Catalytic Asymmetric Diamination of Styrenes

Kilian Muñiz,*[1,2] Laura Barreiro,[1†] R. Martín Romero[1†] and Claudio Martínez[1]

[1] Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, 16 Avgda. Països Catalans, 43007 Tarragona, Spain.
[2] ICREA, Pg. Lluís Companys 23, 08010 Barcelona, Spain

Supporting Information Placeholder

ABSTRACT: An enantioselective catalytic vicinal diamination of styrenes is reported, which proceeds under entirely intermolecular reaction control. It relies on a chirally modified aryliodine(I) catalyst and proceeds within an iodine(I/III) manifold with conventional 3-chloroperbenzoic acid as terminal oxidant. An environmentally benign solvent combination not only adds to the attractiveness of the process, but also slows down the rate of the undesired background reaction. A total of 30 examples are presented, which consistently provide high enantiomeric excesses in the range of 91-98%.

Vicinal diamines represent a family of compounds of high importance in diverse fields of the biomedicinal and pharmaceutical sciences.[1] While the direct vicinal diamination of alkenes has been recognized as a convenient approach toward their synthesis,[2] its challenge rests with the native ability of diamines to function as effective bidentate ligands to conventional transition metal promoters. As an illustrative example, while the Sharpless dihydroxylation[3] and aminohydroxylation[4] can be conducted in a catalytic fashion, the related diamination suffers from strong binding affinity of the diamine product to the osmium atom, thus rendering the process non-catalytic in metal.[4] Catalytic diamination of alkenes has thus remained largely limited to reactions involving intramolecular amination steps,[2c,6] and enantioselective diamination with palladium,[7] copper[8] and titanium[9] catalysts currently requires at least one of the C-N bonds to be formed in an intramolecular reaction.[10] An alternative approach[11] uses homogeneous iodine based redox catalysis,[12] which represents an attractive concept.[13] In this area, enantioselective catalytic transformations that replace existing stoichiometric intermolecular reactions have so far remained elusive.[14] We considered chiral catalysis within the aryliodine(I/III) manifold to broaden the spectrum of catalytic enantioselective diamination reactions to intermolecular reaction control. Redox-active chiral aryl iodine derivatives of type **1** with modification of the chiral pool-derived lactic side chains (Figure 1)[15] have emerged as privileged structures. The preformed diacetoxy aryliodine(III) reagent of compound **1a** had been employed in an enantioselective diamination of styrenes.[16] We here report the first successful iodine(I/III)-catalyzed enantioselective intermolecular diamination.

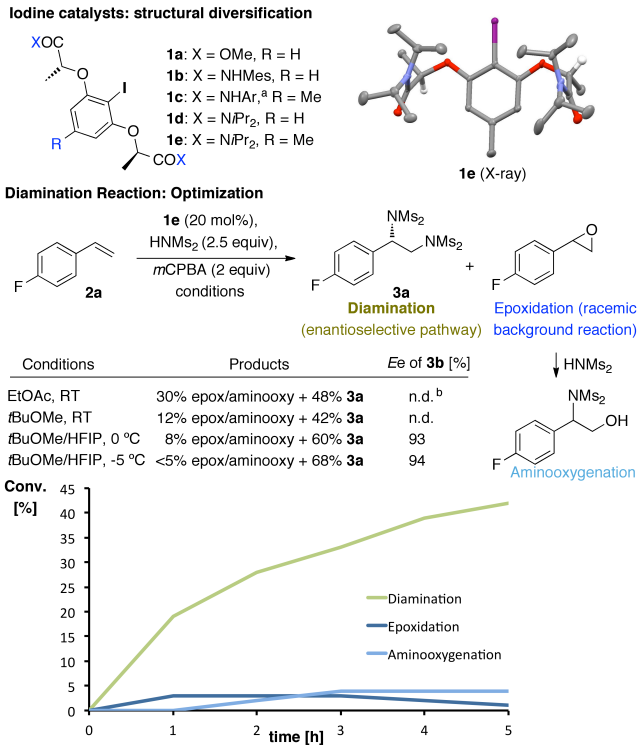
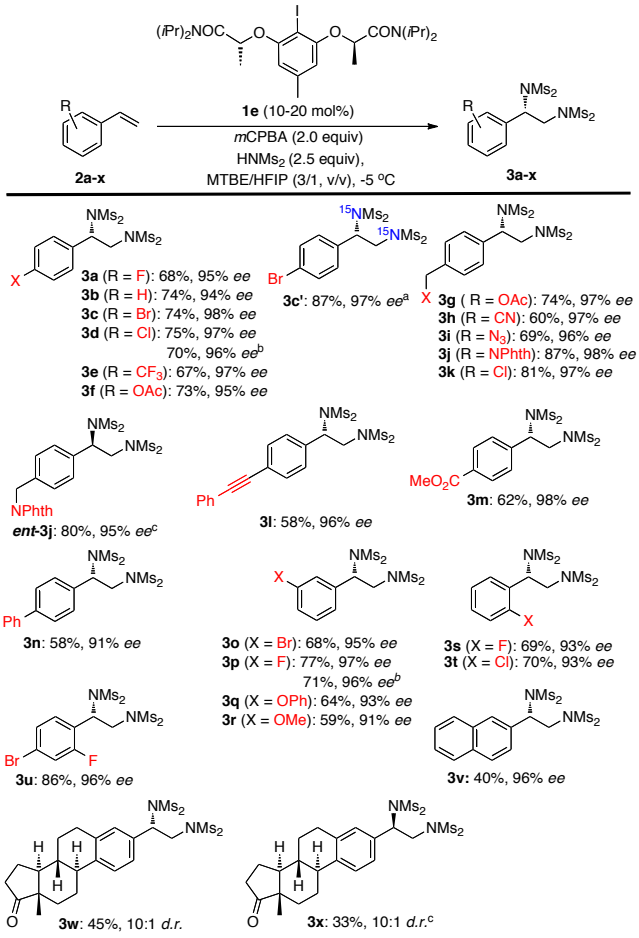


Figure 1. General Structure of Iodine(I) Catalysts **1**, Reaction Optimization of the Catalytic Asymmetric Diamination and Reaction Kinetics. [a] Ar = 2,6-(*i*Pr)$_2$C$_6$H$_3$. [b] n.d. = not determined.

The reaction was optimized exploring various iodine catalysts **1a-e** and oxidants.[17] This extensive screening identified compounds **1d** and **1e** as the only candidates displaying reasonable activity, while *m*CPBA emerged as the only suitable stoichiometric oxidant.[17] Final opti-

mization with **1e** was carried out with 4-fluorostyrene **2a** as substrate, which allowed for an accurate determination of the relative ratio between the diamination product **3a** and undesired epoxidation by ^{19}F NMR analysis. The initially high epoxidation percentage could be reduced changing the solvent to *tert*-butyl methyl ether or *tert*-butyl methyl ether/hexafluoro-2-propanol[18] mixtures and subsequent lowering of the reaction temperature (Figure 1). *m*CPBA is a common oxidant in intramolecular iodine(I/III) catalysis,[12b,19] but had only recently[14b,d] been employed in the corresponding intermolecular alkene functionalization due to its innate high reactivity. Given its particularly high reactivity in the epoxidation of styrene, the use of *m*CPBA appeared challenging at first sight. However, the subsequent exploration provided two important insights. First, this oxidant can be combined with non-chlorinated solvents, which renders the process more benign and attractive. Second, the undesired epoxidation background reaction was found to be kinetically incompetent in the *t*BuOMe/HFIP solvent combination. Figure 1 displays the initial kinetic profile for the catalytic diamination of 4-fluorostyrene, which demonstrates epoxidation (and derivatization to aminooxygenation) to be comparably slow processes.[20] Hence, 4-fluorostyrene derived diamine **3a** was formed in 68% isolated yield and with high 95% enantiomeric excess, while the epoxidation pathway accounted for less than 5% product. These reaction conditions provide the desired entry into catalytic diamination of alkenes under entirely intermolecular reaction control.

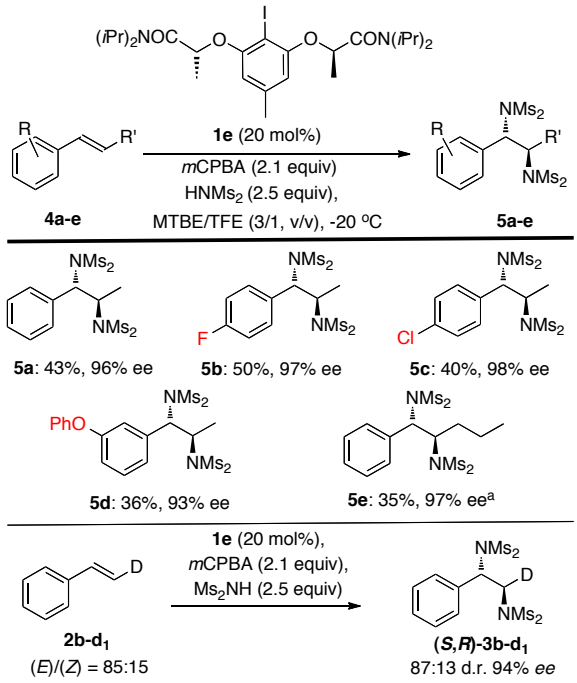
The final conditions are also noteworthy for including a solvent combination outside the usual chlorinated derivatives. The optimized catalyst system exercises generally high enantioselective control in favor of (*S*)-configured diamines **3** as explored for 22 styrenes comprising different substitution patterns at the arene core, which include 2-, 3-, 4- and higher-substituted derivatives and common functional groups from organic chemistry (Scheme 1). The observed efficient face selection is unprecedented in the intermolecular difunctionalization with iodine(III) catalysts. The reactions are usually performed best with 20 mol% catalyst and result in 40-87% isolated yield and consistently high inductions of 91-98% *ee*. To demonstrate the efficiency of the catalyst, experiments with 10 mol% catalyst loading were explored, which for products **3d** and **3p** provided 70-71% yield (equivalent to 7 TON) and 96% *ee*. In addition, the catalysis with ^{15}N labeled bismesylimide provided chiral diamination product **3c'** in isotopically pure form. Previous approaches to mono-labeled diamines required multistep syntheses.[21] The enantiomeric catalyst ***ent*-1e** was synthesized from non-natural lactic acid in order to provide an entry into the enantiomeric series of (*R*)-configured diamines as exemplified for product ***ent*-3j**. Finally, a vinylated estrone derivative was employed to demonstrate complete catalyst control under the chosen reaction conditions. Depending on the catalyst configuration, diamines **3w** and **3x** were obtained each with high 10:1-diastereomeric ratio establishing that in this case the asymmetric induction is independent of the chiral information on the steroid backbone.



Scheme 1. Enantioselective Vicinal Diamination of Styrenes: Scope. [a] With ^{15}N-labeled bismesylimide. [b] With 10 mol% **1e**. [c] With *ent*-**1e** as catalyst.

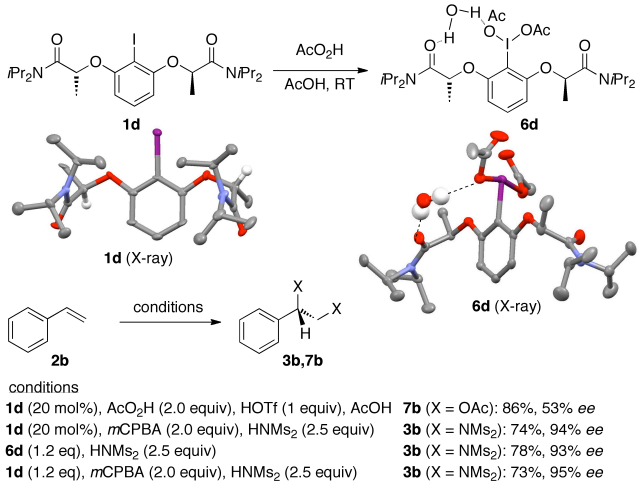
The obtained enantioselectivities from catalysis are significantly higher than the ones from the previous stoichiometric reactions with the preformed diacetoxy reagent from **1a**.[16a] The substrate scope can be enhanced further to include traditionally challenging internal alkenes **4a-e** (Scheme 2). For an efficient reaction outcome, the conditions required slight modification[17] for the diaminations to proceed again with excellent enantiomeric excesses of 93-98% including substrate **4e** with a longer alkyl chain and provide diastereomerically pure products with absolute (2*S*,3*R*)-stereochemistry. Therefore, an identical face-selection is obviously involved in the diamination of terminal and internal alkenes as judged from the absolute configuration at the benzylic stereocenter. This was further corroborated by the expected outcome with deuterated derivative **2b-d$_1$**, which provided the selectively deuterated product **3b-d$_1$** in 94% ee within a clean stereochemistry transfer of the double bond geometry into the corresponding diastereomeric product composition demonstrating that the

overall process is comparable to the one from internal alkenes.



Scheme 2. Enantioselective Vicinal Diamination of Internal Styrenes: Scope. [a] With 5 equiv of $HNMs_2$.

At this point, the exact mode of stereoinduction with the new catalysts **1d** and **1e** remained to be examined. While we had previously identified the formation of a helical chiral environment around the central iodine(III) through intramolecular hydrogen bonding as the decisive motif in catalysts of type **1b** and **1c**,[22] such a supramolecular arrangement is not immediately available for the secondary amides **1d** and **1e**. In addition, the crystal structure analyses from compounds **1d** and **1e**, which correspond to the iodine(I) catalyst states, do not suggest any conformational pre-organization (Figure 1).



Scheme 3. Synthesis, X-Ray Structure and Control Experiments for Compound **6d**.

The corresponding iodine(III) compound **6d** could be obtained from oxidation of **1d**.[17] Single crystal X-ray structural analysis revealed the presence of a water molecule, which engages in double hydrogen bonding (Scheme 3). The resulting 11-membered ring is reminiscent of the chiral helicity induced in the iodine(III) derivatives of **1c** and of the same absolute configuration, but with a significantly enlarged binding pocket for bissulfonimide accommodation,[17] while the structure of **1d** does not reveal any related supramolecular bonding. The intermolecular hydrogen bonding in **6d** promoted by a water molecule can provide a useful explanation for the present high enantioselectivity. Since the terminal oxidant *m*CPBA contains water, the latter is ubiquitously present in the reaction medium throughout catalysis.

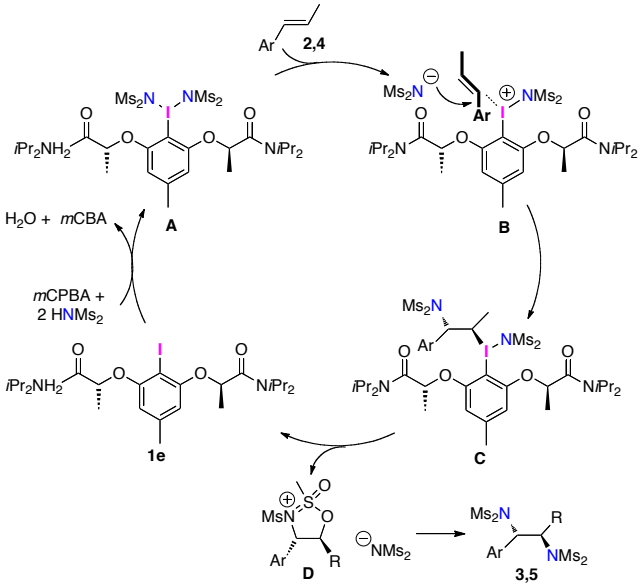


Figure 2. Mechanistic Context for the Enantioselective Catalytic Diamination of Styrenes.

Interestingly, compound **6d** also provides enantioselective diacetoxylation of styrene under both stoichiometric and catalytic reaction control. Upon addition of preformed **6d** to a solution of styrene in the presence of 2.4 equivalents of bismesylimide, the reaction switches selectively into the diamination pathway. Under standard conditions, **1d** provides diamination product with an identical absolute (*S*)-configuration. These observations suggest that the two vicinal difunctionalization reactions proceed through identical enantiotopic differentiation of the prochiral alkene of the styrene substrate. Based on our previous mechanistic insight and on the reported control experiments we suggest the following mechanism for the catalytic cycle (Figure 2). It starts with an oxidation that converts catalyst precursor **1e** to the key catalyst structure, which is in perfect agreement with an earlier observation that bissulfonimides readily enter the iodine(III) center.[23] The helical chirality induced in iodine(III) compounds bearing the bislactamide motif provides a scenario **B** for efficient differentiation of the enantiotopic faces of the styrene substrate. It thereby

provides a diastereomerically highly enriched aminoiodinated catalyst state **C**. The high oxidation state nature of iodine in **C** initiates the reductive displacement of this nucleophuge[24] and thereby regenerates the iodine(I) catalyst state **1e**. In agreement with the overall stereochemistry of the products **5**, an intramolecular displacement by the bissulfonimide is required.[25] The second C-N bond formation takes place through nucleophilic opening of cyclic intermediate **D**[16b] to diamines **3** and **5**, respectively, which represents the hitherto unknown Prevost mechanism[26] in diamine formation. It generates products with the opposite diastereomeric composition as observed in the iodine(I/III)-catalyzed enantioselective diacetoxylation reactions,[27] which proceed through the dioxolonium intermediate of the Woodward mechanism.[28]

In summary, the development of an iodine(I/III)-catalyzed enantioselective diamination of styrenes under intermolecular reaction control has been accomplished for the first time. This protocol acts as an asymmetric gateway to the important class of vicinal diamines[29] and thus facilitates access to entities with particular importance in pharmacophoric and medicinal research. It can be foreseen that this approach of chiral aryliodine catalyst will be an instrumental guide for the development of related transformations.

ASSOCIATED CONTENT

Supporting Information. Experimental details, control experiments and compound characterization (PDF), and details on the X-ray analyses (CIF). The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

* kmuniz@iciq.es

† L. B. and R. M. R. contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

The authors thank Dr. S. Haubenreisser for initial experiments. Financial support of this project was provided by the Spanish Ministry for Economy and Competitiveness and FEDER (CTQ2014-56474R grant to K. M., FPU doctoral grant to R. M. R. and Severo Ochoa Excellence Accreditation 2014-2018 to ICIQ, SEV-2013-0319) and CERCA program of the Government of Catalonia.

REFERENCES

(1) (a) Lucet, D.; Le Gall, T; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37,* 2580. (b) Viso, A.; Fernández de la Pradilla, R.; García, A.; Flores, A. *Chem Rev.* **2005**, *105*, 3167. (c) Viso, A.; Fernández de la Pradilla, R.; Tortosa, M.; García, A.; Flores, A. *Chem Rev*. **2011**, *111*, PR1.

(2) (a) De Jong, S.; Nosal, D. G.; Wardrop, D. J. *Tetrahedron* **2012**, *68*, 4067. (b) Cardona, F.; Goti, A. *Nature Chem.* **2009**, *1*, 269. (c) Martínez, C.; Muñiz, K. *J. Org. Chem*. **2013**, *78*, 2168.

(3) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2024.

(4) (a); Donohoe, T. J.; Callens, C. K. A.; Flores, A.; Lacy, A. R.; Rathi, A. H. *Chem. Eur. J.* **2011**, *17*, 58. (b) Muñiz, K. *Chem. Soc. Rev*. **2004**, *33*, 166.

(5) (a) Muñiz, K.; Nieger, M.; Mansikkamäki, H. *Angew. Chem. Int. Ed*. **2003**, *425*, 5958. (b) Muñiz, K. *New. J. Chem.* **2005**, *29*, 1371.

(6) Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc*. **2005**, *127*, 14586.

(7) Ingalls, E. L.; Sibbald, P. A.; Kaminsky, W.; Michael, F. E. *J. Am. Chem. Soc*. **2013**, *135*, 8854.

(8) (a) Turnpenny, B. W.; Chemler, S. R. *Chem. Sci*. **2014**, *5*, 1786. (b) Sequeira, F. C.; Turnpenny, B. W.; Chemler, S. R. *Angew. Chem. Int. Ed* **2010**, *49*, 6563. (c) Fu, S.; Yang, H.; Li, G.; Deng, Y.; Jiang, H.; Zeng, W. *Org. Lett.* **2015**, *17*, 1018.

(9) Muñiz, K.; Nieger, M. *Chem. Commun*. **2005**, 2729.

(10) For 1,3-butadienes: (a) Zhu Y.; Cornwall R. G.; Du H.; Zhao B.; Shi Y. *Acc. Chem. Res*. **2014**, *47*, 3665. (b) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc*. **2007**, *129*, 11688. (c) Xu, L.; Shi, Y. *J. Org. Chem*. **2008**, *73*, 749. (d) Cornwall, R. G.; Zhao, B.; Shi, Y. *Org. Lett*. **2013**, *15*, 796.

(11) Mizar P.; Laverny A.; El-Sherbini M.; Farid U.; Brown M.; Malmedy F.; Wirth T. *Chem. Eur. J*. **2014**, *20*, 9910.

(12) (a) Uyanik M.; Ishihara K. *Chem. Commun.* **2009**, 2086. (b) Dohi T.; Kita Y. *Chem. Commun.*, **2009**, 2073. (c) Finkbeiner, P.; Nachtsheim, B. *Synthesis* **2013**, *45*, 977.

(13) Application in alkene difunctionalization: Romero, R. M.; Wöste, T. H.; Muñiz, K. *Chem. Asian J.* **2014**, *9*, 972.

(14) (a) Molnár, I. G.; Gilmour, R. *J. Am. Chem. Soc.* **2016**, *138*, 5004. (b) Banik, S. M.; Medley, J. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2016**, *138*, 5000. (c) Molnár, I. G.; Thiehoff, C.; Holland, M. C.; Gilmour, R. *ACS Catal.* **2016**, *6*, 7167. (d) Banik, S. M.; Medley, J. W.; Jacobsen, E. N. *Science* **2016**, *353*, 6294.

(15) (a) Uyanik, M.; Ishihara, K. *J. Synth. Org. Chem. Jpn.* **2012**, *70*, 1116. (b) Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 2175.

(16) (a) Röben, C.; Souto, J. A.; González, Y.; Lishchynskyi, A.; Muñiz, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 9478. (b) Souto, J. A.; González. Y.; Iglesias, Á.; Zian, D.; Lishchynskyi, A.; Muñiz, K. *Chem. Asian J.* **2012**, *7*, 1103.

(17) See Supporting Information for details.

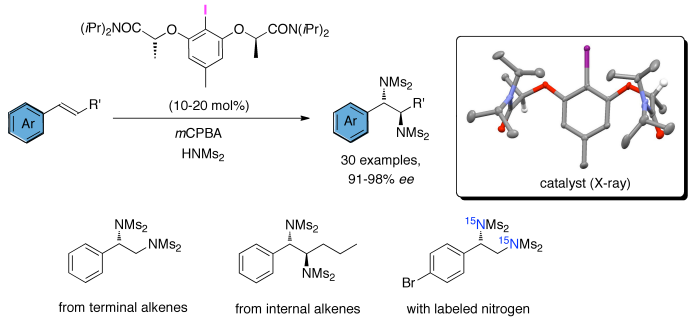
(18) Activation of iodine(III) derivatives with fluorinated alcohols: Colomer, I.; Batchelor-McAuley, C.; Odell, B.; Donohoe, T. J.; Compton, R. G. *J. Am. Chem. Soc*. **2016**, *138*, 8855.

(19) Quideau, S.; Lyvinec, G.; Marguerit, M.; Bathany, K.; Ozanne-Beaudenon, A.; Buffeteau, T.; Cavagnat, D.; Chénedé, A. *Angew. Chem. Int. Ed*. **2009**, *48*, 4605.

(20) This kinetic preference for the enantioselective catalytic pathway over the undesired stoichiometric one is of particular importance. From the investigation of a related achiral iodine-catalysed aziridination reaction, it had been called into question whether such an acceleration in order to overcome the peracid-promoted background reaction could be realised at all: Richardson, R. D.; Desaize, M.; Wirth, T. *Chem. Eur. J.* **2007**, *13*, 6745.

(21) Berger, G.; Gelbcke, M.; Cauët, E.; Luhmer, M.; Nève, J.; Dufrasne, F. *Tetrahedron Lett*. **2013**, *54,* 545.

(22) (a) Haubenreisser, S.; Wöste, T. H.; Martínez, C.; Ishihara, K.; Muñiz, K. *Angew. Chem. Int. Ed.* **2016**, *55*, 413.
(23) (a) Souto, J. A.; Martínez, C.; Velilla, I.; Muñiz, K. *Angew. Chem. Int. Ed.* **2013**, *52,* 1324. (b) Romero, R. M.; Souto, J. A.; Muñiz, K. *J. Org. Chem.* **2016**, *81*, 6118.
(24) Okuyama, T.; Takino, T.; Sueda, T.; Ochiai M. *J. Am. Chem. Soc.* **1995**, *117*, 3360.
(25) Although unprecedented, a direct stereoretentive reductive amination at stage **C** cannot be excluded. For a discussion on the related Csp2-N bond formation, see: Lucchetti, N.; M. Scalone, M.; Fantasia, S.; Muñiz, K. *Angew. Chem. Int. Ed.* **2016**, *55*, 13335.
(26) Prévost, C. *Compt. Rend.* **1933**, *196*, 1129.
(27) Wöste, T. H.; Muñiz, K. *Synthesis* **2016**, *48*, 816.
(28) Woodward, R. B.; Brutcher, F. V. Jr. *J. Am. Chem. Soc.* **1958**, *80*, 209.
(29) Deprotection protocols to free diamines are available and are given in the Supporting Information.



from terminal alkenes

from internal alkenes

with labeled nitrogen