Highly enantioselective Cu-catalysed allylic substitutions with Grignard reagents†

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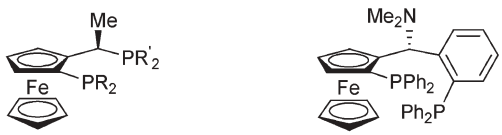
A catalyst system able to perform highly enantioselective Cu-catalysed allylic alkylations with Grignard reagents is described.

Transition metal-catalysed allylic substitution with carbon nucleophiles is a powerful tool for the controlled formation of carbon–carbon bonds.[1] Most enantioselective versions of this reaction have been reported with soft nucleophiles (*i.e.* malonates and related stabilised anions) using Pd as the metal source,[2] although Mo, W, Ru, Rh and Ir catalysts have also been found effective for these nucleophiles.[3] In contrast, the enantioselective allylic alkylation with hard carbon nucleophiles (*i.e.*, organometallic reagents), which allows the introduction of simple alkyl groups in an allylic position, has received far less attention, Cu being the current metal of choice.[4] In 1995, Bäckvall and van Koten reported the first asymmetric Cu-catalysed allylic alkylation with moderate enantioselectivity using Grignard reagents.[5] A few years later, Dübner and Knochel reported a highly enantioselective version using dialkylzinc reagents.[6] Since then, most efforts have been directed towards the development of new efficient Cu catalysts for these organozinc reagents.[7] A notable exception is the highly enantioselective Cu-phosphoramidite[8] catalysed allylic substitution of cinnamyl chlorides with Grignard reagents reported by Alexakis and coworkers in 2004.[9]

Recently, we demonstrated that Cu-catalysed enantioselective 1,4-additions of Grignard reagents to a variety of α,β-unsaturated carbonyl compounds can be achieved with enantioselectivities up to 99% (Fig. 1).[10] Herein, we report that the same catalyst systems can perform regio- and enantioselective allylic alkylations with Grignard reagents. Enantioselectivities up to 98% and excellent regioselectivities can be achieved just by judicious selection of the appropriate ligand and reaction parameters (Scheme 1).



(*R*,*S*)-**1a**, R = Ph, R' = Cy, Josiphos
(*R*,*S*)-**1b**, R = Cy, R' = Ph

(*R*,*S*)-**2**, Taniaphos

Fig. 1 Successful ligands for the enantioselective conjugate addition of Grignard reagents to α,β-unsaturated carbonyl compounds.

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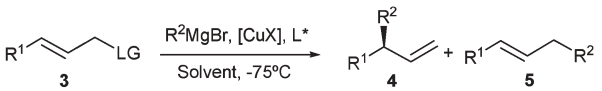


3 **a** R^1 = Ph, LG = Br **e** R^1 = *p*-Cl-Ph, LG = Br
b R^1 = Ph, LG = $OP(O)(OEt)_2$ **f** R^1 = *p*-CO_2Me-Ph, LG = Br
c R^1 = Ph, LG =Cl **g** R^1 = ^{n}Bu, LG = Br
d R^1 = 1-Naphthyl, LG = Br **h** R^1 = $BnOCH_2$, LG =Br

Scheme 1 Cu-catalysed enantioselective allylic alkylation with Grignard reagents.

Furthermore, we describe for the first time a highly enantioselective allylic substitution of linear aliphatic allylic halides with Grignard reagents, and the application of these methodologies to the synthesis of *syn* and *anti* 1,2-dialkyl motifs.

The present study started with the exploration of the ligands (**1a–1b**) found effective in the 1,4-addition to acyclic α,β-unsaturated compounds,[10b,c] using MeMgBr as the Grignard reagent.[11] The results are summarized in Table 1. The allylic alkylation of cinnamyl bromide (**3a**), catalysed by Josiphos (**1a**, 6 mol%) and $CuBr{\cdot}SMe_2$ (5 mol%) in ^{t}BuOMe proceeds with good regioselectivity (**4a** : **5a** = 85 : 15), providing the chiral product **4a** with high enantioselectivity (85% ee, entry 1). The choice of solvent, type of Josiphos ligand,[12] and leaving group (LG) proved to be critical to obtain high selectivities (*i.e.* entries 2–5).[13] However, the nature of

Table 1 Cu-catalysed enantioselective allylic alkylation with Josiphos ligands and Grignard reagents (Scheme 1, L* = **1a** or **1b**)[a,b]

Entry	3	R^2	[Cu]	Solvent	4	4 : 5[c]	ee (%)[c]
1	**a**	Me	$CuBr{\cdot}SMe_2$	^{t}BuOMe	**a**	85 : 15	85
2	**a**	Me	$CuBr{\cdot}SMe_2$	CH_2Cl_2	**a**	49 : 51	73
3[d]	**a**	Me	$CuBr{\cdot}SMe_2$	^{t}BuOMe	**a**	66 : 34	79
4[e]	**b**	Me	$CuBr{\cdot}SMe_2$	^{t}BuOMe	**a**	81 : 19	58
5[f]	**c**	Me	$CuBr{\cdot}SMe_2$	^{t}BuOMe	**a**	0 : 100	—
6	**a**	Me	CuTC	^{t}BuOMe	**a**	60 : 40	84
7	**a**	Me	CuCN	^{t}BuOMe	**a**	85 : 15	86
8	**a**	Me	CuCl	^{t}BuOMe	**a**	85 : 15	84
9	**a**	Me	$Cu(MeCN)_4PF_6$	^{t}BuOMe	**a**	84 : 16	84
10	**a**	Et	$CuBr{\cdot}SMe_2$	^{t}BuOMe	**b**	38 : 62	56
11[g]	**g**	Me	$CuBr{\cdot}SMe_2$	^{t}BuOMe	**c**	82 : 18	46
12	**c**	Et	$Cu(MeCN)_4PF_6$	CH_2Cl_2	**b**	75 : 25	44[h]
13	**g**	Me	$CuBr{\cdot}SMe_2$	CH_2Cl_2	**c**	88 : 12	72[i]
14	**g**	Et	$CuBr{\cdot}SMe_2$	CH_2Cl_2	**d**	94 : 6	69[i]

[a] *Reagents and conditions*: RMgBr (2.50 equiv.), **1a** (6 mol%), $CuBr{\cdot}SMe_2$ (5 mol%), −75 °C, 12 h unless otherwise noted. [b] All conv > 98% (GC) unless otherwise noted. [c] Regio- and enantioselectivity determined by chiral GC; see ESI for details. [d] Reaction carried out with Josiphos **1b**. [e] Conv < 10% (GC). [f] 29% Conv (GC). [g] 50% Conv (GC). [h] EtMgCl (1.15 equiv.) used instead of EtMgBr. [i] 1.15 Equiv. RMgBr. TC = 2-thiophenecarboxylate.

the copper source, which is usually a crucial factor for the selectivity in related Cu-catalysed allylic substitutions,[7,9] did not influence the outcome of the process significantly (entries 6–9).

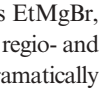
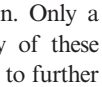
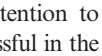
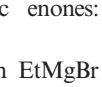
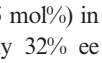
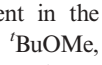
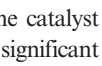
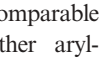
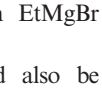
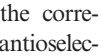
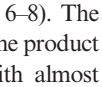
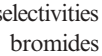
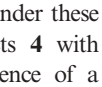
Unfortunately, when other Grignard reagents such as EtMgBr, or aliphatic allylic bromides such as **3g** were applied, the regio- and enantioselectivity of the reactions were affected dramatically (entries 10 and 11). A detailed optimization of the leaving group, and the reaction conditions was, therefore, undertaken. Only a moderate increase in the regio- and enantioselectivity of these reactions could be obtained (entries 12–14). In attempts to further improve the level of stereocontrol, we turned our attention to another ferrocenyl ligand, recently reported to be successful in the conjugate addition of Grignard reagents to cyclic enones: Taniaphos (**2**),[14] (Fig. 1).[10a]

The allylic alkylation of cinnamyl bromide **3a** with EtMgBr catalysed by Taniaphos (**2**, 6 mol%) and $CuBr{\cdot}SMe_2$ (5 mol%) in ^{t}BuOMe, provided a modest regioselectivity and only 32% ee (Table 2, entry 1). However, a dramatic improvement in the selectivity was observed using CH_2Cl_2 instead of ^{t}BuOMe, providing the desired product **4b** with a regioselectivity of 82 : 18 and an excellent ee (96%, entry 2).[15] In addition, the catalyst loading could be reduced to only 1 mol% without significant deterioration in the selectivity obtained (entry 3). Comparable selectivities were achieved in the alkylation of other aryl-substituted allylic bromides (**3d–3e**, Scheme 1) with EtMgBr (entries 4 and 5).

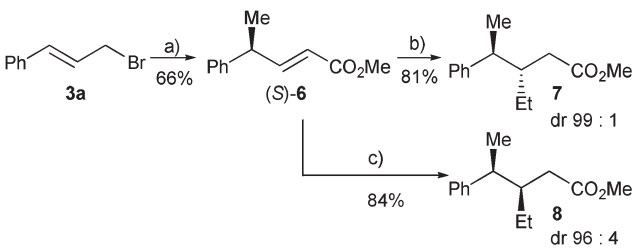
Furthermore, the allylic substitution of **3a** could also be performed with other Grignard reagents, providing the corresponding products **4g–h,a** (Table 2) with excellent enantioselectivities (94–98% ee) and good regioselectivities (entries 6–8). The alkylation with MeMgBr is particularly noteworthy.[11] The product **4a**, as well as the compounds **4i–k** were obtained with almost complete control of the regioselectivity and enantioselectivities $\geqslant$ 96% (entries 8–11).[16] Gratifyingly, aliphatic allylic bromides such as **3g–h** were also excellent substrates, affording under these conditions, almost exclusively, the branched products **4** with enantioselectivities $\geqslant$ 92% (entries 12–15). The presence of a benzyloxy group in the substrate (**3h**) was tolerated providing excellent building blocks (**4l–m**) for natural product synthesis (entries 14 and 15).[17]

In summary, we have demonstrated that the catalyst systems developed recently for the enantioselective conjugate addition of Grignard reagents to α,β-unsaturated carbonyl compounds are also able to perform highly enantioselective allylic alkylations with Grignard reagents. The combination of Taniaphos (**2**) and $CuBr{\cdot}SMe_2$ in CH_2Cl_2 provides excellent regio- and enantioselectivities in the substitution of aliphatic and aromatic allylic bromides. The potential of these two new methodologies for the catalytic and enantioselective preparation of 1,2-dialkyl motifs is shown in Scheme 2.

Table 2 Cu-catalysed enantioselective allylic alkylation with Cu/Taniaphos (**2**) and Grignard reagents (Scheme 1, L* = **2**)[a,b]

Entry	3	R^2	4 : 5[c]	4	Yield[d]	ee (%)[c]
1[e,f]	**a**	Et	31 : 69	 **4b**	99[g]	32 (*S*)
2[f]	**a**	Et	82 : 18	**4b**	99[g]	96 (*S*)
3	**a**	Et	81 : 19	**4b**	92	95 (*S*)
4	**d**	Et	87 : 13	 **4e**	86	90 (*S*)
5	**e**	Et	82 : 18	 **4f**	80	96 (*S*)
6	**a**	^{n}Bu	87 : 13	 **4g**	92	94 (*S*)
7	**a**		91 : 9	 **4h**	93	95 (*S*)
8	**a**	Me	97 : 3	 **4a**	91	98 (*S*)
9	**d**	Me	100 : 0	 **4i**	87	96
10	**e**	Me	99 : 1	 **4j**	95	97
11	**f**	Me	98 : 2	 **4k**	94	97 (*S*)
12[f]	**g**	Me	100 : 0	 **4c**	99[g]	92
13[f]	**g**	Et	100 : 0	 **4d**	99[g]	93
14	**h**	Me	100 : 0	 **4l**	93	92 (*S*)
15	**h**	Et	98 : 2	 **4m**	97	94

[a] *Reagents and conditions*: RMgBr (1.15 equiv.), **2** (1.1 mol%), $CuBr{\cdot}SMe_2$ (1.0 mol%), CH_2Cl_2, −78 °C, 12 h unless otherwise noted. [b] All conversions > 98% (GC). [c] Regio- and enantioselectivities determined by chiral GC or HPLC (see ESI for details). [d] Isolated yield of combined **4** and **5** unless otherwise noted. [e] Reaction in ^{t}BuOMe. [f] Taniaphos (**2**, 6.0 mol%), $CuBr{\cdot}SMe_2$ (5.0 mol%). [g] Conversion (GC).



Scheme 2 *Reagents and conditions*: a) i) MeMgBr (1.15 eq.), **2** (1.1 mol%), $CuBr{\cdot}SMe_2$ (1.0 mol%), CH_2Cl_2, −78 °C; ii) Hoveyda–Grubbs 2nd generation, methyl acrylate (5.0 eq.), CH_2Cl_2, rt; b) EtMgBr (5.0 eq.), (*R*,*S*)-**1b** (6.0 mol%), $CuBr{\cdot}SMe_2$ (5.0 mol%), CH_2Cl_2, −78 °C; c) EtMgBr (5.0 eq.), (*S*,*R*)-**1b** (6.0 mol%), $CuBr{\cdot}SMe_2$ (5.0 mol%), CH_2Cl_2, −78 °C.

The allylic alkylation of **3a** with MeMgBr afforded **4a** with 98% ee. The crude reaction was submitted to cross metathesis with methyl acrylate to afford (*S*)-**6** in 66% overall yield.[18] Gratifyingly, enoate **6** proved to be an excellent substrate for the recently developed enantioselective conjugate addition of Grignard reagents.[10c] Thus, the conjugate addition of EtMgBr to **6**, catalyzed by (*R*,*S*)-**1b** or its enantiomer (*S*,*R*)-**1b**, provided,

respectively, the *anti* and *syn*--1,2-dialkyl substituted esters **7** and **8** with excellent yields and diastereoselectivities.[19] These results demonstrate the efficiency of this chiral catalyst in the control of the configuration at the new stereocenter, independent of the absolute configuration of the chain.[17]

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