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General Route for Preparing β-Nitrocarbonyl Compounds Using Copper Thermal Redox Catalysis

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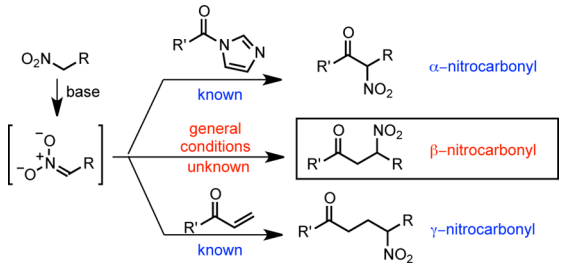
Supporting Information

ABSTRACT: Using a simple copper catalyst, the alkylation of nitroalkanes with α-bromocarbonyls is now possible. This method provides a general, functional group tolerant route to β-nitrocarbonyl compounds, including nitro amides, esters, ketones, and aldehydes. The highly sterically dense, functional group rich products from these reactions can be readily elaborated into a range of complex nitrogen-containing molecules, including highly substituted β-amino acids.

Nitroalkanes are extraordinarily useful intermediates in organic synthesis.[1] These compounds participate in a wide range of carbon−carbon bond-forming reactions (including Henry reactions,[2] conjugate additions,[2] allylations,[3] and arylations[4]), serve as starting materials for the installation of numerous functional groups (including alkylamines, ketones, hydroxyl amines, alkanes),[2] and serve as radical precursors (Scheme 1).[5]

Scheme 1. Synthesis of Nitrocarbonyl Compounds



Among nitroalkanes, nitrocarbonyl compounds are a particularly interesting class, as the two functional groups have widely orthogonal reactivity, making them highly versatile intermediates in complex molecule synthesis.[1] α-Nitrocarbonyls can be easily prepared by acylation of a nitronate anion[6] or by nitration of a carbonyl.[7] Similarly, γ-nitrocarbonyls can be prepared by conjugate addition of a nitronate anion to an α,β-unsaturated carbonyl,[8] or by the addition of an enolate to a nitroalkene.[9] In contrast, however, the synthesis of β-nitrocarbonyls is considerably more challenging. In 1970, Kornblum demonstrated that tertiary α-nitrocarbonyls can undergo coupling with nitronate anions to prepare β-nitroesters and ketones;[10] however, these reactions, which likely proceed via radical intermediates, have not been widely adopted, possibly due to the required starting materials and/or need for light-promoted reaction conditions with many substrates. More recently, MacMillan reported the enantioselective α-nitroalkylation of aldehydes using silylnitronates and organo-SOMO catalysis. While this latter method is extremely elegant and efficient, it is limited to preparation of β-nitroaldehydes and cannot access highly substituted products.[11] While a few additional sundry methods exist,[12] to date, no general method has been reported for the preparation of β-nitrocarbonyls that is general for a wide variety of carbonyl groups with varying substitution and proceeds under synthetically tractable conditions.

One potential entry to β-nitrocarbonyls involves the alkylation of a nitronate anion by a readily available α-bromocarbonyl compound. However, this reaction has been shown to lead to a complex mixture of products, presumably due to the strong preference for nitronate anions to undergo alkylation at oxygen in reactions involving alkyl halide electrophiles.[10,13,14]

We recently reported a simple and inexpensive copper catalyst, prepared in situ from copper bromide and an easily synthesized 1,3-diketimine (nacnac) ligand, that successfully catalyzes the C-alkylation of nitroalkanes using benzyl bromides.[15,16] We believe this reaction proceeds via a benzyl-stabilized radical,[16] which suggests that other alkyl bromides bearing radical-stabilizing groups might be viable coupling partners for the reaction.

We now show that nitroalkanes can be alkylated with α-bromocarbonyls using this copper-catalyzed strategy. This new protocol provides direct access to a wide range of β-nitrocarbonyl compounds, including nitro esters, amides, ketones, and aldehydes with excellent functional group compatibility. Importantly, this method also demonstrates remarkable steric tolerance, and allows the synthesis of β-nitrocarbonyls containing fully substituted vicinal carbons at both the α and β positions. This method can be used to access a range of downstream products, including complex, sterically encumbered β-amino acids.

We began by studying the reaction of ethyl 2-bromovalerate with 1-nitropropane to make β-nitroester **1** (Table 1). Starting with the optimized conditions for alkylation of nitroalkanes using benzyl bromides (20 mol % of CuBr, 20 mol % of diketimine **2**,

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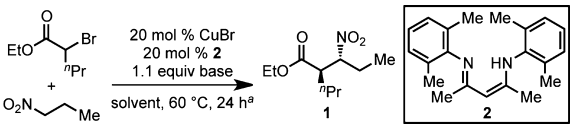
Table 1. Optimization of Reaction Conditions



entry	base	solvent	yield of 1[b] (%)	dr[b]
1	NaOEt	benzene	75	58:42
2	NaOEt	benzene	0[c]	n/a
3	$NaOSiMe_3$	benzene	92 (89)	59:41
4	$NaOSiMe_3$	toluene	69	61:39
5	$NaOSiMe_3$	hexanes	94 (90)	62:38
6	$NaOSiMe_3$	Et_2O	68	62:38
7	$NaOSiMe_3$	dioxane	77	56:44
8	$NaOSiMe_3$	CH_2Cl_2[d]	96 (94)	62:38
9	$NaOSiMe_3$	DMF	4	~50:50

[a]1.2 equiv of 1-nitropropane. [b]Yield and diastereomeric ratio (dr) determined by NMR using 1,3,5-trimethoxybenzene or mesitylene as an internal standard; parenthetical yields are isolated yields of pure material. [c]No copper, no ligand. [d]40 °C.

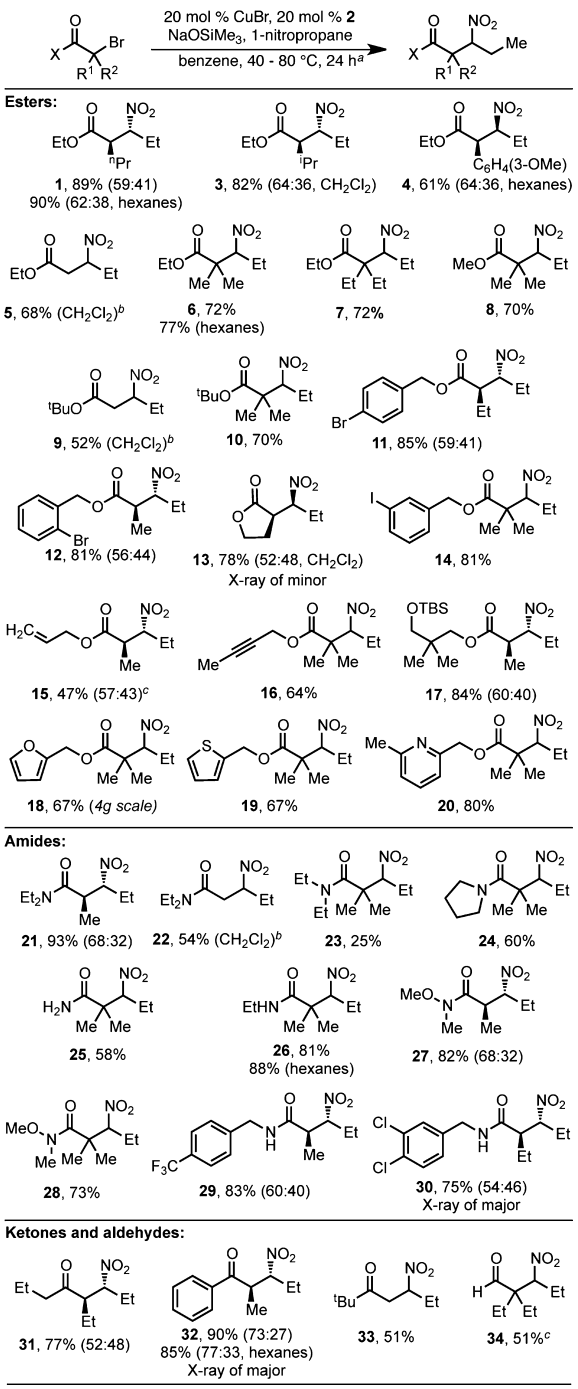
NaOEt, benzene, 60 °C), we were pleased to observe a 75% yield of desired product **1** (entry 1). The nitroester was observed as a 58:42 mixture of diastereoisomers, which was later shown to favor the erythro-isomer, as shown (see below). In the absence of catalyst, none of the desired product was observed (entry 2). When $NaOSiMe_3$ was used as the base, **1** was observed in 92% yield (89% isolated yield) with a similar diastereomeric ratio as above (entry 3). Further studies revealed that the reaction was tolerant of a range of solvents (entries 4−8). Whereas nonpolar solvents generally provided the highest yields, moderate to good yields were observed in all but the most polar solvents investigated (entry 9). Particularly effective solvents include benzene, hexanes, and methylene chloride, all of which provide excellent yield in the model reaction. In subsequent studies, benzene proved to be the most general solvent and was therefore used most often. In many cases, however, hexanes could also be employed. For the sake of comparison, yields in both solvents are reported in some of the studied examples described below. In a few cases, often those involving more polar substrates, other solvents such as dioxane, cyclohexane, or methylene chloride provided superior yields. These cases are denoted in the tables.

The optimized reaction conditions are highly general for the preparation of β-nitrocarbonyl compounds. As shown in Scheme 2 (top), a broad range of α-bromoesters bearing diverse substitution and functional groups participate in the reaction. Branching and aromatic substitution at the α-position (**3** and **4**) do not adversely affect the yield of the reaction. Both primary and tertiary α-bromoesters are also effective substrates. With primary substrates (**5** and **9**), we have found that increased catalyst loading is required to achieve good yields. We assume this relates to the difficulty in forming a primary radical intermediate. However, given the cost of the catalyst, we do not believe this to be a serious impediment.

In contrast, tertiary α-bromo esters react very smoothly with standard catalyst loadings to provide highly substituted β-nitro esters (**6** and **7**). A variety of esters can also be used (**11**, **12**, and **14**). Finally, β-nitrolactones can also be prepared using this route (**13**).

α-Bromo amides also serve as alkylating reagents in this transformation (Scheme 2, middle). *N*,*N*-Dialkylamides bearing a secondary α-bromide react in excellent yield under the optimized reaction conditions (**21**). As with the ester substrates,

Scheme 2. Scope with Respect to α-Bromocarbonyl Compound



[a]Conditions: 1 equiv of α-bromocarbonyl, 1.2−1.4 equiv of nitroalkane, 20 mol % of CuBr, 20 mol % of **2**, and 1.1−1.3 equiv of $NaOSiMe_3$; see the Supporting Information for exact conditions. Diastereomeric ratio determined from NMR of crude product using mesitylene as internal standard. [b]50 mol % of CuBr and **2**. [c]48 h.

primary bromide substrates can also be used, but the yield is slightly attenuated and higher catalyst loading is required (**22**). With tertiary amides bearing a tertiary halogen, the facility of the reaction depends greatly on the nature of the nitrogen substituents.

With amides bearing two alkyl groups, a low yield of the desired product (**23**) was observed, even when forcing

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conditions were employed. We attribute this to the extreme steric encumbrance imparted by the *s-trans* amide substituent in the putative radical intermediate.[17] This hypothesis is supported by the fact that formation of pyrrolidine-derived product **24**, in which the *s-trans* substituent is constrained, is formed in much higher yield under the standard conditions. α-Bromoamides bearing other nitrogen substituents can also be used in the reaction. This includes protic primary (**25**) and secondary amides (**26**). Weinreb amide substrates are also very good substrates in the reaction; products derived from both secondary (**27**) and tertiary bromides (**28**) can be obtained in high yield. The versatility of the Weinreb amide products will allow a broad range of downstream synthetic manipulations.[18]

Finally, with respect to the scope of the α-bromocarbonyl substrate, both α-bromo ketones and aldehydes can be used (Scheme 2, bottom). Ketones both with (**31**) and without (**32**) enolizable protons at the adjacent α-center performed equally well. As with previous examples, reduced substitution at the bromide center of the starting material decreased the yield of the product (**33**). With aldehydes, the degree of substitution at the halogen center proved highly critical. Only tertiary α-bromoaldehydes provided useful yields in the reaction (**34**). In this way, the current reaction is highly complementary to the transformation reported by MacMillan described above.[11]

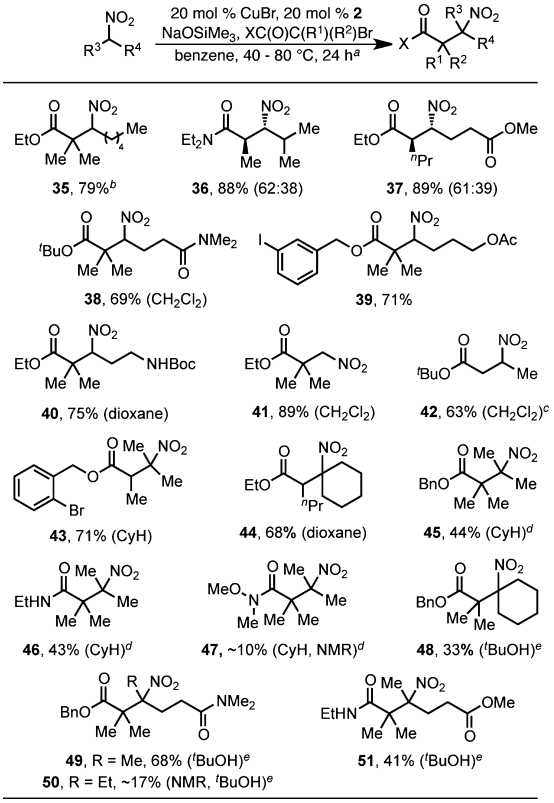
The reaction is also highly robust with respect to the nitroalkane coupling partner (Scheme 3). Longer aliphatic nitroalkanes (**35**), as well as those with β-branching (**36**), are well tolerated. The alkylation of nitromethane proceeded without incident (**41**). Most strikingly, secondary nitroalkanes could also be alkylated using this protocol. This includes the use of secondary (**43** and **44**) *as well as tertiary* (**45**–**51**) α-bromocarbonyls. In the latter case, both simple secondary nitroalkanes, such as 2-nitropropane and nitrocyclohexane, as well as more complex nitroalkanes participated in the reaction with equal facility (**49** and **51**). The products from these reactions lead to fully substituted vicinal carbons bearing a nitrogen center, which are highly challenging to prepare by other means.[19] There does, however, appear to be a steric limit in these reactions (see **47** and **50**); very highly encumbered products are formed in only limited yield.

Finally, more complex nitroalkanes bearing additional functional groups were also well tolerated in the reaction (**37**–**40** and **49**–**51**). These examples, as well as the additional examples in Scheme 2, demonstrate the broad functional group compatibility observed with this transformation. In total, compatible functional groups include aromatic chlorides (**30**), bromides (**11** and **12**), and iodides (**14**), trifluoromethyl arenes (**29**), alkenes (**15**), internal alkynes (**16**), silyl ethers (**17**), esters (**37**), and amides (**38**) located away from the reaction center, acyl-protected alcohols (**39**), and secondary Boc-protected amines (**40**). In addition, a variety of heterocyclic substrates are tolerated in the reaction, including lactones (mentioned above, **13**), furans (**18**), thiophenes (**19**), and pyridines (**20**). Finally, it is notable that the preparation of **18** was accomplished on multigram scale, demonstrating the scalability of these reactions, even on more complex substrates.

Only modest levels of diastereoselectivity were observed in cases where stereoisomers were possible. In most cases, however, the stereoisomers were readily separated by simple chromatography, and in several cases we were able to characterize one of the isomers via X-ray crystallography (see Scheme 2). Correlation of these structures to their ^{1}H NMR spectra revealed that the erythro isomer consistently displayed downfield shifts at the hydrogen atom α to the nitro group compared to the threo isomer.[20] Based upon this analysis, we were able to determine that the erythro isomer was the predominant product in all but two cases (the exceptions were for aromatic product **4** and lactone **13**).[21]

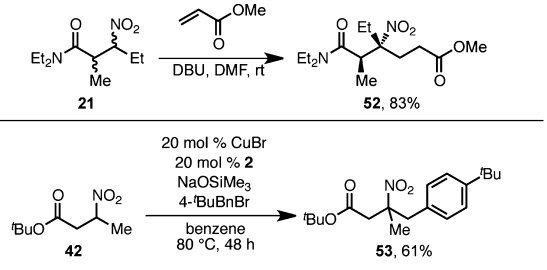
The products from the alkylation reaction are highly useful intermediates for further synthetic manipulations. For example, the products can be elaborated by C–C bond-forming reactions. This includes traditional reactions, such as their use as nucleophiles in conjugate addition reactions (e.g., Scheme 4, top)[22] or our previously reported copper-catalyzed benzylation reaction (e.g., Scheme 4, bottom).[15] Notably, both of these reactions form congested, nitrogen-bearing, fully substituted carbons. The ability to functionalize further α to the nitro group highlights the importance of this transformation compared to

Scheme 3. Scope with Respect to Nitroalkane



[a]Conditions: 1 equiv α-bromocarbonyl, 1.2–1.6 equiv nitroalkane, 20 mol % CuBr, 20 mol % **2**, and 1.1–1.7 equiv $NaOSiMe_3$, see Supporting Information for exact conditions. [b]48 h. [c]50 mol % CuBr and **2**. [d]30 mol % CuBr and **2**, 48 h. [e]40 mol % CuBr and **2**.

Scheme 4. Subsequent C–C Bond-Forming Reactions of Alkylation Products



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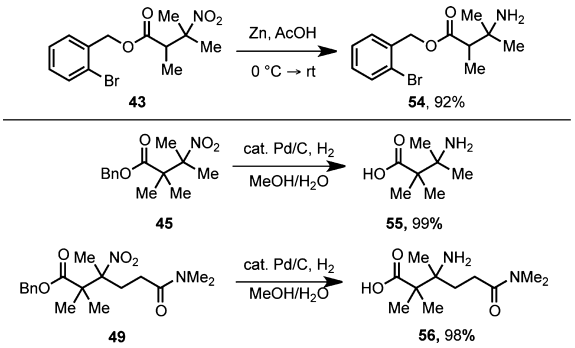
other protocols for preparing β-azacarbonyl compounds, such as the β-aminocarbonyls that result from Mannich reactions.[19]

Moreover, β-nitrocarbonyls are excellent precursors for β-amino acids and their derivatives.[23] For example, Zn/AcOH provides a high-yielding, mild reagent for the selective reduction of the nitro group to the corresponding amine (Scheme 5, top). Alternatively, Pd/C-catalyzed hydrogenolysis of benzyl ester derivatives leads cleanly to the unprotected β-amino acids in very high yield (Scheme 5, bottom).

Scheme 5. Reduction of Alkylation Products



It is particularly notable that this latter reaction works efficiently to prepare a range of highly substituted β-amino acids, including those bearing additional functional groups.

In summary, using copper-catalyzed thermal redox catalysis, we have developed a general and high-yielding route for the preparation of β-nitrocarbonyl compounds from readily available α-bromocarbonyls. The method is applicable to the synthesis of nitro esters, amides, ketones, and aldehydes, and the mild reaction conditions are compatible with a vast range of functional groups. The versatile products from the reaction offer a range of options for additional synthetic manipulations, including ready access to highly substituted β-amino acids and their derivatives.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures; crystallographic and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1.
(2) Ono, N. *The Nitro Group In Organic Synthesis*; John Wiley & Sons: New York, 2001.
(3) (a) Aleksandrowicz, P.; Piotrowska, H.; Sas, W. *Tetrahedron* **1982**, *38*, 1321. (b) Maki, K.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2007**, *63*, 4250. (c) Trost, B. M.; Surivet, J.-P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3122. (d) Tsuji, J.; Yamada, T.; Minami, I.; Yuhara, M.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1987**, *52*, 2988. (e) Wade, P. A.; Morrow, S. D.; Hardinger, S. A. *J. Org. Chem.* **1982**, *47*, 365.
(4) Vogl, E. M.; Buchwald, S. L. *J. Org. Chem.* **2001**, *67*, 106.
(5) (a) Kornblum, N.; Carlson, S. C.; Smith, R. G. *J. Am. Chem. Soc.* **1979**, *101*, 647. (b) Ono, N.; Miyake, H.; Kaji, A. *Chem. Lett.* **1985**, *14*, 635. (c) Tormo, J.; Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 5296.
(6) (a) Bachman, G. B.; Hokama, T. *J. Am. Chem. Soc.* **1959**, *81*, 4882. (b) Baker, D. C.; Putt, S. R. *Synthesis* **1978**, *1978*, 478. (c) Crumbie, R. L.; Nimitz, J. S.; Mosher, H. S. *J. Org. Chem.* **1982**, *47*, 4040. (d) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Gromova, A. V.; Witek, R.; Steel, P. J. *J. Org. Chem.* **2005**, *70*, 9211. (e) Ono, N.; Fujii, M.; Kaji, A. *Synthesis* **1987**, *1987*, 532. (f) Nakamura, K.; Kitayama, T.; Inoue, Y.; Ohno, A. *Tetrahedron* **1990**, *46*, 7471.
(7) (a) Fischer, R. H.; Weitz, H. M. *Synthesis* **1980**, *1980*, 261. (b) Kornblum, N.; Chalmers, M. E.; Daniels, R. *J. Am. Chem. Soc.* **1955**, *77*, 6654. (c) Laikhter, A. L.; Kislyi, V. P.; Semenov, V. V. *Mendeleev Commun.* **1993**, *3*, 20.
(8) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933.
(9) Roca-Lopez, D.; Sadaba, D.; Delso, I.; Herrera, R. P.; Tejero, T.; Merino, P. *Tetrahedron: Asymmetry* **2010**, *21*, 2561.
(10) Kornblum, N.; Boyd, S. D.; Stuchal, F. W. *J. Am. Chem. Soc.* **1970**, *92*, 5783.
(11) Wilson, J. E.; Casarez, A. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 11332.
(12) (a) Miyakoshi, T.; Saito, S.; Kumanotani, J. *Chem. Lett.* **1981**, *10*, 1677. (b) Russell, G. A.; Ros, F. *J. Am. Chem. Soc.* **1982**, *104*, 7349. (c) Kunetsky, R. A.; Dilman, A. D.; Tsvaygboym, K. P.; Ioffe, S. L.; Strelenko, Y. A.; Tartakovsky, V. A. *Synthesis* **2003**, *2003*, 1339.
(13) (a) Kornblum, N.; Boyd, S. D. *J. Am. Chem. Soc.* **1970**, *92*, 5784. (b) Hass, H. B.; Bender, M. L. *J. Am. Chem. Soc.* **1949**, *71*, 1767.
(14) For an isolated case involving a specific substrate class, see: Easton, C. J.; Roselt, P. D.; Tiekink, E. R. T. *Tetrahedron* **1995**, *51*, 7809.
(15) Gildner, P. G.; Gietter, A. A. S.; Cui, D.; Watson, D. A. *J. Am. Chem. Soc.* **2012**, *134*, 9942.
(16) For conceptually related Heck-type reactions, see: (a) Liu, C.; Tang, S.; Liu, D.; Yuan, J.; Zheng, L.; Meng, L.; Lei, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 3638. (b) Nishikata, T.; Noda, Y.; Fujimoto, R.; Sakashita, T. *J. Am. Chem. Soc.* **2013**, *135*, 16372.
(17) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.
(18) Balasubramaniam, S.; Aidhen, I. S. *Synthesis* **2008**, 3707.
(19) (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (c) Tramontini, M.; Angiolini, L. *Mannich Bases, Chemistry and Uses*; CRC Press Inc.: Boca Raton, FL, 1994.
(20) See the Supporting Information for further details regarding this analysis.
(21) With the possible exceptions of **4** and **13**, we believe this product mixture to be kinetic in origin. See the Supporting Information.
(22) Interestingly, this reaction is highly diastereoselective. A 63:37 mixture of diastereomers of starting material affords a single diastereomer of product (NMR). The relative stereochemistry was determined by X-ray crystallography, after reduction to the amine. See the Supporting Information.
(23) (a) Ma, J.-A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290. (b) Juaristi, E.; Soloshonok, V. A *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2005;. (c) Weiner, B.; Szymanski, W.; Janssen, D. B.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2010**, *39*, 1656.

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