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Synthetic Methods

One-Step Catalytic Asymmetric Synthesis of Configurationally Stable Tröger Bases[**]

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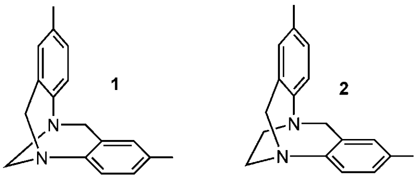
Tröger bases of type **1**,[1] which are the readily made products from condensation reactions of anilines with formaldehyde, have been extensively studied for their interesting properties, reactivity, and a host of applications (Scheme 1).[2] In stereochemistry, Tröger bases are unique, being the first chiral compounds with stereogenic nitrogen atoms to be resolved.[3] Compounds **1** are yet configurationally labile in acidic media[4] and this has limited their use as ligands, auxiliaries, or catalysts.[5] Transformation of methano-bridged Tröger bases **1** into ethano-bridged derivatives **2** is an answer to this problem,[6] but such a solution has been rarely used owing to a lack of general routes to these compounds.[7] Herein, we report a new development in the direct synthesis of ethano-bridged Tröger bases **2** (up to 99% *ee*) from methano-bridged Tröger **1** using rhodium(II)-catalyzed reactions. In a single step, the ethano bridge is constructed, a new carbon quaternary stereogenic center is introduced (up to 49:1 d.r.), and enantiopure bases **1** are transformed into derivatives **2** with very high level of chirality transfer—a remarkable result in both [1,2]-Stevens-like processes and Tröger chemistry.[8]



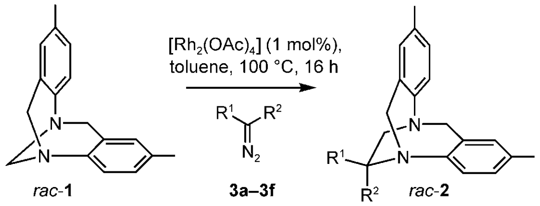
Scheme 1. Methano- (**1**) and ethano-bridged (**2**) Tröger bases.

As mentioned, the development of a general route to enantiopure compounds **2** was desirable and a direct procedure involving metal-catalyzed reactions of α-carbonyl diazo moieties **3** and derivatives **1** was considered. In fact, the metal-catalyzed decomposition of diazo compounds is a powerful method for the generation of electrophilic metal carbenes,[9] which are known to react with tertiary amines to form nitrogen–ylide intermediates.[10] Subsequent [1,2]-Stevens rearrangements can occur with often high diastereoselectivity.[11] However, of relevance to this study, when the migrating carbon atom or the quaternized nitrogen atom are the only stereocenters present on the substrate, important losses in enantiomeric purity are normally observed as a result of the mechanism involved.[12,13]

First, *rac*-**1** was treated with diazo compounds **3a** to **3f** at 100 °C in toluene (Table 1). While the use of **3a** was unproductive, all other diazo compounds **3b** to **3f** afforded the corresponding ethano-bridged Tröger bases in good to excellent yield (**2b** to **2f**, 50–85%). Low diastereomeric ratios (2:1 and 5:1 d.r.) were achieved for the synthesis of **2c** and **2d**,[14] but products **2e** and **2f** were obtained with a good diastereoselectivity (>49:1 and 10:1 d.r., respectively).[15]

The major diastereomer of *rac*-**2f** was isolated by chromatography and found to be a racemic conglomerate that crystallizes as single enantiomers of which the relative

Table 1: Initial screening.[a]



Entry	Diazo	R^1	R^2	Prod.	Yield [%][b]	d.r.[c]
1	**3a**	COMe	COMe	–	–	–
2	**3b**	CO$_2$Et	CO$_2$Et	**2b**	85	–
3	**3c**	CO$_2$Et	COMe	**2c**	80	2:1
4	**3d**	Ph	COMe	**2d**	70	5:1
5	**3e**	Ph	CO$_2$Et	**2e**	50	>49:1
6	**3f**	Ph	CO$_2$Me	**2f**	75	10:1

[a] Typical reaction conditions: *rac*-**1** (0.4 mmol), [Rh$_2$(OAc)$_4$] (1 mol%), toluene(1 mL), 100 °C, 16 h; reported results are the average of at least two experiments. Substituents indicated at positions R^1 and R^2 correspond to that of the major diastereomer of **2**. [b] Yield of isolated product (both diastereomers). [c] Determined by ^{1}H NMR analysis (400 MHz) of the crude reaction mixtures.

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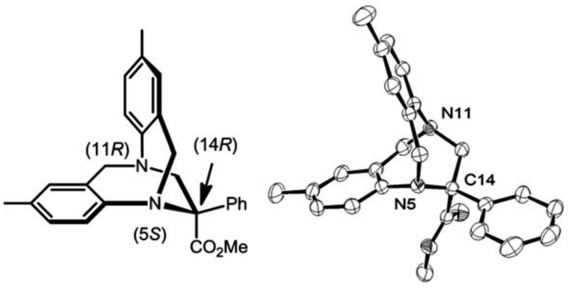
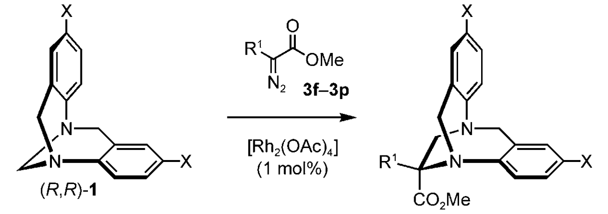


Scheme 2. Drawing of **2 f** (major diastereomer) and ORTEP view of its crystal structure; ($5S_N$,$11R_N$,$14R_C$) enantiomer shown. Hydrogen atoms are omitted for clarity and thermal ellipsoids are drawn at 50% probability.

Table 2: Enantiospecific rearrangement.[a]



Entry	X	Diazo	R^1	Prod.	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Me	**3 e**	Ph	**2 e**	50	>49:1	93
2	Me	**3 f**	Ph	**2 f**	71	10:1	99
3	Me	**3 g**	2-naphthyl	**2 g**	80	9:1	98
4	Me	**3 h**	*p*-MeOC$_6$H$_4$	**2 h**	83	10:1	98
5	Me	**3 i**	*p*-MeC$_6$H$_4$	**2 i**	72	–[e]	98
6	Me	**3 j**	*m*-MeC$_6$H$_4$	**2 j**	70	8:1	98
7	Me	**3 k**	*p*-ClC$_6$H$_4$	**2 k**	78	7.5:1	97
8	Me	**3 l**	*m*-ClC$_6$H$_4$	**2 l**	75	6:1	97
9	Me	**3 m**	*p*-BrC$_6$H$_4$	**2 m**	75	8:1	97
10	Me	**3 n**	*p*-CF$_3$C$_6$H$_4$	**2 n**	70	12:1	97
11	Me	**3 o**	p-FC$_6$H$_4$	**2 o**	50	4:1	96
12	Me	**3 p**	*p*-NO$_2$C$_6$H$_4$	**2 p**	82	20:1	64
13	OMe[f]	**3 f**	Ph	**7**	89	16:1	97

[a] Reaction conditions: (−)-(*R*,*R*)-**1** (0.1 mmol), [Rh$_2$(OAc)$_4$] (1 mol%), dry toluene (0.25 mL), 100 °C, 6 h; major diastereomer of **2** and **7** shown. Reported results are the average of at least two experiments [b] Yield of isolated product (major diastereomer). [c] Determined by ^{1}H NMR analysis (400 MHz) of the crude reactions mixtures. [d] Determined by CSP-HPLC analysis on a chiral stationary phase. [e] Could not be determined. [f] 98% *ee*.

configuration could be determined by X-ray crystallographic analysis ($5S_N$,$11R_N$,$14R_C$ or $5R_N$,$11S_N$,$14S_C$, Scheme 2, see the Supporting Information). All data indicate that this relative configuration is conserved for the major diastereomer within the series of products **2e** to **2p** (Table 2).[16]

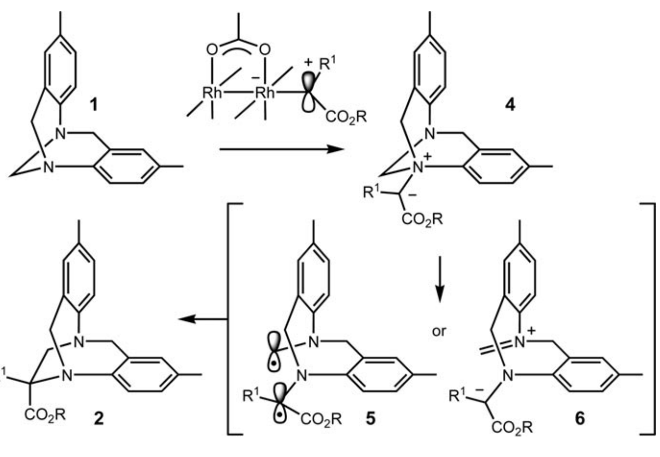
Then, the efficiency of the chirality transfer was tested. Enantiopure (−)-(*R*,*R*)-**1** was used as the substrate.[17–19] Diazo **3b** to **3d** gave corresponding products **2b**, **2c**, and **2d** in low enantiomeric purity (5, 34 and 10% *ee*, respectively for both diastereomers).[12] However, reactions with **3e** and **3f** generated products (−)-**2e** and (−)-**2f** with high enantiomeric excesses (93% and 99% *ee*, respectively).[20] The higher enantiomeric purity of **2f**, and the fact that its major diastereomer could be obtained in better yield of isolated product than that of **2e** (71% vs. 50%, Table 2) led us to use methyl rather than ethyl ester diazo derivatives for the remainder of the study.

The results are summarized in Table 2. Both electron-donating and electron-withdrawing substituents are amenable on the aryl group of the diazo reagent. These functional groups can be introduced at *para*- or at *meta*-positions. Yields of isolated products of the major diastereomer are usually good (70–80%); diastereoselectivity ratios being the only parameters fluctuating from moderate (4:1; Table 2, entry 11) to high (20:1; Table 2, entry 12) values. A slight decrease in enantiomeric purity can be noticed moving in the series from products carrying donor substituents (**2g**–**2j**: OMe, Me) to electron-poor functional groups (**2k**–**2o**: Cl, Br, CF$_3$, F), this effect was particularly noticeable in the reaction of (−)-(*R*,*R*)-**1** and **3p** that yields (−)-**2p** in 64% enantiomeric purity only.

This outcome can be rationalized in terms of the mechanism. It involves the catalytic generation of electrophilic metal carbenoids and additions of Tröger bases **1** to these intermediates (Scheme 3). Stabilized nitrogen ylides of type **4** are generated. Then, radical pair **5** and/or zwitterionic species **6** are formed;[21] these ring-opened intermediates collapse to form ethano-bridged Tröger bases **2**. In reactions of **3b**, **3c**, **3d**, and **3p**, we can hypothesize that the loss of enantiomeric purity results from a stronger stabilization of intermediates **5** or **6** by the electron-withdrawing substituents that surround the reactive carbon center. These intermediates **5** or **6** have then a longer life-time and the opportunity to racemize through a complete planarization of the core.

For the reactions with substrates **3f** to **3o** that proceed with high enantiospecificity, care was taken to determine the absolute configuration of products **2** with certainty.[19] The configuration was established by vibrational circular dichroism (VCD) in view of the rigidity of compounds **2**.[22] Infrared absorption and VCD spectra were measured for solutions (CCl$_4$) of the major diastereomer of both (+)- and (−)-**2f** and compared to the averaged spectrum calculated for ($5S_N$,$11R_N$,$14R_C$)-**2f** (Figure 1).[19,23]

Conformational analysis showed only two possible conformations;[24] the most stable having a geometry close to that determined by X-ray crystallographic analysis. The geometry



Scheme 3. Mechanistic rationale.

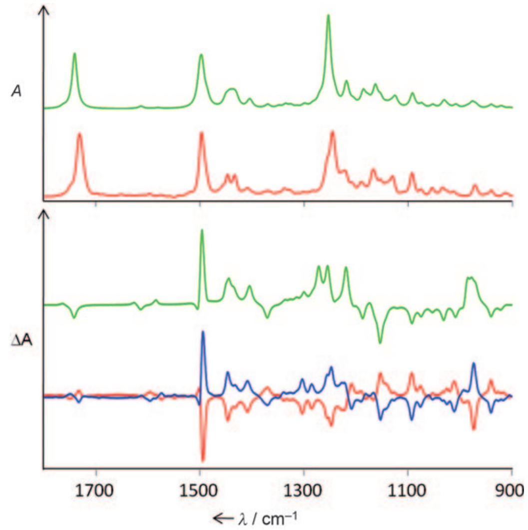
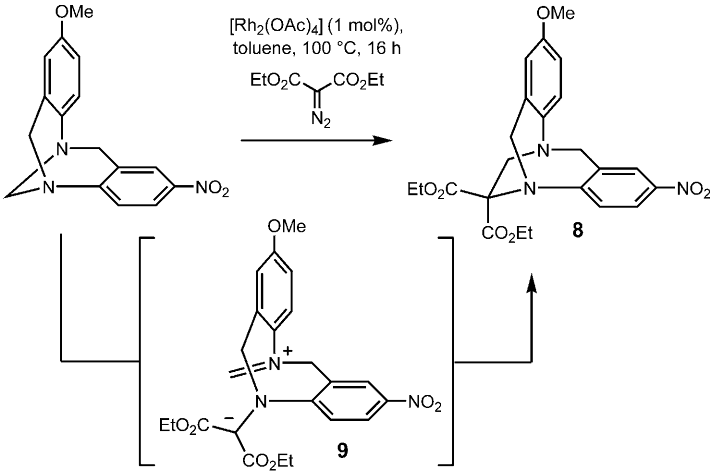


Figure 1. Experimental IR absorption (top) and VCD (bottom) spectra (CCl_4, 298 K) of (−)-**2f** (red) and (+)-**2f** (blue). Calculated spectrum of ($5S_N$,$11R_N$,$14R_C$)-**2f** (green).

optimizations, vibrational frequencies, IR absorption; and VCD intensities were calculated by using density functional theory (DFT).[25] Overall, a good agreement between the experimental and theoretical spectra was observed, thus allowing the assignment of a ($5S_N$,$11R_N$,$14R_C$) configuration for (+)-**2f**. The enantiospecific rearrangement occurs, therefore, with retention of configuration.

An electron-rich Tröger base was also used as a substrate (X = OMe, 98% *ee*; Table 2, entry 13) and its treatment with **3f** afforded product **7** with excellent diastereoselectivity (16:1 d.r.) and enantiospecificity (97% *ee*). Finally, an unsymmetrically substituted Tröger base was prepared carrying electron-donating and electron-withdrawing substituents on the two aromatic rings, respectively (OMe and NO_2; Scheme 4).[26] A single regioisomer was obtained from its reaction with diester **3b**. Interestingly, product **8** (> 49:1 d.r., 71% yield) arises from the reaction of the electron-poor nitrogen atom only (*para* to the nitro group). This result, at first glance surprising, can be rationalized considering a preferred formation of intermediate **9** (Scheme 2). In this intermediate, the cationic nitrogen atom is stabilized by the *para*-OMe group while the electron-density on the other nitrogen atom is efficiently delocalized towards the nitro substituent.



Scheme 4. Regioselectivity.

In conclusion, this paper reports the one-step rhodium(II)-catalyzed reaction of methano-bridged Tröger bases and diazo esters to yield highly enantioenriched, configurationally stable ethano-bridged Tröger derivatives. The process is general, enantiospecific (up to 99% *ee*, retention of configuration), diastereoselective (quaternary carbon center introduction, up to 49:1 d.r.), and represents an interesting regioselective outcome.

Experimental Section

Representative procedure: In a 5 mL screw-cap vial equipped with a magnetic stirring bar, Tröger base (−)-(*R*,*R*)-**1** (0.40 mmol, 100.0 mg) was introduced along with dry toluene (1.0 mL) and 1.76 mg [$Rh_2(OAc)_4$] (1 mol%). Diazo compound **3f** (0.40 mmol) was added in one portion and the cap was placed at the top (unscrewed). The reaction mixture was introduced into an already-heated oil bath (100 °C) and stirred for 1 h. Then, **3f** (0.40 mmol) was added in one portion again and the resulting solution stirred for another 5 h at 100 °C. The reaction was monitored by ESI-MS. After completion, the mixture was cool to 20 °C and the solvent removed under reduced pressure. After NMR spectroscopic analysis of the crude reaction mixture, the desired product was purified by column chromatography on silica gel (eluent: hexanes/acetone = 20:1) to give (−)-**2f** as a white solid (113 mg, 71%).

CCDC 806457 (**2f**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Keywords: carbenoids · diazo compounds · rearrangement · rhodium · Tröger bases

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[1] J. Tröger, *J. Prakt. Chem.* **1887**, *36*, 225–245.
[2] S. Sergeyev, *Helv. Chim. Acta* **2009**, *92*, 415–444; B. Dolensky, J. Elguero, V. Kral, C. Pardo, M. Valik, *Adv. Heterocycl. Chem.* **2007**, *93*, 1–56; M. Demeunynck, A. Tatibouet, *Prog. Heterocycl. Chem.* **1999**, *11*, 1–20; E.-i. Kim, S. Paliwal, C. S. Wilcox, *J. Am. Chem. Soc.* **1998**, *120*, 11192–11193; S. Sergeyev, F. Diederich, *Angew. Chem.* **2004**, *116*, 1770–1773; *Angew. Chem. Int. Ed.* **2004**, *43*, 1738–1740; M. D. H. Bhuiyan, K. X. Zhu, P. Jensen, A. C. Try, *Eur. J. Org. Chem.* **2010**, 4662–4670; E. B. Veale, T. Gunnlaugsson, *J. Org. Chem.* **2010**, *75*, 5513–5525; S. Sergeyev, D. Didier, V. Boitsov, A. Teshome, I. Asselberghs, K. Clays, C. M. L. V. Velde, A. Plaquet, B. Champagne, *Chem. Eur. J.* **2010**, *16*, 8181–8190; A. Tatar, J. Cejka, V. Kral, B. Dolensky, *Org. Lett.* **2010**, *12*, 1872–1875; T. Weilandt, U. Kiehne, J. Bunzen, G. Schnakenburg, A. Lutzen, *Chem. Eur. J.* **2010**, *16*, 2418–2426; X. Du, Y. L. Sun, B. E. Tan, Q. F. Teng, X. J. Yao, C. Y. Su, W. Wang, *Chem. Commun.* **2010**, *46*, 970–972.

[3] V. Prelog, P. Wieland, *Helv. Chim. Acta* **1944**, *27*, 1127–1134.

[4] O. Trapp, G. Trapp, J. W. Kong, U. Hahn, F. Vögtle, V. Schurig, *Chem. Eur. J.* **2002**, *8*, 3629–3634; D. A. Lenev, K. A. Lyssenko, D. G. Golovanov, V. Buss, R. G. Kostyanovsky, *Chem. Eur. J.* **2006**, *12*, 6412–6418.

[5] M. S. Sigman, D. R. Jensen, *Acc. Chem. Res.* **2006**, *39*, 221–229; Y. M. Shen, M. X. Zhao, J. Xu, Y. Shi, *Angew. Chem.* **2006**, *118*, 8173–8176; *Angew. Chem. Int. Ed.* **2006**, *45*, 8005–8008.

[6] Y. Hamada, S. Mukai, *Tetrahedron: Asymmetry* **1996**, *7*, 2671–2674; D. A. Lenev, D. G. Golovanov, K. A. Lyssenko, R. G. Kostyanovsky, *Tetrahedron: Asymmetry* **2006**, *17*, 2191–2194; C. Michon, A. Sharma, G. Bernardinelli, E. Francotte, J. Lacour, *Chem. Commun.* **2010**, *46*, 2206–2208.

[7] The presence of the ethano bridge on **2** avoids the conventional racemization pathway via an achiral iminium intermediate; the geometry of the core being essentially unchanged by the ring expansion.

[8] Previous syntheses of compounds **2** only afford racemates using enantiopure methano-bridged Tröger derivatives **1** as substrates. A quaternization of one nitrogen atom occurs and it induces a fast ring opening leading to achiral iminium intermediates and hence to a racemization.

[9] T. Ye, M. A. McKervey, *Chem. Rev.* **1994**, *94*, 1091–1160; M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, New York, **1998**; H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861–2903; A. Padwa, *Helv. Chim. Acta* **2005**, *88*, 1357–1374; Y. Zhang, J. Wang, *Chem. Commun.* **2009**, 5350–5361; M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev.* **2010**, *110*, 704–724.

[10] F. G. West, J. S. Clark, *Nitrogen, Oxygen Sulfur Ylide Chem.* **2002**, 115–134; F. F. West, *Mod. Rhodium-Catal. Org. React.* **2005**, 417–431; J. Sweeney, *Chem. Soc. Rev.* **2009**, *38*, 1027–1038.

[11] J. A. Vanecko, H. Wan, F. G. West, *Tetrahedron* **2006**, *62*, 1043–1062.

[12] R. K. Hill, T. H. Chan, *J. Am. Chem. Soc.* **1966**, *88*, 866–867; K. W. Glaeske, F. G. West, *Org. Lett.* **1999**, *1*, 31–33; M.-H. Gonçalves-Farbos, L. Vial, J. Lacour, *Chem. Commun.* **2008**, 829–831.

[13] For a rare exception, see: E. Tayama, S. Nanbara, T. Nakai, *Chem. Lett.* **2006**, *35*, 478–479.

[14] The presence of two different substituents around the diazo moiety leads to the formation of a new carbon stereocenter on the ethano bridge, and hence the formation of diastereomers.

[15] W.-J. Zhao, M. Yan, D. Huang, S.-J. Ji, *Tetrahedron* **2005**, *61*, 5585–5593; E. Ciganek, *J. Org. Chem.* **1970**, *35*, 862–864; M. Regitz, W. Bartz, *Chem. Ber.* **1970**, *103*, 1477–1485.

[16] The phenyl and ester substituents occupy what appears to be the less- and more-crowded positions on the ethano bridge, respectively.

[17] The absolute configuration of (+)-**1** was originally misassigned in 1967: S. F. Mason, G. W. Vane, K. Schofiel, R. J. Wells, J. S. Whitehurst, *J. Chem. Soc. B* **1967**, 553-556.

[18] S. H. Wilen, J. Z. Qi, P. G. Williard, *J. Org. Chem.* **1991**, *56*, 485–487.

[19] A. Aamouche, F. J. Devlin, P. J. Stephens, *J. Am. Chem. Soc.* **2000**, *122*, 2346–2354.

[20] As expected, the reaction with (+)-(*S*,*S*)-**1** gave the enantiomeric product (+)-**2 f** with the same *ee* value and with exactly the same yield and diastereoselectivity as in the racemic series.

[21] In [1,2]-Stevens rearrangements, a diradical mechanism is often considered, see: Y. Maeda, Y. Sato, *J. Chem. Soc. Perkin Trans. 1* **1997**, 1491–1493; K. Chantrapromma, W. D. Ollis, I. O. Sutherland, *J. Chem. Soc. Perkin Trans. 1* **1983**, 1049–1061.

[22] L. A. Nafie, T. A. Keiderling, P. J. Stephens, *J. Am. Chem. Soc.* **1976**, *98*, 2715–2723; T. B. Freedman, X. Cao, R. K. Dukor, L. A. Nafie, *Chirality* **2003**, *15*, 743–758; P. J. Stephens, F. J. Devlin, J. J. Pan, *Chirality* **2008**, *20*, 643–663.

[23] The averaged spectrum of minor diastereomer ($5S_N$,$11R_N$,$14S_C$)-**2 f** was calculated and shown not to fit the experimental spectrum.

[24] See the Supporting Information.

[25] B3LYP and CAM-B3LYP functionals combined with 6-311+G(d,p) and/or TZVP basis set were used. Frequencies were scaled by a factor of 0.98 with B3LYP and 0.96 with CAM-B3LYP. Infrared absorption and VCD spectra were constructed from calculated dipole and rotational strengths assuming Lorentzian band shape with a half-width at half maximum of 6 cm^{-1}. All calculations were performed using Gaussian09 Revision A02.

[26] B. Dolenský, M. Valik, D. Sykora, V. Kral, *Org. Lett.* **2005**, *7*, 67–70; C. Pardo, M. Ramos, A. Fruchier, J. Elguero, *Magn. Reson. Chem.* **1996**, *34*, 708–710.