Synthesis of Enantiopure 5-Substituted 2,3-Methanopyrrolidines by Cyclization of Enantiopure α-Branched α-*N*-Homoallylamino Nitriles

Sabrina Ouizem, Fabrice Chemla,* Franck Ferreira,* Alejandro Perez-Luna*

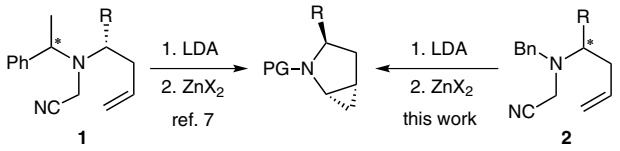
UPMC – Univ Paris 06, Institut Parisien de Chimie Moléculaire (UMR CNRS 7201), Institut de Chimie Moléculaire (FR 2769), Case 183, 4 Place Jussieu 75252 Paris Cedex 05, France
Fax +33(1)44277567; E-mail: fabrice.chemla@upmc.fr; E-mail: franck.ferreira@upmc.fr; E-mail: alejandro.perez_luna@upmc.fr

Received: 13.03.2012; Accepted: 28.03.2012

Abstract: The preparation of 5-substituted 2,3-methanopyrrolidines by the stereoselective cyclization of zincated α-amino nitriles derived from enantiopure α-branched homoallylamines has been investigated. The formation of *trans* adducts in excellent diastereoselectivities (up to >98:2) and good yields (up to 71%) is observed. The absolute configuration and enantiomeric excess are dependent on the nitrogen protecting group.

Key words: cyclization, zinc, carbenoids, stereoselective synthesis, bicyclic compounds

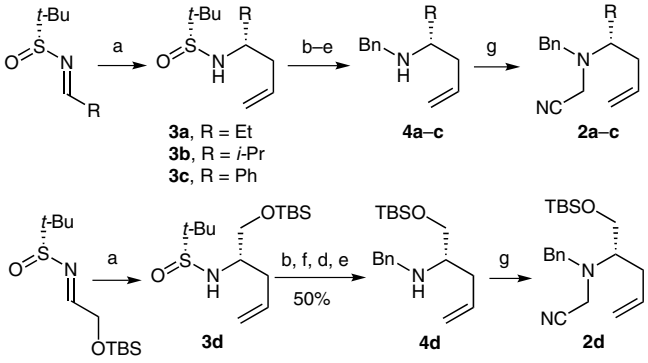
2,3-Methanopyrrolidines {2-azabicyclo[3.1.0]hexane derivatives} are interesting molecules that have attracted interest both for their use as scaffolds in biologically active peptide mimics[1,2] and as synthetic intermediates for nitrogen-containing compounds.[3] In contrast with the preparation of 2,3-methanopyrrolidines in racemic form,[1a,3,4] general synthetic methods for the preparation of enantiopure 2,3-methanopyrrolidines are not common.[1b–e,5–7]



Scheme 1

In this context, we recently reported the diastereoselective formation of 2,3-methanopyrrolidines from α-*N*-(1-phenylethyl)-*N*-homoallylamino nitriles by treatment with LDA and transmetalation with a zinc salt (Scheme 1).[7] In the case of α-branched substrates **1**, the stereochemical outcome of the cyclization was governed by the homoallylic stereocenter, and a stereospecific inversion was observed. Unfortunately, difficulties associated both with the control of the stereoselectivity in preparation of substrates **1** and with the removal of the 1-phenyl-ethyl chiral auxiliary made it difficult to use this reaction for a general approach to 2,3-methanopyrrolidines. We reasoned that these drawbacks might be avoided starting from α-*N*-(benzyl)-*N*-homoallylamino nitriles **2** derived from readily available enantiopure α-branched homoallylic amines.[8] First, according to our results with adducts **1**, cyclization of **2** should provide stereospecifically enantiopure 5-substituted *N*-benzyl-2,3-methanopyrrolidines. Second, according to a recent report,[9] removal of the benzyl nitrogen protecting group without altering the 2-azabicyclo[3.1.0]hexane framework should be straightforward.

We chose to prepare the required substrates by the route depicted in Scheme 2. Diastereomerically pure sulfinamides **3a**–**d** were isolated in good yields (57–92%) from the reaction of the parent enantiopure *tert*-butanesulfinylimines[10] and allylmagnesium bromide in CH_2Cl_2.[11] Acidic removal of the sulfinyl auxiliary followed by reductive amination of benzaldehyde provided efficiently secondary *N*-benzyl α-branched homoallylic amines **4a**–**c**. In the case of **3d**, removal of the auxiliary with HCl also led to desilylation of the protected alcohol. An additional silylation step to reinstall the *tert*-butyldimethylsilyl group prior to the reductive amination sequence was thus required. Compound **4d** was nevertheless obtained from **3d** in 50% yield. Finally, α-*N*-(benzyl)-*N*-homoallylamino nitriles **2a**–**d** were obtained in 54–95% yield by alkylation of **4a**–**d** with bromoacetonitrile in DMF in the presence of K_2CO_3.

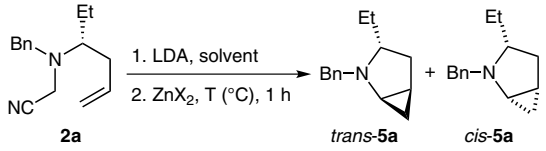


Scheme 2 *Reagents and conditions*: (a) allylmagnesium bromide, CH_2Cl_2, –78 °C to r.t., 57% (**3a**), 86% (**3b**), 83% (**3c**), 92% (**3d**); (b) 4 M HCl–dioxane solution, 0 °C; (c) aq Na_2CO_3; (d) benzaldehyde, CH_2Cl_2, r.t.; (e) $NaBH_4$, MeOH, 0 °C to r.t., 42% (**4a**), 41% (**4b**), 68% (**4c**) (over four steps); (f) TBSCl, imidazole, CH_2Cl_2, r.t.; (g) bromoacetonitrile, K_2CO_3, DMF, r.t., 75% (**2a**), 54% (**2b**), 95% (**2c**), 93% (**2d**).

We initiated our cyclization studies with prototypical ethyl-substituted amino nitrile **2a** (Scheme 3, Table 1). As observed in our previous works,[7] full metalation of **2a** in

SYNLETT 2012, 23, 1374–1378
Advanced online publication: 14.05.2012
DOI: 10.1055/s-0031-1291046; Art ID: ST-2012-D0232-L

Et_2O required treatment with two equivalents LDA at 0 °C. As anticipated, addition of $ZnBr_2$ (4 equiv) following lithiation led to the formation of methanopyrrolidine **5a** in 40% yield but as a *trans*/*cis* mixture (88:12) of diastereomers. Formation of *cis*-**5a** was unexpected as cyclization of α-branched *N*-(1-phenyl-ethyl)-amino nitriles had always shown an excellent *trans* selectivity.



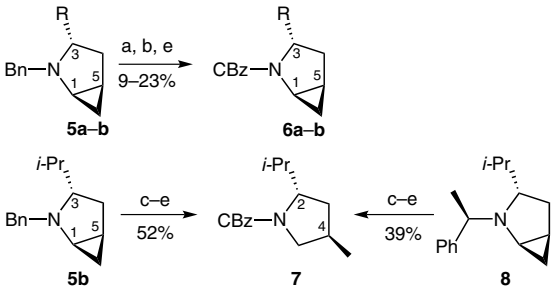
Scheme 3

Table 1 Optimization of the Diastereoselectivity in the Cyclisation of **2a**

Entry	LDA (equiv)	Solvent	ZnX_2 (equiv)	Temp (°C)	Yield of **5a** (%)[a]	Ratio *trans*/*cis*[b]
1	2.4[c]	Et_2O	$ZnBr_2$ (4)	r.t.	40	88:12
2	2.4[d]	THF	$ZnBr_2$ (4)	r.t.	31	87:13
3	2.4[d]	THF	$ZnBr_2$ (4)	0	28	87:13
4	2.4[d]	THF	$ZnBr_2$ (4)	–20	<5	n.d.
5	2.4[d]	THF	$ZnBr_2$ (1.5)	r.t.	19	65:35
6	2.4[d]	THF	$ZnBr_2$ (8)	r.t.	<5	n.d.
7	2.4[d]	THF	ZnI_2 (4)	r.t.	41	83:17
8	–[e]	THF	$Zn(NiPr_2)_2$ (2)	r.t.	29	61:39
9	–[f]	THF	$Zn(TMP)_2$ (2)	r.t.	29	64:36
10	1.2[d]	THF	$ZnBr_2$ (4)	r.t.	46	>98:2

[a] Isolated yield after silica gel chromatography.
[b] Diastereoselectivity determined by ^1H NMR analysis of the crude reaction mixture.
[c] Conditions: 0 °C, 1 h.
[d] Conditions: –80 °C, 1 h.
[e] Compound **2a** was reacted directly with a 2:1 mixture of lithium diisopropylamide/$ZnBr_2$.
[f] Compound **2a** was reacted directly with a 2:1 mixture of lithium tetramethylpiperidide/$ZnBr_2$.

Seeking to improve both the yield and the diastereoselectivity, we studied the influence of several reaction conditions (Table 1). Metalation of **2a** was achieved in THF using 2.4 equivalents LDA at –78 °C. However, this solvent change had little impact on the reaction outcome (Table 1, entry 2). Conversely, the product yield was found to be dependent on the reaction temperature (Table 1, entries 3 and 4) and, interestingly, we found that no cyclization occurred below –20 °C. The same stereoselectivity (dr = 87:13) was, however, obtained at 0 °C and at room temperature. We then investigated the influence of the zinc salt. It was found that either lower (1.5 equiv, Table 1, entry 5) or higher (8 equiv, Table 1, entry 6) amounts of zinc bromide led to significantly lower yields. The use of ZnI_2 instead of $ZnBr_2$ led to **5a** in slightly improved 41% yield, but with a lower diastereomeric ratio of 83:17 (Table 1, entry 7). Interestingly, reaction of **2a** with zinc diisopropylamide [$Zn(NiPr_2)_2$] or zinc tetramethylpiperidide [$Zn(TMP)_2$] without any additional base also resulted in the formation of methanopyrrolidine, albeit in lower yield (29%) and selectivities (*trans*/*cis* = 61:39 and 64:36, respectively; Table 1, entries 8 and 9). Following these observations, we reasoned that excess LDA would have a deleterious effect on the reaction outcome when $ZnBr_2$ was used if ligand exchange between diisopropylamide and bromide occurred. We thus carried out the deprotonation of **2a** with 1.2 equivalents LDA at –78 °C. Following treatment with four equivalents $ZnBr_2$, methanopyrrolidine **5a** was obtained in 46% yield and as a single *trans* diastereomer. The relative configuration between the ethyl group and the cyclopropane ring was assigned following transformation of **5a** into previously reported Cbz-protected methanopyrrolidine **6a** (Scheme 4).

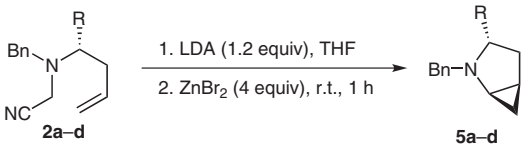


Scheme 4 *Reagents and conditions*: (a) $ClCO_2CH(Cl)CH_3$, CH_2Cl_2, reflux; (b) MeOH, reflux; (c) H_2 (1 atm), $Pd(OH)_2$ on carbon (20% Pd), MeOH, r.t.; (d) 4 M HCl dioxane solution; (e) $ClCO_2Bn$ (CBz-Cl), Et_3N, CH_2Cl_2, r.t.

Adduct **6a** allowed for determination of enantiomeric excess by HPLC.[12] It was found that **5a** was produced from **2a** in 60% ee (Scheme 5, Table 2). The 1*R*,3*R*,5*R* configuration of the major enantiomer was assigned by comparison of the HPLC retention times with enantiopure (1*R*,3*R*,5*R*)-**6a**.[7] Hence, cyclization of **2a** occurred with partial loss of the stereochemical integrity of the homoallylic stereocenter.

The reaction of other substrates was next considered (Scheme 5, Table 2). Cyclization of amino nitrile **2b** having a secondary substituent (*i*-Pr) led to **5b** in good 67% isolated yield, excellent diastereoselectivity and in basically enantiomerically pure form (97% ee measured after transformation to **6b**[13]). The 1*R*,3*S*,5*R* configuration was assigned by transformation into **7** (Scheme 4), the configuration of which was determined by comparison of the HPLC retention times with enantiopure (2*S*,4*R*)-**7**[14] obtained from known **8**.[7] The 5-phenyl-substituted methanopyrrolidine **5c** was obtained from **4c** in low 23% yield and only 88:12 dr. Complete diastereoselectivity but low yield (34%) was obtained in the cyclization of **4d** having a silyloxymethyl substituent. Furthermore, we were not able to

find suitable conditions to determine the enantiomeric excess of **5d**.



Scheme 5

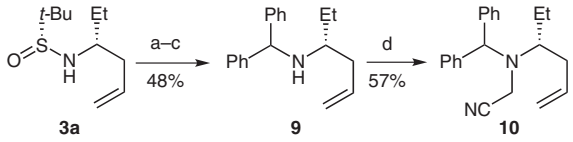
Table 2 Cyclization of α-Amino Nitriles **5a**–**d** under the Optimized Conditions[15]

Entry	R	Product	Yield (%)[a]	Ratio *trans*/*cis*[b]	ee (%)
1	Et	**5a**	46	>98:2	60[c]
2	*i*-Pr	**5b**	67	98:2	97[c]
3	Ph	**5c**	23	88:12	–
4	CH_2OTBS	**5d**	34	>98:2	n.d.[d]

[a] Isolated yield after silica gel chromatography.
[b] Diastereoselectivity determined by ^1H NMR analysis of the crude reaction mixture.
[c] The enantiomeric excess was measured by HPLC following transformation to products **6a**,**b** (see text).
[d] Suitable conditions for ee measurement could not be found.

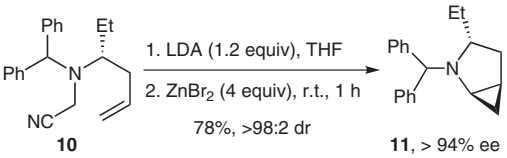
While disappointing from a synthetic standpoint, the cyclization of α-*N*-(benzyl)-*N*-homoallylamino nitriles remains interesting from a mechanistic perspective. Similarly to the reaction of α-branched α-*N*-(1-phenyl-ethyl)-*N*-homoallylamino nitriles, diastereoselective formation of *trans*-5-substituted 2,3-methanopyrrolidines is observed. In sharp contrast, however, retention of the configuration of the homoallylic stereocenter is observed for the major or exclusive enantiomer formed.

Intrigued by the difference of behavior with respect to the nitrogen protecting group, we decided to study the cyclization of **10** having a bulkier, still achiral, benzhydryl protecting group. Enantiopure α-branched *N*-benzhydryl homoallylic secondary amine **9** was prepared in 48% yield from **3a** in a sequence involving reductive amination of benzophenone. Alkylation with bromoacetonitrile provided **10** in 57% yield (Scheme 6).



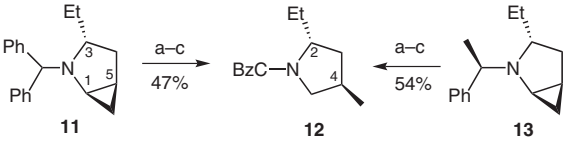
Scheme 6 *Reagents and conditions*: (a) 4 M HCl dioxane solution, 0 °C; (b) benzophenone, $TiCl_4$, Et_3N, CH_2Cl_2, r.t.; (c) $NaBH_4$, MeOH, 0 °C to r.t., 48% (over 3 steps); (d) bromoacetonitrile, K_2CO_3, DMF, r.t., 57%.

Reaction of enantiopure *N*-(benzhydryl)amino nitrile **10** under our optimized conditions (1.2 equiv LDA, 4 equiv $ZnBr_2$ in THF) provided methanopyrrolidine **11** in a very good 78% isolated yield, as a single *trans* diastereomer and in ee >94% (Scheme 7).



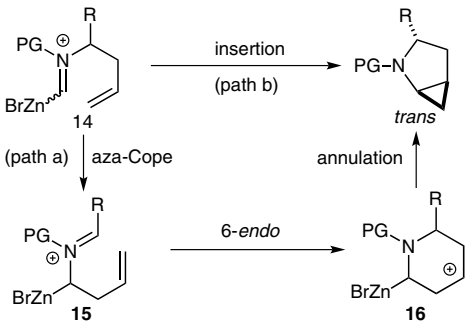
Scheme 7

Removal of the benzhydryl group could only be achieved through hydrogenolysis with $Pd(OH)_2$ on carbon, but opening of the cyclopropane ring was observed. The enantiomeric excess was therefore measured on **12**[16] (Scheme 8). The 2*R*,4*R* configuration of the enantiomer produced from **11** was established by comparison of the HPLC retention times with enantiopure (2*R*,4*R*)-**12** prepared from known **13**.[7] Accordingly, the configuration of methanopyrrolidine **11** was determined to be 1*R*,3*R*,5*R*, indicating that cyclization of **10** occurs with retention of configuration of the homoallylic stereocenter.



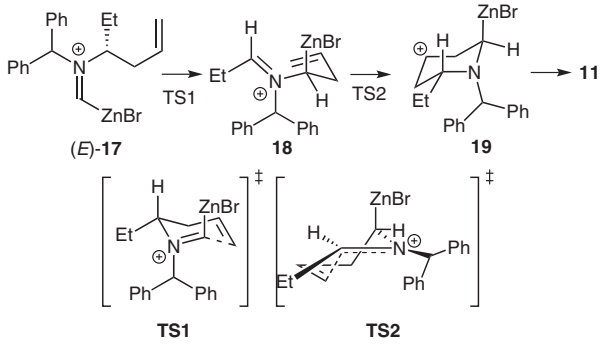
Scheme 8 *Reagents and conditions*: (a) H_2 (1 atm), $Pd(OH)_2$ on carbon (20% Pd), MeOH, r.t.; (b) 4 M HCl dioxane solution; (c) $ClCO_2Bn$ (CBzCl), Et_3N, CH_2Cl_2, r.t.

The stereochemical outcomes observed for the differently protected α-branched α-*N*-homoallylamino nitriles cannot be explained by a single mechanistic rationale. In the case of (1-phenyl-ethyl)-protected α-amino nitriles, the proposed mechanism involved the formation of zincioiminium ions **14** from zincated α-amino nitriles, followed by an aza-Cope rearrangement (Scheme 9, path a) providing configurationally stable (2-azoniaallyl)zinc **15** that then undergoes 6-*endo* cyclization to afford **16** that annulates to the *trans*-5-substituted 2,3-methanopyrrolidines.[7] Direct insertion of the zincioiminium ions **14**[17] (Scheme 9, path b) was ruled out because it did not account for the stereospecific inversion of the homoallylic stereocenter.



Scheme 9

The stereoselective formation of product **11** from **10** is consistent with the same mechanistic picture (Scheme 10). Formation of zincioiminium ion (*E*)-**17** should be stereoselective as a result of the presence of the bulky benzhydryl group.[18] Aza-Cope rearrangement through **TS1** wherein the ethyl substituent occupies an equatorial position would afford **18**. The 6-*endo* cyclization should occur through **TS2** in which the C–Zn bond is parallel to the π-system of the C=N bond to stabilize the adjacent cationic center by hyperconjugative effects (Linderman's model).[19] Finally, from intermediate **19** thus formed, annulation through a W-conformation[20] would afford **11**.

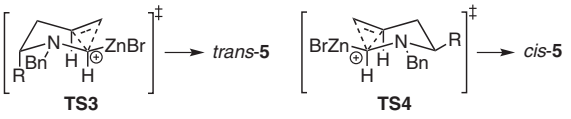


Scheme 10

Following this model, however, cyclization of amino nitriles **2** having a less bulkier benzyl nitrogen protecting group should involve an initial aza-Cope rearrangement, as in the case of *N*-(1-phenyl-ethyl)amino nitriles, wherein both the homopropargylic substituent and the zinc atom occupy an equatorial position. Inversion of the configuration of the homoallylic stereocenter should be observed. Thus, formation of *N*-(benzyl) 2,3-methanopyrrolidines **5** does not take place predominantly via a mechanism involving an aza-Cope rearrangement.

Given literature precedents on intramolecular cyclopropanation of α-*N*-(homoallyl)amino carbenes,[4a,21] our results are best explained by a mechanism involving a direct insertion of the zincioiminium ion carbenoid (Scheme 9, path b). According to this picture, formation of *trans*-methanopyrrolidines **5** results from transition state **TS3** where the R group occupies an equatorial position to prevent a gauche interaction with the benzyl group on the tetrahedral nitrogen (Scheme 11). Note that the formation of *cis*-methanopyrrolidines (i.e., *cis*-**5**), that was not observed in the cyclization of *N*-(1-phenylethyl)amino nitriles proceeding via an aza-Cope–6-*endo*-annulation sequence, can be readily explained by an insertion via **TS4**. We cannot, however, provide for the moment a satisfactory explanation for this mechanistic shift and for the partial inversion observed with ethyl-substituted amino nitrile **2a**.

In conclusion, the formation of *trans*-5-substituted 2,3-methanopyrrolidines by cyclization of benzyl- or benzhydryl-protected enantiopure α-branched *N*-homoallylamino nitriles has been investigated. While excellent



Scheme 11

results can be obtained for specific substrates, the approach remains rather narrow in terms of synthetic scope. Importantly, however, we have observed a remarkable dependence of the stereochemical outcome of the cyclization on the nitrogen protecting group, indicative of a mechanistic difference between on the one hand 1-phenylethyl- and benzhydryl-protected substrates and on the other hand benzyl-protected ones.

Acknowledgment

S.O. thanks MESR for a PhD grant.

References and Notes

(1) (a) Switzer, F. L.; Van Halbeek, H.; Holt, E. M.; Stammer, C. H. *Tetrahedron* **1989**, *45*, 6091. (b) Hanessian, S.; Reinhold, U.; Gentile, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1881. (c) Hanessian, S.; Reinhold, U.; Saulnier, M.; Claridge, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2123. (d) Magnin, D. R.; Robl, J. A.; Sulsky, R. B.; Augeri, D. J.; Huang, Y.; Simpkins, L. M.; Taunk, P.; Betebenner, D. A.; Robertson, J. G.; Abboa-Offei, B.; Wang, A.; Cap, M.; Xing, L.; Tao, L.; Sitkoff, D. F.; Malley, M. F.; Gougoutas, J. Z.; Khanna, A.; Huang, Q.; Han, S.-P.; Parker, R. A.; Hamann, L. G. *J. Med. Chem.* **2004**, *47*, 2587. (e) Mykhailiuk, P. K.; Afonin, S.; Palamarchuk, G. V.; Shishkin, O. V.; Ulrich, A. S.; Komarov, I. V. *Angew. Chem. Int. Ed.* **2008**, *47*, 5765.

(2) Saxagliptin, a dipeptide-containing a 2,3-methanopyrrolidine subunit is currently marketed for treatment of type 2 diabetes: Augeri, D. J.; Robl, J. A.; Betebenner, D. A.; Magnin, D. R.; Khanna, A.; Robertson, J. G.; Wang, A.; Simpkins, L. M.; Taunk, P.; Huang, Q.; Han, S.-P.; Abboa-Offei, B.; Cap, M.; Xin, L.; Tao, L.; Tozzo, E.; Welzel, G. E.; Egan, D. M.; Marcinkeviciene, J.; Chang, S. Y.; Biller, S. A.; Kirby, M. S.; Parker, R. A.; Hamann, L. G. *J. Med. Chem.* **2005**, *48*, 5025.

(3) (a) Recent examples: Larquetoux, L.; Kowalska, J. A.; Six, Y. *Eur. J. Org. Chem.* **2004**, 3517. (b) Larquetoux, L.; Ouhamou, N.; Chiaroni, A.; Six, Y. *Eur. J. Org. Chem.* **2005**, 4654. (c) Madelaine, C.; Six, Y.; Buriez, O. *Angew. Chem. Int. Ed.* **2007**, *46*, 8046. (d) Madelaine, C.; Ouhamou, N.; Chiaroni, A.; Vedrenne, E.; Grimaud, L.; Six, Y. *Tetrahedron* **2008**, *64*, 8878. (e) Madelaine, C.; Buriez, O.; Crousse, B.; Florent, I.; Grellier, P.; Retailleau, P.; Six, Y. *Org. Biomol. Chem.* **2010**, *8*, 5591.

(4) (a) Couty, S.; Meyer, C.; Cossy, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6726. (b) Couty, S.; Meyer, C.; Cossy, J. *Tetrahedron* **2009**, *65*, 1809. (c) Madelaine, C.; Buzas, A. K.; Kowalska-Six, J. A.; Six, Y.; Crousse, B. *Tetrahedron Lett.* **2009**, *50*, 5367.

(5) Hercouet, A.; Bessières, B.; Le Corre, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1267.

(6) Simpkins, L. M.; Bolton, S.; Pi, Z.; Sutton, J. C.; Kwon, C.; Zhao, G.; Magnin, D. R.; Augeri, D. J.; Gungor, T.; Rotella, D. P.; Sun, Z.; Liu, Y.; Slusarchyk, W. S.; Marcinkeviciene, J.; Robertson, J. G.; Wang, A.; Robl, J. A.; Atwal, K. S.;

Zahler, R. L.; Parker, R. A.; Kirby, M. S.; Hamann, L. G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6476.
(7) Ouizem, S.; Cheramy, S.; Botuha, C.; Chemla, F.; Ferreira, F.; Perez-Luna, A. *Chem. Eur. J.* **2010**, *16*, 12668.
(8) (a) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (c) Yus, M.; Gonzalez-Gomez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774.
(9) Wolan, A.; Soueidan, M.; Chiaroni, A.; Retailleau, P.; Py, S.; Six, Y. *Tetrahedron Lett.* **2011**, *52*, 2501.
(10) (a) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869. (b) Lin, G.-Q.; Xu, M.-H.; Zhong, Y.-W.; Sun, X.-W. *Acc. Chem. Res.* **2008**, *41*, 831. (c) Ferreira, F.; Botuha, C.; Chemla, F.; Pérez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162. (d) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.
(11) (a) Rech, J. C.; Yato, M.; Duckett, D.; Ember, B.; LoGrasso, P. V.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 490. (b) Yendapally, R.; Lee, R. E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1607.
(12) Daicel Chiralpak AD column [(4.6 mm × 250 mm, 5 μm); hexane–*i*-PrOH (95:5), flow rate = 1.0 mL min^{-1}, detection λ = 220 nm]: t_R [(1*S*,3*S*,5*S*)-**6a**] = 10.4 min; t_R [(1*R*,3*R*,5*R*)-**6a**] = 11.1 min. Racemic **6a** was prepared from racemic **4a** obtained by reaction of allylmagnesium bromide with (*E*)-*N*-benzylpropan-1-imine.
(13) Daicel Chiralpak AD column [(4.6 mm × 250 mm, 5 μm); hexane–*i*-PrOH (95:5), flow rate = 0.8 mL min^{-1}, detection λ = 220 nm]: t_R [(1*S*,3*R*,5*S*)-**6b**] = 13.9 min; t_R [(1*R*,3*S*,5*R*)-**6b**] = 15.0 min. Racemic **6b** was prepared from racemic **4b** obtained by reaction of allylmagnesium bromide with (*E*)-*N*-benzyl-2-methylpropan-1-imine.
(14) Daicel Chiralpak AD column [(4.6 mm × 250 mm, 5 μm); hexane–*i*-PrOH (98:2), flow rate = 0.4 mL min^{-1}, detection λ = 220 nm]: t_R [(2*R*,4*S*)-**7**] = 52.4 min; t_R [(2*S*,4*R*)-**7**] = 53.2 min. Racemic **7** was prepared from racemic **4b** obtained by reaction of allylmagnesium bromide with (*E*)-*N*-benzyl-2-methylpropan-1-imine.
(15) **Procedure for the Preparation of 5a–d (Table 2) and 11 – Preparation of 5b is Representative**
Diisopropylamine (0.17 mL, 1.2 mmol) was added at r.t. to *n*-BuLi (2.4 M in hexane, 0.50 mL, 1.2 mmol). Once the gummy mixture formed, dry THF (1.5 mL) was added, and the solution was cooled to –80 °C. A solution of α-amino nitrile (**2b**, 243 mg, 1 mmol) in dry THF (1.5 mL) was added dropwise. After 1 h of stirring at –80 °C, $ZnBr_2$ (1.0 M in dry THF, 4.0 mL, 4.0 mmol) was added at once, and the cooling bath was removed and replaced by a water bath. Once the temperature of the solution reached r.t., the bath was removed, and the mixture was stirred for 2 h. An aq solution of NH_4Cl–NH_3 (2:1; 10 mL) and ethanolamine (1 mL) were added. The biphasic mixture was stirred vigorously during 30 min before the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography over silica gel afforded **5b** (144 mg, 67%). $[\alpha]_D^{20}$ +230.5 (*c* 1.89, $CHCl_3$). IR (neat): 3029, 2954, 1494, 1453, 1157, 733, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.02 (dt, *J* = 8.1, 5.5 Hz, 1 H), 0.63–0.66 (m, 1 H), 0.91 (d, *J* = 7.0 Hz, 3 H), 0.96 (d, *J* = 6.8 Hz, 3 H), 1.25–1.35 (m, 1 H), 1.80–1.83 (m, 2 H), 1.90–1.94 (m, 1 H), 2.19–2.25 (m, 1 H), 2.55–2.58 (m, 1 H), 3.23 (d, *J* = 12.7 Hz, 1 H), 3.91 (d, *J* = 12.7 Hz, 1 H), 7.25–7.45 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.1, 13.5, 15.8, 20.5, 27.8, 28.2, 41.4, 57.0, 64.1, 126.8, 128.3, 129.1, 140.5. HRMS: *m*/*z* $[M - H]^+$ calcd for $C_{15}H_{22}N_1$: 216.17468; found: 216.17453.
(16) Daicel Chiralpak AD column [(4.6 mm × 250 mm, 5 μm); hexane–*i*-PrOH = 98:2, flow rate = 0.8 mL min^{-1}, detection λ = 220 nm]: t_R [(2*S*,4*S*)-**12**] = 13.5 min; t_R [(2*R*,4*R*)-**12**] = 14.5 min. Racemic **12** was prepared from racemic **9** obtained by reaction of allylmagnesium bromide with (*E*)-*N*-benzhydrylpropan-1-imine.
(17) (a) Bégis, G.; Cladingboel, D. E.; Motherwell, W. B. *Chem. Commun.* **2003**, 2656. (b) Bégis, G.; Cladingboel, D. E.; Motherwell, W. B.; Sheppard, T. D.; Tocher, D. A. *Synthesis* **2005**, 3186. (c) Motherwell, W. B.; Bégis, G.; Cladingboel, D. E.; Jerome, L.; Sheppard, T. D. *Tetrahedron* **2007**, *63*, 6462. (d) Bégis, G.; Cladingboel, D. E.; Jerome, L.; Motherwell, W. B.; Sheppard, T. D. *Eur. J. Org. Chem.* **2009**, 1532. (e) Jerome, L.; Sheppard, T. D.; Aliev, A. E.; Motherwell, W. B. *Tetrahedron Lett.* **2009**, *50*, 3709.
(18) Johnson, B. F.; Marrero, E. L.; Turley, W. A.; Lindsay, H. A. *Synlett* **2007**, 893.
(19) Linderman, R. J.; Anklekar, T. V. *J. Org. Chem.* **1992**, *57*, 5078.
(20) Beruben, D.; Marek, I.; Normant, J. F.; Platzer, N. *J. Org. Chem.* **1995**, *60*, 2488.
(21) (a) Casey, C. P.; Vollendorf, N. W.; Haller, K. J. *J. Am. Chem. Soc.* **1984**, *106*, 3754. (b) Soderberg, B. C.; Hegedus, L. S. *Organometallics* **1990**, *9*, 3113. (c) Ogawa, A.; Takami, N.; Sekigushi, M.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992**, *114*, 8729. (d) Barluenga, J.; Aznar, F.; Gutierrez, I.; Llorca-Baragano, M. A. *Org. Lett.* **2002**, *4*, 4273.

