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Diastereoselective Access to Nonracemic 2-*cis*-Substituted and 2,6-*cis*-Disubstituted Piperidines

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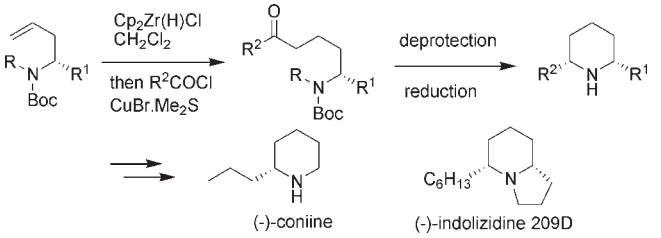
ABSTRACT



Access to nonracemic amino ketones via a hydrozirconation/transmetalation/acylation sequence applied to Boc-protected 1-aminobut-3-enes is presented. This method was applied to the stereoselective synthesis of cyclic imines (or iminiums) which were diastereoselectively converted into 2-*cis*-substituted and 2,6-*cis*-disubstituted piperidines. The potential of this approach in the field of alkaloid synthesis was illustrated by the synthesis of (−)-coniine and (−)-indolizidine 209D. Furthermore, access to indolizidines bearing a quaternary center could also be envisioned through this strategy.

Omnipresent in both naturally occurring and biologically active molecules,[1] nitrogen-containing heterocycles are crucial synthetic targets. Thus, efforts to develop new methodologies for building this class of molecules are of continuous interest.[2] Classical disconnection implies N−C bond-forming condensation or displacement as the ring-closure step. Such a strategy typically involves the prerequisite generation of an electrophilic site onto substrates bearing an amine precursor. Emerging from this approach, cross-metathesis[3] and hydroformylation,[4] applied to unsaturated amines, allow a general access to several N-heterocycles.

We have previously described the preparation of 2-substituted pyrrolidines via hydrozirconation of homoallylic amines. The resulting zirconocenes **I** are subsequently converted into the corresponding iodo intermediates **II**,

(1) (a) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon Press: New York, 1999; Vol. 13, pp 1−161. (b) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679–3681. (c) Pu, X.; Ma, D. *J. Org. Chem.* **2003**, *68*, 4400–4405. (c) Vazzana, I.; Budriesi, R.; Terranova, E.; Ioan, P.; Ugenti, M. P.; Tasso, B.; Chiarini, A.; Sparatore, F. *J. Med. Chem.* **2007**, *50*, 334–343.

(2) (a) Cossy, J.; Vogel, P. In *Studies in Natural Products Chemistry, Part H*; Atta-ur-Raman, Ed.; Elsevier: Amsterdam, 1993; Vol. 12, pp 275−363. (b) Angle, S. R.; Breittenbucher, J. G. In *Studies in Natural Products Chemistry, Part J*; Atta-ur-Raman, Ed.; Elsevier: Amsterdam, 1995; Vol. 16, pp 453−502. (c) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1791–1813. (d) Guilloteau-Bertin, B.; Comèpre, D.; Gil, L.; Marazano, C.; Das, B. C. *Eur. J. Org. Chem.* **2000**, 1391–1399. (e) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953–2989. (f) Davis, F. A.; Rao, A.; Carroll, P. J. *Org. Lett.* **2003**, *5*, 3855–3857. (g) Fujita, K.; Fujii, T.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 3525–3528. (h) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701–1729. (i) Davis, F. A.; Zhang, J.; Li, Y.; Xu, H.; DeBrosse, C. *J. Org. Chem.* **2005**, *70*, 5413–5419. (j) Amat, M.; Escolano, C.; Lozano, O.; Gomez-EsquéA.; Griera, R.; Molins, E.; Bosch, J. *J. Org. Chem.* **2006**, *71*, 3804–3815. (k) Van Brabandt, W.; Van Landeghem, R.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 1105–1108. (l) Fadel, A.; Lahrache, N. *J. Org. Chem.* **2007**, *72*, 1780–1784. (m) Lebrun, S.; Couture, A.; Deniau, E.; Grandclaudon, P. *Org. Lett.* **2007**, *9*, 2473–2476. (n) Noël, R.; Vanucci-Bacqué, C.; Fargeau-Bellassoued, M.-C.; Lhommet, G. *Eur. J. Org. Chem.* **2007**, 476–486.

(3) (a) Liu, H.; Su, D.; Cheng, G.; Xu, J.; Wang, X; Hu, Y. *Org. Biomol. Chem.* **2010**, *8*, 1899–1904. (b) Bates, R. W.; Lu, Y. *J. Org. Chem.* **2009**, *74*, 9460–9465.

(4) (a) Airiau, E.; Spangenberg, T.; Girard, N.; Schoenfelder, A.; Salvadori, J.; Taddei, M.; Mann, A. *Chem.—Eur. J.* **2008**, *14*, 10938–10948. (b) Spangenberg, T.; Breit, B.; Mann, A. *Org. Lett.* **2009**, *11*, 261–264. (c) Airiau, E.; Girard, N.; Mann, A.; Salvadori, J.; Taddei, M. *Org. Lett.* **2009**, *11*, 5314–5317. (d) Airiau, E.; Spangenberg, T.; Girard, N.; Breit, B.; Mann, A. *Org. Lett.* **2010**, *12*, 528–531. (e) Arena, G.; Zill, N.; Salvadori, J.; Girard, N.; Mann, A.; Taddei, M. *Org. Lett.* **2011**, *13*, 2294–2297.

(5) (a) Ahari, M.; Joosten, A.; Vasse, J.-L.; Szymoniak, J. *Synthesis* **2008**, 61–68. (b) Delaye, P.-O.; Pradhan, T. K.; Lambert, E.; Vasse, J.-L.; Szymoniak, J. *Eur. J. Org. Chem.* **2010**, 3395–3406.

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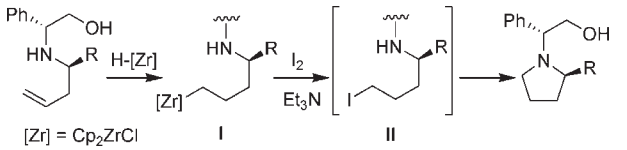
which spontaneously cyclize to afford the pyrrolidines (Scheme 1).[5]

Scheme 1. Hydrozirconation/Iodination-Mediated Synthesis of Pyrrolidines



When considering the aminozirconocene **I** involved in the above strategy, one may distinguish a bis-nucleophilic entity, opening the way to coupling with divalent electrophiles (Figure 1). Thus, applied to homoallylic amines, the sequence hydrozirconation/coupling with an acyl chloride would provide an alternative to the Rh-catalyzed hydroacylation.[6] In turn, such a strategy would allow an access to substituted piperidines by successive reaction of the C- and the N-poles of a 4-aminobutylzirconocene (Figure 1).

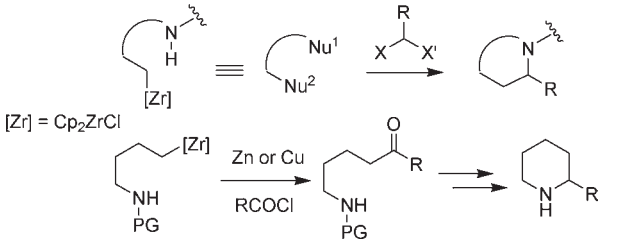


Figure 1. Approach toward piperidines.

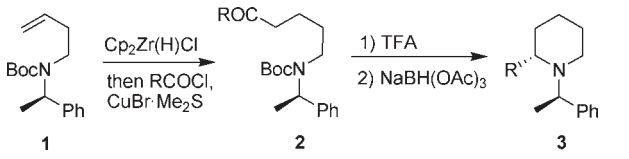
In this paper, we present a synthetic methodology that allows the preparation of enantiopure piperidines via a sequential hydrozirconation/acylation followed by an intramolecular reductive amination.

The feasibility of the approach was first tested starting from the *N*-Boc-protected amine **1**.[7] In that case, a complete hydrozirconation of the substrate was obtained using 1.1 equiv of the Schwartz reagent.

Although zirconocenes are easily converted into the corresponding halides, they are inert toward most classical electrophiles. The transmetalation typically to Al,[8] Zn,[9] or Cu[10] is a method of choice to readily form more nucleophilic organometallic species.[11] Therefore, benzoyl chloride was added in the presence of a transmetalating agent to perform the acylation.

While the use of $AlCl_3$, $ZnBr_2$, or $Zn(OTf)_2$ was unsuccessful, both CuI and $CuBr\cdot SMe_2$ afforded the expected product. Acylation of alkylzirconocenes is reported to require a catalytic amount of copper salt, but in our case, best results were obtained with an equimolar loading of $CuBr\cdot SMe_2$. Several acyl chlorides have been tested in these optimal conditions, leading to the corresponding amino ketones **2** (Table 1). Finally, Boc-deprotection under standard conditions, followed by reductive amination using $NaBH(OAc)_3$, gave the 2-substituted piperidines **3** with generally good diastereoselectivities.[12]

Table 1. Synthesis of Piperidines **3**



entry	R	**2** (yield, %)	**3** (yield, %)[a]	dr[b]
1	Ph	**2a** (71)	**3a** (69)	13:1
2	2-BrC_6H_4	**2b** (70)	**3b** (53)	4:1
3	*n*-C_3H_7	**2c** (56)	**3c** (69)	12:1
4	*n*-C_4H_9	**2d** (62)	**3d** (78)	16:1
5	*c*-C_3H_5	**2e** (53)	**3e** (69)	15:1

[a] Yields refer to the major isomer isolated in the diastereomerically pure form. [b] Determined by ^1H NMR on the crude mixture.

Thus, piperidines **3a**–**e** bearing an aryl (entries 1 and 2) or an alkyl group (entries 3 and 4) at the 2-position were obtained in good yield. Most compounds were obtained in a highly diastereoselective manner, except **3b**. Nevertheless, all compounds could be isolated in diastereomerically pure form after column chromatography.

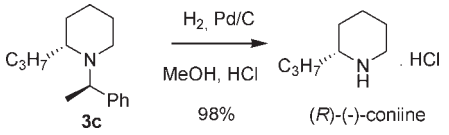
Good diastereoselectivity in this reaction was previously observed[13] and postulated to result from an hydride addition occurring onto the more accessible face of an iminium

(6) Kim, G.; Lee, E.-j *Tetrahedron: Asymmetry* **2001**, *12*, 2073–2076.
(7) For the preparation of **1**, see the Supporting Information.
(8) (a) Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1977**, *99*, 638–640. (b) Zhao, C.; Li, P.; Cao, X.; Xi, Z. *Chem.—Eur. J.* **2002**, *8*, 4292–4298.
(9) (a) Wipf, P.; Nunes, R. L. *Tetrahedron* **2004**, *60*, 1369–1379. (b) Wipf, P.; Pierce, J. G. *Org. Lett.* **2005**, *7*, 3537–3740. (c) Wipf, P.; Kendall, C. *Chem.—Eur. J.* **2002**, *8*, 1779–1784.
(10) (a) Wipf, P. *Synthesis* **1993**, 537–557. (b) Wipf, P.; Takahashi, H. *J. Chem. Soc., Chem. Commun.* **1996**, 2675–2676. (c) Yoshifuji, M.; Loots, M.; Schwartz, J. *Tetrahedron Lett.* **1997**, *15*, 1303–1306. (d) Sato, A.; Ito, H.; Yamaguchi, Y.; Taguchi, T. *Tetrahedron Lett.* **2000**, *41*, 10239–10243. (e) Doherty, S.; Knight, J. G.; Robins, E. G.; Scanlan, T. H.; Champkin, P. A.; Clegg, W. *J. Am. Chem. Soc.* **2001**, *123*, 5110–5111. (f) Sato, A.; Ito, H.; Okada, M.; Nakamura, Y.; Taguchi, T. *Tetrahedron Lett.* **2005**, *46*, 8381–8383.
(11) For zirconocene transmetalation to others metals, see: (a) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853–12910. (b) Lipshutz, B. H.; Pfeiffer, S. S.; Noson, K.; Tomioka, T. *Titanium and Zirconium in Organic Synthesis*; Wiley: Weinheim, 2002. (c) Wipf, P.; Kendall, C. *Topics in Organometallic Chemistry*; Takahashi, T., Ed.; Springer: Berlin, 2004; Vol. 8, p 1.
(12) The stereochemistry of **3a** was assigned by comparison with known isomers: Fujita, K-I; Fujii, T.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 3525–3528.
(13) Adriaenssens, L. V.; Austin, C. A.; Gibson, M.; Smith, D.; Hartley, R. C. *Eur. J. Org. Chem.* **2006**, 4998–5001.
(14) Hates, J. F.; Shipman, M.; Twin, H. *Chem. Commun.* **2001**, 1784–1785. (b) Girard, N.; Pouchain, L.; Hurvois, J.-P.; Moinet, C. *Synlett* **2006**, 1679–1682.

that adopts a conformation minimizing the steric interactions.[14]

Such an approach constitutes a simple access toward enantiomerically pure free piperidines as exemplified by the synthesis of (*R*)-(−)-coniine[4e,15] obtained by hydrogenolysis[16] of **3c** (Scheme 2).

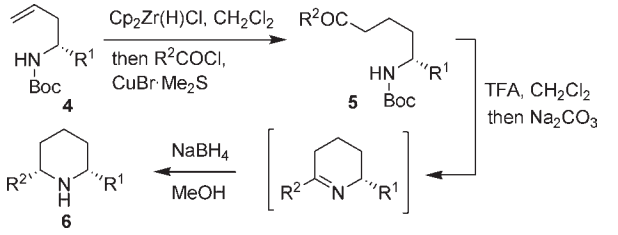
Scheme 2. Synthesis of (−)-Coniine



To extend the potential of the method, we next turned our attention toward the synthesis of 2,6-disubstituted piperidines. For that purpose, a series of enantiomerically pure *N*-Boc-protected 2-substituted homoallylic amines **4** were prepared according to a known procedure.[17]

The hydrozirconation/acylation sequence was next applied to **4** using 2 equiv of the Schwartz reagent, since one is consumed by the NH-carbamate, and 2 equiv of the copper salt.

Table 2. Synthesis of Piperidines **6**



entry	R^1	R^2	**5** (yield, %)	**6**[b] (yield, %)	dr
1[a]	Ph	Me	**5a** (69)	**6a** (72)	>19:1
2[a]	2-OMeC_6H_4	Ph	**5b** (45)	**6b** (73)	>19:1
3	Ph	Ph	**5c** (70)	**6c** (77)	>19:1
4	Ph	3-ClC_6H_4	**5d** (50)	**6d** (87)	>19:1
5	Ph	2-BrC_6H_4	**5e** (56)	**6e** (81)	>19:1
6	Ph	*c*-C_3H_5	**5f** (51%)	**6f** (88)	>19:1
7[c]	Ph	*i*-Bu	**5g** (72)	**6g** (73)	>19:1
8	*i*-Bu	Ph	**5h** (63)	*ent*-**6g** (70)	6.5:1
9	(*E*)-PhCH=CH	Ph	**5i** (56)	**6i** (47)	4:1
10	$(CH_2)_3$-OBn	*n*-C_6H_{13}	**5j** (47)	**6j** (58)	5.5:1

[a] Racemic material was used as substrate. [b] Yields refer to the major isomer isolated in the diastereomerically pure form. [c] CuI was used as the transmetalating agent.

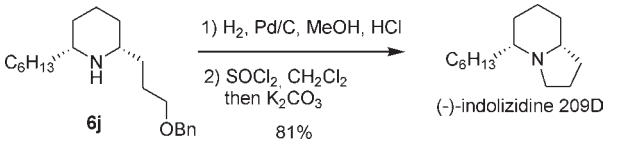
The sequence appears as quite general to afford diversely *cis*-2,6-disubstituted piperidines (Table 2).[18] Thus, piperidines substituted by two aryl groups (entries 2−5), an aryl and an aliphatic group (entries 1 and 6−8), and also two alkyl groups (entry 10) were obtained. Furthermore, access to each enantiomer of **6g** was allowed by inverting the order of introduction of the substituents R^1 and R^2 (entry 7 and 8). Piperidine **6i** with a vinyl fragment could also be prepared owing to the selective hydrozirconation of the less substituted C=C double bond (entry 9).

The diastereoselectivity observed in the reduction step may be rationalized through an axial hydride addition occurring from a half-chair-like conformation that might be favored when the R^1 substituent is located in a pseudoequatorial position (Figure 2).

Figure 2. Plausible origin of the *cis*-selectivity.

To illustrate the synthetic potential of the method, the synthesis of indolizidine 209D[6,19] was achieved. Thus, **6j** was subjected to hydrogenolysis under acidic conditions to give the corresponding hydroxy ammonium. The chloro ammonium was then generated with $SOCl_2$, and cyclization was promoted by the addition of K_2CO_3 to provide the target alkaloid (Scheme 3).

Scheme 3. Synthesis of Indolizidine 209D



Additionally, an extension toward piperidines bearing a quaternary center at the 2-position was initiated. Thus, the

(15) For recent asymmetric synthesis of coniine see:(a) Passarella, D.; Barilli, A.; Belinghieri, F.; Fassi, P; Riva, S.; Sacchetti, Silvani, A.; Danieli, B. *Tetrahedron: Asymmetry* **2005**, *16*, 2225–2229. (b) Yamashita, Y.; Mizuki, Y.; Kobayashi, S. *Tetrahedron Lett.* **2005**, *46*, 1803–1806.

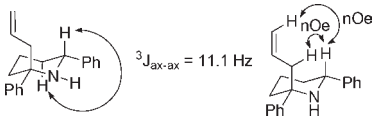
(16) (a) Fujita, K-I; Fujii, T.; Komatsubara, A.; Enoki, Y.; Yamaguchi, R. *Heterocycles* **2007**, *74*, 673–682. (b) Fellah, M; Santerem, M; Lhommet, G.; Mouries-Mansuy, V. *J. Org. Chem.* **2010**, *75*, 7803–7808. (c) Miao, L.; Di Maggio, S. C.; Shu, M.; Trudell, M. L. *Org. Lett.* **2009**, *11*, 1579–1582. (d) Breuning, M.; Steiner, M. *Tetrahedron: Asymmetry* **2008**, *19*, 1978–1983.

(17) Vilaivan, T.; Winotapan, C.; Banphavichit, V.; Shinada, T.; Ohfune, Y. *J. Org. Chem.* **2005**, *70*, 3464–3471.

(18) The *cis* configuration of **6a** was assigned by comparison with the known compound: Katritzky, A. R.; Qiu, G.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1998**, *63*, 6699–6703. The stereochemistry of all other compounds was deduced by analogy.

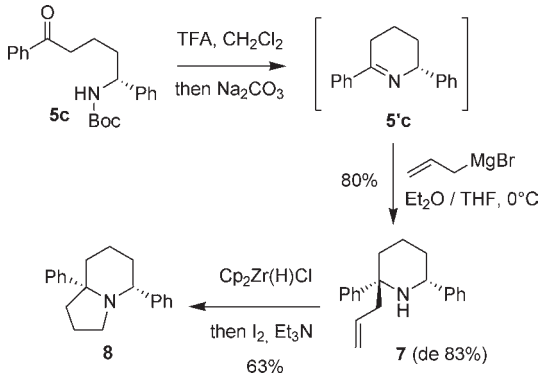
(19) For a previous synthesis of indolizidine 209D, see: (a) Åhman, J.; Somfai, P. *Tetrahedron* **1995**, *51*, 9747–9756. (b) Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W. K.; Blickensdorf, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 10183–10194.

(20) The *cis* configuration was deduced from NOE experiments; see the Supporting Information.



addition of allylmagnesium bromide onto the cyclic imine **5′c** intermediate was tested as a model experiment. In this case, a high diastereoselectivity was observed, affording the *cis* piperidine **7**,[20] isolated in its pure diastereomeric form, in 80% yield starting from **5c**. Further cyclization through hydrozirconation/iodination[5] provided the indolizidine **8** in 63% yield (Scheme 4).

Scheme 4. Synthesis of Piperidines **8**



In summary, applied to protected homoallylic amines, the hydrozirconation/acylation sequence allows access to protected amino ketones, ideal precursors of cyclic imines (or iminiums). The methodology thus consists of the sequential activation of the C- and N-termini of homoallylic amines toward a trivalent electrophile. This approach was applied to the diastereoselective synthesis of 2-*cis*-substituted and *cis*-2,6-disubstituted piperidines, opening the way to alkaloid synthesis, as illustrated by the synthesis of (−)-coniine and (−)-indolizidine 209D. Moreover, an access to piperidines bearing a stereocontrolled quaternary center is exemplified.

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Supporting Information Available. Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.