Tetrahedron Letters 52 (2011) 1348–1350

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Homocoupling of aldimines mediated by zirconocene: synthesis of vicinal diamines and imidazolidines

Mohamad Soueidan [a], Florence Hélion [a,*], Jean-Louis Namy [a], Jan Szymoniak [b]

[a] Equipe de Catalyse Moléculaire, CNRS (UMR 8182), ICMMO, Bât 420, Université Paris-Sud, 91405 Orsay, France
[b] Institut de Chimie Moléculaire de Reims, CNRS (UMR 6229), Université de Reims, 51687 Reims Cedex 2, France

ARTICLE INFO

Article history:
Received 4 October 2010
Revised 12 January 2011
Accepted 14 January 2011
Available online 20 January 2011

Keywords:
Lanthanides
Zirconocene
Aldimine coupling
Imidazolidine

ABSTRACT

The reductive coupling of imines in the presence of the lanthanide-originated zirconocene equivalent allows the synthesis of vicinal diamines or imidazolidines under mild conditions in good yields with high diastereoselectivity.

The pinacol coupling of imines to vicinal diamines is an important reaction in organic synthesis because vicinal diamines[1] constitute a class of compounds that have found widespread applications as medicinal products.[2] Furthermore, some vicinal diamines are used as chiral ligands in asymmetric synthesis[3] and as chiral resolving agents.[4] A variety of reductants[5] including active metals have been developed for this purpose: for example, samarium(II) iodide,[5a–c] indium,[5d] Pb/Al bimetal redox system,[5e] Zn–Cu couple,[5f] niobium,[5g] LVT (low valent titanium).[5h] In all cases, the diastereoselectivity of the reaction (*dl and meso*) was moderate.

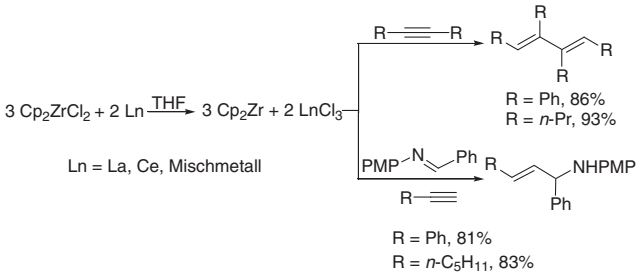
Recently we have explored the potential of $Cp_2Zr(II)$,[6–8] generated under mild conditions by reduction of Cp_2ZrCl_2 with a pure lanthanide metal (La) or Mischmetall (an alloy of Ce, La, Nd and Pr), to induce coupling reactions (Scheme 1).[9]

Herein, we report that the La-generated $Cp_2Zr(II)$ can be applied to the synthesis of vicinal diamines[1] and imidazolidines.[10] These products were obtained in good yields with high diastereoselectivity by reductive couplings of imines under mild conditions.

The optimized procedure for intermolecular reductive coupling of *N*-aryl or *N*-alkyl imines is as follows: a mixture of Cp_2ZrCl_2 (0.5 mmol) and the powdered La (0.66 mmol) was stirred at 50 °C in 4 mL of THF until a deep red colour appeared (10 min). A solution of the imine (1 mmol) in 1 mL of THF was then added, and the reaction was carried out at 50 °C for 12 h. The mixture was then cooled to room temperature, hydrolysed under argon by HCl 0.1 M and extracted with dichloromethane. The chromatographic purification of the crude product afforded vicinal diamines **1**.

Results are presented in Table 1. 1,2-Diamines **1** were obtained in good yields (70–95%) and with excellent to total diastereoselectivity: (*dl*)-isomers were obtained as major products (*dl*/*meso*: 91/9–100/0). In no case was the reduction of aldimines to amines (R^2CH_2–NHR^1) observed. In contrast, coupling of a *N*-aryl ketimine such as phenyl-(1-phenyl-ethylidene)-amine (Table 1, entry 6) under the same conditions was not observed. Only *N*-phenyl-1-phenylethanamine **2f** was obtained in 30% yield. Unfortunately, attempts to have a procedure catalytic in zirconium failed.[11]

To explain these results, we propose a mechanistic rationale involving the initial formation of the zirconaaziridine **A** and the successive aldimine (R^3 = H) insertion into **A** affording the azazirconacycle **B** stereoselectively. Subsequently, the hydrolysis of **B** gives diamine (*d,l*)-**1**. With ketimines (Table 1, entry 6), the steric

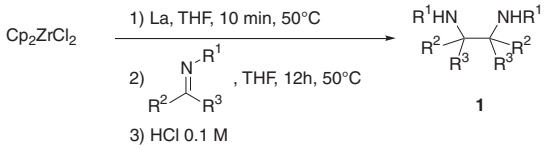


Scheme 1. Coupling reactions induced by $Cp_2Zr/LnCl_3$.

* Corresponding author. Tel.: +33 1 69 15 47 43; fax: +33 1 69 15 46 80.
E-mail address: florence.helion@u-psud.fr (F. Hélion).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.01.075

Table 1
Coupling of *N*-aryl imines: formation of vicinal diamines **1**



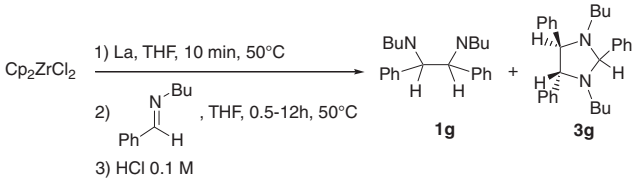
Entry	R^1	R^2	R^3	Products, yield[a] (%) (*dl*/*meso*)[b]
1	Ph	Ph	H	**1a**, 70 (91/9)
2	Ph	*p*-MeO–C_6H_4	H	**1b**, 76 (94/6)
3	Ph	*p*-Me_2N–C_6H_4	H	**1c**, 95 (94/6)
4	Ph	*p*-Me–C_6H_4	H	**1d**, 94 (95/5)
5	Ph	Naphthyl	H	**1e**, 70 (100/0)
6	Ph	Ph	Me	**1f**, 0[c]
7	*n*-C_4H_9	Ph	H	**1g**, 90 (100/0)
8	*n*-C_5H_{11}	Ph	H	**1h**, 85 (90/10)
9	*n*-C_3H_7	*p*-Me–C_6H_4	H	**1i**, 90 (100/0)
10	*n*-C_3H_7	*p*-MeO–C_6H_4	H	**1j**, 85 (100/0)

[a] Isolated yields: entries 1–6: purification by chromatography, entries 7–10: purification by Celite® filtration.
[b] Ratio determined by ^{1}H NMR.
[c] Only 50% of phenyl-(1-phenyl-ethylidene)-amine was converted to *N*-phenyl-1-phenylethanamine **2f** (isolated yield 30%).

bulk would prevent the formation of **B**[12] from A. Interestingly, the formation of **A** is supported by a partial (50%) incorporation of deuterium into **2f** after deuterolysis. Besides, the reaction of a *N*-trimethylsilylzirconaaziridine with an *N*-trimethylsilylimine gives the expected (*d*,*l*)-diamine as a major product (isolated yield 78%, *dl*/*meso*: 98/2).[13] Moreover, it is generally admitted that radical coupling of imines gives *meso*-diamines as major products.[5k,o,14] Therefore, the formation of the (*d*,*l*)-vicinal diamine **1** with an excellent stereoselectivity gives support to the mechanistic Scheme 2.

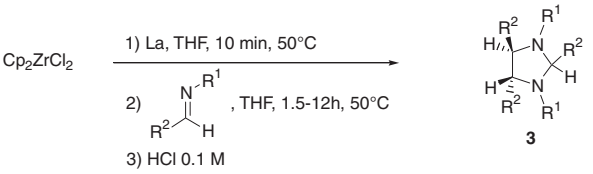
The monitoring of the benzylidene–phenylamine coupling reaction showed a rapid conversion to diamine **1a** (after 20 min, 80% conversion was observed, based on ^{1}H NMR analysis of the crude product). Nevertheless, the total conversion was obtained after 12 h. Unexpectedly, a similar monitoring with *N*-alkyl aldimines such as benzylidene–butyl-amine showed that imidazolidine **3g** was obtained together with diamine **1g** (Scheme 3). The ratio diamine **1g**/imidazolidine **3g** gradually increased, **1g** being the major product after the 4 h-reaction time. Analogous observations have been reported recently.[15]

Synthesis of imidazolidines **3** was optimized by using 1.5 mmol of alkyl-imines instead of 1 mmol as described above. Hydrolysis was completed after 12 h. Results are collected in Table 2. It should be mentioned that *N*-alkyl aldimines were converted to imidazolidines **3** in good yields (70–85%) except for **3o**. In all cases only *dl*



Scheme 3. Reaction of benzylidene–butylamine.

Table 2
Formation of imidazolidines **3**



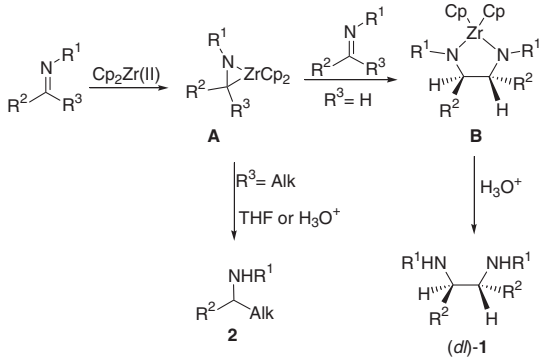
Entry	R^1	R^2	*T* (h)	Products, yield (%)
1	*n*-C_4H_9	Ph	1.5	**3g**, 83
2	*n*-C_5H_{11}	Ph	1.5	**3h**, 82
3	*n*-C_3H_7	*p*-Me–Ph	1.5	**3i**, 85[a]
4	*n*-C_3H_7	*p*-MeO–Ph	1.5	**3j**, 75
5	*n*-C_3H_7	Ph	1.5	**3m**, 80
6	*n*-C_3H_7	Furanyl	1.5	**3n**, 78
7	*n*-C_3H_7	Pyridinyl	12	**3o**, 70

[a] 5% of the diamine **1i** was observed in the crude product (determined by ^{1}H NMR).

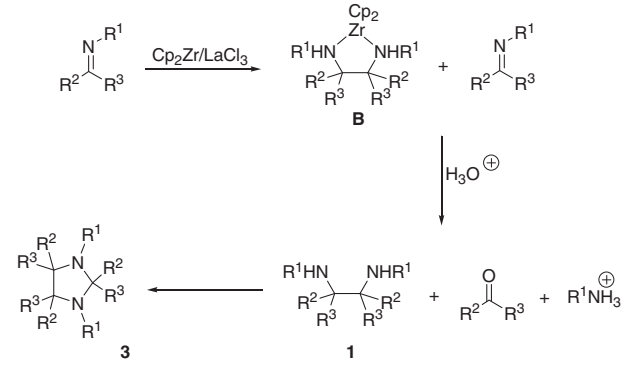
isomers were obtained.[16] It would be noticed that diazazirconacyclopentanes **B** do not react directly with additional equivalent of imines since imidazolidines **3** are obtained in very low yields when reactions are performed for a long period but with a short-time hydrolysis. Besides, it is known that acidic hydrolysis conditions are compatible with the hydrolysis of *N*-alkylimines to aldehydes and the formation of imidazolidines.[15b,17] Consequently, the formation of imidazolidines **3** can be rationalized as follows: imines are partly converted (1.5 mmol of imine for 0.5 mmol of zirconocene) to diazazirconacyclopentanes **B**. During hydrolysis, **B** gives corresponding diamines **1** and residual *N*-alkyl aldimines are hydrolysed to aldehydes, thus diamines **1** react slowly (12 h) with aldehydes to give corresponding imidazolidines **3** (Scheme 4).

An additional experiment showed that under hydrolysis conditions applied, metallic species (from Zr or La) were not involved in the reaction of diamines with aldehydes to give imidazolidines **3**. Since a mixture of diamine **1g**, benzaldehyde, HCl 0.1 M in THF, yields in a 12 h-reaction time the imidazolidine **3g**.

It can be noticed that during monitoring the formation of five-membered ring aminals **3** from *N*-aryl aldimines was not observed,



Scheme 2. Mechanistic proposal for the synthesis of amines **1** and **2**.



Scheme 4. Mechanistic proposal for synthesis of imidazolidines **3**.

probably due to the lesser sensitivity to hydrolysis. When reactions with *N*-aryl aldimines were stopped at an early stage, *N*-aryl aldimines were recovered after hydrolysis. Under the same conditions *N*-alkyl aldimines were not recovered.

In conclusion, dimerization of aromatic imines was carried out by using $Cp_2Zr(II)$ to afford the corresponding vicinal diamines **1** in excellent yields and high diastereoselectivity. In addition, we found a simple method to prepare only *dl*-isomer five-membered ring aminals **3** in good yields. These products are interesting in synthesis as precursors of chiral imidazolinium salts.[18] Besides they constitute important parts of biologically active compounds.[17]

Acknowledgements

We thank the CNRS and the Ministère de l'Enseignement Supérieur et de la Recherche for their financial support.

References and notes

1. (a) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580–2627; (b) Robertson, G. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pinacol Coupling Reaction-sin; Pergamon Press: Oxford, 1991; Vol. 3, pp 563–611.
2. (a) Li, G.; Chang, H. T.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, *35*, 451–454; (b) Reedijk, J. *Chem. Commun.* **1996**, 801–806; (c) Pashini, A.; Zunino, F. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 615–624.
3. (a) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97–102; (b) Seyden Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley & Sons, Inc.: New York, 1995. p 61.
4. (a) Fulwood, R.; Parker, D. *J. Chem. Soc., Perkin Trans. 2* **1994**, 57–64; (b) Alexakis, A.; Frutos, J. C.; Mutti, S.; Mangeny, P. *J. Org. Chem.* **1994**, *59*, 3326–3334.
5. (a) Enholm, E. J.; Forbes, D. C.; Holub, D. P. *Synth. Commun.* **1990**, *20*, 981–987; (b) Liao, P.; Huang, Y.; Zhang, Y. *Synth. Commun.* **1997**, *27*, 1483–1486. and references cited therein; (c) Aurrecoechea, J. M.; Fernández-Acebes, A. *Tetrahedron Lett.* **1992**, *33*, 4763–4766; (d) Kalyanam, N.; Venkateswara Rao, G. *Tetrahedron Lett.* **1993**, *34*, 1647–1648; (e) Tanaka, H.; Dhimane, H.; Fujita, H.; Ikemoto, Y.; Torii, S. *Tetrahedron Lett.* **1988**, *29*, 3811–3814; (f) Shimizu, M.; Iida, T.; Fujisawa, T. *Chem. Lett.* **1995**, 609–610; (g) Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 3152–3154; (h) Mangeney, P.; Tejero, T.; Alexakis, A.; Grosjean, F.; Normant, J. *Synthesis* **1988**, 255–257; (i) Tanaka, H.; Nakahara, T.; Dhimane, H.; Torii, S. *Synlett* **1989**, 51–52; (j) von Betschart, C.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 2215–2231; (k) Eisch, J. J.; Kaska, D. D.; Peterson, C. J. *J. Org. Chem.* **1966**, *31*, 453–456; (l) Jones, D. S.; Srinivasan, A.; Kasina, S.; Fritzberg, A. R.; Wilkening, D. W. *J. Org. Chem.* **1989**, *54*, 1940–1943. and references cited therein; (m) Smith, J. G.; Ho, I. *J. Org. Chem.* **1972**, *37*, 653–656; (n) Selvakumar, K.; Harrod, J. F. *Angew. Chem., Int. Ed.* **2001**, *40*, 2129–2131; (o) Rangareddy, K.; Selvakumar, K.; Harrod, J. F. *J. Org. Chem.* **2004**, *69*, 6843–6850.
6. (a)For reviews, see: *Titanium and Zirconium in Organic Synthesis*; Marrek, I., Ed.; Wiley-VCH: Weinheim, 2002; (b) Negishi, E. *Dalton Trans.* **2005**, 827–848; (c)*New Aspects of Zirconium Containing Organic Compounds*; Marek, I., Ed.Topics in Organometallic Chemistry; Springer: Berlin, 2005; Vol. 10, (d)*Metallocenes in Regio-and Stereoselective Synthesis In Topics in Organometallic Chemistry*; Takahashi, T., Ed.; Springer: Berlin, 2005; Vol. 8, Negishi, T. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 755–769.
7. Earlier works employed Na or Mg as reductants typically in the presence of alkynes or bipyridine, see for example: (a) Watt, G. W.; Drummond, F. O., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 826–828; (b) Wailes, P. C.; Weigold, H. *J. Organomet. Chem.* **1971**, *28*, 91–95.
8. Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829–2832.
9. Denhez, C.; Médégan, S.; Hélion, F.; Namy, J.-L.; Vasse, J.-L.; Szymoniak, J. *Org. Lett.* **2006**, *8*, 2945–2947.
10. (a) Viso, A.; Fernandez de la Pradilla, R.; Garcia, A.; Guerrero-Strachan, C.; Alonso, M.; Tortosa, M.; Flores, A.; Martinez-Ripoll, M.; Fonseca, I.; André, I.; Rodriguez, A. *Chem. Eur. J.* **2003**, *9*, 2867–2876; (b)Duhamel, L., Patai, S., Eds.The Chemistry of Amino, Nitroso and Nito Compounds and their Derivatives; Wiley: New York, 1982; Vol. 2, pp 849–890.
11. Soueidan, M.; Hélion, F.; Namy, J.-L.; Szymoniak, J. *Tetrahedron Lett.* **2010**, *51*, 115–117.
12. Talukdar, S.; Banerji, A. *J. Org. Chem.* **1998**, *63*, 3468–3470.
13. Buchwald, S. L.; Watson, B. T.; Wannamaker, M. W.; Dewan, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 4486–4494.
14. (a) Machrouhi, F.; Namy, J.-L. *Tetrahedron Lett.* **1999**, *40*, 1315–1318; (b) Nishino, T.; Nishiyama, Y.; Sonoda, N. *Heteroat. Chem.* **2002**, *13*, 131–135; (c) Hanato, B.; Ogawa, A.; Hirao, T. *J. Org. Chem.* **1998**, *63*, 9421–9424.
15. (a) Zhu, Z.; Wang, J.; Zhang, Z.; Xiang, X.; Zhou, X. *Organometallics* **2007**, *26*, 2499–2500; (b) Grat, A.; Sinault, L.; Fusaro, M. B.; Vallet, A.-L.; Seu, C.; Kilgore, J. L.; Baum, M. M. *Organometallics* **2010**, *29*, 1997–2000.
16. *Materials and methods*. All reactions were performed under an atmosphere of argon using standard Schlenk techniques. Prior to use tetrahydrofuran was distilled under argon from sodium benzophenone ketyl. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Brucker 360 AVANCE. Chemical shifts are reported in delta (δ) units, expressed in parts per million (ppm). ^{13}C NMR spectra were recorded in $CDCl_3$ on a Brucker 250 DPX. Chemical shifts are reported in delta (δ) units, expressed in parts per million (ppm). Coupling constants are expressed in hertz (Hz). High-resolution mass spectra (HRMS) were obtained with a MAT-95-S Finnigan. GC–MS were obtained with a DSQ-Thermo electron instrument. *2,4-(Di-furane-2-yl)-5-(furane-3-yl)-1,3-dipropylimidazolidine* (**3n**): Purification: eluent pentane/EtOAc (90:10). Yellow oil. Yield (78%). ^{1}H NMR ($CDCl_3$): δ 0.70 (t, J = 7.4, 3H), 0.72 (t, J = 7.4, 3H), 1.20–1.50 (m, 4H), 1.90 (m, 1H), 2.21 (m, 1H), 2.76 (m, 2H), 4.18 (d, J = 7.4, 1H), 4,29 (d, J = 7.4, 1H), 4.89 (s, 1H), 6.20–6.50 (m, 6H), 7.35 (d, J = 1.7, 1H), 7.41 (d, J = 2.1, 1H), 7.43 (d, J = 1.9, 1H). ^{13}C NMR ($CDCl_3$): δ 155.7, 155.2, 152.5, 142.3, 142.0, 141.8, 110.0, 109.8, 109.2, 107,1, 78.1, 65.5, 63.5, 56.2, 49.2, 21.8, 20.9, 11.7, 11.5. HRMS: [M$^+$] calcd for $C_{21}H_{26}N_2O_3$+[Na$^+$] 377.1836; found, 377.1846. *1,3-Dipropyl-2,4,5-dipyridinylimidazolidine* (**3o**): Purification: eluent pentane/EtOAc (90:10). Incolored oil. Yield (70%). ^{1}H NMR ($CDCl_3$): δ 0.56 (t, J = 7.4, 3H), 0.61 (t, J = 7.4, 3H), 1.15 (m, 4H), 1.95–2.15 (m, 2H), 2.45–2.70 (m, 2H), 3.86 (d, J = 7.9, 1H), 4.09 (d, J = 7.9, 1H), 5.05 (s, 1H), 7.25 (m, 2H), 7.38 (dd, J = 7.9, J = 4.7, 1H), 7.56 (dt, J = 7.9, J = 2.0, 1H), 7.62 (dt, J = 7.9, J = 2.0, 1H), 7.96 (dt, J = 7.9, J = 2.0, 1H), 8.38 (d, J = 2.2, 1H), 8.43 (d, J = 2.2, 1H), 8.52 (dd, J = 4.7, J = 1.8, 1H), 8.54 (dd, J = 4.7, J = 1.8, 1H), 8.61 (dd, J = 4.7, J = 1.8, 1H), 8.80 (d, J = 2.2, 1H). ^{13}C NMR ($CDCl_3$): δ 150.6, 150.1, 149.6, 149.5, 149.4, 137.8, 136.9, 135.9, 135.2, 135.1, 134.6, 123.4, 123.2, 83.1, 74.4, 72.7, 55.2, 48.0, 21.6, 21.1, 11.5, 11.4. HRMS: [M$^+$] calcd for $C_{24}H_{29}N_5$+[Na$^+$] 410.2315; found, 410.2322.
17. (a) Kallen, R. G.; Jencks, W. P. *J. Biol. Chem.* **1966**, *241*, 5851–5864; (b) Benkovic, S. J.; Benkovic, P. H.; Comfort, D. R. *J. Am. Chem. Soc.* **1969**, *91*, 5270–5279; (c) Benkovic, S. J.; Benkovic, P. H.; Chrzanowski, R. *J. Am. Chem. Soc.* **1970**, *92*, 523–528.
18. Jurčík, V.; Wilhelm, R. *Tetrahedron: Asymmetry* **2006**, *17*, 801–810.