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Synthesis of Enantiopure Dehydropiperidinones from α-Amino Acids and Alkynes via Azetidin-3-ones

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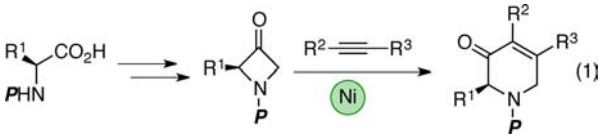
ABSTRACT

Chiral dehydropiperidinones were synthesized in enantiopure form from α-amino acids and alkynes via azetidin-3-ones.

Substituted piperidines are found in numerous natural alkaloids, pharmaceuticals, and agrochemicals as a privileged structural motif.[1] Although a wide variety of methods for their synthesis have been developed,[2] new pathways leading to their enantiopure forms starting from readily available substances are still in demand. We now report the synthesis of chiral dehydropiperidinones[3] in enantiopure form from α-amino acids and alkynes via azetidin-3-ones (eq 1).[4]



We previously reported the nickel-[5] and rhodium-catalyzed[6] insertion of alkynes and alkenes into carbon–carbon single bonds of cyclobutanones to construct complex carbocyclic skeletons. This straightforward synthetic strategy based on carbon–carbon bond activation[7] significantly improved the step as well as atom economies of the synthesis of chiral benzobicyclo[2.2.2]octenones.[5d] On the basis of these results, we next directed our attention to azetidin-3-ones, which were readily synthesized in enantiopure form from α-amino acids according to Seebach's method (Scheme 1).[8] For example, commercially available *N*-Boc-(L)-alanine was treated with ethyl chloroformate/triethylamine, and subsequently

(1) (a) Escolano, C.; Amat, M.; Bosch, J. *Chem.—Eur. J.* **2006**, *12*, 8198. (b) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139. (c) Chemler, S. A. *Curr. Bioact. Compd.* **2009**, *5*, 2.

(2) For recent examples of enantioselective synthesis of substituted piperidine derivatives, see: (a) Stead, D.; Carbone, G.; O'Brein, P.; Campos, K. R.; Coldham, I.; Sanderson, A. *J. Am. Chem. Soc.* **2010**, *132*, 7260. (b) Beng, T. K.; Gawley, R. E. *J. Am. Chem. Soc.* **2010**, *132*, 12216. (c) Cui, L.; Li, C.; Zhang, L. *Angew. Chem., Int. Ed.* **2010**, *49*, 9178. (d) Seki, H.; Georg, G. I. *J. Am. Chem. Soc.* **2010**, *132*, 15512. (e) Nadeau, C.; Aly, S.; Belyk, K. *J. Am. Chem. Soc.* **2011**, *133*, 2878. (f) Seel, S.; Thaler, T.; Takatsu, K.; Zhang, C.; Zipse, H.; Straub, B. F.; Mayer, P.; Knochel, P. *J. Am. Chem. Soc.* **2011**, *133*, 4774. (g) Wong, H.; Garnier-Amblard, E. C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2011**, *133*, 7517 and references cited therein.

(3) For synthesis of dehydropiperidinones, see: (a) Cassldy, M. P.; Padwa, A. *Org. Lett.* **2004**, *6*, 4029. (b) Donohoe, T. J.; Fishlock, L. P.; Basutto, J. A.; Bower, J. F.; Procopiou, P. A.; Thompson, A. L. *Chem. Commun.* **2009**, 3008. (c) Husain, I.; Saquib, M.; Bajpai, V.; Kumar, B.; Shaw, A. K. *J. Org. Chem.* **2011**, *76*, 8930.

(4) During preparation of this manuscript, Aïssa and Louie independently reported a closely related nickel-catalyzed reaction, giving achiral dehydropiperidinone using nonsubstituted azetidin-3-ones except for one example: (a) Ho, K. Y. T.; Aïssa, C. *Chem.—Eur. J.* **2012**, *18*, 3486. (b) Kumar, P.; Louie, J. *Org. Lett.* **2012**, *14*, 2026.

(5) (a) Murakami, M.; Ashida, S.; Matsuda, T. *J. Am. Chem. Soc.* **2005**, *127*, 6932. (b) Murakami, M.; Ashida, S.; Matsuda, T. *J. Am. Chem. Soc.* **2006**, *128*, 2166. (c) Ashida, S.; Murakami, M. *Chem. Commun.* **2006**, 4599. (d) Liu, L; Ishida, N.; Murakami, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 2485.

(6) For rhodium-catalyzed alkene insertion reactions into cyclobutanones, see: (a) Murakami, M.; Itahashi, T.; Ito, Y. *J. Am. Chem. Soc.* **2002**, *124*, 13976. (b) Matsuda, T.; Fujimoto, A.; Ishibashi, M.; Murakami, M. *Chem. Lett.* **2004**, *33*, 876.

(7) For reviews on transition-metal-catalyzed cleavage of carbon–carbon bonds: (a) Miura, M.; Satoh, T. *Top. Organomet. Chem.* **2005**, *14*, 1. (b) Kondo, T.; Mitsudo, T. *Chem. Lett.* **2005**, *34*, 1462. (c) Nečas, D.; Kotora, M. *Curr. Org. Chem.* **2007**, *11*, 1566. (d) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (e) Winter, C.; Krause, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 2460. (f) Seiser, T.; Cramer, N. *Org. Biomol. Chem.* **2009**, *7*, 2835. (g) Murakami, M.; Matsuda, T. *Chem. Commun.* **2011**, *47*, 1100. (h) Aïssa, C. *Synthesis* **2011**, 3389.

(8) (a) Podlech, J.; Seebach, D. *Helv. Chim. Acta* **1995**, *78*, 1238. (b) Wang., J; Hou, Y.; Wu, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2277.

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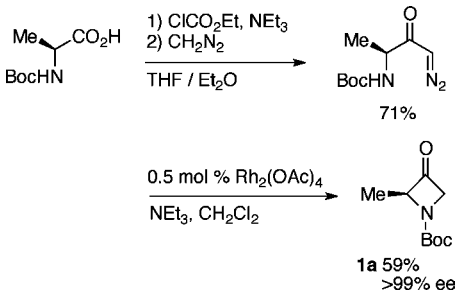
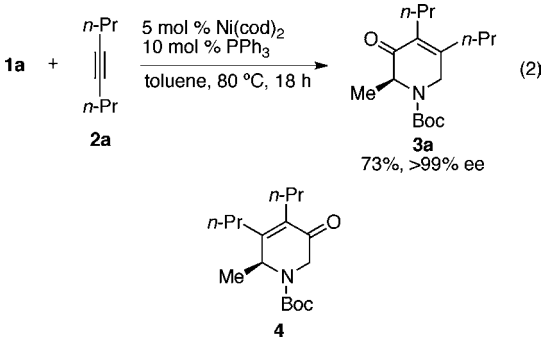
Scheme 1. Synthesis of Azetidin-3-ones



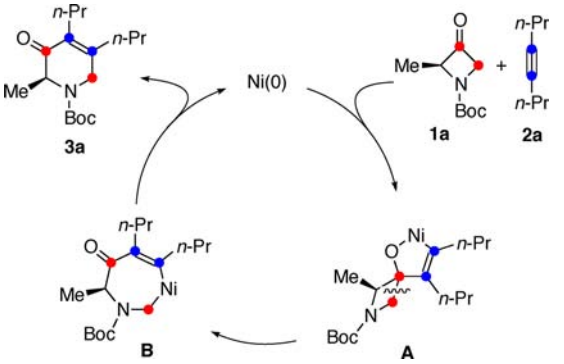
with diazomethane, to afford the diazomethyl ketone. Upon treatment of this species with dimeric rhodium(II) acetate, cyclization spontaneously occurred with the release of molecular nitrogen to furnish azetidin-3-one **1a** with stereochemical integrity.

The azetidinone **1a** thus obtained was next reacted with 4-octyne (**2a**, 1.5 equiv) in the presence of $Ni(cod)_2$ (5 mol %) and PPh_3 (10 mol %)[9] in toluene (eq 2). The insertion of **2a** between the carbonyl carbon and the α-methylene carbon successfully took place at 80 °C to afford (*S*)-α-methylpiperidinone **3a** in 73% isolated yield. Analysis of **3a** by HPLC verified that the stereochemical integrity was retained again. Compound **4**, the isomer possibly arising from insertion between the carbonyl carbon and the other α-carbon having a methyl substituent on it, was not formed.



Thus, the single bond between the carbonyl carbon and the α-methylene carbon was site-selectively cleaved, and the carbon−carbon triple bond was inserted therein. We assume the mechanistic pathway shown in Scheme 2, which involves oxidative cyclization on nickel(0),[10,11] as in the case of cyclobutanones.[5a] Initially, the carbonyl group of azetidin-3-one **1a** and alkyne **2a** are coupled on nickel(0) to afford spirocyclic oxanickelacyclopentene **A**, which possesses two kinds of strained carbons located γ to nickel,

Scheme 2. Plausible Mechanism



i.e., a methylene carbon and a methyl-substituted carbon. Whereas both are potentially amenable to migration onto nickel by β-elimination, the methylene carbon selectively migrates, probably due to steric reasons. As a result, the two rings are merged to expand into seven-membered nickelacycle **B**.[12] Finally, reductive elimination gives six-membered ring product **3a** with regeneration of the nickel(0) catalyst.

Various dehydropiperidinones were synthesized in an analogous manner to **3a** (Table 1). First, *N*-Boc- and *N*-Cbz-azetidin-3-ones **1b**−**1e** were prepared in enantiopure form from the corresponding α-amino acids, i.e., phenylalanine, valine, lysine, and methionine respectively, by Seebach's method.[8] When subjected to the nickel catalysis, they all underwent alkyne insertion without any difficulties which the presence of the amino and thio functionalities might potentially bring forth. The corresponding piperidinones **3b**−**3e** were obtained in moderate to good isolated yields (entries 1−4). Stereochemical integrity was retained with **1c** derived from valine, whereas a very slight but measurable racemization was detected with **1b**, **1d**, and **1e**. Unsubstituted achiral azetidin-3-ones **1f**−**h**[13] also underwent the insertion reaction. In addition to carbamate-type *N*-protective groups, benzhydryl and *p*-toluenesulfonyl groups were also suitable for the nitrogen substituent (entries 5 and 6). Whereas PPh_3 was the choice of ligand with carbamates **1a**−**e**,**h** and sulfonamide **1g**, the use of more electron-donating PCy_3 gave better results with benzhydryl-protected azetidin-3-one **1f**. Good to high regioselectivities were observed with unsymmetrical alkynes **2b**−**e**. The bulkier *tert*-butyl and phenyl groups were placed selectively at the β-position (entries 2 and 7). This regioselectivity is explained based on sterics; when undergoing oxidative cyclization, the sterically demanding ketonic carbonyl carbon prefers to couple with the sp carbon attached to a less bulky substituent. Unlike the previous case with cyclobutanones,[5a] it was possible to insert alkynylstannanes **2d** and **2e** to give 2-stannylpiperidinones exclusively

(9) The use of NHC and other phosphine ligands including PCy_3, which was the ligand of choice for the reaction of cyclobutanones, gave a lower yield.

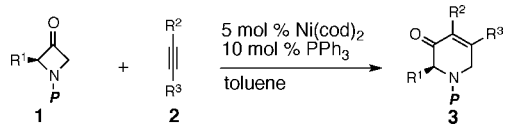
(10) For nickel-catalyzed reactions through oxidative cyclization between unsaturated hydrocarbons and carbonyl compounds, see: (a) *Modern Organonickel Chemistry*; Tamaru, Y., Ed.; Willey-VCH: Weinheim, Germany, 2005. (b) Ikeda, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5120. (c) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890. (d) Moslin, R. M.; Miller-Moslin, K.; Jamison, T. F. *Chem. Commun.* **2007**, 4441 and references cited therein.

(11) For direct observation of oxidative cyclization of carbonyls with alkenes, see: Ogoshi, S.; Oka, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2004**, *126*, 11082.

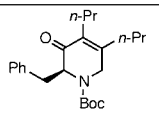
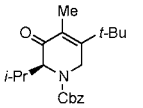
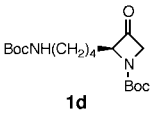
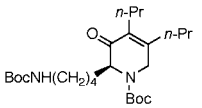
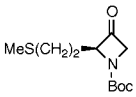
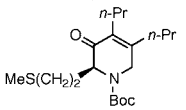
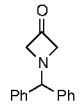
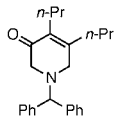
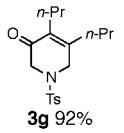
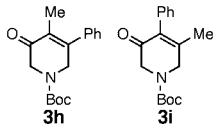
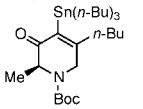
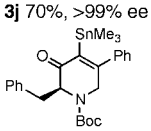
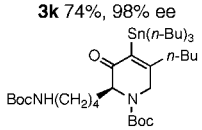
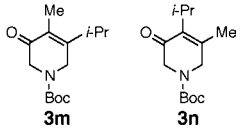
(12) For related reactions involving β-carbon elimination of spirocyclic metalacycles, see: (a) Murakami, M.; Takahashi, K.; Amii, H.; Ito, Y. *J. Am. Chem. Soc.* **1997**, *119*, 9307. (b) Matsuda, T.; Tsuboi, T.; Murakami, M. *J. Am. Chem. Soc.* **2007**, *129*, 12596. See also ref 5.

(13) An azetidinol to be oxidized to **1f**, *N*-H azetidinol hydrochloride to be derivatized to **1g**, and azetidin-3-one **1h** itself are commercially available.

Table 1. Insertion of Alkynes into Azetidin-3-ones[a]



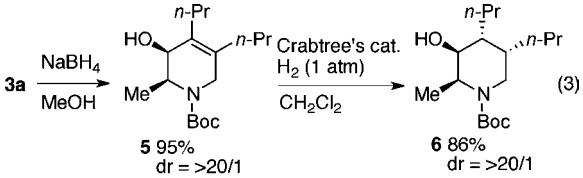
1 + 2 → 3

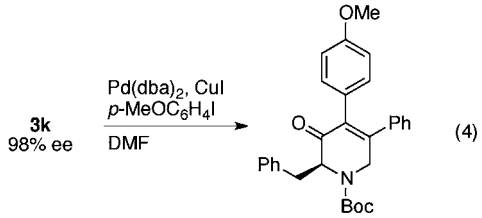
entry	1	2	3[b]
1	 **1b**	**2a**	 **3b** 84%, 97% ee
2	 **1c**	 **2b**	 **3c** 56%, >99% ee
3	 **1d**	**2a**	 **3d** 83%, 98% ee
4	 **1e**	**2a**	 **3e** 74%, 97% ee
5[c,d,e]	 **1f**	**2a**	 **3f** 82%
6[c,f]	 **1g**	**2a**	 **3g** 92%
7[c,f]	 **1h**	 **2c**	 **3h** (**3h**:**3i** = 95:5) **3i** 76%
8	**1a**	 **2d**	 **3j** 70%, >99% ee
9	**1b**	 **2e**	 **3k** 74%, 98% ee
10	**1d**	**2d**	 **3l** 76%, >99% ee
11[c,f]	**1h**	 **2f**	 **3m** (**3m**:**3n** = 61:39) **3n** 86%

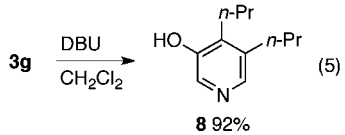
[a] Reaction conditions: 1.0 equiv of **1**, 1.5 equiv of **2**, 5 mol % $Ni(cod)_2$, 10 mol % PPh_3, toluene, 80 °C, 18 h unless otherwise noted. [b] Isolated yields. [c] 1.1 equiv of **2**. [d] Rt, 15 h. [e] PCy_3 was used instead of PPh_3. [f] 60 °C, 15 h.

(entries 8–10). The selectivity observed with **2d** and **2e** can be ascribed to the less electronegative nature of tin, which renders its α-carbon to be charged negatively. The positively charged carbonyl carbon prefers to couple with the negatively charged α-carbon rather than with the *β*-carbon.[14] The stannyl group thus set at the 2-position regioselectively could serve as the synthetic basis for allowing further carbon–carbon bond formation (vide infra). In contrast, less imbalanced unsymmetrical alkyne **2f** (R^2 = Me, R^3 = *i*-Pr) afforded a mixture of regioisomers (entry 11). Terminal alkynes such as 1-octyne and phenylethyne failed to participate in the insertion reaction because of their facile self-oligomerization.

Thus, the present insertion reaction renders it possible to derive dehydropiperidinones with various substituents, even containing functionalities, from natural α-amino acids. Further derivatization of the enantiopure products demonstrated their synthetic utility. Reduction of the piperidinone **3a** with sodium borohydride furnished piperidinol **5** stereoselectively with the arising hydroxyl group being oriented *cis* to the α-methyl substituent (95% yield, dr = >20:1, eq 3). Further stereoselective hydrogenation of **5** by the well-established method using Crabtree's catalyst afforded tetrasubstituted piperidine **6** in 86% yield.[15] The cross-coupling reaction of the stannyl-substituted dehydropiperidinone **3k** with 4-iodoanisole produced 4-anisylpiperidine **7** (77%, 98% ee, eq 4), which was unavailable with regioselective control from unsymmetrical anisylphenylethyne. Upon treatment of **3g** with DBU, *p*-toluenesulfinate was eliminated to give 4,5-disubstituted 3-hydroxypyridine **8**,[3b] which is the core structure of both pyridoxines and pyridinolines[16] (eq 5).







In summary, we have described the nickel-catalyzed reaction of azetidin-3-ones that selectively insert a triple

(14) For disscussions on the regioselectivity of oxidative cyclization on nickel, see: (a) Miller, K. M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 4130. (b) Miller, K. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 15342. (c) Sa-ei, K.; Montgomery, J. *Org. Lett.* **2006**, *8*, 4441. (d) Saito, N.; Katayama, T.; Sato, Y. *Org. Lett.* **2008**, *10*, 3829. (e) Malik, H. A.; Chaulagain, M. R.; Montgomery, J. *Org. Lett.* **2009**, *11*, 5734.

bond into one of their carbon−carbon bonds to furnish dehydropiperidinones. When combined with Seebach's method for azetidinone synthesis, the present reaction provides a reliable synthetic pathway to enantiopure piperidines with various substituents including functionalized ones starting from α-amino acids.

(15) The stereochemistry of **6** was assigned based on the premise that Crabtree's catalyst hydrogenates a cyclohexenol derivative selectively from the side *cis* to the directing hydroxyl group: Crabtree, R. G.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655.

(16) Fujimoto, D.; Moriguchi, T.; Ishida, T.; Hayashi, H. *Biochem. Biophys. Res. Commun.* **1978**, *84*, 52.

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

The authors declare no competing financial interest.