COMMUNICATION

ChemComm
www.rsc.org/chemcomm

A catalytic and iterative route to β-substituted esters *via* highly enantioselective conjugate addition of dimethylzinc to unsaturated malonates†

Julia Schuppan, Adriaan J. Minnaard and Ben L. Feringa*

Department of Organic and Molecular Inorganic Chemistry, Stratingh Institute, University of Groningen, Nijenborgh 4, 9749 AG Groningen, The Netherlands

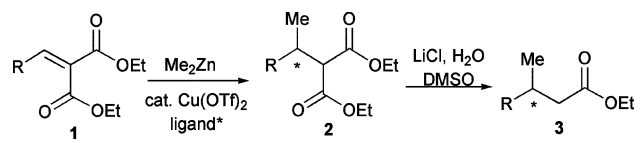
Received (in Cambridge, UK) 5th December 2003, Accepted 28th January 2004
First published as an Advance Article on the web 24th February 2004

Using the chiral phosphoramidite ligand (*S*,*R*,*R*)-L1 in the conjugate addition of dimethylzinc to acyclic unsaturated malonates, enantioselectivities of up to 98% have been obtained for the first time. An iterative and stereodivergent route to 3,5-dimethyl esters that takes advantage of this asymmetric catalysis has been developed.

Among several methods for catalytic asymmetric carbon–carbon bond formation, the copper-catalyzed conjugate addition of organozinc reagents to unsaturated carbonyl compounds is a widely used key transformation.[1] To date, efficient protocols for the conversion of both cyclic and acyclic enones, as well as nitroalkenes, have been developed featuring excellent stereocontrol.[1,2] Highly enantioselective additions have also been reported for lactones.[3,4] On the other hand, similar conjugate addition to acyclic unsaturated esters remains a major challenge, in particular, realizing the synthetic potential of optically active β-substituted esters as chiral building blocks in organic synthesis. In earlier studies, only moderate stereocontrol was achieved in the 1,4-addition of diethylzinc to nitro-substituted unsaturated esters[4] and malonates.[5] Recently, Hird and Hoveyda described the addition of diorganozinc reagents to *N*-acyloxazolidinones with excellent enantioselectivity applying peptide-based phosphine ligands.[6] We wish to report the development of a highly enantioselective, copper-catalyzed 1,4-addition to acyclic malonates employing monodentate phosphoramidite ligands.[7] Furthermore, an iterative and stereodivergent route to 3,5-dimethyl esters is presented.

Since simple acyclic unsaturated esters are not reactive in the conjugate addition of dialkylzincs, we focused on unsaturated malonates **1** (Scheme 1).[8] The products **2** can easily be converted into the monoesters **3** by dealkoxycarbonylation.[9] In view of the prominent role of the resulting structural motif in numerous natural products, the enantioselective introduction of a methyl substituent using Me_2Zn is considered the most important goal.

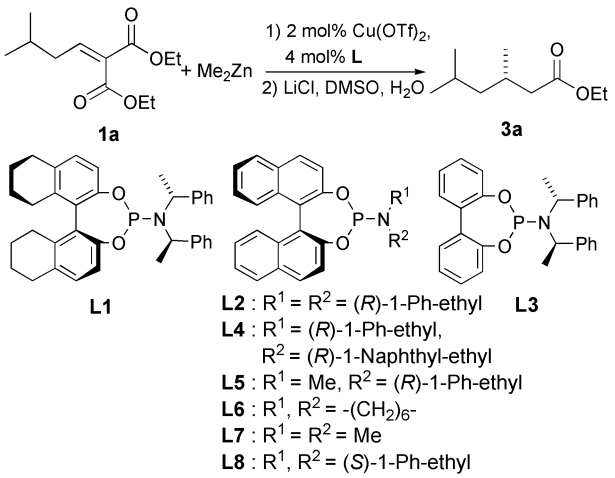
Diethyl isopentylidene malonate (**1a**) was chosen as a model substrate and a variety of phosphoramidite ligands were screened using 2 mol% of catalyst (Cu : L ratio 1 : 2; Scheme 2). The best results were obtained with ligands **L1**, **L2** and **L3**. Full conversion was reached within 1–2 h, producing ees of up to 94% (Table 1). These three ligands share the same amine part, but differ in the diol backbone. Exchanging the phenylethyl substituent at nitrogen for an alkyl group (**L5**–**L7**) decreased both conversion and ee (entries 5–7). Altering the configuration of the amine moiety from *S*,*R*,*R* in **L2** to *S*,*S*,*S* in **L8** resulted in a significantly lower reaction rate and reversed stereoselectivity, providing the *R*-enantiomer of **3a** as the major product.



Scheme 1

† Electronic supplementary information (ESI) available: experimental procedures and spectral data for all products. See http://www.rsc.org/suppdata/cc/b3/b315871c/

To further optimize the reaction conditions, **L1** and **L2** were tested in different solvents (Table 2). In toluene, an ee of 95% was obtained for both ligands. This could be improved to an excellent value of 97% ee by using heptane as the solvent. Diethyl ether and



Scheme 2 Conjugate addition of dimethylzinc to unsaturated malonic ester **1a**.

Table 1 Effect of the ligand in asymmetric conjugate addition of Me_2Zn to **1a** at −40 °C in toluene

Entry	Ligand	Conversion (%)	Time/h	ee[a] (%)
1	**L1**	100	2	94
2	**L2**	100	1	93
3	**L3**	100	2	93
4	**L4**	99	1	91
5	**L5**	84	21	90
6	**L6**	41	2	59
7	**L7**	22	21	21
8	**L8**	92	21	26[b]

[a] The configuration of the major product, (*S*)-**2a**, was determined by comparison of the optical rotation with literature data (see ESI†). [b] *R*-Enantiomer of **2a** obtained.

Table 2 Effect of the solvent in asymmetric conjugate addition of Me_2Zn to **1a** at −60 °C

Entry	Ligand	Solvent	Time[a]/h	ee (%)
1	**L1**	Toluene	4	95
2	**L2**	Toluene	2	95
3	**L1**	Heptane	24	97
4	**L2**	Heptane	20	97
5	**L1**	Diethyl ether	20	94
6	**L2**	Diethyl ether	4	94
7	**L1**	CH_2Cl_2	20	82
8	**L2**	CH_2Cl_2	4	88

[a] All conjugate additions were run to complete conversion.

DOI: 10.1039/b315871c

dichloromethane also lead to full conversion within 20 h, but somewhat lower ees were observed. As a general trend, it was found that longer reaction times were required to reach full conversion when using **L1** as compared to **L2**, whereas the ees were similar with both ligands.

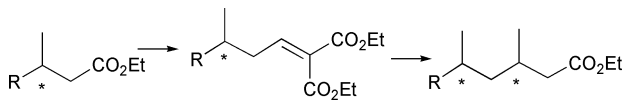
Under the optimized conditions, a number of unsaturated malonates were tested (Table 3). For linear alkyl substituents, excellent ees of up to 96% and full conversion within 25 h were achieved (entries 1–13). A second substituent at the γ-position lowers the reactivity of the system (entries 14–19); however, for the isopropyl-substituted malonic ester **1e**, an excellent ee of 98% was obtained using ligand **L1** in toluene. With the exception of substrate **1f**, in general, **L1** gave slightly higher ees than **L2**.

Table 3 Asymmetric conjugate addition of dimethylzinc to unsaturated malonic esters **1b**–**1f**[a]

Entry	Di-ester	R	Ligand	Solvent	Con-version (%)	Time/ h	ee[b] (%)
1	**1b**	Pr	**L1**	Toluene	100	21	95
2	**1b**	Pr	**L2**	Toluene	98	4	94
3	**1b**	Pr	**L1**	Heptane	98	21	96
4	**1b**	Pr	**L2**	Heptane	100	20	96
5	**1b**	Pr	**L1**	Diethyl ether	100	21	94
6	**1c**	Et	**L1**	Toluene	100	24	96
7	**1c**	Et	**L2**	Toluene	100	24	92
8	**1c**	Et	**L1**	Heptane	80	24	92
9	**1c**	Et	**L2**	Heptane	45	24	90
10	**1d**	$(CH_2)_2Ph$	**L1**	Toluene	98	2	86
11	**1d**	$(CH_2)_2Ph$	**L2**	Toluene	100	25	82
12	**1d**	$(CH_2)_2Ph$	**L1**	Heptane	98	25	66
13	**1d**	$(CH_2)_2Ph$	**L2**	Heptane	97	25	42
14	**1e**	*i*Pr	**L1**	Toluene	60	68	98
15	**1e**	*i*Pr	**L2**	Toluene	42	68	96
16	**1e**	*i*Pr	**L1**	Heptane	10	68	n.d.
17	**1e**	*i*Pr	**L2**	Heptane	8	68	n.d.
18	**1f**	1-Furyl	**L1**	Toluene	80	25	90
19	**1f**	1-Furyl	**L2**	Toluene	57	25	94

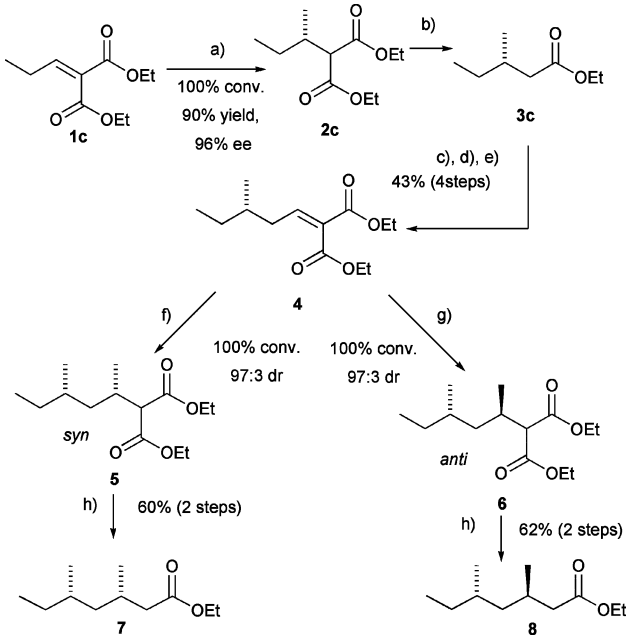
[a] All conjugate additions run at −60 °C. [b] The configuration of the major product was determined by comparison of the optical rotation with literature data (see ESI†). n.d.: not determined.

An attractive aspect of the new methodology is that it provides the basis for an iterative catalytic protocol (Scheme 3). In this way, the stereoselective construction of 3,5-dimethyl carbonyl motifs can be achieved, which are common in numerous naturally occurring compounds.[10]



Scheme 3 Iterative 1,4-addition.

Thus, diethyl propylidene malonate (**1c**) was subjected to an asymmetric conjugate addition providing, after decarboxylation, (*S*)-ethyl 3-methylpentanoate (**3c**) in excellent yield and enantioselectivity (Scheme 4). A sequence involving reduction of the ester moiety to the corresponding alcohol, oxidation to the aldehyde and subsequent Knoevenagel condensation gave access to unsaturated diester **4**. Subjecting **4** to a second catalytic asymmetric conjugate addition, again using ligand **L1** (configuration *S*,*R*,*R*) resulted in the *syn*-dimethylated product (*S*,*S*)-**5**, with an excellent selectivity of 97 : 3. With ligand *ent*-**L2** (configuration *R*,*S*,*S*) in the second conjugate addition, the other diastereomer, *anti*-(*S*,*R*)-**6** was formed and, again, very high selectivity (dr 97 : 3) was observed. The diastereoisomers **5** and **6** can easily be distinguished by NMR, GC and optical rotation (see ESI†). Apparently, the stereocenter present in substrate **4** has no influence on the stereochemical outcome of the second conjugate addition step. This nearly complete stereocontrol governed by the chiral catalyst in subsequent 1,4-additions



Scheme 4 *Reagents and conditions*: (a) 2 mol% $Cu(OTf)_2$, 4 mol% **L1**, 1.5 eq. Me_2Zn, toluene, −60 °C; (b) LiCl, H_2O, DMF; (c) DiBAL-H; (d) Dess–Martin oxidation; (e) diethyl malonate, pyridine, Ac_2O; (f) 3 mol% $Cu(OTf)_2$, 6 mol% **L1**, 1.5 eq. Me_2Zn, toluene, −60 °C; (g) 3 mol% $Cu(OTf)_2$, 6 mol% *ent*-**L2**, 1.5 eq. Me_2Zn, toluene, −60 °C; (h) LiCl, H_2O, DMSO.

provides a powerful tool in the new iterative scheme to *syn* and *anti* products (Scheme 4).

In summary, we have shown that excellent stereocontrol can be achieved in the catalytic conjugate addition of dimethylzinc to unsaturated malonic esters and that the methodology can be applied iteratively, thus allowing the construction of either *syn*- or *anti*-3,5-dimethyl carbonyl compounds.

This project was financially supported by the European Network COMBICAT (HPRN-CT-2000-00014).

Notes and references

1 (*a*) N. Krause and A. Hoffmann-Roder, *Synthesis*, 2001, 171–196; (*b*) B. L. Feringa, R. Naasz, R. Imbos and L. A. Arnold, in *Modern Organocopper Chemistry*, ed. N. Krause, Wiley-VCH, Weinheim, 2002; (*c*) A. Alexakis and C. Benhaim, *Eur. J. Org. Chem.*, 2002, 3221–3236.
2 (*a*) B. L. Feringa, M. Pineschi, L. A. Arnold, R. Imbos and A. H. M. de Vries, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2620–2623; (*b*) I. H. Escher and A. Pfaltz, *Tetrahedron*, 2000, **56**, 2879–2888; (*c*) H. Mizutani, S. J. Degrado and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2002, **124**, 779–781; (*d*) A. Duursma, A. J. Minnaard and B. L. Feringa, *J. Am. Chem. Soc.*, 2003, **125**, 3700–3701.
3 (*a*) M. Kanai, Y. Nakagawa and K. Tomioka, *Tetrahedron*, 1999, **55**, 3843–3854; (*b*) M. Yan, L.-W. Yang, K.-Y. Wong and A. C. S. Chan, *Chem. Commun.*, 2000, 115–116; (*c*) M. T. Reetz, A. Gosberg and D. Moulin, *Tetrahedron Lett.*, 2002, **43**, 1189–1191.
4 J. P. G. Versleijen, A. M. Leusen van and B. L. Feringa, *Tetrahedron Lett.*, 1999, **40**, 5803–5806.
5 A. Alexakis and C. Benhaim, *Tetrahedron: Asymmetry*, 2001, **12**, 1151–1157.
6 A. W. Hird and A. Hoveyda, *Angew. Chem., Int. Ed.*, 2003, **42**, 1276–1279.
7 B. L. Feringa, *Acc. Chem. Res.*, 2000, **33**, 346–353.
8 In accordance with observations by Alexakis *et al*. (see ref. 5), we found modest ees for the addition of Et_2Zn to malonates **1**, attributed to a significant uncatalyzed reaction.
9 A. P. Krapcho, *Synthesis*, 1982, 805–822.
10 See (*a*) A. Gambacorta, D. Tofani, P. Lupattelli and A. Tafi, *Tetrahedron Lett.*, 2002, **43**, 2195–2198 and references therein; (*b*) N. Tabata, Y. Ohyama, H. Tomoda, T. Abe, M. Namikoshi, Y. Yamaguchi, R. Masuma and S. Omura, *J. Antibiot.*, 1999, **52**, 815–826; (*c*) M. A. Calter and W. Liao, *J. Am. Chem. Soc.*, 2002, **124**, 127–129.