Pergamon

TETRAHEDRON

Tetrahedron 54 (1998) 15731–15738

A Comparative Study of C2-Symmetric Bis(aziridine) Ligands in Some Transition Metal-Mediated Asymmetric Transformations

David Tanner,*[a] Fredrik Johansson,[a,b] Adrian Harden[b] and

Pher G. Andersson*[b]

[a]Department of Organic Chemistry, The Technical University of Denmark
Building 201, DK-2800 Lyngby, Denmark.

[b]Department of Organic Chemistry, University of Uppsala
Box 531, S-751 21 Uppsala, Sweden.

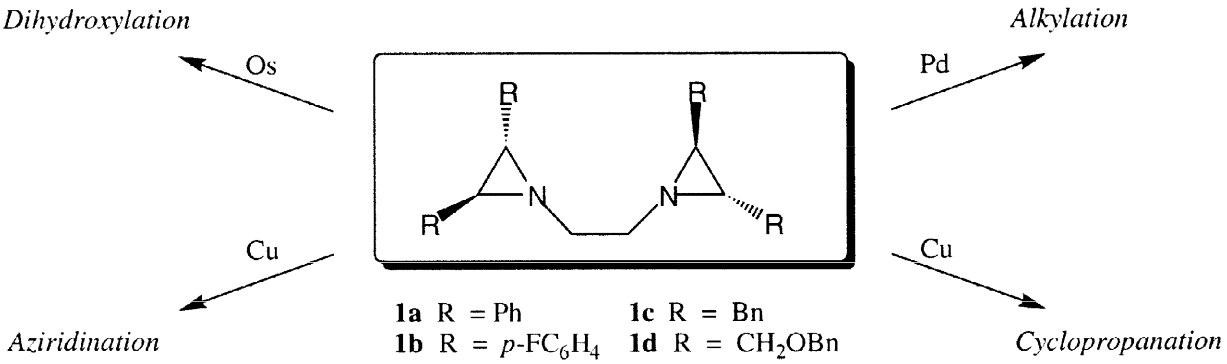
Received 7 September 1998; revised 7 October 1998; accepted 22 October 1998

Abstract:

A comparative study has been made of the performance of differently substituted C_2-symmetric bis(aziridine) ligands in a variety of metal-mediated asymmetric reactions. The metals studied were osmium (dihydroxylation), palladium (allylic alkylation) and copper (cyclopropanation and aziridination), the ligands being chosen so as to allow evaluation of both electronic and steric effects. The electronic effects were most pronounced for complexes of palladium, which seem to bind rather loosely to this type of ligand. For the other metals, steric effects play a more important role.

We have earlier reported [1a,b] on the use of C_2-symmetric bis(aziridines) as chiral ligands in a variety of asymmetric transformations (both stoichiometric and catalytic) mediated by transition metals (Fig. 1). It was demonstrated [1b] that ligands with a two-carbon tether between the aziridine rings (presumably forming five-membered chelates) are much superior to the corresponding species with longer tether lengths, irrespective of the metal used.

Fig. 1.



1a R = Ph　**1c** R = Bn
1b R = p-FC_6H_4　**1d** R = CH_2OBn

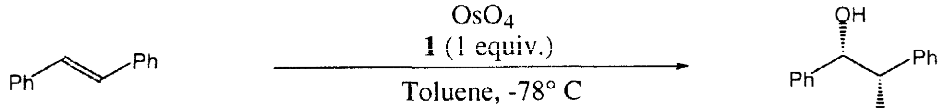
PII: S0040-4020(98)00987-9

In this paper we present a comparative study of the performance of ligands **1a-d** in the reactions shown above. This set of ligands was chosen in order to study *electronic* (**1a** *vs.* **1b**) and *steric* (**1a** *vs.* **1c**, **1d**) effects. The decision to study electronic effects of substituents was based on knowledge of the special bonding situation [2] in three-membered rings. Cromwell *et al.* [3a] have studied "hyperconjugative" stabilisation [3b] in 2,3-disubstituted aziridines and such effects should also be present in **1a**, due to orbital interactions between the two phenyl moieties transmitted via the "bent" bonds of the three-membered ring. This effect is maximised when the planes of the aryl groups are arranged nearly perpendicular to the plane of the heterocyclic ring, *i.e.* when the π-orbital axis of the arene is parallel to the aziridine ring plane (Fig. 2, a). In our analysis, we have also taken into account the possible effect of an alternative hyperconjugative interaction upon the geometry at nitrogen, and concluded that overlap of the nitrogen lone-pair with the aromatic rings should increase as the nitrogen approaches planarity; this requires the π-orbital axis of the aryl groups to be arranged as shown in Fig. 2, b. This could in turn manifest itself in a lower barrier to pyramidal inversion [4] at nitrogen (since a planar nitrogen is involved in the transition state for the inversion) and we have found that this is indeed the case, by a comparison of the inversion barriers for **1a** and **1c** [5]. While the effects of substituents on *nitrogen* upon the barrier to aziridine *N*-inversion are well documented [4], the effects of substituents on *carbon* have not been widely appreciated, although a number of examples can be found [4].

Fig. 2

The first reaction studied was the osmium-mediated dihydroxylation [6] of *trans*-stilbene, and the results are presented in Table 1.

Table 1.



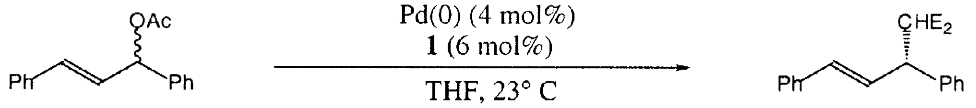
Ligand	Yield	*ee* %	Abs. conf.
1a	90	95	*S,S*
1b	75	83	*S,S*
1c	78	33	*S,S*
1d	61	6	*S,S*

For experimental procedure and determination of *ee* and absolute configuration see ref. [1b].

As far as steric effects are concerned, it is not surprising to note that the *ee* drops sharply as the phenyl groups on the ligand become further removed from the coordination site. Due to its very poor performance, ligand **1d** was not considered for the catalytic reactions discussed below. There is also a weak, but appreciable, electronic effect of ligand **1b** (*vide infra*).

For palladium-catalysed asymmetric allylic alkylation [7], 1,3-diphenylpropenyl acetate has become the standard substrate for testing new ligands (Table 2). Our original ligand **1a** gives essentially complete asymmetric induction due to a striking deviation from square planar geometry of the intermediate π-allyl complex [7b]. However, the binding of this ligand to palladium is not particularly strong since the π-allyl species in the catalytic reaction decomposes quite readily in solution upon heating above 45° C.

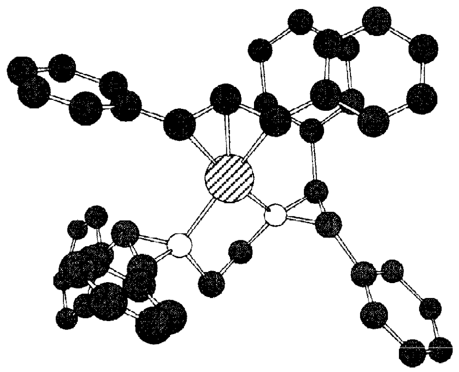
Table 2.



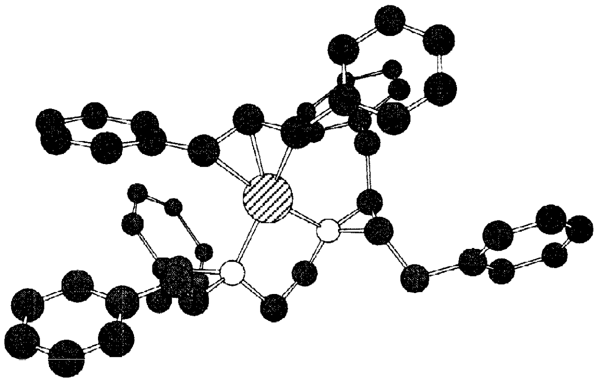
Ligand	Yield %	*ee* %	Abs. conf.
1a	89	> 99	*R*
1b	N.R.	-	-
1c	60	> 99	*R*

For experimental procedure and determination of *ee* and absolute configuration see ref. [7b].

The introduction of a *p*-fluoro substituent (**1b**) [8] would be expected to further weaken the binding between palladium and the nitrogen lone pairs because of the inductive effect of fluorine. In practice, it was observed that ligand **1b** did not promote any catalytic reaction. Attempted preparation of the putative intermediate (which was very simple [7b] for **1a**) was not possible either. On the other hand, the benzyl substituted ligand **1c** gave the same excellent level of asymmetric induction as **1a**, and the preparation of the π-allyl palladium complex presented no problems. The complex has been characterised by NMR spectroscopy and the results of MM2 calculations are shown below. It is instructive to compare the structure with that of the complex from **1a**.



MM2 calculated structure **A** (from ligand **1a**)

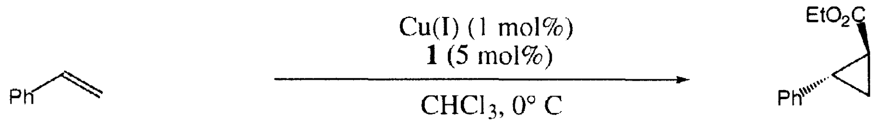


MM2 calculated structure **B** (from ligand **1c**)

The deviation from square planarity in B is slightly less than that in A, but the same type of argument as presented previously [7b,c] can be used to explain the absolute configuration obtained in the product (attack by the nucleophile at the sterically less hindered and more electrophilic terminus of the π-allyl moiety) [7d]. Any inductive effect of the benzyl substituents would be expected to be opposite to that of the *p*-fluorophenyl group.

Ligand **1a** induced moderate levels of enantioselectivity in the copper catalysed cyclopropanation [1b, 9] of styrene. Interestingly, in this case ligand **1b** matched the performance of **1a** almost exactly (Table 3) indicating that the copper complexes of **1a** and **1b** are much less sensitive towards electronic effects compared to the corresponding palladium species. Somewhat surprisingly, ligand **1c** gave substantially higher levels of asymmetric induction. Using the model proposed by Pfaltz [9a] for the rationalisation of the stereochemical outcome of this type of reaction, it is not clear why the benzyl substituted derivative should be more efficient, but it must be borne in mind that the observed effect is dependent on only small differences in the free energy of activation.

Table 3.

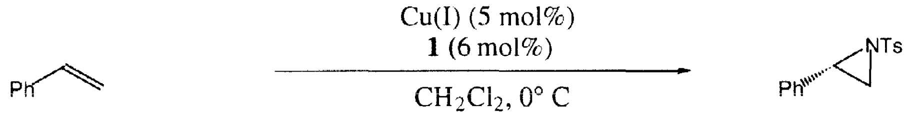


Ligand	Yield %	*trans* / *cis*	*ee* % (*trans*)	Abs. conf. (*trans*)
1a	82	3 : 1	60	1*S*, 2*S*
1b	60	3 : 1	58	1*S*, 2*S*
1c	73	3 : 1	90	1*S*, 2*S*

For experimental procedure and determination of *ee* and absolute configuration see ref. [1b].

Finally, copper catalysed aziridination[1b, 10] of styrene was studied using ligands **1a** - **c**. In contrast to the cyclopropanation reaction, there was now a marked difference between **1a** and **1b**. Another very interesting feature was the extremely poor performance of **1c**; these results casts doubt on the proposal recently advanced by Jacobsen [11] who has suggested a close resemblance between the transition states for the cyclopropanation and aziridination processes. This point is under further investigation.

Table 4.



Ligand	Yield %	*ee* %	Abs. conf.
1a	68	33	*S*
1b	59	9	*S*
1c	62	7	*S*

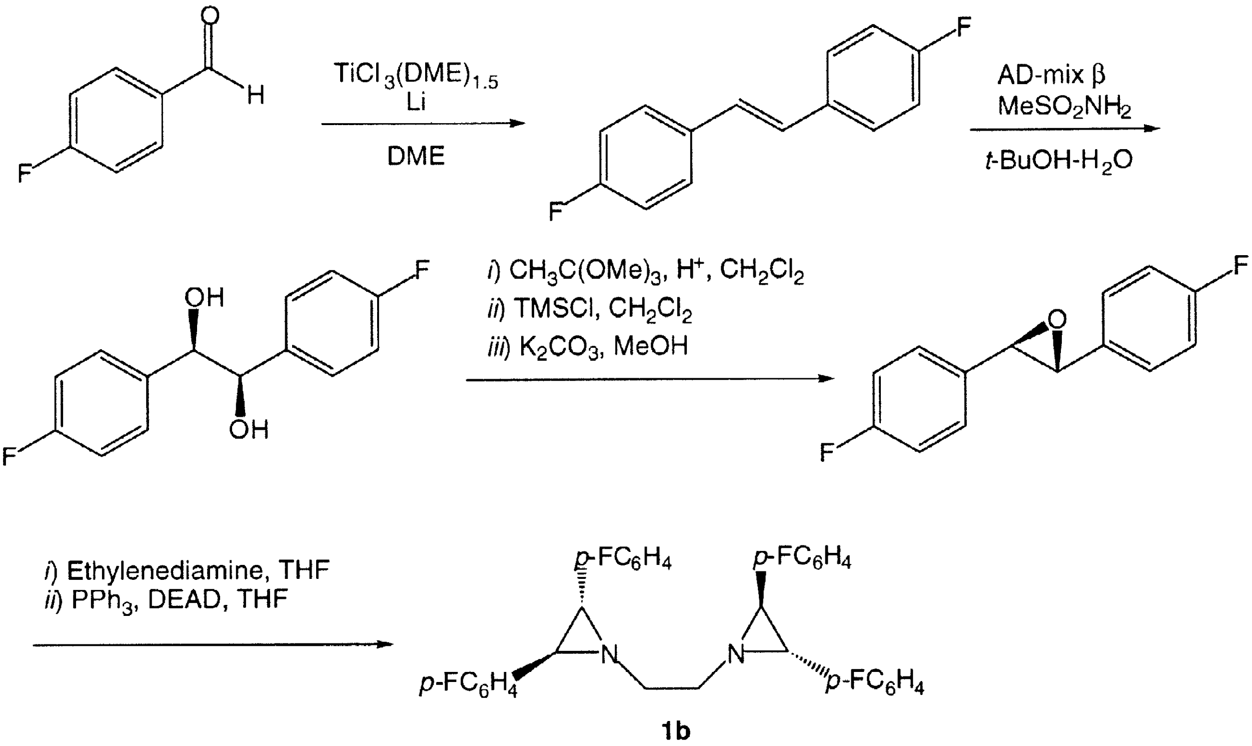
For experimental procedure and determination of *ee* and absolute configuration see ref. [1b].

Conclusion

In conclusion, we have shown that easily available C_2-symmetric bis(aziridines) can act as ligands for a variety of transition metal-mediated asymmetric syntheses. The best results in terms of enantioselectivity (95 to >99% e.e.) were obtained for osmium-mediated asymmetric dihydroxylation and palladium-catalyzed allylic alkylation reactions. An *e.e.* of 90% was obtained for the copper-catalyzed cyclopropanation of styrene, while the corresponding aziridination reaction gave only 33%, at best. As could be expected, steric effects of the substituents on the aziridine ring carbons play an important role in determining reactivity and enantioselectivity, but we have also observed an interesting and unusual electronic effect of a *p*-fluorophenyl group, particularly in the reactions involving palladium complexes.

Experimental

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AC-250 or a Varian XL-300 instrument ($CDCl_3$/TMS). Mass spectra were recorded on a Finnigan MAT INCOS 50 instrument at 70 eV. IR spectra were recorded on a Perkin-Elmer 1600 FTIR instrument. Enantiomeric excess (*e.e.*) was determined by chiral HPLC using an OD-H column. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by Mikroanalytisches Laboratorium, Institut für Physikalische Chemie, University of Vienna, Austria. and Mikro Kemi AB, Uppsala, Sweden. Toluene was dried over sodium hydride and distilled under nitrogen atmosphere. The synthesis of ligands **1a** [1b], **1c**, and **1d** [1c] has been described previously. Ligand **1b** was synthesised as shown below.



Synthesis of ligand **1b**.

(i) McMurry coupling of *p*-fluorobenzaldehyde. Commercially available $TiCl_3(DME)_{1.5}$ (50 g, 170 mmol) was placed under argon in a flame-dried 250 mL flask equipped with a reflux condenser. Anhydrous DME (150 mL) was added, followed by lithium wire (3.5 g, 510 mmol) which had been cut into small pieces, etched with methanol and washed with pentane. The resultant black mixture was refluxed for 1.5 h before dropwise addition of neat *p*-fluorobenzaldehyde (5.36 g, 43 mmol). After 20 h of reflux, the mixture was allowed to cool to room temperature before being diluted with pentane (100 mL) and filtered through celite. Solid material remaining in the reaction flask was extracted with pentane (3 x 100 mL) and dichloromethane (100 mL), the extracts were filtered through celite, and the filter cake was washed with dichloromethane (200 mL). The combined organics were evaporated to dryness in vacuo and the residue was taken up in the minimum amount of dichloromethane before being filtered through a short plug of silica gel. Removal of the solvent in vacuo gave the *trans* alkene (2.7 g, 58%) as a crystalline solid (m.p. 133 - 137^{o}C) which could be used directly in the next step. For analysis, a small sample was purified by flash chromatography on silica gel, eluting first with hexane and then 1% ethyl acetate in hexane. Rf (EtOAc-hexane, 1:19) 0.41. ^{1}H NMR: 7.46 (4 H, m), 7.06 (4 H, m), 6.99 (2 H, s). ^{13}C NMR: 162.4 (d, J_{CF} 244 Hz), 133.3, 127.9 (d, J_{CF} 12.5) 127.2, 115.6 (d, J_{CF} 18.8). IR (KBr): 2924, 1896, 1601, 1506, 1234, 968, 838. Anal. Calc. for $C_{14}H_{10}F_2$: C, 77,77%; H, 4.66. Found: C, 77.56; H, 4.73.

(ii) Sharpless Asymmetric Dihydroxylation. Commercially available AD-mix ß (11.3 g) was dissolved in a mixture of tert-butanol (40 mL) and water (40 mL) and cooled with stirring to 0^{o}C before addition of methanesulfonamide (0.77 g, 8.1 mmol) and the alkene from above (1.75 g, 8.1 mmol). The reaction mixture was allowed to reach room temperature slowly and was then stirred for 20 h before addition of Na_2SO_3 (12.13 g, 96.3 mmol). The resultant mixture was stirred for 45 min, and dichloromethane (50 mL) was added. The phases were separated and the aqueous phase was extracted with dichloromethane (3 x 50 mL). The combined organic phases were washed with 2 M KOH solution (40 mL) and dried over $MgSO_4$. After removal of the solvents, the residue was purified by flash chromatography (20 - 80% ether in pentane) to give the chiral 1,2-diol (3.68 g, 91%) as a crystalline solid (m.p. 82 - 83^{o}C). Rf (EtOAc-hexane, 1:1) 0.45. ^{1}H NMR: 6.99 - 6.81 (8 H, m), 4.49 (2 H, s), 3.56 (2 H, bs). ^{13}C NMR: 162.3 (d, J_{CF} 250), 135.3 (d, J_{CF} 3), 128. 5 (d, J_{CF} 6.3), 115.0 (d, J_{CF} 19), 78.5. IR (KBr): 3373, 2932, 1893, 1607, 1514, 1237, 989, 860, 835. Anal. Calc. for $C_{14}H_{12}F_2O_2$: C, 67.20; H, 4.83. Found: C, 67.05; H, 4.90. $[\alpha]_D$ +76.8 (c 1.0, CH_2Cl_2).

(iii) To a solution of the diol from above (0.537 g, 2.14 mmol) in dichloromethane (20 mL) under argon was added p-toluenesulfonic acid (5 mg, 0.03 mmol) followed by trimethyl orthoacetate (0.32 mL, 2.57 mmol). After 1 h, TLC (ethyl acetate - hexane, 1:1) indicated complete reaction and the volatiles were removed in vacuo. ^{1}H NMR analysis of the crude product indicated that the expected cyclic orthoacetate was the only product formed. The crude product was dissolved with stirring under argon in dichloromethane and trimethylsilyl chroride (0.38 mL, 2.99 mmol) was added. The course of the reaction was monitored by TLC (ethyl acetate - hexane, 1:9) which indicated essentially complete conversion after 3 h at room temperature. The volatiles were removed in vacuo and the residue was dissolved in methanol (20 mL) followed by addition of potassium carbonate (0.59 g, 4.28 mmol). The resultant mixture was stirred at room temperature for 20 h, filtered, and the solvents were removed in vacuo. The residue was partitioned between ethyl acetate (50 mL) and brine (20 mL), the phases were separated, and the organic phase was washed with saturated aqueous ammonium chloride (20 mL) and brine (20 mL). After drying over $MgSO_4$, the organic phase was evaporated to dryness and the residue was purified by flash chromatography (ethyl acetate - hexane) to yield the desired trans epoxide (0.33 g, 66% based on the diol) as a crystalline solid (m.p. 102 - 105^{o}C). R_f (EtOAc- hexane, 1:9) 0.55. ^{1}H NMR: 7.39 - 7.28 (4 H, m), 7.08 (4 H, m), 3.83 (2 H, s). ^{13}C NMR: 162.8 (d, J_{CF} 250), 132.7 (d, J_{CF} 6.3), 127.1 (d, J_{CF} 6.3), 115.5 (d, J_{CF} 19), 62.2. IR (KBr): 3002, 1899, 1773, 1605, 1514, 1453, 1228, 862, 822. Anal. Calc. for $C_{14}H_{10}F_2O$: C, 72.41; H, 4.34. Found: C, 72.33; H, 4.44. $[\alpha]_D$ +219.3 (c 1.01, CH_2Cl_2). (This material was shown to be of >98% e.e. by chiral HPLC (Chiralcel OD-H column) after a control experiment with the racemic *trans* epoxide prepared by standard mCPBA epoxidation of the alkene from the McMurry coupling reaction described above.)

(iv) The epoxide from above (1.63 g, 7.02 mmol) was dissolved with stirring under nitrogen in refluxing THF (3 mL). The source of heat was removed briefly and ethylenediamine (250 µL, 3.72 mmol) was added dropwise. The resultant mixture was stirred at reflux for 65 h and the volatiles were removed in vacuo. ^{1}H NMR spectroscopic analysis of the residue indicated only minor amounts of unreacted epoxide. The crude product was taken up in THF (25 mL) and triphenylphosphine (2.44 g, 9.3 mmol) was added with stirring under nitrogen at room temperature. The resultant mixture was cooled to 0^{o}C and diethyl azodicarboxylate (1.46 mL, 9.3 mmol) was added. The mixture was allowed to reach room temperature and was stirred for 16 h before being partitioned between ether and water. The organic phase was washed with water, then with brine, dried over $MgSO_4$, and evaporated to dryness to give a residue which was purified by flash chromatography (40% ether in pentane) followed by two recrystallisations from hexane (23 mL). There was obtained 0.770 g (42% based on the epoxide) of ligand 1b as an analytically pure crystalline solid (m.p. 135.5 - 136^{o}C). R_f (EtOAc -hexane, 1:3) 0.48. ^{1}H NMR: 7.20 (8 H, bm), 7.00 (8 H, bm), 3.09 (4H, bs), 2.40 (4 H, m). ^{13}C NMR: 162.9 (d, J_{CF} 250), 131.3 (b), 127.5 (b), 115.1 (d, J_{CF} 19), 52.5, 49.5 (b), 45.3 (b). (Some of the signals in both the ^{1}H and ^{13}C NMR spectra are broadened at room temperature due to slow pyramidal inversion at nitrogen.) IR (KBr): 3448, 3069, 2982, 2952, 2851, 1896, 1604, 1509, 1229, 1209, 839, 756. Anal. Calc. for $C_{30}H_{24}F_4N_2$: C, 73.76; H, 4.95. Found: C, 73.87; H, 5.09. $[\alpha]_D$ -91.0 (c 1.0, CH_2Cl_2).

Acknowledgements.

We thank the *Swedish Natural Science Research Council, Danish National Research Council, NORFA* and the *Swedish Foundation for Strategic Research* for generous financial support, Dr. A. Gogoll for obtaining NMR data for ligand 1c and Dr. P-O. Norrby for preparing Fig. 3. A. H. thanks the EPSRC for a stipend.

References and Notes

[1] (a) Tanner, D.; Andersson, P. G.; Harden, A.; Somfai, P. *Tetrahedron Lett.* 1994, *35*, 4631. (b) Tanner, D.; Harden, A.; Johansson, F.; Wyatt, P.; Andersson, P. G.; *Acta Chem. Scand.* 1996, *50* 361. (c) Andersson, P. G.; Johansson, F.; Tanner, D. *Tetrahedron*, **1998**, *54*, 11549.

[2] For discussion see: (a) Wiberg, K. B. *Acc. Chem. Res.* 1996, *29*, 229. (b) de Meijere, A. *Angew. Chem. Int. Ed. Engl.* 1979, *18*, 809. (c) Gilchrist, T. L. *Heterocyclic Chemistry 2nd ed.*; Longman: Harlow, 1992.

[3] (a) Cromwell, N. H.; Graff, M. A. *J. Org. Chem.* 1952, *17*, 414. (b) For a discussion of hyperconjugative effects, see: Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: Chichester, 1976; pp. 80-85.

[4] Jennings, W. B.; Boyd, D. R. *Cyclic Organonitrogen Stereodynamics*: Lambert, J.; Takeuchi, Y, Eds.; VCH: New York, 1992; pp. 77-123.

[5] Inversion barriers determined by DNMR methods: 60 kJ mol^{-1} (**1a**) and 84 kJ mol^{-1} (**1c**).

[6] For a leading reference see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* 1994, *94*, 2483. For other examples using dinitrogen ligands see: (a) Hanessian, S.; Meffre, P.; Girard, M.; Beaudin, S.; Sancéau, J. Y.; Bennani, Y. *J. Org. Chem.* 1993, *58*, 1991. (b) Nakajima, M.; Tomioka, K.; Iitaka, Y.; Koga, K. *Tetrahedron* 1993, *49*, 10793.

[7] (a) For an excellent review, see: Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* 1996, *96*, 395. (b) Andersson, P. G.; Harden, A.; Tanner, D.; Norrby, P-O. *Chem. Eur. J.* 1995, *1*, 12. (c) von Matt, P.; Lloyd-Jones, G. C.; Minidis, A. B. E.; Pfaltz, A.; Macko, L.; Neuburger, M.; Zehnder, M.; Rüegger, H.; Pregosin, P. S. *Helv. Chim. Acta* 1995, *78*, 265. (d) The ^{13}C chemical shift differences between the terminal atoms of the π-allyl are: 18.4 ppm (A) and 14.8 ppm (B).

[8] For a recent review of the often surprising and unpredictable effects of fluorine substituents, see: Schlosser, M. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1497.

[9] (a) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helv. Chim. Acta* 1988, *71*, 1553. (b) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron, Lett.*, 1990, *31*, 6005. (c) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* 1991, *113*, 726. (d) Bedekar, A. V.; Andersson, P. G. *Tetrahedron Lett.* 1996, *37*, 4073. (e) Bedekar, A. V.; Koroleva, E. B.; Andersson, P. G. *J. Org. Chem.* **1997**, *62*, 2518. (f) Temme, O.; Taj, S.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 6007.

[10] (a) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* 1993, *115*, 5326. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* 1993, *115*, 5328.

[11] Li, Z.; Quan, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* 1995, *117*, 5889.