Different influence of polyoxygenation on the catalytic activity of amido vs. amino isoborneols.

E. M. Márquez Sánchez-Carnerero, T. de las Casas Engel, B. Lora Maroto, S. de la Moya Cerero*

Dpto. de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, Spain. E-mail: santmoya@quim.ucm.es, belora@quim.ucm.es

Abstract

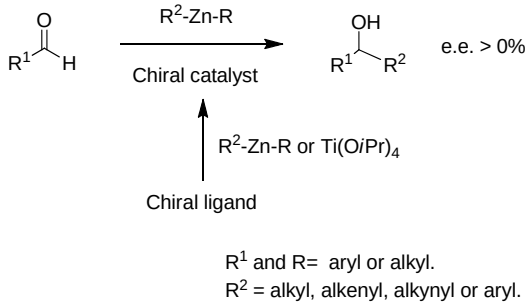
A new series of polyoxygenated amido isoborneols has been synthesized and tested on the enantioselective addition of diethylzinc to benzaldehyde and the results compared to a series of related amino isoborneols. The observed different behavior has been explained on the basis of catalytic quelates previously proposed by us.

Keywords

Asymmetric catalysis / Zinc / Hydroxyamides / Amino isoborneols / Chiral pool / Structure–activity relationships.

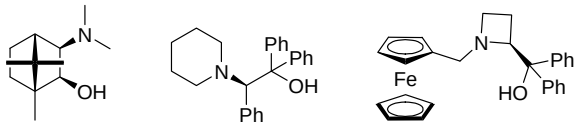
Introduction

One of the most synthetically useful methods to create a carbon-carbon bond in an asymmetric way is the enantioselective addition of organozinc reagents to aldehydes.[1] Additionally, the reaction leads to secondary alcohols, which are valuable synthetic intermediates for the preparation of natural products or new materials with interesting physicochemical properties[2] (sch. 1).



Scheme 1. Enantioselective addition of organozinc reagents to aldehydes.

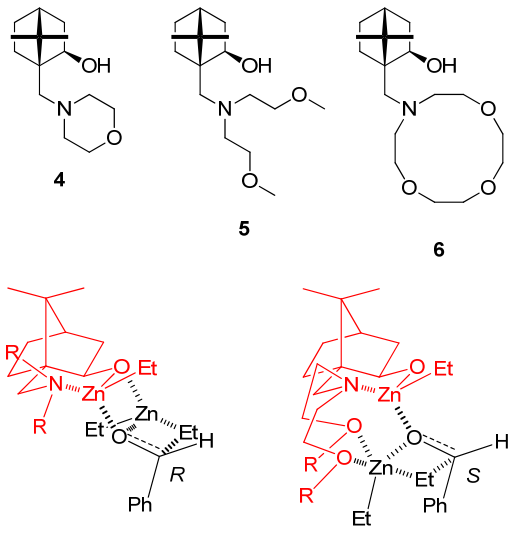
Although many chiral ligands have been described so far for the reaction, most of them being *N,N*-dialkyl amino alcohols (*e. g.* Noyori's DAIB **1**[3], Pericàs's ephedrine analogue **2**[4] or Wang's ferrocene amino alcohol **3**[5], fig. 1), there is still a search for a really versatile ligand, able to promote the addition of a wide range of organozinc reagents to a wide range of substrates. Moreover, the synthesis leading to the most efficient ligands are frequently long and racemic resolution or asymmetric synthesis steps are often required in their preparation.



1 **2** **3**

Figure 1. Some efficient ligands for the addition of organozinc reagents to aldehydes.

In the search of new versatile ligands, research on how the structural features of the ligands affect their catalytic activity is necessary. However, not many studies on this topic have been carried on up to date. In this sense, we have reported a study on the effect of polyoxygenation on the catalytic activity of a series of amino isoborneols. We explained the behavior of these ligands by the competition of a new transition state where the two additional oxygen atoms in the ligand acted as a pincer, directing the reactive diethylzinc molecule to the *si* face of benzaldehyde (fig. 2).[6]



4 **5** **6**

Figure 2. Polyoxygenated amino isoborneols and the proposed competitive TS's. (Catalytic chelate in red).

On the other hand, we have found that some amido isoborneols have a catalytic activity comparable to related amino isoborneols and, thus, we have described ketopinic acid-derived C_2-symmetric bis(hydroxyamides) as efficient ligands to promote the enantioselective addition of diethylzinc to aldehydes.[7] The advantage of the ligands having an amido group is that they are easily prepared and much more inert than their analogous amines. The activity of these ligands could be modulated as well by polyoxygenation of their amine moieties, as it has been the case for related amino isoborneols. However, the effect of polyoxygenation in amido isoborneols has not been studied yet.

Results and discussion

Thus, following our investigations, we were interested in studying the effect that polyoxygenation has on the catalytic activity of amido isoborneols. We synthesized ligands **7** to **9** for this purpose. These ligands are obtained in two straightforward steps from ketopinic acid: amidation followed by chemo- and stereoselective reduction of the keto group (fig 3, see experimental section).

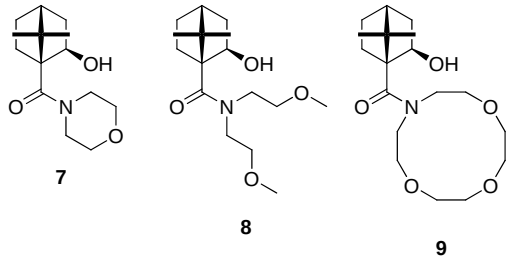


Figure 3. Polyoxygenated amido isoborneols.

The catalytic activity of these ligands was evaluated in the enantioselective addition of diethylzinc to benzaldehyde. The results are shown in table 1. The catalytic activity of ligands **4** to **6** has been included for comparison.[6]

The data from table 1 show that there is no change in the catalytic activity of hydroxyamides **7 - 9**, due to the different number of oxygen atoms present in the structure of the ligand. On the contrary, the related amino alcohols **4** to **6** did show different

Table 1: Catalytic activity of ligands **4-9** on the addition of diethylzinc to benzaldehyde.[a]

Entry	Ligand	1-Phenylpropan-1-ol		
		Yield (%)[b]	*ee* (%)[c]	Configuration
1	**4**[6]	99	72	*R*
2	**5**[6]	99	36	*S*
3	**6**[6]	99	52	*R*
4	**7**	94	82	*R*
5	**8**	98	78	*R*
6	**9**	98	78	*R*

[a] Benzaldehyde/diethylzinc/ligand: 1/2/0.05. 1 mL additional hexne, 5 h, r.t. [b] Determined by GC. [c] Determined by chiral HPLC quiral (Chiralpak IC).

behavior, depending on the polyoxygenation.[6] This different behavior can be explained on the basis of the empiric catalyst models used previously by us for amino and amido isoborneols (fig. 4), which corroborates our hypothesis.[7a]

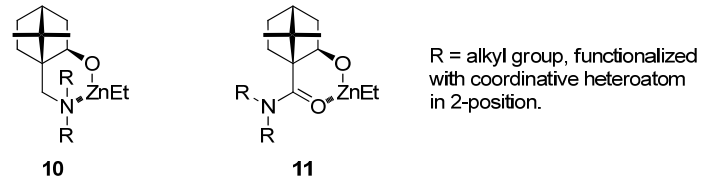


Figure 4. Proposed catalysts for amino isoborneols (**10**) and amido isoborneols (**11**).

Thus, for amino isoborneols, the groups attached to the nitrogen coordinating the catalytic zinc are near the active site of the catalyst, therefore they have an influence on the catalytic activity, as it has been actually observed. However, in the amido isoborneols, the catalytic zinc coordinates to the carbonyl oxygen, which places the alkyl groups far away from the catalytic site. Hence, they don't affect the activity of the catalyst.

Conclusion

The different influence of polyoxygenation in the catalytic activity of amido and amino isoborneols on the enantioselective addition of diethylzinc to benzaldehyde corroborates the different zinc quelate models proposed for each type of ligands and leads us to

conclude that, unlike amino isoborneols, it is not possible to modulate the catalytic activity of amido isoborneols by introducing oxygen atoms in the amine moiety.

General experimental procedure

General considerations: Common solvents were dried and distilled by standard procedures. All starting materials and reagents were obtained commercially and used without further purifications. Flash chromatography purifications were performed on silica gel (230-400 mesh ASTM). Melting points are uncorrected. NMR spectra were recorded at 20 ºC in $CDCl_3$ and the residual solvent peak was used as internal standard. FTIR spectra were obtained using the thin-layer technique. GC analyses were realized at 120ºC in a chromatograph equipped with a capillary silicon-gum (SGL-1) column and a FID, and using nitrogen as mobile phase. Chiral-HPLC analyses were realized at r.t. in a chromatograph equipped with a capillary Chiralpak-IC column and a DAD, and using hexane / isopropanol (98:2) as mobile phase. MS were recorded using the EI (70 eV) or ESI ionization techniques. HRMS were realized using the peak-matching method (EI) or FTMS (ESI).

Ligand 7: (1*S*,2*R*)-7,7-dimethyl-1-[(morpholin-4-yl)carbonyl]norbornan-2-ol (7): A two-necked round-bottom flask, equipped with a magnetic stirrer was charged with (1*S*)-7,7-dimethyl-1-[(morpholin-4-yl)carbonyl]norbornan-2-one[8] (150 mg, 0.6 mmol), methanol (10 mL) and $NaBH_4$ (91 mg, 2.4 mmol). The mixture was stirred under argon for 24 h. Then, H_2O (5 mL) was added and the resulting mixture was concentrated under reduced pressure (methanol elimination). The obtained residue was diluted with ethyl acetate (5 mL). H_2O (3 mL) was added, and the resulting layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 3 mL). The combined organic layers were washed with brine (1 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration and solvent evaporation under reduced pressure, the residue was purified by flash column chromatography (silica gel, $CHCl_3$) to obtain (1*S*,2*R*)-7,7-dimethyl-1-[(morpholin-4-yl)carbonyl]norbornan-2-ol **7** (133 mg, 88% yield) as a white solid. M.p.: 163-165ºC. $[\alpha]_D^{20}$ –10.1 (*c* 0.975, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 4.16 (dd, J = 7.9, 4.3 Hz, 1H), 3.75-3.64 (m, 8H), 2.06-1.75 (m, 5H), 1.65 (dd, J = 4.3, 4.3 Hz, 1H), 1.53-1.45 (m, 1H), 1.38 (s, 3H), 1.19-1.11 (m, 1H), 1.15 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz), δ:

171.9 (C), 78.0 (CH), 67.0 (CH_2), 60.6 (C), 50.6 (C), 44.81 (CH_2), 44.76 (CH), 41.5 (CH_2), 29.9 (CH_2), 27.0 (CH_2), 22.1 (CH_3), 21.6 (CH_3) ppm. FTIR, ν: 3508 (w), 3376 (broad, w), 1738 (str), 1117 (m) cm^{-1}. MS (ESI) *m/z* (%): 252 (100). HRMS (FTMS-ESI) *m/z*: 252.1600 (calcd. for $C_{14}H_{22}NO_3$: 252.1605).

Ligand 8: (1*S*)-1-{[Bis(2-methoxyethyl)amino]carbonyl}-7,7-dimetilnorbornan-2-one: Over a solution of (1*S*)-ketopinic acid (291 mg, 1.6 mmol) in CH_2Cl_2 at r.t. were added *N*-3-[(dimethylamino)propyl]-*N´*-ethylcarbodiimide hydrochloride (EDC·HCl, 346 mg, 1.8 mmol), 4-(dimethylamino)pyridine (DMAP, 220 mg, 1.8 mmol) and bis(2-methoxyethyl)amine (239 mg, 1.8 mmol). The reaction mixture was stirred for 24 h. Then, $CHCl_3$ (3 mL) and H_2O (3 mL) were added to the mixture and the obtained phases separated. The organic phase was washed with 10% HCl (1 x 3 mL), water (1 x 3 mL), 10% NaOH (2 x 3 mL), water (1 x 3 mL) and brine (1 x 3 mL), and dried over $MgSO_4$. After filtration and solvent elimination, (1*S*)-1-{[Bis(2-methoxyethyl)amino]carbonyl}-7,7-dimetilnorbornan-2-one was obtained (366 mg, 77% yield). $[\alpha]_D^{20}$ –24.5 (*c* 0.55, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 3.70-3.31 (m, 8H), 3.31 (s, 6H), 2.46 (ddd, *J* = 18.4, 4.7, 2.6 Hz, 1H), 2.33-2.19 (m, 1H), 2.16-1.91 (m, 3H), 1.88 (d, *J* = 18.4 Hz, 1H), 1.47-1.36 (m, 1H), 1.17 (s, 3H), 1.16 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 212.9 (C), 169.9 (C), 72.0 (CH_2), 70.8 (CH_2), 68.1 (C), 59.2 (CH_3), 51.1 (C), 48.7 (CH_2), 47.1 (CH_2), 44.6 (CH_2), 43.5 (CH), 28.2 (CH_2), 27.4 (CH_2), 21.8 (CH_3), 21.2 (CH_3) ppm. FTIR, ν: 1741 (str), 1632 (str), 1119 (str) cm^{-1}. MS (ESI) *m/z* (%): 320 (100), 298 (1). HRMS (FTMS-ESI) *m/z*: 298.2026 (Calcd. for $C_{16}H_{28}NO_4$: 298.2013). **(1*S*,2*R*)-1-{[Bis(2-methoxyethyl)amino]carbonyl}-7,7-dimetilnorbornan-2-ol (8)**: 150 mg (0.5 mmol) of (1*S*)-1-{[Bis(2-methoxyethyl)amino]carbonyl}-7,7-dimetilnorbornan-2-one were reacted following the experimental procedure for the preparation of **7**. Purification by column chromatography hexanes /ethyl acetate (1/1). 147 mg (97% yield). Colorless oil. $[\alpha]_D^{20}$ +12.3 (*c* 0.81, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 4.40 (brs, 1H), 4.13 (m, 1H), 3.67-3.28 (m, 8H), 3.32 (s, 6H), 1.94-1.85 (m, 2H), 1.82-1.71 (m, 2H), 1.54 (dd, *J* = 4.2, 4.2 Hz, 1H), 1.50-1.45 (m, 1H), 1.34 (s, 3H), 1.15-1.06 (m, 1H), 1.11 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 173.1 (C), 76.9 (CH), 70.8 (CH_2), 69.5 (CH_2), 61.2 (C), 58.8 (CH_3), 50.4 (C), 47.5 (CH_2), 45.5 (CH_2), 44.6 (CH), 39.7 (CH_2), 29.6 (CH_2), 27.2 (CH_2), 22.3 (CH_3), 21.1 (CH_3) ppm. FTIR, ν: 3446 (broad, w), 1628 (str), 1115 (m) cm^{-1}. MS

(ESI) *m/z* (%): 621 (100), 322 (73). HRMS (FTMS-ESI) *m/z*: 322.1979 (calcd. for $C_{16}H_{29}NNaO_4$: 322.1989).

Ligand 9: (1*S*)-7,7-Dimethyl-1-[(1,4,7-trioxa-10-azacyclododecan-10-yl)carbonyl]norbornan-2-one: 293 mg (1.6 mmol) of ketopinic acid were reacted following the experimental procedure for the preparation of (1*S*)-1-{[Bis(2-methoxyethyl)amino]carbonyl}-7,7-dimetilnorbornan-2-one. 376 mg (83% yield). M.p.: 85-87ºC. $[\alpha]_D^{20}$ –19.3 (*c* 0.460, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 3.99-3.24 (m, 16H), 2.48 (ddd, *J* = 18.4, 4.4, 2.7 Hz, 1H), 2.35-1.93 (m, 4H), 1.89 (d, *J* = 18.4 Hz, 1H), 1.48-1.37 (m, 1H), 1.20 (s, 3H), 1.18 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 213.1 (C), 170.2 (C), 71.7 (CH_2), 71.5 (CH_2), 71.0 (CH_2), 70.7 (CH_2), 68.3 (C), 51.2 (C), 49.9 (CH_2), 48.3 (CH_2), 44.2 (CH_2), 43.5 (CH), 28.4 (CH_2), 27.5 (CH_2), 22.0 (CH_3), 21.2 (CH_3) ppm. FTIR, ν: 1738 (str), 1626 (str), 1119 (m) cm^{-1}. MS (ESI) *m/z* (%): 362 (100), 340 (1). HRMS (FTMS-ESI) *m/z*: 340.2115 (Calcd. for $C_{18}H_{30}NO_5$: 340.2118). **(1*S*,2*R*)-7,7-Dimethyl-1-[(1,4,7-trioxa-10-azacyclododecan-10-yl)carbonyl]norbornan-2-ol (9)**: 150 mg (0.4 mmol) of (1*S*)-7,7-Dimethyl-1-[(1,4,7-trioxa-10-azacyclododecan-10-yl)carbonyl]norbornan-2-one were reacted following the experimental procedure for the preparation of **7**. Purification by column chromatography hexanes /ethyl acetate (1/1). 149 mg (99% yield). White solid. M.p.: 115-116ºC. $[\alpha]_D^{20}$ –15.6 (*c* 0.390, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 4.74 (d, *J* =4.8 Hz, 1H), 4.54-4.29 (m, 1H), 4.21 (dd, *J* = 4.3, 4.3 Hz, 1H), 4.11-3.94 (m, 1H), 3.74-3.44 (m, 12H), 3.02-2.62 (m, 2H), 2.02-1.90 (m, 2H), 1.84-1.73 (m, 2H), 1.59-1.51 (m, 2H), 1.36 (s, 3H), 1.26-1.11 (m, 1H), 1.16 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 174.1 (C), 76.4 (CH), 69.0 (CH_2), 60.8 (C), 50.6 (C), 49.1 (CH_2), 44.7 (CH), 39.9 (CH_2), 29.9 (CH_2), 27.5 (CH_2), 22.6 (CH_3), 21.0 (CH_3) ppm. FTIR, ν: 3457 (broad, d), 1627 (str), 1128 (m) cm^{-1}. MS (ESI) *m/z* (%): 364 (100), 342 (1). HRMS (FTMS-ESI) *m/z*: 342.2268 (calcd. for $C_{18}H_{32}NO_5$: 342.2275).

Typical procedure for the enantioselective ethylation of aldehydes: Into a 10 mL round-bottom flask, equipped with a magnetic stirrer under argon, containing **5** (0.05 mmol) in dry hexane (1 mL), diethylzinc solution (2.0 mmol, 1.0 M in hexanes) was added at room temperature. The mixture was stirred at this temperature for 5 min. The corresponding aldehyde (1.0 mmol) was then added and the reaction mixture was stirred at room temperature for 5 h. The reaction was quenched by the addition of 10% HCl (3

mL). The resulting mixture was extracted with ether (3 x 3 mL). The combined organic layers were submitted to celite filtration and solvent evaporation. The obtained residue was dissolved in HPLC-grade hexanes and submitted to analysis by GC and chiral HPLC. **1-Phenylpropan-1-ol:** Chiralpak IC, 260 nm, 2-propanol/hexanes (2:98), 1.3 mL/min. t_R = 7.3 min (*R*), 7.8 (*S*).

Acknowledgements

We thank MEC (CTQ2007-67103-C02/BQU), UCM-CM (910107) and Santander-UCM (PR34/07-15782) for supporting this work.

References

1. Some reviews are: (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed.* **1991**, *30*, 49. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. (c) Knochel, P.; Millot, N.; Rodrigues, A. L. *Org. React.* **2001**, *58*, 417. (d) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757. (e) Pu, L.; *Tetrahedron* **2003**, *59*, 9873. (f) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (g) Zhu, H.-J.; Jiang, J.-X.; Ren, J.; Yan, Y.-M.; Pitmann, C. U. *Curr. Org. Synth.* **2005**, *2*, 547. (h) Ramón, D. J.; Yus, M. *Chem. Rev.* **2006**, *106*, 2126. (i) Hatano, M.; Miyamoto, T.; Ishihara, K. *Curr. Org. Chem.* **2007**, *11*, 127. (j) Trost, B.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963. (k) Somanathan, R.; Flores-Lopez, L. Z.; Montalbo-Gonzalez, R.; Chavez, D.; Parra-Hake, M.; Aguirre, G. *Mini-Rev. Org. Chem.* **2010**, *7*, 10.
2. Some interesting examples are described in ref. 1a y 1h. On the use of the reaction for the preparation of chiral liquid crystals, see: (a) Armstrong, J. D.; McWilliams, J. C. Patent No. US 5977371. Recent examples on the preparation of chiral building blocks of interest are: (b) Sedelmeir, J. Carsten B. *J. Org. Chem.* **2007**, *72*, 8859. (c) Yang, Y.; Zhu, S.-F.; Zhou, C.-Y.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2008**, *130*, 14052.
3. Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071.
4. Rodríguez-Escrich, S; Reddy, K. S.; Jimeno, C.; Colet, G.; Rodríguez-Escrich, C.; Solà, L.; Vidal-Ferran, A.; Pericàs, M. A. *J. Org. Chem.* **2008**, *73*, 5340.
5. (a) Wang, M.-C.; Zhang, Q.-J.; Wang, X.-D.; Ding, X.; Jing, T.-T.; Song, M.-P. *J. Org. Chem.* **2008**, *73*, 168. (b) Wang, M.-C.; Zhang, Q.-J.; Li, G.-W.; Liu, Z.-K. *Tetrahedron: Asymmetry* **2009**, *20*, 288.
6. Márquez Sánchez-Carnerero, E.; de las Casas Engel, T.; Lora Maroto, B.; de la Moya Cerero, S. *Tetrahedron: Asymmetry* **2009**, *20*, 2655.
7. (a) de las Casas Engel, T.; Lora Maroto, B.; García Martínez, A.; de la Moya Cerero, S. *Tetrahedron: Asymmetry* **2008**, *19*, 646. (b) de las Casas Engel, T.; Lora Maroto, B.; de la Moya Cerero, S. *Eur. J. Org. Chem.* **2010**, *9*, 1717.
8. Hari, Y.; Aoyama, T. *Synthesis* **2005**, 583.