JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Synthesis of Alkaloid (−)-205B via Stereoselective Reductive Cross-Coupling and Intramolecular [3+2] Cycloaddition

Dexi Yang and Glenn C. Micalizio*

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

Supporting Information

ABSTRACT: An asymmetric synthesis of alkaloid (−)-205B, a tricyclic member of the architecturally diverse family of natural products isolated from the skin of neotropical poison frogs, is described that proceeds through two recently developed stereoselective synthetic methods: (1) Ti-mediated allylic alcohol−imine reductive cross-coupling and (2) intramolecular [3+2] cycloaddition of a glyoxylate-based homoallylic nitrone. The utility of this latter cycloaddition process for the assembly of the stereochemically dense piperidine core of 205B is noteworthy, as this method enables direct [3+2] cycloaddition of an intermediate homoallylic (*E*)-nitrone via a pathway that is stereochemically unscathed by competitive [3,3]-sigmatropic rearrangement processes. Overall, the synthesis is asymmetric, concise, and highly stereoselective—features which point to the potential future utility of these chemical methods in natural product synthesis and medicinal chemistry.

Due to the pioneering and focused efforts of John Daly at the National Institutes of Health, it has become clear that neotropical frogs are a rich source of architecturally unique alkaloids.[1] To date, over 800 heterocycles spanning more than 20 structural classes have been discovered from anuran skin, many of which are sequestered unchanged from dietary sources (ants, mites, beetles, and millipedes). Despite the rich structural diversity associated with this class, the majority of these natural products lack pharmacological characterization, due, in part, to their low natural abundance. As a result, chemical synthesis stands as an enabling tool for future evaluation of this potentially important class of natural products. In this regard, the azatricyclododecene (−)-205B, isolated from *Dendrobates pumilio*,[2] has risen as a target of interest due to its intriguing structure and the synthesis-driven discovery that the unnatural enantiomer blocks the α7 nicotinic acetylcholine receptor in a selective fashion (Figure 1).[3] Since Toyooka's pioneering synthesis of (+)-205B,[4] Smith and Comins have independently

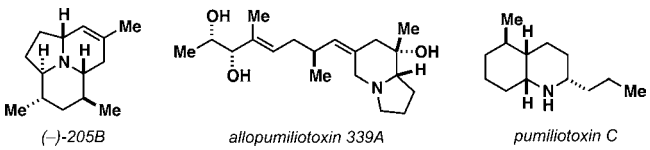

Figure 1. Structurally diverse alkaloids from the skin of the neotropical poison frog *Dendrobates pumilio*.

reported syntheses of the natural antipode through chemical pathways that have secured the utility of anion relay chemistry and dihyropyridone-based functionalization processes to access the heterocyclic core of this target.[5] Here, we report a conceptually unique synthesis of (−)-205B that proceeds by two stereoselective synthetic methods that have recently emerged from our laboratories: (1) Ti-mediated reductive cross-coupling between an aldehyde and an allylic alcohol (via the intermediacy of a TMS-imine)[6] and (2) path-selective intramolecular [3+2] cycloaddition of a glyoxylate-based homoallylic nitrone.[6] The current studies document the first demonstrations of these reaction processes in natural product synthesis.

While related to the structure of coccinelline (Figure 2A), the stereochemically dense piperidine core of 205B presents a challenge not easily addressed with the elegant two-directional synthesis that Stevens demonstrated for the former[7]—a strategy undoubtedly inspired by Robinson's classic tropinone synthesis,[8] and one that explored the stereochemical course of an intermolecular Mannich reaction on a six-membered ring-containing iminium ion (Figure 2B). We suspected that a related approach to 205B, while potentially elegant, would likely be substantially less effective for a number of reasons. As illustrated in Figure 2C, the primary amine required for 205B is not symmetric and can engage in iminium ion formation with either of the terminal acetals (paths A and B)—each path presenting different obstacles. Adding to the mounting uncertainty surrounding a coccinelline-inspired annulation en route to 205B, the likely multistep nature of any modern asymmetric synthesis of the requisite chiral primary amine starting material dissuaded us from the pursuit of such an annulation process.

Aiming to avoid these issues, we abandoned a strategy for annulation that targets the simultaneous generation of the C2a and C5a stereocenters, favoring a late stage annulation of the relatively unfunctionalized indolizidine onto a pre-existing piperidine core (**1**→205B; Figure 2D).[9] This piperidine was inturn envisioned to derive from functional group manipulation of the 1-aza-7-oxabicyclo[2.2.1]heptane **2**, itself generated by a highly stereoselective [3+2] cycloaddition of an intermediate homoallylic nitrone generated by condensation of **3** with butylglyoxylate (**4**). In this manner, the C5a−C6 bond was targeted as a key site for assembly of the densely functionalized piperidine core, rather than relying on C5−C5a bond construction via the intermediacy of a six-membered ring

Received: July 5, 2012
Published: September 7, 2012

dx.doi.org/10.1021/ja306362m | *J. Am. Chem. Soc.* 2012, 134, 15237−15240

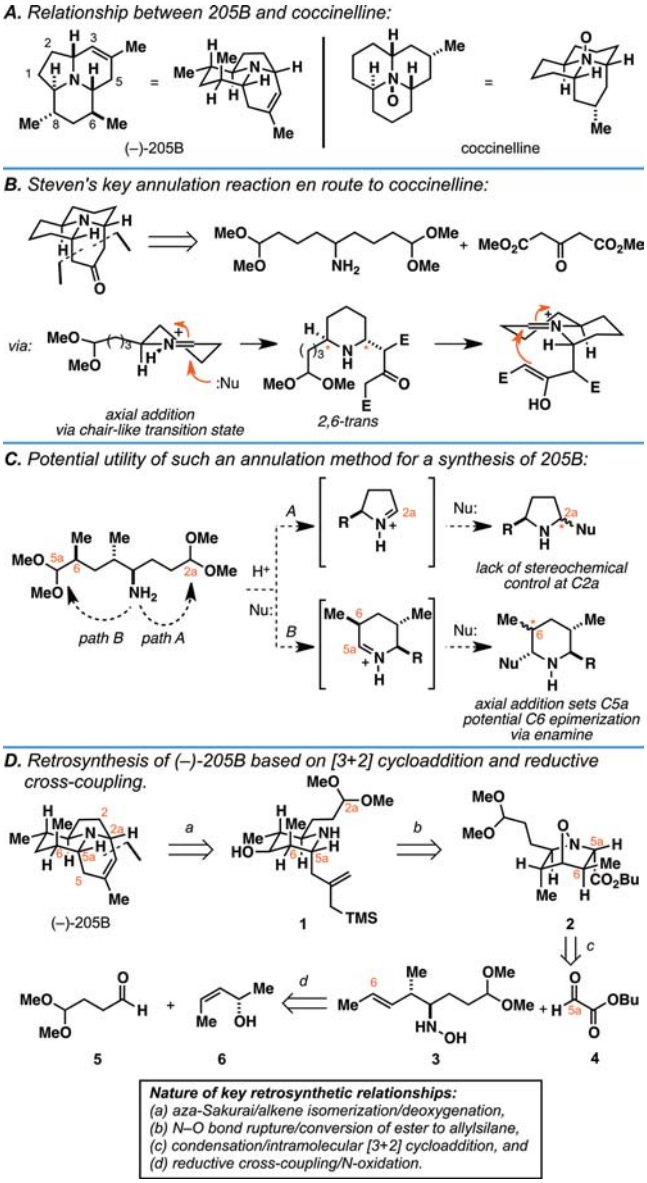

Figure 2. Strategic considerations and retrosynthesis of (−)-205B.

iminium ion intermediate. Finally, the stereodefined acyclic intermediate **3** could derive from enantioselective Ti-mediated reductive cross-coupling of a TMS-imine (generated *in situ* from the aliphatic aldehyde **5**) with a simple chiral allylic alcohol **6**.[10]

Our pursuits began with attempted reductive cross-coupling of aldehyde **5** with allylic alcohol **6** and quickly led to the identification of a limitation in our Ti-mediated reductive cross-coupling technology.[6] In short, allylic alcohol **6** is not a robust substrate for Ti-mediated coupling, with all attempts leading to low conversion and poor stereoselection (alkene geometry). Given the documented success of related coupling reactions with allylic alcohols that bear groups larger than Me- at the allylic position,[6,11] we opted to pursue reductive cross-coupling with an allylic alcohol that was functionally equivalent to **6** but contained a suitable substituent at the allylic position to facilitate reductive cross-coupling. As illustrated in Figure 3, reaction of aldehyde **7** with the TMS-substituted allylic alcohol **8**[12] proceeds effectively by sequential treatment of the aldehyde (2 equiv) with LiHMDS (2 equiv) (to generate the TMS-imine *in situ*), $Ti(O\textit{i}\text{-}Pr)_4$/*s*-BuLi (to form the azatitanacyclopropane from the TMS-imine), and the allylic alcohol **8** (1 equiv). In contrast to previous reports that employ the Li-alkoxide of the allylic alcohol in Ti-mediated reductive cross-coupling reactions, use of the free alcohol in this procedure avoided potential Peterson elimination.[13] Overall, the primary homoallylic amine **9** was produced as a single isomer in 57% yield, with complete transfer of absolute stereochemical information.

The stereochemical course of this coupling reaction is consistent with the empirical model depicted in Figure 4. Directed carbometalation is proposed to occur through a boat-like transition state geometry (**A**) that allows for alignment of the σ_{C-Ti} bond with $\pi_{C=C}$ bond, where minimization of allylic-1,3 strain (A1,3)[14] and nonbonded steric interactions about the developing C−C bond combine to define a highly stereoselective C−C bond-forming process. Subsequent *syn*-elimination of the oxatitanacyclobutane intermediate **17**,[15] and hydrolysis of the resulting inorganic complex leads to the homoallylic amine product **9**. Competing transition state geometries for this alkoxide-directed Ti-mediated coupling are thought to be destabilized by substantial nonbonded steric interactions (A1,3 and/or eclipsing interactions about the developing C−C bond; highlighted in **B**−**D** of Figure 4).

Returning to the synthesis, oxidation of the primary homoallylic amine **9** was straightforward by sequential exposure to $(BzO)_2$ and hydrazine. Heating a solution of this species with butylglyoxylate resulted in a highly stereoselective annulation process that likely proceeds by formation of the (*E*)-homoallylic nitrone and direct intramolecular [3+2] cycloaddition to deliver the stereodefined 1-aza-7-oxabicyclo[2.2.1]heptane **11** in 67% yield (dr ≥ 20:1). The complexity of this annulation process deserves comment as this glyoxylate-based nitrone annulation is rather unique among related intramolecular cycloaddition processes. Homoallylic nitrones are well known to undergo two competitive reaction processes: (1) direct [3+2] cycloaddition with the pendant alkene, or (2) sequential aza-Cope rearrangement/intramolecular [3+2] cycloaddition.[6,16] This latter pathway can provide a stereochemically distinct product to that derived from direct [3+2] cycloaddition. Unlike homoallylic nitrones generated from aliphatic aldehydes, those derived from glyoxylates have been observed to preferentially react by way of a direct [3+2] cycloaddition through the (*E*)-isomer. Overall, bicyclic products are typically observed with outstanding levels of stereoselection, unscathed by potential competitive [3,3]-sigmatropic rearrangement chemistry typical of aliphatic nitrones.[6]

With the densely functionalized heterocycle **11** in hand, the butyl ester was homologated by a simple three-step sequence to the α-trimethylsilylmethyl-substituted enoate **13**. Reduction to the allylic alcohol and deoxygenation with allylic transposition (NBSH, PPh_3, DIAD, NMM)[17] then delivered the allylic silane **14** in 55% yield (over the two-step sequence). Reductive cleavage of the N−O bond (Zn, HOAc), followed by stirring in 3 N HCl/THF resulted in iminium ion formation (**E**) and cyclization to deliver tricyclic product **15** in 82% yield.

While this acid-promoted cyclization reaction proved to be an effective tandem process to establish the tricyclic core of the natural product, the success of this sequence may speak to the relative rates of aza-Sakurai ring closure and aza-Cope rearrangement of the intermediate bicyclic iminium ion **E**. As illustrated in Figure 5, direct aza-Sakurai-based ring closure would lead to the observed product **15**, while competitive aza-

dx.doi.org/10.1021/ja306362m | J. Am. Chem. Soc. 2012, 134, 15237−15240

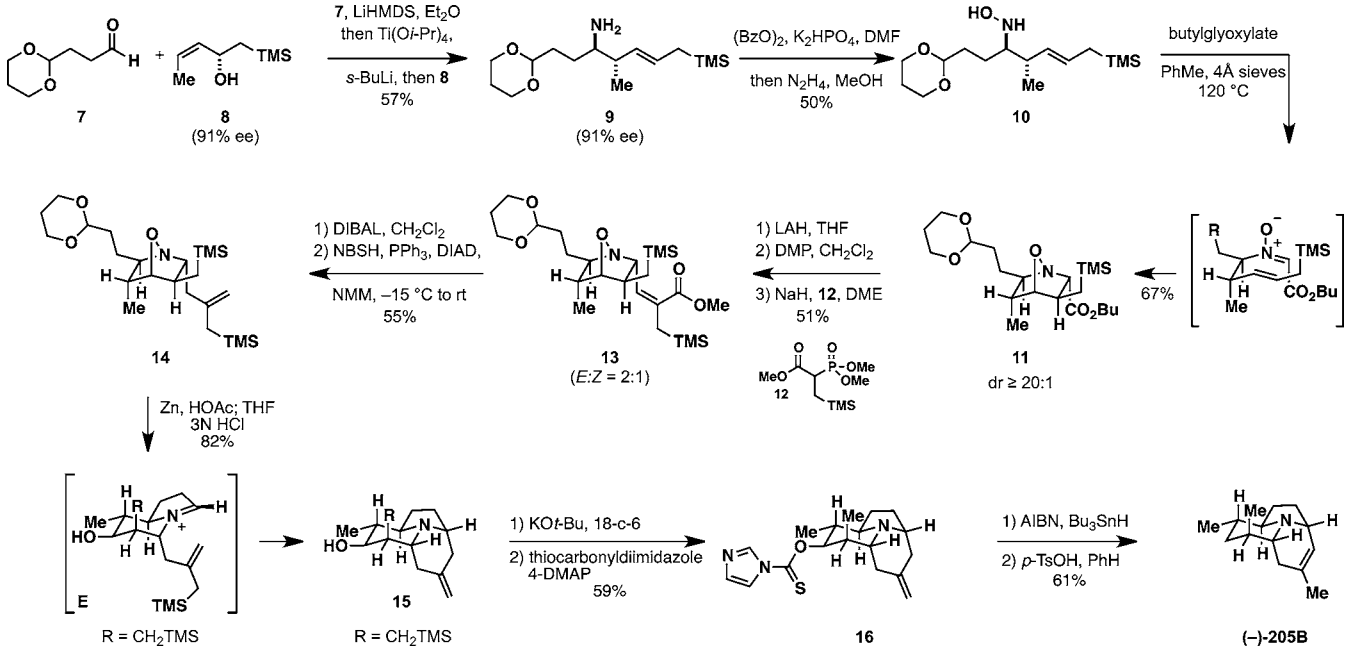

Figure 3. Asymmetric synthesis of (−)-205B via Ti-mediated reductive cross-coupling and stereoselective intramolecular [3+2] cycloaddition.

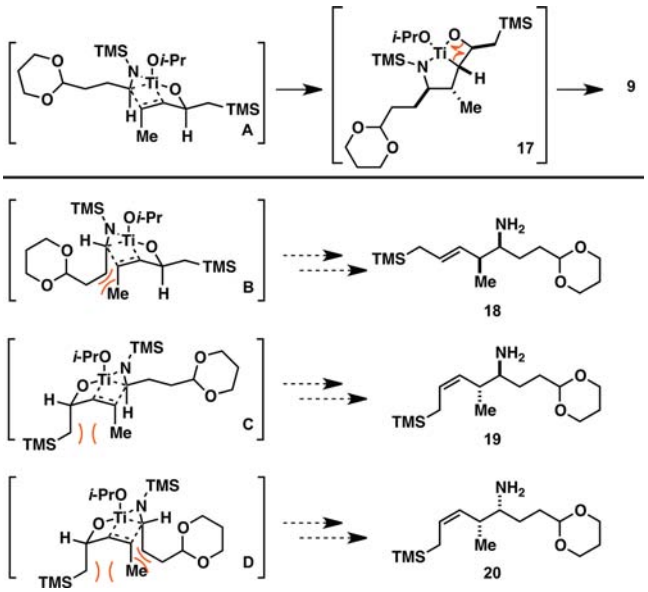

Figure 4. Stereochemical course of the reductive cross-coupling reaction between aldehyde **7** and allylic alcohol **8**.

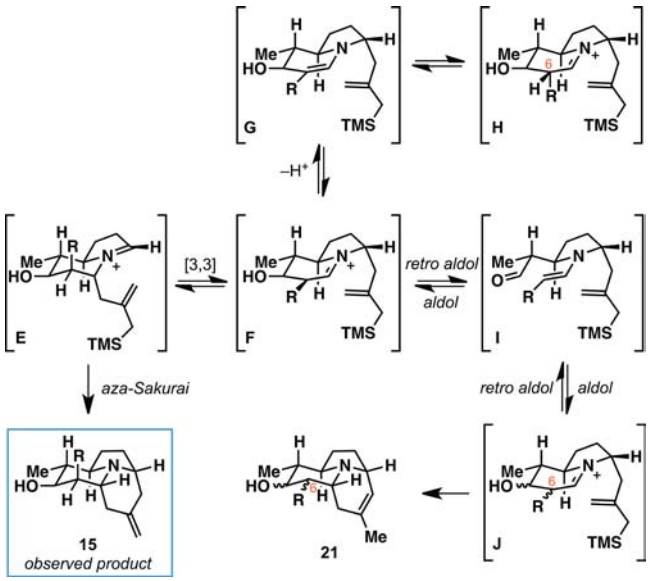

Figure 5. Success of the cationic annulation may reflect an increased rate for aza-Sakurai vs [3,3]-rearrangement and resulting competitive fragmentation and epimerization pathways.

Cope rearrangement could deliver an isomeric iminium ion **F** that has the potential to proceed through a variety of reaction pathways capable of scrambling the C6 stereochemistry. For example, loss of a proton would provide a means to generate an enamine **G** that could be in equilibrium with the isomeric iminium ion **H**. Alternatively, **F** could undergo thermodynamic equilibration by retro aldol/aldol (**F**→**I**→**J**). While the lack of an observed isomeric product in this cyclization does not rigorously exclude the possibility of competitive aza-Cope rearrangement of **E**, the results certainly support the conclusion that the 1-aza-7-oxabicyclo[2.2.1]heptane **14** is a viable intermediate en route to the azatricyclododecene core of 205B, and that this cyclization process is not effected by the potential pitfalls delineated in Figure 5.

To complete the asymmetric synthesis of (−)-205B, a means to remove the remaining TMS-substituent, accomplish deoxygenation at C7, and selectively isomerize the alkene was required. The first of these goals was met by treatment with KO*t*-Bu/18-crown-6—a procedure known to effect hydroxyl-directed desilylation.[18] Next, treatment with thiocarbonyldiimidazole furnished the functionalized azatricyclododecene **16** in 59% yield (over two steps). Deoxygenation by treatment with tributyltin hydride and AIBN[19] was followed by acid-mediated alkene isomerization to deliver (−)-205B in 61% yield.

In conclusion, we report a concise asymmetric synthesis of (−)-205B that demonstrates the utility of two stereoselective synthetic methods that have recently emerged from our laboratory: (1) Ti-mediated reductive cross-coupling of allylic

dx.doi.org/10.1021/ja306362m | J. Am. Chem. Soc. 2012, 134, 15237−15240

alcohols with aldehydes through the intermediacy of a TMS-imine and (2) path-selective intramolecular [3+2] cycloaddition of glyoxylate-based homoallylic nitrones.[6] Overall, the combined use of these methods defines a highly stereoselective synthesis of a rare alkaloid that belongs to a family of natural products that likely possess potent and diverse neurological functions. We look forward to exploring the pharmacological profile of synthetic (−)-205B and establishing the scope and limitations of these powerful chemical methods in stereoselective synthesis.

■ ASSOCIATED CONTENT

Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

micalizio@scripps.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support of this work by the National Institutes of Health−NIGMS (GM80266 and GM80266-04S1).

■ REFERENCES

(1) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556−1575.

(2) (a) Tokuyama, T.; Nishimori, N.; Shimada, A.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1987**, *43*, 643−652. (b) Tokuyama, T.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Anal. Asoc. Quim. Argentina* **1998**, *86*, 291−298. Notably, skins of 3620 frogs were required in the original isolation paper to deliver only 13 mg of (−)-205B.

(3) Tsuneki, H.; You, Y; Toyooka, N.; Kagawa, S.; Kobayashi, S.; Sasaoka, T.; Nemoto, H.; Kimura, I.; Dani, J. A. *Mol. Pharmacol.* **2004**, *66*, 1061−1069.

(4) Toyooka, N.; Fukutome, A.; Shinoda, H.; Nemoto, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 3808−3810.

(5) (a) Smith, A. B.; Kim, D.-S. *Org. Lett.* **2005**, *7*, 3247−3250. (b) Tsukanov, S. V.; Comins, D. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8626−8628.

(6) Yang, D.; Micalizio, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 9216−9219.

(7) Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032−7035.

(8) Robinson, R. *J. Chem. Soc., Trans.* **1917**, *111*, 762−768.

(9) (a) Grieco, P. A.; Fobare, W. F. *Tetrahedron Lett.* **1986**, *27*, 5067−5070. (b) Hosomi, A.; Sakurai, H. *Tetrahdron Lett.* **1976**, *17*, 1295−1298. (c) Yang, D.; Micalizio, G. C. *J. Am. Chem. Soc.* **2009**, *131*, 17548−17549. A related ring closure based on an intramolecular Mannich cyclization was a key reaction in Toyooka's total synthesis of (+)-205B (see ref 4).

(10) During review of this manuscript, it was suggested that modern asymmetric imine allylation chemistry may be suitable to afford direct access to the stereodefined (*E*)-*anti*-homoallylic primary amine precursor to **3**. We recognize that a variety of alternative strategies that embrace the reactivity of allylic and propargylic organometallic reagents may be suitable to prepare the desired intermediate for intramolecular nitrone cycloaddition. That said, we are unaware of any synthetic method capable of delivering the desired (*E*)-*anti*-homoallylic hydroxylamine (or primary amine) from the corresponding aldimine or aldoxime. Related transformations include the following. (a) Chelation-controlled addition reactions of chiral crotylsilanes for the synthesis of (*E*)-*anti*-homoallylic carbamates: Schaus, J. V.; Jain, B.; Panek, J. S. *Tetrahedron* **2000**, *56*, 10263−10274. (b) Asymmetric crotylation reactions (addition of a C4-unit) of imines: Ramachandran, P. V.; Burghardt, T. E. *Chem.—Eur. J.* **2005**, *11*, 4387−4395. It is well established that asymmetric crotylation of oximes remains a challenging problem, so direct conversion to a homoallylic hydroxylamine is not readily available. For a discussion, see: (c) White, J. D.; Hansen, J. D. *J. Org. Chem.* **2005**, *70*, 1963−1977. We note that the established asymmetric crotylation chemistry of aldimines delivers products that contain a terminal alkene, not the desired (*E*)-disubstituted olefin. Perhaps crossed olefin metathesis with propylene could emerge as a solution for the conversion of such terminal alkenes to the desired product, but we favored an approach that would obviate the need for a chiral allylic organometallic reagent and the use of olefin metathesis catalysts. Finally, imine propargylation could serve as an entry to **3** but would suffer from moderate *anti*/*syn* selectivities. See: (d) Song, Y.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **2002**, *43*, 8635−8637. Additional functional group manipulations would be required to access the desired primary homoallylic amine product. Overall, the present solution that is based on Ti-mediated reductive cross-coupling of a TMS-imine with a chiral allylic alcohol offers a superbly enantio- and stereoselective alternative to chemistry that may emerge from developments centered on controlling the reactivity of allylic organometallic reagents and/or functional group manipulation chemistry of the products that are known to be accessible from such chemistry.

(11) (a) Chen, M. Z.; McLaughlin, M.; Takahashi, M.; Tarselli, M. A.; Yang, D.; Umemura, S.; Micalizio, G. C. *J. Org. Chem.* **2010**, *75*, 8048−8059. (b) Takahashi, M.; McLaughlin, M.; Micalizio, G. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 3648−3652.

(12) Compound **8** was prepared by asymmetric reduction of the corresponding enone: (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553. (b) Corey, E. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2100−2117.

(13) Ager, D. J. *Org. React.* **1990**, *38*, 1−223.

(14) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.

(15) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611−3613. (b) Hartley, R. C.; Li, J.; Main, C. A.; McKiernan, G. J. *Tetrahedron* **2007**, *63*, 4825−4864.

(16) (a) Wuts, P. G. M.; Jung, Y.-W. *J. Org. Chem.* **1988**, *53*, 1957−1965. (b) For a review of [3 + 2] nitrone cycloaddition reactions to alkenes, see: Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1−173.

(17) Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, *37*, 4841−4844. In our hands, freshly prepared NBSH proved to be quite unstable after drying under high vacuum for 48h. For example, in the presence of air, a minor tap of the vial containing this material resulted in the generation of red smoke followed immediately by an aggressive flame/explosion. While the reported preparation of NBSH calls for drying under vacuum at 23 °C for 14 h, in efforts to achieve a similar melting point to that reported in the literature one batch of material was dried under vacuum for 48 h. This was the only modification made to the literature procedure.

(18) (a) Hudrlik, P. F.; Holmes, P. E.; Hudrlik, A. M. *Tetrahedron Lett.* **1988**, *29*, 6395−6398. (b) Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 6809−6811. (c) Heitzman, C. L.; Lambert, W. T.; Mertz, E.; Shotwell, J. B.; Tinsley, J. M.; Va, P.; Roush, W. R. *Org. Lett.* **2005**, *7*, 2405−2408.

(19) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585. (b) For a review of radical chemistry associated with thiocarbonyls, see: Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413−1432.