ORGANIC LETTERS

2009
Vol. 11, No. 21
4982−4985

Convergent Synthesis of Piperidines by the Union of Conjugated Alkynes with Imines: A Unique Regioselective Bond Construction for Heterocycle Synthesis

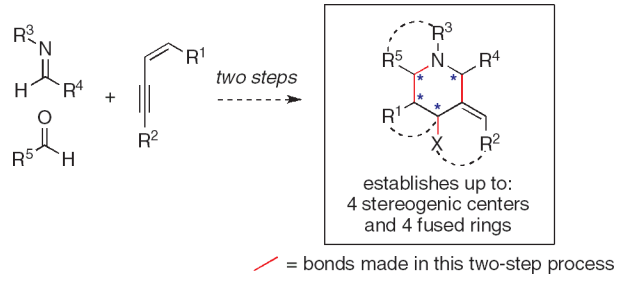
Ming Z. Chen and Glenn C. Micalizio*

Department of Chemistry, The Scripps Research Institute, Scripps Florida, Jupiter, Florida 33458

micalizio@scripps.edu

Received September 18, 2009

ABSTRACT



A two-step process is described for the union of aromatic imines, conjugated alkynes, and aldehydes that results in a stereoselective synthesis of highly substituted piperidines. This synthetic process has been made possible by defining a unique regioselective functionalization of conjugated alkynes that establishes a suitably functionalized substrate for subsequent heterocycle-forming cationic annulation. Given the flexibility of the coupling process, heterocycles can be accessed through a process that establishes up to four stereogenic centers and four fused rings.

Substituted piperidines are structural motifs found in a variety of natural products and small molecules of biomedical relevance.[1] Despite the significant advances made that define chemical methods suitable for the construction of this heterocyclic core, the stereocontrolled preparation of highly substituted piperidines remains a challenge in chemical synthesis.[2] Of the many methods available, cationic annulation of suitably functionalized amines with aldehydes (via Pictet−Spengler or aza-Prins cyclization) has long been recognized as a useful pathway to a subset of functionalized piperidines.[3,4] Aside from problems associated with the control of these cationic annulation reactions, preparation of complex unsaturated amine substrates suitable for these heterocycle-forming processes can be cumbersome. Here, we describe a bimolecular bond construction for the selective union of conjugated alkynes with imines as a means to establish appropriate functionality for subsequent stereoselective cationic annulation. Specifically, the process described

(1) (a) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679–3681. (b) Källström, S.; Leino, R. *Bioorg. Med. Chem.* **2008**, *16*, 601–635.

(2) For recent reviews, see: (a) Escolano, C.; Amat, M.; Bosch, J. *Chem.—Eur. J.* **2006**, *12*, 8198–8207. (b) Cossy, J. *Chem. Rec.* **2005**, *5*, 70–80. (c) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701–1729. (d) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953–2989.

(3) (a) Bohlmann, F.; Winterfeldt, E.; Overwien, H.; Pagel, H. *Chem. Ber.* **1962**, *95*, 944–948. (b) Grob, C. A.; Wohl, R. A. *Helv. Chem. Acta* **1966**, *49*, 2175–2189. (c) Cope, A. C.; Burrows, W. D. *J. Org. Chem.* **1966**, *29*, 3099–3103.

(4) For recent reviews of cationic annulation reactions in heterocycle synthesis, see: (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367–4416. (b) Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857–873. (c) Overman, L. E. *Aldrichim. Acta* **1995**, *28*, 107–120. (d) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311–2352. (e) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797–1842.

10.1021/ol902169k CCC: $40.75
Published on Web 10/09/2009

defines a two-step, three-component coupling reaction between conjugated alkynes, imines, and aldehydes for the stereoselective synthesis of piperidines containing up to four stereogenic centers and four fused rings.

From the outset, we sought a bimolecular alkyne−imine coupling that would enable the synthesis of allylic amines well suited for cationic annulation (**1** → **2**, and **2** + **3** → **4**; Figure 1). With this goal in mind, we were aware of the

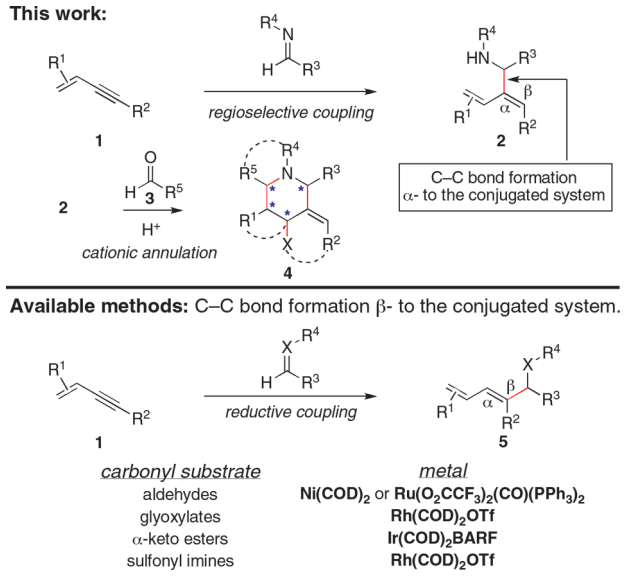


Figure 1. Regioselective union of conjugated alkynes with imines for heterocycle synthesis.

numerous methods available for metal-catalyzed reductive coupling of conjugated alkynes with carbonyl electrophiles. Unfortunately, the selectivity of these coupling reactions is uniformly dictated by the presence of π-conjugation and delivers an isomeric product to that required for the heterocycle synthesis of interest here (**2** vs **5**; Figure 1).[5]

Recently, we have defined a Ti-mediated alkyne−imine coupling reaction for the synthesis of allylic amines and γ-lactams where a tethered alkoxide directs regioselective functionalization of an internal alkyne and overrides the influence of simple nonbonded steric interactions.[6] The knowledge gleaned from this study served as a guiding principle for the design of the first step of the heterocycle synthesis described here. While targeting a bond construction that, as in our previous studies, would require stoichiometric quantities of Ti(O-*i*-Pr)$_4$, the potential of such a process in complex heterocycle synthesis and the inability to generate the desired substitution in **2** with available catalytic methods drove our investigation of this chemistry.

As illustrated in Figure 2, alkoxide-directed C−C bond formation provides an exceptionally powerful means to

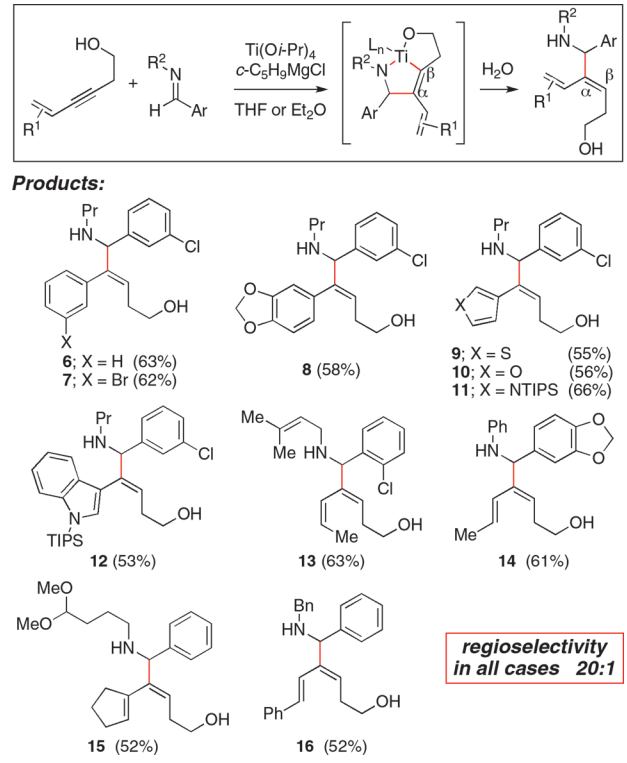


Figure 2. Alkoxide-directed union of conjugated alkynes with imines.

deliver the unique regioisomer required here, where C−C bond formation occurs α-to the conjugated π-system, in opposition to that expected from the electronic effects that dictate the regiochemical course of related reductive coupling reactions.[5] The selective production of **6**−**12** highlights the effectiveness of this reductive cross-coupling reaction with a variety of aromatic and heteroaromatic conjugated alkynes. While demonstrating the compatibility of the coupling reaction with electron rich aromatics, aromatic halides, thiophenes, furans, pyrroles, and indoles, these reactions provided single regioisomers of coupled products in 52−66% yield.

The successful formation of **13**−**16** demonstrates that this metal-mediated coupling process is equally effective with enyne-containing substrates. Here, high regioselectivity is possible in a chemoselective coupling process, where no

(5) (a) Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221–4223. (b) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1364–1367. (c) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698–3699. (d) Miller, K. M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 4130–4131. (e) Miller, K. M.; Jamison, T. F. *Org. Lett.* **2005**, *7*, 3077–3080. (f) Kong, J.-R.; Cho, C.-W.; Krische, M. J. *J. Am. Chem. Soc.* **2005**, *125*, 11269–11276. (g) Sa-ei, K.; Montgomery, J. *Org. Lett.* **2006**, *8*, 4441–4443. (h) Komanduri, V.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 16448–16449. (i) Cho, C.-W.; Krische, M. J. *Org. Lett.* **2006**, *8*, 3873–3876. (j) Ngai, M.-Y.; Barchuk, A.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 280–281. (k) Cho, C.-W.; Skucas, E.; Krische, M. J. *Organometallics* **2007**, *26*, 3860–3867. (l) Hong, Y.-T.; Cho, C.-W.; Skucas, E.; Krische, M. J. *Org. Lett.* **2007**, *9*, 3745–3748. (m) Patman, R. L.; Chaulagain, M. R.; Williams, V. M.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2066–206. For coupling reactions of isolated alkynes with activated imines: (n) Skucas, E.; Kong, J. R.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 7242–7243. (o) Barchuk, A.; Ngai, M.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 8432–8433. (p) Ngai, M.; Barchuk, A.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 12644–12645.

(6) McLaughlin, M.; Takahashi, M.; Micalizio, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3912–3914.

evidence was found for the functionalization of the conjugated alkene of the starting enyne.

With a site-selective convergent coupling reaction in hand, we shifted our attention to exploring the unique reactivity of the allylic amine products derived from this coupling process. As anticipated on the basis of well-precedented Pictet−Spengler chemistry,[4e] cationic annulation of substrates containing conjugated aromatics defines a concise pathway to polysubstituted fused bicyclic heterocycles (Figure 3).

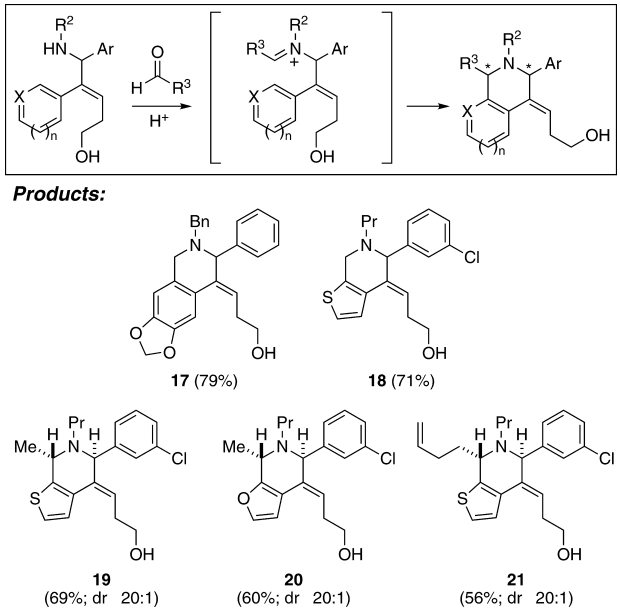


Figure 3. Cationic annylation via Pictet−Spengler-like cyclization.

While the generation of **17** and **18** (via acid-promoted addition to 1,3,5-trioxane in EtOH or CH_3CN) demonstrates the basic reactivity profile of interest with electron-rich and heteroaromatic systems, the formation of **19**−**21** highlights that good levels of stereocontrol are possible in convergent annulation with aldehydes. In all cases, high selectivity for the formation of the 2,6-trans-disubstituted piperidines was observed (dr ≥ 20:1).

Moving on, cationic annulation of the 1,3-diene-containing allylic amines (derived from reductive cross-coupling of enynes with aromatic imines) provides a unique opportunity for the rapid generation of complex heterocycles. Here, cationic annulation terminated by C−O bond formation defines a concise pathway to bi-, tri-, and tetracyclic piperidines with typically very high levels of stereoselection (Figure 4).[7,8]

Our preliminary investigation of this reaction pathway indicated that the stereochemical course of the annulation

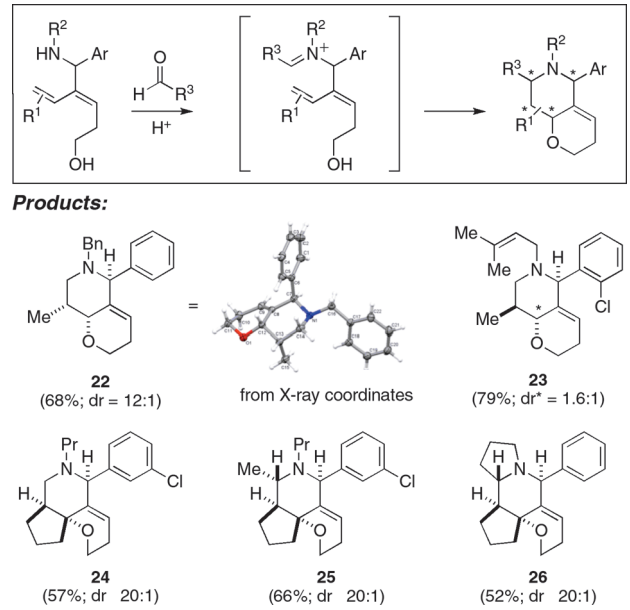


Figure 4. Cationic annulation via aza-Prins-initiated cyclization.

reaction is complex. For example, cyclization of an enyne bearing a (*Z*)-disubstituted alkene leads to the generation of a bicyclic product **22** with good levels of stereoselection (dr = 12:1), while cyclization of a related isomeric enyne proceeds with very low levels of stereoselection (i.e., **23** is derived from the (*E*)-disubstituted alkene and is produced as a 1.6:1 mixture of stereoisomers). This observed lack of stereospecificity is consistent with stepwise cyclization terminated by diastereoselective addition to an intermediate allylic carbocation.[9]

In an effort to enhance diastereoselection, we examined the cyclization of enynes where the alkene was constrained in a five-membered ring. Perhaps due to the expected preference for formation of a cis-fused saturated aza-indane over the trans-fused isomer, all cationic annulation reactions with this subset of enynes proceeded with very high levels of diastereoselection (**24**−**26**; dr ≥ 20:1 in all cases). As observed previously in the annulation reaction of substrates containing conjugated aromatics, in these more complex cyclization reactions, stereoselection was observed for the formation of the central piperidine bearing 2,6-trans-substitution (i.e., **25** and **26**).

This regioselective reductive cross-coupling reaction between enynes and aromatic imines can be rendered asymmetric. As depicted in Figure 5, use of a phenylglycine-modified aromatic

(7) For examples of annulation reactions between iminium ions and 1,3-dienes, see: (a) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768–1769. (b) Grieco, P. A.; Kaufman, M. D. *J. Org. Chem.* **1999**, *64*, 6041–6048. (c) Liu, J.; Sung, R. P.; Peters, S. D. *Org. Lett.* **2004**, *6*, 3989–3992.

(8) For an interesting example of a tandem aza-Prins reaction followed by intramolecular C−O bond formation in the context of total synthesis, see: Lee, H. M.; Nieto-Oberhuber, C.; Shair, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 16864–16866.

(9) Resubjecting each diastereomer of **23** to the reaction conditions did not lead to any observable interconversion. As such, the mixture of products obtained in this annulation reaction is deemed likely to result from a stepwise process entailing formation of a secondary allylic cation followed by C−O bond formation, not stereospecific cationic cyclization followed by acid-promoted isomerization of the product.

(10) The relative stereochemistry of products **29** and **31** was assigned in analogy to previously described alkoxide-directed reductive cross-coupling reactions of chiral imine **28** (see ref 6 and literature cited therein). For the initial report that describes use of a phenylglycine-based imine in diastereoselective reductive coupling of aromatic imines with terminal alkynes, see: Fukuhara, K.; Okamoto, S.; Sato, F. *Org. Lett.* **2003**, *5*, 2145–2148.

imine (**28**) leads to moderate stereoselection in the formation of the functionalized allylic amines **29** (dr = 85:15) and **31** (dr = 75:25).[10]

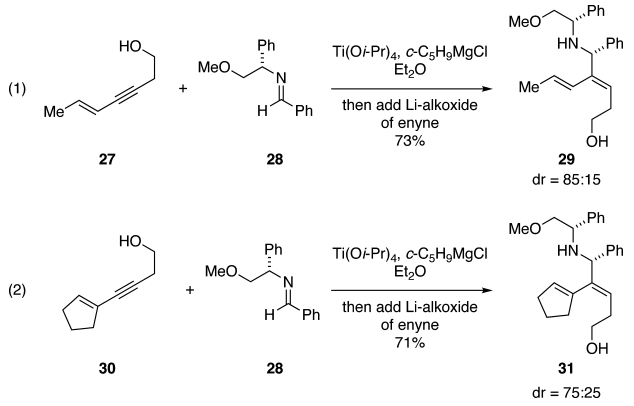


Figure 5. Preliminary studies in asymmetric synthesis.

In conclusion, we have described a two-step three-component coupling process for the synthesis of stereodefined and highly substituted piperidines. Site-selective union of readily available conjugated alkynes with aromatic imines provides a means of accessing allylic amine products not readily available with other reductive cross-coupling methods (where C−C bond formation occurs α- to the conjugated π-system). As a result of the unique selectivity of this alkyne-imine cross-coupling reaction, subsequent cationic annulation with carbonyl electrophiles defines a powerful pathway to highly substituted piperidines. The complex annulation processes discovered are typically highly selective, generating up to four stereogenic centers (dr is typically ≥20:1) and four fused rings. Due to the rapid access to structural complexity afforded by this chemical process and ubiquitous presence of substituted piperidines in natural products and small molecules of biomedical relevance, we anticipate that this two-step, three-component coupling process will be of great utility in chemical synthesis. The ease of use, low cost, and unique reactivity profile of Ti(O-*i*-Pr)$_4$ combine to define a powerful system of increasing utility in defining unique and highly regioselective bond constructions in organic chemistry.[11,12]

Acknowledgment. We gratefully acknowledge financial support of this work by the American Cancer Society (RSG-06-117-01), Boehringer Ingelheim, Eli Lilly & Co., and the National Institutes of Health-NIGMS (GM80266 and GM80266-04S1).

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

OL902169K

(11) It is instructive to compare the cost associated with running reductive cross-coupling chemistry based on stoichiometric Ti(O-*i*-Pr)$_4$ with reported processes that employ substoichiometric quantities of Ni, Rh, Ir, and Ru catalysts. For a hypothetical reductive cross-coupling reaction run on a 1 mol scale, the following costs are associated with the purchase of required metal (in each case the typical mol % reported for each system has been used for the calculation): 1 mol of Ti(O-*i*-Pr)$_4$ = $18; 10 mol % Ni(COD)$_2$ = $591; 5 mol % [Rh(COD)$_2$]OTf = $4391; 5 mol % [Ir(COD)$_2$]BARF = $6465; 5 mol % Ru(O$_2CCF_3$)$_2$(CO)(PPh$_3$)$_2$ = $11,612 (costs calculated for purchase from Strem 2008 catalogue). While typically 2 equivalents of Grignard reagent are employed in the reduction of the Ti(IV) alkoxide (additional $184), the cost of required ligands associated with the other systems is not factored into the costs listed above. Finally, the analysis presented above is based on published procedures that report catalyst loadings between 5 and 10 mol %, with associated turnover numbers between 5 and 20.

(12) While the removal of toxic metal impurities in reaction products is a problem that surfaces in many applications of metal-catalyzed reactions in pharmaceutical process chemistry (i.e., Pd-, Ni-, or Ru-), the byproducts of this Ti(O-*i*-Pr)$_4$-mediated coupling reaction include *i*-PrOH, Mg salts, simple hydrocarbons, and TiO$_2$—a nontoxic species encountered daily in toothpaste, sunscreen, and paint.