Pergamon

Tetrahedron Letters 44 (2003) 8893–8895

TETRAHEDRON LETTERS

Conceptually new chiral tertiary C_2 symmetric diamines in asymmetric synthesis

Jean-Claude Kizirian,[a] Jean-Claude Caille[b] and Alexandre Alexakis[a,*]

[a]*Université de Genève, Department of Organic Chemistry, 30 quai Ernest Ansermet, CH-1211 Genève 4, Switzerland*
[b]*PPG-SIPSY, Z. I. La croix cadeau B.P. 79. 49242 Avrille Cedex, France*

Received 5 August 2003; revised 11 September 2003; accepted 19 September 2003

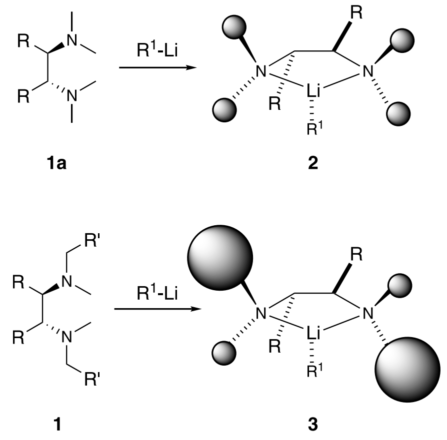
Abstract—New chiral diamines were prepared, based on the cyclohexane diamine core. The two different substituents on each nitrogen allow this heteroatom to become a stereogenic center upon chelation with a metal, such as lithium. The enantioselective addition of MeLi to imines, with ee's up to 68%, illustrates the validity of this concept.

Since the development of asymmetric synthesis, the design of new chiral ligands has become an important issue to improve enantioselectivity of organic reactions. Diamines have been widely used as efficient chiral inductors, particularly tertiary diamines, which have found applications in many asymmetric processes.[1] These types of reactions are particularly interesting when catalytic amounts of ligand can be used, and several examples have recently been reported in the literature.[2]

Our project has focused on the development of a conceptually new class of C_2 symmetric tertiary diamines in which the nitrogens can become a stereogenic center in the reactive species. In a cyclic chelated intermediate, the conformation of the nitrogens will be locked, and space discrimination will be determined by the *N*-substituents. It is expected that the bulky substituent on nitrogen would adopt a *trans* relationship with the R group of the carbon backbone. This situation will be possible when the diamine is associated with a metal, and this principle can be tested in all reactions where the two species are combined (Scheme 1).

Among the reactions available to validate our concept, we have chosen to study the addition of organolithium reagents to imines. Organolithium reagents are very useful nucleophiles in organic synthesis due to their wide availability, but to date only a few efficient catalytic asymmetric transformations have been described because of their high reactivity. Nucleophilic additions to imines have shown good levels of enantioselectivity,[3] but the development of new systems is still needed to improve those results.

Diamines are interesting tools for this purpose because they are easily available in enantiomerically pure form, many structural varieties are possible, and they are easily tunable with respect to the nitrogen substituents. Based on the cyclohexanediamine backbone we have synthesized ligands **1a–j** with different substitution at nitrogen, the goal being to make the nitrogen chiral in the chelated species, in order to obtain better spacial discrimination in the asymmetric reaction.

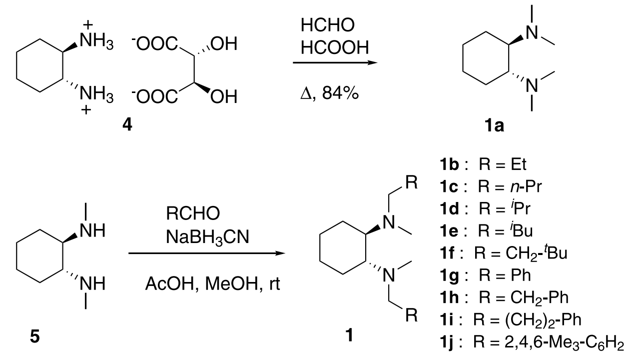


Scheme 1.

Keywords: asymmetric synthesis; diamines; organolithiums; imines; C_2 symmetry.

* Corresponding author. Tel.: +41 22 379 6522; fax: +41 22 379 3215; e-mail: alexandre.alexakis@chiorg.unige.ch

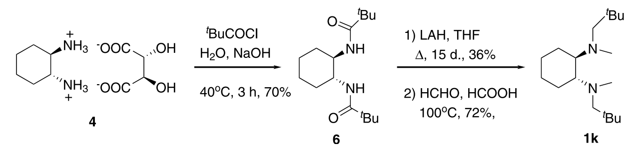
0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.09.171



Scheme 2.

Table 1. Reductive amination of *N*,*N*′-dimethyl-1,2-cyclohexanediamine producing ligands **1a**–**j**

Entry	Product	R	Yield (%)
1	**1b**	Et	68
2	**1c**	^{n}Pr	89
3	**1d**	^{i}Pr	72
4	**1e**	^{i}Bu	82
5	**1f**	CH_2^tBu	83
6	**1g**	Ph	49
7	**1h**	CH_2Ph	82
8	**1i**	CH_2CH_2Ph	75
9	**1j**	2,4,6-Me_3-C_6H_2	87

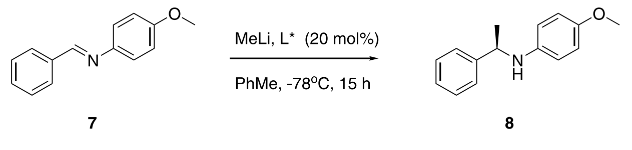


Scheme 3.

Table 2. Enantioselective addition of MeLi to imine **7** with ligands **1a** and **1g**

Entry	Ligand	Yield (%)	Ee (%)[a]
1	**1a** (2 equiv.)	78	20 (*R*)
2	**1g** (2 equiv.)	78	48 (*R*)
3	**1g** (20 mol%)	94	40 (*R*)

[a] Determined by supercritical fluid chromatography.



Scheme 4.

Starting directly from the tartaric acid salt of 1,2-cyclohexanediamine,[4] we have obtained ligand **1a** (R = H) on a large scale by an Eschweiler–Clark reaction while the other diamines (R ≠ H) have been prepared by reductive amination of *N*,*N*′-dimethyl-1,2-cyclohexanediamine[5] with the appropriate aldehyde (Scheme 2). The ligands **1b**–**j** were obtained in good yield after bulb-to-bulb distillations (Table 1).[6]

All the diamines **1a**–**j** were readily obtained, except when R was a bulky group (e.g. ligand **1k**, R = ^{t}Bu). Thus, ligand **1k** was prepared by a different route. The bis-amide **6** was prepared from cyclohexanediamine tartaric acid salt **4** with pivaloyl chloride in basic aqueous media.[5c] Reduction with lithium aluminium hydride in refluxing THF gave, after 2 weeks, the secondary diamine in moderate yield. Eschweiler–Clark bis-methylation occurred efficiently to produce ligand **1k** (Scheme 3).

As preliminary work, we have studied the addition of methyllithium to imine **7**. Many ligands have already been tested in this reaction, showing the lack of efficient diamine systems in this field.[3,7] The stoechiometric use of ligand **1a** and **1g** led to an increase in enantioselectivity which is consistent with our starting hypothesis. In **1a**, the nitrogens bear twice the same substituent (NMe_2), whereas in **1g**, the nitrogens act as new stereogenic centers (Table 2). As described by Tomioka,[7a] we have also observed that substoechiometric amounts of ligand (20%) are sufficient to catalyze the reaction at −78°C (Scheme 4).

Two series of ligands with alkyl chains have been used: the first one with a substituent β to the nitrogen (ligands **1d**, **1k**), and the second one with the substituent γ to the nitrogen (ligands **1e**, **1f**) (Table 3). The linear chain gives, as expected, only a slight improvement of ee (entries 1, 4). When a branching of this chain is introduced, a large difference in behavior is then observed. In the β series, the selectivity is strongly reduced even with an isopropyl substituent (entries 2, 3) while in the γ series, the substitution is beneficial and the best result is obtained with the more hindered ligand **1f** (entries 5, 6).

The influence, on the ee, of the distance of the steric hindrance from the nitrogen has also been examined with the phenyl series. We have moved the phenyl moiety away from the nitrogen by means of several methylene spacer units. The best ee was obtained with ligand **1h**, while with three methylene groups (**1i**), the selectivity decreased. It is interesting to note that ligand **1g** which belongs to the β series gives an increase in ee, in contrast to the other members of this series. However, when the hindered group is a mesityl, the selectiv-

Table 3. Enantioselective addition of MeLi to imine **7** with ligands substituted by an alkyl chain

Entry	Ligand (20 mol%)	Yield (%)	Ee (%)[a]
1	**1b**	93	24 (*R*)
2	**1d**	94	0
3	**1k**	76	0
4	**1c**	93	34 (*R*)
5	**1e**	94	53 (*R*)
6	**1f**	98	67 (*R*)

[a] Determined by supercritical fluid chromatography.

Table 4. Enantioselective addition of MeLi to imine **7** with ligands substituted by an aromatic chain

Entry	Ligand	Yield (%)	Ee (%)[a]
1	**1g** (1 equiv.)	78	48 (*R*)
2	**1g** (20%)	94	40 (*R*)
3	**1h** (20%)	98	68 (*R*)
4	**1h** (5%)	72	43 (*R*)
5	**1h** (1%)	62	32 (*R*)
6	**1i** (20%)	93	58 (*R*)
7	**1j** (20%)	95	0

[a] Determined by supercritical fluid chromatography.

ity disappears completely. This last result is consistent with the behavior of the ligands of the β series.

The amount of ligand **1h** was decreased from 100% to 5 mol% and 1 mol%. The product was still obtained with good conversion (Table 4, entries 4 and 5) but with significant erosion of selectivity (respectively 43% and 32%).

In conclusion, we have prepared a new class of diamine ligands that give interesting levels of enantioselectivity in the addition of methyllithium to an imine. We have checked that substoichiometric amounts of this type of ligand are sufficient to catalyze the reaction without large loss of selectivity. The improved results with our new ligands compared to the classic one, **1a**, demonstrate the validity of our initial hypothesis concerning the stereogenicity of the nitrogens when they bear different substituents. These results are very promising and the study of other reactions of the new ligands is in progress in our laboratory as well as the examination of the scope and limitations of this concept.

Acknowledgements

The authors wish to thank PPG-SIPSY for financial support.

References

1. (a) Snyder, J. K.; Tokles, M. *Tetrahedron Lett.* **1986**, *34*, 3951; (b) Tomioka, K.; Nakajima, M.; Koga, K. *J. Am. Chem. Soc.* **1987**, *109*, 6213; (c) Oishi, T.; Hirama, M. *J. Org. Chem.* **1989**, *54*, 5834; (d) Hirama, M.; Oishi, T.; Itô, S. *J. Chem. Soc., Chem. Commun.* **1989**, 665; (e) Fuji, K.; Tanaka, K.; Miyamoto, H. *Tetrahedron Lett.* **1992**, *33*, 4021; (f) Falorni, M.; Giacomelli, G.; Marchetti, M.; Culeddu, N.; Lardicci, L. *Tetrahedron: Asymmetry* **1991**, *4*, 287; (g) Mazaleyrat, J. P.; Cram, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 4585; (h) Kanoh, S.; Muramoto, H.; Maeda, K.; Kawaguchi, N.; Motoi, M.; Suda, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2244; (i) Tomioka, K.; Nakajima, M.; Koga, K. *Chem. Lett.* **1987**, 65; (j) Seebach, D.; Kalinowski, H. O.; Bastani, B.; Crass, G.; Daum, H.; Dörr, H.; DuPreez, N. P.; Ehrig, V.; Langer, W.; Nüssler, C.; Oei, H. A.; Schmidt, M. *Helv. Chim. Acta* **1977**, 301; (k) Colombo, L.; Gennari, C.; Poli, G.; Scolastico, C. *Tetrahedron* **1982**, *17*, 2725; (l) Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455; (m) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552; (n) Li, X.; Schenkel, L. B.; Kozlowski, M. *Org. Lett.* **2000**, *7*, 875; (o) Würthwein, E. U.; Behrens, K.; Hoppe, D. *Chem. Eur. J.* **1999**, *12*, 3459; (p) Matsubara, S.; Hashimoto, Y.; Okano, T.; Utimoto, K. *Synlett* **1999**, *9*, 1411.
2. (a) Li, X.; Yang, J.; Kozlowski, M. *Org. Lett.* **2001**, *8*, 1137; (b) Nakajima, M.; Miyoshi, I.; Kanayama, K.; Hashimoto, S. I.; Noji, M.; Koga, K. *J. Org. Chem.* **1999**, *64*, 2264; (c) Oriyama, T.; Taguchi, H.; Terakado, D.; Sano, T. *Chem. Lett.* **2002**, 26; (d) Tanner, D.; Johansson, F.; Harden, A.; Andersson, P. G. *Tetrahedron* **1998**, *54*, 15731; (e) Gamez, P.; Fache, F.; Lemaire, M. *Tetrahedron: Asymmetry* **1995**, *3*, 705.
3. (a) Andersson, P. G.; Johansson, F.; Tanner, D. *Tetrahedron* **1998**, *54*, 11549; (b) Denmark, S. E.; Nakajima, N.; Niçaise, O. *J. Am. Chem. Soc.* **1994**, *116*, 8797; (c) Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron: Asymmetry* **1993**, *7*, 1603.
4. Larrow, J. F.; Jacobsen, E. *Org. Syn.* **1998**, *75*, 1.
5. (a) Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754; (b) Alexakis, A.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1992**, *57*, 1224; (c) Alexakis, A.; Chauvin, A.-S.; Stouvenel, R.; Vrancken, E.; Mutti, S.; Mangeney, P. *Tetrahedron: Asymmetry* **2001**, *12*, 1171.
6. All novel compounds gave satisfactory spectroscopic and analytical data. For compound **1d**, see: Hoffman, R. W.; Klute, W. *Chem. Eur. J.* **1996**, *2*, 694.
7. (a) Inoue, I.; Shindo, M.; Koga, K.; Kanai, M.; Tomioka, K. *Tetrahedron: Asymmetry* **1995**, *10*, 2527; (b) Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875; (c) Arrasate, S.; Lete, E.; Sotomayor, N. *Tetrahedron: Asymmetry* **2001**, *12*, 2077.