Investigation of the Effects of the Structure and Chelate Size of Bis-oxazoline Ligands in the Asymmetric Copper-Catalyzed Cyclopropanation of Olefins: Design of a New Class of Ligands

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A set of novel, C_2-symmetric bis-oxazoline ligands has been synthesized by mounting two oxazoline rings onto an optically active 1,3-dioxolane backbone. This design allows for the control of both orientation as well as the proximity of the oxazolinyl R-groups around the reactive site. As a result of the twist imparted by the 1,3-dioxolane ring, the stereogenic oxazolinyl substituents can be brought either toward or away from the complexed metal in a controllable fashion. Starting from L-amino alcohols and either L- or D-tartaric acid, two sets of ligands (**6b**−**e** and **7a,b**) were synthesized and evaluated in the copper-catalyzed cyclopropanation of olefins. The comparison of benzyl and isopropyl derivatives of these ligands with previously reported five- and six-membered bis-oxazolines clearly indicates the beneficiary effect of the larger chelate size and the chiral tether of the tartrate-derived ligand. The effect of the different oxazolinyl groups along with the different substituents on the dioxolane tethers was also investigated. The influence of the alkyl group of the diazoacetate was studied, and the diazoacetate derived from (−)-8-phenylmenthol was found to be superior to (−)-menthyl diazoacetate. The cyclopropanation of vinyl acetate, a relatively unexplored substrate for this reaction, furnished cyclopropanol derivatives in good optical purity.

Introduction

The C_2-symmetric chiral bis-oxazolines have emerged as an efficient class of ligands in an increasing number of asymmetric transformations over the last few years.[1] Since the first use of the structurally similar semicorrins in asymmetric cyclopropanation of olefins by Pfaltz,[1a] the bis-oxazoline unit has been found to be an excellent chiral ligand for numerous asymmetric reactions. Pfaltz showed its utility in a number of applications,[2a] which in addition to cyclopropanation also included Ir-catalyzed transhydrogenation of ketones and Pd-catalyzed nucleophilic allylic substitution.[3] Masamune[2c,d] and Evans[2e,f] further developed the Cu-catalyzed asymmetric cyclopropanation of olefins into a highly enantioselective process. Jacobsen[4] recently introduced Cu-catalyzed aziridination of imines in the presence of bis-oxazolines with moderate enantioselectivity. Evans[5] demonstrated the asymmetric version of Cu-catalyzed aziridination of olefins with [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane in the presence of bis-oxazolines. Corey[6a,b] and Evans[6c,d,h] utilized these ligands with remarkable success for the Mg-, Cu-, and Fe-catalyzed asymmetric Diels−Alder cycloaddition reactions, and recently, Jørgensen[6f] reported on the Cu-catalyzed hetero Diels−Alder reactions of glyoxylates. Helmchen et al.[7] were the first to report on the Rh-catalyzed hydrosilylation of ketones with these ligands. Addition of alkyllithium reagents to imines[8] and Cu-catalyzed allylic oxidation[9] are other recent applications of bis-oxazolines. Addition of trimethylsilyl cyanide[10] and silylketene acetal[11] to aldehydes are other examples where excellent enantioselectivities have been achieved. Porter and co-workers[12] used bis-oxazolines as chiral auxiliaries in their enantioselective free-radical-initiated addition of allyltributylstannane. The schematic representation of the wide applications of bis-oxazolines is presented in Figure 1. However, the asymmetric cyclopropanation of olefins is by far the most successful application of the Cu(I)/bis-oxazoline catalytic system.

The conformationally rigid framework of the metal chelate with the presence of stereocenters close to the donor nitrogen atoms imposes a well-ordered chiral

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(1) (a) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339. (b) Bolm, C. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 542. (c) Pfaltz, A. *Acta. Chem. Scand.* **1996**, *50*, 189.

(2) For various bis-oxazoline-mediated organic syntheses see the following for cyclopropanation of olefins: (a) Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232. (b) Reiser, O. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 547. (c) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005. (d) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373. (e) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. (f) Evans, D. A.; Woerpel, K. A.; Scott, M. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 430. (g) Tokunoh, R.; Tomiyama, H.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 2449.

(3) Nucleophilic allylic substitution: von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566.

(4) Aziridination of imines: Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 676.

(5) Aziridination of olefins: Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328.

(6) Diels−Alder reactions: (a) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728. (b) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807. (c) Evans, D. A.; Miller, S. J.; Leckta, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460. (d) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798. (e) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007. (f) Johannsen, M.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757. (g) Desimoni, G.; Faita, G.; Righetti, P. P. *Tetrahedron Lett.* **1996**, *37*, 3027. (h) Evans, D. A.; Kozlowski, M. C.; Tedrow, J. S. *Tetrahedron Lett.* **1996**, *37*, 7481.

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(8) Addition of organolithium reagents to imines: (a) Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C. *J. Am. Chem. Soc.* **1994**, *116*, 8797. (b) Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C.; Faucher, A. M.; Edwards, J. P. *J. Org. Chem.* **1995**, *60*, 4884.

(9) Allylic oxidation of olefins: (a) Gokhale, A. S.; Minidis, A. B. E.; Pfaltz, A. *Tetrahedron Lett.* **1995**, *36*, 1831. (b) Andrus, M. B.; Argade, A. B.; Chen, X.; Pamment, M. G. *Tetrahedron Lett.* **1995**, *36*, 2945.

(10) Addition of trimethylsilyl cyanide to aldehydes: Corey, E. J.; Wang, Z. *Tetrahedron Lett.* **1993**, *34*, 4001.

(11) Aldol additions to aldehydes: Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814.

(12) Free-radical addition of alkyl iodides to olefins: Wu, J. H.; Radinov, R.; Porter, N. D. *J. Am. Chem. Soc.* **1995**, *117*, 11029.

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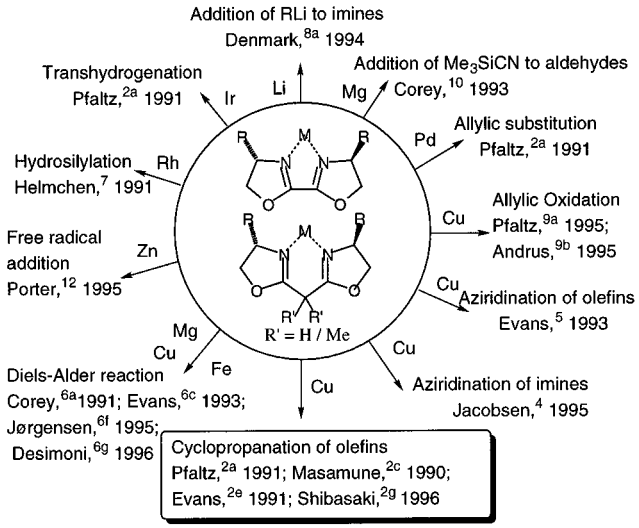


Figure 1.

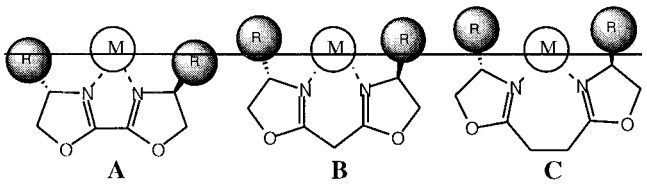


Figure 2.

environment at the catalytic site. The relatively easy accessibility and the possibility to modify the chiral centers also allow for fine-tuning of the ligand structure for specific applications. The size of the chelate in the reactive metal complex of bis-oxazolines is another important feature of the catalyst since it will control the orientation of the substituents on the two oxazolines around the metal ion. As the bite angle of the bidentate bis-oxazoline ligand increases from a five-membered chelate in **A** to a six-membered chelate in **B**, the R-groups will come in closer proximity to the metal ion, and this effect will be even more pronounced in a seven-membered chelate system, **C**, as shown in Figure 2. It should also be noted that the chelated metal ion will be more deeply embedded in complex **C**, as the larger chelate size will push the R-groups upward toward the substrate.

Bis-oxazolines forming five- and six-membered chelates are the most widely used ligands of this type. Recently, Corey[13] has reported a new catalyst for the intramolecular cyclopropanation in the asymmetric synthesis of sirenin, where the two oxazoline rings are fixed on a biaryl framework at the 2,2′ positions, increasing the size of chelate to a nine-membered ring. However, few investigations have been focused on the seven-membered chelate systems, and we therefore decided to explore this factor in order to better understand the influence of the chelate size on the reactivity/selectivity of bis-oxazoline ligands.

Methods for the preparations of bis-oxazolines **1**−**5** (R = *i*-Pr) are available in the literature,[2c,e,14] and to compare the effect of the chelate size we chose the cyclopropanation of styrene with ethyl diazoacetate catalyzed by CuOTf as the model reaction.

(13) Grant, T. G.; Noe, M. C.; Corey, E. J. *Tetrahedron Lett.* **1995**, *36*, 8745.

(14) Bolm, C.; Weickhardt, K.; Zehnder, M.; Ranff, T. *Chem. Ber.* **1991**, *124*, 1173.

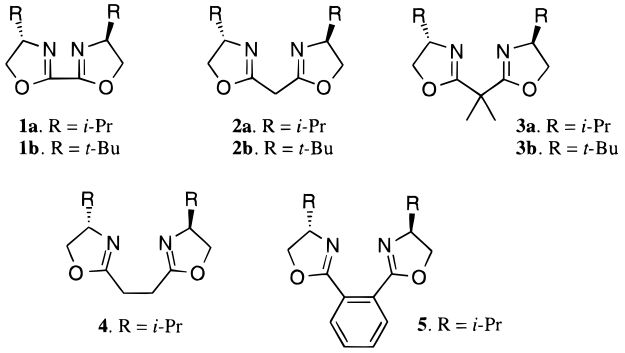


Figure 3.

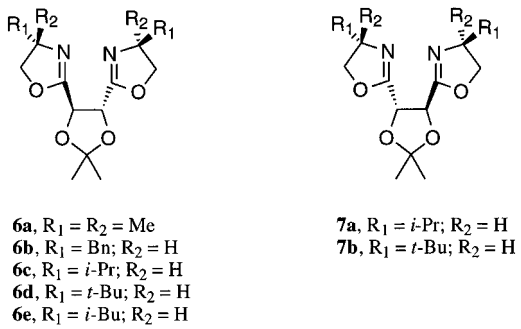


Figure 4.

The bis-oxazolines of type **1**, where the oxazoline rings are directly connected and thus form a five-membered chelate with Cu, give *trans* product with poor enantioselectivity[2e] (3% ee for **1a**; Figure 3). On the other hand, the ligands in which the oxazoline rings are separated by one carbon atom, of the type **2** and **3**, lead to a six-membered chelate and have been found to be more effective in Cu-catalyzed cyclopropanation. Masamune[2c] used ligand **2a** and obtained the *trans* product with 46% ee in the cyclopropanation of styrene under similar conditions. Evans et al.[2e] obtained the *trans* product in the same reaction with 49% ee with the use of **3a** and could enhance the selectivity to 99% with **3b**. It is noteworthy that the use of *t*-Bu derivatives of **2** and **3** has been found to be crucial in order to achieve high asymmetric induction in cyclopropanation as well as in several other catalytic reactions.[2a,c]

We have recently reported[15] a series of new bis-oxazoline ligands[16] capable of forming seven-membered chelates and their use in the asymmetric Cu-catalyzed cyclopropanation of olefins. In this paper, we present full experimental details for their preparation, along with a comparative study on the effect of the chelate size on the selectivity/reactivity of this important class of C_2-symmetric ligands (Figure 4).

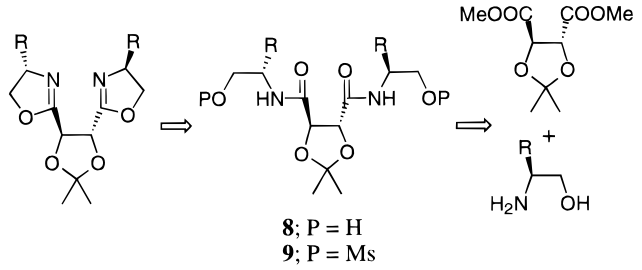
Synthesis of Bis-oxazolines

In the design of our new ligands it was crucial to have a rigid, cyclic backbone, and 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylic acid dimethyl ester was selected for this purpose since both enantiomeric forms are readily avail-

(15) Bedekar, A. V.; Andersson, P. G. *Tetrahedron Lett.* **1996**, *37*, 4073.

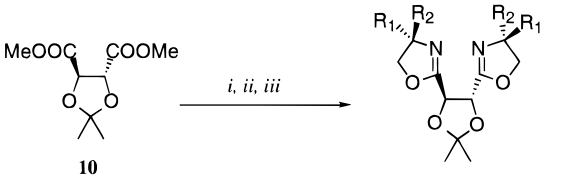
(16) After the publication of our preliminary results on the asymmetric cyclopropanation of olefins with this new class of ligands, two other groups have reported on similar ligands: (a) Harm, A. M.; Knight, J. G.; Stemp, G. *Synlett* **1996**, 677. (b) Harm, A. M.; Knight, J. G.; Stemp, G. *Tetrahedron Lett.* **1996**, *37*, 6189. (c) Imai, Y.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron: Asymmetry* **1996**, *7*, 2453.

Scheme 1



8; P = H
9; P = Ms

Scheme 2[a]



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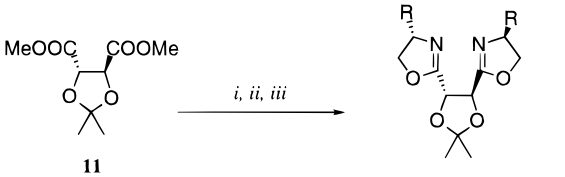
6a; $R_1 = R_2 = Me$
6b; $R_1 = Bn$; $R_2 = H$
6c; $R_1 = i\text{-Pr}$; $R_2 = H$
6d; $R_1 = t\text{-Bu}$; $R_2 = H$
6e; $R_1 = i\text{-Bu}$; $R_2 = H$



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7a; R = *i*-Pr
7b; R = *t*-Bu

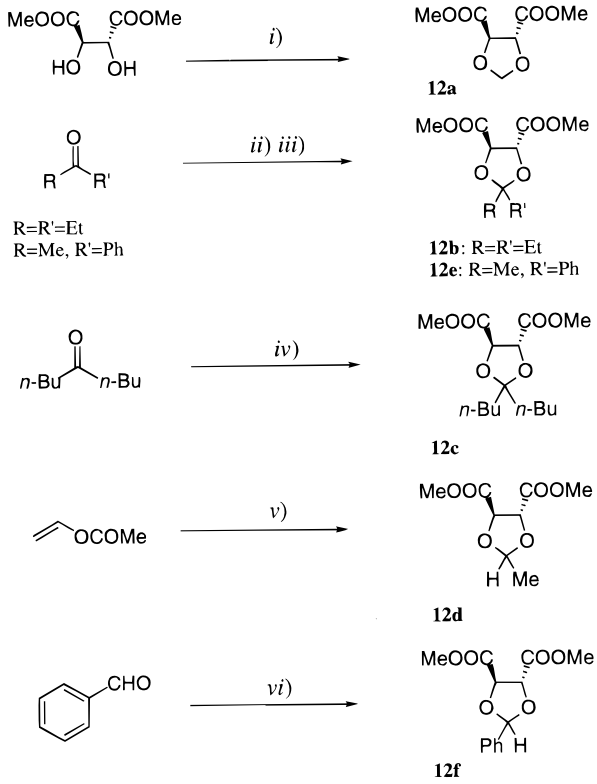
[a] Key: (i) L-amino alcohol, NaCN, MeOH, 45 °C; (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C; (iii) KOH, MeOH−H_2O (50−84% overall yield).

able.[17] Although there are several synthetic methods available for the preparation of oxazolines, many of these methods utilize acidic reagents or require drastic reaction conditions. The acid-sensitive nature of the dioxolane ring of the tether precluded the use of acidic reagents such as zinc chloride,[14] dichlorodimethylstannane,[2c] methanesulfonic acid,[6b] etc., otherwise used for the synthesis of oxazolines. Instead, another approach using the method recently reported by Denmark[8b] for the preparation of bis-oxazolines was investigated and found to be compatible with the dioxolane ring (Scheme 1).

The dimethyl 2,3-*O*-isopropylidenetartrates were converted into the corresponding dihydroxy diamides **8** under cyanide-catalyzed (10 mol %) neutral conditions[18] in warm methanol. The crude samples of these dihydroxy diamides were treated with methanesulfonyl chloride (MsCl) (2.2 equiv) and Et_3N (4.4 equiv) in dichloromethane at 0 °C to afford the corresponding bismesylates **9**, which were treated with an aqueous methanolic solution of NaOH (8 equiv) to afford the bis-oxazolines in good to moderate overall yield (Scheme 2). In all cases, the intermediate dihydroxy diamides and bis-mesylates were too unstable to tolerate flash chromatographic purifications; thus, the crude material was used immediately in the following step. The final ligands were conveniently purified by flash chromatography on silica gel in the presence of triethylamine.

The *i*-Pr derivative, **6c**, was found to be the most effective for the asymmetric cyclopropanation of styrene.

Scheme 3[a]

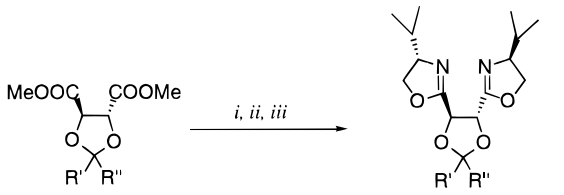


[a] Key: (i) $ZnCl_2$, paraformaldehyde, 150 °C (64%); (ii) trimethyl orthoformate, *p*-toluenesulfonic acid, MeOH; (iii) (+)-dimethyl tartrate, MeOH (80−90%); (iv) (+)-dimethyl tartrate, refluxing benzene (64%); (v) (+)-dimethyl tartrate, HgO, $BF_3{\cdot}Et_2O$, Et_2O (66%); (vi) $ZnCl_2$, (+)-dimethyl tartrate (65%).

To study the effect of different substitutions on the tether dioxolane ring, on which two oxazoline rings are mounted, a series of another set of ligands, **13a**−**f**, derived from L-valinol was synthesized. For the synthesis of these different *i*-Pr derivatives of bis-oxazolines by the same reaction sequence as shown in Scheme 2, the corresponding dioxolane diesters were required (Scheme 3). There are several methods available for the preparation of tartrate dioxolanes from ketones, but no general pathway was found to be useful for all the required derivatives, and after much investigation we had to rely on different syntheses for each derivative of the dioxolane diesters. For instance, the diester **12a** with two hydrogens instead of alkyl groups could not be prepared from paraformaldehyde and dimethyl tartrate by *p*-toluenesulfonic acid-catalyzed acetalization but was instead obtained when $ZnCl_2$ was used as a catalyst, as described by Seebach.[19] The dioxolane diesters **12b** and **12e** were prepared from diethyl ketone and acetophenone, respectively, by treatment with trimethyl orthoformate and a catalytic amount of *p*-toluenesulfonic acid in methanol, followed by treatment with (+)-dimethyl tartrate, as described in the literature.[20] However, this method could not be applied to the preparation of the *n*-Bu analogue, **12c**, which was instead synthesized *via* acid-catalyzed reaction of 5-nonanone and (+)-dimethyl tartrate in refluxing benzene with continuous removal of water over 4 days.[19] 2-Methyl-1,3-dioxolane-4,5-dicarboxylic acid dimethyl ester (**12d**) was prepared from (+)-dimethyl tartrate and

(17) Mash, E. A.; Nelson, K. A.; van Deusen, S.; Hemperly, S. B. *Org. Synth.* **1990**, *68*, 92.
(18) Högberg, T.; Ström, P.; Ebner, M.; Rämsby, S. *J. Org. Chem.* **1987**, *52*, 2033.
(19) Seebach, D.; Beck, A. K.; Imwinkelried, R.; Roggo, S.; Wonnacott, A. *Helv. Chim. Acta* **1987**, *70*, 954.
(20) McClelland, R. A.; Engell, K. M.; Larsen, T. S.; Sorensen, P. E. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2199.

Scheme 4[a]



12a; R'=R''=H
12b; R'=R''=Et
12c; R'=R''=*n*-Bu
12d; R'=Me, R''=H
12e; R'=Me, R''=Ph
12f; R'=Ph, R''=H

13a; R'=R''=H
13b; R'=R''=Et
13c; R'=R''=*n*-Bu
13d; R'=Me, R''=H
13e; R'=Me, R''=Ph
13f; R'=Ph, R''=H

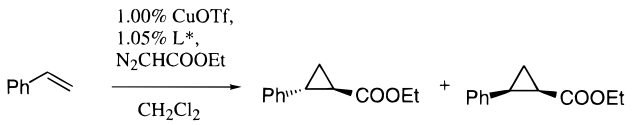
[a] Key: (i) L-valinol, NaCN, MeOH, 45 °C; (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C; (iii) KOH, MeOH−H_2O (32−78% overall yield).

vinyl acetate by the action of red HgO and BF_3·Et_2O, as described by Seebach.[21] The derivative **12f**, with phenyl and hydrogen substituents at the 2,2 position of dioxolane, was prepared via $ZnCl_2$-catalyzed acetalization of benzaldehyde and (+)-dimethyl tartrate, as reported earlier[22] (Scheme 3).

The series of *i*-Pr derivatives, **13a**−**f**, was synthesized via the dihydroxy diamides and the bis-mesylates prepared from the corresponding diesters, **12a**−**f**, and optically pure L-valinol (Scheme 4).

Results and Discussion

The Cu-catalyzed cyclopropanation of olefins with different diazoacetates in the presence of tartrate-tethered bis-oxazolines was investigated in detail in order to determine the efficiency of the new ligand system. To compare various derivatives of ligands, as well as the different reaction conditions, styrene was chosen as a standard substrate. Different Cu salts and complexes were employed, and the best results were obtained using CuOTf·1/2C_6H_6[23] in accordance with literature observations.[2e] In the first part, different *i*-Pr derivatives of bis-oxazolines, which will form different chelate sizes in their complexes with copper, were investigated to determine the influence of the chelate size on the enantioselectivity in this reaction. The cyclopropanation of styrene was carried out with ethyl diazoacetate in the presence of 1.00 mol % of CuOTf and 1.05 mol % of chiral ligand in dry dichloromethane.



The beneficial effect of an increased chelate size is evident from the data presented in Table 1. While the five-membered chelate formed with ligand **1a** resulted in a nearly nonselective reaction, ligands **2a** and **3a**, which form six-membered chelates, gave rise to considerably higher enantioselectivities. It has been proposed[24] that the copper−ligand complex first reacts with the alkyl diazoacetate to form a metal−carbene complex which then is attacked by the olefin to form the cyclopropanated product. The steric interactions between the alkyl groups of the ligand and the carboxy group of the carbenoid intermediate will determine the approach of the olefin and hence the stereochemical outcome of the reaction. With an increase of the bite angle, the substituents on the oxazoline rings will come closer toward the metal and the carboxy group in the intermediate, resulting in a more severe interaction.

Table 1. Comparison of Enantioselectivities Using *i*-Pr-substituted Bis-oxazolines in the Cu-Catalyzed Cyclopropanation of Styrene with Ethyl Diazoacetate

entry	ligand	% yield[a]	diastereoselectivity *trans*:*cis*	% ee[b] *trans*	% ee[c] *cis*	ref
1	**1a**	d	66:34	3	8	2e
2	**2a**	76	71:29	36	15	2c
3	**3a**	d	69:31	49	45	2e
4	**4**	49	64:36	59	30	f
5	**5**	12	64:36	8	e	f
6	**6c**	76	70:30	84	65	f
7	**7a**	77	67:33	68	73	f

[a] Isolated. [b] Determined by HPLC analysis using a CHIRALCEL OD-H column. [c] Determined by optical rotation. [d] Not reported. [e] Not determined. [f] This work.

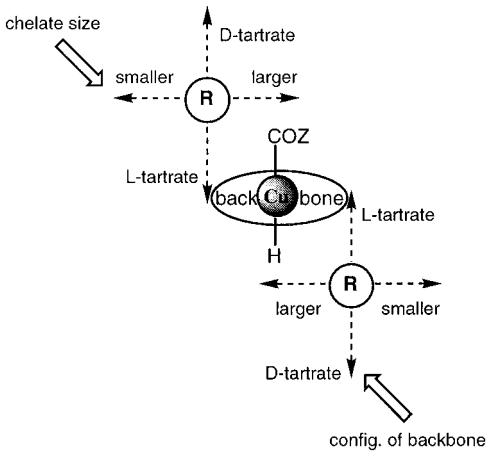


Figure 5. Positioning of the oxazoline R-groups as a function of the chelate size and the configuration of the ligand backbone.

To investigate this effect further, we conducted the same experiment with bis-oxazoline **4**, tethered with an ethylene unit, and capable of forming a seven-membered chelate with Cu. The *trans* product was formed in 59% ee, which is substantially higher than for **2a** and **3a**. This observation clearly supports the assumption that in the seven-membered chelate the substituents on the two oxazoline rings will be brought closer to the metal as the bite angle is increased (Figures 2 and 5), which in turns results in a higher enantioselectivity for the reaction. The other bis-oxazoline **5** tethered by a benzene ring, however, resulted in a considerable drop in both catalytic activity (12% yield) as well as enantioselectivity (8% ee).

Encouraged by the results obtained using ligand **4**, we decided to concentrate on making a bis-oxazoline with a more rigid two-carbon tether. One such way to restrict the flexibility of this bidentate ligand would be to attach the two oxazoline rings onto the tartrate backbone as demonstrated by Seebach[19,25] and Narasaka[26] in their TADDOL ligands. Other examples of the beneficiary

(21) Seebach, D.; Plattner, D. A.; Beck, A. K.; Wang, Y. M.; Hunziker, D.; Petter, W. *Helv. Chim. Acta* **1992**, *75*, 2171.
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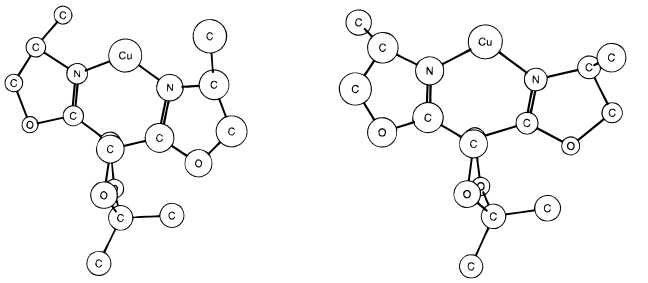
(23) Solomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 3300.
(24) (a) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helv. Chim. Acta* **1988**, *71*, 1553. (b) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919. (c) Brookhart, M.; Studabaker, W. B. *Chem. Rev.* **1987**, *87*, 411.
(25) Seebach, D.; Weidmann, B.; Widler, L. In *Modern Synthetic Methods*; Scheffold, R., Ed.; John Wiley and Sons, Inc.: New York, 1983; Vol. 3, p 217.
(26) Narasaka, K.; Iwasaka, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340.



6 **7**

Figure 6. CS Chem3D presentation of L-tartrate ligand **6** and D-tartrate ligand **7**.

effect of placing the donor centers on a cyclic backbone compared to a linear one is pointed out by Jacobsen[27] in his work on Mn(salen)-catalyzed epoxidations. For this purpose, the 1,3-dioxolane ring was selected due to its easy preparation and readily availability in both antipodes starting from (+)- or (−)-tartaric acid. Another benefit with this system lies in the additional chiral centers in the ligand, which gives us a chance to study the effect of different combination of the tartrate and oxazolinyl chirality. In the rigid tartrate derived ligands, **6** and **7** (Figures 5 and 6), the two oxazoline rings are slightly twisted (instead of being nearly coplanar as in **1**−**3**), pushing the oxazolinyl R groups (represented in Figure 6 as a carbon atom for simplicity) either toward the metal ion as in **6c** (prepared from L-valinol and L-tartrate) or away from it in **7a** (prepared from L-valinol and D-tartrate). We were pleased to find that the rigid bis-oxazoline **7a** with a D-tartrate backbone having a wide angle between the *i*-Pr groups led to an enantioselectivity of 68% for the *trans* product. This could be improved considerably to 84% by the use of **6c**, derived from L-tartrate, where the *i*-Pr groups are much closer to the metal ion as depicted in Figures 5 and 6. The model cyclopropanation was carried out in CH_2Cl_2 using 1.00 mol % of CuOTf and 1.05 mol % of ligand **6c**. The alkyl diazoacetate was slowly added with a syringe pump to a solution of styrene, 1.00 mol % of CuOTf, and 1.05 mol % of the ligand at 0 °C, and the reaction mixture was stirred at room temperature for 24 h. Keeping the reaction temperature constant at 0 °C throughout the reaction time (28 h) resulted in similar enantioselectivity but with considerable drop in chemical yield. It was also observed that the enantioselectivity remained unaffected when 1.00 mol % of CuOTf and 2.00 mol % of ligand was used.

Having established that the *i*-Pr derivative of **6** with a backbone derived from the naturally occurring (+)-tartaric acid was superior among the bis-oxazoline ligands in Table 1 for the model reaction, we further investigated the other structural features of these new ligands.

Seebach[21,25] and Narasaka[26] have demonstrated the effect of the ketal substituents on the efficiency of their TADDOL catalysts for asymmetric Diels−Alder and carbonyl addition reactions. Narasaka observed that C_1-symmetric ligands having two different substituents on the ketal were superior to the corresponding C_2-symmetric analogues. This observation prompted us to prepare a series of C_2- and non-C_2-symmetric ligands, **13a**−**f**, having different substituents on the dioxolane ring. These ligands were then evaluated in the Cu-catalyzed cyclopropanation of styrene with ethyl diazoacetate, and the results are presented in Table 2.

Table 2. Effect of Different Substituents of the Dioxolane Ring of the *i*-Pr Derivative of Bis-oxazolines in the Cu-Catalyzed Cyclopropanation of Styrene with Ethyl Diazoacetate

entry	ligand	R′	R″	% yield[a]	diastereoselectivity[b] *trans*:*cis*	% ee[c,d] *trans*
1	**13a**	H	H	53	70:30	50
2	**6c**	Me	Me	76	70:30	84
3	**13b**	Et	Et	71	73:27	74
4	**13c**	*n*-Bu	*n*-Bu	60	54:46	25
5	**13d**	Me	H	59	67:33	51
6	**13f**	Ph	H	26	74:26	66
7	**13e**	Me	Ph	50	72:28	69

[a] Isolated. [b] Determined by ^{1}H NMR analysis of crude sample. [c] Determined by HPLC analysis using a CHIRACEL OD-H column. [d] The configuration was established to be 1*R*,2*R* in all the examples by the sign of optical rotation.

Table 3. Effect of Different Oxazolinyl Groups of Bis-oxazolines in the Cu-Catalyzed Cyclopropanation of Styrene with Ethyl Diazoacetate

entry	ligand	confgn of tartrate backbone	R	% yield[a]	diastereo-selectivity[b] *trans*:*cis*	% ee[c] *trans* (confgn[d])	% ee[d] *cis* (confgn[d])
1	**6a**	L	Me_2	58	58:42	18 (1*S*,2*S*)	*e*
2	**6b**	L	Bn	77	68:32	50 (1*R*,2*R*)	39 (1*R*,2*S*)
3	**6c**	L	*i*-Pr	76	70:30	84 (1*R*,2*R*)	65 (1*R*,2*S*)
4	**6d**	L	*t*-Bu	78	64:36	2 (1*R*,2*R*)	*e*
5	**6e**	L	*i*-Bu	80	73:27	77 (1*R*,2*R*)	70 (1*R*,2*S*)
6	**7a**	D	*i*-Pr	77	67:33	68 (1*R*,2*R*)	73 (1*R*,2*S*)
7	**7b**	D	*t*-Bu	85	70:30	84 (1*R*,2*R*)	85 (1*R*,2*S*)

[a] Isolated. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by chiral HPLC analysis using a CHIRALCEL OD-H column. [d] Determined by chiroptical comparison. [e] Not determined.

As shown in Table 2, the presence of two geminal methyl groups on the dioxolane ring resulted in optimum selectivity for the reaction. Replacing the methyl groups by hydrogen drastically decreased the selectivity. On the other hand, increasing the size of the dioxolane substituents from methyl to ethyl gave a slightly lower enantioselectivity (74% ee for the *trans* product; Table 2, entry 3) compared to the dimethyl analogue (84% ee; Table 2, entry 2). The ligand **13c**, with the even larger *n*-Bu substituents, was less efficient, which is in accordance with the observation made by Narasaka for the TADDOL-catalyzed asymmetric Diels−Alder reactions. However, introduction of two different substituents on the dioxolane ring did not improve the selectivity (Table 2, entries 5−7).

A number of bis-oxazolines prepared from different 1,2-amino alcohols with the 2,2-dimethyldioxolane tether prepared from (+)- and (−)-tartaric acid were next compared in the reaction under investigation (Table 3). The ligand **6a**, with a *gem*-dimethyloxazolinyl substituent, gave very poor asymmetric induction. Its failure to induce enantioselectivity in the reaction indicates that the presence of the chiral backbone alone is not responsible for enantioselective addition of the carbene to the olefin. The benzyl derivative, **6b**, gave the cyclopropanation products of styrene with 50 and 39% ee for *trans* and *cis* isomers, respectively. Masamune[2c] previously reported that the benzyl derivative of bis-oxazoline **2** with

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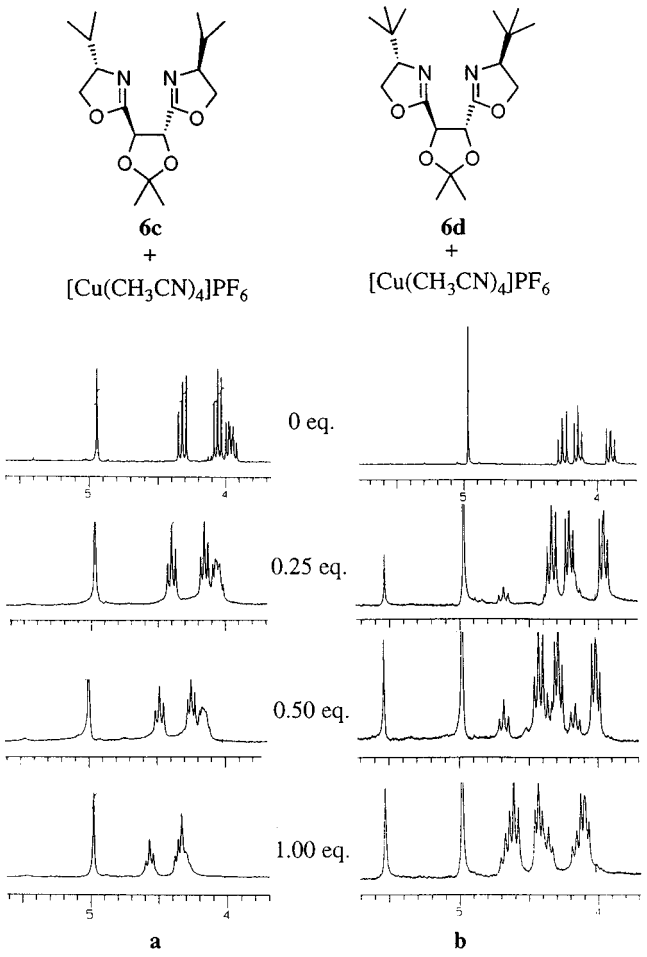

Figure 7. ^{1}H NMR study of the complex formation between the ligands **6c**, **6d**, and $[Cu(CH_3CN)_4]PF_6$ in $CDCl_3$.

methylene backbone gave the same products in 36 and 15% ee under similar reaction conditions. This again shows the considerable beneficial effect of the twisted oxazoline rings mounted on the tartrate backbone.

The bulkier *tert*-butyl derivative, **6d**, with the tether prepared from L-tartaric acid, was expected to give even higher enantioselectivities compared to the sterically less demanding *i*-Pr derivative, **6c** (Table 3, entry 4). Contrary to expectations, this ligand resulted in the formation of almost racemic products, although the chemical yield was high. The *t*-Bu derivative of the bis-oxazoline with a dioxolane tether prepared from D-tartaric acid, **7b**, however, proved to be a much more effective ligand giving the *trans* and *cis* cyclopropanated products with 84 and 85% ee, respectively. The *t*-Bu derivative of bis-oxazoline **3b** was observed to be by far the most effective of the ligands studied for the model reaction, because the large substituents are capable of efficiently controlling the olefin approach. In the case of **6d**, the combination of two bulky *t*-Bu oxazolinyl groups and the inward twist of the L-tartrate backbone resulted in a severe steric hindrance. This does not leave sufficient space for the copper to simultaneously coordinate with both nitrogens of the oxazoline rings. Hence, with **6d**, the reaction is probably catalyzed by free or monocoordinated Cu, leading to optically inactive products in high yield. In the case of ligand **7b** the oxazoline rings are twisted outward by the D-tartrate-derived backbone, allowing enough space for bis-oxazoline to complex with the copper. The *trans* product of cyclopropanation of styrene catalyzed by **7b** was found to be as enantiomerically enriched as that

Table 4. Solvent Effect on the Cu-Catalyzed Cyclopropanation of Styrene with Ethyl Diazoacetate in the Presence of 6c

entry	solvent	% yield[a]	diastereoselectivity[b] *trans*:*cis*	% ee[c] *trans*
1	CH_2Cl_2	76	70:30	84
2	$CHCl_3$	54	67:33	73
3	Styrene	48	74:26	63
4	THF	34	80:20	37
5	Toluene	36	78:22	59
6	Pentane	d		

[a] Isolated. [b] Determined by ^{1}H NMR analysis of crude mixture. [c] Determined by chiral HPLC analysis using a CHIRALCEL OD-H column. [d] No reaction.

Table 5. Cyclopropanation of Styrene with Various Diazoacetates in the Presence of 6c

entry	diazoacetate	% yield[a]	diastereo-selectivity[b] *trans*:*cis*	% ee/% de *trans*	% ee/% de *cis*
1	ethyl	76	70:30	84	65
2	*tert*-butyl	84	82:18	88[c]	84[d]
3	(−)-menthyl	86	85:15	89[e]	89[e]
4	(−)-8-phenylmenthyl	80	80:20	96[d]	91[d]

[a] Isolated. [b] Determined by ^{1}H NMR analysis of the crude sample. [c] Determined by optical rotation of the acid. [d] Determined by chiral HPLC analysis using a CHIRALCEL OD-H column. [e] Determined by GC analysis.

for *i*-Pr derivative **6c**, but the *cis* product was also obtained with equal optical purity, 85% ee (Table 3, entry 7).

The conclusion that the ligand **6d** failed to form a uniform bidentate complex with CuOTf due to its large oxazolinyl substituents was also supported by ^{1}H NMR study of separate experiments in which the ligands were treated with various cuprous complexes. The ligands **6c** and **6d** were treated with different concentrations of $[Cu(CH_3CN)_4]PF_6$[28] and analyzed by ^{1}H NMR spectroscopy. The comparison is presented in Figure 7. The *i*-Pr ligand **6c** showed a single set of signals with downfield shift of the oxazolinyl protons (Figure 7a) indicating rapid complex formation. On the other hand, the *t*-Bu derivative **6d** gave rise to at least two sets of signals upon addition of the cuprous complex (Figure 7b), indicating the formation of a mixture of ligand-copper complexes. A similar pattern of signals was observed when ligands **6c** and **6d** were treated with $CuOTf\cdot 1/2C_6H_6$ and $[Cu(CH_3CN)_4]ClO_4$,[28] but the signals were not as sharp and clear as those observed for $[Cu(CH_3CN)_4]PF_6$.

A systematic study of solvent effect on the cyclopropanation of styrene in the presence of **6c** was carried out to establish the best conditions for this reaction, and the results are presented in Table 4. Dichloromethane and chloroform were very suitable solvents, with the former being marginally superior in all respects. Performing the reaction in neat styrene resulted in a considerable drop in both chemical and optical yields, but the level of stereochemical induction was maintained. In tetrahydrofuran and toluene even lower yields and enantioselectivities were observed. The reaction could not be carried out in pentane due to the insolubility of the catalyst in this medium.

The influence of the diazoacetate substituent on the selectivity in the cyclopropanation of styrene was also studied using different ester groups (Table 5). Not unexpectedly, sterically demanding diazoacetates, such as *tert*-butyl and menthyl diazoacetate, resulted in increased diastereoselectivities and enantioselectivities.

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Table 6. Cyclopropanation of Different Olefins with Various Diazoacetates

entry	olefin	diazoacetate	ligand	% yield[a] (*trans*:*cis*)[b]	% ee/% de
1	1,1-diphenyl-ethylene	*tert*-butyl	**6c**	90	92[c]
2	α-methyl-styrene	(−)-menthyl	**6c**	70	85 (*trans*)[d]
				(57:43)	63 (*cis*)[d]
3	vinyl acetate	ethyl	**6c**	44	64 (*trans*)[e]
				(75:25)	60 (*cis*)[e]
4	vinyl acetate	(−)-menthyl	**6c**	64	74 (*trans*)[d]
				(72:28)	88 (*cis*)[d]
5	vinyl acetate	(−)-menthyl	**7b**	51	62 (trans)[d]
				(72:28)	80 (*cis*)[d]

[a] Isolated. [b] Determined by ^{1}H NMR analysis of crude mixture. [c] Determined by optical rotation of the acid. [d] Determined by GC analysis. [e] Established by ^{1}H NMR analysis with chiral shift reagent.

We also prepared (−)-8-phenylmenthyl diazoacetate, a new diazoester, from (−)-8-phenylmenthol in analogy with the method reported[24a] for the preparation of (−)-menthyl diazoacetate. Cyclopropanation of styrene with this (−)-8-phenylmenthyl diazoacetate in the presence of bis-oxazoline **6c** gave *trans* and *cis* products with 96 and 91% de, respectively.

The efficiency of the new ligand system for the cyclopropanation was not restricted to monosubstituted olefins. The cyclopropanation of 1,1-diphenylethylene with **6c**/CuOTf and *tert*-butyl diazoacetate gave the *R* enantiomer in 92% ee and 90% yield (Table 6).

Another interesting class of substrates consists of enol derivatives that will form optically active precursors to cyclopropanols upon asymmetric cyclopropanation. Despite the synthetic utility of these in organic synthesis,[29] there are only a few reports[30] on the enantioselective cyclopropanation of such substrates in the literature. We therefore chose to study the cyclopropanation of vinyl acetate with our new ligand system (Table 6, entries 3−5). Using ligand **6c**, the cyclopropanated products could be obtained in much higher enantioselectivities than what has previously been reported[30a] with chiral dirhodium complexes.

Summary. By introducing a tartrate backbone between the two oxazoline rings, we have synthesized a new class of bis-oxazoline ligands that have shown high enantioselectivity in cyclopropanation of olefins compared to the corresponding conventional ligands having a methylene bridge between the two oxazoline rings. The valine-derived ligand **6c** was found to be superior to the analogous ligands **2a** and **3a**, but less selective than ligand **3b**, which in turn is derived from the more expensive *tert*-leucine. This new ligand should find many applications in asymmetric reactions catalyzed by C_2-symmetric ligands as recently reported by Ikeda[16c] for hydrosilylation of ketones.

Experimental Section

Optical rotations were recorded on a thermostated Perkin-Elmer 241 polarimeter using a 1.0 dm cell. ^{1}H and ^{13}C NMR spectra were recorded for $CDCl_3$ solutions at 400/300 and 100.4 /75.5 MHz (Varian Unity 400/Varian XL 300), respectively. Chemical shifts for protons are reported using the residual ^{1}H in $CDCl_3$ as the internal reference (δ 7.26). Carbon shifts are referenced to the ^{13}C signal of $CDCl_3$ at 77.0 ppm. Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer. Mass spectra were recorded on a INCOS 50 GC/MS system. Melting points were determined on a Leitz apparatus and are uncorrected. GC analysis was performed on Varian 3400 capillary gas chromatograph using a 25 m SE 54 column. HPLC analyses were performed on a Waters M 45 pump coupled with a Varian 9065 polychrom diode array detector. Toluene, methylene chloride, and chloroform were dried over calcium hydride and freshly distilled under nitrogen. Styrene and α-methylstyrene were distilled prior to use. THF and diethyl ether were distilled over sodium/benzophenone under nitrogen. Preparative TLC plates, SIL G-100 UV_{254}, were purchased from Macherey-Nagel. Ethyl diazoacetate was purchased from Aldrich Co., and *tert*-butyl diazoacetate was prepared according to a literature procedure.[31] CuOTf·1/2C_6H_6 was prepared according to a previously described procedure,[23] and (−)-8-phenylmenthyl diazoacetate was prepared in a similar procedure[24a] as described for (−)-menthyl diazoacetate. (4*R*,5*R*)-2,2-Dimethyl-1,3-dioxolane-4,5-dicarboxylic acid dimethyl ester (**10**) and (4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylic acid dimethyl ester (**11**) were synthesized according to a previously described procedure.[17] It is the first step in the preparation of the following ligands.

General Procedure for the Synthesis of Ligands. Unless otherwise mentioned, the bis-oxazoline ligands were prepared according to the three-step process outlined below.

(−)-(4*R*,5*R*)-Bis[(*S*)-4-isopropyloxazolin-2-yl]-2,2-dimethyl-1,3-dioxolane (6c). To a solution of L-2-amino-3-methyl-1-butanol (L-valinol) (0.84 g, 8.07 mmol) in dry methanol (12 mL) was added (4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylic acid dimethyl ester (**10**) (0.80 g, 3.67 mmol) together with a catalytic amount of NaCN (18 mg, 0.03 mmol). The reaction mixture was stirred under inert atmosphere at 45 °C for 24 h. After being cooled to room temperature, the solution was concentrated to give an oil that was dissolved in ethyl acetate (25 mL) and washed with water (5 mL). The organic phase was dried ($MgSO_4$), and evaporation of the solvent yielded a yellow oily product pure enough to be used in the next step without further purification: ^{1}H NMR (300 MHz) δ 7.20 (bd, J = 8.0 Hz, 2 H), 4.58 (s, 2 H), 3.75 (m, 4 H), 3.65 (m, 2 H), 1.92 (m, 2 H), 1.53 (s, 6 H), 0.98 (d, J = 6.8 Hz, 6 H), 0.96 (d, J = 6.1 Hz, 6 H).

To an ice-cooled solution of the dihydroxy diamide (1.21 g, 3.37 mmol) and Et_3N (1.53 g, 15.1 mmol) in CH_2Cl_2 (15 mL) was added MsCl (0.96 g, 8.4 mmol) slowly. The mixture was allowed to warm to room temperature, stirred for 1 h, and washed with water (3 mL). The organic phase was dried (Na_2SO_4) and concentrated to dryness *in vacuo* to give a yellow oil, which was used in the next reaction without purification.

The bis-mesylated compound was treated with NaOH (0.14 g, 3.4 mmol in 24 mL of a 5:1 MeOH/H_2O mixture). The reaction mixture was stirred at room temperature for 2 days, at which point no trace of the starting material could be seen on TLC (5% v/v MeOH in $CHCl_3$). The solvent was removed and the residual oil dissolved in CH_2Cl_2 (25 mL), washed with water (5 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by flash chromatography (1.5% triethylamine, 20% chloroform in pentane) gave the ligand **6c** as a pale yellow, low-melting solid in 77% overall yield: $[\alpha]^{21}_D = -137.7$ (c = 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz) δ 4.94 (s, 2 H), 4.31 (dd, J = 9.7, 8.3 Hz, 2 H), 4.05 (app t, J = 8.3 Hz, 2 H), 3.97 (m, 2 H), 1.78 (m, 2 H), 1.51 (s, 6 H), 0.95 (d, J = 6.8 Hz, 6 H), 0.87 (d, J = 6.8 Hz, 6 H); ^{13}C NMR (75.5 MHz) δ 163.1, 112.7, 74.0, 72.0, 71.7, 32.4, 26.4, 18.6, 17.9; IR (CCl_4, cm^{-1}) 2960, 1673; MS (EI) m/z (rel intensity) 324 ($M^+ - 15$; 47), 281 (11), 267 (18), 223 (100), 195 (19), 154 (77), 114 (42), 85 (43), 79 (57). Anal. Calc for $C_{17}H_{28}N_2O_4$: C, 62.94; H, 8.70; N, 8.63. Found: C, 62.64; H, 8.56; N, 8.47.

(−)-(4*R*,5*R*)-Bis(4,4-dimethyloxazolin-2-yl)-2,2-dimethyl-1,3-dioxolane (6a). The ligand **6a** was prepared from **10** (0.50 g, 2.29 mmol) and 2-amino-2-methyl propanol (0.45 g, 5.04 mmol) in 46% overall yield (colorless oil) following the same procedure as reported for **6c**: $[\alpha]^{21}_D = -32.5$ (c = 1.17, CH_2Cl_2); ^{1}H NMR (300 MHz) δ 4.87 (s, 2 H), 4.00 (s, 4 H), 1.49 (s, 6 H), 1.28 (s, 6 H), 1.26 (s, 6 H); ^{13}C NMR (75.5 MHz) δ

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161.5, 112.6, 79.6, 74.0, 67.4, 18.1, 27.9, 26.3; IR (neat, cm^{-1}) 3125, 2975, 1675, 1225; MS (EI) *m/z* (rel intensity) 316 (M^+ − 36, <1), 275 (90), 233 (30), 216 (39), 191 (42), 178 (60), 163 (35), 137 (100), 112 (33), 98 (26), 82 (24), 70 (23). Anal. Calcd for $C_{15}H_{24}N_2O_4$: C, 60.79; H, 8.16; N, 9.45. Found: C, 60.58; H, 8.09; N, 9.28.

(−)-(4*R*,5*R*)-Bis[(*S*)-4-benzyloxazolin-2-yl]-2,2-dimethyl-1,3-dioxolane (6b). The ligand **6b** was prepared from **10** (1.00 g, 4.58 mmol) and L-phenylalaninol (1.52 g, 10.1 mmol) in 84% overall yield (colorless oil) following the same procedure as reported for **6c**: $[\alpha]^{21}_D = -82.5$ ($c = 1.00$, CH_2Cl_2); ^{1}H NMR (300 MHz) δ 7.29 (m, 5 H), 7.21 (m, 10 H), 4.91 (s, 2 H), 4.46 (m, 2 H), 4.28 (app t, $J = 9.0$ Hz, 2 H), 4.08 (app t, $J = 9.0$ Hz, 2 H), 3.14 (dd, $J = 13.8$, 5.2 Hz, 2 H), 2.68 (dd, $J = 13.7$, 8.5 Hz, 2 H), 1.52 (s, 6 H); ^{13}C NMR (75.5 MHz) δ 163.8, 137.4, 129.1, 128.5, 126.5, 112.8, 73.9, 72.4, 67.3, 41.3, 26.3; IR (neat, cm^{-1}) 2987, 2935, 1670, 1382, 1248; MS (EI) *m/z* (rel intensity) 420 (M^+, 34), 405 (14), 329 (72), 271 (41), 260 (20), 243 (33), 202 (40), 117 (54), 91 (100). Anal. Calcd for $C_{25}H_{28}N_2O_4$: C, 71.41; H, 6.71; N, 6.66. Found: C, 71.25; H, 6.79; N, 6.58.

(−)-(4*R*,5*R*)-Bis[(*S*)-4-*tert*-butyloxazolin-2-yl]-2,2-dimethyl-1,3-dioxolane (6d). The ligand **6d** was prepared from **10** (0.80 g, 3.67 mmol) and L-*tert*-leucinol (0.95 g, 8.07 mmol) in 54% overall yield (white solid) following the same procedure as reported for **6c**: mp 91−93 °C; $[\alpha]^{21}_D = -117.5$ ($c = 1.00$, CH_2Cl_2); ^{1}H NMR (300 MHz) δ 4.97 (s, 2 H), 4.26 (dd, $J =$ 10.2, 8.8 Hz, 2 H), 4.15 (app t, $J = 8.5$ Hz, 2 H), 3.90 (dd, $J =$ 7.9, 5.7 Hz, 2 H), 1.51 (s, 6 H), 0.88 (s, 18 H); ^{13}C NMR (75.5 MHz) δ 163.2, 112.7, 75.6, 74.0, 69.3, 33.6, 29.4, 25.7; IR (CCl_4, cm^{-1}) 2958, 1675, 1247; MS (EI) *m/z* (rel intensity) 337 (M^+ − 15, 17), 295 (10), 237 (100), 168 (30), 112 (36), 84 (16). Anal. Calcd for $C_{19}H_{32}N_2O_4$: C, 64.75; H, 9.15; N, 7.95. Found: C, 64.78; H, 9.20; N, 7.87.

(−)-(4*R*,5*R*)-Bis[(*S*)-4-(1-methylpropyl)oxazolin-2-yl]-2,2-dimethyl-1,3-dioxolane (6e). The ligand **6e** was prepared from **10** (0.70 g, 3.21 mmol) and L-isoleucinol (0.83 g, 7.06 mmol) in 50% overall yield (colorless oil) following the same procedure as reported for **6c**: $[\alpha]^{21}_D = -120.9$ ($c = 1.12$, CH_2Cl_2); ^{1}H NMR (300 MHz) δ 4.92 (s, 2 H), 4.28 (m, 2 H), 1.72 (m, 2 H), 1.49 (m, 10 H), 1.15 (dddq, $J = 14.3$, 13.9, 7.4, 7.4 Hz, 2 H), 0.89 (t, $J = 7.4$ Hz, 6 H), 0.80 (d, $J = 6.8$ Hz, 6 H); ^{13}C NMR (75.5 MHz) δ 162.9, 112.6, 74.0, 70.6, 70.2, 38.6, 26.3, 25.9, 14.1, 11.5; IR (neat, cm^{-1}) 2963, 1673, 1382; MS (EI) *m/z* (rel intensity) 352 (M^+, 1), 337 (42), 295 (32), 237 (100), 209 (17), 168 (50), 153 (18), 128 (19), 110 (21). Anal. Calcd for $C_{19}H_{32}N_2O_4$: C, 64.75; H, 9.15; N, 7.95. Found: C, 64.66; H, 9.03; N, 7.87.

(+)-(4*S*,5*S*)-Bis[(*S*)-4-isopropyloxazolin-2-yl]-2,2-dimethyl-1,3-dioxolane (7a). The method described for the preparation of **6c** was also used to prepare the ligands with D-tartrate backbone. The ligand **7a** was prepared from **11** (0.60 g, 2.75 mmol) and L-valinol (0.62 g, 6.05 mmol) in 73% overall yield (colorless oil) following the same procedure as reported for **6c**: $[\alpha]^{21}_D = -12.7$ ($c = 0.99$, CH_2Cl_2); ^{1}H NMR (300 MHz) δ 4.96 (s, 2 H), 4.32 (app. t, $J = 9.1$ Hz, 2 H), 4.06 (app t, $J = 9.1$ Hz, 2 H), 3.98 (ddd, $J = 9.1$, 7.6, 6.1 Hz, 2 H), 1.78 (dqq, $J = 14.0$, 6.7, 6.5 Hz, 2 H), 1.51 (s, 6 H), 0.95 (d, J = 6.6 Hz, 6 H), 0.88 (d, $J = 6.7$ Hz, 6 H); ^{13}C NMR (75.5 MHz) δ 163.1, 112.6, 74.1, 72.1, 70.6, 32.3, 26.3, 18.6, 17.8; IR (CCl_4, cm^{-1}) 2960, 1673, 1371, 1242; MS (EI) *m/z* (rel intensity) 324 (M^+, 11), 309 (57), 281 (19), 267 (24), 223 (100), 195 (23), 154 (80), 114 (55), 85 (49), 69 (39). Anal. Calcd for $C_{17}H_{28}N_2O_4$: C, 62.94; H, 8.70; N, 8.63. Found: C, 63.08; H, 8.66; N, 8.53.

(+)-(4*S*,5*S*)-Bis[(*S*)-4-*tert*-butyloxazolin-2-yl]-2,2-dimethyl-1,3-dioxolane (7b). The ligand **7b** was prepared from **11** (0.60 g, 2.75 mmol) and L-*tert*-leucinol (0.71 g, 6.05 mmol) in 52% overall yield (white solid) following the same procedure as reported for **6c**: mp 117−119 °C; $[\alpha]^{21}_D = -40.8$ ($c = 0.98$, CH_2Cl_2); ^{1}H NMR (300 MHz) δ 4.96 (s, 2 H), 4.27 (app t, $J =$ 8.0 Hz, 2 H), 4.14 (app t, $J = 8.0$ Hz, 2 H), 3.91 (app t, $J = 8.0$ Hz, 2 H), 1.51 (s, 6 H), 0.89 (s, 18 H); ^{13}C NMR (75.5 MHz) δ 162.9, 112.6, 75.8, 74.2, 69.3, 33.6, 26.2, 25.7; IR (CCl_4, cm^{-1}) 2958, 1675, 1365, 1246; MS (EI) *m/z* (rel intensity) 337 (M^+ − 15, 17), 295 (11), 237 (100), 168 (29), 112 (34), 84 (15). Anal. Calcd for $C_{19}H_{32}N_2O_4$: C, 64.75; H, 9.15; N, 7.95. Found: C, 64.60; H, 9.25; N, 8.03.

(−)-(4*R*,5*R*)-Bis[(*S*)-4-isopropyloxazolin-2-yl]-1,3-dioxolane (13a). The ligand **13a** was prepared from **12a** (0.50 g, 2.47 mmol) and L-valinol (0.56 g, 5.43 mmol) in 78% overall yield following the same procedure as reported for **6c**. Cyclization of the intermediate bis-mesylate with KOH required only 1 day. Purification by flash chromatography (2% $CHCl_3$, 1.5% Et_3N in pentane) gave the pure compound as a colorless oil in 78% yield: $[\alpha]^{21}_D = -136.4$ ($c = 1.00$, CH_2Cl_2); ^{1}H NMR (400 MHz) δ 5.23 (s, 2 H), 4.94 (d, $J = 1.5$ Hz, 2 H), 4.33 (dd, $J = 9.6$, 8.3 Hz, 2 H), 4.05 (app t, $J = 8.2$ Hz, 2 H), 3.97 (ddd, $J = 9.7$, 8.1, 6.1 Hz, 2 H), 1.78 (m, 2 H), 0.96 (d, $J = 6.7$ Hz, 6 H), 0.89 (d, $J = 6.7$ Hz, 6 H); ^{13}C NMR (100.4 MHz) δ 163.1, 127.5, 96.9, 74.0, 72.2, 70.9, 32.4, 18.6, 18.0; IR (CCl_4, cm^{-1}) 2961, 1674; MS (EI) *m/z* (rel intensity) 296 (M^+, 16), 251 (83), 223 (100), 195 (59), 184 (16), 154 (93), 140 (34), 112 (34), 84 (27), 69 (62). Anal. Calcd for $C_{15}H_{24}N_2O_4$: C, 60.79; H, 8.16; N, 9.45. Found: C, 60.56; H, 7.99; N, 9.23.

(−)-(4*R*,5*R*)-Bis[(*S*)-4-isopropyloxazolin-2-yl]-2,2-diethyl-1,3-dioxolane (13b). The ligand **13b** was prepared from **12b** (0.28 g, 1.14 mmol) and L-valinol (0.26 g, 2.51 mmol) in 32% overall yield (pale yellow oil) following the same procedure as reported for **6c**: $[\alpha]^{21}_D = -106.1$ ($c = 1.08$, CH_2Cl_2); ^{1}H NMR (300 MHz) δ 4.88 (s, 2 H), 4.30 (dd, $J = 9.1$, 8.7 Hz, 2 H), 4.04 (app t, $J = 8.4$ Hz, 2 H), 3.96 (dd, $J = 9.4$, 6.1 Hz, 2 H), 1.75 (m, 6 H), 0.95 (d, $J = 6.7$ Hz, 12 H), 0.86 (t, $J = 6.7$ Hz, 6 H); ^{13}C NMR (75.5 MHz) δ 162.9, 116.5, 74.3, 72.0, 70.6, 32.4, 29.8, 18.7, 17.9, 7.8; IR (CCl_4, cm^{-1}) 2964, 2879, 1673, 1466; MS (EI) *m/z* (rel intensity) 352 (M^+, 6), 285 (23), 172 (59), 142 (35), 111 (29), 98 (21), 86 (35), 69 (89). Anal. Calcd for $C_{19}H_{32}N_2O_4$: C, 64.75; H, 9.15; N, 7.95. Found: C, 64.73; H, 8.92; N, 8.05.

(−)-(4*R*,5*R*)-Bis[(*S*)-4-isopropyloxazolin-2-yl]-2,2-dibutyl-1,3-dioxolane (13c). The ligand **13c** was prepared from **12c** (1.00 g, 3.31 mmol) and L-valinol (0.75 g, 7.28 mmol) in 35% overall yield (colorless oil) following the same procedure as reported for **6c**. The methanolic KOH treatment of the bis-mesylate required 4 days to reach completion: $[\alpha]^{21}_D = -40.5$ ($c = 1.26$, CH_2Cl_2); ^{1}H NMR (400 MHz) δ 4.88 (s, 2 H), 4.32 (dd, $J = 9.7$, 8.3 Hz, 2 H), 4.06 (dd, $J = 8.1$, 6.7 Hz, 2 H), 3.96 (m, 2 H), 1.74 (m, 4 H), 1.34 (bm, 8 H), 0.97 (m, 6 H), 0.89 (app t, $J = 6.7$ Hz, 12 H); ^{13}C NMR (100.4 MHz) δ 116.2, 77.7, 74.2, 72.1, 70.6, 64.2, 57.4, 37.2, 36.8, 32.4, 29.0, 25.8, 25.6, 22.8, 19.5, 18.7, 18.5, 18.0, 14.0; IR (CCl_4, cm^{-1}) 2960, 1731, 1273; MS (EI) *m/z* (rel intensity) 413 (M^+ - 30, 78), 387 (31), 285 (28), 172 (65), 142 (38), 130 (13), 104 (35), 85 (58), 69 (87). Anal. Calcd for $C_{23}H_{40}N_2O_4$: C, 67.61; H, 9.87; N, 6.86. Found: C, 67.48; H, 10.05; N, 6.65.

(−)-(4*R*,5*R*)-Bis[(*S*)-4-isopropyloxazolin-2-yl]-2-methyl-1,3-dioxolane (13d). The ligand **13d** was prepared from **12d** (1.40 g, 6.86 mmol) and L-valinol (1.56 g, 15.09 mmol) in 34% overall yield (colorless oil) following the same procedure as reported for **6c**. The methanolic KOH treatment of the bis-mesylate required 1 day to reach completion: $[\alpha]^{21}_D = -147.4$ ($c = 1.25$, CH_2Cl_2); ^{1}H NMR (400 MHz) δ 5.39 (q, $J = 4.8$ Hz, 1 H), 4.90 (m, 2 H), 4.31 (m, 2 H), 4.04 (m, 2 H), 3.96 (m, 2 H), 1.78 (m, 2 H), 1 (m, 3 H), 0.95 (m, 6 H), 0.88 (m, 6 H); ^{13}C NMR (100.4 MHz) δ 163.6, 163.1, 104.0, 74.7, 74.2, 72.1, 72.0, 70.9, 70.7, 46.3, 32.4, 29.4, 19.4, 18.7, 18.6, 18.0; IR (CCl_4, cm^{-1}) 2960, 1729, 1675; MS (EI) *m/z* (rel intensity) 310 (M^+, <1%), 291 (41), 246 (41), 194 (37), 178 (19), 151 (100), 110 (31), 96 (13), 68 (30). Anal. Calcd for $C_{16}H_{26}N_2O_4$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.95; H, 8.52; N, 9.15.

(−)-(4*R*,5*R*)-Bis[(*S*)-4-isopropyloxazolin-2-yl]-2-methyl-2-phenyl-1,3-dioxolane (13e). The ligand **13d** was prepared from **12e** (0.60 g, 2.14 mmol) and L-valinol (0.49 g, 4.71 mmol) in 25% overall yield (colorless oil) following the same procedure as reported for **6c**: $[\alpha]^{21}_D = -99.7$ ($c = 1.01$, CH_2Cl_2); ^{1}H NMR (300 MHz) δ 7.54 (m, 2 H), 7.27 (m, 3 H), 5.00 (m, 2 H), 4.34 (m, 1H), 4.05 (m, 2 H), 3.99 (m, 1 H), 3.89 (app t, $J = 8.0$ Hz, 1 H), 3.67 (m, 1 H), 1.78 (s, 3 H), 1.60 (m, 2 H), 0.95 (d, $J =$ 6.8 Hz, 3 H), 0.87 (d, $J = 6.8$ Hz, 3 H), 0.84 (d, $J = 6.8$ Hz, 3 H), 0.76 (d, $J = 6.7$ Hz, 3 H); ^{13}C NMR (75.5 MHz) δ 162.6, 142.5, 128.0, 127.8, 125.5, 112.4, 74.4, 73.8, 72.0, 71.8, 70.7, 70.4, 32.4, 32.2, 28.3, 18.6, 18.5, 17., 17.8; IR (CCl_4, cm^{-1}) 2873, 1673, 1371; MS (EI) *m/z* (rel intensity) 386 (M^+, 9%), 371 (23), 327 (100), 223 (15), 105 (22). Anal. Calcd for $C_{22}H_{30}N_2O_4$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.22; H, 7.61; N, 7.09.

(−)-(4*R*,5*R*)-Bis[(*S*)-4-isopropyloxazolin-2-yl]-2-phenyl-1,3-dioxolane (13f). The ligand **13f** was prepared from **12f** (1.00 g, 3.76 mmol) and L-valinol (0.85 g, 8.27 mmol) following the same procedure as reported for **6c**. Purification was performed on preparative TLC on silica gel first treated with triethylamine and then eluted with a solution of 2% MeOH and 2% Et_3N in chloroform to yield the ligand **13f** in 45% overall yield as a colorless oil: $[\alpha]^{21}_D = -72.5$ ($c = 1.00$, CH_2Cl_2); ^{1}H NMR (400 MHz) δ 7.58 (d, $J = 6.2$ Hz, 2 H), 7.37 (m, 3 H), 6.10 (s, 1 H), 5.10 (m, 2 H), 4.34 (dd, $J = 9.2$, 12.3 Hz, 2 H), 4.09 (dd, $J = 6.1$, 13.6 Hz, 2 H), 3.99 (m, 2 H), 1.79 (m, 2 H), 0.98 (d, $J = 6.7$ Hz, 6 H), 0.90 (d, $J = 6.7$ Hz, 6 H); ^{13}C NMR (100.4 MHz) δ 163.4, 162.9, 135.8, 129.7, 128.2, 127.3, 106.1, 74.9, 74.4, 72.2, 72.1, 70.0, 70.8, 32.5, 32.4, 18.7, 18.6, 18.2; IR (CCl_4, cm^{-1}) 2960, 1731; MS (EI) *m*/*z* (rel intensity) 372 (M^+, 3), 327 (41), 267 (16), 251 (100), 223 (21), 154 (34), 132 (15), 105 (35), 91 (17), 77 (24), 69 (19). Anal. Calcd for $C_{21}H_{28}N_2O_4$: C, 67.72; H, 7.58; N, 7.52. Found: C, 67.66; H, 7.51; N, 7.41.

(−)-8-Phenylmenthyl Diazoacetate. A solution of chloroacetyl chloride (2.67 g, 23.7 mmol) in 10 mL of dry ether was added *via* a syringe pump during 2 h to a mixture of 8-phenylmenthol (5.50 g, 23.7 mmol) and pyridine (1.87 g, 23.7 mmol) in 50 mL of dry ether at 0 °C. The reaction was stirred for 2 h at 22 °C, and the precipitate was removed by filtration. The solution was washed with 2 M HCl (20 mL) followed by saturated $NaHCO_3$ (10 mL) and brine (10 mL) and dried ($MgSO_4$).The 8-phenylmenthyl chloroacetate obtained in quantitative yield on concentration of this solution was used without purification in next step.

Crude 8-phenylmenthyl chloroacetate (7.30 g, 23.7 mmol) in a mixture of DMF (80 mL) and 25% aqueous ammonia solution (40 mL) was stirred for 96 h at 22 °C. The mixture was then extracted with ether (3 × 100 mL), and the combined organic phases was washed with saturated $NaHCO_3$ (50 mL), dried (Na_2SO_4), and concentrated to give 5.80 g crude 8-phenylmenthyl glycinate (85%).

A mixture of crude 8-phenylmenthyl glycinate (5.8 g, 20.1 mmol), isopentyl nitrite (2.82 g, 24.1 mmol), and AcOH (0.34 mL, 6.00 mmol) in $CHCl_3$ (40 mL) was heated to reflux for 4 h until the ninhydrin test was no longer positive. The mixture was diluted with CH_2Cl_2 (100 mL) and washed with 1 N H_2SO_4 (25 mL), water (25 mL), saturated $NaHCO_3$ (25 mL), and again with water (25 mL). The organic phase was filtered through cotton, evaporated *in vacuo*, and purified by chromatography to afford (−)-8-phenylmenthyl diazoacetate (4.4 g, 73%) as yellow oil: $[\alpha]^{25}_D = -13.7$ ($c = 1.25$, $CHCl_3$); ^{1}H NMR (400 MHz) δ 7.27 (m, 4 H), 7.15 (m, 1 H), 4.00 (td, $J = 10.7$, 4.4 Hz, 1 H), 4.21 (s, 1 H), 2.00 (ddd, $J = 12.3$, 10.6, 3.5 Hz, 1 H), 1.93 (m, 1 H), 1.69 (dq, J =13.3, 3.4 Hz, 1 H), 1.64 (m, 1 H), 1.48 (m, 1 H), 1.33 (s, 3 H), 1.23 (s, 3 H), 1.10 (dd, J =12.8, 3.2 Hz, 1 H), 0.99 (app d, $J = 10.8$ Hz, 1 H), 0.92 (m, 1 H), 0.87 (d, $J = 6.4$ Hz, 3 H); ^{13}C NMR (100.4 MHz) δ 151.4, 127.8, 125.3, 125.0, 74.7, 50.8, 46.2, 42.1, 39.7, 34.5, 31.3, 27.7, 26.6, 24.9, 21.7; IR ($CDCl_3$, cm^{-1}) 2112, 1681; MS (EI) *m*/*z* (rel intensity) 272 ($M^+ - 28$, 10), 119 (100), 105 (13), 91 (29), 69 (10). Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 71.65; H, 8.06; N, 9.10.

General Procedure for the Asymmetric Cyclopropanation. A mixture of CuOTf·1/2C_6H_6 (3.5 mg, 0.014 mmol) and ligand **6c** (4.7 mg, 0.015 mmol) was stirred in dry CH_2Cl_2 (1 mL) under argon for 30 min. This solution was cooled to 0 °C, and styrene (1.56 g, 14 mmol) was added, followed by slow addition of a CH_2Cl_2 solution (2.5 mL) of ethyl diazoacetate (159 mg, 1.4 mmol) over 5 h *via* syringe pump. The reaction mixture was allowed to warm to room temperature and was stirred for an additional 16 h, and then quenched with a 10% aqueous solution of NH_4Cl (5 mL). The solution was diluted with Et_2O (25 mL), washed with water (5 mL) and brine (5 mL), and dried ($MgSO_4$). The solvents were evaporated *in vacuo*, which afforded the crude cyclopropanated products as a mixture of *cis* and *trans* isomers. The ratio of *trans* to *cis* product was determined by ^{1}H NMR spectroscopy to be 70:30 in the crude mixture. The cyclopropanes were isolated by flash chromatography (2% ethyl acetate in pentane; 76% combined yield). Optical purity could be determined by HPLC analysis for the *trans* isomer (CHIRALCEL OD-H column, 0.5 mL/min flow rate, 10% *i*-PrOH in hexane as eluent, 84% ee), while comparison of optical rotation[2f] was used for the *cis* compound (65% ee), the absolute configuration being confirmed by the sign of the optical rotation [*trans*: (1*R*,2*R*), *cis*: (1*R*,2*S*)].

Cyclopropanation of 1,1-Diphenylethylene with *tert*-Butyl Diazoacetate. A mixture of CuOTf·1/2C_6H_6 (3.0 mg, 0.012 mmol) and ligand **6c** (4.1 mg, 0.013 mmol) was stirred in dry CH_2Cl_2 (1 mL) under argon, for 30 min. This solution was cooled to 0 °C, and 1,1-diphenyethylene (0.22 g, 1.2 mmol) was added, followed by slow addition of a CH_2Cl_2 solution (2.5 mL) of *tert*-butyl diazoacetate (200 mg, 1.4 mmol) over 5 h *via* syringe pump. The reaction mixture was allowed to warm to room temperature, stirred for an additional 16 h, and then quenched with a 10% aqueous solution of NH_4Cl (5 mL). The solution was diluted with Et_2O (25 mL), washed with water (5 mL) and brine (5 mL), and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* afforded the crude product. The product was isolated by column chromatography (2% ethyl acetate in pentane; 0.32 g, 90% yield). The absolute configuration of the pure *tert*-butyl ester was established as described by Evans[2e] to be *R* [92% ee; $[\alpha]_D$ −194 (*c* 0.29; $CHCl_3$) for the acid obtained upon hydrolysis of the *tert*-butyl ester].

Cyclopropanation of α-methylstyrene with (−)-Menthyl Diazoacetate. The mixture of CuOTf·1/2C_6H_6 (12.2 mg, 0.048 mmol) and **6c** (16.11 mg, 0.050 mmol) was stirred in CH_2Cl_2 (2.5 mL) under argon for 30 min. This solution was cooled to 0 °C, and α-methylstyrene (0.57 g, 4.8 mmol) was added, followed by slow addition of a CH_2Cl_2 solution (3.5 mL) of (−)-menthyl diazoacetate (1.3 g, 5.8 mmol) over 5 h *via* syringe pump. The reaction mixture was allowed to warm to room temperature, stirred for an additional 16 h, and then quenched with a 10% aqueous solution of NH_4Cl (5 mL). The solution was diluted with Et_2O (25 mL), washed with water (5 mL) and brine (5 mL), and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* afforded the crude product as a mixture of *trans* and *cis* cyclopropanated products. The optical purity of the crude products was determined by GC analyses.

Cyclopropanation of Vinyl Acetate with (−)-Menthyl Diazoacetate. The mixture of CuOTf·1/2C_6H_6 (8.4 mg, 0.033 mmol) and **6c** (11.4 mg, 0.035 mmol) was stirred in CH_2Cl_2 (1.5 mL) under argon for 30 min. This solution was cooled to 0 °C, and vinyl acetate (280 mg, 3.3 mmol) was added, followed by slow addition of a CH_2Cl_2 solution (3.0 mL) of (−)-menthyl diazoacetate (920 mg, 4.1 mmol) over 5 h. The reaction mixture was allowed to warm to room temperature, stirred for an additionnal 16 h, and then quenched with a 10% aqueous solution of NH_4Cl (5 mL). The solution was diluted with Et_2O (35 mL), washed with water (5 mL) and brine (5 mL), and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* afforded the crude product as a mixture of *trans* and *cis* cyclopropanated products. The optical purity of the crude products was determined by GC analyses.The crude product was purified by chromatography (2% ethyl acetate in pentane) to yield 0.60 g (64% combined yield) of *cis*- and *trans*-cyclopropanes.

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