Copper-catalyzed asymmetric allylic substitution with aryl and ethyl Grignard reagents†

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Phenyl- and ethyl-magnesium bromides undergo regioselective asymmetric allylic substitution with high enantioselectivity under the catalysis of chiral amidophosphane–copper(I) complexes.

Transition metal-catalyzed asymmetric allylic substitution has proven to be an efficient method in C–C bond-forming reactions to obtain enantiomerically enriched compounds.[1] Extensive accounts report a wide variety of metals (Pd, Ir, Mo, Rh and Ru) that use soft stabilized nucleophiles for the reaction.[2] In contrast, copper enables the transfer of hard nonstabilized nucleophiles such as alkyl groups in the form of organometallic species to be delivered in the allylic position with high regioselectivity.[3] Rapid growth of Cu-catalyzed asymmetric allylic alkylation (AAA) over the past decade has occurred. By using Grignard or dialkylzinc reagents with unsymmetrically substituted allylic substrates, a branched chiral product (S_N2' product) could be obtained in high regio- and stereocontrol with excellent enantioselectivity.[4] However, the transfer of sp^2 and sp carbon have not been well exploited and most of the reports were limited to symmetrically substituted allylic substrates utilizing transition metals other than copper as catalysts.[5]

Recently, Hoveyda and co-workers have developed an efficient Cu-catalyzed AAA with diarylzinc as well as vinylaluminium reagents under the control of Cu–NHC complexes.[6] Moreover, Alexakis and co-workers have disclosed the Ir-catalyzed regioselective allylic substitution with arylzinc reagents in high enantioselectivity.[7]

We have been involved in the development of catalytic asymmetric reactions applying chiral amidophosphanes, such as **1a–e** (Fig. 1), as chiral ligands for copper- or rhodium-catalyzed reactions. These chiral amidophosphane ligands have enabled catalytic asymmetric conjugate arylation and alkylation of cycloalkenones with arylboronic acids,[8] Grignard reagents[9] and diorganozincs.[10]

Since the π-allylcopper(III) species is a common intermediate in conjugate addition as well as in allylic alkylation chemistry,[11] we expected that amidophosphane ligands could provide regio- and enantioselective transfer of an aryl moiety in Cu-catalyzed allylic alkylation. Herein, we report that chiral copper-amidophosphane complexes can perform, for the first time, regio- and enantioselective allylic arylation with aryl-

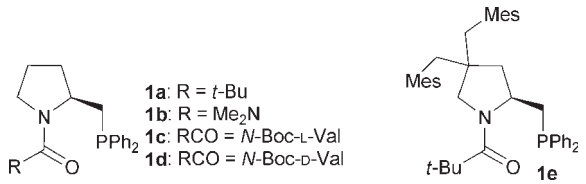


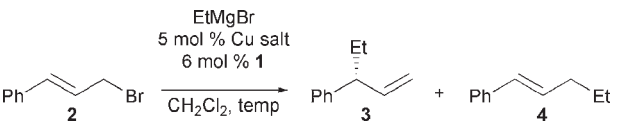
Fig. 1 Amidophosphane ligands.

magnesium bromides that affords the S_N2' product as the major regioisomer with high enantioselectivity.

We started our study with the reaction of cinnamyl bromide (**2**) (1 mmol) and EtMgBr. Using amidophosphane **1a**[9d] (6 mol%) and CuBr·SMe_2 (5 mol%) in CH_2Cl_2 (10 mL) at −78 °C, S_N2' product **3** with 78% ee was obtained along with S_N2 product **4** (100% conversion, **3** : **4** = 66 : 34) (Table 1, entry 1). This result encouraged us to perform further optimization of the allylic alkylation.

Increasing the concentration of the reaction medium to 0.4 M of **2** from 0.1 M gave higher 88% enantioselectivity with slight decrease in regioselectivity (entries 2 and 3). However, choice of the copper source, which is usually a crucial factor for the selectivity in Cu-catalyzed allylic alkylation, did not influence the outcome of the process significantly (entries 5–7), except for copper cyanide giving **3** with 9% ee (entry 4),

Table 1 Optimization of Cu–**1**-catalyzed asymmetric allylic alkylation with EtMgBr[a]



Entry	Cu salt	1	T/°C	Conv.[b] (%)	3 : 4[b]	ee[c] (%)
1[d]	CuBr·SMe_2	**1a**	−78	100	66 : 34	78
2[e]	CuBr·SMe_2	**1a**	−78	100 (100)	63 : 37	85
3	CuBr·SMe_2	**1a**	−78	100	61 : 39	88
4	CuCN	**1a**	−78	100	62 : 38	9
5	$Cu(OTf)_2$	**1a**	−78	100	63 : 37	90
6	$(CuOTf)_2·C_6H_5Me$	**1a**	−78	100 (91)	65 : 35	90
7	$Cu(MeCN)_4BF_4$	**1a**	−78	100 (95)	62 : 38	91
8	$Cu(MeCN)_4BF_4$	**1a**	−60	100	69 : 31	86
9	$Cu(MeCN)_4BF_4$	**1a**	−40	100	73 : 27	78
10	$Cu(MeCN)_4BF_4$	**1b**	−78	100	57 : 43	60
11	$Cu(MeCN)_4BF_4$	**1c**	−78	100	58 : 42	40
12	$Cu(MeCN)_4BF_4$	**1d**	−78	100	60 : 40	44
13	$Cu(MeCN)_4BF_4$	**1e**	−78	100	63 : 37	88

[a] 0.4 M concentration of **2**. EtMgBr (1.3 equiv., 3.0 M Et_2O solution) diluted with 0.5 mL CH_2Cl_2 was added over 30 min. [b] Conversion (conv.) and regioselectivity (**3** : **4**) were determined by achiral GC. Isolated yields are given in parentheses. [c] Determined by chiral GC. [d] 0.1 M concentration of **2**. [e] 0.25 M concentration of **2**.

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and slightly better enantioselectivity (91% ee) was obtained with $Cu(MeCN)_4BF_4$ (entry 7).

The reaction using allylic substrates having chloride, acetate and phosphate as a leaving group, failed to improve the enantioselectivity. The reaction at higher temperature (−60 °C, −40 °C) improved the regioselectivity[12] at the expense of the enantioselectivity (entries 8 and 9).

Although a number of amidophosphane ligands were also screened, **1a** was found to be the best. The use of **1b**[9d] having a dimethylcarbamoyl group resulted in lower enantio- and regioselectivity (60% ee, **3** : **4** = 57 : 43) (entry 10). Using amino-acid-connected amidophosphanes **1c** and **1d**,[13] the products were obtained with lower enantioselectivities and slightly lower regioselectivities (entries 11 and 12). Amidophosphanes **1e**[14] having two mesitylmethyl groups on the pyrrolidine ring gave comparable results (entry 13). Thus, the best conditions were determined to be those in entry 7, giving **3** with 91% ee as a 62 : 38 mixture with **4**.

In contrast to many excellent reports on Cu-catalyzed AAA with *alkyl* Grignard reagents, examples on those with *aryl* Grignard reagents are rare and suffer from low reactivity in addition to poor regio- and/or enantioselectivity (up to 21% ee).[15] We then applied our catalyst to this more challenging arylation reaction. As depicted in Table 2, entry 1, we first examined the reaction of (*E*)-1-bromooct-2-ene (**5a**) with PhMgBr under our aforementioned conditions, **1a** (6 mol%) and $Cu(MeCN)_4BF_4$ (5 mol%), to give the corresponding S_N2' product **6a** with 56% ee. S_N2 product **7a** was also obtained (**6a** : **7a** = 62 : 38) as a mixture of *E* : *Z* isomers (88 : 12). The sense of enantiofacial selectivity was opposite to that in the reactions in Table 1.[16]

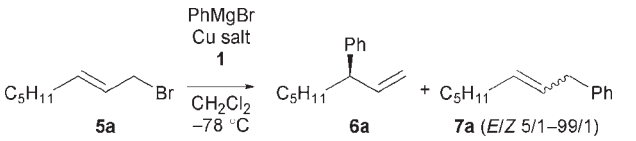
The enantioselectivity was improved when Cu(I) and the ligand were used in 1 : 2 ratio (entry 2) and was further improved when just 2 mol% Cu salt and 4.4 mol% **1a** were employed to afford **6a** with 72% ee and a 71 : 29 ratio of **6a** : **7a** (entry 3). Further decrease of the catalyst loading led to lower enantioselectivity (entry 4).

Other copper salts were tested. Copper(I) thiophencarboxylate (CuTC) was found to be as efficient as $Cu(MeCN)_4BF_4$ (entry 5), while CuCN expectedly gave higher regioselectivity (87 : 13) albeit with 12% ee (entry 6). The use of $CuBr{\cdot}SMe_2$, CuOTf and $Cu(OTf)_2$ had deleterious effects on regio- and enantioselectivity (entries 7–9).

Different amidophosphane ligands were screened in the reaction of **5a** with PhMgBr. In contrast to the reaction with cinnamyl bromide (**2**) and EtMgBr (Table 1, entry 10), the carbamoyl amidophosphane ligand **1b** was proven to be an alternative ligand to **1a**, producing the desired chiral product **6a** with 73% ee in 69 : 31 regioisomeric ratio (entry 10). The amino-acid-connected ligands **1c** and **1d** showed lower regioselectivity and poor enantioselectivity (entries 11 and 12). In addition, ligand **1e** having more bulky substituents did not improve the selectivity of the reaction (entry 13).

Finally, the addition rate of PhMgBr was found to be of significance. The slower was the addition, the higher were the regio- and enantioselectivity (entries 14, 16 and 17). Simultaneous slow addition of **5a** and PhMgBr made only slight improvement (entry 15). When CuTC–**1a** and CuTC–**1b** complexes were used, **6a** with 81% ee was obtained in 76 : 24 and 73 : 27 regioselectivity, respectively (entries 18 and 19).

Table 2 Optimization of Cu–**1**-catalyzed asymmetric allylic arylation with PhMgBr[a]



Entry	Cu salt/mol%	**1**/mol%	Conv.[b] (%)	**6a** : **7a**[b]	ee[c] (%)
1	$Cu(MeCN)_4BF_4$/5	**1a**/6	100 (100)	62 : 38	56
2	$Cu(MeCN)_4BF_4$/5	**1a**/10	100 (94)	64 : 36	66
3	$Cu(MeCN)_4BF_4$/2	**1a**/4.4	100 (90)	71 : 29	72
4	$Cu(MeCN)_4BF_4$/1	**1a**/2.2	100	70 : 30	60
5	CuTC[d]/2	**1a**/4.4	100 (93)	73 : 27	69
6	CuCN/2	**1a**/4.4	100	87 : 13	12
7	$CuBr{\cdot}SMe_2$/2	**1a**/4.4	100	64 : 36	57
8	$(CuOTf)_2{\cdot}C_6H_5Me$/1	**1a**/4.4	100	66 : 34	59
9	$Cu(OTf)_2$/2	**1a**/4.4	100	64 : 36	60
10	$Cu(MeCN)_4BF_4$/2	**1b**/4.4	100 (89)	69 : 31	73
11	$Cu(MeCN)_4BF_4$/2	**1c**/4.4	100	55 : 45	17
12	$Cu(MeCN)_4BF_4$/2	**1d**/4.4	100	55 : 45	16
13	$Cu(MeCN)_4BF_4$/2	**1e**/4.4	100	63 : 37	38
14[e]	$Cu(MeCN)_4BF_4$/2	**1a**/4.4	100 (96)	72 : 28	71
15[f]	$Cu(MeCN)_4BF_4$/2	**1a**/4.4	100	70 : 30	74
16[g]	$Cu(MeCN)_4BF_4$/2	**1a**/4.4	100	74 : 26	76
17[h]	$Cu(MeCN)_4BF_4$/2	**1a**/4.4	100 (91)	75 : 25	79
18[h]	CuTC/2	**1a**/4.4	100 (99)	76 : 24	81
19[h]	CuTC/2	**1b**/4.4	100 (87)	73 : 27	81

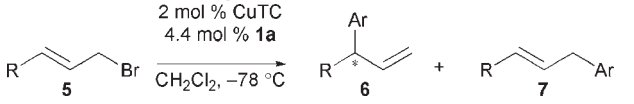
[a] PhMgBr (1.3 equiv., 3.0 M Et_2O solution) diluted with 0.5 mL CH_2Cl_2 was added over 30 min. [b] Conversion (conv.) and regioselectivity (**6a** : **7a**) were determined by achiral GC. Isolated yields are given in parentheses. [c] Determined by chiral GC. [d] CuTC = copper(I) thiophencarboxylate. [e] PhMgBr (1.3 equiv.) was added over 1 h. [f] Both **5a** and PhMgBr (1 equiv.) were independently added over 1 h at the same time. [g] PhMgBr (1.3 equiv.) was added over 2 h. [h] PhMgBr (1.3 equiv.) was added over 4 h.

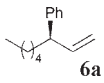
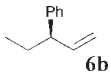
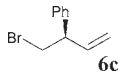
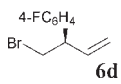
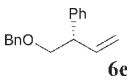
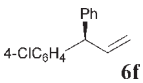
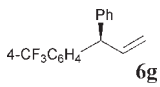
With the optimized conditions in hands, other substrates were applied to the reaction (Table 3). Aliphatic allylic bromide **5b** (entry 2) afforded the product **6b** with 67% ee and high regioselectivity (83 : 17). Gratifyingly, difunctionalized allylic substrate, *trans*-1,4-dibromo-2-butene (**5c**), was also a promising substrate in the reactions using PhMgBr and 4-FC_6H_4MgBr, which exclusively afforded the S_N2' products **6c** and **6d** in 80 and 72% ee, respectively (entries 3 and 4).[17] In these reactions, (*E*)-1,4-diphenylbut-2-ene and 3,4-diphenybut-1-ene (entry 3), and (*E*)-1,4-bis-(4-fluorophenyl)but-2-ene and 3,4-bis(4-fluoropheny)but-1-ene (entry 4) were also obtained in 5, 7, 9 and 10% yield, respectively. These results clearly indicate that the apparently exclusive S_N2' selectivity in entries 3 and 4 should be due to further reactions of the once-formed S_N2 products with the Grignard reagents.

Interestingly, inversion of the sense of enantiofacial selectivity was observed in the reaction of substrate **5d** having a benzyloxy group to give product **6e** with 34% ee and 66 : 34 regioselectivity (entry 5). To the best of our knowledge, these regio- and enantioselectivities are unprecedentedly high in Cu-catalyzed allylic arylation using aryl Grignard reagents.

In the reactions of aryl-type substrates **5e** and **5f**, **6f** and **6g** were formed in 71 and 77% ee, respectively, with low S_N2'-regiocontrol probably due to the bulky phenyl group causing severe steric and/or electronic repulsion with the incoming nucleophilic species (entries 6 and 7).[18]

Table 3 CuTC–**1a**-catalyzed asymmetric allylic arylation[a]



Entry	R	Ar	Product	Conv.[b] (%)	6 : 7[b]	ee[c] (%)
1[d]	C_5H_{11} **5a**	Ph	 **6a**	100 (99)	76 : 24	81
2	Et **5b**	Ph	 **6b**	100 (100)	83 : 17	67
3	$BrCH_2$ **5c**	Ph	 **6c**	100 (89)	100 : 0	80
4	$BrCH_2$ **5c**	4-FC_6H_4	 **6d**	100 (81)	100 : 0	72
5	$BnOCH_2$ **5d**	Ph	 **6e**	100 (100)	66 : 34	34[e]
6	4-ClC_6H_4 **5e**	Ph	 **6f**	100 (100)	18 : 82	71
7[f]	4-$CF_3C_6H_4$ **5f**	Ph	 **6g**	(93)	16 : 84	77

[a] ArMgBr (1.3 equiv.) diluted with 1 mL CH_2Cl_2 was added over 4 h. [b] Conversion (conv.) and regioselectivity (**6** : **7**) were determined by ^{1}H NMR or GC. Isolated yields are given in parentheses. [c] Determined by chiral GC. [d] Table 2, entry 18. [e] Determined after conversion to the corresponding alcohol by debenzylation using BCl_3. [f] Both **5f** and PhMgBr (1 equiv.) were independently added over 4 h at the same time.

In conclusion, we have developed regio- and enantioselective allylic substitution with arylmagnesium bromide as well as ethylmagnesium bromide, using chiral amidophosphane–copper(I) complexes as catalysts. It is noteworthy that unprecedentedly high regio- and enantioselectivities were achieved in the asymmetric arylation of aliphatic and difunctionalized brominated substrates with aryl Grignard reagents by the present protocol.

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