

Total Synthesis of Sedum Alkaloids via Catalyst Controlled aza-Cope Rearrangement and Hydroformylation with Formaldehyde

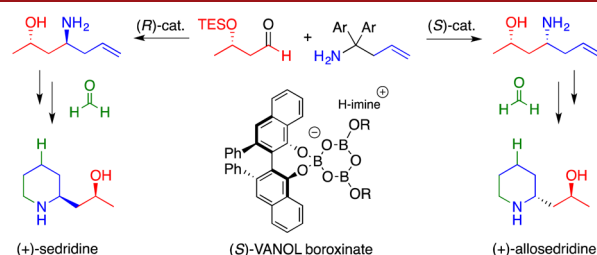
Hong Ren and William D. Wulff*

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824,
United States

Wulff@chemistry.msu.edu

Received October 8, 2012

ABSTRACT



The catalytic asymmetric aminoallylation of chiral aldehydes is developed as a new method for the catalyst controlled synthesis of *syn*- and *anti*-1,3-aminoalcohols. This methodology is highlighted in the synthesis of the sedum alkaloids (+)-sedridine and (+)-allosedridine both of which have their final carbon incorporated during closure of the piperidine ring via a hydroformylation with formaldehyde.

The sedum alkaloids exist widely in nature, and these types of alkaloids have memory-enhancing properties and are effective in the treatment of cognitive disorders.¹ The most commonly occurring members of this alkaloid family are 2-substituted piperidines with various combinations of hydroxyl functionalities in the side chains, featuring the

(1) Meth-Cohn, O.; Yu, C. Y.; Lestage, P.; Lebrun, M. C.; Cagniard, D. H.; Renard, P. *Eur. Pat.* 1050531, 2000.

(2) For a review, see: Bates, R. W.; Sa-Ei, K. *Tetrahedron* **2002**, 58, 5957–5978.

(3) For examples after 2008, see: (a) Chen, L.-J.; Hou, D.-R. *Tetrahedron: Asymmetry* **2008**, 19, 715–720. (b) Chang, M. Y.; Lin, C. Y.; Wu, T. C.; Sun, P. P. *J. Chin. Chem. Soc.* **2008**, 55, 421–430. (c) Rice, G. T.; White, M. C. *J. Am. Chem. Soc.* **2009**, 131, 11707–11711. (d) Wang, G.; Vedejs, E. *Org. Lett.* **2009**, 11, 1059–1061. (e) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Smith, A. D. *Tetrahedron* **2009**, 65, 10192–10213. (f) Lebrun, S.; Couture, A.; Deniau, E.; Grandclaude, P. *Chirality* **2010**, 212–216. (g) Shaikh, T. M.; Sudalai, A. *Eur. J. Org. Chem.* **2010**, 3437–3444. (h) Coldham, I.; Leonori, D. *J. Org. Chem.* **2010**, 75, 4069–4077. (i) Bates, R. W.; Lu, Y. *Org. Lett.* **2010**, 12, 3938–3941. (j) Boussonniere, A.; Ranaivondrambola, T.; Lebreton, J.; Mathe-Allainmat, M. *Synthesis* **2010**, 2456–2462. (k) Liu, J.-D.; Chen, Y.-C.; Zhang, G.-B.; Li, Z.-Q.; Chem, P.; Du, J.-Y.; Tu, Y.-Q.; Fan, C.-A. *Adv. Synth. Catal.* **2011**, 353, 2721–2730. (l) Riva, E.; Rencurosi, A.; Gagliardi, S.; Passarella, D.; Martinelli Chem.—*Eur. J.* **2011**, 17, 6221–6226. (m) Satyalakshmi, G.; Suneel, K.; Shinde, D. B.; Das, B. *Tetrahedron: Asymmetry* **2011**, 22, 1000–1005. (n) Bhat, C.; Tilve, S. *Tetrahedron Lett.* **2011**, 52, 6566–6568.

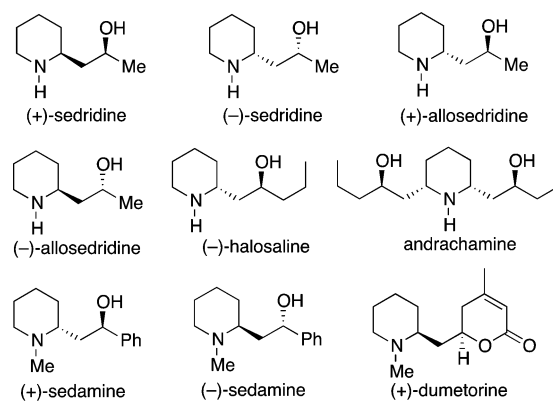
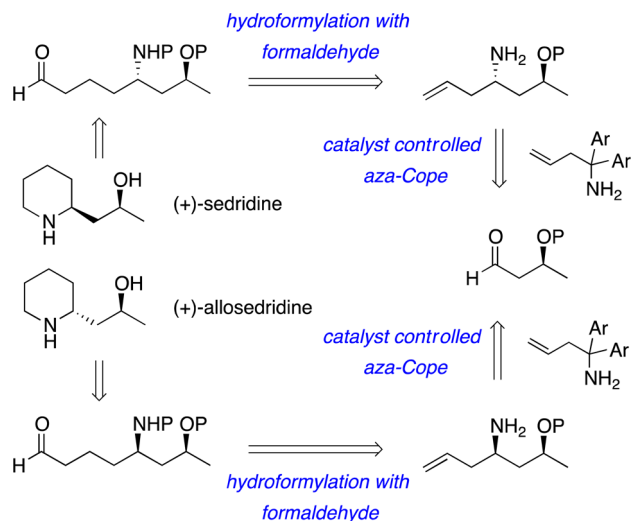


Figure 1. Sedum and related alkaloid natural products.

1,3-amino alcohol moiety, and a select set are shown in Figure 1.² A review of the syntheses of sedum alkaloids has appeared,² and the field has remained very active.³

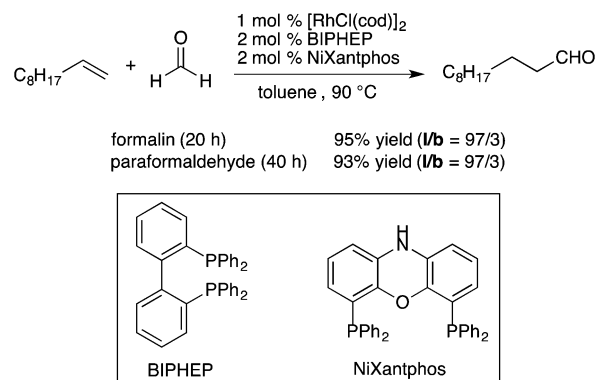
Our efforts in this field began with an interest in developing an approach to the sedum alkaloids that has a

Scheme 1. Retrosynthesis of (+)-Sedridine and (+)-Allosedridine

hydroformylation with formaldehyde and a catalyst controlled asymmetric aza-Cope rearrangement (or amino-allylation) as the key steps (Scheme 1). The catalyst controlled aza-Cope rearrangement was envisioned to be featured in ordered stereoselective syntheses of (+)-sedridine and (+)-allosedridine which constitute one of the diastereomeric pairs of natural products in the sedum alkaloid family.⁴

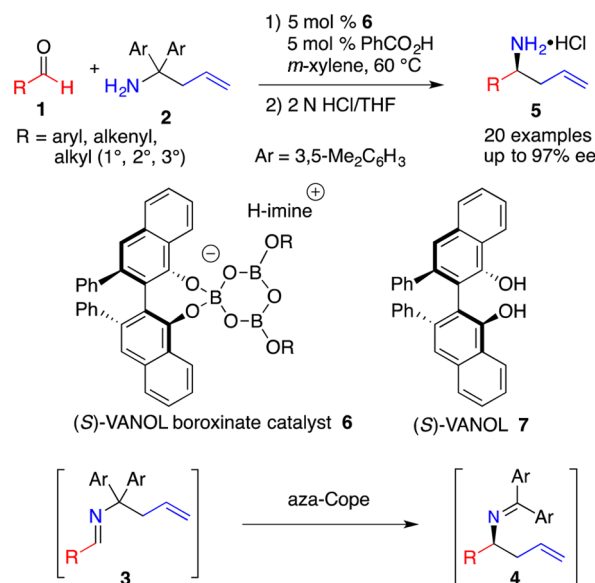
Conventionally, hydroformylation utilizes syngas (CO/H₂) in the presence of a transition metal catalyst to give homologous linear and/or branched aldehydes. A recent innovation in hydroformylation chemistry features an experimentally convenient alternative using formaldehyde as a syngas substitute. This synthetically attractive method was recently described by Morimoto and co-workers when they smartly applied two types of in situ generated catalysts to separately direct the two cooperative catalytic processes involved: (1) decarbonylation of an aldehyde and (2) hydroformylation of an olefin (Scheme 2).⁵ This dual catalyst system provides homologated aldehydes in excellent yields and with very high linear to branched ratios. The intention for the application of this hydroformylation in the synthesis of sedum alkaloids will be to incorporate it into an intramolecular amidocarbonylation⁶ that takes the alkenyl amino alcohol directly to a piperidine ring.

The key transformation in the synthesis of sedridine and allosedridine involves an aza-Cope rearrangement of an in situ generated imine **3** to give imine **4** which upon hydrolysis provides the homoallylic amine **5** in high asymmetric inductions over a broad range of aromatic, alkenyl, and aliphatic substrates.⁷ The successful catalyst system results

Scheme 2. Hydroformylation with Formaldehyde

from the incorporation of a molecule of benzoic acid into the VANOL boroxinate catalyst **6**.^{7,8}

The pertinent issue to address here is whether the presence of a chiral center in the aldehyde **1** (Scheme 3) will interfere with the normal operations of the boroxinate/benzoate catalyst in the aza-Cope rearrangement? If the answer is no then this reaction would represent a new method for the controlled synthesis of *syn*- and *anti*-1,3-aminoalcohols. The controlled synthesis of both *syn*- and *anti*-1,3-aminoalcohols from a single substrate have been

Scheme 3. Direct Aminoallylation of Nonchiral Aldehydes

(4) For leading references, see ref 3s and: (a) Butruille, D.; Fodor, G.; Huber, C. S.; Letourneau, F. *Tetrahedron* **1971**, 27, 2055–2067.

(5) Makado, G.; Morimoto, T.; Sugimoto, Y.; Tsutsumi, K.; Kagawa, N.; Kiuchi, K. *Adv. Synth. Catal.* **2010**, 352, 299–304.

(6) For a review on intramolecular amidocarbonylation, see: Chiou, W.; Lee, S.; Ojima, I. *Can. J. Chem.* **2005**, 83, 681–692.

(7) Ren, H.; Wulff, W. D. *J. Am. Chem. Soc.* **2011**, 133, 5656–5659.

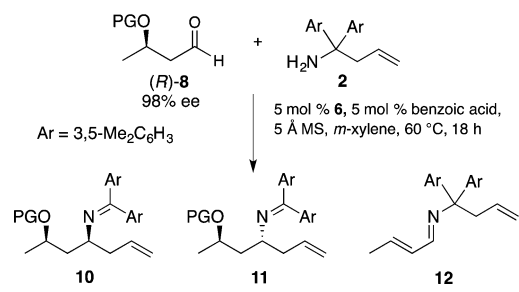
(8) (a) Hu, G.; Gupta, A. K.; Huang, R. H.; Mukherjee, M.; Wulff, W. D. *J. Am. Chem. Soc.* **2010**, 132, 14669–14675. (b) Veticatt, M. J.; Desai, A. A.; Wulff, W. D. *J. Am. Chem. Soc.* **2010**, 132, 13104–13107.

(9) (a) Pillim, R. A.; Russowsky, D.; Dias, L. C. *J. Chem. Soc., Perkin Trans. I* **1990**, 1213–1214. (b) Keck, G. E.; Truong, A. P. *Org. Lett.* **2002**, 4, 3131–3134. (c) Davis, F. A.; Gaspari, P. M.; Nolt, B. M.; Xu, P. *J. Org. Chem.* **2008**, 73, 9619–9626. (d) Gonzalez-Gomez, J. C.; Foubelo, F.; Yus, M. *Synthesis* **2009**, 2083–2088. (e) De Lamo Marin, S.; Catala, C.; Kumar, S. R.; Valleix, A.; Wagner, A.; Mioskowski, C. *Eur. J. Org. Chem.* **2010**, 3985–3989.

reported from β -aminoketones⁹ and β -borylamines.¹⁰ We only know of a single example where a catalyst controlled process can be used to access *syn*- or *anti*-1,3-aminoalcohols from a single substrate.^{11,12}

The initial screen of chiral aldehydes was carried out with the TBS protected aldehyde (*R*)-**8a** derived from the commercially available methyl (*R*)-3-hydroxybutyrate (Table 1). The diastereoselectivity is nearly equal and

Table 1. Direct Aminoallylation of Chiral β -Alkoxy Aldehydes



entry ^a	series	ligand	PG	conv (%) ^b	(10 + 11): 12 ^c	10 : 11 ^d	% yield (10 + 11) ^e
1	a	(<i>R</i>)-VANOL	TBS	73 (70)	3:1	33:1	48
2	a	(<i>S</i>)-VANOL	TBS	72 (67)	4:1	1:23	44
3	b	(<i>R</i>)-VANOL	Bn	(80)	4:1	nd	nd
4	c	(<i>R</i>)-VANOL	TBDPS	(52)	1:10	nd	nd
5 ^f	d	(<i>R</i>)-VANOL	TES	100	100:0	1:20	87
6 ^f	d	(<i>S</i>)-VANOL	TES	100	100:0	26:1	74

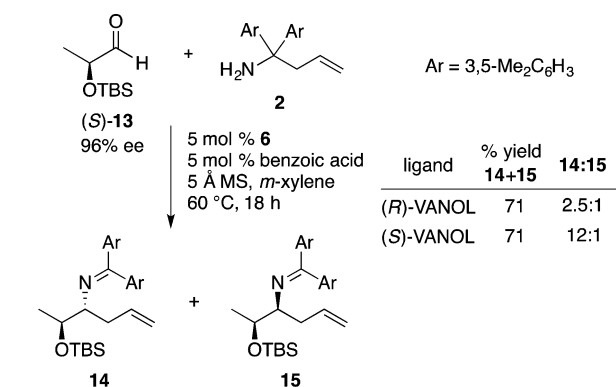
^a Unless otherwise specified all reactions were run at 0.2 M in amine **2** with 1.1 equiv of **8**. The catalyst was prepared from 1 equiv of the ligand, 2 equiv of 2,4,6-trimethylphenol, 3 equiv of H₂O, and 3 equiv BH₃·SMe₂. nd = not determined. ^b Calculated from the ¹H NMR spectrum of the crude reaction mixture from the ratio (**10** + **11**):**2** (or **2** + imine **9**) and the isolated yield of **10** + **11**. The value in parentheses based on the ratios of **2** (or **2** + imine **9**), **10**, **11**, and **12** and assuming no other products are formed. In most cases, the unreacted material is in the form of amine **2**, but in some cases a small amount of imine **9** formed from **8** and **2** is present. ^c Determined from the ¹H NMR spectrum of the crude reaction mixture. ^d Isolated ratio. ^e Isolated yield of a mixture of **10** + **11** after chromatography on silica gel. ^f Reaction performed on (*S*)-**8** also of 98% ee. This reaction gives the enantiomer of **10** and **11**.

opposite with the (*R*)- and (*S*)-ligands of VANOL (33:1 vs 1:23), and thus this is a case of catalyst control (entries 1 and 2). The total yield of **10a** and **11a** was low, and the elimination product **12** was observed as a byproduct. The reaction of the benzyl protected aldehyde **8b** with amine **2** gave a 4:1 mixture of aza-Cope product (**10b** + **11b**) and byproduct **12** (entry 3). Incorporation of a larger protecting group (TBDPS) lead to a mixture largely consisting of the eliminated imine **12** (entry 4). However, when the sterically less hindered triethylsilyl protecting group (TES) was installed, the formation of **12** was completely shut

down (Table 1, entry 5) giving an 87% yield and a 20:1 diastereoselectivity in favor of **11** with (*R*)-VANOL and a 74% yield and a 26:1 diastereoselectivity in favor of **10** with (*S*)-VANOL (these two reactions were with (*S*)-**8**).

The interplay of the catalyst with a pre-existing α -chiral center was also investigated. As shown in Scheme 4, the reaction of the chiral aldehyde (*S*)-**13** is not under catalyst control but rather displays a matched and mismatched relationship. A 12:1 selectivity was observed for the matched case with the (*S*)-VANOL catalyst resulting in a 71% isolated yield. The same diastereomer predominated in the mismatched case with the (*R*)-VANOL catalyst, but the selectivity dropped to 2.5:1. The stereochemistry of **14** was assigned as anti since the matched case would be expected to be with the *Re*-face addition to the imine with the (*S*)-VANOL catalyst since this is the preference with nonchiral aldehydes.⁷

Scheme 4. Direct Aminoallylation of a Chiral α -Alkoxy Aldehyde



When Morimoto's protocol was applied to an intramolecular amidocarbonylation with a homoallylic amine, some branched hydroformylation and other side products were obtained. When formalin, which contains methanol as a stabilizer, was utilized as the formaldehyde source, a significant amount of the 2-alkoxypiperidine **18** was observed in the ¹H NMR spectrum of the crude reaction mixture (Table 2, entry 1). *para*-Formaldehyde gave didehydropiperidine **17** and its five-membered analog **19** along with some of the olefin isomerization product **20**. Even with less than complete regio- and chemoselection, the didehydropiperidine **17** could be obtained in 73% isolated yield (Table 2, entry 3).¹³

The intramolecular amidocarbonylation was then applied to the synthesis of (–)-coniine **22**. The chiral center is installed in acyclic amine **21** in 83% yield and 95% ee with catalytic asymmetric direct aminoallylation of *n*-butanal as shown in Scheme 5.⁷ The piperidine ring is closed using the intramolecular amidocarbonylation in 71% yield. Subsequent reduction of the double bond and cleavage of Boc

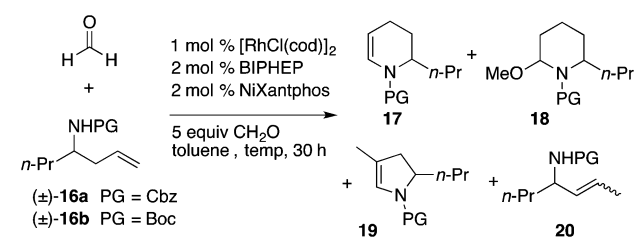
(10) Sole, C.; Whiting, A.; Gulyas, H.; Fernandez, E. *Adv. Synth. Catal.* **2011**, 353, 376–384.

(11) Jha, V.; Kondekar, N. B.; Kumar, P. *Org. Lett.* **2010**, 12, 2762–2765.

(12) Another example would presumably be a catalyst controlled process if the enantiomer of the enzyme was available: Millet, R.; Traff, A. M.; Petrus, M. L.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2010**, 132, 15182–15184.

(13) 2-Alkoxypiperidines and didehydropiperidines are both useful intermediates for the synthesis of piperidine compounds,⁶ and in the present case both could be reduced to provide access to the target alkaloids. This possibility was not pursued in the present work.

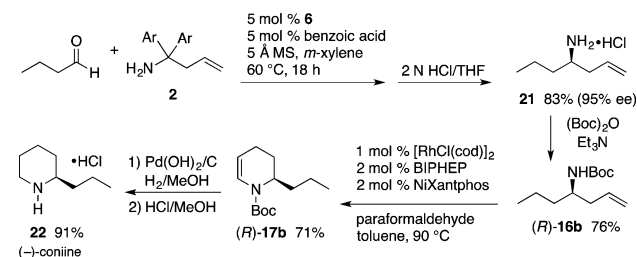
Table 2. Optimization of the Intramolecular Amidocarbonylation with Formaldehyde



entry ^a	PG	formaldehyde source	temp (°C)	yield 17 (%) ^b	17:19:20 ^c
1	Cbz	formalin	90	46	— ^d
2	Cbz	paraformaldehyde	90	69	6:1:1
3	Boc	paraformaldehyde	90	73	6:1:1
4 ^e	Boc	paraformaldehyde	90	nd	2:3:0

^a Unless otherwise specified all reactions were run at 0.15 M in 16 with 5.0 equiv of formaldehyde. nd = not determined. ^b Isolated yield after chromatography on silica gel. ^c Calculated from the ¹H NMR spectrum of the crude reaction mixture. ^d A 38% yield of **18** also formed in this reaction. ^e PPTS (5 mol %) was added to this reaction.

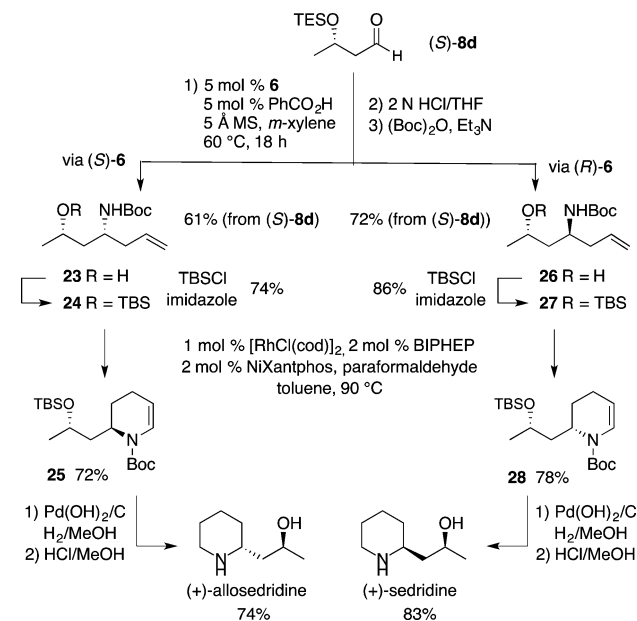
Scheme 5. Synthesis of (–)-Coniine



give the target compound (–)-coniine **22** in 91% yield over two steps.

Finally, we coupled the catalyst controlled aza-Cope rearrangement and intramolecular amidocarbonylation in the total synthesis of (+)-sedridine and (+)-allosedridine (Scheme 6). Chiral aldehyde (*S*)-**8d** was subjected to a diastereoselective aza-Cope rearrangement catalyzed by the boroxinate catalyst **6** derived from (*R*)-VANOL (Scheme 6). Following hydrolysis and protection with a Boc group, purification gave **26** as a single diastereomer in 72% yield over three steps in a one-pot fashion. After protection an intramolecular amidocarbonylation reaction afforded **28** in 78% yield. Reduction and deprotection

Scheme 6. Synthesis of (+)-Sedridine and (+)-Allosedridine



gave (+)-sedridine in 83% yield. (+)-Allosedridine was obtained in a similar manner utilizing the boroxinate catalyst **6** derived from (*S*)-VANOL which allowed for the isolation of **23** in 61% yield as a single diastereomer. Protection with TBS and hydroformylation with formaldehyde gave **25** in 72% yield and subsequently a final conversion to (+)-allosedridine in 74% yield in two steps.

This work has demonstrated that chiral aldehydes bearing a β -alkoxy group will undergo a chiral Brønsted acid catalyzed 2-aza-Cope rearrangement with an in situ generated imine to give either *syn*- or *anti*-1,3-homoallylic amino alcohols depending on the absolute configuration of the catalyst. This catalyst controlled 2-aza-Cope rearrangement is coupled with a syngas-free hydroformylation in a highly stereoselective synthesis of (+)-sedridine and (+)-allosedridine from the same β -alkoxy aldehyde.

Acknowledgment. Support provided by the National Institute of General Medical Sciences (GM094478).

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

The authors declare no competing financial interest.