

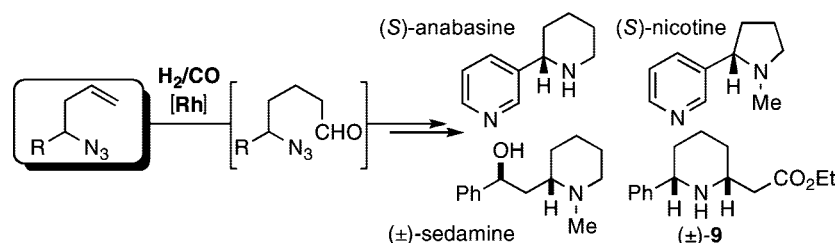
Hydroformylation of Homoallylic Azides:  
A Rapid Approach toward AlkaloidsThomas Spangenberg,<sup>†,‡</sup> Bernhard Breit,<sup>\*,‡</sup> and André Mann<sup>\*,†</sup>

Département de Pharmacochimie de la Communication Cellulaire, UMR 7175-LC-1  
ULP/CNRS, Faculté de Pharmacie, 74 route du Rhin BP 60024,  
F-67401 Illkirch, France, and Institut für Organische Chemie and Biochemie, Freiburg  
Institute of Advanced Studies (FRIAS), Albert-Ludwigs-Universität Freiburg,  
Albertstrasse 21, D-79104 Freiburg, Germany

andre.mann@pharma.u-strasbg.fr; bernhard.breit@chemie-freiburg.de

Received October 6, 2008

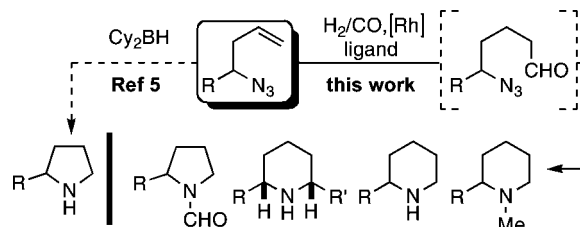
## ABSTRACT



Unprecedented hydroformylation of homoallylic azides combined with useful one-pot operations provides an expeditious access to alkaloids.

In natural products and pharmaceuticals, the piperidine core is one of the most encountered and has been recognized as a privileged structure in medicinal chemistry.<sup>1</sup> Indeed over 12,000 discrete piperidine entities have been mentioned in clinical or preclinical studies over the past decade.<sup>2</sup> To date, a variety of approaches to piperidines have been developed,<sup>3</sup> but general and efficient methods meeting the criteria of atom economy are still desirable. Following our interest in the preparation of piperidine-related alkaloids,<sup>4</sup> we envisioned using homoallylazides as direct precursors for the piperidine core. Indeed homoallylazides have already been used for the

synthesis of pyrrolidines<sup>5</sup> by means of a hydroboration–cycloalkylation reaction (Figure 1). However, the extension



**Figure 1.** Strategy to access pyrrolidine and piperidine alkaloids.

of this strategy for the preparation of piperidine rings has proven to be troublesome because the corresponding azido olefins were prone to [3 + 2] cycloadditions.<sup>6</sup> Conversely,

<sup>†</sup> Département de Pharmacochimie de la Communication Cellulaire, UMR 7175-LC-1 ULP/CNRS.

<sup>‡</sup> Albert-Ludwigs-Universität Freiburg.

(1) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. J. *Med. Chem.* **1988**, *31*, 2235.

(2) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679.

(3) (a) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781. (b) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693. (c) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701.

(4) (a) Spangenberg, T.; Airiau, E.; Bui The Thuong, M.; Donnard, M.; Billet, M.; Mann, A. *Synlett* **2008**, 2859. (b) Airiau, E.; Spangenberg, T.; Girard, N.; Schoenfelder, A.; Salvadori, J.; Taddei, M.; Mann, A. *Chem.–Eur. J.* **2008**, *14*, 10938.

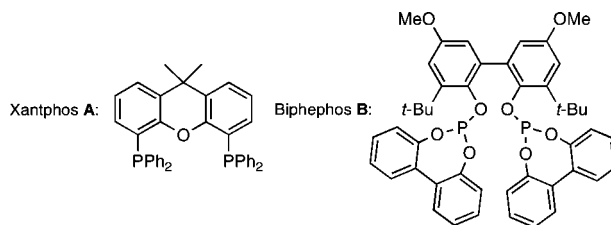
(5) (a) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151. (b) Jegou, J. M.; Carboni, B.; Vaultier, M.; Carrié, R. *Chem. Commun.* **1989**, 142. (c) Jegou, J. M.; Carboni, B.; Vaultier, M. *Bull. Soc. Chim. Fr.* **1992**, 129, 554.

**Table 1.** Optimization of the Hydroformylation Conditions

$\text{1a} \xrightarrow[\text{Rh(CO)}_2(\text{acac}), \text{ligand L, solvent}]{\text{H}_2/\text{CO (1:1), 5 bar}} \text{2a : linear} + \text{branched} + \text{isomerized}$

entry	loading <sup>a</sup>	L	solvent/temp	time (h)	l/b	iso %	yield % <sup>c</sup> (convn) <sup>b</sup>
1	1/2/50	A	THF/65	10	86/14	5	37 (62) <sup>d</sup>
2	1/2/50	B	THF/65	6	>95/5	<5	87 (99)
3	1/2/50	B	Tol/65	6	>95/5	<5	87 (99)
4	1/3/100	B	THF/rt	24 <sup>e</sup>	>95/5	10	83 (99)
5	1/3/100	B	THF/65	4	>95/5	<5	87 (99)
6	1/3/100	B	MeOH/50	4	>95/5	<5	87 (99)

<sup>a</sup> Rh(CO)<sub>2</sub>(acac)/L/**1a**. <sup>b</sup> Conversion and percentage of isomerized product as the l/b ratio were determined by crude <sup>1</sup>H NMR. <sup>c</sup> Isolated after silical gel chromatography. <sup>d</sup> Total oxidation of the phosphorus was observed by crude <sup>31</sup>P NMR. <sup>e</sup> 1 atm of *syngas*.



a carbon homologation of the terminal double bond could provide a solution. Indeed if the azide function would be compatible with the conditions of a linear regioselective hydroformylation, the transformation of the azide to a basic amine would allow the formation of a cyclic imine, a direct precursor of aza-heterocycles. This sequence would represent a new synthetic pathway to piperidines (Figure 1). Hydroformylation is a prototype of an atom-economic<sup>7</sup> reaction and an attractive synthetic valorisation of alkenes. A new carbon–carbon bond is formed by addition of H<sub>2</sub> and CO with concomitant formation of an aldehyde function under mild conditions allowing, for instance, further transformations in a one-pot processes.<sup>8</sup> In the present case this strategy is of particular interest as azides are relatively inert to classical chemical transformations, but if properly activated they can offer an exploding diversity of chemical reactivities.<sup>9</sup> Additionally they represent an inexpensive orthogonal protection of the amine function to a broad range of reaction conditions and functional groups. Herein we report our first results using hydroformylation of homoallylic azides in the syntheses of piperidinyll alkaloids or analogues.

From the literature data no report was available on the elusive stability of the azide group under hydroformylation conditions. Therefore two main questions had to be addressed: (i) the reduction of the azide to an amine in the presence of Rh(I) and hydrogen (one partner in the *syngas*) and (ii) the oxidation of usual phosphine ligands (e.g., Xantphos **A**) for Rh(I) during the hydroformylation via a Staudinger reaction at the expense of the azide. A preliminary experiment with Xantphos revealed a poor regioselectivity and conversion (Table 1, entry 1).

Proscribing phosphine ligands, it is well-known that phosphite ligands such as Biphephos, **B**, a sterically hindered

bis-phosphite ligand, greatly favors the linear/branched ratio (l/b) with a high turnover frequency.<sup>10</sup> In addition, phosphites are more electronically deficient than phosphines, thus reacting very slowly with azides. Initial experiments were performed on a model homoallylazide **1a**, and the results are depicted in Table 1. Indeed, the hydroformylation was operating at low pressure of *syngas* (5 bar) in THF, toluene, and MeOH (entries 2–6), with Biphephos as a ligand and Rh(CO)<sub>2</sub>(acac) as a precatalyst. The chemical conversion of the terminal olefin and the regioselectivity in favor of the linear aldehyde **2a** were excellent, but more interestingly, the azido function remained intact. Even the room temperature atmospheric pressure protocol gave good results (entry 4) albeit demanding a longer reaction time.<sup>11</sup> With a low catalyst/ligand loading good yields were obtained with excellent regioselectivity. The reaction time could be reduced to 4 h for reaching complete conversion (entry 5), and different solvents (THF, toluene, MeOH) can be used. Finally we achieved our first goal, the regioselective generation of an aldehyde from an alkene, in the presence of an azide via hydroformylation under mild conditions.

We next examined the scope of the reaction by subjecting to hydroformylation a broad range of azido alkenes **1a–h** and **4**, carrying various substituents such as alkyl, allyl, aryl, heteroaryl, and substituted aryl groups (Table 2). Preparations of **1a–1h** were uneventful using standard methods.<sup>12,13</sup>

Using our optimized conditions, the desired  $\delta$ -azido-aldehydes **2a–h** could be isolated in good to excellent yields (entries 1–8). The use of methanol as solvent in the presence of a catalytic amount of *p*TSA·H<sub>2</sub>O (10 mol %) allowed the direct transformation of **1a** into the corresponding ketal **3** in 90% yield (entry 9). Finally, subjecting **4**, a 1,2-disubstituted olefin, to hydroformylation in the presence of triphenylphos-

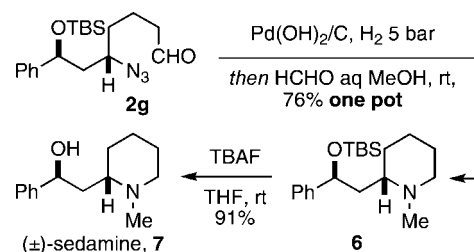
**Table 2.** Scope of the Reaction

$  \begin{array}{c}  \text{H}_2/\text{CO (1:1) 5 bar} \\  \text{Rh}(\text{CO})_2(\text{acac}) \text{ 1 mol \%} \\  \text{biphephos 3 mol \%} \\  \text{THF, 65 }^\circ\text{C, 4 h}  \end{array}  \rightarrow  $			
entry	substrate	product	yield <sup>a</sup>
1			87%
2			92%
3			83%
4			84%
5			92%
6			89%
7			89%
8			87%
9			90 <sup>b</sup>
10			51% <sup>c</sup> (convn 79%)

<sup>a</sup> Isolated yield after silica gel chromatography. <sup>b</sup> Rh(CO)<sub>2</sub>(acac) 1 mol %, biphephos 3 mol %, *p*TSA·H<sub>2</sub>O 10 mol %, H<sub>2</sub>/CO (1:1) 5 bar, MeOH [0.04 M], 50 °C, 4 h. <sup>c</sup> Rh(CO)<sub>2</sub>(acac) 2 mol %, triphenylphosphite 8 mol %, H<sub>2</sub>/CO (1:1) 20 bar, THF [0.04 M], 65 °C, 24 h.

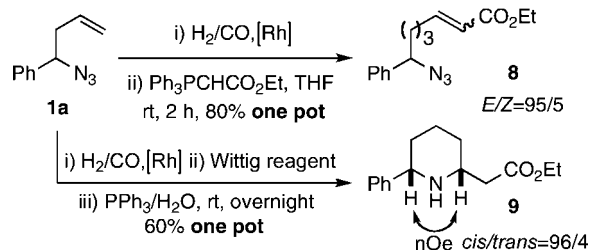
phite as coligand at high pressure of *syngas* (20 bar) led to the branched azido-aldehyde **5** in a moderate yield with incomplete conversion (entry 10).

With this practical method in hand, we first embarked on the synthesis of a well-known alkaloid, (±)-sedamine (**7**), starting from **2g**.<sup>4,14</sup> The *N*-methyl piperidine **6** was obtained with the following one-pot reduction protocol (Scheme 1): azido-aldehyde **2g** was reduced to the primary amine with Pearlman's catalyst in presence of aqueous formaldehyde. After TBS deprotection in **6**, (±)-sedamine was obtained in 34% overall yield in eight steps from benzaldehyde. This new procedure represents an alternative to the piperidine syntheses by ring-closing metatheses from 1,3-hydroxy homoallyl-amines, if atom- and step-economy are considered.<sup>3a,15</sup>

**Scheme 1.** Synthesis of (±)-Sedamine


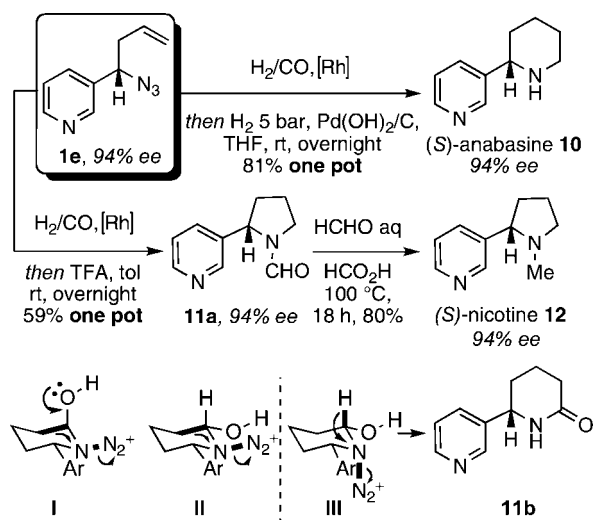
Next, the azido group was considered as an orthogonal protection of the amino function with respect to the aldehyde in compounds **1a–h**. Indeed the aldehyde function produced by hydroformylation can be employed for performing a Wittig reaction in a one-pot manner.<sup>15</sup> For instance the generation of an  $\alpha,\beta$ -unsaturated ester can be amenable to an in situ aza-Michael addition via the nitrene generated from the azido group. With this sequence, the formation of 2,6-disubstituted piperidine rings could be expected.

To illustrate this strategy, we first investigated a one-pot hydroformylation/Wittig olefination using **1a** as azido-olefin and ethyl-(triphenylphosphoranylidene)-acetate as the Wittig reagent. Thus the hydroformylation reaction was performed on **1a** (entry 1, Table 2), the gas was released, and then the Wittig reagent was added into the crude reaction mixture, which produced enoate **8** in 80% isolated yield. When enoate **8** was directly submitted to the classical Staudinger conditions, piperidine **9** (*cis/trans* = 96/4) was obtained in a one-pot fashion with an overall yield of 60%. To our knowledge this sequence represents, the first one-pot hydroformylation/Wittig olefination/Staudinger reaction/Michael addition (Scheme 2).

**Scheme 2.** One-Pot Access to 2,6-Disubstituted Piperidine **9**


Finally the chiral pyridinyl-homoallylazide **1e**<sup>16</sup> was recognized as an ideal substrate for a hydroformylative skeletal diversity oriented synthesis of two major alkaloids from *Nicotiana tabacum*, (*S*)-anabasine (**10**) and (*S*)-nicotine (**12**). Thus after hydroformylation of azido-alkene **1e**, replacement of the *syngas* by hydrogen allowed reduction of the azide followed by an intramolecular domino reductive amination in the presence of Pearlman's catalyst. This one-pot sequence allowed us to obtain (*S*)-anabasine (**10**) in 81% yield and 94% ee (four steps from 3-pyridinecarboxaldehyde, 61% overall yield; Scheme 3).

**Scheme 3.** Diversity Oriented Synthesis of (*S*)-Anabasine and (*S*)-Nicotine via a One-Pot Hydroformylation/Hydrogenation and Hydroformylation/Schmidt Rearrangement



The synthesis of (*S*)-nicotine (**12**) from azido-alkene/aldehyde **1e/2e** required the construction of a pyrrolidine unit from an open chain structure. Recently Aubé showed that  $\gamma$ - or  $\delta$ -azidoalkyl aldehydes were amenable to lactams or formamides via an intramolecular Schmidt rearrangement.<sup>17</sup> Therefore homochiral aldehyde **2e**, with an aryl residue next to the azido group, is a good candidate to explore the intramolecular azido-aldehyde conversion into the corresponding chiral formamide. Indeed (*S*)-nicotine was prepared from **1e** by performing the hydroformylation reaction in toluene followed by the addition of TFA upon *syngas* removal. Full conversion was observed, formamide **11a** was by far the major adduct over lactam **11b** (**11a/11b** = 4/1). Finally pure formamide **11a** was treated with formic acid and aqueous formaldehyde to furnish (*S*)-nicotine (**12**) (five steps from 3-pyridine carboxaldehyde, 35% overall yield, 94% ee).<sup>18</sup> As a rationale, the formation of formamide **11a** can be explained by the two favorable conformers **I** and **II** where the equatorial leaving group is antiperiplanar to the migrating alkyl group. Although the large aryl group is in the equatorial position in both **I** and **II** conformers, the anomeric effect probably favors conformer **I**. Noteworthy and contrary to Aubé's observations, the lactam product **11b** is formed in traceable quantities, demonstrating that hydride

migration is possible in larger ring sizes through the postulated conformer **III**.

In conclusion, we have shown that azides are compatible with certain conditions of hydroformylation. Thus, starting from easily accessible homoallylic azides, we could implement the hydroformylation reaction in several one-pot protocols (hydrogenation/Wittig olefination/Staudinger reaction/Michael addition/Schmidt rearrangement) representing new ways for the expeditive assembly of piperidine- and pyrrolidine-containing alkaloids in an atom-economic manner. Extension of this methodology toward the synthesis of other alkaloids is underway.

**Acknowledgment.** This work was supported by the Ministère délégué à l'Enseignement Supérieur et à la Recherche (T.S.). The authors thank P. Wehrung and P. Buisine (IFR85) for HRMS analyses, G. Ferenbach (ALU Freiburg) for chiral HPLC analyses, and Dr. M. Keller (ALU Freiburg) for helpful NMR experiments.

**Supporting Information Available:** Detailed experimental procedures and spectral and analytical data for all of the compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL802314G

- (6) (a) Pearson, W. H.; Lin, K.-C. *Tetrahedron Lett.* **1990**, *31*, 7571. (b) Martin, M.-T.; Marazano, C. *J. Org. Chem.* **2002**, *67*, 1890.
- (7) Trost, B. M. *Angew. Chem., Int. Ed.* **1995**, *34*, 259.
- (8) For a review of one-pot and tandem reactions using hydroformylation, see: Eilbracht, P.; Bärfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbick, R.; Schmidt, A. *Chem. Rev.* **1999**, *99*, 3329.
- (9) For a review on the chemistry of azides, see: Bräse, V.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188.
- (10) Cuny, G. D.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 2066.
- (11) Seiche, W.; Schuschkowski, A.; Breit, B. *Adv. Synth. Catal.* **2005**, *347*, 1488.
- (12) (a) Zallom, J.; Roberts, D. C. *J. Org. Chem.* **1981**, *46*, 5173. (b) Alper, P. B.; Hung, S.-C.; Wong, C.-H. *Tetrahedron Lett.* **1996**, *37*, 6029. (c) Lundquist, J. T., IV; Pelletier, J. C. *Org. Lett.* **2001**, *3*, 781.
- (13) Homoallylic azides were prepared from their corresponding alcohols via allylation (**1a–1f**) or Sakurai reactions (**1g**) followed by a  $S_N2$  reaction and finally from primary amines via a diazo transfer reaction (**1h**): see Supporting Information.
- (14) (a) Batey, R. A.; Thadani, A. N.; Smil, D. V.; Lough, A. J. *Synthesis* **2000**, *7*, 990. (b) Borah, J. C.; Boruwa, J.; Barua, N. C. *Lett. Org. Chem.* **2006**, *3*, 140.
- (15) Breit, B.; Zahn, S. K. *Angew. Chem., Int. Ed.* **1999**, *38*, 969. Breit, B.; Zahn, S. K. *Angew. Chem., Int. Ed.* **2001**, *40*, 1910. Breit, B.; Zahn, S. K. *Tetrahedron* **2005**, *61*, 6171.
- (16) Felpin, F.-X.; Girard, S.; Vo-Thanh, G.; Robins, R. J.; Villiéras, J.; Lebreton, J. *J. Org. Chem.* **2001**, *66*, 6305.
- (17) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449. Lee, H.-L.; Aubé, J. *Tetrahedron* **2007**, *63*, 9007.
- (18) Mahboobi, S.; Wiegerebe, W. *Arch. Pharma.* **1988**, *321*, 175.