Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 1877–1880
Tetrahedron Letters

Copper-catalyzed enantioselective conjugate addition of Grignard reagents to acyclic enones using monodentate phosphoramidite ligands

Beatriz Maciá, M. Ángeles Fernández-Ibáñez, Nataša Mršić, Adriaan J. Minnaard *, Ben L. Feringa *

Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG, Groningen, The Netherlands

Received 3 December 2007; revised 17 December 2007; accepted 3 January 2008
Available online 8 January 2008

Dedicated to Professor Miguel Yus on the occasion of his 60th birthday

Abstract

Herein, we report efficient catalysts based on phosphoramidites for the asymmetric copper-catalyzed conjugate addition of Grignard reagents to acyclic α,β-unsaturated ketones. A variety of Grignard reagents can be added to aliphatic and aromatic acyclic enones with good yields and moderate to good enantioselectivities.

Keywords: Conjugate addition; Grignard reagents; Phosphoramidites; Asymmetric catalysis

The conjugate addition (CA) of organometallic reagents to enones is one of the most widely used synthetic methods for carbon–carbon bond formation.[1] Enantioselective metal-catalyzed versions of this key transformation[2] have been studied extensively with cyclic enones and chalcones using dialkylzinc,[3] organomagnesium,[4] organoboron[5] and silicon reagents.[6] However, for the more challenging acyclic enones, the progress has been limited. Only two notable examples of highly enantioselective CA to acyclic enones have been reported, despite the enormous synthetic potential of the resulting enantiopure β-substituted linear ketones as building blocks for natural product synthesis. The first example, reported by Hoveyda et al., comprises the asymmetric Cu-catalyzed CA of dialkylzinc reagents using peptidic phosphine ligands[7] and the second one consists of the Cu-catalyzed CA of Grignard reagents using Josiphos ligand reported from our laboratories.[8]

Among all the ligands used so far in the field of Cu-catalyzed 1,4-addition of organometallic reagents, phosphoramidites stand out for being readily accessible, cheap and very easy to modify.[9] The excellent enantioselectivities that phosphoramidite ligands give in the CA of dialkylzinc reagents to enones,[10] encouraged us to use them as ligands for the CA of Grignard reagents.

Phosphoramidites and Grignard reagents have been combined before with success in the asymmetric Cu-catalyzed allylic substitution[11] and the Cu-catalyzed ring opening of oxabicyclic alkenes.[12] The fact that conjugate additions and allylic substitutions are mechanistically related,[13] stimulated us to search for effective catalysts based on phosphoramidites for the CA of Grignard reagents.

In this Letter, recent advances in catalytic asymmetric conjugate addition of Grignard reagents are discussed. The first examples of the use of phosphoramidites in the

* Corresponding authors. Tel.: +31 50 363 42 35; fax: +31 50 363 42 96 (B.L.F.).
E-mail address: B.L.Feringa@rug.nl (B. L. Feringa).

0040-4039/$ - see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2008.01.019

enantioselective Cu-catalyzed conjugate addition of Grignard reagents to the challenging class of acyclic aliphatic enone substrates are reported. Good levels of stereocontrol (up to 80% ee) are achieved with Cu(I) halides, alkylmagnesium bromides and readily available phosphoramidites as ligands.

In a systematic search for the optimal ligand, copper source and halide in the Grignard reagent, we initially tested several types of phosporamidites, but the enantioselectivities were consistently poor. The first promising results were achieved with ligands (*R*)-**L1**[14] and (*R*)-**L2**[14] and $CuBr{\cdot}SMe_2$, which gave 40% and 54% ee, respectively, in the addition of EtMgBr to the model substrate (*E*)-3-nonen-2-one (**1a**).[15] The combination of structural elements of these two ligands gave rise to the design of 3,3′-dimethyl-octahydro-BINOL derivatives (*S*)-**L3** and (*R*)-**L4** (Fig. 1).[16] The addition of EtMgBr to **1a** was studied at different temperatures and in different solvents with these new ligands (Table 1). In toluene at −30 °C, both ligands **L3** and **L4** gave the same enantioselectivity in the model reaction, although the regioselectivity (1,4-addition *vs* 1,2-addition product) was slightly better with ligand **L4** (entries 1 and 2). Different solvents were also evaluated[17] and *t*-BuOMe was found to give the same enantioselectivity in the reaction as toluene (entries 2 and 3). Lower temperatures (−50 °C) led to a significant decrease of regioselectivity (entry 4) while higher temperatures (0 °C) produced a slight decrease in enantioselectivity (entry 5).

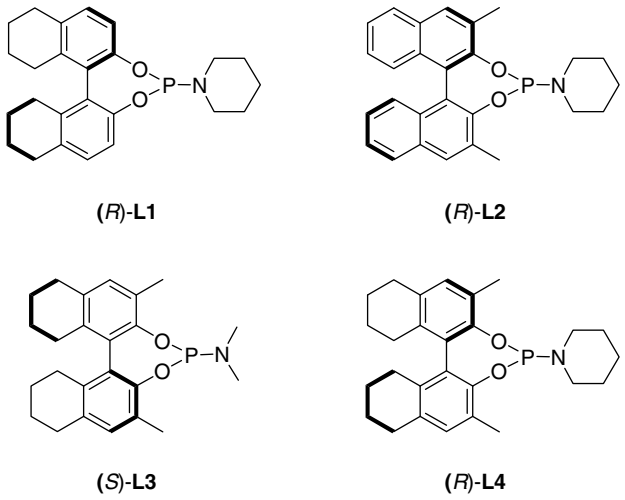


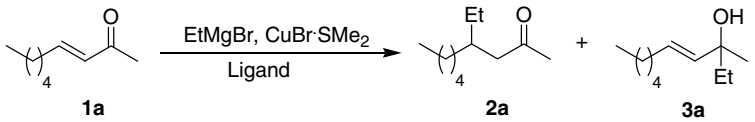
Fig. 1. Chiral phosphoramidites used in this study.

Next, we examined the influence on the enantioselectivity of the ligand/copper ratio as well as the catalyst loading in the addition of EtMgBr to the model substrate **1a** (Table 2). From these results we concluded that with a copper to ligand ratio ranging from 1:1 to 1:2, the addition was equally effective, as long as the catalyst loading was $\geqslant$6 mol % (entries 1, 4 and 6). Higher catalyst loadings did not produce any increase in enantioselectivity (entries 2 and 5). Other ligand/copper ratios were investigated without observing improvement in the enantioselectivity (entries 3 and 6).

Having established the optimal protocol, the addition of different Grignard reagents as well as a variety of aliphatic and aromatic linear enones was examined. The results are summarized in Table 3. Reactions were typically carried out at −30 °C, with 6 mol % of (*R*)-**L4** and 5 mol % of $CuBr{\cdot}SMe_2$ in toluene, for aromatic substrates, and in *t*-BuOMe, for the more volatile aliphatic substrates. A solution of Grignard reagent in *t*-BuOMe[18] was added dropwise to the mixture of substrate and ligand-copper complex at −30° C,[19] and full conversion was achieved in less than 1 h.

The conjugate addition of different Grignard reagents to linear aliphatic substrates (3-nonen-2-one and 4-hexen-3-one) occurred smoothly within 1 h at −30 ° C with excellent yields and good to moderate enantioselectivities (Table 3, entries 1-6). When linear alkyl Grignard reagents (MeMgBr, EtMgBr) were used as nucleophiles, **2a**, **2b** and **2d** were obtained with 52–80% ee (entries 1, 2 and 4). Gratifyingly, for the challenging bulky Grignard reagents, *i*-PrMgBr and *i*-BuMgBr, enantioselectivities were found to be 56% and 80% ee, respectively (entries 3 and 5). Addition of the sp^2 hybridized Grignard reagent PhMgBr

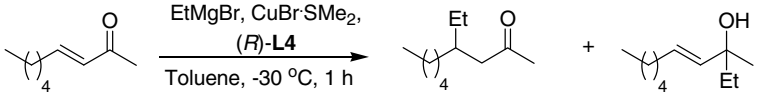
Table 1
Addition of EtMgBr to (*E*)-3-nonen-2-one (**1a**)[a,b]



Entry	Ligand	Solvent	Temp (°C)	**2a**:**3a**	ee[c] (%)
1	(*S*)-**L3**	Toluene	−30	97/3	60
2	(*R*)-**L4**	Toluene	−30	99/1	61
3	(*R*)-**L4**	*t*-BuOMe	−30	99/1	60
4	(*R*)-**L4**	Toluene	−50	90/10	54
5	(*R*)-**L4**	Toluene	0	99/1	55

[a] Reagents and conditions: **1a** (1 equiv), EtMgBr (1.2 equiv), $CuBr{\cdot}SMe_2$ (5 mol %), ligand (6 mol %), 1 h.
[b] All conversions >99% (GC–MS).
[c] Determined by chiral GC (see Supplementary data).

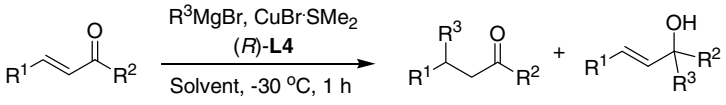
Table 2
Addition of EtMgBr to (*E*)-3-nonen-2-one (**1a**)[a,b]



Entry	Ratio ligand/CuBr·SMe_2 (mol %/mol %)	**2a**:**3a**	ee[c] (%)
1	1/1 (6/5)	99/1	60
2	1/1 (11/10)	99/1	60
3	1.5/1 (8/5)	99/1	60
4	2/1 (6/2.5)	82/18	48
5	2/1 (11/5)	99/1	60
6	3/1 (13/4)	98/2	55

[a] Reagents and conditions: **1a** (1 equiv), EtMgBr (1.2 equiv), CuBr·SMe_2 (*x* mol %), (R)-**L4** (*x* mol %), toluene, −30 °C, 1 h.
[b] All conversions >99% (GC–MS).
[c] Determined by chiral GC (see Supplementary data).

Table 3
Addition of Grignard reagents to enones[a,b]



Entry	**1**	R^1	R^2	R^3	**2**/**3**	Yield[c] (%)	ee[d] (%)
1	**1a**	*n*-Pent	Me	Me	99/1	81 (**2a**)	52 (S)[e]
2	**1a**	*n*-Pent	Me	Et	>99/1	85 (**2b**)	60 (S)[e]
3	**1a**	*n*-Pent	Me	*i*-Pr	>99/1	88 (**2c**)	56 (−)
4	**1b**	Me	Et	Et	>99/1	nd[f] (**2d**)	80
5	**1b**	Me	Et	*i*-Bu	>99/1	40[f] (**2e**)	80
6	**1b**	Me	Et	Ph	80/20	72 (**2f**)	54 (R)[e]
7	**1c**	*n*-Pent	*t*-Bu	Me	98/2	68 (**2g**)	66 (−)
8	**1d**	*i-Pr*	Me	Et	>99/1	92 (**2h**)	68 (+)
9	**1e**	Ph	Me	Et	98/2	80 (**2i**)	30 (S)[e]
10	**1e**	Ph	Me	*i-Pr*	>99/1	79 (**2j**)	22 (R)[e]
11	**1e**	Ph	Me	*i*-Bu	>99/1	50 (**2k**)	60 (+)
12	**1f**	2-Furyl	Me	Et	98/2	56 (**2l**)	52 (+)
13	**1g**	2-Thienyl	Me	Et	99/1	68 (**2m**)	44 (+)

[a] Reagents and conditions: **1** (1 equiv), R^3MgBr (1.2 equiv), CuBr·SMe_2 (5 mol %), (*R*)-**L4** (6 mol %), in *t*-BuOMe or toluene at −30 °C, 1 h.
[b] All conversions >99% (GC–MS).
[c] Isolated yield.
[d] Determined by chiral GC or HPLC.
[e] Absolute configuration determined by correlation with known compounds (see Supplementary data).
[f] Volatile product.

proceeded in good yield and with moderate enantioselectivity (entry 6).

We next studied the influence of the enone structure on the efficiency of the asymmetric CA. Ethyl ketone **1b** led to an increase in enantioselectivity compared to the methyl ketone **1a** (Table 3, entries 2 and 4), while substrate **1c** with a *t*-butyl substituent, gave comparable results to the methyl ketone **1a** (entries 2 and 7). Bulky substituents, like *i*-Pr on the β-position of the aliphatic enone, did not affect the enantioselectivity of the process. Thus, ketone **2h** was obtained from enone **1d** with 68% ee (entry 8); this selectivity is better than that already described for the same reaction using Josiphos ligand.[8]

Finally, we studied the addition of Grignard reagents to aryl-substituted substrates (Table 3, entries 9–13). The regioselectivity of the addition was excellent in all cases, and much higher than previously reported with Josiphos ligand.[8] Enantioselectivities varied from 30% to 52% for the addition of EtMgBr to benzylideneacetone (**1e**) and furyl and thienyl derivatives **1f** and **1g** (entries 9, 12 and 13). Addition of *i*-PrMgBr to **1e** proceeded with low enantioselectivity (entry 10), while the bulky Grignard reagent *i*-BuMgBr gave 60% ee (entry 11).

In conclusion, this study shows that CuBr·SMe_2/**L4** is an active catalyst for the addition of Grignard reagents to acyclic enones, providing optically active β-substituted

acyclic ketones in good yields and enantioselectivities up to 80%. Studies towards the elucidation of the mechanism of this transformation are currently in progress.

Acknowledgements

Financial support from the Dutch Ministry of Economics Affairs (ETT scheme; Grant No's.: EEKT-97107 and 99104). M.A.F.-I. thanks the Spanish Ministry of Education and Science for a postdoctoral fellowship. We thank T. D. Tiemersma-Wegman (GC and HPLC) and A. Kiewiet (MS) for technical assistance. A generous gift of (*S*)-BINOL and (*R*)-3,3′-dimethyl-BINOL from DSM is gratefully acknowledged.

Supplementary data

Experimental procedures, spectroscopic data of the ligands and analytical data of the reaction products. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.01.019.

References and notes

1. Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*, Tetrahedron Organic Chemistry Series 9; Pergamon Press: Oxford, UK, 1992.
2. For reviews, see: (a) Feringa, B. L.; de Vries, A. H. M. Asymmetric Chemical Transformations. In *Advances in Catalytic Processes 1*; Doyle, M. D., Ed.; JAI Press, 1995; (b) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221–3236; (c) Christoffers, J.; Koripelly, G.; Rosiak, A.; Roessle, M. *Synthesis* **2007**, 1279–1300.
3. (a) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 3, pp 1105–1120; (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171–196; (c) Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. In *Modern Organocopper Chemistry*; Krause, N., Ed.; VCH: Weinheim, Germany, 2002; pp 224–258; (d) Shintani, R.; Fu, G. C. *Org. Lett.* **2002**, *4*, 3699–3702; (e) Wan, H.; Hu, Y.; Liang, Y.; Gao, S.; Wang, J.; Zheng, Z.; Hu, X. *J. Org. Chem.* **2003**, *68*, 8277–8280.
4. (a) Feringa, B. L.; Badorrey, R.; Peña, D.; Harutyunyan, S. R.; Minnaard, A. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5834–5838; (b) Martin, D.; Kehrli, S.; D'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416–8417.
5. See, for example: (a) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052–5058; (b) Ma, Y.; Song, C.; Ma, C.; Sun, Z.; Chai, Q.; Andrus, M. B. *Angew. Chem., Int. Ed.* **2003**, *42*, 5871–5874 and references cited therein.
6. (a) Yamasaki, K.; Hayashi, T. *Chem. Rev.* **2003**, *103*, 2829–2844; (b) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169–196; (c) Oi, S.; Taira, A.; Honna, Y.; Inoue, Y. *Org. Lett.* **2003**, *5*, 97–99 and references cited therein.
7. (a) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779–781. For other examples of CA of dialkylzinc reagents to acyclic enones, see: (b) Borner, C.; Dennis, M. R.; Sinn, E.; Woodward, S. *Eur. J. Org. Chem.* **2001**, 2435–2446 and references cited therein.
8. (a) López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2004**, *126*, 12784–12785. For asymmetric CA of Grignard reagents to acyclic α,β-unsaturated esters and thioesters, see: (b) López, F.; Harutyunyan, S. R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 2752–2756; (c) Ruiz, B. M.; Geurts, K.; Fernández-Ibáñez, M. A.; ter Horst, B.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2007**, *9*, 5123–5126. For a review on enantioselective CA with Grignard reagents, see: (d) López, F.; Minnaard, A. J.; Feringa, B. L. *Acc. Chem. Res.* **2007**, *40*, 179–198.
9. Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346–353.
10. (a) de Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed.* **1996**, *35*, 2374–2376; (b) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed.* **1997**, *36*, 2620–2623.
11. Falciola, C. A.; Tissot-Croset, K.; Alexakis, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5995–5998.
12. Zhang, W.; Wang, L.-X.; Shi, W.-J.; Zhou, Q.-L. *J. Org. Chem.* **2005**, *70*, 3734–3736.
13. Woodward, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 5560–5562 and references cited therein.
14. Duursma, A.; Boiteau, J.-G.; Lefort, L.; Boogers, J. A. F.; De Vries, A. H. M.; De Vries, J. G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2004**, *69*, 8045–8052.
15. Reaction conditions: (*E*)-3-nonen-2-one (0.25 mmol), ligand (6 mol %), $CuBr{\cdot}SMe_2$ (5 mol %), toluene (2 mL), −30 °C, 1 h.
16. For the preparation of ligands **L3** and **L4**, see Supplementary data.
17. The reaction of (*E*)-3-nonen-2-one (0.25 mmol) and EtMgBr using **L4** (6 mol %), $CuBr{\cdot}SMe_2$ (5 mol %) at −30 °C in dichloromethane and diethyl ether resulted in 10–20% ee.
18. Grignard reagent solutions in diethyl ether caused a drastic drop in enantioselectivity.
19. Addition of the substrate to the mixture of Grignard reagent and phosphoramidite complex led to a decrease in enantioselectivity.