Asymmetric Syntheses of 3-Substituted-cyclohexanone Derivatives by Stereoselective Conjugate Addition to Chiral 2-Substituted-2-cyclohexen-1-ones

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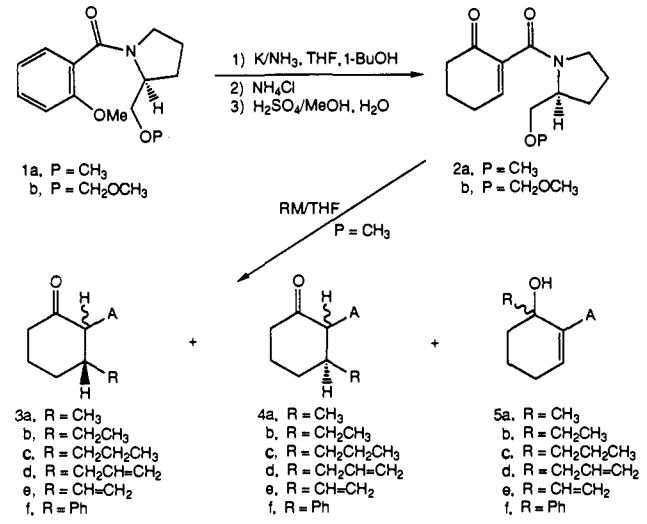
Abstract: Chiral 2-substituted-2-cyclohexen-1-one **2a** is prepared from **1a** by Birch reduction followed by acid-catalyzed hydrolysis–olefin migration. Conjugate additions of organometallic reagents to **2a** occur with good to excellent diastereoselectivities (Table I). Enone **2b**, which contains an additional potentially coordinating oxygen atom on the side chain of the chiral auxiliary, gave about the same stereoselectivity as **2a**. The chiral auxiliary (*S*)-(+)-2-(methoxymethyl)pyrrolidine can be removed from the product of conjugate addition by treatment with hydroxylamine hydrochloride and sodium acetate in 95% ethanol at 60 °C to give an oxime of a 3-substituted cyclohexanone (e.g., **3a** + **4a** → **6**). The C2 carboxyl substituent is retained by treatment of the conjugate addition product with *N*-methylhydroxylamine hydrochloride and *p*-toluenesulfonic acid in benzene at reflux; 1-methyl-4,5,6,7-tetrahydro-4-substituted-2,1-benzisoxazolin-3-ones **10a–10d** are obtained in 73–91% isolated yields. In the preparation of **10c** it was demonstrated that the chiral auxiliary could be easily recovered in 81% yield as the *p*-toluenesulfonic acid salt. Benzisoxazolin-3-one **10d** (98.7% ee) gives (3*R*)-(+)-3-phenylcyclohexanone on treatment with lithium in NH_3/THF solution.

The alkali metal in ammonia reduction of benzamide **1** and stereoselective alkylation of the resulting chiral amide enolate has provided a variety of enantiomerically pure cyclohexane derivatives.[1] As a complement to this process, we now report asymmetric syntheses of 3-substituted-cyclohexanone derivatives by stereoselective conjugate additions of organometallic reagents to the chiral 2-substituted-2-cyclohexen-1-one **2a**.[2] This versatile acceptor is readily prepared from **1** by Birch reduction followed by acid-catalyzed hydrolysis–olefin migration (Scheme I). Whereas the Birch reduction–alkylation sequence is ideally suited to the construction of quaternary carbon atoms, the new conjugate addition methodology provides convenient access to tertiary stereocenters on targeted cyclohexane rings.

Outstanding recent advances have been made toward development of enantioselective conjugate addition reactions of chiral organometallic reagents to 2-cyclohexen-1-one.[3] However, the substrate-linked chiral auxiliary approach offers the opportunity to obtain enantiomerically pure 3-substituted-cyclohexanone derivatives by separation of diastereomerically related conjugate addition products. Indeed, Posner and co-workers have obtained excellent results for the stereoselective addition of organometallic reagents to chiral vinyl sulfoxides derived from 2-cyclohexen-1-one.[4a] Related methods involving conjugate addition reactions also are available for the control of absolute configuration at C3 of cyclohexanone derivatives.[4c,d]

Scheme I



Results and Discussion

The conjugate addition reactions of Grignard reagents to acyclic α,β-unsaturated amides of ephedrine have been reported.[5] Reaction of **2a** with CH_3MgCl in ether gave a 41% yield of a 1.4:1

(1) Schultz, A. G. *Acc. Chem. Res.* **1990**, *23*, 207.

(2) (a) For the first practical asymmetric synthesis by conjugate addition of organometallic reagents, the asymmetric synthesis of 3-substituted-alkanoic acids by conjugate addition of organolithium reagents to chiral 2-(1-alkenyl)oxazolines, see: Meyers, A. I.; Whitten, C. E. *J. Am. Chem. Soc.* **1975**, *97*, 6266. At about the same time, an efficient asymmetric synthesis of β-substituted aldehydes by stereoselective conjugate addition of Grignard reagents to chiral α,β-unsaturated aldimines also was developed; see: Hashimoto. S.; Yamada, S.; Koga, K. *J. Am. Chem. Soc.* **1976**, *98*, 7450. (b) After our study of conjugate addition reactions of **2** was well under way, an asymmetric synthesis of 3-substituted-2-*exo*-methylenecyclohexanones via conjugate addition of $R_2CuLi/ZnBr_2$ to (*S*)-2-[[2-(methoxymethyl)-1-pyrrolidinyl]-methyl]-2-cyclohexen-1-one followed by in situ elimination of the chiral auxiliary was reported; see: Tamura, R.; Watabe, K.-I.; Katayama, H.; Suzuki, H.; Yamamoto, Y. *J. Org. Chem.* **1990**, *55*, 408. For other examples of the use of (*S*)-(+)-2-(methoxymethyl)pyrrolidine in asymmetric synthesis via addition–elimination reactions, see: Fuji, K.; Node, M.; Nagasawa, H.; Naniwa, Y.; Taga, T.; Machida, K.; Snatzke, G. *J. Am. Chem. Soc.* **1989**, *111*, 7921. Fuji, K.; Node, M.; Abe, H.; Itoh, A.; Masaki, Y.; Shiro, M. *Tetrahedron Lett.* **1990**, *31*, 2419. (c) For a review of noncatalytic additions to α,β-unsaturated carbonyl compounds, see: Tomioka, K.; Koga, K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 2, pp 201–224.

(3) (a) Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.* **1986**, *108*, 7114. (b) Bertz, S. H.; Dabbagh, G.; Sundararajan, G. *J. Org. Chem.* **1986**, *51*, 4953. (c) Dieter, R. K.; Tokles, M. *J. Am. Chem. Soc.* **1987**, *109*, 2040. (d) Yamamoto, K.; Kanoh, M.; Yamamoto, N.; Tsuji, J. *Tetrahedron Lett.* **1987**, *28*, 6347. (e) Villacorta, G. M.; Rao, Ch. P.; Lippard, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 3175. (f) Jansen, J. F. G. A.; Feringa, B. L. *J. Org. Chem.* **1990**, *55*, 4168. (g) Rossiter, B. E.; Eguchi, M. *Tetrahedron Lett.* **1990**, *31*, 965.

(4) (a) For conjugate additions to chiral 2-cyclohexenone sulfoxides, see: Posner, G. H.; Frye, L. L.; Hulce, M. *Tetrahedron* **1984**, *40*, 1401. Posner, G. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 2, pp 225–241; Posner, G. H. *Acc. Chem. Res.* **1987**, *20*, 72. (b) For conjugate addition reactions of a chiral acetal derivative of 2-carboxy-2-cyclohexen-1-ol, see: Herradon, B.; Seebach, D. *Helv. Chim. Acta* **1989**, *72*, 690. (c) For conjugate additions to (*R*)- and (*S*)-5-(trimethylsilyl)-2-cyclohexen-1-one, see: Asaoka, M.; Shima, K.; Takei, H. *Tetrahedron Lett.* **1987**, *28*, 5669. Asaoka, M.; Takenouchi, K.; Takei, H. *Ibid.* **1988**, *29*, 325. Asaoka, M.; Shima, K.; Takei, H. *J. Chem. Soc., Chem. Commun.* **1988**, 430. Asaoka, M.; Shima, K.; Fujii, N.; Takei, H. *Tetrahedron* **1988**, *44*, 4757. (d) For synthesis of nonracemic 3-substituted cyclohexanone derivatives by homoconjugate addition, see: Taber, D. F.; Saleh, S. A.; Korsmeyer, R. W. *J. Org. Chem.* **1980**, *45*, 4699.

(5) (a) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1981**, 913. (b) For the conjugate addition reactions of Grignard reagents to chiral oxazepines in the presence of nickel chloride, see: Mukaiyama, T.; Takeda, T.; Osaki, M. *Chem. Lett.* **1977**, 1165. (c) For an asymmetric synthesis of α-hydroxycycloalkanones, which involves stereoselective 1,2-addition of Grignard and organolithium reagents to α-ketoenamines prepared from (*S*)-(+)-2-(methoxymethyl)pyrrolidine and cycloalkane-1,2-diones, see: Fujisawa, T.; Watanabe, M.; Sato, T. *Chem. Lett.* **1984**, 2055.

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Table I. Stereoselectivity and Regioselectivity of Organometallic Addition to **2a**

entry	reaction conditions[a]	distribn of 3 and 4 (% de)[b]	% yield[c] 3 + 4	% yield[c] 5 (dr)[f]
1	1.5 equiv of CH_3MgCl[d]	1:1	8	41 (1.4:1)
2	3.6 equiv of CH_3MgCl, 1.0 equiv of $ZnCl_2$, 5.0 equiv of Me_3SiCl	5:1 (67)	80	*e*
3	4.0 equiv of CH_3Li, 1.2 equiv of $ZnBr_2$	4:1 (60)	89	9 (1:1)
4	3.6 equiv of CH_3CH_2MgBr, 1.2 equiv of $ZnBr_2$	30:1 (94)	54	16 (3:1)
5	3.6 equiv of $CH_3CH_2CH_2MgCl$, 1.2 equiv of $ZnBr_2$	30:1 (94)	57	10 (2:1)
6	3.6 equiv of CH_2=$CHCH_2MgBr$, 1.2 equiv of $ZnBr_2$	36:1 (95)	19	78 (3:1)
7	1.2 equiv of CH_2=$CHCH_2MgBr$, 10% $CuBr_2$, 5.0 equiv of Me_3SiCl	>3:1 (>94)	36[g]	trace
8	3.6 equiv of CH_2=$CHMgBr$, 1.2 equiv of $ZnBr_2$	>30:1 (>94)	73	e
9	1.5 equiv of $PhMgBr$[d]	1:1	37	35 (2:1)
10	2.0 equiv of PhMgBr, 1.0 equiv of CuBr, 5.0 equiv of Me_3SiCl	5:1 (67)	99	*e*
11	3.6 equiv of PhMgBr, 1.2 equiv of $ZnBr_2$	32:1 (94)	49	49 (2:1)

[a] Reactions were performed in freshly distilled THF at 0 °C. [b] Distributions of **3** and **4** were determined by HPLC analyses of each mixture of *trans*-**3** and *trans*-**4** separated from *cis*-**3** and *cis*-**4** by flash column chromatography. Each mixture of *cis*-**3** and *cis*-**4** was converted to a second mixture of *trans*-**3** and *trans*-**4**. Each duplicate set of trans isomers so obtained had identical composition by HPLC analysis. [c] Yields are for isolated materials. [d] This reaction performed in ether. [e] None detected by ^1H NMR analysis. [f] Diasteromer ratio (dr) determined by ^1H NMR analysis. [g] Substantial **2a** and some of the isomeric β,γ-enone were recovered in this experiment.

mixture of carbonyl addition products **5a**[5c] and only 8% of a 1:1 mixture of conjugate addition products **3a** and **4a** (Table I, entry 1). However, treatment of **2a** with excess CH_3MgCl in the presence of anhydrous $ZnBr_2$ and chlorotrimethylsilane[6a] provided an 80% isolated yield of a 5:1 mixture of conjugate addition products **3a** and **4a** (entry 2). The yield of conjugate addition products was increased to 89% by utilization of CH_3Li in place of the Grignard reagent, but with some erosion of the stereoselectivity (entry 3). More sterically demanding Grignard reagents such as CH_3CH_2MgBr (entry 4) and $CH_3CH_2CH_2MgBr$ (entry 5) provided substantially better stereoselectivities (94% diastereomeric excess). Isolated yields for these reactions were in the moderate to good range, and some selectivity was observed for the product **5** of carbonyl addition. By contrast, the products **3e** and **4e** of vinyl group conjugate addition are obtained in high yield with excellent diastereoselectivity (>30:1, entry 8). In this case, carbonyl addition products were not observed.

Conjugate addition of the allyl group is currently problematic. While the stereoselectivity for conjugate addition of CH_2=CH-CH_2MgBr is excellent (entries 6 and 7), reaction conditions that worked well with alkyl Grignard reagents gave mainly carbonyl addition products with the allylic reagent (entry 6). Carbonyl addition was virtually eliminated, and the yield of **3d** + **4d** was increased to 36% by the use of 10% $CuBr_2$[6b] and chlorotrimethylsilane additives (entry 7). Substantial **2a** along with some of the isomeric β,γ-enone was recovered in this experiment, suggesting that some of the organometallic reagent is consumed by deprotonation of **2a**. It is possible that allylic conjugate addition can be further optimized, although an abbreviated survey of reaction variants that have been reported to promote allylic ligand transfer[7] were ineffective with **2a**.

The uncatalyzed addition of PhMgBr to **2a** gave both conjugate and 1,2-addition products without stereocontrol (entry 9); however, nearly quantitative yields of **3f** + **4f** (5:1) were obtained with the CuBr and chlorotrimethylsilane additives (entry 10). The stereoselectivity of conjugate addition was increased to 94% de when anhydrous $ZnBr_2$ was used (entry 11).

Enone **2b**, which contains an additional potentially coordinating oxygen atom on the side chain of the chiral auxiliary, gave about the same stereoselectivity as **2a**. The highest selectivity for methyl group addition to **2b** (5:1 product ratio of **3a** and **4a**; 72% yield) was obtained with the CH_3Li and $ZnBr_2$ reagent. PhMgBr in the presence of CuBr and chlorotrimethylsilane gave **3f** and **4f** (3.5:1) in only 46% yield; conditions that produced excellent stereoselectivities with **2a** (entry 11 of Table I) gave a 2.8:1 mixture of **3f** and **4f** (42% yield) with **2b**.

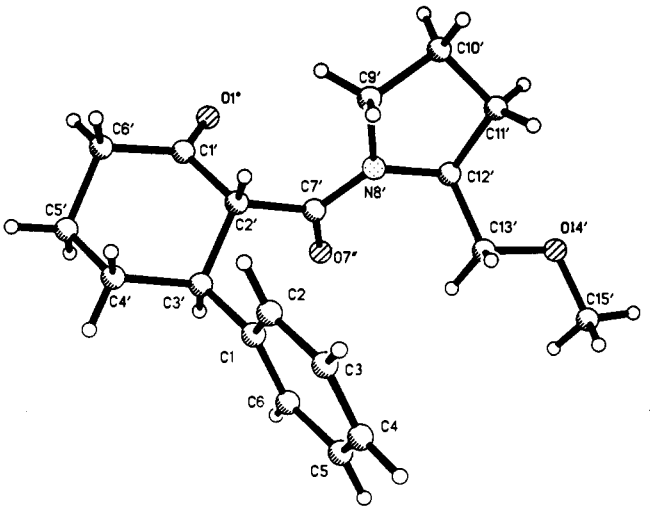
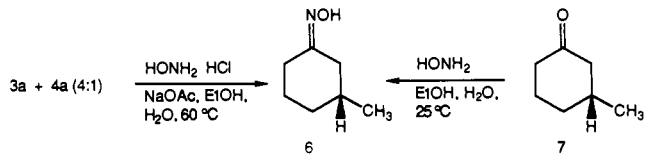
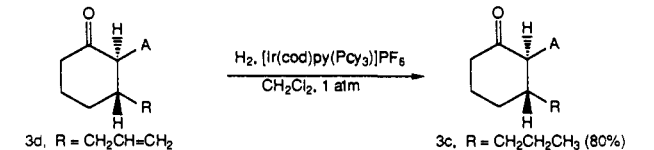


Figure 1. Molecular structure of *trans*-**4f**.

The stereochemical sense of addition of organometallic reagents to **2a** was determined by chemical interconversions and an X-ray diffraction study. Treatment of the 4:1 mixture of **3a** and **4a** with hydroxylamine hydrochloride and sodium acetate in 95% ethanol at 60 °C provided oxime **6**. The rotation of this material was compared to the oxime obtained from (*R*)-(+)-3-methylcyclohexanone; the sign and magnitude confirmed the assignment of structures of **3a** and **4a**.



Vinyl and allyl group addition products were related to the alkyl series by hydrogenation of the olefinic bond. Thus, **3d** and **3e** gave **3c** and **3b**, respectively. An X-ray structure determination was obtained for the trans isomer of the minor product of phenyl Grignard addition to **2a**; the molecular structure of *trans*-**4f** is shown in Figure 1.

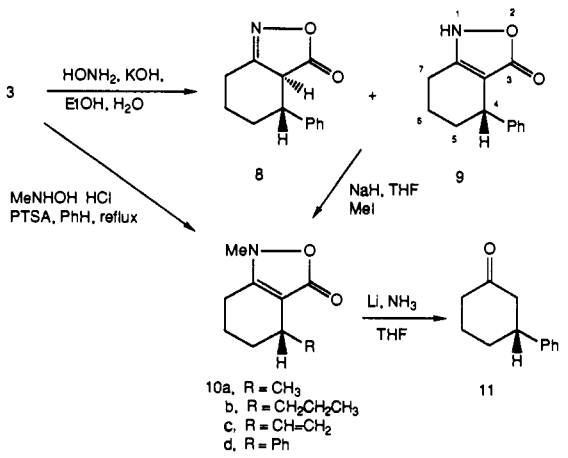


It is believed that the stereoselectivity of conjugate addition to **2a** (and **2b**) is a result of conformational effects. Low-energy conformations of **2a** have the amide carbonyl group nearly or-

(6) (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015, 6019. Alexakis, A.; Berlan, J.; Besace, Y. *Ibid.* **1986**, *27*, 1047. (b) Sakata, H.; Aoki, Y.; Kuwajima, I. *Tetrahedron Lett.* **1990**, *31*, 1161.

(7) Use of the Lipshutz modification gave no reaction at −78 °C and reagent decomposition at 0 °C, see: Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Smith, R. A. J. *J. Am. Chem. Soc.* **1990**, *112*, 4404.

Scheme II



thogonal to the plane of the enone system. This orientation allows rotation about the amide CO–N bond as observed in ^{1}H NMR experiments with **2a** (and **2b**). Coplanarity of carbonyl groups, as suggested by the two-dimensional drawing of **2a**, would suffer from severe steric destabilization; amide rotational isomerization would be precluded because of steric interactions between the side chain of the chiral auxiliary and C3 of the cyclohexenone ring.

The relative orientation of the amide and ketone carbonyl group in **2a** is probably very similar to that determined for *trans*-**4f** (Figure 1). With use of the molecular structure of *trans*-**4f** as a model for **2a**, it is observed that the hydrogen atoms at C9′ (and the side chain attached to C12′ in the alternative amide rotational isomer) would very effectively shield the β-face of C3′ from attack by the organometallic reagent. This model explains why conjugate addition of a methyl group to **2a** occurs with good stereoselectivity at the α-face, while larger alkyl, vinyl, and aryl groups add nearly exclusively to the α-face.

While the chiral auxiliary can be removed to provide oximes of 3-substituted-cyclohexanones (e.g., **3a** → **6**), the strategic value of this asymmetric conjugate addition process is expected to be enhanced by transformations that utilize the C2 carboxyl substituent (e.g., Scheme II). Reaction of **3f** with hydroxylamine under mildly basic conditions gives the tautomerically related tetrahydro-2,1-benzisoxazolin-3-ones **8** and **9** in 81% isolated yield.[8] This mixture undergoes N-methylation[9] to give 1-methyl-4,5,6,7-tetrahydro-4-phenyl-2,1-benzisoxazolin-3-one (**10d**). Alternatively, 1-methylbenzisoxazolin-3-ones were prepared directly from the β-ketoamide by treatment with *N*-methylhydroxylamine hydrochloride and *p*-toluenesulfonic acid in benzene at reflux.[10] In this way **10a–10d** were obtained in 73–91% yields; in the preparation of **10c**, it was demonstrated that the chiral auxiliary could be easily recovered in 81% yield as the *p*-toluenesulfonic acid salt.

Chiral benzisoxazolin-3-ones should have interesting utility in asymmetric synthesis. With regard to syntheses of 3-substituted-cyclohexanones, treatment of **10d** (98.7% ee) with lithium in NH_3/THF solution gave (3*R*)-(+)-3-phenylcyclohexanone (**11**). A rotation of $[\alpha]^{22}_D$ +20.5° (*c* 0.58, $CHCl_3$) was determined for (3*R*)-**11** (98.7% ee).[11] It is noteworthy that reduction of the aromatic ring in **10d** did not occur during the conversion of **10d** to **11**.

Conclusion

We have described a new method for asymmetric syntheses by stereoselective conjugate addition of organometallic reagents to a chiral 2-substituted-α,β-unsaturated carbonyl derivative. The prototype process (**2a** → **3** + **4**) features (1) convenient access to the chiral 2-substituted-2-cyclohexen-1-one, (2) good to excellent stereocontrol for conjugate addition of alkyl, aryl, and vinyl ligands, and (3) efficient recovery of the chiral auxiliary. Application of the method to other substrates and target structures is under investigation.

Experimental Section

General Procedures. ^{1}H spectra were recorded at 200 MHz; tetramethylsilane was used as the internal standard. Analytical TLC was performed on silica gel F-254 plates. Solvents and reagents were distilled under nitrogen as follows: tetrahydrofuran (THF) from sodium/benzophenone; *tert*-butyl alcohol from CaH_2; chlorotrimethylsilane (neat). Organometallic reagents were purchased from Aldrich: methylmagnesium chloride (3.0 M solution in THF); methyllithium (1.4 M solution in Et_2O); ethylmagnesium bromide (2.0 M solution in THF); propylmagnesium chloride (2.0 M solution in Et_2O); allylmagnesium chloride (2.0 M solution in THF); vinylmagnesium bromide (1.0 M solution in THF); phenylmagnesium bromide (3.0 M solution in Et_2O). Zinc chloride was purchased as a 1.0 M solution in Et_2O. All other solvents and reagents were of reagent grade quality and were utilized without further purification. Solutions were concentrated by a Buchi rotary evaporator. Residual solvent was removed by a vacuum pump. Elemental analyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, MI.

(2′*S*)-2-[[2′-[(Methoxymethoxy)methyl]pyrrolidinyl]carbonyl]cyclohex-2-en-1-one (2b). Ammonia (100 mL) was added to a stirred solution of **1b**[12] (3.01 g, 10.9 mmol) and *tert*-butyl alcohol (1.03 mL, 10.9 mmol) in THF (50 mL) cooled to −78 °C. Potassium metal (1.27 g, 32.7 mmol) was added, and the mixture was stirred for 0.5 h. The reaction mixture was quenched with excess ammonium chloride. After the mixture was warmed to room temperature, the residue was partitioned between water (30 mL) and methylene chloride (100 mL). The organic phase was concentrated at reduced pressure. The residue was diluted with methanol (20 mL) and water (3 mL), and then concentrated sulfuric acid was added until the solution tested acidic. After being stirred for 0.5 h, the mixture was concentrated at reduced pressure. Water (30 mL) and methylene chloride (100 mL) were added. The organic phase was washed with saturated sodium bicarbonate solution and water and then dried over magnesium sulfate. Filtration, concentration at reduced pressure, and flash chromatography (silica gel, ethanol/ethyl acetate (1:9)) afforded **2b** (1.9 g, 66%) as a viscous oil (2.3:1 mixture of amide rotational isomers): ^{1}H NMR ($CDCl_3$) δ 1.7–2.25 (m, 6 H), 2.35–2.58 (m, 4 H), 3.32 and 3.37 (s, 3 H), 3.15–3.42 (m, 2 H), 3.6–3.86 (m, 2 H), 4.25–4.40 (m, 1 H), 4.54 and 4.58–4.70 (s and m, 2 H), 7.11–7.15 (m, 1 H); $[\alpha]^{22}_D$ −59.6° (*c* 2.02, $CHCl_3$); IR (film) 2950, 2870, 1670, 1620, 1410 cm^{-1}; chemical ionization mass spectrum, *m*/*z* (relative intensity) 268 (M^+ + 1, 100), 236 (30), 224 (10). Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92. Found: C, 62.54; H, 8.16.

(2′*S*)-2-[[2′-(Methoxymethyl)pyrrolidinyl]carbonyl]cyclohex-2-en-1-one (2a) was prepared from **1a**[12] (1.83 g, 7.72 mmol) as described for the preparation of **2b**. Flash chromatography (silica gel, ethanol/ethyl acetate (1:10)) afforded **2a**, a colorless oil, as a 2:1 mixture of amide rotational isomers (1.13 g, 65%): ^{1}H NMR ($CDCl_3$) δ 1.7–2.15 (m, 6 H), 2.4–2.6 (m, 4 H), 3.12–3.3 (m, 2 H), 3.26 and 3.38 (s, 3 H), 3.38–3.55 (m, 1 H), 3.55–3.85 (m, 1 H), 4.22–4.38 (m, 1 H), 7.05–7.18 (m, 1 H); $[\alpha]^{22}_D$ −97.6° (*c* 4.96, $CHCl_3$); IR (film) 2950, 2880, 2820, 1675, 1620, 1415 cm^{-1}; chemical ionization mass spectrum, *m*/*z* (relative intensity) 238 (M^+ + 1, 100). Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07. Found: C, 65.72; H, 8.05.

(2*R*/*S*,2′*S*,3*R*)-2-[[2′-(Methoxymethyl)pyrrolidinyl]carbonyl]-3-methylcyclohexan-1-one (3a) and (2*R*/*S*,2′*S*,3*S*)-2-[[2′-(Methoxymethyl)pyrrolidinyl]carbonyl]-3-methylcyclohexan-1-one (4a) (Table I, Entry 2). A stirred solution of **2a** (124 mg, 0.52 mmol) and zinc chloride (71 μL, 0.52 mmol) in THF (5 mL) was cooled to 0 °C, and then chlorotrimethylsilane (282 mg, 2.6 mmol) was added. A solution of methylmagnesium chloride in (46 μL, 1.8 mmol) was added. The mixture was stirred at 0 °C for 2 h and then at room temperature for 12 h.

(8) For the preparation of isoxazolin-5-ones by the reaction of β-keto esters with hydroxylamine, see: (a) Katritzky, A. R.; Oksne, S. *Proc. Chem. Soc.* **1961**, 387. (b) Beccalli, E. M.; Marchesini, A.; Gelmi, M. L.; Pilati, T. *J. Org. Chem.* **1987**, *52*, 1666 and references cited therein. Preparation of the 4-unsubstituted-tetrahydrobenzisoxazolin-3-one analogue of **8** and **9** is described in: Katritzky, A. R.; Oksne, S.; Boulton, A. J. *Tetrahedron* **1962**, *18*, 777.

(9) (a) Kohler, E. P.; Blatt, A. H. *J. Am. Chem. Soc.* **1928**, *50*, 504. (b) Van Rompuy, L.; Schamp, N.; DeKimpe, N.; Van Parijs, R. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2503. (c) Doleschall, G. *Tetrahedron Lett.* **1987**, *28*, 2993.

(10) Saeki, S.; Honda, H.; Hamana, M. *Chem. Pharm. Bull.* **1983**, *31*, 1474.

(11) The optical rotation of "optically pure" (3*R*)-(+)-3-phenylcyclohexanone is listed as $[\alpha]^{25}_D$ +14.35 (*c*, 9.674, $CHCl_3$) in: *Dictionary of Organic Compounds*; Buckingham, J., Ed.; Chapman and Hall: New York, 1982; Vol. 5, p 4614. This assignment is in error; for a discussion of this point, see ref 3b.

(12) Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828. **1a** is available in both *R* and *S* modifications from Aldrich.

Aqueous ammonium chloride was added, the aqueous phase was washed with methylene chloride (2 × 25 mL), and the combined organic phases were dried over magnesium sulfate. Concentration at reduced pressure and flash chromatography (silica gel, ethyl acetate/hexane (1:1)) afforded a mixture of *cis*-**3a** and *cis*-**4a** (29 mg, 22%) and a mixture of *trans*-**3a** and *trans*-**4a** (77 mg, 58%).

3a and 4a (cis isomers): colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.95–1.12 (m, 3 H), 1.46–2.55 (m, 11 H), 2.6–3.0 (m, 1 H), 3.31, 3.34, and 3.35 (s, 3 H), 3.05–3.72 (m, 4 H), 4.86–4.95, 4.95–4.10, 4.16–4.34, and 4.38–4.52 (m, 1 H); IR (film) 2940, 2860, 1700, 1625 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 254 (M^+ + 1, 100). Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15. Found: C, 66.46; H, 9.12.

3a and 4a (trans isomers): colorless oil, isolated as a 5:1 mixture; ^{1}H NMR ($CDCl_3$) δ 0.95–1.1 (m, 3 H), 1.22–2.6 (m, 11 H), 3.34 and 3.39 (s, 3 H), 3.02–3.9 (m, 5 H), 3.9–4.08 and 4.22–4.48 (m, 1 H); $[\alpha]^{24}_D$ −81.1° (*c* 0.57, $CHCl_3$); IR (film) 2940, 2920, 2860, 1700, 1630 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 254 (M^+ + 1, 100), 236 (8). Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15. Found: C, 66.02; H, 9.20.

Epimerization of *cis*-3a/4a to *trans*-3a/4a. A solution of *cis*-**3a/4a** (20 mg, 0.08 mmol) and sodium hydroxide (8 mg, 0.2 mmol) in methanol (5 mL) was stirred at room temperature for 2 h. The mixture was concentrated at reduced pressure, and then methylene chloride (10 mL) and water (3 mL) were added. The organic phase was dried over magnesium sulfate. Concentration at reduced pressure afforded a mixture of **3a** and **4a** as trans isomers (20 mg, 100%).

(4*R*/*S*)-1,4-Dimethyl-4,5,6,7-tetrahydro-2,1-benzisoxazolin-3-one (10a). A 5:1 mixture of **3a** and **4a** (50 mg, 0.2 mmol), *N*-methylhydroxylamine hydrochloride (20.0 mg, 0.24 mmol), and *p*-toluenesulfonic acid monohydrate (40 mg, 0.02 mmol) in benzene (10 mL) were stirred at reflux for 2 h. The solution was washed with saturated sodium bicarbonate solution and dried over magnesium sulfate. Concentration at reduced pressure and flash chromatography (silica gel, ethyl acetate/hexane (1:1)) afforded **10a** (24 mg, 73%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.21 (d, *J* = 6.9 Hz, 3 H), 1.3–1.48 (m, 1 H), 1.65–2.0 (m, 3 H), 2.3–2.4 (m, 2 H), 2.5–2.7 (m, 1 H), 3.2 (s, 3 H); $[\alpha]^{22}_D$ −59.4° (*c* 0.18, $CHCl_3$); IR (film) 2930, 2860, 1725, 1615 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 168 (M^+ + 1, 100). Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84. Found: C, 64.47; H, 7.76.

3a, 4a, and (1*R*/*S*,2′*S*)-2-[[2′-(Methoxymethyl)pyrrolidinyl]carbonyl]-1-methylcyclohex-2-en-1-ol (5a) (Table I, Entry 3). Methyllithium (53 μL, 3.4 mmol) was added to a stirred solution of zinc bromide (225 mg, 1 mmol) in THF (5 mL) at 0 °C. To this mixture was added a solution of **2a** (198 mg, 0.84 mmol) in THF (5 mL). After the mixture was stirred for 6 h, aqueous ammonium chloride was added. The aqueous phase was washed with methylene chloride (2 × 15 mL), and the combined organic phases were dried over magnesium sulfate. Concentration at reduced pressure and flash chromatography (silica gel, ethyl acetate/hexane (1:1)) afforded a 4:1 mixture of *trans*-**3a** and *trans*-**4a** (189 mg, 89%); $[\alpha]^{21}_D$ −76.3° (*c* 3.78, $CHCl_3$).

Also isolated was **5a** (20 mg, 9%) as a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 1.1–1.35 (m, 3 H), 1.4–2.6 (m, 10 H), 3.34 and 3.35 (s, 3 H), 3.2–3.8 (m, 4 H), 4.15–4.5 (m, 1 H), 4.85–5.0 (m, exchangeable with D_2O, 1 H), 5.88–6.0 and 6.0–6.13 (m, 1 H); IR (film) 3420, 2960, 2920, 2870, 2820, 1590 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 254 (M^+ + 1, 100), 236 (45). Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15. Found: C, 66.21; H, 9.09.

(3*R*/*S*)-3-Methyl-1-oximidocyclohexane (6). A stirred solution of **3a** and **4a** (189 mg, 0.75 mmol; prepared as described in Table I, entry 3), hydroxylamine hydrochloride (69.5 mg, 0.99 mmol), and sodium acetate (123 mg, 1.49 mmol) in 95% ethanol (20 mL) was heated to 60 °C for 20 h. The mixture was concentrated at reduced pressure, and the residue was partitioned between water (5 mL) and methylene chloride (15 mL). The organic phase was dried over magnesium sulfate. Concentration at reduced pressure and flash chromatography (silica gel, ethyl acetate/hexane (1:3)) afforded **6** (26 mg, 27%): $[\alpha]^{22}_D$ −28.5° (*c* 0.52, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.96 and 0.99 (d, *J* = 6 Hz, 3 H), 1.05–2.1 (m, 7 H), 2.25–2.45 (m, 1 H), 3.1–3.3 (m, 1 H), 9.4–10.1 (m, exchangeable with D_2O, 1 H); IR ($CHCl_3$ solution) 3250, 2920, 1655 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 128 (M^+ + 1, 100), 110 (28). Anal. Calcd for $C_7H_{13}NO$: C, 66.10; H, 10.30. Found: C, 66.10; H, 10.38.

(3*R*)-3-Methyl-1-oximidocyclohexane. A solution of (*R*)-(+)-3-methylcyclohexanone (7) (1.0 g, 8.9 mmol), hydroxylamine hydrochloride (700 mg, 10.0 mmol), and sodium hydroxide (400 mg, 10.0 mmol) in 90% ethanol (55 mL) was stirred at room temperature for 1h. The mixture was concentrated at reduced pressure, and the residue was partitioned between ether (50 mL) and water (20 mL). The organic phase was dried over magnesium sulfate. Concentration at reduced pressure and flash chromatography (silica gel, ethyl acetate/hexane (1:3)) afforded (−)-**6** (950 mg, 84%); $[\alpha]^{23}_D$ −40.0° (*c* 1.9, $CHCl_3$).

(2*R*/*S*,2′*S*,3*R*)-2-[[2′-(Methoxymethyl)pyrrolidinyl]carbonyl]-3-ethylcyclohexan-1-one (3b), (2*R*/*S*,2′*S*,3*S*)-2-[[2′-(Methoxymethyl)-pyrrolidinyl]carbonyl]-3-ethylcyclohexan-1-one (4b), and (1*R*/*S*,2′*S*)-2-[[2′-(Methoxymethyl)pyrrolidinyl]carbonyl]-1-ethylcyclohex-2-en-1-ol (5b) (Table I, Entry 4). A stirred solution of **2a** (125 mg, 0.53 mmol) and zinc bromide (135 mg, 0.60 mmol) in THF (6 mL) was cooled to 0 °C. Ethylmagnesium bromide (120 μL, 1.80 mmol) was added, and after being stirred at 0 °C for 2 h, the mixture was allowed to warm to room temperature. After the mixture was stirred for an additional 12 h, aqueous ammonium chloride was added. The aqueous phase was washed with methylene chloride (2 × 20 mL), and the combined organic phases were dried over magnesium sulfate. Concentration at reduced pressure and flash chromatography (silica gel, ethyl acetate/hexane (1:1)) afforded a mixture of *cis*-**3b** and *cis*-**4b** (46 mg, 33%), a mixture of *trans*-**3b** and *trans*-**4b** (30 mg, 21%), and **5b** (23 mg, 16%).

3b and 4b (cis isomers): colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, *J* = 7.4 Hz, 3 H), 1.2–2.4 (m, 13 H), 3.33 and 3.38 (s, 3 H), 2.72–3.8 (m, 5 H), 3.95–4.12 and 4.12–4.27 (m, 1 H); IR (film) 2960, 2870, 1700, 1630 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 268 (M^+, + 1, 100). The mixture of *cis*-**3b/4b** was epimerized to *trans*-**3b/4b** (91% yield) by the method used for **3a/4a**.

3b and 4b (trans isomers): colorless oil, isolated as a 30:1 mixture; ^{1}H NMR ($CDCl_3$) δ 0.92 and 0.94 (t, *J* = 7.3 Hz, 3 H), 1.05–2.6 (m, 13 H), 3.15 (d, *J* = 10.8 Hz, 1 H), 3.33 and 3.38 (s, 3 H), 3.2–3.5 (m, 1H), 3.56 (d, *J* = 10.8 Hz, 1 H), 3.65–3.9 (m, 2 H), 4.24–4.38 (m, 1 H); IR (film) 2960, 2930, 2870, 1700, 1635 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 268 (M^+ + 1, 100). Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.43. Found: C, 67.33; H, 9.49.

5b: colorless oil, isolated as a 3:1 mixture of diastereomers; ^{1}H NMR ($CDCl_3$) δ 0.8–1.05 (m, 3 H), 1.4–2.4 (m, 12 H), 3.35 (s, 3 H), 3.30–3.7 (m, 4 H), 4.15–4.42 (m, 1 H), 4.42–4.5 and 4.82–4.92 (m, exchangeable with D_2O, 1 H), 5.97–6.08 and 6.08–6.2 (m, 1 H); IR (film) 3420, 2915, 2870, 1590 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 267 (M^+ + 1, 100), 250 (96); an acceptable analysis could not be obtained.

(2*R*/*S*,2′*S*,3*R*)-2-[[2′-(Methoxymethyl)pyrrolidinyl]carbonyl]-3-propylcyclohexan-1-one (3c), (2*R*/*S*,2′*S*,3*S*)-2-[[2′-(Methoxymethyl)-pyrrolidinyl]carbonyl]-3-propylcyclohexan-1-one (4c), and (1*R*/*S*,2′*S*)-2-[[(Methoxymethyl)pyrrolidinyl]carbonyl]-1-propylcyclohex-2-en-1-ol (5c) (Table I, Entry 5). The procedure described for entry 4 was followed with **2a** (140 mg, 0.59 mmol) and propylmagnesium chloride (93 μL, 1.8 mmol). Flash chromatography (silica gel, ethyl acetate/hexane (1:1)) afforded a mixture of *cis*-**3c** and *cis*-**4c** (48 mg, 29%), a mixture of *trans*-**3c** and *trans*-**4c** (46 mg, 28%), and **5c** (17 mg, 10%).

3c and 4c (cis isomers): colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.8–1.0 (m, 3 H), 1.15–1.52 (m, 4 H), 1.52–2.48 (m, 11 H), 3.33 and 3.39 (s, 3 H), 2.76–3.95 (m, 5 H), 4.0–4.12 and 4.15–4.28 (m, 1 H); IR (film) 2950, 2860, 1700, 1630 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 282 (M^+ + 1, 100). The mixture of *cis*-**3c**/*cis*-**4c** was epimerized to *trans*-**3c/4c** by the method used for **3a/4a**.

3c and 4c (trans isomers): colorless oil, isolated as a 30:1 mixture; ^{1}H NMR ($CDCl_3$) δ 0.85–0.96 (m, 3 H), 1.05–2.6 (m, 15 H), 3.14 (d, *J* = 10.8 Hz, 1 H), 3.33 and 3.38 (s, 3 H), 3.2–3.5 (m, 1 H), 3.55 (d, *J* = 10.8 Hz, 1 H), 3.65–3.88 (m, 2 H), 4.24–4.38 (m, 1 H); IR (film) 2960, 2860, 1700, 1630 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 282 (M^+ + 1, 100). Anal. Calcd for $C_{16}H_{27}NO_3$: C, 68.31; H, 9.67. Found: C, 68.13; H, 9.81.

5c: cololess oil, isolated as a 2:1 mixture of diastereomers; ^{1}H NMR ($CDCl_3$) δ 0.8–1.05 (m, 3 H), 1.1–2.3 (m, 14 H), 3.35 (s, 3 H), 3.1–4.0 (m, 4 H), 4.1–4.6 (m, 1 H), 5.94–6.05 and 6.05–6.15 (m, 1 H); IR (film) 3400, 2960, 2870, 1590 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 282 (M^+ + 1, 100), 264 (52); an acceptable analysis could not be obtained.

(4*R*/*S*)-1-Methyl-4,5,6,7-tetrahydro-4-propyl-2,1-benzisoxazolin-3-one (10b) was prepared as described for **10a** utilizing a 30:1 mixture of *trans*-**3c** and *trans*-**4c** (44 mg, 0.16 mmol). Flash chromatography (silica gel, ethyl acetate/hexane (1:1)) afforded **10b** as a colorless oil (26 mg, 87%): ^{1}H NMR ($CDCl_3$) δ 0.89–0.96 (m, 3 H), 1.15–1.58 (m, 4 H), 1.65–2.0 (m, 4 H), 2.3–2.38 (m, 2 H), 2.4–2.58 (m, 1 H), 3.17 (s, 3 H); $[\alpha]^{22}_D$ −58.5° (*c* 0.2, $CHCl_3$); IR (film) 2950, 2930, 2860, 1730, 1625 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 196 (M^+ + 1, 100). Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.77. Found: C, 67.54; H, 8.76.

(2*S*/*R*,2′*S*,3*R*)-2-[[2′-(Methoxymethyl)pyrrolidinyl]carbonyl]-3-allylcyclohexan-1-one (3d), (2*R*/*S*,2′*S*,3*S*)-2-[[2′-(Methoxymethyl)-pyrrolidinyl]carbonyl]-3-allylcyclohexan-1-one (4d), and (1*R*/*S*,2′*S*)-2-[[2′-(Methoxymethyl)pyrrolidinyl]carbonyl]-1-allylcyclohex-2-en-1-ol (5d) (Table I, Entry 6). The procedure described for entry 4 was fol-

lowed with **2a** (150 mg, 0.63 mmol) and allylmagnesium chloride (120 μL, 2.30 mmol). Flash chromatography (silica gel, ethyl acetate/hexane (1:1)) afforded a mixture of *cis*-**3d** and *cis*-**4d** (14 mg, 8%), a mixture of *trans*-**3d** and *trans*-**4d** (19 mg, 11%), and **5d** (138 mg, 78%).

3d and 4d (cis isomers): colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.5–2.6 (m, 13 H), 2.7–3.15 (m, 1 H), 3.35 and 3.38 (s, 3 H), 3.15–3.72 (m, 4 H), 3.95–4.12 and 4.12–4.3 (m, 1 H), 4.92–5.15 (m, 2 H), 5.6–5.85 (m, 1 H); IR (film) 3060, 2920, 2860, 1700, 1630 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 280 (M^+ + 1, 100), 238 (8). The mixture of *cis*-**3d**/*cis*-**4d** was epimerized to *trans*-**3d**/*trans*-**4d** by the method used for **3a**/**4a**.

3d and 4d (trans isomers): colorless oil, isolated as a 36:1 mixture; ^{1}H NMR ($CDCl_3$) δ 1.2–2.6 (m, 13 H), 3.34 and 3.38 (s, 3 H), 3.17 (d, *J* = 10.4 Hz, 1 H), 3.2–3.5 (m, 1 H), 3.60 (d, *J* = 10.4 Hz, 1 H), 3.65–3.90 (m, 2 H), 4.2–4.38 (m, 1 H), 4.95–5.12 (m, 2 H), 5.65–5.92 (m, 1 H); IR (film) 3060, 2920, 1700, 1630 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 280 (M^+ + 1, 100); an acceptable analysis could not be obtained.

5d: colorless oil, isolated as a 3:1 mixture of diastereomers; ^{1}H NMR ($CDCl_3$) δ 1.5–2.3 (m, 10 H), 2.3–2.5 (m, 2 H), 3.35 (s, 3 H), 3.3–3.72 (m, 4 H), 4.18–4.4 (m, 1 H), 4.92–5.12 (m, 2 H), 5.12–5.35 (m, exchangeable with D_2O, 1 H), 5.62–5.9 (m, 1 H), 6.0–6.1 and 6.12–6.22 (m, 1 H); IR (film) 3400, 3060, 2930, 1590 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 280 (M^+ + 1, 100), 262 (40). Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02. Found: C, 68.62; H, 8.96.

3d and 4d (Table I, Entry 7). A stirred solution of **2a** (100 mg, 0.42 mmol), copper(II) bromide (9.0 mg, 0.04 mmol), and trimethylsilyl chloride (0.27 mL, 2.1 mmol) in THF (5 mL) was cooled to 0 °C, and allylmagnesium chloride (25 μL, 0.5 mmol) was added. The mixture was stirred at 0 °C for 2 h and then was allowed to warm to room temperature. After the mixture was stirred for an additional 12 h, aqueous ammonium chloride was added. The aqueous phase was washed with methylene chloride (2 × 15 mL), and the combined organic phases were dried over magnesium sulfate. Concentration at reduced pressure and flash chromatography (silica gel, ethyl acetate/hexane (1:1)) afforded a mixture of *cis*-**3d** and *cis*-**4d** (21 mg, 18%) and a mixture of *trans*-**3d** and *trans*-**4d** (22 mg, 18%, product ratio of >32:1).

Conversion of *trans*-3d/4d to *trans*-3c/4c. A sample of *trans*-**3d**/**4d** (10 mg, >32:1) and [Ir(cod)py(PCy_3)]PF_6[13] (2 mg) in methylene chloride (5 mL) was stirred under hydrogen for 1 h. The mixture was concentrated at reduced pressure, ether (5 mL) was added, and the solution was filtered through filter paper under vacuum. Concentration at reduced pressure and flash chromatography (silica gel, ethyl acetate/hexane (1:1)) afforded *trans*-**3c**/**4c** (8 mg, 80%) as a 60:1 mixture of diastereomers.

(2*R*/*S*,2′*S*,3*S*)-2-[[2′-(Methoxymethyl)pyrrolidinyl]carbonyl]-3-vinylcyclohexan-1-one (3e) and (2*R*/*S*,2′*S*,3*R*)-2-[[2′-(Methoxymethyl)pyrrolidinyl]carbonyl]-3-vinylcyclohexan-1-one (4e). The procedure described for entry 7 was followed with **2a** (100 mg, 0.42 mmol) and vinylmagnesium bromide (0.2 mL, 1.5 mmol). Flash chromatography (silica gel, ethyl acetate/hexane (1:1)) afforded a mixture of *trans*-**3e** and *trans*-**4e** (66 mg, 59%, 1:1.5 mixture of diastereomers determined by HPLC and ^{1}H NMR analysis). Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74. Found: C, 67.98; H, 8.80.

Flash chromatography (silica gel, ethyl acetate/hexane (1:2)) afforded separation of *trans*-**3e** and *trans*-**4e**. *trans*-**3e** was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.5–2.62 (m, 10 H), 2.95–3.2 (m, 1 H), 3.2–3.28 (m, 1 H), 3.33 and 3.38 (s, 3 H), 3.28–3.5 (m, 2 H), 3.65–3.88 (m, 2 H), 4.22–4.35 (m, 1 H), 4.94–5.2 (m, 2 H), 5.65–5.88 (m, 1 H); IR (film) 2920, 2870, 1705, 1635 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 266 (M^+ + 1, 100). *trans*-**4e** also was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.5–2.15 (m, 8 H), 2.15–2.4 (m, 1 H), 2.42–2.62 (m, 1 H), 3.23 and 3.32 (s, 3 H), 2.9–3.88 (m, 6 H), 3.88–4.02 and 4.3–4.44 (m, 1 H), 4.92–5.2 (m, 2 H), 5.58–5.88 (m, 1 H); IR (film) 2920, 2870, 1705, 1635 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 266 (M^+ + 1, 100).

3e and 4e (Table I, Entry 8). The procedure described for entry 4 was followed with **2a** (100 mg, 0.42 mmol) and vinylmagnesium bromide (0.2 mL, 1.5 mmol). HPLC analysis of the crude product gave a ratio of >30:1 for *trans*-**3e** and *trans*-**4e**. Flash chromatography (silica gel, ethyl acetate/hexane (1:1)) afforded a mixture of *cis*-**3e** and *cis*-**4e** (14 mg, 13%) and a mixture of *trans*-**3eand** *trans*-**4e** (67 mg, 60%).

3e and 4e (cis isomers): colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.5–2.22 (m, 8 H), 2.25–2.72 (m, 3 H), 3.34 and 3.38 (s, 3 H), 2.85–3.73 (m, 5 H), 3.88–4.04 and 4.13–4.3 (m, 1 H), 4.95–5.2 (m, 2 H), 5.6–5.92 (m, 1 H); $[\alpha]^{27}_D$ −72.1° (*c* 0.28, $CHCl_3$); IR (film) 2940, 2870, 1700, 1630 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 266 (M^+ + 1, 100). The mixture of *cis*-**3e**/*cis*-**4e** was epimerized to *trans*-**3e**/*trans*-**4e** by the method used for **3a**/**4a**. Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74. Found: C, 67.42; H, 9.02.

(4*R*/*S*)-1-Methyl-4,5,6,7-tetrahydro-4-vinyl-2,1-benzisoxazolin-3-one (10c). A 2:1 mixture of *trans*-**3e** and *trans*-**4e** (40 mg, 0.15 mmol), *N*-methylhydroxylamine hydrochloride (13.4 mg, 0.16 mmol), and *p*-toluenesulfonic acid monohydrate (28.5 mg, 0.15 mmol) in benzene (5 mL) was heated to reflux for 12 h. The solution was decanted, washed with saturated sodium bicarbonate solution, and dried over magnesium sulfate. Concentration at reduced pressure and flash chromatography (silica gel, ethyl acetate/hexane (1:1)) afforded **10c** as a colorless oil (22 mg, 83%): ^{1}H NMR ($CDCl_3$) δ 1.6–1.9 (m, 4 H), 2.3–2.42 (m, 2 H), 3.15–3.3 (m, 1 H), 3.22 (s, 3 H), 5.0–5.17 (m, 2 H), 5.78–5.96 (m, 1 H); IR (film) 3070, 2930, 2860, 1725, 1620 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 180 (M^+ + 1, 100). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31. Found: C, 66.73; H, 7.43.

The residual benzene-insoluble oil from the reaction flask was washed with ethyl acetate (2 × 10 mL). The oil was soluble in methylene chloride (10 mL). Magnesium sulfate was added, and this mixture was stirred at room temperature for 1 h. Filtration and concentration at reduced pressure provided (2*S*)-2-(Methoxymethyl)pyrrolidine *p*-toluenesulfonate as a light brown oil (35 mg, 81%). The product was crystallized from ethyl acetate to give colorless crystals: mp 67–8 °C; ^{1}H NMR ($CDCl_3$) δ 1.7–2.13 (m, 4 H), 2.36 (s, 3 H), 2.95 and 3.34 (s, 3 H), 3.25–3.48 (m, 2 H), 3.52–3.72 (m, 2 H), 3.75–3.98 (m, 1 H), 7.19 (d, *J* = 7.9 Hz, 2 H), 7.74 (*J* = 8.2 Hz, 2 H), 8.4–8.7 (m, 1 H), 9.15–9.45 (m, 1 H); $[\alpha]^{22}_D$ −3.7° (*c* 3.82, $CHCl_3$); IR (film) 3300–2300 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 173 (26), 116 (100).

A sample of *trans*-**3e**/*trans*-**4e** (ratio >30:1) was converted to **10c** as previously described; $[\alpha]^{22}_D$ +21.3° (*c* 0.73, $CHCl_3$).

Hydrogenation of *trans*-**3e** (19 mg, 0.07 mmol) by the procedure used to obtain *trans*-**3c**/**4c** from *trans*-**3d**/**4d** gave *trans*-**3b** in 79% yield.

(2*R*/*S*,2′*S*,3*S*)-2-[[2′-(Methoxymethyl)pyrrolidinyl]carbonyl]-3-phenylcyclohexan-1-one (3f) and (2*R*/*S*,2′*S*,3*R*)-2-[[2′-(Methoxymethyl)pyrrolidinyl]carbonyl]-3-phenylcyclohexan-1-one (4f) (Table I, Entry 10). To a stirred mixture of **2a** (120 mg, 0.50 mmol) and copper(I) bromide (72 mg, 0.5 mmol) in THF (10 mL) at 0 °C was added chlorotrimethylsilane (0.32 mL, 2.5 mmol). Phenylmagnesium bromide (60 μL, 1.0 mmol) was added, and the mixture was stirred at 0 °C for 2 h. The reaction mixture was allowed to warm to room temperature and stirred for an additional 12 h. Aqueous ammonium chloride was added. The aqueous phase was washed with methylene chloride (2 × 20 mL), and the combined organic phases were dried over magnesium sulfate. Concentration at reduced pressure and flash chromatography (silica gel, ethyl acetate/hexane (1:1)) afforded a mixture of *cis*-**3f** and *cis*-**4f** (53 mg, 33%) and a mixture of *trans*-**3f** and *trans*-**4f** (105 mg, 66%).

3f and 4f (cis isomers): colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.15–1.9 (m, 6 H), 2.1–2.65 (m, 4 H), 3.25, 3.28, and 3.31 (s, 3 H), 2.65–3.5 (m, 5 H), 3.70–3.74 and 3.75–3.82 (m, 1 H), 3.87–4.05 and 4.05–4.20 (m, 1 H), 7.2–7.4 (m, 5 H); $[\alpha]^{25}_D$ +5.0° (*c* 1.06, $CHCl_3$); IR (film) 3060, 3020, 2930, 2870, 1690, 1620 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 316 (M^+ + 1, 100). The mixture of *cis*-**3f**/*cis*-**4f** was epimerized by the method used for **3a**/**4a**. Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99. Found: C, 72.37; H, 8.06.

3f and 4f (trans isomers): the 5:1 mixture of diastereomers was resubjected to flash chromatography (silica gel, ethyl acetate/hexane (1:2)) to give *trans*-**3f** as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.55–2.20 (m, 8 H), 2.3–2.72 (m, 2 H), 2.85–3.08 (m, 2 H), 3.24 and 3.34 (s, 3 H), 3.1–3.4 (m, 1 H), 3.52–3.85 (m, 3 H), 3.96–4.12 (m, 1 H), 7.12–7.4 (m, 5 H); $[\alpha]^{22}_D$ −45.1° (*c* 1.03, $CHCl_3$); IR (film) 3060, 3020, 2930, 2870, 1700, 1630 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 316 (M^+ + 1, 100), 270 (10). Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99. Found: C, 72.08; H, 7.90.

Also obtained was *trans*-**4f**, which was crystallized from ethyl acetate/hexane (1:6): mp 111–116 °C; ^{1}H NMR ($CDCl_3$) δ 1.2–2.24 (m, 8 H), 2.3–2.54 (m, 1 H), 2.54–2.7 (m, 1 H), 2.86 (dd, *J* = 9.6 Hz, *J* = 6.6 Hz, 1 H), 3.01 and 3.22 (s, 3 H), 3.05–3.7 (m, 5 H), 3.86 and 4.15–4.32 (m, 1 H), 7.1–7.35 (m, 5 H); $[\alpha]^{22}_D$ −6.1° (*c* 0.16, $CHCl_3$); IR (solution cell, $CDCl_3$) 3060, 3020, 2920, 2850, 1700, 1630 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 316 (M^+ + 1, 100), 270 (6). Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99. Found: C, 72.41; H, 8.07.

3f, 4f, and (1*R*/*S*,2′*S*)-2-[[2′-(Methoxymethyl)pyrrolidinyl]carbonyl]-1-phenylcyclohex-2-en-1-ol (5f) (Table I, Entry 11). The procedure described for entry 4 was followed with **2a** (200 mg, 0.84 mmol) and phenylmagnesium bromide (0.2 mL, 3 mmol). Flash chromatography (silica gel, ethyl acetate/hexane (1:1)) afforded a mixture of *cis*-**3f** and *cis*-**4f** (68 mg, 26%): $[\alpha]^{22}_D$ +14.5° (*c* 1.36, $CHCl_3$), a

(13) Crabtree, R. H.; Felkin, H.; Fellebeen-Khan, T.; Morris, G. E. *J. Organomet. Chem.* **1979**, *168*, 183.

mixture of *trans*-**3f** and *trans*-**4f** [61 mg, 23%; $[\alpha]^{25}_D$ -44.4° (*c* 1.22, $CHCl_3$)], and **5f** (130 mg, 49%).

5f: colorless oil, isolated as a 2:1 mixture of diastereomers; ^1H NMR ($CDCl_3$) δ 1.6–2.68 (m, 10 H), 3.0 and 3.29 (s, 3 H), 2.8–3.82 (m, 4 H), 3.85–4.15 (m, 1 H), 5.3–5.5 and 5.6–5.75 (m, exchangeable with D_2O, 1 H), 6.1–6.28 and 6.28–6.4 (m, 1 H), 7.12–7.36 (m, 3 H), 7.36–7.5 (m, 2 H); $[\alpha]^{22}_D$ -15.0° (*c* 0.99, $CHCl_3$); IR (film) 3470, 3050, 3010, 2920, 2870, 1625, 1590 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 316 (M^+ + 1, 96), 298 (100). Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99. Found: C, 72.32; H, 8.12.

(3a*S*,4*S*)-4,5,6,7-Tetrahydro-4-phenyl-2,1-benzisoxazol-3(3a*H*)-one (8) and 4,5,6,7-Tetrahydro-4-phenyl-2,1-benzisoxazolin-3(1*H*)-one (9). A 5:1 mixture of *trans*-**3f** and *trans*-**4f** (51 mg, 0.16 mmol), hydroxylamine hydrochloride (11.1 mg, 0.16 mmol), and potassium hydroxide (17.9 mg, 0.32 mmol) in 95% ethanol (5 mL) were stirred at room temperature for 48 h. The mixture was concentrated at reduced pressure, and water (5 mL) and methylene chloride (20 mL) were added. The organic phase was washed with brine and dried over magnesium sulfate. Concentration at reduced pressure and flash chromatography (silica gel, ethyl acetate/hexane (1:1)) afforded a 1:1 mixture of **8** and **9** (28 mg, 81%): ^1H NMR ($CDCl_3$) δ 1.5–1.88 (m, 3 H), 2.0–2.55 (m, 3 H), 2.78–2.94 and 3.75–3.85 (m, 2 H), 3.35 (d, *J* = 11.8 Hz, 0.65 H), 7.1–7.45 (m, 5 H); $[\alpha]^{24}_D$ -10.5° (*c* 0.55, $CHCl_3$); IR (film) 3100, 2950, 2860, 1700, 1600 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 216 (M^+ + 1, 100), 198 (6). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09. Found: C, 72.46; H, 6.02.

(4*R*/*S*)-1-Methyl-4,5,6,7-tetrahydro-4-phenyl-2,1-benzisoxazolin-3-one (10d). Sodium hydride (48 mg, 0.2 mmol) was added to a mixture of **8** and **9** (25.8 mg, 0.12 mmol) in THF (5 mL). After the mixture was stirred at room temperature for 1 h, methyl iodide (36 μL, 0.58 mmol) was added and the mixture was stirred for an additional 12 h. Water (2 mL) was added, and the aqueous phase was washed with methylene chloride (10 mL). The organic phase was washed with brine and dried over magnesium sulfate. Concentration at reduced pressure and flash chromatography (silica gel, ethyl acetate/hexane (1:1)) afforded **10d** (10 mg, 38%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.7–1.88 (m, 3 H), 1.9–2.14 (m, 1 H), 2.3–2.6 (m, 2 H), 3.28 (s, 3 H), 3.81–3.86 (m, 1 H), 7.1–7.36 (m, 5 H); IR (film) 3020, 2930, 2850, 1730, 1620 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 230 (M^+ + 1, 100). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59. Found: C, 73.16; H, 6.74.

A mixture (1:2) of *trans*-**3f** and *trans*-**4f** (150 mg, 0.47 mmol) was converted to **10d** by treatment with *N*-methylhydroxylamine as described for **10a**. The product, a colorless oil, was obtained with 28.9% ee (Chiracel OJ HPLC column, hexane/ethanol (1:1), 1.0 mL/min, 40 °C; retention times (+)-**10d** 6.65 min, (-)-**10d** 9.07 min);[14] $[\alpha]^{22}_D$ +15.5 (*c* 1.69, $CHCl_3$).

A chromatographically homogeneous sample of *trans*-**3f** (96 mg, 0.3 mmol) was converted to (4*S*)-**10d** by treatment with *N*-methylhydroxylamine in 91% yield as described for **10a**: mp 95–7 °C; $[\alpha]^{24}_D$ -56.3° (*c* 1.20, $CHCl_3$). The product was obtained with 98.7% ee as determined by the chiral HPLC analysis.[14]

(3*R*)-3-Phenylcyclohexanone (11). A stirred solution of (4*S*)-**10d** (82 mg, 0.36 mmol, 98.7% ee) in THF (5 mL) was cooled to -78 °C, and then ammonia (15 mL) was added. Lithium (7 mg, 1 mmol) was added, and the mixture was allowed to warm to -33 °C and then was refluxed for 1 h. Ammonium chloride was added, and the mixture was partitioned between water (5 mL) and methylene chloride (20 mL). The organic phase was washed with brine and dried over magnesium sulfate. Concentration at reduced pressure and flash chromatography (silica gel, ethyl acetate/hexane (1:1)) afforded **11** (38 mg, 61%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.55–2.0 (m, 2 H), 2.0–2.22 (m, 2 H), 2.25–2.7 (m, 4 H), 2.85–3.15 (m, 1 H), 7.05–7.42 (m, 5 H); $[\alpha]^{22}_D$ +20.5° (*c* 0.58, $CHCl_3$),[11] IR (film) 3050, 3020, 2920, 2850, 1705 cm^{-1}; chemical ionization mass spectrum, *m/z* (relative intensity) 175 (M^+ + 1, 100). Chiral HPLC comparisons of this material to racemic **11** confirmed the enantiomeric purity determined for (4*S*)-**10d** (98.7% ee).

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Supplementary Material Available: Experimental procedures and structures for compounds **11a**, **11b**, **12a**, **12b**, **14**, **15**, **16**, and **17** and tables of characterization data for products of organometallic addition to **2b**, crystal data, atomic coordinates and isotropic thermal parameters, bond lengths, bond angles, anisotropic thermal parameters, and hydrogen atom coordinates and isotropic thermal parameters (12 pages). Ordering information is given on any current masthead page.

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Asymmetric Syntheses of 1,6-Dialkyl-1,4-cyclohexadiene Derivatives

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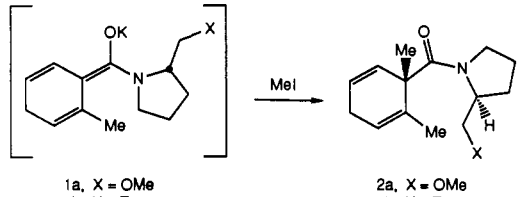
Abstract: Ortho-lithiation–alkylation of tertiary benzamide **3** provides a series of 2-substituted chiral benzamides **3a–g** (Scheme I). Birch reduction of **3a–j** followed by alkylation of the resulting chiral amide enolate with MeI at -78 °C gives 1,6-dialkyl-1,4-cyclohexadiene derivatives **4a–j** with excellent diastereoselectivities (Table I). Applications of this asymmetric synthesis are illustrated by conversions of **4g** to enantiomerically pure bicyclic lactone **9** and octalone **11** (Scheme III) and **4j** to hexahydro-9-anthracenone **14** (Scheme IV).

We have described the generation of enolate **1a** by potassium in ammonia reduction of the chiral benzamide **3** and alkylation of **1a** with methyl iodide to give the 1,4-cyclohexadiene **2a** in 90% isolated yield with a diastereoisomeric excess (de) of >98%.[1]



1a, X = OMe
b, X = Et

2a, X = OMe
b, X = Et

Enolate **1b**, prepared to test the importance of internal chelation arguments, gave **2b** with only slightly reduced de. The assignment of a specific configuration to enolate **1a** rested on circumstantial evidence rather than definitive spectroscopic data. Enolate configuration **1a** places the vinyl methyl substituent distant from the large, solvated alkoxide substituent. Aggregation of the enolate also probably increases the effective size of the alkoxide relative to the substituents on the nitrogen atom.

We now report a significant extension of this methodology to a wide range of 2-substituted-benzamide analogues (**3a–j**), which

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