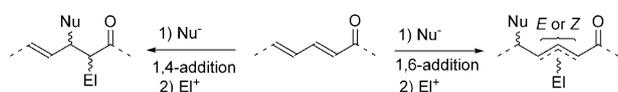


Homogeneous Catalysis

Iron-Catalyst-Switched Selective Conjugate Addition of Grignard Reagents: $\alpha,\beta,\gamma,\delta$ -Unsaturated Amides as Versatile Templates for Asymmetric Three-Component Coupling Processes**

Satoshi Okada, Kyohei Arayama, Ryuji Murayama, Takumi Ishizuka, Keiichi Hara, Naoki Hirone, Takeshi Hata, and Hirokazu Urabe*

Conjugate addition of Grignard reagents to α,β -unsaturated carbonyl compounds is one of the most fundamental methods for carbon–carbon bond formation and is usually carried out with copper catalysis.^[1,2] Among the various kinds of carbonyl compounds employed for this procedure, dienic substrates have not been amply investigated, presumably as a result of the accumulated difficulties in controlling both regio- and stereoselections, as shown in Scheme 1.^[3,4] We report herein

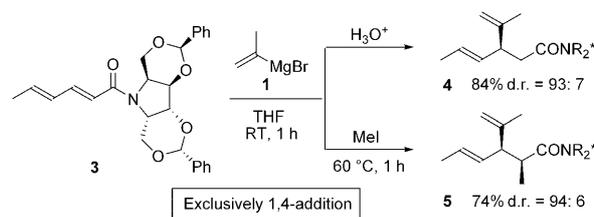


Scheme 1. Conjugate addition to dienic carbonyl compounds.

that $\alpha,\beta,\gamma,\delta$ -unsaturated amides work as a simple yet versatile template to circumvent this problem, where the absence or presence of an iron catalyst, rather than the aforementioned copper catalyst, is another key to achieving clear-cut reactions.

While 1,4-regioselective addition of Grignard reagents to $\alpha,\beta,\gamma,\delta$ -unsaturated amides was documented almost twenty-five years ago, we revisited this reaction using (*E,E*)-*N,N*-diethyl-2,4-hexadienamides as a dienic substrate.^[5] After surveying various Grignard reagents, we found that using isopropenylmagnesium bromide (**1**) results in an excellent 1,4-:1,6-selectivity of 94:6 in THF without any other additive(s) to give (*E*)-*N,N*-diethyl-3-isopropenyl-4-hexenamides (**2**) in a synthetically acceptable 65% yield. This result

allowed us to explore asymmetric 1,4-addition by using a chiral amide group.^[6] Among several such candidates,^[7] amide **3**, incorporating a sugar-derived pyrrolidine unit (Scheme 2),^[8] showed exclusive 1,4-regioselectivity and sat-



Scheme 2. 1,4-Addition of Grignard reagent and successive alkylation.

isfactory product yield (**4**, 84%), both of which were more enhanced than those of **2**, probably as a result of the ether functionality present in the chiral auxiliary (see below). We also found that conjugate addition was highly stereoselective, giving **4** in 93:7 diastereoselectivity. More importantly, the subsequent alkylation of the resultant enolate also proceeded in a highly stereoselective manner to give **5** (Scheme 2), which consists of a 94:6 mixture of two major diastereoisomers with two other isomers being formed in trace amounts.^[9,10] This ratio (94:6) reflects that of the addition product **4** (93:7), thus suggesting that the stereochemistry of methylation is perfectly controlled by the proximate chiral amide auxiliary, which is further evidenced by the fact that the isomeric ratio of **5** did not change after the removal of amide auxiliary, as shown in Equation (1).

Scheme 3 illustrates a proposed reaction course. The reaction should proceed via a less hindered conformation **3** (rather than **3'**), in which the reacting Grignard reagent **1** is fixed at the depicted position in **6** by the chelation of magnesium to the carbonyl and acetal oxygen atoms. From the intermediate **6**, the alkenyl (*R*) group migrates to the diene carbon β to the carbonyl group, to account for the higher 1,4-selectivity and better product yield (of **4**) than for the simple diethylamide **2**. In addition, alkylation of the resulting enolate **7** most likely proceeds from the side where the magnesium coordinates (as in **8**), to produce **5**.

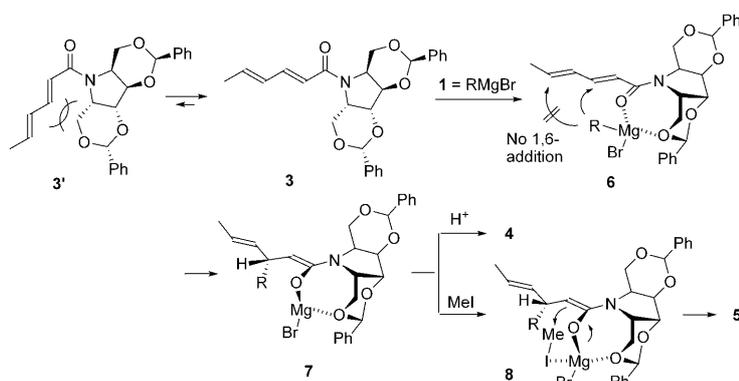
Results for the above three-component coupling process, incorporating different amides, Grignard reagents, and organic halides, are listed in Table 1. The chiral enolate generated by the 1,4-addition was alkylated with activated halides, such as methyl iodide, allyl bromide, propargyl

[*] S. Okada,^[†] K. Arayama,^[†] R. Murayama, T. Ishizuka, K. Hara, N. Hirone, Dr. T. Hata, Prof. Dr. H. Urabe
Department of Biomolecular Engineering, Graduate School of Bioscience and Biotechnology
Tokyo Institute of Technology
4259-B-59 Nagatsuta-cho, Midori-ku, Yokohama, Kanagawa 226-8501 (Japan)
Fax: (+81) 45-924-5849
E-mail: hurabe@bio.titech.ac.jp
Homepage: <http://www.urabe-lab.bio.titech.ac.jp>

[†] These authors contributed equally to this work.

[**] This work was supported by a Grant-in-Aid for Scientific Research on Priority Area (No.16073208) and a Grant-in-Aid for Young Scientists (B) (No. 20750071, to T.H.) from the Ministry of Education, Culture, Sports, Science and Technology (Japan).

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.200801928>.



Scheme 3. Proposed reaction course for 1,4-addition.

bromide, and benzyl bromide (other than entry 4), and also a less reactive primary-alkyl iodide (Table 1, entry 4) in good yields with exclusive regioselectivity and excellent diastereoselectivities.^[10] α -Hexyl- and α -silylvinyl Grignard reagents

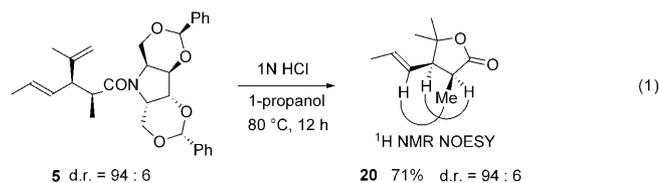


Table 1: Three-component coupling process based on 1,4-addition of Grignard reagents according to Scheme 2.^[a]

Entry	Substrate	Grignard Reagent	Alkylation	Product ^[b]	Yield [%] ^[c]	d.r. ^[d]
1			MeI		74	94:6
2					66	95:5
3					44	94:6
4			C ₆ H ₁₃ I		62	94:6
5			MeI		73	92:8
6			MeI		53	97:3
7 ^[e]			BnBr ^[f]		65	94:6
8 ^[e]			MeI		76	95:5
9 ^[e]			MeI		87	93:7

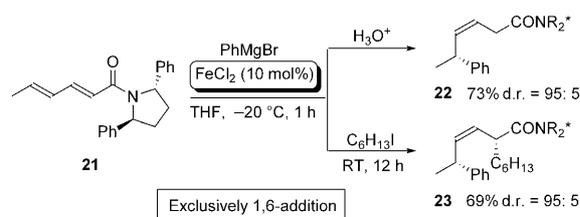
[a] Molar ratio: dienamide/Grignard reagent/alkylating agent = 1:2:4. [b] The most abundant diastereoisomer is depicted. Absolute stereochemistries of 9–13 and 17–19 were deduced based on that of 5 by analogy. [c] Yields that are not necessarily optimized. [d] The ratio of two major diastereoisomers. Two other isomers, which were formed in less than trace amounts and could not be isolated nor characterized, are omitted. [e] NR₂* is the same as that in 3. [f] Alkylation was performed at room temperature for 12 h.

also gave the products **12** and **13** with high asymmetric induction (Table 1, entries 5 and 6). Variation in the amide substrates (**14**–**16**) further illustrated the synthetic flexibility of this method (Table 1, entries 7–9).

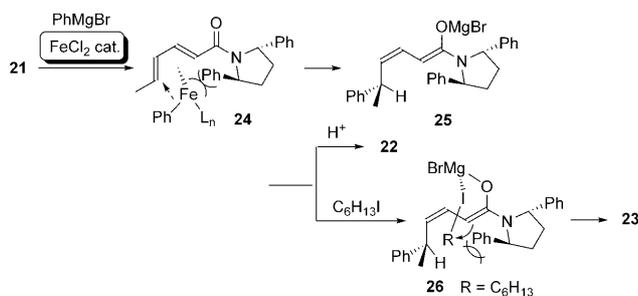
The chiral auxiliary in **5** was readily removed by acidic hydrolysis, as shown in Equation (1),^[11] to give lactone **20**, which has thermodynamically less stable *cis*-substituents on its five-membered ring. This stereochemical outcome and the separately confirmed structure of **4** were used to assign the depicted absolute stereochemistry to **5**.

Regio- and stereoselective 1,6-addition of Grignard reagents to $\alpha,\beta,\gamma,\delta$ -unsaturated amides is complementary to the above 1,4-addition as illustrated in Scheme 1. While we reported that the exclusive 1,6-selective addition of aryl Grignard reagents to $\alpha,\beta,\gamma,\delta$ -unsaturated esters and amides was viable with an iron catalyst,^[12–15] the remote asymmetric induction from a chiral amide portion to the carbon δ to the carbonyl, which is categorized as 1,7-chirality transfer,^[16] appeared quite difficult. Nonetheless, of the chiral esters and amides tested,^[17] amide **21**^[18] (see Scheme 4) was most promising. The iron-catalyzed 1,6-addition of PhMgBr to **21** proceeded with exclusive regioselectivity and high diastereoselectivity to give **22**, or the same addition followed by the stereoselective alkylation of the resulting enolate gave **23** as a 95:5 mixture of two (of a possible four) diastereoisomers.

In these products, the amide moiety and the incoming aryl group are *cis* to each other about the carbon–carbon double bond, which suggests that the reaction most likely proceeds via the *s-cis*-diene iron complex **24**^[12,19] to generate **25** (and subsequently **22** or **23**) as shown in Scheme 5. This olefin geometry is in stark contrast to that



Scheme 4. Iron-catalyzed 1,6-addition and successive alkylation.



Scheme 5. Proposed reaction course for 1,6-addition. L_n = ligands.

in copper-catalyzed reactions, where the carbonyl and the introduced alkyl groups are usually *trans*.^[4a–c,f,g] The same intermediate **24** could account for the anomalously high level of 1,7-chirality transfer, because the amide auxiliary efficiently blocks one plane of the *s-cis*-diene, whereas the iron complexation takes place from another side (**21**→**24**, Scheme 5) to promote efficient asymmetric delivery of the Ph group (**24**→**25**), which is followed by highly stereoselective alkylation (**26**→**23**). Thus, throughout the reaction, the iron catalyst should play three roles; to control 1) the regiochemistry of the conjugate addition, 2) the olefinic geometry of the product, and 3) the efficient remote chiral induction.

Table 2 shows the generality of this reaction. The 1,6-addition and the subsequent alkylation of **21** could be carried out with a variety of aryl Grignard reagents and alkylating agents to produce the desired products, **23** and **27–31** (Table 2, entries 1–6). The same reaction sequence with differently substituted amides **32** and **33** gave the products **34** and **35**, in very high diastereomeric ratios, without any complication (Table 2, entries 7 and 8).

In conclusion, switching between exclusive 1,4- and 1,6-additions of Grignard reagents to $\alpha,\beta,\gamma,\delta$ -unsaturated amides is now possible, owing to the absence or presence of an iron catalyst. Moreover, $\alpha,\beta,\gamma,\delta$ -unsaturated amides can be utilized as a simple yet versatile template for asymmetric three-component coupling process by the present one-pot reaction.

Experimental Section

(2*S*,3*R*,*E*)-2-Methyl-3-(1-methylethenyl)-4-hexenamide (**5**, derived from 1,3:4,6-di-*O*-benzylidene-2,5-dideoxy-2,5-imino-L-*iditol*): isopropenylmagnesium bromide (**1**) (0.53 M in THF, 0.377 mL, 0.200 mmol) was added to a stirred solution of **3** (43.4 mg, 0.100 mmol, ca. 100% *ee*) in THF (2.0 mL) at -20°C under argon. The solution was rapidly warmed to room temperature and was stirred at the same temperature for 1 h. Iodomethane (0.025 mL, 0.400 mmol) was added to this solution at room temperature, and the solution was stirred at 60°C for 1 h. The reaction was cooled to room temperature and was terminated by the addition of an aqueous saturated NH_4Cl solution (2.0 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 , and concentrated in vacuo to give a crude oil, which was purified by column chromatography on silica gel (hexane/ethyl acetate) to afford **5** (36.5 mg, 74%) as a white solid. ^1H NMR spectroscopic analysis of isolated **5** revealed that the diastereoselectivity was 94:6, which is comparable to the value detected at the crude stage.

Table 2: Three-component coupling process based on the iron-catalyzed 1,6-addition according to Scheme 4.^[a]

Entry	Substrate	ArMgBr	Alkylation	Product ^[b]	Yield [%] ^[c]	d.r. ^[d]
1		PhMgBr	MeI		67	95:5
2	21	PhMgBr			58	95:5
3	21	PhMgBr			55	94:6
4	21	PhMgBr	$\text{C}_6\text{H}_{13}\text{I}$		69	95:5
5	21		$\text{C}_6\text{H}_{13}\text{I}$		63	96:4
6	21		$\text{C}_6\text{H}_{13}\text{I}$		70	94:6
7 ^[e]		PhMgBr	$\text{C}_6\text{H}_{13}\text{I}$		71	96:4
8 ^[e]		PhMgBr	MeI ^[f]		68	97:3

[a] Molar ratio: dienamide/ FeCl_2 /ArMgBr/alkylating agent = 1:0.1:2.5:5. [b] The most abundant diastereoisomer is depicted. Absolute stereochemistries of **27–31**, **34** and **35** were deduced by analogy based on that of **23**. [c] Yields that are not necessarily optimized. [d] The ratio of two major diastereoisomers. Two other isomers, which were formed in trace amounts and could not be isolated or characterized, are omitted. [e] NR_2^* is the same as that in **21**. [f] Alkylation was performed at 0°C for 12 h.

(2*R*,5*R*,*Z*)-*N,N*-[(1'*S*,4'*S*)-1',4'-Diphenyl-1',4'-butylidene]-2-hexyl-5-phenyl-3-hexenamide (**23**): PhMgBr (1.0 M in THF, 0.250 mL, 0.250 mmol) was added over 7 min to a stirred solution of **21** (31.7 mg, 0.100 mmol, 97% ee^[20]) and FeCl₂ (1.3 mg, 0.010 mmol) in THF (1.0 mL) in a 30 mL round-bottomed flask at -20 °C under argon to give a dark brown to black homogeneous solution. After the solution was stirred at the same temperature for 1 h, 1-iodohexane (0.074 mL, 0.500 mmol) was added. The solution was warmed to room temperature and stirred for 12 h. The reaction was terminated by the addition of 1 M aqueous HCl (1.0 mL) at room temperature. The reaction mixture was diluted with ethyl acetate and the organic layer was separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with an aqueous saturated NaHCO₃ solution, dried over Na₂SO₄, and concentrated in vacuo to give a crude oil, ¹H NMR spectroscopic analysis of which revealed that the diastereoselectivity was 95:5 and that the regio- and olefinic stereoisomers were absent. The product was purified by column chromatography on silica gel (hexane/ethyl acetate) to afford **23** (33.3 mg, 69%) as a white solid, having the same isomeric composition as above.

Products **5** and **23** were fully characterized by ¹H NMR, ¹³C NMR spectroscopy, IR, elemental analyses, and appropriate derivatizations. Their spectroscopic data and detailed structural determinations are shown in the Supporting Information.

Received: April 24, 2008

Published online: July 29, 2008

Keywords: amides · asymmetric reaction · conjugate addition · Grignard reagents · iron

- [1] Reviews on Grignard reagents: for transition-metal-mediated reactions, see: a) H. Urabe, F. Sato in *Handbook of Grignard Reactions* (Eds.: G. S. Silverman, P. E. Rakita), Marcel Dekker, New York, **1996**, pp. 577–632. For conjugate addition, see: b) L. Miginiac in *Handbook of Grignard Reactions* (Eds.: G. S. Silverman, P. E. Rakita), Marcel Dekker, New York, **1996**, pp. 391–396. For nucleophilic reactions, see: c) B. J. Wakefield, *Organomagnesium Methods in Organic Synthesis* Academic Press, London, **1995**.
- [2] For reviews on copper-mediated conjugate addition of Grignard reagents, see: a) B. H. Lipshutz in *Organometallics in Organic Synthesis. A Manual, 2nd ed.* (Ed.: M. Schlosser), Wiley, New York, **2002**, pp. 665–815; b) B. H. Lipshutz, S. Sengupta in *Organic Reactions, Vol. 41* (Ed.: L. A. Paquette), Wiley, New York, **1992**, pp. 135–631; c) B. H. Lipshutz in *Comprehensive Organic Synthesis, Vol. 1* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 107–138; d) J. A. Kozlowski in *Comprehensive Organic Synthesis, Vol. 4* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 169–198.
- [3] 1,4-Selective addition to $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds is little documented. For copper-catalyzed 1,4-addition to 2,4-dienoates, see: a) Y. Yamamoto, S. Yamamoto, H. Yatagai, Y. Ishihara, K. Maruyama, *J. Org. Chem.* **1982**, *47*, 119–126. For 1,4-addition of Grignard reagents to $\alpha,\beta,\gamma,\delta$ -unsaturated amides: b) F. Barbot, A. Kadib-Elban, P. Miginiac, *Tetrahedron Lett.* **1983**, *24*, 5089–5090.
- [4] For copper-mediated 1,6-addition to 2,4-dienoates, see: a) E. J. Corey, C. U. Kim, R. H. K. Chen, M. Takeda, *J. Am. Chem. Soc.* **1972**, *94*, 4395–4396; b) E. J. Corey, R. H. K. Chen, *Tetrahedron Lett.* **1973**, *14*, 1611–1614; c) B. Ganem, *Tetrahedron Lett.* **1974**, *15*, 4467–4470; d) Reference [3a]; e) P. Wipf, M. Grenon, *Can. J. Chem.* **2006**, *84*, 1226–1241; f) T. den Hartog, S. R. Harutyunyan, D. Font, A. J. Minnaard, B. L. Feringa, *Angew. Chem.* **2008**, *120*, 404–407; *Angew. Chem. Int. Ed.* **2008**, *47*, 398–401. To 2,4-dienamide, see: g) Reference [3b]. To 2,4-dienones, see: h) F. Barbot, A. Kadib-Elban, P. Miginiac, *J. Organomet. Chem.* **1983**, *255*, 1–9; i) E. J. Corey, N. W. Boaz, *Tetrahedron Lett.* **1985**, *26*, 6019–6022; j) S. P. Modi, J. O. Gardner, A. Milowsky, M. Wierzba, L. Forgiione, P. Mazur, A. J. Solo, W. L. Duax, Z. Galdecki, P. Grochulski, Z. Wawrzak, *J. Org. Chem.* **1989**, *54*, 2317–2321; k) H. Liu, L. M. Gayo, R. W. Sullivan, A. Y. H. Choi, H. W. Moore, *J. Org. Chem.* **1994**, *59*, 3284–3288; l) M. Uerdingen, N. Krause, *Tetrahedron* **2000**, *56*, 2799–2804. To enyoates, see: m) N. Krause, A. Gerold, *Angew. Chem.* **1997**, *109*, 194–213; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 186–204.
- [5] Although 1,4-addition of Grignard reagents to $\alpha,\beta,\gamma,\delta$ -unsaturated amides was reported (reference [3b]), the precise regioselectivities were not described and low to moderate product yields were reported. In our group, among alkyl, alkenyl, and aryl Grignard reagents, only isopropenyl-like reagents proved satisfactory for this study. For Grignard conjugate addition to α,β -unsaturated amides, see reference [1b].
- [6] For reviews on asymmetric conjugate additions, see: a) B. E. Rossiter, N. M. Swingle, *Chem. Rev.* **1992**, *92*, 771–806; b) A. Alexakis in *Organocopper Reagents A Practical Approach* (Ed.: R. K. Taylor), Oxford University Press, Oxford, **1994**, pp. 160–182; c) A. Alexakis, C. Benhaim, *Eur. J. Org. Chem.* **2002**, 3221–3236; d) J. Christoffers, G. Koripelly, A. Rosiak, M. Rössle, *Synthesis* **2007**, 1279–1300; e) F. López, A. J. Minnaard, B. L. Feringa, *Acc. Chem. Res.* **2007**, *40*, 179–188.
- [7] Similar amides derived from prolinol or α,α -diphenylprolinol and amide **21** showed lower product yields and/or diastereoselectivities.
- [8] a) Y. Masaki, H. Oda, K. Kazuta, A. Usui, A. Itoh, F. Xu, *Tetrahedron Lett.* **1992**, *33*, 5089–5092; b) T. M. K. Shing, *Tetrahedron* **1988**, *44*, 7261–7264; c) N. Baggett, P. Stribblehill, *J. Chem. Soc. Perkin Trans. 1* **1977**, 1123–1126. The antipode of **3** can be prepared from commercially available L-mannitol.
- [9] For reviews on three-component coupling reactions based on conjugate addition, see: a) M. J. Chapdelaine, M. Hulce in *Organic Reactions, Vol. 38* (Ed.: L. A. Paquette), Wiley, New York, **1990**, pp. 225–653; b) H.-C. Guo, J.-A. Ma, *Angew. Chem.* **2006**, *118*, 362–375; *Angew. Chem. Int. Ed.* **2006**, *45*, 354–366.
- [10] Precedents of three-component coupling process based on conjugate addition of organometallic reagents to acyclic chiral α,β -unsaturated carbonyl compounds followed by alkylation are as follows. In these reactions, the alkylation was achieved with reactive halides and a less reactive, higher primary-alkyl iodide, such as C₆H₁₃I, was not included; a) L. S. Liebeskind, M. E. Welker, *Tetrahedron Lett.* **1985**, *26*, 3079–3082; b) K. Totani, S. Asano, K. Takao, K. Tadano, *Synlett* **2001**, 1772–1776; c) Y. Arai, M. Kasai, K. Ueda, Y. Masaki, *Synthesis* **2003**, 1511–1516; d) E. Reyes, J. L. Vicario, L. Carrillo, D. Badia, U. Uria, A. Iza, *J. Org. Chem.* **2006**, *71*, 7763–7772.
- [11] For hydrolysis of amides, see: T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 2nd ed., Wiley, New York, **1991**, pp. 270–275 and pp. 349–357.
- [12] K. Fukuhara, H. Urabe, *Tetrahedron Lett.* **2005**, *46*, 603–606.
- [13] For conjugate addition of Grignard reagents to α,β -unsaturated carbonyl compounds, few reports described an iron-catalyzed version: a) M. S. Kharasch, D. C. Sayles, *J. Am. Chem. Soc.* **1942**, *64*, 2972–2975; b) S. R. Jensen, A.-M. Kristiansen, J. Munch-Petersen, *Acta Chem. Scand.* **1970**, *24*, 2641–2647; c) T. Mukaiyama, T. Takeda, K. Fujimoto, *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3368–3372; d) Z. Lu, G. Chai, S. Ma, *J. Am. Chem. Soc.* **2007**, *129*, 14546–14547.
- [14] Rh- or Ir-catalyzed 1,6-addition of arylboron or -zinc reagents to 2,4-dienones or -dienoates has been recently reported: a) T. Hayashi, S. Yamamoto, N. Tokunaga, *Angew. Chem.* **2005**, *117*, 4296–4299; *Angew. Chem. Int. Ed.* **2005**, *44*, 4224–4227; b) G. de La Herrán, C. Murcia, A. G. Csáky, *Org. Lett.* **2005**, *7*, 5629–5632; c) T. Nishimura, Y. Yasuhara, T. Hayashi, *Angew. Chem.*

- 2006**, *118*, 5288–5290; *Angew. Chem. Int. Ed.* **2006**, *45*, 5164–5166.
- [15] For reviews on iron-mediated organic reactions, see: C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217–6254.
- [16] Examples of acyclic 1,*n*-asymmetric induction where *n* is more than five are rare; a) H. J. Mitchell, A. Nelson, S. Warren, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1899–1914; b) A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307–1370.
- [17] A similar amide derived from α,α -diphenylprolinol and amide **3** showed lower diastereoselectivities.
- [18] a) D. J. Aldous, W. M. Dutton, P. G. Steel, *Tetrahedron: Asymmetry* **2000**, *11*, 2455–2462; b) W. F. Jarvis, M. D. Hoey, A. L. Finocchio, D. C. Dittmer, *J. Org. Chem.* **1988**, *53*, 5750–5756. The antipode of **21** is also available by this method.
- [19] For *s-cis*-diene-iron complexes, see: a) *Comprehensive Organometallic Chemistry*, Vol. 4 (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, Oxford, **1982**, pp. 243–649; b) M. F. Semmelhack in *Organometallics in Organic Synthesis. A Manual*, 2nd ed. (Ed.: M. Schlosser), Wiley, New York, **2002**, pp. 1006–1121; c) D. C. Knölker, *Chem. Rev.* **2000**, *100*, 2941–2961.
- [20] Although we used a sample of 97% *ee* for this study, the parent amine of 99% *ee* is also available. See reference [18].
-