Organic LETTERS

Letter

pubs.acs.org/OrgLett

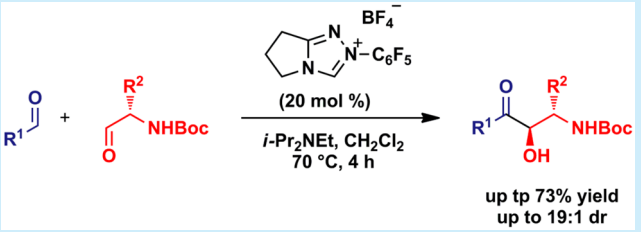
Chemo- and Diastereoselective *N*-Heterocyclic Carbene-Catalyzed Cross-Benzoin Reactions Using *N*-Boc-α-amino Aldehydes

Pouyan Haghshenas and Michel Gravel*

Department of Chemistry, University of Saskatchewan, 110 Science Place, Saskatoon, Saskatchewan S7N 5C9, Canada

Supporting Information

ABSTRACT: *N*-Boc-α-amino aldehydes are shown to be excellent partners in cross-benzoin reactions with aliphatic or heteroaromatic aldehydes. The chemoselectivity of the reaction and the facial selectivity on the amino aldehyde allow cross-benzoin products to be obtained in good yields and good diastereomeric ratios. The developed method is utilized as the key step in a concise total synthesis of D-*arabino*-phytosphingosine.



Enantioenriched α-hydroxy ketones are convenient building blocks for a variety of synthetic transformations as well as important structural features present in a wide array of natural products.[1] A typical synthetic approach toward this motif relies on preformation of a ketone's C−C bond followed by α-hydroxylation.[2] However, achieving desirable enantio- and/or diastereoselectivities in such reactions has remained a challenge. In addition, controlling the regioselectivity of hydroxylation in the case of aliphatic ketones is particularly problematic.

In contrast to the α-hydroxylation of ketones, disconnection at the central carbon−carbon bond represents a more efficient strategic approach to α-hydroxy ketones as it introduces the stereogenic center while assembling the carbon chain (Figure 1).[3] *N*-Heterocyclic carbene (NHC)-catalyzed cross-benzoin

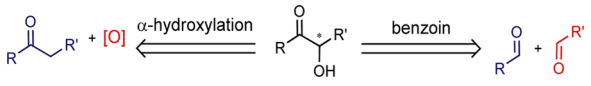


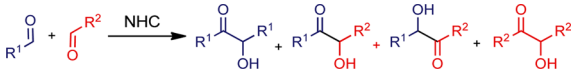
Figure 1. Retrosynthetic strategies toward α-hydroxy ketones.

reactions are potentially useful for such purposes. These types of reactions directly couple two aldehydes in an umpolung fashion to produce α-hydroxy ketones in a single step. The generally accepted mechanism[4] involves the formation of a "Breslow intermediate" between the NHC and an aldehyde.[5] This intermediate then attacks another molecule of aldehyde (C−C bond formation step) followed by ejection of the catalyst to form the desired α-hydroxy ketone product.

In order to devise a viable synthetic strategy toward these motifs, it is crucial to control the chemoselectivity of the reaction, i.e., control of the aldehyde being attacked by the NHC and by the Breslow intermediate, respectively. Without such control, a mixture of all four possible products (two homobenzoin and two cross-benzoin[6] products) will be obtained (Scheme 1).

Controlling the chemoselectivity in the NHC-catalyzed cross-benzoin reaction remains the most important challenge despite significant efforts to address the issue in recent years. A number

Scheme 1. Products of NHC-Catalyzed Benzoin Reaction



of studies have addressed the chemoselectivity of NHC-catalyzed cross-benzoin reactions, most of which rely on substrate modifications to control the selectivity. One strategy consists of utilizing highly reactive ketones as they can only enter the catalytic cycle in the C−C bond-forming step.[7] Another approach makes use of a stoichiometric amount of preformed silylated Breslow intermediate which could only participate as the nucleophile in the C−C bond-forming step.[8] However, when two aldehydes are used as coupling partners, the product ratio is often difficult to control and even to predict.

In 1977, Stetter and co-workers demonstrated that *ortho*-chloro aromatic aldehydes or sterically hindered aliphatic aldehydes can be coupled chemoselectively in some cases.[9] Müller and co-workers later showed the coupling of *ortho*-substituted aromatic aldehydes with other aromatic aldehydes bearing an electron-withdrawing group using thiamine-dependent enzymes.[10] Later, in 2011, Glorius and co-workers showed that similar results could be obtained by using thiazolium-derived NHC precatalysts.[11] The same group reported on the use of paraformaldehyde as a formaldehyde equivalent in the synthesis of hydroxymethyl ketones.[12] Han, Ryu, and Yang showed the catalyst-dependent chemoselectivity in the coupling of aromatic aldehydes with a large excess of acetaldehyde.[13] Glorius and co-workers showed that electron-deficient benzaldehyde derivatives can be used as electrophiles toward the Breslow intermediate formed between an NHC and isobutyraldehyde or benzaldehyde.[11] Connon and Zeitler have discovered that *N*-C_6F_5 triazolium salts could be used to selectively couple aliphatic aldehydes with aromatic aldehydes, particularly *ortho*-halogen-

Received: July 19, 2016

DOI: 10.1021/acs.orglett.6b02123
Org. Lett. XXXX, XXX, XXX−XXX

ated ones.[14] Recent kinetic studies have shed light on the origins of the observed chemoselectivity of this system.[15] We have shown that a slightly more hindered triazolium salt could be used to couple a wider variety of aromatic and aliphatic aldehydes.[16]

The factors affecting chemoselectivity in cross-benzoin reactions are quite complex. In addition to the structure of the catalyst and that of the substrates, the potential reversibility of the reaction can play an important role in the product distribution. Connon, Zeitler, and co-workers have demonstrated that the interplay between steric bulk and the electronic nature of the substrates is critical to the chemoselectivity in cross-acyloin reactions catalyzed by C_6F_5-triazolylidenes.

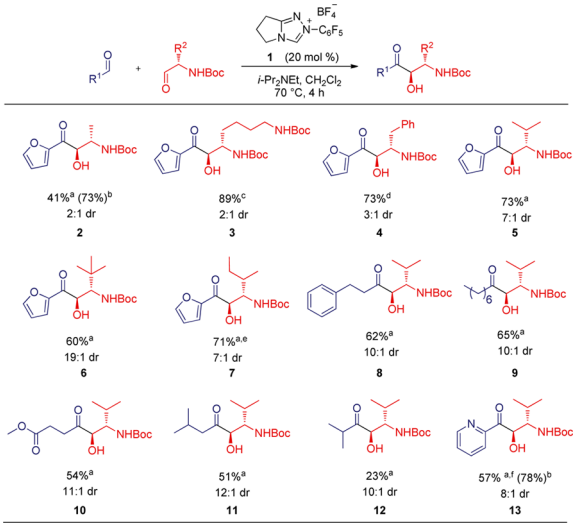
Despite the recent body of work in this area, the synthetically useful cross-benzoin reaction between two aliphatic aldehydes remains a challenge. We wondered whether installing a bulky electron-withdrawing group close to the reaction center could lead to chemoselectivity in such cases. *N*-Boc-protected α-amino aldehydes were chosen as suitable substrates due to the tunability of both their steric and electronic properties. The use of these readily available chiral pool-derived substrates can also lead to diastereofacial selectivity during C−C bond formation. It is worth noting that very few examples of diastereoselective benzoin reactions have been reported.[17]

The choice of catalyst, base,[18] and solvent was determined through an optimization study (see the Supporting Information). We were gratified to find that by using catalyst **1** the corresponding α-hydroxy-β-amino ketone was obtained as the major product with good diastereoselectivity with the undesired cross-benzoin and *N*-Boc-L-valinal homobenzoin reaction pathways suppressed. Although good yields of cross-benzoin products are obtained using 1.5 equiv of the achiral aldehyde partner, the use of 3 equiv leads to an increase in yield by ca. 10%, and this stoichiometry was used throughout the rest of our study.

Having established optimized conditions, the scope of the reaction was explored using a variety of *N*-Boc-protected amino aldehydes[19] and heteroaromatic or aliphatic aldehydes (Scheme 2). *N*-Boc-amino aldehydes bearing unbranched substituents such as *N*-Boc-alaninal, *N*-Boc-phenylalaninal, and *N*,*N*′-bis-Boc-L-lysinal furnished the desired product with good yields and moderate diastereomeric ratios (**2**−**4**).[20] Increased bulk on the α-substituent of the amino aldehyde improved the diastereoselectivity, as shown in the case of L-valine, L-*tert*-leucine, and L-isoleucine derivatives (**5**−**7**).[21] Importantly, good yields were obtained by using aliphatic aldehydes as coupling partners, including one bearing an ester functionality (**8**−**10**). Interestingly, higher diastereoselectivities were observed when using aliphatic aldehydes compared to heteroaromatic aldehydes.[22] β-Branching in the donor aldehyde is well tolerated (**11**). However, and as expected, the presence of α-branching in both aldehyde partners resulted in lower yields (**12**). Benzaldehyde and its derivatives are not suitable for this reaction, as their use results in the formation of a complex mixture of homo- and cross-benzoin products (not shown). Other heteroaromatic aldehydes such as 2-pyridine carboxaldehyde afforded good yields and diastereomeric ratios under the reaction conditions (**13**). It should be noted that separation of diastereomers is often difficult by chromatography, highlighting the importance of diastereoselectivity in this process. This problem can be circumvented through the diastereoselective reduction of the product, giving rise to easily separable aminodiols (vide infra).

The relative configuration of the cross-benzoin products was initially established as depicted via computational methods (see the SI) and later confirmed through the synthesis of a known

Scheme 2. Scope of the Cross-Benzoin Reaction[g]



[a]Isolated yield of major diastereomer. [b]Overall yield of diastereomers determined by ^{1}H NMR analysis using dimethyl terephthalate as the internal standard. [c]Isolated yield of a 2:1 mixture of diastereomers. [d]Isolated yield of a 3:1 mixture diastereomers. [e]Isolated yield of a 13:1 mixture of the two diastereomers. [f]Product is air sensitive. [g]Reaction conditions: 1 equiv of *N*-Boc-amino aldehyde, 3 equiv of aliphatic or heteroaromatic or aromatic aldehyde.

natural product (vide infra). The diastereoselectivity of the reaction can be predicted using a Cram-chelate model involving a hydrogen bond between the carbamate and the aldehyde (Figure 2).[23]

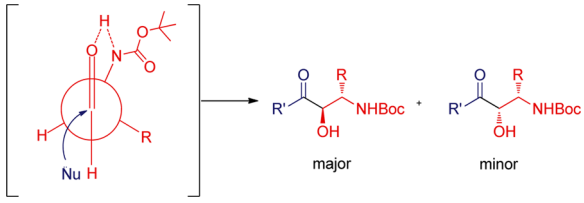


Figure 2. Rationale for diastereoselectivity.

All α-amino aldehyde substrates used in this study were enantiomerically enriched and derived from naturally occurring amino acids. The racemization of these reactants under the basic reaction conditions was a matter of concern.[24] Gratifyingly, comparison of a representative cross-benzoin product (**8**) with a racemic sample showed no erosion of the enantiomeric ratio (>98:2 er) following the reaction (see the SI).

To gain mechanistic insight into the reaction, two experiments were carried out using a 1:1 ratio of the two aldehydes and monitored by ^{1}H NMR spectroscopy. In the NHC-catalyzed cross-benzoin reaction between hydrocinnamaldehyde (**14**) and valine derivative **15**, the rate of formation of the desired cross-benzoin product (**8**) is comparable to the rate of consumption of both starting materials (Figure 3a and SI). The formation of the undesired homobenzoin dimer of hydrocinnamaldehyde (**16**) is much slower than formation of **8**. This suggests that the observed major product is kinetically favored. Subjecting **8** to reaction conditions did not lead to the formation of the minor diastereomer, homobenzoin products, or the starting aldehydes. Therefore, the cross-benzoin product is formed irreversibly under the reaction conditions. Although the exact factors

DOI: 10.1021/acs.orglett.6b02123
Org. Lett. XXXX, XXX, XXX−XXX

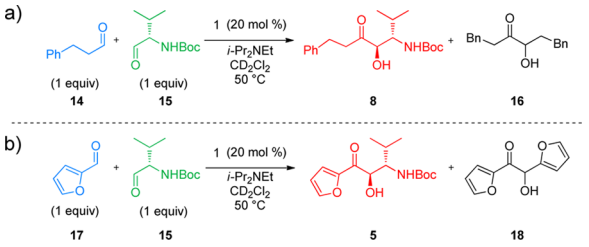


Figure 3. (a) ^{1}H NMR monitoring experiment for the reaction between **14** and **15**; (b) ^{1}H NMR monitoring experiment for the reaction between **17** and **15**.

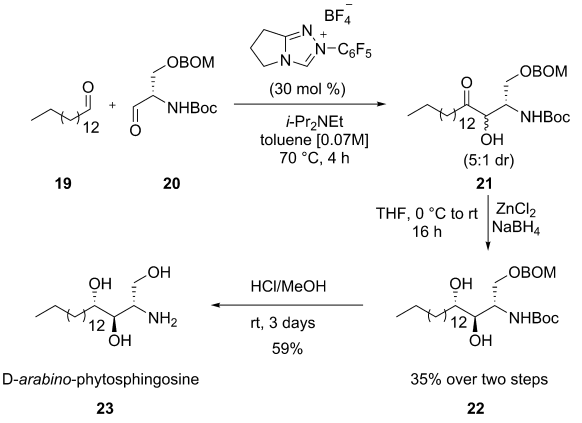
dictating chemoselectivity in this case remain unclear, it can be concluded that the reaction is under kinetic control. When *N*-Boc-L-valinal was subjected to standard reaction conditions without the partner aldehyde, the homobenzoin product was obtained in 49% NMR yield. To determine the importance of this homobenzoin pathway, the crude mixtures from the reactions depicted in Scheme 2 were carefully analyzed by ^{1}H NMR spectroscopy. Only trace quantities (3−8% NMR yield) of this product were present, suggesting that either the formation of the Breslow intermediate with the amino aldehydes is possible but not preferred in the presence of aliphatic or heteroaromatic aldehydes or that a subsequent step is rate-limiting and responsible for the observed chemoselectivity.[15,16b]

A similar experiment was performed for the cross-benzoin reaction involving furfural and **15** (Figure 3b and SI). This experiment suggests a different rationale for the formation of the major product. The rate of formation of **18** is faster than the formation of the desired cross-benzoin product (**5**). However, after partial formation of **18**, a retro-benzoin reaction leads to the steady production of the cross-benzoin product (**5**). These results highlight an important point: chemoselectivity at every step of the mechanism is not necessary to obtain high yields of cross-benzoin product. In this case, a presumably unfavorable formation of the Breslow intermediate with the amino aldehyde combined with reversibility of the homobenzoin reaction of furfural leads to formation of the desired cross-benzoin product over time. Furthermore, the reversibility of the cross-benzoin reaction pathway was verified through a crossover experiment by subjecting **4** and *trans*-chalcone to reaction conditions, and the expected Stetter product was observed (see the SI).

The absence of a method to address chemoselectivity in the NHC-catalyzed cross-benzoin reaction between aliphatic aldehydes has limited its use in total synthesis. Having developed a viable method, we set out to demonstrate its application in a concise synthesis of the sphingoid base D-*arabino*-phytosphingosine (Scheme 3). Sphingoid bases are key building blocks of sphingolipids, which play crucial structural and signaling functions.[25] The biological importance of phytosphingosines[26] and their difficult isolation have spurred wide interest in their chemical synthesis.[27]

Initial efforts toward the NHC-catalyzed cross-benzoin reaction of **19** and **20** under previously optimized conditions proved disappointing. Reaction optimization revealed that moderate yield and diastereoselectivity can be achieved using conditions depicted in Scheme 3. The resulting diastereomeric mixture (**21**) was subjected to stereoselective hydroxyl-directed reduction using $ZnCl_2$/$NaBH_4$. The reaction proceeded smoothly with a >20:1 diastereomeric ratio to afford **22** in 35% yield over two steps. This two-step process provides rapid and stereocontrolled access to amino diols bearing three contiguous

Scheme 3. Concise Total Synthesis of D-*arabino*-Phytosphingosine



stereocenters. Finally, simultaneous removal of BOM- and Boc-protecting groups using MeOH/HCl led to the formation of D-*arabino*-phytosphingosine (**23**). Spectroscopic data, optical rotation, and the melting point of the product match the previously reported values for the title compound (see the SI). Despite the moderate yield of the key cross-benzoin step, this strategic bond formation enables the shortest synthesis of this natural product to date.[27b,28] To our knowledge, no other total synthesis has utilized a cross-benzoin reaction between aliphatic aldehydes.

In summary, the use of α-amino aldehydes in NHC-catalyzed cross-benzoin reactions provides chemoselectivity through a combination of steric hindrance and electronic activation. The method affords the desired products diastereoselectively and in good yield for a variety of aldehydes. This method is the first example of both chemoselective cross-benzoin reaction between aliphatic aldehydes and of diastereoselectivity in intermolecular NHC-catalyzed benzoin reactions. NMR studies and a crossover experiment highlight the subtle interplay between reversibility and kinetic control and inform on the origin of chemoselectivity using different aldehydes. However, in order to firmly establish the origins of diastereo- and chemoselectivity, more thorough mechanistic studies are required. Finally, the value of the developed method is demonstrated through a concise synthesis of D-*arabino*-phytosphingosine.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02123.

Experimental procedures and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: michel.gravel@usask.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Natural Sciences and Engineering Research Council of Canada, the Canada Foundation for Innovation, and the University of Saskatchewan for financial support. This research was enabled in part by support provided by WestGrid

DOI: 10.1021/acs.orglett.6b02123
Org. Lett. XXXX, XXX, XXX−XXX

(www.westgrid.ca) and Compute Canada Calcul Canada (www.computecanada.ca).

REFERENCES

(1) (a) Hanessian, S. *Total Synthesis of Natural Products: The "Chiron" Approach*; Pergamon Press: Oxford, 1983; Vol. 3. (b) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2012**, *41*, 4150.

(2) For selected reviews, see: (a) Davis, F.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919. (b) Adam, W.; Lazarus, M.; Saha-Möller, C. R.; Schreier, P. *Acc. Chem. Res.* **1999**, *32*, 837. (c) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893. (d) Vilaivan, T.; Bhanthumnavin, W. *Molecules* **2010**, *15*, 917. (e) Merritt, E. A.; Olofsson, B. *Synthesis* **2011**, *2011*, 517. (f) Dong, D.-Q.; Hao, S.-H.; Wang, Z.-L.; Chen, C. *Org. Biomol. Chem.* **2014**, *12*, 4278. For selected examples of enantioselective α-hydroxylation of ketones, see: (g) Morikawa, K.; Park, J.; Andersson, P. G.; Hashiyama, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 8463. (h) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 1080. (i) Kawasaki, M.; Li, P.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 3795. (j) Basdevant, B.; Legault, C. Y. *Org. Lett.* **2015**, *17*, 4918.

(3) For recent reviews on NHC-catalyzed transformations, see: (a) Grossmann, A.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 314. (b) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511. (c) Thai, K.; Sánchez-Larios, E.; Gravel, M. In *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*; Wiley−VCH: Weinheim, 2013; pp 495−522. (d) Scheidt, K. A.; O'Bryan, E. A. Acyloin Coupling Reactions. In *Comprehensive Organic Synthesis II*, 2nd ed.; Marek, I., Knochel, P., Eds.; Elsevier, 2014; Vol. 3, pp 621−655. (e) Bugaut, X., Benzoin and Aza-benzoin. In *Comprehensive Organic Synthesis II*; Marek, I., Knochel, P., Ed.; Elsevier: 2014; Vol. 1, pp 424−470. (f) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485. (g) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307.

(4) The involvement of a radical pair pathway has recently been proposed: Rehbein, J.; Ruser, S.-M.; Phan, J. *Chem. Sci.* **2015**, *6*, 6013.

(5) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.

(6) The terms "acyloin reaction" and "cross-acyloin reaction" are often used to describe benzoin reactions involving aliphatic aldehydes.

(7) (a) Hachisu, Y.; Bode, J. W.; Suzuki, K. *J. Am. Chem. Soc.* **2003**, *125*, 8432. (b) Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3492. (c) Enders, D.; Niemeier, O.; Balensiefer, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1463. (d) Enders, D.; Niemeier, O.; Raabe, G. *Synlett* **2006**, *2006*, 2431. (e) Li, Y.; Feng, Z.; You, S.-L. *Chem. Commun.* **2008**, 2263. (f) Enders, D.; Henseler, A. *Adv. Synth. Catal.* **2009**, *351*, 1749. (g) Ema, T.; Oue, Y.; Akihara, K.; Miyazaki, Y.; Sakai, T. *Org. Lett.* **2009**, *11*, 4866. (h) Enders, D.; Grossmann, A.; Fronert, J.; Raabe, G. *Chem. Commun.* **2010**, *46*, 6282. (i) Takada, A.; Hashimoto, Y.; Takikawa, H.; Hikita, K.; Suzuki, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2297. (j) Rose, C. A.; Gundala, S.; Fagan, C.-L.; Franz, J. F.; Connon, S. J.; Zeitler, K. *Chem. Sci.* **2012**, *3*, 735. (k) Thai, K.; Langdon, S. M.; Bilodeau, F.; Gravel, M. *Org. Lett.* **2013**, *15*, 2214.

(8) Mathies, A.; Mattson, A.; Scheidt, K. *Synlett* **2009**, *2009*, 377.

(9) Stetter, H.; Dambkes, G. *Synthesis* **1977**, *1977*, 403.

(10) Pohl, M.; Lingen, B.; Müller, M. *Chem. - Eur. J.* **2002**, *8*, 5288.

(11) Piel, I.; Pawelczyk, M. D.; Hirano, K.; Fröhlich, R.; Glorius, F. *Eur. J. Org. Chem.* **2011**, *2011*, 5475.

(12) Kuhl, N.; Glorius, F. *Chem. Commun.* **2011**, *47*, 573.

(13) (a) Jin, M. Y.; Kim, S. M.; Han, H.; Ryu, D. H.; Yang, J. W. *Org. Lett.* **2011**, *13*, 880. (b) Jin, M. Y.; Kim, S. M.; Mao, H.; Ryu, D. H.; Song, C. E.; Yang, J. W. *Org. Biomol. Chem.* **2014**, *12*, 1547.

(14) (a) O'Toole, S. E.; Rose, C. A.; Gundala, S.; Zeitler, K.; Connon, S. J. *J. Org. Chem.* **2011**, *76*, 347. (b) Rose, C.; Gundala, S.; Connon, S.; Zeitler, K. *Synthesis* **2011**, *2011*, 190.

(15) Collett, C. J.; Massey, R. S.; Taylor, J. E.; Maguire, O. R.; O'Donoghue, A. C.; Smith, A. D. *Angew. Chem., Int. Ed.* **2015**, *54*, 6887.

(16) (a) Langdon, S. M.; Wilde, M. M. D.; Thai, K.; Gravel, M. *J. Am. Chem. Soc.* **2014**, *136*, 7539. (b) Langdon, S. M.; Legault, C. Y.; Gravel, M. *J. Org. Chem.* **2015**, *80*, 3597.

(17) (a) Müller, C. R.; Pérez-Sánchez, M.; Domínguez de María, P. *Org. Biomol. Chem.* **2013**, *11*, 2000. (b) Stockton, K. P.; Greatrex, B. W.; Taylor, D. K. *J. Org. Chem.* **2014**, *79*, 5088. (c) Kang, B.; Sutou, T.; Wang, Y.; Kuwano, S.; Yamaoka, Y.; Takasu, K.; Yamada, K. *Adv. Synth. Catal.* **2015**, *357*, 131.

(18) The use of the weak base CsOAc led to a lower diastereomeric ratio (5:1) compared to the selected DIPEA (7:1) after the same period of time (4 h). The use of the stronger base DBU also led to a lower diastereomeric ratio and raises the issue of racemization of the starting α-amino aldehyde.

(19) In order to improve the reactivity and/or diastereoselectivity of the reaction, various protecting groups such as tosyl, Fmoc, Moc, *N*,*N*′-Bis(Bn), *N*-Bn-*N*-Boc, *N*-tosyl-*N*-Boc, *N*-phthalamide, and *N*-Bn-*N*-PMB were employed. Unfortunately, none of these improved the reaction outcome.

(20) Although the fate of the unaccounted for *N*-Boc-amino aldehyde is still unclear, we were able to isolate a small amount of aldehyde−NHC adduct consistent with an S_NAr pathway: Zhao, X.; Glover, G. S.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *Synlett* **2013**, *24*, 1229.

(21) Although sterically similar, the use of *N*-Boc-phenylglycinal results in poor yields and low diastereomeric ratios under these reaction conditions.

(22) The reasons for the somewhat better diastereoselectivities observed with aliphatic aldehydes are unclear at this point.

(23) The proposed Cram-chelate model was further validated by subjecting *N*-Boc-*N*-Bn-alaninal to the reaction conditions. The other diastereomer was favored in this experiment. Work is ongoing, and results will be reported in due course.

(24) (a) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236. (b) Myers, A. G.; Zhong, B.; Movassaghi, M.; Kung, D. W.; Lanman, B. A.; Kwon, S. *Tetrahedron Lett.* **2000**, *41*, 1359. (c) Gryko, D.; Chalko, J.; Jurczak, J. *Chirality* **2003**, *15*, 514.

(25) (a) Brodesser, S.; Sawatzki, P.; Kolter, T. *Eur. J. Org. Chem.* **2003**, *2003*, 2021. (b) Curfman, C.; Liotta, D. *Methods Enzymol.* **2000**, *311*, 391. (c) Howell, A. R.; Ndakala, A. J. *Curr. Org. Chem.* **2002**, *6*, 365. (d) Liao, J.; Tao, J.; Lin, G.; Liu, D. *Tetrahedron* **2005**, *61*, 4715.

(26) (a) Natori, T.; Morita, M.; Akimoto, K.; Koezuka, Y. *Tetrahedron* **1994**, *50*, 2771. (b) Li, H.; Matsunaga, S.; Fusetani, N. *Tetrahedron* **1995**, *51*, 2273. (c) Kobayashi, S.; Furuta, T.; Hayashi, T.; Nishijima, M.; Hanada, K. *J. Am. Chem. Soc.* **1998**, *120*, 908. (d) Kolter, T.; Sandhoff, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1532. (e) Mormeneo, D.; Casas, J.; Llebaria, A.; Delgado, A. *Org. Biomol. Chem.* **2007**, *5*, 3769. (f) Lee, D. H.; Kim, S. H.; Ahn, K. H.; Kim, S. K.; Choi, J. M.; Ji, J. E.; Won, J. H.; Park, Y. H.; Lim, C.; Kim, S.; Kim, D. K. *Arch. Pharmacal Res.* **2011**, *34*, 229.

(27) For recent syntheses of phytosphingosines, see: (a) Lee, Y. M.; Baek, D. J.; Lee, S.; Kim, D.; Kim, S. *J. Org. Chem.* **2011**, *76*, 408. (b) Mu, Y.; Jin, T.; Kim, G.-W.; Kim, J.-S.; Kim, S.-S.; Tian, Y.-S.; Oh, C.-Y.; Ham, W.-H. *Eur. J. Org. Chem.* **2012**, *2012*, 2614. (c) Calder, E. D. D.; Zaed, A. M.; Sutherland, A. *J. Org. Chem.* **2013**, *78*, 7223. (d) Sarabia, F.; Vivar-Garcia, C.; Garcia-Ruiz, C.; Sanchez-Ruiz, A.; Pino-Gonzalez, M. S.; Garcia-Castro, M.; Chammaa, S. *Eur. J. Org. Chem.* **2014**, *2014*, 3847.

(28) (a) Mulzer, J.; Brand, C. *Tetrahedron* **1986**, *42*, 5961. (b) Imashiro, R.; Sakurai, O.; Yamashita, T.; Horikawa, H. *Tetrahedron* **1998**, *54*, 10657. (c) Shirota, O.; Nakanishi, K.; Berova, N. *Tetrahedron* **1999**, *55*, 13643. (d) Azuma, H.; Tamagaki, S.; Ogino, K. *J. Org. Chem.* **2000**, *65*, 3538. (e) Jung, D. Y.; Kang, S.; Chang, S. B.; Kim, Y. H. *Synlett* **2005**, 2183. (f) Enders, D.; Paleček, J.; Grondal, C. *Chem. Commun.* **2006**, *55*, 655. (g) Mormeneo, D.; Casas, J.; Llebaria, A.; Delgado, A. *Org. Biomol. Chem.* **2007**, *5*, 3769. (h) Kim, S.; Lee, N.; Lee, S.; Lee, T.; Lee, Y. M. *J. Org. Chem.* **2008**, *73*, 1379.

DOI: 10.1021/acs.orglett.6b02123
Org. Lett. XXXX, XXX, XXX−XXX