ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 5843–5845

www.rsc.org/chemcomm

COMMUNICATION

Stereoselective synthesis of *syn* and *anti* 1,2-hydroxyalkyl moieties by Cu-catalyzed asymmetric allylic alkylation†

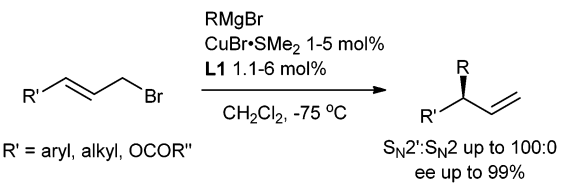
Martín Fañanás-Mastral, Bjorn ter Horst, Adriaan J. Minnaard and Ben L. Feringa*

Received 24th November 2010, Accepted 1st April 2011
DOI: 10.1039/c0cc05161f

A stereoselective synthesis of 1,2-hydroxyalkyl moieties is described herein. These valuable building blocks are obtained with complete regiocontrol and excellent stereocontrol both for the *syn* or the *anti* products, by choosing the appropriate enantiomer of the ligand in a copper-catalyzed asymmetric allylic alkylation of δ-alkoxy-substituted allyl bromides.

1,2-Hydroxyalkyl moieties are key subunits in a diverse array of natural products and pharmaceuticals, and their synthesis has been a prime objective for synthetic organic chemists for many years.[1] A variety of methods has been reported for the direct and enantioselective assembly of these important moieties, the aldol reaction being the most important transformation for their construction.[2] Furthermore, alternative strategies such as crotylations,[3] allenylations,[4] selective radical processes[5] and sequential substitutions[6] are of high importance. Despite their great versatility, most of these methods need a chiral auxiliary or rely on substrate control for stereoselectivity. Because of this, the development of catalytic asymmetric reactions for the synthesis of these subunits with the stereochemistry under catalyst control continues to be highly warranted.

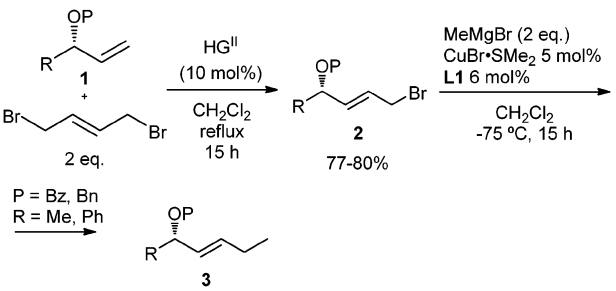
Recently, it has been reported by our group that copper-catalyzed asymmetric allylic alkylation (AAA) with Grignard reagents can be achieved with excellent regio- and enantioselectivities on *C*-substituted and ester-substituted allyl bromides (Scheme 1).[7,8] We envisioned that this AAA with MeMgBr on δ-alkoxy-substituted allyl bromides as substrates could give rise to the stereoselective formation of 1,2-hydroxymethyl units.



Scheme 1 Asymmetric Cu-catalyzed AAA and *hetero*-AAA (for the ligand structure see Fig. 1).

Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG, Groningen, The Netherlands. E-mail: b.l.feringa@rug.nl; Fax: +31 50 363 4296; Tel: +31 50 363 4235

† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data. See DOI: 10.1039/c0cc05161f

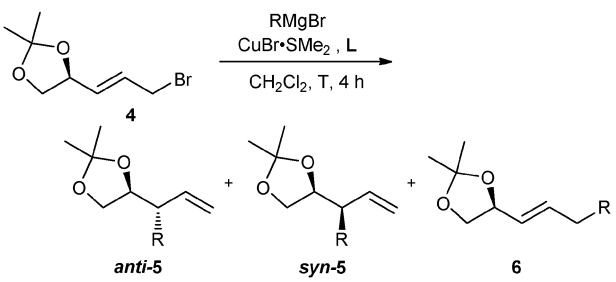


Scheme 2 Preparation and reactivity of allyl bromides **2**.

We first prepared allyl bromides **2** by reacting the corresponding benzoate- and benzyl-protected allyl alcohols **1** with 1,4-dibromo-2-butene in the presence of 10 mol% of the Hoveyda–Grubbs second generation catalyst. However, the subsequent copper-catalyzed reaction with MeMgBr only gave rise to the undesired α-substituted product **3** (Scheme 2).

When alternative protecting groups, such as TBDPS or MOM, were used no reaction was observed. Taking into account that the alkoxy substituent may be too bulky, we decided to use allyl bromide **4** (Scheme 3) which is easily obtained in three steps from commercially available 1,2:5,6-di-*O*-isopropylidene-D-mannitol.[9,10] In this case the alkoxy substituent is part of a dioxolane ring which might reduce the steric problem.

To our delight, the reaction with MeMgBr using CuBr·SMe$_2$ and (*R,R*)-(+)-taniaphos **L1** (Fig. 1) as a catalyst at −75 °C gave rise to compound ***anti*-5a** as the major product of the reaction together with a small amount of the linear product **6** (Table 1, entry 1). The use of the other enantiomer



Scheme 3 Cu-catalyzed AAA on **4**.

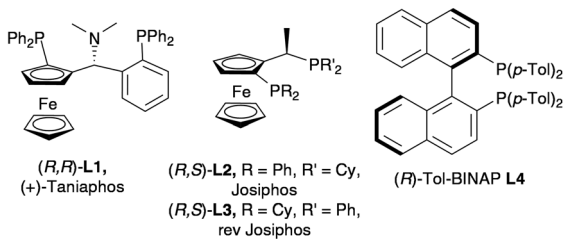


Fig. 1 Screened ligands.

Table 1 Screening of ligands and conditions with MeMgBr (Scheme 3)[a]

Entry	L	T/°C	*anti*-**5a**[b] (%)	*syn*-**5a**[b] (%)	**6**[b] (%)
1	(*R*,*R*)-(+)-**L1**	−75	92	0	8
2	(*S*,*S*)-(−)-**L1**	−75	33	28	39
3[c]	—	−75	0	0	100
4	PPh_3[d]	−75	39	1	60
5	(*R*,*S*)-**L2**	−75	62	4	34
6	(*S*,*R*)-**L2**	−75	59	8	33
7	(*R*,*S*)-**L3**	−75	73	0	27
8	(*S*,*R*)-**L3**	−75	33	27	40
9	(R)-**L4**	−75	51	0	49
10	(S)-**L4**	−75	49	4	47
11	(*R*,*R*)-(+)-**L1**	−80	100	0	0
12	(*S*,*S*)-(−)-**L1**	−80	10	90	0

[a] *Reagents and conditions*: MeMgBr (1.5 eq.), CuBr·SMe_2 (5 mol%), **L** (6 mol%), CH_2Cl_2, 4 h. [b] Based on GC analysis. [c] 1 eq. CuBr·SMe_2 + 2 eq. MeMgBr. [d] 10 mol%.

of this ligand ((*S*,*S*)-(−)-taniaphos **L1**), under the same conditions, led to a mismatch situation and afforded an almost 1 : 1 : 1 mixture of both the *anti* and *syn* isomers of **5a** and the linear product **6** (entry 2).

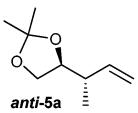
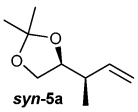
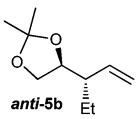
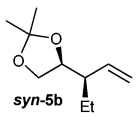
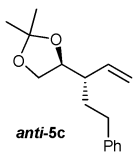
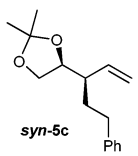
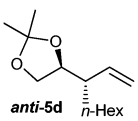
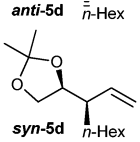
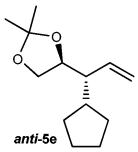
To investigate the role of the catalyst in this process we studied a variety of conditions (Table 1).

When the reaction was carried out using a magnesium cuprate without any ligand (entry 3) we only observed the formation of the linear product **6**. Also the use of PPh_3 as the ligand led preferentially to the formation of the linear product (entry 4). Various chiral phosphines (Fig. 1) were also tested as ligands, but in all cases (entries 5–10) lower selectivities were obtained as those observed for taniaphos (entries 1 and 2).

Remarkably, when the temperature was decreased to −80 °C, we observed complete selectivity towards the *anti* product using (+)-taniaphos **L1** as the ligand (entry 11). After purification ***anti*-5a** was obtained in 91% yield. The use of the same temperature (−80 °C) in the reaction with the (−)-enantiomer of the ligand (entry 12) led to a more dramatic change in the product ratio. In this case we could also direct the reaction towards the *syn* isomer with high selectivity (90 : 10). Noteworthily, the small amount of minor isomer was readily removed by column chromatography to provide pure ***syn*-5a** in 85% yield.

This dramatic change in the diastereoselectivity of this AAA of allyl bromide **4** with MeMgBr catalyzed by Cu–taniaphos can be explained on the basis of recent observations by Bertz, Ogle and co-workers in the preparation and characterization of the first examples of both σ-allyl and π-allyl Cu^{III} complexes.[11] It has been shown that temperature has a major influence on the regioselectivity (S_N2 or S_N2' pathways) in the substitution reactions of allylic substrates with organocopper(I) reagents. In analogy with the proposed mechanism by Goering and co-workers for the copper-catalyzed allylic alkylation of allylic carboxylates with Grignard reagents,[12] a catalytic cycle which involves the formation of a Cu^{III} σ-complex intermediate could be proposed for the mechanism of the AAA with Grignard reagents catalyzed by Cu–taniaphos. This Cu^{III} σ-complex (see ESI† for further details) would yield the *anti* or *syn* product, depending on the configuration of the catalyst, *via* reductive elimination at −80 °C (Table 1, entries 11 and 12). Upon raising the temperature to −75 °C (entries 1 and 2), conversion of the σ-complex to the π-complex can occur,[11] resulting in a lower regioselectivity (see ESI†).

Table 2 Cu-catalyzed stereoselective synthesis of 1,2-hydroxyalkyl substrates (Scheme 3, **L** = **L1**)[a]

Entry	**L1**	R	**5**	*anti*[b,c] (%)	*syn*[b,c] (%)
1	(*R*,*R*)-(+)-**L1**	Me	 ***anti*-5a**	100 (91)	0
2	(*S*,*S*)-(−)-**L1**	Me	 ***syn*-5a**	10	90 (85)
3	(*R*,*R*)-(+)-**L1**	Et	 ***anti*-5b**	100 (89)	0
4	(*S*,*S*)-(−)-**L1**	Et	 ***syn*-5b**	12	88 (80)
5	(*R*,*R*)-(+)-**L1**	$PhCH_2CH_2$	 ***anti*-5c**	100 (84)	0
6	(*S*,*S*)-(−)-**L1**	$PhCH_2CH_2$	 ***syn*-5c**	13	87 (72)
7	(*R*,*R*)-(+)-**L1**	*n*-Hex	 ***anti*-5d**	100 (87)	0
8	(*S*,*S*)-(−)-**L1**	*n*-Hex	 ***syn*-5d**	11	89 (79)
9	(*R*,*R*)-(+)-**L1**	*c*-C_5H_9	 ***anti*-5e**	100 (80)	0

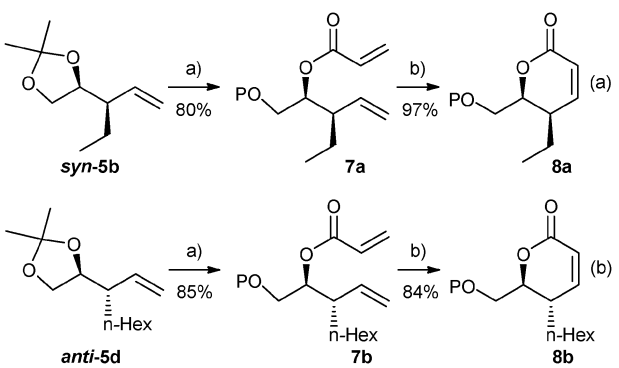
[a] *Reagents and conditions*: **4** (0.5 mmol, 1 eq.), RMgBr (1.5 eq.), CuBr·SMe_2 (2 mol%), **L1** (2.4 mol%), CH_2Cl_2, −80 °C, 4 h. [b] Based on GC analysis. [c] Isolated yield in parenthesis.

The diminished stereoselectivity is attributed to a change of exclusive catalyst control to competing chiral substrate control.

In addition, the catalyst loading could be reduced to only 2 mol% without deterioration in the selectivity obtained (Table 2, entries 1 and 2). Using these optimized conditions, the allylic alkylation of **4** was performed using different Grignard reagents with high selectivities in all cases (Table 2). Again, when (+)-taniaphos was used as the ligand, the *anti* isomers were obtained selectively (entries 1, 3, 5 and 7). The (−)-enantiomer of the ligand was slightly less selective, but led to the *syn* product with very high ratios (entries 2, 4, 6 and 8) and in all cases the minor isomer could be readily removed by column chromatography. An important feature is that the reaction is readily scalable to 5 mmol with similar results as shown for entries 4 and 7. Noteworthily, the reaction also provided the *anti* isomer with total selectivity when a cyclic Grignard reagent was used in combination with (+)-taniaphos (entry 9). However, when (−)-taniaphos was used with this Grignard reagent, a strong mismatch effect was observed and the products were obtained in a 20 : 20 : 60 *syn* : *anti* : linear ratio. PhMgBr was also used but in this case no reaction was observed at −80 °C and the starting material was recovered.

The optically active *syn* and *anti* 1,2-hydroxyalkyl moieties **5** obtained this way are versatile chiral building blocks for natural products. The presence of a double bond[13] in their structure together with the presence of a protected primary alcohol functionality opens a wide array of possible transformations. An example of the synthetic potential of compounds **5** is shown in Scheme 4. A three-step deprotection–protection sequence starting with compound ***syn*-5b** afforded diolefin **7a** in 80% combined yield. The latter was converted, by a ring-closing metathesis,[14] into γ-ethyl substituted α,β-unsaturated δ-lactone **8a** in 97% yield (Scheme 4a).

This type of γ-ethyl substituted lactones is of great interest because of its presence in a large number of natural products that possess important biological activities including pironetin,[15] phostalomycins[14b,16] and bitungolides.[17] This new methodology represents a catalytic alternative to the chiral boron-mediated pentenylation[14b] which proceeds in the same fashion as the chiral auxiliary-assisted asymmetric crotylation.[3] As an additional proof of the versatility of this methodology, we applied this synthetic route to compound ***anti*-5d** and obtained γ-hexyl substituted α,β-unsaturated δ-lactone **8b** in a comparable yield (Scheme 4b). These examples show that this new methodology gives access to *cis* and *trans* disubstituted δ-lactones with total stereocontrol and with the possibility of introducing different alkyl groups at the γ-position in a general fashion.



Scheme 4 *Reagents and conditions*: (a) (i) AcOH, H_2O, rt; (ii) TBDPSCl (1.1 eq.), imidazole (1.1 eq.), DMAP (cat.), DMF, 0 °C to rt; (iii) acryloyl chloride (1.5 eq.), $^iPr_2EtN$ (2 eq.), CH_2Cl_2, 0 °C; (b) Grubbs 2nd generation (5 mol%), CH_2Cl_2, 0.01 M, reflux, 12 h. P = TBDPS.

In summary, we have described a stereoselective synthesis of *syn* and *anti* 1,2-hydroxyalkyl structures based on a copper-catalyzed asymmetric allylic alkylation of δ-alkoxy-substituted allylic bromides with Grignard reagents. The use of a dioxolane-containing allylic bromide is crucial for the regiochemistry while the *syn–anti* stereochemistry of the product can be tuned using the appropriate enantiomer of the chiral catalyst.

Financial support from The Netherlands Organization for Scientific Research (NWO-CW) is acknowledged. M.F.-M. is grateful to the Spanish Ministry of Science and Innovation (MICINN) for a postdoctoral grant.

Notes and references

1 (*a*) K.-S. Yeung and I. Paterson, *Chem. Rev.*, 2005, **105**, 4237; (*b*) B. Schetter and R. Mahrwald, *Angew. Chem., Int. Ed.*, 2006, **45**, 7506; (*c*) J. Li and D. Menche, *Synthesis*, 2009, 2293.
2 (*a*) *Modern Aldol Reactions*, ed. R. Mahrwald, Wiley-VCH, Weinheim, 2004; (*b*) I. Paterson, in *Asymmetric Synthesis—The Essentials*, ed. M. Christmann and S. Bräse, Wiley-VCH, Weinheim, 2007, pp. 293–298; (*c*) B. M. Trost and C. S. Brindle, *Chem. Soc. Rev.*, 2010, **39**, 1600.
3 R. W. Hoffmann, in *Stereocontrolled Organic Synthesis*, ed. B. M. Trost, Blackwell Scientific Publications, Cambridge, 1994, 259–274.
4 J. A. Marshall, *Chem. Rev.*, 2000, **100**, 3163.
5 Y. Guindon, K. Houde, M. Prévost, B. Cardinal-David, S. R. Landry, B. Daoust, M. Bencheqroun and B. Guérin, *J. Am. Chem. Soc.*, 2001, **123**, 8496.
6 (*a*) S. Hanessian, J. Ma and W. Wang, *J. Am. Chem. Soc.*, 2001, **123**, 10200; (*b*) A. Whitehead, J. P. McParland and P. R. Hanson, *Org. Lett.*, 2006, **8**, 5025.
7 (*a*) F. López, A. W. van Zijl, A. J. Minnaard and B. L. Feringa, *Chem. Commun.*, 2006, 409; (*b*) K. Geurts, S. P. Fletcher and B. L. Feringa, *J. Am. Chem. Soc.*, 2006, **128**, 15572.
8 For reviews on Cu-catalalyzed AAA, see: (*a*) S. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard and B. L. Feringa, *Chem. Rev.*, 2008, **108**, 2824; (*b*) A. Alexakis, J. E. Bäckvall, N. Krause, O. Pàmies and M. Diéguez, *Chem. Rev.*, 2008, **108**, 2796.
9 (*a*) J. A. Marshall, J. D. Trometer and D. G. Cleary, *Tetrahedron*, 1989, **45**, 391; (*b*) A. R. Ellwood, A. J. P. Mortimer, D. A. Tocher and M. J. Porter, *Synlett*, 2008, 2199.
10 The (*S*)-enantiomer of allyl bromide **4** was chosen for our studies but also the (*R*)-enantiomer is readily available from L-ascorbic acid: C. Hubschwerlin, *Synthesis*, 1986, 962.
11 E. R. Bartholomew, S. H. Bertz, S. Cope, M. Murphy and C. A. Ogle, *J. Am. Chem. Soc.*, 2008, **130**, 11244.
12 C. C. Tseng, S. D. Paisley and H. L. Goering, *J. Org. Chem.*, 1986, **51**, 2884.
13 For an example of versatile use of a terminal olefin, see: T. den Hartog, B. Maciá, A. J. Minnaard and B. L. Feringa, *Adv. Synth. Catal.*, 2010, **352**, 999.
14 (*a*) A. Fürstner and K. Langemann, *J. Am. Chem. Soc.*, 1997, **119**, 9130; (*b*) S. Shibahara, M. Fujino, Y. Tashiro, K. Takahashi, J. Ishihara and S. Hatakeyama, *Org. Lett.*, 2008, **10**, 2139.
15 S. Kobayashi, K. Tsuchiya, T. Harada, M. Nishide, T. Kurokawa, T. Nakagawa, N. Shimada and K. Kobayashi, *J. Antibiot.*, 1994, **47**, 697.
16 S. Fushimi, S. Nishikawa, A. Shimazu and H. Seto, *J. Antibiot.*, 1989, **42**, 1019.
17 S. Sirirath, J. Tanaka, I. I. Ohtani, T. Ichiba, R. Rachmat, K. Ueda, T. Usui, H. Osada and T. Higa, *J. Nat. Prod.*, 2002, **65**, 1820.