DOI: 10.1002/adsc.200800086

β- and γ-Disubstituted Olefins: Substrates for Copper-Catalyzed Asymmetric Allylic Substitution

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Received: February 9, 2008; Published online: April 18, 2008

Dedicated to Professor Andreas Pfaltz on the occasion of his 60th birthday.

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

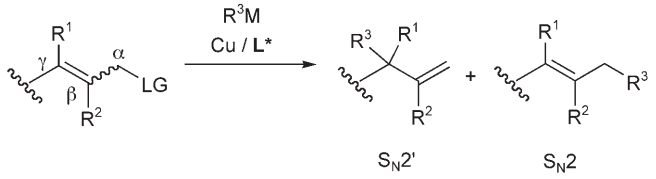
Abstract: The copper-catalyzed asymmetric allylic alkylation has shown through many examples that it is a powerful means to generate stereogenic centers with mono β- and γ-substituted olefinic substrates. However, little has been reported about more substituted olefinic patterns, such as β-disubstituted allylic electrophiles. In this paper, we show that a simple procedure using easily accessible Grignard reagents and as low as 3 mol% of copper/ligand can promote high to nearly perfect enantioselectivities (up to >99% *ee*) with very good γ-selectivities on a wide panel of aliphatic or aromatic β-disubstituted substrates.

Keywords: allylic alkylation; allylic compounds; asymmetric catalysis; copper; nucleophilic substitution

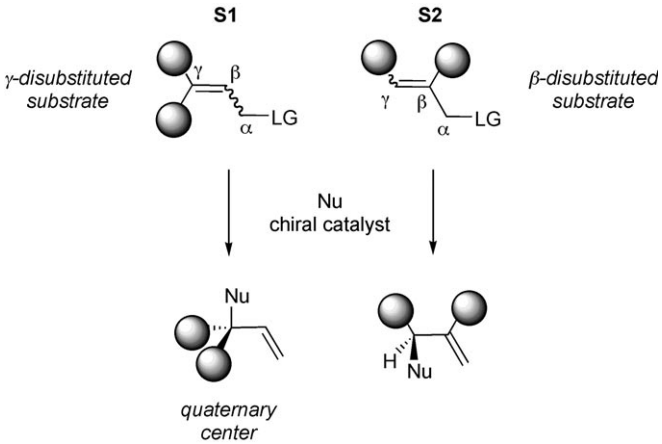
Introduction

The allylic alkylation, also known as an S_N2' reaction, has become a key reaction for creating carbon-carbon bonds.[1] In the literature many metals have been found to catalyze such reactions with the use of a wide diversity of soft or hard nucleophiles.[2] Catalytic amounts of copper usually enable a highly γ-regioselective process using different organometallic reagents as nucleophilic sources.[3] Numerous enantioselective variants have been developed over the past years with a range of easily accessible organometallic reagents such as Grignard reagents,[4] organozinc[5–6] and more recently alkylaluminum[7] reagents, all of which have been used with considerable success.

The olefinic patterns in early studies from our group or others on the asymmetric Cu-catalyzed S_N2' reaction were limited to simple γ- and β- monosubstituted frameworks ($R^1 = R^2 = H$; Scheme 1). Trisubstituted allylic substrates – such as **S1** and **S2**, if *E* and *Z* isomers are not a problematic issue – can also undergo asymmetric allylic substitution (Scheme 2) but have been poorly documented until recently. The formation of quaternary carbon stereogenic centers could be realized through S_N2' substitution of γ-disubstituted allylic substrates (**S1**). However, few groups



Scheme 1.



Scheme 2.

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have managed to exploit this reaction with good regio-, chemo- and enantioselectivities, with the notable exception of the work of Hoveyda and co-workers.[6] Conversely, β-disubstituted olefinic systems (**S2**-type allylic substrates) had not yet been covered, other than in stereoselective additions to Baylis–Hilman-derived allylic electrophiles as described by Woodward and co-workers.[8] In addition, this last example was mechanistically closer to a conjugate (Michael) addition, followed by elimination of the chloride through the allylic rearrangement of the intermediate enolate. In 2006, a preliminary report by our group described the first successful attempts on these unexplored β-disubstituted target structures.[9]

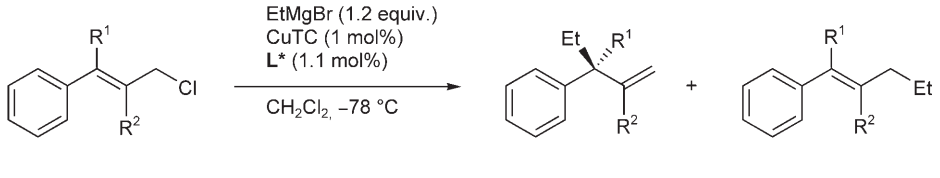
Result and Discussion

With the simplest model of trisubstituted olefins at hand, namely β-methylcinnamyl chloride (**1**) and γ-methylcinnamyl chloride (**2**) (Scheme 3), we conducted a screening of different biphenol-[10] and binaphthol-based[11,12] phosphoramidite ligands (Figure 1).

Results for the first study on *trans*-(3-chloro-2-methylprop-1-enyl)benzene **1** are listed in Table 1. The allylic substitution of **1** by the slow addition of ethylmagnesium bromide, catalyzed by copper thiophenecarboxylate (CuTC; 1 mol%) and different phosphoramidite ligands (1.1 mol%), gave adducts (**3**) with poor-to-good γ/α ratios and provided high enantiomeric excesses of up to 96% *ee* with ligand (*S,SS*)-**L2** (Table 1, entry 2). Similar results were obtained with the *para*-methoxy-substituted ligand **L8** of same diastereomeric nature, which suggested that there was no electronic effect of the methoxy function on the stereoselectivity of the reaction. Conversely, the *ortho*-methoxy substituents present on ligand (*S,SS*)-**L5**, otherwise highly effective in different reactions with copper or iridium catalysis on unsubstituted cinnamyl substrates,[12,13] affected negatively the asymmetric outcome with lower *ee* values of 80% (Table 1, entry 6). Interestingly, although most equivalent combinations of (*S*)-binaphthol unit and (*S,S*)-amines would enable a similar positive rotation in products **3a**, the later ligand **L5** produced the enantiomer (−)-**3a**. This observation suggests that the *ortho*-methoxy moieties are coordinating/chelating and would modify the conformation of the intermediate copper catalyst.

To further improve the selectivity in favor of the γ product, catalyst loading of CuTC/**L2** was increased to an optimal amount of 3 mol% (Table 2, entry 3), which afforded 92% S_N2'-selectivity and in parallel improved the enantioselectivity from 96% to 98% *ee*. By accelerating the reaction and thus preventing the formation of a dialkyl-cuprate complex in the reaction medium, the catalyst loading is an important parameter that favors the formation of the branched product (**3a**).[2,12c,14]

Because the formation of enantiomerically enriched quaternary centers is highly valuable and could easily be accessed through an asymmetric allylic substitution, the γ-methylcinnamyl chloride (**2**) was subjected



Scheme 3. Enantioselective allylic substitution of β-methylcinnamyl (**1**) and γ-methylcinnamyl chlorides (**2**).

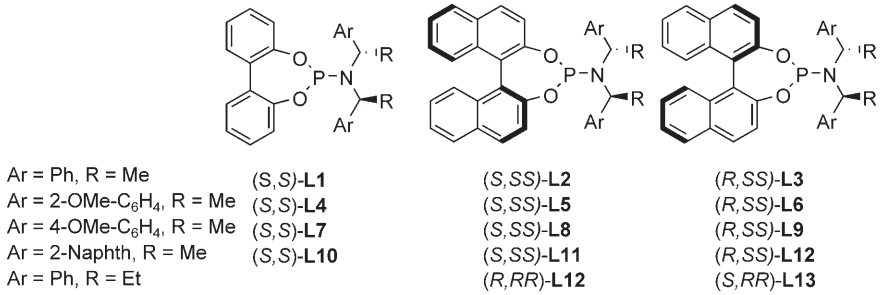


Figure 1. Ligands used for the stereoselective allylic substitution of trisubstituted allylic halides.

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Table 1. Ligand screening for the copper-catalyzed allylic substitution of β-methylcinnamyl chloride (**1**) with ethylmagnesium bromide (L* = **L1–L12**; Figure 1).

Entry[a]	Substrate	Ligand	Yield [%][b]	S_N2'/ S_N2[c]	*ee* [%][d]
1	**1** (R^1 = H, R^2 = Me)	**L1** (*SS*)	(>99)	65/35	53 (+)
3	**1** (R^1 = H, R^2 = Me)	**L2** (*S,SS*)	(>99)	87/13	96 (+)
2	**1** (R^1 = H, R^2 = Me)	**L3** (*R,SS*)	(>99)	30/70	27 (−)
4	**1** (R^1 = H, R^2 = Me)	**L4** (*SS*)	(>99)	89/11	81 (−)
6	**1** (R^1 = H, R^2 = Me)	**L5** (*S,SS*)	(>99)	87/13	80 (−)
5	**1** (R^1 = H, R^2 = Me)	**L6** (*R,SS*)	(>99)	73/27	61 (−)
7	**1** (R^1 = H, R^2 = Me)	**L7** (*SS*)	(>99)	71/29	52 (+)
9	**1** (R^1 = H, R^2 = Me)	**L8** (*S,SS*)	(>99)	86/14	96 (+)
8	**1** (R^1 = H, R^2 = Me)	**L9** (*R,SS*)	(>99)	37/63	26 (−)
10	**1** (R^1 = H, R^2 = Me)	**L10** (*SS*)	81	56/44	15 (+)
12	**1** (R^1 = H, R^2 = Me)	**L11** (*S,SS*)	78	59/41	71 (+)
11	**1** (R^1 = H, R^2 = Me)	**L12** (*R,SS*)	89	31/69	22 (−)

[a] *Conditions:* **1** (1 mmol), CuTC (1 mol%), and L* (1.1 mol%) in CH_2Cl_2 (2 mL) at −78 °C with addition of EtMgBr in Et_2O (1.2 equiv.) over 1 h.
[b] Yield of isolated products after purification by column chromatography on silica gel, (in parentheses, conversion determined by GC-MS).
[c] Ratio determined by ^{1}H NMR spectroscopy and GC-MS.
[d] Enantiomeric excess determined by GC analysis on chiral stationary phase.

Table 2. Variation of the catalyst loading [CuTC/(*S,SS*)-**L2**] for the addition of ethylmagnesium bromide (1.2 equiv.) to β-methylcinnamyl chloride (**1**).

Entry	Substrate	Cat. loading [mol%]	Conv. [%]	S_N2'/ S_N2	*ee* [%]
1	**1**	1	>99	87/13	96 (+)
2	**1**	2	>99	90/10	96 (+)
3	**1**	3	>99 (87)	92/8	98 (+)

Table 3. Ligand screening for the copper-catalyzed allylic substitution of γ-methylcinnamyl chloride (**2**) with ethylmagnesium bromide (L* = **L1–L12**; Scheme 3)

Entry[a]	Substrate	Ligand	Conv. [%][b]	S_N2'/ S_N2[c]	*ee* [%][d]
1	**2** (R^1 = Me, R^2 = H)	**L1** (*SS*)	>99	70/30	29 (−)
2	**2** (R^1 = Me, R^2 = H)	**L2** (*S,SS*)	>99	44/56	26 (−)
3	**2** (R^1 = Me, R^2 = H)	**L3** (*R,SS*)	>99	59/41	11 (−)
4	**2** (R^1 = Me, R^2 = H)	**L4** (*SS*)	>99 (54)	86/14	20 (+)
5	**2** (R^1 = Me, R^2 = H)	**L5** (*S,SS*)	>99	77/23	35 (+)
6	**2** (R^1 = Me, R^2 = H)	**L6** (*R,SS*)	>99	44/56	30 (−)
7	**2** (R^1 = Me, R^2 = H)	**L7** (*SS*)	>99	80/20	26 (−)
8	**2** (R^1 = Me, R^2 = H)	**L8** (*S,SS*)	>99	61/39	15 (−)
9	**2** (R^1 = Me, R^2 = H)	**L9** (*R,SS*)	>99	73/27	20 (−)
10	**2** (R^1 = Me, R^2 = H)	**L10** (*SS*)	>99	46/54	20 (−)
11	**2** (R^1 = Me, R^2 = H)	**L11** (*S,SS*)	>99	87/13	5 (−)
12	**2** (R^1 = Me, R^2 = H)	**L12** (*R,SS*)	>99	52/48	7 (−)

[a] *Conditions:* same as Table 1.
[b] Yield of isolated products after purification by column chromatography on silica gel, (in parentheses, conversion determined by GC-MS).
[c] Ratio determined by ^{1}H NMR spectroscopy and GC-MS.
[d] Enantiomeric excess determined by GC analysis on chiral stationary phase.

to the same panel of phosphoramidite ligands used above. As summarized in Table 3, using our developed methodology with organomagnesium reagents under CuTC catalysis, only moderate regioselectivities and poor *ee* values were obtained. The bis-*ortho*-methoxyphosphoramidite ligand (*S,SS*)-**L5** developed by our group, which afforded excellent enantioselectivities on less substituted cinnamyl-type substrates, gave our best result for the formation of **4a** with a poor 35% *ee* and 77% branched product (Table 3, entry 5). Such a process with ethylmagnesium bromide and catalytic CuTC/**L5** being obviously not optimal on the trisubstituted olefin **2**, we additionally attempted the *in situ* generation of an ethylzinc reagent (Et_2Zn or EtZnBr) – starting from the corresponding Grignard reagent and zinc dibromide (0.5 or 1 equivalent) in THF[13] – using ligand (*S,SS*)-**L5**. These last conditions afforded excellent regioselectivities (branched-to-linear ratio > 99:1), alas as a racemic mixture.

Aryl β-Disubstituted Allylic Chlorides

With the set of optimal conditions for β-disubstituted aryl allylic chlorides at hand, we investigated differently substituted cinnamyl substrates, with electron-richer or poorer aryl scaffolds and with higher substi-

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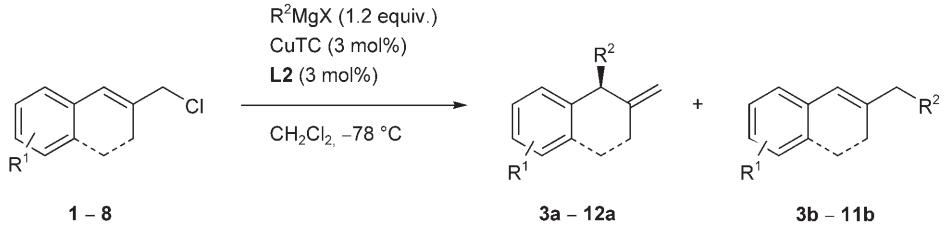
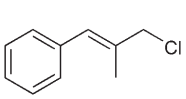
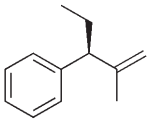
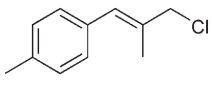
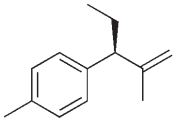
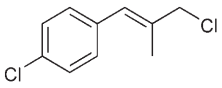
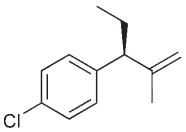
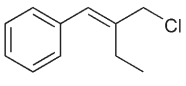
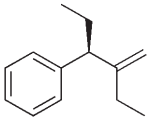
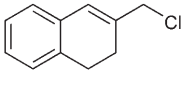
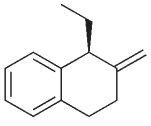


Scheme 4. Stereoselective S_N2' alkylation on allylic chlorides **1**–**8**.

tution at the β-position (Scheme 4). Results for the addition of ethylmagnesium bromide catalyzed with CuTC (3 mol%) and chiral ligand (*S*,SS)-**L2** are collected in Table 4. Overall results are comparable to the model reaction on **1** (Table 4, entry 1) with very good enantioselectivities for either *para*-tolyl (**5**) or *para*-chlorophenyl (**6**) substrates, both affording 96% *ee* (Table 4, entries 2 and 3). Owing to the higher steric hindrance generated by the β-ethyl group on compound **7**, we observed a slight decrease in regio- and enantioselectivities with 83% γ-selectivity and 92% *ee* (Table 4, entry 4). At last, the 3-(chloromethyl)-1,2-dihydronaphthalene (**8**) presented a noteworthy advantage to the cinnamyl derivatives, as its structure is configurationally locked as a *trans* isomer. This allowed for a highly asymmetric allylic substitution with an ethylmagnesium reagent reaching up to 98% *ee* for **12a**. Conversely, the lower flexibility of the bicyclic allylic electrophiles or its electronically richer nature afforded a γ-selectivity close to the ones observed for **9** and **11** with a branched-to-liner ratio of 83/17.

Table 4. Enantioselective Cu-catalyzed allylic alkylation on **1–8** with EtMgBr (R^2 = Et; Scheme 4).

Entry[a]	Substrate	Product	Yield [%][b]	S_N2'/S_N2[c]	*ee* [%][d]
1	 **1**	 **3a**	87	92:8	98 (+)
2	 **5**	 **9a**	85	84:16	96 (+)
3	 **6**	 **10a**	87	92:8	96 (+)
4	 **7**	 **11a**	83	83:17	92 (+)
7	 **8**	 **12a**	87	83:17	98 (+)

[a] *Conditions:* same as Table 1.
[b] Yield of isolated products after purification by column chromatography on silica gel.
[c] Ratio determined by ^{1}H NMR spectroscopy and GC-MS.
[d] Enantiomeric excess determined by GC analysis on chiral stationary phase.

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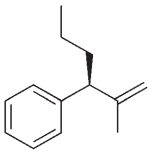
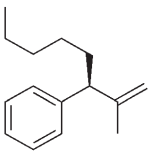
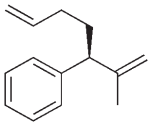
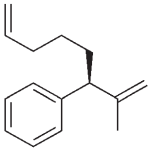
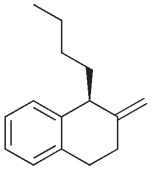
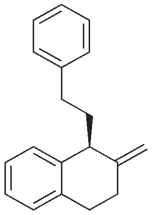
With these encouraging results at hand, other linear Grignard reagents were tested, as illustrated in Table 5. Very good enantioselectivities of up to 98% *ee* were achieved in the allylic substitution of substrates **1** and **8** using linear saturated organomagnesium reagents with the CuTC/**L2** catalytic mixture to give products **13**–**18**. The lower branched-to-linear ratios of 79/21 and 82/18 obtained, respectively, with both but-3-enylmagnesium bromide (Table 5, entry 3) and pent-4-enyl bromide (Table 5, entry 5) were im-

Table 5. Enantioselective allylic alkylation of **1** and **8** with R^2MgX (Scheme 4).

Entry	Substrate	R^2MgX	Product	Yield [%][a]	b/l[b]	*ee* [%][c]
1	**1**	*n*-propylMgCl	 **13a**	85	84/16	97 (+)
2	**1**	*n*-hexylMgCl	 **14a**	83	83/17	96 (+)
3	**1**	but-3-enylMgBr	 **15a**	84	79/21	95 (+)
4[d]	**1**	but-3-enylMgBr	**15a**	(>99)	89/11	97 (+)
5	**1**	pent-4-enylMgBr	 **16a**	87	82/18	93 (+)
6[d]	**1**	pent-4-enylMgBr	**16a**	(>99)	87/13	96 (+)
7	**8**	*n*-butylMgCl	 **17a**	62	71/29	98 (+)[16]
8	**8**	$PhCH_2CH_2MgBr$	 **18a**	62	78/22	96.5 (+)

[a] Yield of isolated products after purification by column chromatography on silica gel, (in parentheses, conversion determined by GC-MS).
[b] Ratio determined by ^1H NMR spectroscopy and GC-MS.
[c] Enantiomeric excess determined by GC analysis on chiral stationary phase.
[d] Slow addition of the Grignard reagent over a period of four hours.
[e] Ligand (*R,SS*)-**L3** was used.

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proved by a slower addition of the reagent over a period of four hours (to 89 and 87% γ-selectivity for **15a** and **16a**, respectively). This also afforded a slight increase in the enantiomeric excess. However such a methodology could not be transposed to secondary organomagnesium reagents. Indeed, when using isopropylmagnesium chloride on **1** in the presence of ligand (*S,SS*)-**L2** – although regioselectivities were in favor of the branched product (γ/α 86/14) – the *ee* dropped below 28% *ee*. The diastereomeric ligand (*R,SS*)-**L3**, on the other hand, yielded 52% *ee*.[15] Both *n*-butylmagnesium and phenethylmagnesium halide reagents would yield excellent enantiomeric excess on the bicyclic substrate **8**, affording 98% *ee* and 97% *ee* for **17a** and **18a**, respectively (Table 5, entries 7 and 8).

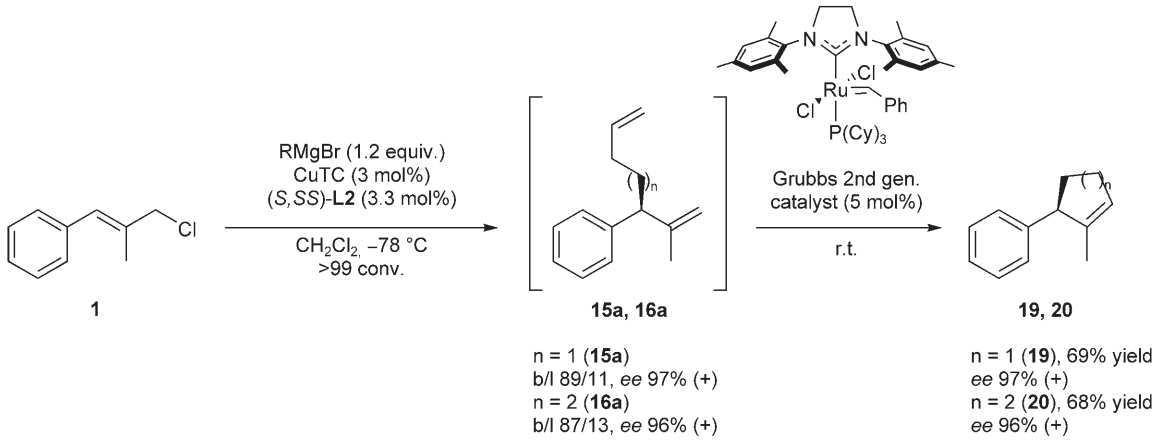
Additionally, as described previously by our group,[17] chiral compounds **15a** and **16a**, generated by the addition of the corresponding Grignard reagent on **1**, could undergo a one-pot ring-closing metathesis (**19**–**20**) upon treatment with the Grubbs second generation catalyst in a completely stereoretentive fashion (Scheme 5).[18]

Aliphatic β-Disubstituted Allylic Halides

To broaden the scope of the copper-catalyzed procedure employing the phosphoramidite ligand (*S,SS*)-**L2** and to circumvent the problem of *E:Z* isomeric ratio present in the cinnamyl substrates, we looked at aliphatic endocyclic allylic chlorides. These allylic electrophiles were again configurationally locked as *trans* isomers and looked like a very interesting class of β-disubstituted allylic substrates in comparison to the results disclosed some years ago by Gais and co-workers.[19] Indeed, this group had described the enantioselective addition of various organocuprate and organocopper reagents to optically active endocyclic allylic sulfoximines. By using these chiral auxiliaries as leaving groups, they obtained S_N2' rearrangement products with low-to-high enantioselectivities (27–90% *ee*). The stoichiometric organocopper reagent prepared *in situ* stood out as the choice reagent for a highly selective γ-substitution (>92% S_N2). Gratifyingly, the addition of different Grignard reagents promoted by 3 mol% of the copper catalyst proceeded with high selectivity towards the γ-substitution product and delivered adducts **23a–f** and **24a–f** with excellent enantiomeric excess of up to >99% (Scheme 6).

Although, in our first substitution assays, a short ligand screening was done for the addition of *n*-butylmagnesium chloride to the five-membered ring substrate **21** (Table 6, entries 1–3), the best ligand was found to be (*S,SS*)-**L2** which, as mentioned earlier, afforded excellent enantioselectivities on the β-methylcinnamyl substrates. We were pleased to observe that the chiral adduct (+)-**23a** was obtained with 98% *ee* and 96% γ-selectivity (Table 6, entry 2). In regard to the five-membered ring substrate **21**, this asymmetric methodology constantly provided very high selectivities of 97–98% *ee* throughout the array of linear Grignard reagents tested, displayed in Table 6. This copper-catalyzed process could be used on a preparative synthesis for **23b** on a one gram-scale, allowing a slower addition time of the *n*-hexylmagnesium reagent (Table 6, entry 5). The latter compound was obtained with equally good stereoselectivities and was the starting point for the asymmetric synthesis of Indolizidine frameworks.[20] Other useful transformations can be envisioned on the exocyclic double bond (such as oxidation to a ketone or selective epoxidation)[21] or deprotection of the *tert*-butoxide in **23c–24c**. Moreover, the absolute configuration of the *exo*-methylenic adducts **23a–f** and **24a–f** was ascertained by comparison with literature data.[19,22]

The six-membered ring allylic chloride **22** afforded equally good *ee* values and γ selectivities whatever the Grignard reagents employed. Once again, a small array of phosphoramidite ligands – **L2/L3**, **L5/L6** and



Scheme 5. One-pot Cu-catalyzed enantioselective S_N2' reaction and ring-closing metathesis.

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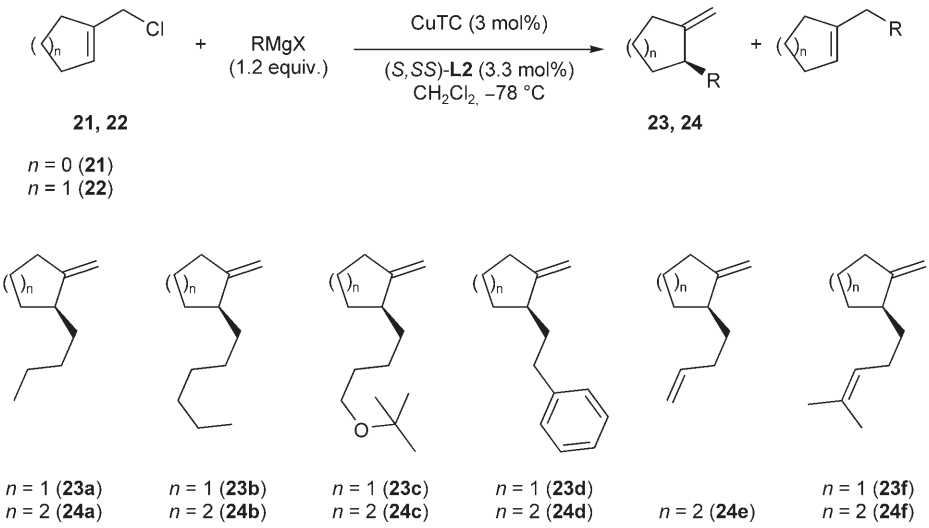

Scheme 6.

Table 6. Asymmetric CuTC-catalyzed allylic alkylation on endocyclic 1-(chloromethyl)cyclopent-1-ene **21** with RMgX (Scheme 6; L* = **L1–L6**).

Entry	Substrate	RMgX	L*	Product	Conv. [%][a]	γ/α[b]	*ee* [%][c]
1	**21**	*n*-butylMgCl	**L2**	**23a**	>99 (10)	96/4	98 (+,*S*)
2	**21**	*n*-butylMgCl	**L3**	**23a**	>99	63/37	29 (+,*S*)
3	**21**	*n*-butylMgCl	*ent*-**L6**	**23a**	>99	91/9	29 (−,*R*)
4	**21**	*n*-hexylMgBr	**L2**	**23b**	>99 (44)	97/3	98 (+)
5[d]	**21**	*n*-hexylMgBr	**L2**	**23b**	>99 (91)	98/2	98 (+)
6	**21**	*t*-BuO$(CH_2)_4$MgBr	**L2**	**23c**	96 (60)	98/2	97 (+)[e]
7	**21**	$PhCH_2CH_2MgCl$	**L2**	**23d**	>99	97/3	98 (+)
8	**21**	4-methylpent-3-enylMgBr	**L2**	**23f**	>99	98/2	95 (+)

[a] Conversion determined by GC-MS (in parentheses, yield of isolated products after purification by column chromatography on silica gel).
[b] Ratio determined by ^{1}H NMR spectroscopy and GC-MS.
[c] Enantiomeric excess determined by GC analysis on chiral stationary phase.
[d] Reaction with 4 mmol of material; addition of RMgX over 4 h.
[e] Determined by GC analysis of **23g** [R = $(CH_2)_4OCOCF_3$].

L12/**L13** – were tested for their asymmetric induction of the allylic substitution reaction of the six-membered ring chloride **22**. Nevertheless, from analysis of Table 7 it becomes clear that the previously established ligand (*S*,*SS*)-**L2** was once again the most successful throughout the different magnesium reagents used. Remarkable and unprecedented enantioselectivities up to >99% *ee* are obtained for compounds **24a–f** in the Cu-catalyzed asymmetric S_N2' alkylation on the six-membered ring chloride **22** (Table 7). The highest enantioselectivity for such a reaction was recorded for the addition of 4-methylpent-3-enylmagnesium bromide to **22** with 3 mol% CuTC/**L2** loading, to afford **24f** with 99.6% *ee* and a 98:2 branched-to-linear ratio (Table 7, entry 12).

It is conceivable that a certain degree of π-π stacking or π-cation interactions could be involved in the transition state and thus govern the stereocontrol of the reaction. Indeed, if one considers the six-membered ring *n*-butyl adduct (**24a**) and the closely related 3-butenyl product (**24e**), the optical purity is significantly increased from 97% *ee* to 99.2% *ee* (Table 7, entries 1 and 11). Furthermore, other reagents, containing a similar unsaturation at related sites, fostered even better asymmetric outcome. Indeed, phenethylmagnesium reagent and the terpenic 4-methylpent-3-enyl Grignard reagent afforded each 99.4% *ee* and 99.6% *ee* for **24d** and **24f**, respectively (Table 7, entries 10 and 12), the highest enantioselectivities recorded for copper-catalyzed allylic alkylation and more importantly on aliphatic substrates (Figure 2).

The reactivity of the seven-membered ring substrate was subsequently studied to ascertain whether it exhibited the same selectivity trends as the six- and five-membered ring systems. Reaction of substrate **25** with *n*-butyl- and phenethylmagnesium reagent in the

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Table 7. Asymmetric CuTC-catalyzed allylic alkylation on endocyclic 1-(chloromethyl)cyclohex-1-ene **22** with RMgX (Scheme 6; L* = **L1–L4**).

Entry	Substrate	R	L*	Product	Conv. [%][a]	γ/α[b]	*ee* [%][c]
1	**22**	*n*-butyl	**L2**	**24a**	73	81/19	97 (+)
2[d]	**22**	*n*-butyl	*ent*-**L5**	**24a**	75	44/66	75 (−)
3	**22**	*n*-butyl	*ent*-**L6**	**24a**	>99	70/30	88 (+)
4	**22**	*n*-hexyl	**L2**	**24b**	>99 (67)	97/3	98 (+)
5	**22**	*t*-BuO$(CH_2)_4$	**L2**	**24c**	>99 (58)	91/9	98.9 (+)
6	**22**	*t*-BuO$(CH_2)_4$	**L3**	**24c**	94	73/27	74 (−)
7	**22**	*t*-BuO$(CH_2)_4$	**L12**	**24c**	>99	75/25	94 (−)
8	**22**	*t*-BuO$(CH_2)_4$	**L13**	**24c**	80 (42)	58/42	67 (+)
9	**22**	$PhCH_2CH_2$	**L1**	**24d**	>99	72/28	87 (−,*S*)
10	**22**	$PhCH_2CH_2$	**L2**	**24d**	>99 (78)	85/15	99.4 (+,*R*)
11	**22**	3-butenyl	**L2**	**24e**	>99 (83)	97/3	99.2 (+)
12	**22**	4-methylpent-3-enyl	**L2**	**24f**	>99 (99)	98/2	99.6 (+)

[a] Conversion determined by GC-MS (in parentheses, yield of isolated products after purification by column chromatography on silica gel).
[b] Ratio determined by ^1H NMR spectroscopy and GC-MS.
[c] Enantiomeric excess determined by GC analysis on chiral stationary phase.
[d] Catalyst loading CuTC/L* 1 mol%.

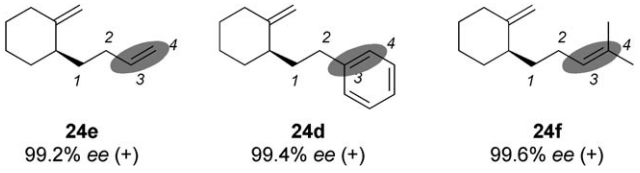
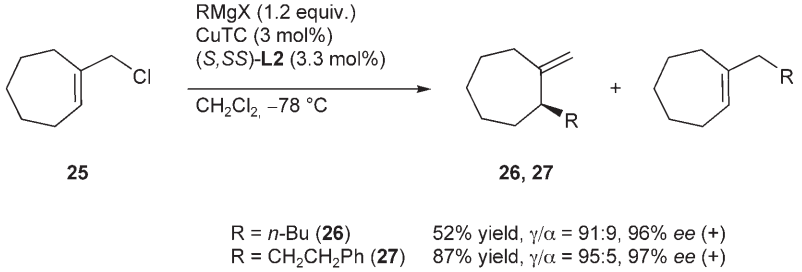


Figure 2.

presence of 3 mol% of CuTC/(*S,SS*)-**L2** proceeded with a high γ-selectivity and gave the exocyclic alkenes **26** and **27**, respectively (Scheme 7). Once again, this catalytic system efficiently controlled the enantioselective issue with 96% *ee* for **26** and 97% *ee* for **27**; the results are thus comparable to those obtained for other substitutions in this series.

We then applied the aforementioned highly efficient protocol for the asymmetric allylic substitution of β-disubstituted allylic substrates to chloride **28** (Scheme 8). Our initial trial was conducted by a slow addition of phenethylmagnesium bromide catalyzed by copper(I) thiophenecarboxylate and (*S,SS*)-**L2** (Table 8). In contrast to our previous results, this allylic substitution afforded only moderate enantioselectivities of 70% *ee* for **29** with 3 mol% catalyst loading (Table 8, entry 1) and 74% *ee* when using up to 5 mol% CuTC/(*S,SS*)-**L2** (Table 8, entry 2). We ascribed the poorer chiral results to the lower flexibility of the substrate **28** and thus ventured in further screening of ligands for the optimization of the asymmetric induction.

We looked into smaller biphenol-based ligands or phosphine-amines, such as SimplePhos structures,[23] but the optical purity of the diverse adducts dropped close to zero. Finally, (*R,RR*)-**L5** stood out as the specific choice ligand for the rigid β-disubstituted compound **28**, promoting a better regio- and enantiocontrolled allylic substitution for **29**, with an enantiomeric excess of up to 75% *ee* when increasing the catalyst loading to an optimal 5 mol% (Table 8, entry 4). Under similar conditions, products **30** and **31** were obtained with 71% *ee* and 84% *ee*, respectively, albeit with a moderate γ-selectivity (Table 8, entries 6 and 8).



Scheme 7. Cu-catalyzed asymmetric allylic substitution of seven-membered ring **25**.

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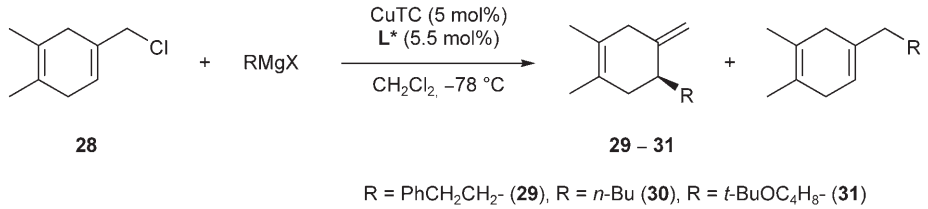


Scheme 8. S_N2'-allylic reaction on rigid endocyclic allylic chloride (**28**).

Table 8. Enantioselective Cu-catalyzed alkylation of **28**.

Entry	R	L*	Cu/L* [mol%]	Product	Conv. [%][a]	S_N2'/S_N2[b]	*ee* [%][c]
1	$PhCH_2CH_2$-	(*S,SS*)-**L2**	3	**29**	72 (30)	70/30	72 (+)
2	$PhCH_2CH_2$-	(*S,SS*)-**L2**	5	**29**	65	78/22	74 (+)
3	$PhCH_2CH_2$-	(*R,RR*)-**L5**	3	**29**	86	86/14	74 (+)
4	$PhCH_2CH_2$-	(*R,RR*)-**L5**	5	**29**	>98	90/10	75 (+)
5	*n*-butyl-	(*S,SS*)-**L2**	5	**30**	82	31/69	55
6	*n*-butyl-	(*R,RR*)-**L5**	5	**30**	85	57/43	71
7	*t*-$BuO(CH_2)_4$-	(*S,SS*)-**L2**	5	**31**	>99	47/53	65 (+)
8	*t*-$BuO(CH_2)_4$-	(*R,RR*)-**L5**	5	**31**	>99 (62)	70/30	84 (+)

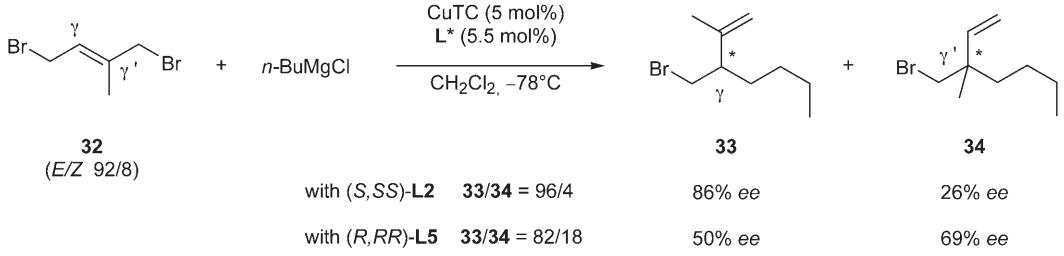
[a] Conversion determined by ^{1}H NMR (in parentheses, yield of isolated products after purification by column chromatography on silica gel).
[b] Ratio determined by ^{1}H NMR spectroscopy and GC-MS.
[c] Enantiomeric excess determined by GC analysis on chiral stationary phase.

Unsymmetrical 1,4-Dibromo-2-methylbut-2-ene

Having achieved promising results in the allylic subsitution on 1,4-bishalo-2-butene, (up to 94% *ee* on 1,4-dibromo-2-butene),[24] and moreover high asymmetric induction on the more substituted endocyclic allylic chlorides (**21**) (>99% *ee*), we envisioned to combine these two types of allylic electrophiles in the compound 1,4-dibromo-2-methylbut-2-ene (**32**). We anticipated that such a challenging unsymmetrical allylic electrophile would react regioselectively towards the incoming nucleophile depending on the selected ligand (Scheme 9). Indeed, when subjecting **32** to *n*-butylmagnesium chloride in the presence of ligand (*S,SS*)-**L2**, the substitution took place preferentially at the γ-position (tertiary-to-quaternary ratio 96/4), acting as if the compound was a pure β-disubtituted substrate. This produced the chiral adduct **33** with up to 86% *ee*. Under these conditons, the minor quaternary coumpound (**34**) (4%) would only afford 26% *ee*. Conversely, using the bis-*ortho*-methoxyphosphoramidite (*R,RR*)-**L5**, up to 20% of the quaternary chiral homo-allylic bromide was formed with 69% *ee*. Although this last result was recorded on the minor product **34**, this is to our knowledge the best enantioselectivity reported for the copper-catalyzed allylic substitution using Grignard reagents (Scheme 9).

Conclusions

In conclusion, we have described the first method for the copper-catalyzed enantioselective alkylation of β-disubstituted allylic chlorides (bromides) with organomagnesium reagents through the use of a simple chiral phosphoramidite ligand (*S,SS*)-**L2** and promo-



Scheme 9. Unsymmetrical substrate **32** used in Cu-catalyzed asymmetric allylic alkylation (AAA).

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tion by copper thiophenecarboxylate (CuTC). This identified process could be further applied to a variety of substrates with equally high ranges of stereoselectivities (up to >99% *ee*), with a single exception on highly rigid frameworks where another ligand was preferred. Moreover, compound **23b** is a precursor for the asymmetric synthesis of the indolizidine backbone, and was thus prepared on a gram-scale. We have also illustrated that fine tuning of the ligand can promote regioselectivity upon an unsymmetrical allylic dibromide **32**, which in one case has started to enable interesting enantioselectivities for the formation of chiral quaternary centers, moreover on a highly functionalized substrate.

Experimental Section

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 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 cold bath. The Grignard reagent (3 M in diethyl ether, 1.2 equiv.) diluted in CH_2Cl_2 (0.6 mL) was added over 60 min *via* 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 flash column chromatography. Gas chromatography on a chiral stationary phase gave the enantiomeric excess of the S_N2' product.

(+)-(*R*)-1-Methylene-2-(4-methylpent-3-enyl)cyclohexane (24f): yield: 99%; SiO_2, pentane, $R_F = 0.95$; IR (neat): $\nu =$ 3065 (w), 2962 (w), 2925 (s), 2855 (m), 1784 (w), 1645 (m), 1445 (s), 1376 (m), 1107 (w), 981 (w), 888 (s), 832 (m), 629 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.12$ (t, $J =$ 7.0 Hz, 1H), 4.65 (s, 1H), 4.56 (s, 1H), 2.26–2.20 (m, 1H), 2.05–1.94 (m, 4H), 1.79–1.72 (m, 1H), 1.69 (s, 3H), 1.63–1.20 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 153.2$, 131.5, 125.0, 105.6, 42.8, 35.0, 34.0, 32.4, 29.0, 26.0, 25.9, 24.4, 17.8; MS (EI mode): *m/z* (%) = 178 (9), 135 (31), 109 (13), 95 (12), 93 (12), 83 (14), 82 (100), 81 (17), 79 (12), 69 (15), 67 (36), 55 (24), 41 (38); HR-MS (EI mode): *m/z* = 178.1722, calcd. for $C_{13}H_{22}$: 178.1719; $[\alpha]_D^{22}$: +31.30 (*c* 1.28, $CHCl_3$) for 99.56% *ee*. The *ee* was measured by chiral GC with a Chirasil Dex CB, helium flow (program: 70–0–1–170–5) R_T: 38.80 (−), 38.93 (+).

Supporting Information

Preparation procedures of starting materials and spectral analysis of different chiral products are available in the supporting information.

Acknowledgements

The authors thank the Swiss National Research Foundation (no. 20–068095.02), and COST action D24/0003/01 (OFES contract no. C02.0027) for financial support, and BASF for a generous gift of chiral amines.

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