, 2H), 7.21–7.16 (m, 3H), 5.04 (t, J = 1.2 Hz, 1H), 4.86 (s, 1H), 3.49 (d, J = 10.1 Hz, 1H), 3.41 (d, J = 10.1 Hz, 1H), 2.56–2.38 (m, 2H), 1.80 (s, 3H), 1.81–1.63 (m, 2H), 1.26 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 146.8, 142.5, 128.6 (2×), 128.4 (2×), 126.0, 113.7, 43.8, 43.6, 31.2, 22.9, 19.5 ppm; MS (EI mode): *m*/*z* (%): 268 (1), 266 (1), 164 (39), 162 (40), 131 (13), 117 (11), 105 (79), 104 (97), 92 (22), 91 (88), 84 (17), 83 (100), 82 (13), 81 (21), 79 (14), 77 (13), 69 (14), 67 (15), 65 (12), 55 (23); the enantiomeric excess was measured by chiral GC with a Hydrodex B6-TBDM, hydrogen flow (program: 120–0–1–170); t_R = 33.98 (+), 34.32 (−).

(+)-1-[(2-Cyclohexylbut-3-enyloxy)methyl]benzene (32): R_f = 0.79 (silica gel, pentane); $[\alpha]_D^{28} = +5.9$ (c = 1.00 in $CHCl_3$) for 36% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5H), 5.71 (ddd, J = 9.1, 10.3, 17.0 Hz, 1H), 5.07 (d, J = 10.3 Hz, 1H), 5.03 (d, J = 17.7 Hz, 1H), 4.51 (s, 2H), 3.47 (m, 2H), 2.22–2.15 (m, 1H), 1.72–1.61 (m, 5H), 1.28–0.87 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.0, 128.4, 128.4, 127.7, 127.6, 127.6, 116.3, 73.1, 71.8, 50.0, 38.6, 31.3, 29.6, 26.8, 26.7 ppm; MS (EI mode): *m*/*z* (%): 244 (4), 171 (1), 161 (2), 153 (5), 135 (11), 123 (7), 104 (9), 91 (100), 81 (44), 67 (18), 55 (15); the enantiomeric excess was measured by chiral SFC with an OD-H column (program: 0–5–1–15; 200 bar, 2 mL min^{-1}, 30 °C); t_R = 5.85 (−), 6.69 (+).

(−)-(*R*)-1-[(2-Ethylbut-3-enyloxy)methyl]benzene (33): R_f = 0.5 (silica gel, pentane/Et_2O 98:2); (ref. [16a]) $[\alpha]_D^{28} = +19.0$ (c = 1.1 in $CHCl_3$) for 94% *ee* on *ent*-**33**); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.33 (m, 4H), 7.30–7.26 (m, 1H), 5.66 (ddd, ^1J = 8.3 Hz, ^2J = 9.8 Hz, ^3J = 17.9 Hz, 1H), 5.10–5.06 (m, 2H), 4.52 (s, 2H), 3.40 (d, J = 6.3 Hz, 2H), 2.31–2.22 (m, 1H), 1.62–1.52 (m, 1H), 1.34–1.23 (m, 1H), 0.88 ppm (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.2, 138.8, 128.5, 127.7, 127.6, 115.6, 73.7, 73.1, 45.9, 24.2, 11.6 ppm; MS (EI mode): *m*/*z* (%): 190 (5), 189 (4), 104 (6), 92 (11), 91 (100), 65 (13); the enantiomeric excess was measured by chiral HPLC with an OD-H column (5 μL, 99.8:0.2 *n*Hex/*i*PrOH, 1 mL min^{-1}, 40 °C); t_R = 5.66 (−), 6.14 (+).

(+)-(*R*)-1-[(2-Methylbut-3-enyloxy)methyl]benzene (34): R_f = 0.85 (silica gel, pentane); (ref. [16a]: $[\alpha]_D^{28} = -6.0$ (c = 1.1 in $CHCl_3$) for 92% *ee* on *ent*-**34**); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.27 (m, 5H), 5.81 (ddd, ^1J = 17.2 Hz, ^2J = 10.4 Hz, ^3J = 6.8 Hz, 1H), 5.08 (dt, ^1J = 17.4 Hz, ^4J = 1.8 Hz, 1H), 5.02 (d, ^2J = 10.3 Hz, 1H), 4.53 (s, 2H), 3.35 (dd, J = 6.6, 39.6 Hz, 1H), 3.35 (dd, J = 6.6, 21.5 Hz, 1H), 2.51 (m, J = 6.6 Hz, 1H), 1.04 ppm (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.5, 138.6, 128.5, 127.7, 127.6, 114.2, 75.2, 73.1, 38.0, 16.8 ppm; MS (EI mode): *m*/*z* (%): 176 (5), 175 (5), 92 (12), 91 (100), 65 (15), 55 (9); the enantiomeric excess was measured by chiral HPLC with an OD-H column (5 μL, 99.9:0.1 *n*Hex/*i*PrOH, 0.5 mL min^{-1}, 15 °C); t_R = 16.68 (+), 18.41 (−).

(+)-2-Phenethylbut-3-en-1-ol (36): R_f = 0.36 (silica gel, pentane/Et_2O 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.26 (m, 2H), 7.20–7.17 (m, 3H), 5.65 (ddd, ^1J = 8.8 Hz, ^2J = 10.1 Hz, ^3J = 17.2 Hz, 1H), 5.24 (dd, ^1J = 1.5 Hz, ^2J = 10.1 Hz, 1H), 5.19 (dd, ^1J = 1.0 Hz, ^2J = 17.2 Hz, 1H), 3.61–3.43 (m, 2H), 2.74–2.53 (m, 2H), 2.32–2.23 (m, 1H), 1.80–1.54 (m, 2H), 1.50 ppm (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.3, 139.7, 128.5, 128.5, 125.9, 118.2, 65.7, 46.7, 33.4, 32.6 ppm; the enantiomeric excess was measured by chiral GC with a Chirasil-Dex CB column, helium flow (program: 80–0–1–170); t_R = 61.51, 62.42.

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