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Skeletally Diverse Small Molecules Using a Build/Couple/Pair Strategy

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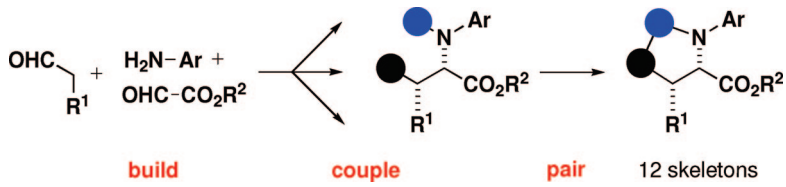
ABSTRACT



Intermolecular couplings of simple building blocks using catalytic, stereoselective cross-Mannich reactions followed by intramolecular functional group-pairing reactions of easily accessed variants of the Mannich products are explored as a route to skeletally diverse small molecules. The synthetic pathway yields products having 12 different skeletons using only three steps and has the potential to enable substantial stereochemical diversification in the future.

Small molecules are widely used as probes in biology and drugs in medicine.[1] One approach to their discovery involves, in part, an upfront investment in chemistry; specifically, the complete synthesis of a transformative small-molecule screening collection.[2] The properties of compounds in such a collection should possess have been discussed elsewhere, as has a synthesis strategy that might facilitate their production.[3] We describe an application of this "build/couple/pair" strategy here, illustrating how intramolecular, functional group-pairing reactions can facilitate the synthesis of skeletally diverse small molecules. A recent application of this strategy proved effective in generating stereochemically and skeletally diverse small molecules, but the requirement for a pre-existing stereogenic center in aldehyde-containing building blocks, which imparted face selectivity during a Petasis reaction, limited the diversity of steroisomers. In this case, only one face of the imine was accessible to the nucleophile, resulting in *anti*-diastereoselectivity.[4] We reasoned that organocatalytic enantioselective additions to electrophilic imines might increase the degree of stereochemical diversity.[5] Here, we explore the use of catalytic, enantioselective Mannich reactions using achiral aldehydes as the nucleophile in cross-coupling reactions of highly electrophilic imines derived from primary amines and ethyl glyoxylate.[5b] Although, in principle, recent advances in this area would provide access to all four steroisomeric products, we have in this study focused on the *syn*-diastereomeric

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(1) Schreiber, S. L. *Nat. Chem. Biol.* **2005**, *1*, 64–66.
(2) Spiegel, D. A.; Schroeder, F. C.; Duvall, J. R.; Schreiber, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 14766–14767.
(3) (a) Nielsen, T. E.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 48–56. (b) Schreiber, S. L. *Nature* **2009**, *457*, 153–154.
(4) Kumagai, N.; Muncipinto, G.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3635–3638.
(5) (a) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827–833. (b) Córdova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866–1867. (c) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3677–3680. (d) Notz, W.; Tanaka, F.; Watanabe, S.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F., III. *J. Org. Chem.* **2003**, *68*, 9624–9634. (e) Chowdari, N. S.; Suri, J. T.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2507–2510. (f) Ibrahem, I.; Córdova, A. *Chem. Commun.* **2006**, 1760–1762. (g) Mitsumori, S.; Zhang, H.; Ha-Yeon Cheong, P.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 1040–1041.

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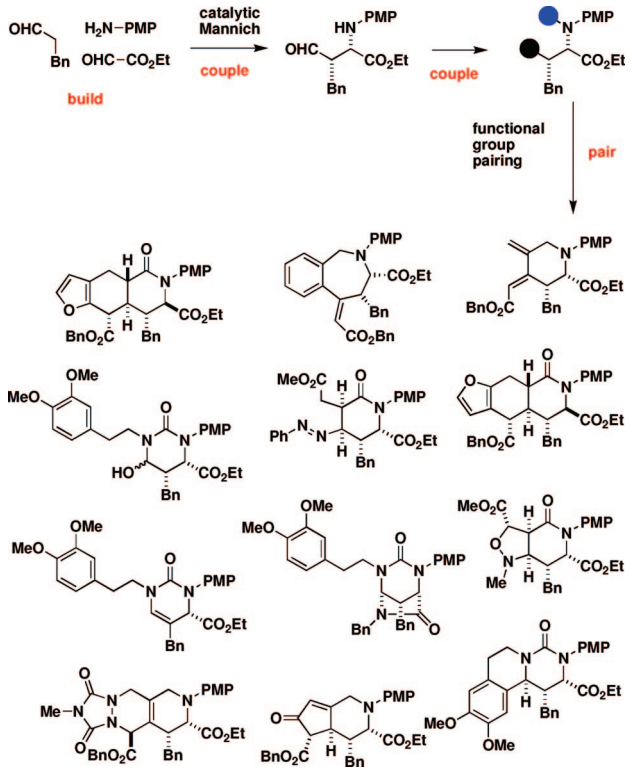
products. Our initial aim was to establish conditions that permit (1) the attachment of functional groups to the amine and aldehyde functionalities and (2) intramolecular, functional group-pairing reactions that would result in products having diverse skeletons (Scheme 1).

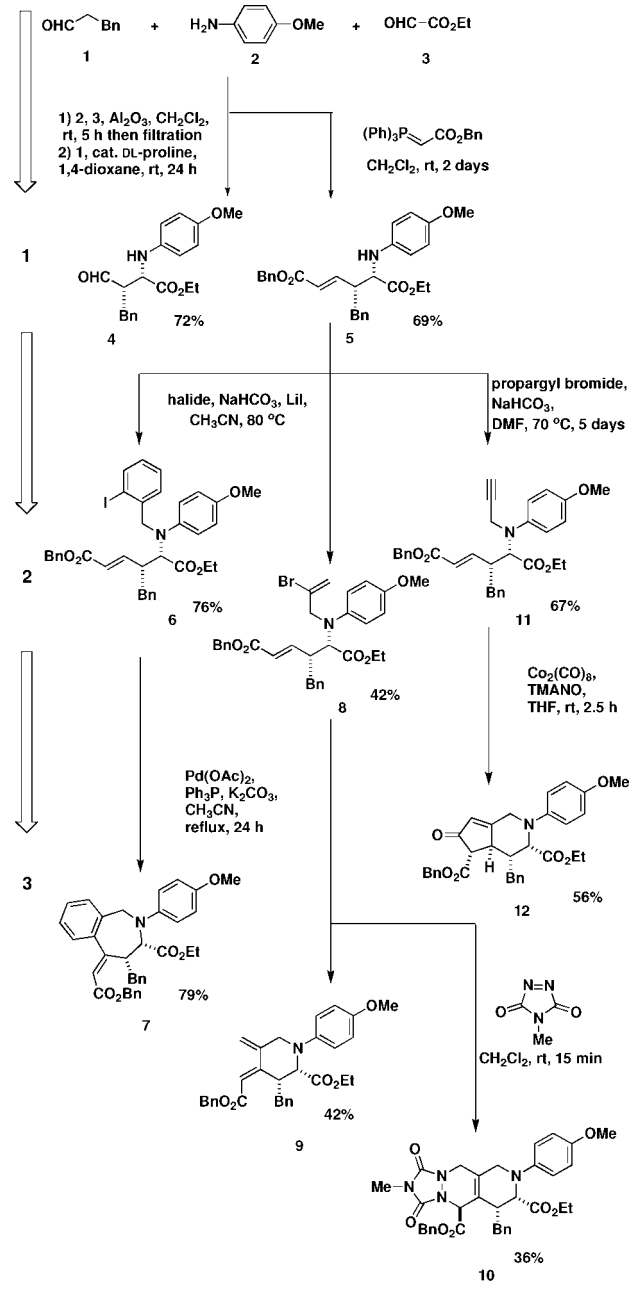
Scheme 1. Build/Couple/Pair Strategy Yielding Skeletally Diverse Small Molecules



We initiated the current research with commercially available achiral reagents **1**, **2**, and **3** to minimize the overall number of synthetic steps (Scheme 2). Stereochemical control of the coupling step was achieved by using an organocatalytic asymmetric cross-Mannich reaction.[5b] (As noted, extensions of this chemistry should exploit the full potential of analogous enantio- and diastereoselective Mannich reactions coupled to analogous derivatization and cyclization reactions. Such reactions would enable the synthesis of both stereochemically and skeletally diverse products, provided that the cyclization reactions proceed with both diastereomeric Mannich products.)

The first reaction was a three-component, cross-Mannich reaction using a simple aldehyde to afford the *syn*-product **4** stereoselectively in 72% yield. A one-pot Wittig reaction proceeded at room temperature and gave *E*-alkene **5** with high stereoselectivity in 69% yield. The *E*-alkene **5** was also alkylated to give **6**, **8**, and **11**. Benzyl compound **6** was cyclized by using a Heck reaction to give 6/7-fused bicyclic compound **7** in 79% yield. Allyl compound **8** was cyclized by using another Heck reaction to give diene **9** in 42% yield[6] or a one-pot Heck/Diels−Alder-cascade sequence to give tricyclic compound **10** with a 5/6/6-fused ring system.

Scheme 2. Cyclizations of *N*-Alkylated Intermediates

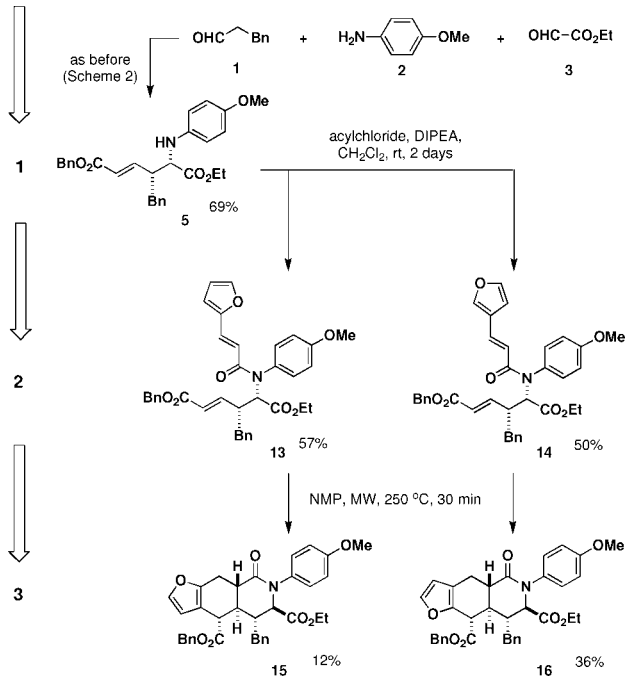


The structure of **10** was confirmed by X-ray crystallographic analysis. A Pauson−Khand reaction of propargyl compound **11** proceeded diastereoselectively to give azabicyclo compound **12**.[7]

The *E*-alkene **5** was further transformed via one-pot acylations to give **13** and **14** in 57% and 50% yields, respectively (Scheme 3). Attempts to achieve microwave-assisted intramolecular Diels−Alder reactions using furans **13** and **14** gave poor results when performed below 200 °C. Above this temperature only diesters **15** and **16**, resulting

(6) Nagasawa, K.; Ishihara, H.; Zako, Y.; Shimizu, I. *J. Org. Chem.* **1993**, *58*, 2523–2529.
(7) Günter, M.; Gais, H.-J. *J. Org. Chem.* **2003**, *68*, 8037–8041.

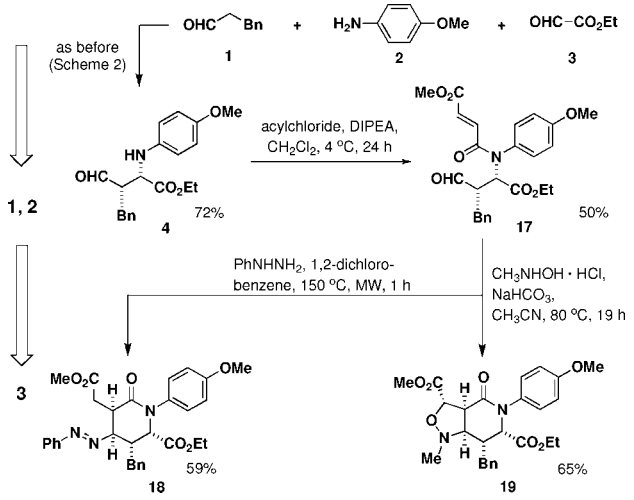
Scheme 3. Cyclizations of *N*-Acylated Intermediates



from cyclization, olefin isomerization, and epimerization, were isolated.[8] The stereochemistry of tricyclic compound **15** was confirmed by X-ray crystallographic analysis.

Next, we examined a sequence where the amine moiety of aminoaldehyde **4** was acylated in the second step (Scheme 4). A hydrazone of **17** was transformed to give lactam **18**

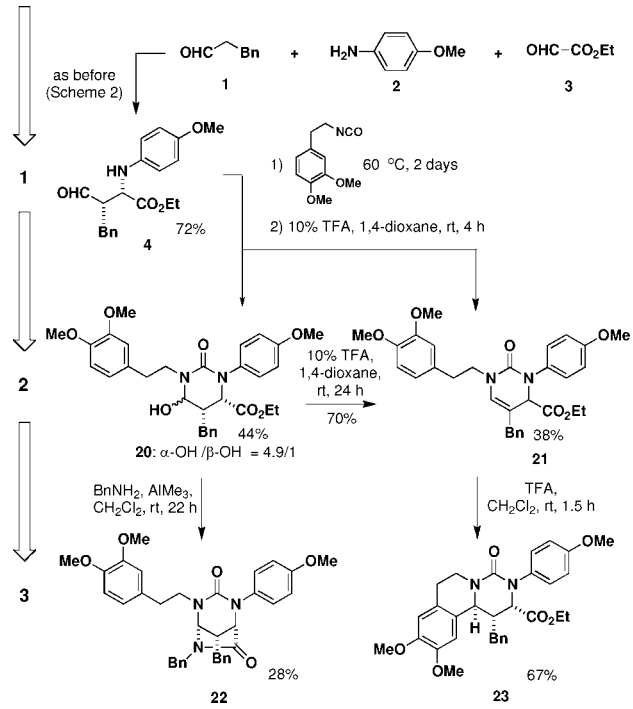
Scheme 4. Cyclizations of *N*-Acylaminoaldehyde Derivatives



presumably via either an intramolecular Michael addition or an ene reaction.[9] A nitrone derived from **17** underwent an intramolecular 1,3-dipolar cycloaddition to give the fused isoxazolidine **19** in 65% yield.[10] Compound **19** was obtained as a single isomer, and the assignment of its stereochemistry was based on NOESY experiments.

We next investigated a reaction sequence where the aminoaldehyde **4** was acylated to form a urea in the second step (Scheme 5).

Scheme 5. Cyclizations of *N*-Acylaminoaldehyde Derivatives

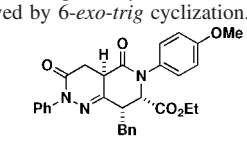


Following urea formation and mild acidic treatment, aminoaldehyde **4** was converted into cyclic compounds **20** and **21**. The hemiaminal **20** was obtained as an inseparable mixture of α-OH and β-OH ($\alpha/\beta = 4.9$) and was converted into compound **21** following treatment with aqueous TFA. The hemiaminal **20** was also converted into the bridged bicycle **22** by Weinreb amidation and in situ cyclization.[11]

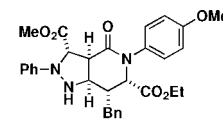
Compound **21** was converted into the tricycle **23** by a Pictet−Spengler reaction under conditions more acidic than those required to form **21**.[12] After column chromatography, **23** was obtained as a single isomer in 67% yield. This structure was confirmed by X-ray crystallographic analysis.

(8) (a) Cooper, J. A.; Cornwall, P.; Dell, C. P.; Knight, D. W. *Tetrahedron Lett.* **1988**, *29*, 2107–2110. (b) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179–14233.

(9) (a) Snider, B. B.; Conn, R. S. E.; Sealfon, S. *J. Org. Chem.* **1979**, *44*, 218–221. (b) Grigg, R.; Dowling, M.; Jordan, M. W.; Sridharan, V. *Tetrahedron* **1987**, *43*, 5873–5886. Lactam **18a** was also obtained in 11% yield. It was probably formed via azo-hydrazo prototropy reaction of **18**, followed by 6-*exo-trig* cyclization.



18a



18b

Furthermore, a hydrazone of **17** underwent intramolecular 1,3-dipolar cycloaddition reaction via hydrazone-azomethine imine isomerization to afford the fused pyrazolidine **18b** in 9% yield.

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In conclusion, using a *syn*-selective cross-Mannich reaction in the context of the build/couple/pair strategy, we obtained skeletally diverse small molecules with 12 different skeletons within three steps starting from commercially available reagents. In addition to incorporating the compounds now available by the pathway described here into the Broad Institute screening collection, we aim to use this strategy with enantio- and diastereomeric products resulting from *syn*- and *anti*-selective Mannich reactions.[5] Results of small-molecule screens using the compounds synthesized here and in the future will be made available on the public database ChemBank.[13]

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

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