Tetrahedron Letters 50 (2009) 4741-4743

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Construction of a new type of chiral bidentate NHC ligands: copper-catalyzed asymmetric conjugate alkylation

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ARTICLE INFO

Article history: Received 29 April 2009 Revised 29 May 2009 Accepted 5 June 2009 Available online 9 June 2009

ABSTRACT

We synthesized in three steps simple chiral bidentate NHC compounds that carry an achiral coordinating group as N-substituent and revealed that they serve as efficient chiral auxiliaries for the copper-catalyzed asymmetric conjugate addition of dialkylzinc to acyclic enones (up to 97% ee).

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Recently, optically active N-heterocyclic carbene compounds (NHC compounds) have attracted significant attention for their application in asymmetric synthesis.^{1,2} In 1962, Wanzlick reported the seminal study on the unique catalytic performance of NHC compounds³ and, in 1968, Öfele reported the synthesis of NHCtransition metal complexes.⁴ Subsequent to these studies, a stable NHC was synthesized⁵ and the catalysis of NHCs has been intensively studied.^{2,6,7} Furthermore, the ligating properties of NHC compounds have attracted increasing attention because of the discovery of unprecedented catalysis by transition-metal NHC complexes, such as the ruthenium catalyst for olefin metathesis^{1c} and the palladium catalyst for C-C bond formation.^{1e} Moreover, Burgess and co-workers reported the asymmetric hydrogenation of alkenes using a Ir-chiral NHC complex as the catalyst.^{8a} Since then, various chiral-NHC ligands have been introduced, and their transition-metal complexes have been used as the catalysts for asymmetric reactions such as hydrogenation,^{1b,8} olefin metathesis,^{1c,9} allylic substitution,^{1a,10} and the aerobic oxidation of alcohols.¹¹

Conjugate addition to enones is a useful method not only for C– C bond formation but also for the generation of a stereogenic center. Thus, the asymmetric version of the conjugate addition has been extensively studied,¹² and chiral NHC–transition metal complexes have also been found to be efficient catalysts for conjugate addition reactions.¹³ Among the NHC ligands, bidentate NHC ligands bearing a chiral or dynamically induced chiral coordinating N-substituent generally induce high asymmetry. Mauduit's group has reported that the addition of various dialkylzinc to cyclic enones in the presence of **1a** proceeds with high enantioselectivity (up to 93% ee).^{13a,b} Alexakis and co-workers have also reported that the copper-mediated addition of Grignard reagents to β -substitued cyclic enones in the presence of **1b** proceeds with high enantioselectivity.^{13e} Moreover, Hoveyda and co-workers reported the highly enantioselective addition of alkyl- and aryl-zincs and alkyl-

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and aryl-aluminums to β -substituted cyclic enones in the presence of NHC derivatives **2** and **3**, respectively (up to 97% ee).^{13c,d} The Nsubstituent of **3** is achiral but it is conformationally fixed to induce an axial chirality upon the chelate formation.^{13d} However, good substrates for these addition reactions are mostly limited to cyclic enones (Fig. 1).

On the other hand, it is known that, when the N-substituent in 4,5-*trans*-1,3,4,5-tetrasubstituted 4,5-dihydroimidazolium salts is an arylmethyl group, the aryl group is *anti* to the vicinal C-substituent.^{13f,g,14} Thus, we expected that the NHC ligands **4**, bearing an achiral N₁-(*m*-substituted *o*-hydroxy)benzyl and N₃-aryl groups, would form a broad chiral coordination sphere around the metal center upon complex formation (Fig. 2 and Scheme 1) and that the complex, dialkylzinc, and enone would combine therein to give a postulated bimetallic intermediate in the conjugate addition.^{12,15} Moreover, it was expected that the ligands **4a**-**f** were synthesized in a modular manner. Indeed, the ligands **4a**-**f** were synthesized in three steps from (1*R*,2*R*)-1,2-diphenylethyrenediamine (Scheme 1): (i) Buchwald amination,¹⁶ (ii) reductive amination, and (iii) imidazolium formation.^{14b}



2a: R=H, Binaphthyl 2b: R=Ph, Biphenyl

Ha-2 6-Eta

Figure 1. Previous examples of chiral bidentate NHC ligands.

1a: R=*i*-Pr **1b**: R=*t*-Bu



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Figure 2. An expected structure of a metal-NHC complex



Scheme 1. Synthesis of NHC ligands 4.

With a series of imidazolium salts in hand, we first examined the reaction of chalcone using diethylzinc, triethylaluminum, or ethylmagnesium chloride as the alkylating agent in the presence of $Cu(OTf)_2$ and the imidazolium salt **4a** in tetrahydrofuran (THF) at $-20 \degree C$ (Table 1, runs 1–3). The reaction with diethylzinc gave among the best results (run 1). The use of the imidazolium salt **4b** improved the enantioselectivity to 94%, albeit with moderate yield (run 4). The use of *N*,*N*-dimethylformamide (DMF) as the sol-

Table 1

Optimization of the asymmetric addition reaction of diethylzinc to chalcone using in situ prepared NHC-Cu complexes as the catalyst^a

Run	Ligand	4/Cu/base (mol %)	Solvent	Temp (°C)	Yield ^b (%)	ee ^c (%)
1	4a	5/2.5/5.5	THF	-20	>99	89 ^d
2 ^e	4a	5/2.5/5.5	THF	-20	28	52
3 ^f	4a	5/2.5/5.5	THF	-20	24	8
4	4b	5/2.5/5.5	THF	-20	35	94
5	4b	5/2.5/5.5	DMF	-20	81	97
6	4b	5/2.5/5.5	DMF	-10	95	97
7	4b	5/2.5/5.5	DMF	rt	47	91
8	4c	5/2.5/5.5	DMF	-10	52	82
9	4d	5/2.5/5.5	DMF	-10	81	84
10	4e	5/2.5/5.5	DMF	-10	69	85
11	4f	5/2.5/5.5	DMF	-10	52	86
12	4b	2.5/2.5/2.8	DMF	-10	93	97 ^d
13 ^g	4b	1/1/1.1	DMF	-10	99 (98) ^{d,h}	97 (97) ^{d,h}
14	4b	0.1/0.1/0.1	DMF	-10	50	90
15	4b	1/0/0	DMF	-10	21	64

^a Reaction was carried out with a molar ratio of chalcone (0.1 mmol), diethylzinc (0.15 mmol), and solvent (0.5 mL) in the presence of the described amounts of ligand, $Cu(OTf)_2$ and *t*-BuONa under N₂.

^b Isolated vield.

- ^c Determined by HPLC with DAICEL CHIRALCEL AD-H (hexane/*i*-PrOH = 99:1).
- ^d The absolute configuration of the product was *S*. (See Ref. 18.)
- ^e Triethylaluminum was used.
- ^f Ethylmagnesium chloride was used.
- ^g The reaction was run on a 0.5-mmol scale.
- ^h The reaction was run on a 5.0-mmol scale.

vent remarkably improved both the enantioselectivity and the chemical yield (run 5). Moreover, the reaction at -10 °C provided a better result (97% ee, 95%) (run 6). The reactions at room temperature reduced the enantioselectivity and yield (run 7). The reactions were further examined using **4c**-**f** as the ligands at -10 °C, but no improvement was observed in enantioselectivity and chemical yield (runs 8–11). We next examined the reaction using reduced catalyst loading (runs 12–14). The reactions proceeded without diminishing enantioselectivity even at 1 mol% catalyst loading (run 13). The reaction could be carried out even on a 5 mmol scale.¹⁷ However, further reduction of catalyst loading diminished both the enantioselectivity and yield (run 14). The reaction in the absence of copper salt was slow and less enantioselective (run 15).

Under the optimized reaction conditions, we examined the conjugate addition reaction of dialkylzinc to various acyclic enones (Table 2). The reactions with chalcone derivatives proceeded with high enantioselectivities (up to 97% ee), irrespective of dialkylzinc (runs 1–6). The reactions of *E*-alkenyl phenyl ketones (\mathbb{R}^1 = alkyl) also proceeded with high enantioselectivities (94–95% ee) and yields (90–>99%) (runs 7–9). In contrast, the conjugate addition to benzal acetone (\mathbb{R}^2 = Me) showed almost no enantioselectivity (run 10). However, the use of *n*-BuLi as the base was found to induce a reversed enantioselectivity, albeit with low selectivity (run 11). Thus, we examined the reaction using ligands **4c**–**f** in the presence of *n*-BuLi in THF, and a moderate enantioselectivity of 69% was obtained when **4f** was used (run 12). An identical enantioselectivity was also obtained in the reaction of 5-methyl-3-hexen-2-one (run 13).

As aforementioned, conjugate addition to cyclic enones often proceeds with high enantioselectivity, while the selectivity of the addition to acyclic substrates is generally lower due to the *s*-cis/*s*-trans conformational flexibility.^{12,20,21} However, some of the

Table 2

Asymmetric conjugate reaction of dialkylzinc to acyclic enones^a

 $B^{1} \xrightarrow{\text{O}} B^{2} \xrightarrow{\text{I}/1/1.1 (1mol %), R^{3}_{2}Zn} B^{3} \xrightarrow{\text{R}^{3}} B^{1} \xrightarrow{\text{R}^{3}} B^{1}$

	11 1	n Divir,	N ₂ , -10	-0 n		
Run	R ¹	R ²	R ³	Time (h)	Yield ^b (%)	ee (%)
1	p-Cl-C ₆ H ₄	Ph	Et	2	>99	97 ^{c,d}
2	p-MeO-C ₆ H ₄	Ph	Et	12	62	96 ^{c,d}
3	Ph	p-Cl-C ₆ H ₄	Et	2	>99	97 ^c
4	Ph	p-MeO-C ₆ H ₄	Et	12	56	96 ^{d,e}
5	Ph	Ph	Me	12	86	95 ^c
6	Ph	Ph	<i>i</i> -Pr	2	54	92 ^c
7	Me	Ph	Et	2	90	95 ^f
8	i-Pr	Ph	Et	2	>99	94 ^g
9	n-Pentyl	Ph	Et	2	90	94 ^f
10	Ph	Me	Et	12	62	2
11 ⁱ	Ph	Me	Et	24	67	-7
12 ^j	Ph	Me	Et	24	70	-69 ^{h,k}
13 ^j	<i>i</i> -Pr	Me	Et	24	39 ¹	69 ^{m,n}

 a Reaction was carried out with a molar ratio of enone (0.5 mmol), dialkylzinc (0.75 mmol), and DMF (2.5 mL) under N2 at -10 °C.

^b Isolated yield.

^c Determined by HPLC with DAICEL CHIRALCEL AD-H (hexane/i-PrOH = 99:1).

^d The absolute configuration of the product was *S*. (See Ref. 18.)

^e Determined by HPLC with DAICEL CHIRALPAC IA (hexane/i-PrOH = 90:10).

^f Determined by HPLC with DAICEL CHIRALCEL OD-H (hexane).

- ^g Determined by GLC with CP CP-CHIRASIL-DEX CB (30 m), 120 °C, 35 cm/s.
- * Determined by GLC with CF CF-CHIKASIL-DEX CB (50 m), 120 C, 55 C
- Determined by HPLC with DAICEL CHIRALCEL AD-H (hexane/i-PrOH = 99.5:0.5).

The reaction was run in THF with *n*-BuLi as the base.

^j The reaction was run in THF with *n*-BuLi as the base in the presence of **4f**.

- ^k The absolute configuration of the product was *R*. (See Ref. 18.)
- ¹ Determined by GLC using bicyclohexyl as the internal standard.
- ^m Determined by GLC with SUPELCO GAMMA-DEX 225 (30 m), 55 °C, 50 cm/s.

ⁿ The configuration of the product has not been determined.

reactions that proceed through a highly ordered transition state proceed with high enantioselectivity.^{12,15,20} Although the mechanism of the present reaction is unclear, it is likely that the reaction also proceeds through an ordered transition state, from the catalyst structure bearing a precoordinating substituent. Thus, we examined the reaction of 2-cyclohexen-1-one; however, the reaction showed poor selectivity.²² This result suggests that a π -complex intermediate formed from the *s*-cis isomer of enone participates in the present reaction.^{15b}

In conclusion, we introduced new bidentate NHC ligands that can be prepared in a modular fashion, and we revealed that they serve as efficient chiral auxiliaries for the copper-catalyzed asymmetric conjugate addition reaction of dialkylzinc to acyclic enones. We believe that this study expands the utility of chiral bidentate NHC ligands in asymmetric synthesis.

Acknowledgments

The authors acknowledge the financial support from a Grant-in-Aid for Scientific Research on Priority Areas 18037056 'Advanced Molecular Transformations of Carbon Resources' and Specially Promoted Research 18002011 from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References and notes

- For recent reviews on the catalysis of transition metal-NHC complexes, see: (a) Douthwaite, R. E. Coord. Chem. Rev. 2007, 251, 702-717; (b) Gade, L. H.; Bellemin-Laponnaz, S. Coord. Chem. Rev. 2007, 251, 718-725; (c) Colacino, E.; Martinez, J.; Lamaty, F. Coord. Chem. Rev. 2007, 251, 726-764; (d) Dragutan, V.; Dragutan, I.; Delaude, L.; Demonceau, A. Coord. Chem. Rev. 2007, 251, 765-794; (e) Nolan, S. P. N-Heterocyclic Carbenes in Synthesis; Wiley-VCH: Weinheim, Germany, 2006; (f) Diez-González, S.; Nolan, S. P. Annu. Rep. Chem., Sect. B 2005, 101, 171-191; (g) César, V.; Bellemin-Laponnaz, S.; Gade, L. H. Chem. Soc. Rev. 2004, 33, 619-636.
- For recent reviews on the catalysis of the NHC compounds, see: (a) Enders, D.; Niemeier, O.; Henseler, A. Chem. Rev. 2007, 107, 5606–5655; (b) Marion, N.; Díez-González, S.; Nolan, S. P. Angew. Chem., Int. Ed. 2007, 46, 2988–3000; (c) Zeitler, K. Angew. Chem., Int. Ed. 2005, 44, 7506–7510; (d) Enders, D.; Balensiefer, T. Acc. Chem. Res. 2004, 37, 534–541; (e) Nair, V.; Bindu, S.; Sreekumar, V. Angew. Chem., Int. Ed. 2004, 43, 5130–5135.
- (a) Wanzlick, H. W. Angew. Chem., Int. Ed. Engl. 1962, 1, 75–80; (b) Wanzlick, H. W.; Esser, F.; Kleiner, H. J. Chem. Ber. 1963, 96, 1208–1212; (c) Wanzlick, H.-W.; Schönherr, H.-J. Angew. Chem., Int. Ed. Engl. 1968, 7, 141–142.
- (a) Öfele, K. J. Organomet. Chem. 1968, 12, P42–P43; (b) Öfele, K.; Herberhold, M. Angew. Chem., Int. Ed. Engl. 1970, 9, 739–740; (c) Öfele, K. J. Organomet. Chem. 1970, 22, C9–C11.
- 5. Arduengo, A. J., III; Harlow, R. L.; Kline, M. J. Am. Chem. Soc. 1991, 113, 361-363.
- (a) Díez-González, S.; Nolan, S. P. Coord. Chem. Rev. 2007, 251, 874–883; (b) Hermann, W. A. Angew. Chem., Int. Ed. 2002, 41, 1290–1309; (c) Green, J. C.; Scurr, R. G.; Arnold, P. L.; Cloke, G. N. Chem. Commun. 1997, 20, 1963–1964.
- (a) Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G. R. J. Angew. Chem., Int. Ed. Engl. 1995, 34, 2371–2374; (b) Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J.-P.; Ebel, K.; Brode, S. Angew. Chem., Int. Ed. Engl. 1995, 34, 1021–1023.
- Selected recent examples: (a) Powell, M. T.; Hou, D.-R.; Perry, M. C.; Cui, X.; Burgess, K. J. Am. Chem. Soc. 2001, 123, 8878–8879; (b) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K. J. Am. Chem. Soc. 2003, 125, 113–123; (c) Bappert, E.; Helmchen, G. Synlett 2004, 1789–1793; (d) Song, C.; Ma, C.; Ma, Y.; Feng, W.; Ma, S.; Chai, Q.; Andrus, M. B. Terahedron Lett. 2005, 46, 3241–3244.
- Selected recent examples: (a) Seiders, T. J.; Ward, D. W.; Grubbs, R. H. Org. Lett. 2001, 3, 3225–3228; (b) Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. J. Am. Chem. Soc. 2002, 124, 4954–4955; (c) Gillingham, D. G.; Kataoka, O.; Garber, S. B.; Hoveyda, A. H. J. Am. Chem. Soc. 2004, 126, 12288– 12290; (d) Van Veldhuizen, J. J.; Campbell, J. E.; Giudici, R. E.; Hoveyda, A. H. J. Am. Chem. Soc. 2005, 127, 6877–6882; (e) Funk, T. W.; Berlin, J. M.; Grubbs, R. H. J. Am. Chem. Soc. 2006, 128, 1840–1846; (f) Berlin, J. M.; Goldberg, S. D.; Grubbs, R. H. Angew. Chem., Int. Ed. 2006, 45, 7591–7595; (g) Fournier, P.-A.; Collins, S. K. Organometallics 2007, 26, 2945–2949.

- Selected recent examples: (a) Tominaga, S.; Oi, Y.; Kato, T.; An, D. K.; Okamoto, S. *Tetrahedrone Lett.* **2004**, 45, 5585–5588; (b) Larsen, A. O.; Leu, W.; Oberhuber, C. N.; Campbell, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 11130–11131.
- 11. Jensen, D. R.; Sigmann, M. S. Org. Lett. 2003, 5, 63-65
- For recent reviews on asymmetric conjugate addition reaction, see: (a) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pamies, O.; Diéguez, M. Chem. Rev. 2008, 108, 2796–2823; (b) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. Synthesis 2007, 1279–1300; (c) López, F.; Minnaard, A. J.; Feringa, B. L. Acc. Chem. Res. 2007, 40, 179–188; (d) Alexakis, A.; Benhaim, C. Eur. J. Org. Chem. 2002, 3221–3236; (e) Krause, N.; Hoffmann-Röder, A. Synthesis 2001, 171–196; (f) Feringa, B. L. Acc. Chem. Res. 2000, 33, 346–353; (g) Tomioka, K.; Nagaoka, Y. In Comprehensive Asymmetric Catalysis; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; pp 1105–1120; (h) Yamaguchi, M. In Comprehensive Asymmetric Catalysis; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; pp 1121–1139.
- For recent selected examples, see: (a) Clavier, H.; Coutable, L.; Toupet, L.; Guillemin, J.-C.; Mauduit, M. J. Organomet. Chem. 2005, 690, 5237-5254; (b) Clavier, H.; Coutable, L.; Guillemin, J.-C.; Mauduit, M. Tetrahedron: Asymmetry 2005, 921-924; (c) Lee, K.-S.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. J. Am. Chem. Soc. 2006, 128, 7182-7184; (d) May, T. L.; Brown, M. K.; Hoveyda, A. H. Angew. Chem., Int. Ed. 2008, 47, 7358-7362; (e) Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. J. Am. Chem. Soc. 2006, 128, 8416-8417; (f) Matsumoto, Y.; Tomioka, K. Tetrahedron Lett. 2006, 47, 5843-5846; (g) Matsumoto, Y.; Yamada, K.-I.; Tomioka, K. J. Org. Chem. 2008, 73, 4578-4581.
- (a) Faller, J. W.; Fontaine, P. P. Organometallics 2006, 25, 5887–5893; (b) Winn, C. L.; Guillen, F.; Pytkowicz, J.; Roland, S.; Mangeney, P.; Alexakis, A. J. Organomet. Chem. 2005, 690, 5672–5695.
- (a) Ito, K.; Eno, S.; Saito, B.; Katsuki, T. Tetrahedron Lett. 2005, 46, 3981–3985;
 (b) Hajra, A.; Yoshikai, N.; Nakamura, E. Org. Lett. 2006, 8, 4153–4155.
- Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. Acc. Chem. Res. 1998, 31, 805–818.
- 17. Typical experimental procedure for the asymmetric 1,4-conjugate addition of diethylzinc to enones in the presence of imidazolium salt 4b: Imidazolium salt 4b (3.5 mg, 0.05 mmol) and t-BuONa (0.5 mg, 0.055 mmol) were stirred in THF (1.0 mL) under a nitrogen atmosphere at room temperature. After 30 min, Cu(OTf)₂ (1.8 mg, 0.05 mmol) was added to the mixture, and the whole mixture was stirred for another 30 min. THF was removed in vacuo, and the residue was re-dissolved in 25 mL of DMF. Chalcone (1.0 g, 5.0 mmol) was added to the mixture, and the mixture was cooled to -10 °C. Then, a hexane solution of diethylzinc (7.0 mL, 7.5 mmol) was slowly added to the reaction mixture. After 90 min, the reaction was guenched with saturated NH₄Cl aq (5.0 mL), and the mixture was extracted twice with AcOEt (5.0 mL). The combined organic phases were washed with saturated brine $(2 \times 5.0 \text{ mL})$ and dried over MgSO₄. After removal of the solvent, the residue was chromatographed on silica gel (hexane/AcOEt = 50:1 to 20:1) to afford the product (1.2 g, 98%). The enantiomeric excess of the product was determined to be 97% by HPLC analysis using DAICEL CHIRALCEL AD-H (hexane/i-PrOH = 99:1).
- 18. The specific rotations of the products are given below: (a) 1,3-Diphenyl-1-pentanone (97% ee): $[\alpha]_D^{24} + 7.1 (c 2.0, EtOH); lit.^{19a} [96\% ee, (S)-isomer: <math>[\alpha]_D^{24} + 6.07 (c 5.85, EtOH)]$ (Table 1, run 13). (b) 3-(4-Chlorophenyl)-1-phenyl-1-pentanone (97% ee): $[\alpha]_D^{24} + 1.9 (c 2.0, EtOH); lit.^{14a} [99\% ee, (S)-isomer: <math>[\alpha]_D^{24} + 1.5 (c 1.13, EtOH)]$ (Table 2, run 1). (c) 3-(4-Methoxyphenyl)-1-phenyl-1-pentanone (96% ee): $[\alpha]_D^{24} + 1.5 (c 2.0, EtOH); lit.^{19a} [96\% ee (S)-isomer: <math>[\alpha]_D^{24} + 15.5 (c 0.98, EtOH)]$ (Table 2, run 2). (d) 1-(4-Methoxyphenyl)-3-phenyl-pentanone (96% ee): $[\alpha]_D^{25} 2.3 (c 2.1, EtOH); lit.^{19a} [97\% ee (S)-isomer: <math>[\alpha]_D^{24} 4.0 (c 2.2, EtOH)]$ (Table 2, run 4). (e) 1,3-Diphenyl-1-butanone (95\% ee): $[\alpha]_D^{25} + 13.4 (c 2.0, CCI_4); lit.^{19b} [82\% ee (R)-isomer: <math>[\alpha]_D^{24} 20.9 (c 2.0, EtOH); lit.^{15a} [90\% ee, (S)-isomer; <math>[\alpha]_D^{24} + 25.4 (c 0.16, EtOH)]$ (Table 2, run 12).
- (a) Shi, M.; Wang, C.-J.; Zhang, W. Chem. Eur. J. 2004, 10, 5507–5516; (b) Kanazawa, Y.; Tsuchiya, Y.; Kobayashi, K.; Shiomi, T.; Itoh, J.-I.; Kikuchi, M.; Yamamoto, Y.; Nishiyama, H. Chem. Eur. J. 2006, 12, 63–71; (c) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. J. Am. Chem. Soc. 2002, 124, 5262– 5263.
- (a) Harutyunyan, S. R.; López, F.; Browne, W. R.; Correa, A.; Peña, D.; Badorrey, R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 9103– 9118; (b) García, J. M.; González, A.; Kardak, B. G.; Odriozola, J. M.; Oiarbide, M.; Razkin, J.; Palomo, C. *Chem. Eur. J.* **2008**, *14*, 8768–8771.
- With acyclic enones ees of conjugate addition are generally <90%. For exceptions, see: (a) Hu, X.; Chen, H.; Zhang, X. Angew. Chem., Int. Ed. 1999, 38, 3518–3521; (b) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. J. Am. Chem. Soc. 2002, 124, 779–781; (c) Duncan, A. P.; Leighton, J. L. Org. Lett. 2004, 6, 4117–4119; (d) Takahashi, Y.; Yamamoto, Y.; Katagiri, K.; Danjo, H.; Yamaguchi, K.; Imamoto, T. J. Org. Chem. 2005, 70, 9009–9012.
- 22. The reaction of 2-cyclohexen-1-one and diethylzinc in the presence of **4f** at -10 °C for 24 h was poorly selective (3% ee, 54% yield).