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Highly Diastereoselective Michael Reactions Using β-Nitrocarbonyl Nucleophiles

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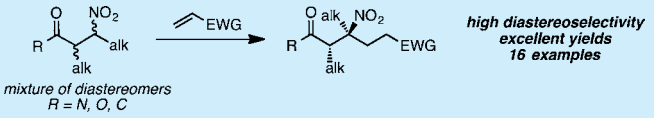
Supporting Information

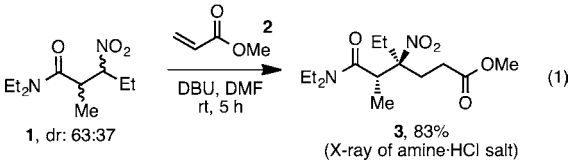
ABSTRACT: We have discovered a highly diastereoselective Michael reaction of α-substituted, β-nitrocarbonyl compounds to deliver highly functionalized stereodiads containing fully substituted nitrogen-bearing centers. Good to excellent yields and diastereoselectivities are observed. This transformation is tolerant of various types of carbonyl groups on the nucleophilic partner, as well as a range of unsaturated electrophiles. Mechanistic investigations are consistent with internal hydrogen bonding in the nitroalkane tautomer as the major factor in the control of diastereoselectivity in these transformations.



Nitroalkanes are highly versatile intermediates in organic synthesis.[1] These compounds are able to undergo a variety of carbon−carbon bond forming reactions such as arylations,[2] allylations,[3] Henry reactions,[1] and conjugate additions.[1] Nitroalkanes also serve as starting materials for the installation of a variety of other functional groups, such as amines, ketones, and alkanes.[1]

Recently, as a method for rapidly preparing complex nitroalkanes, our group has developed several copper-catalyzed procedures for the C-alkylation of nitroalkanes using simple alkyl halide electrophiles.[4−6] In the course of these studies, we developed conditions for the preparation of β-nitrocarbonyl compounds via the alkylation of nitroalkanes with α-bromocarbonyls.[7,8] Although these reactions proceed in excellent yields with good functional group tolerance, diastereoselectivity in the reactions was modest (ca. 66:33).

In an effort to demonstrate the utility of these products in downstream synthesis, we previously reported a single example using β-nitroamide **1** as the nucleophile in a Michael reaction with methyl acrylate (eq 1).[7] To our surprise, despite the fact



(1)

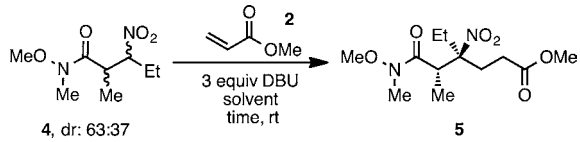
that a 63:37 diastereomeric mixture of the β-nitroamide was brought into the reaction, a single detectable diastereomer of product **3** emerged from the reaction in high yield. The relative stereochemistry of the product was determined by X-ray crystallography, after reduction to the corresponding amine. No examples of diasteroselective Michael additions of this type have been previously reported. In fact, very few alkylation reactions of β-nitrocarbonyl compounds of any type have ever been described.[9,10]

We recognized these Michael adducts could potentially be of interest for the synthesis of complex nitrogen-containing molecules, as the products contain a fully substituted nitrogen-bearing stereocenter in a highly functionalized environment. As such, we chose to investigate the generality of this Michael reaction.

Herein we report that good to excellent levels of diastereoselectivity are observed using a range of β-nitrocarbonyl nucleophiles and several different classes of Michael acceptors. In addition, we briefly investigated the mechanism of this reaction, allowing us to offer a model to rationalize the observed diastereoselectivity.

Before exploring the generality of the transformation, we wanted to investigate the reaction conditions for the Michael reaction. To do so, the reaction of β-nitro-Weinreb amide **4** with excess (3 equiv) methyl acrylate (**2**) was investigated (Table 1). We were pleased to find that high yield and high diastereoselectivity were also observed in this system (entry 1),

Table 1. Optimization of Reaction Conditions



entry	solvent	time (h)	equiv **2**	yield **5** (%)[a]	dr[a]
1	DMF	5	3	96	>95:5
2	MeCN	5	3	96	>95:5
3	CH_2Cl_2	5	3	39	>95:5
4	MeCN	1	3	95	>95:5
5	MeCN	1	1.5	71	>95:5

[a]Yield and diastereoselectivity determined by NMR using 1,3,5-trimethoxybenzene as an internal standard.

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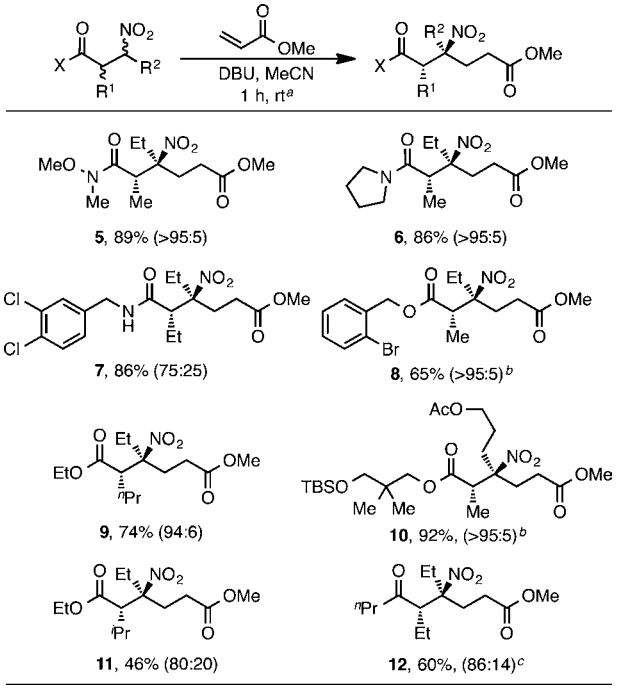
which was comparable to the previously investigated diethylamide substrate (**1**). We found that the reaction could also be run in other polar solvents such as acetonitrile (entry 2), but was less efficient in less polar solvents such as dichloromethane (entry 3). Acetonitrile also proved easier to remove from the products and was therefore selected for further studies. We also found the reaction to be relatively rapid, affording nearly quantitative yields in just 1 h (entry 4). A variety of other mild organic and inorganic bases were also examined, but none were as effective as DBU (see Supporting Information). Finally, attempts to lower the equivalents of methyl acrylate used in the reaction led to lower yields (entry 5). In all cases, however, high diastereoselectivity (>95:5) was observed.

With the optimized conditions in hand, we began to examine the scope of the reaction with respect to the β-nitrocarbonyl nucleophile. A variety of carbonyl moieties were well tolerated under the reaction conditions (Scheme 1). The model Weinreb

Scheme 1. Scope with Respect to β-Nitrocarbonyls



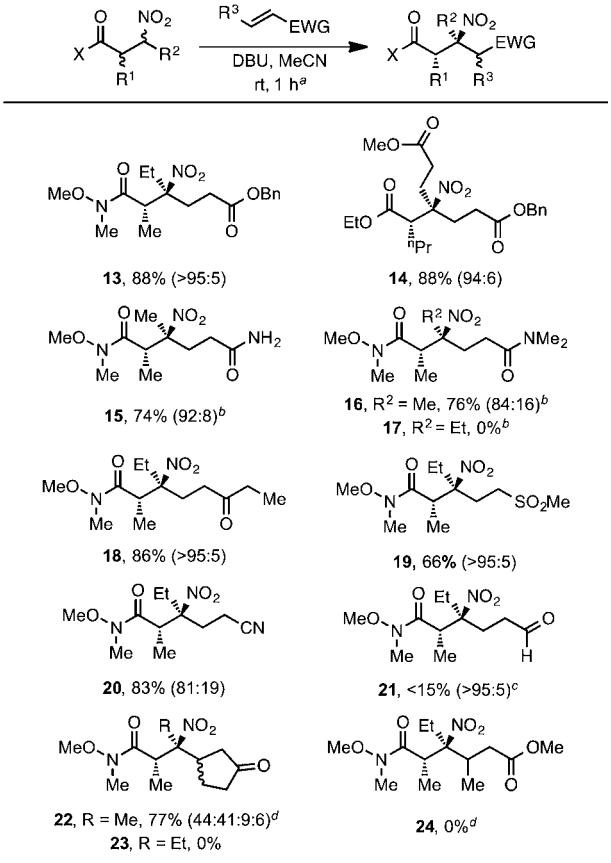
[a]3 equiv of methyl acrylate, 3 equiv of DBU. Diastereomeric ratios determined by NMR. Yields are for isolated product. [b] Reaction run at −40 °C for 24 h, base = 1,1,3,3-tetramethylguanidine. [c] Reaction run at 0 °C for 24 h, base = 1,1,3,3-tetramethylguanidine.

amide product **5** was isolated in 89% yield. Substrates bearing other tertiary amides (e.g., cyclic amide **6**) also participated equally well in the Michael reaction, providing high yield and diastereoselectivity. Secondary amides (**7**) also participated, but with slightly eroded levels of diastereoselectivity.

β-Nitroesters can also be used in this method. Substrates bearing linear alkyl groups α to the ester were well tolerated, leading to high yielding, highly diastereoselective reactions (**8**–**10**). Branched α-substituents, however, resulted in both lower yield and selectivity, reflecting the greater steric demands of the nucleophile (**11**). Somewhat surprisingly, even β-nitroketones proved to be competent starting materials in the reaction, providing reasonable yield and diastereoselectivity (**12**).

In the case of the ketone substrate (as well as some esters) significant levels of byproducts resulting from denitration of the starting materials were observed under the standard reaction conditions. These alkenes presumably arise via the E_{1CB} elimination of an equivalent of nitrous acid from these more acidic starting materials. This side reaction was suppressed using the more sterically encumbered base 1,1,3,3-tetramethylguandidine (TMG) and lowering the reaction temperature (see Schemes 1 and 2). Notably, the denitration reaction appears to be sensitive to the steric environment; no byproducts from the denitration of the Michael adducts have been observed.[11]

Scheme 2. Scope with Respect to Michael Acceptor



[a]3 equiv of Michael acceptor, 3 equiv of DBU. Diastereomeric ratios determined by NMR. Yields are for isolated product unless otherwise noted. [b] Reaction run at 40 °C for 2 h. [c] Reaction run at −40 °C for 24 h, base = 1,1,3,3-tetramethylguanidine. Yield determined by NMR. [d] Reaction run at 0 °C for 24 h.

We also examined the scope of the transformation with respect to Michael acceptors (Scheme 2). Other acrylate esters such as benzyl acrylate (**13** and **14**) afforded high yield and excellent diastereoselectivity.

Less electrophilic acrylamide derivatives (**15** and **16**) also afforded good yields, but required slightly elevated temperatures and longer reaction times (40 °C, 2 h). In addition, when using acrylamide derivatives, increasing the steric bulk at the α position of the β-nitrocarbonyl had a profound effect on the reactivity. When the substituent was larger than methyl, the reaction did not proceed (**16** vs **17**). Attempts to circumvent this steric limitation were unsuccessful; increasing the temperature afforded increased elimination of the nitro group from the starting material, and variation of the base led to poor conversion. Vinyl ketones (**18**) and sulfones (**19**) proved to

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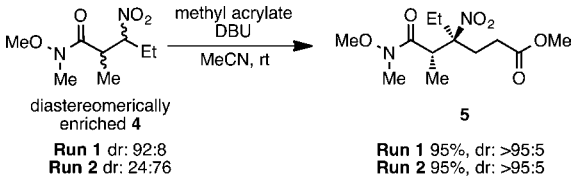
be excellent and highly selective substrates. Unsaturated nitriles also led to high yielding reactions with respectable levels of stereoselectivity (**20**). These products provide a variety of functional handles for downstream synthetic manipulation. With acrolein, good diastereoselectivity was observed (**21**); however, the formation of polymer byproducts severely suppressed the yield, even at cryogenic temperatures (−40 °C, 24 h).

We also briefly investigated more substituted Michael acceptors. Those incorporating internal cyclic alkenes, such as cyclopentenone, provided reasonable reactivity with nonsterically demanding β-nitrocarbonyls. However, stereocontrol in these systems was poor (**22**). With somewhat more sterically demanding nucleophiles, no product was observed (**23**). Likewise, acyclic Micheal acceptors bearing either α- or β-substituents failed in the reaction. For example, product **24** was not observed.

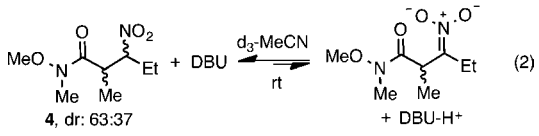
As shown in Schemes 1 and 2, the reaction demonstrates excellent functional group tolerance. In addition to the functional groups described above, aryl chlorides (**7**), aryl bromides (**8**), silyl ethers and acyl protected alcohols (**10**), and distal esters (**14**) all afford excellent yields with high diastereoselectivity of the desired products.

We next sought to examine the origin of the diastereoselectivity observed in the Michael reaction. First, we established that the dr of the product is independent of that of the starting material by using diastereomerically enriched[12] samples of β-nitroamide **4** (Scheme 3).

Scheme 3. Product Diastereomeric Ratio is Not a Function of Starting Material Stereochemistry



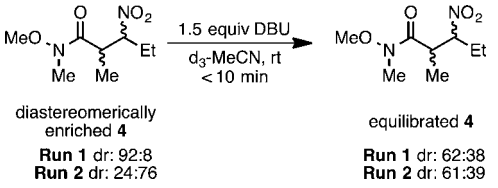
Next, we examined the thermodynamics of the reaction of DBU and β-nitroamide **4** in d_3-MeCN at rt (eq 2). No



nitroanate anion and only free DBU and **4** were observed by ^{1}H NMR, even after extended reaction times. This suggests that any deprotonation event is endothermic under the reaction conditions.

Finally, to understand the kinetics of deprotonation of the β-nitrocarbonyl starting materials, we studied the epimerization of β-nitroamide **4** in the presence of DBU in d_3-MeCN at rt using diastereomerically enriched samples. The reactions were monitored by ^{1}H NMR. Independent of the diastereomeric ratio of the starting sample, compound **4** equilibrates to an approximate 60:40 ratio of diastereomers within 10 min (Scheme 4 and Supporting Information). This time frame is much faster than the time course of the Michael reaction, which requires approximately 1 h to complete, suggesting that deprotonation is also rapid under these conditions.

Scheme 4. Epimerization Studies of 4



Given these observations, a possible rationale for the observed diastereoselectivity is outlined in Figure 1. Rapid,

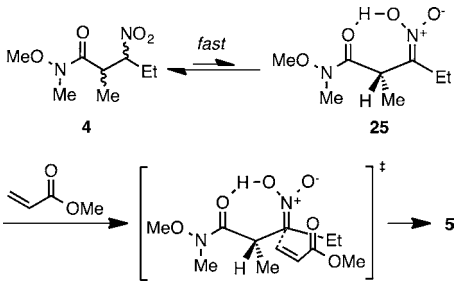


Figure 1. Possible model for observed diastereoselectivity.

reversible deprotonation of the nitroalkane could establish a small concentration of the highly nucleophilic tautomer **25**. Intramolecular hydrogen bonding to the adjacent carbonyl would organize compound **25** as shown. From this intermediate, the Michael acceptor would be expected to react at the face away from the alkyl group α to the carbonyl, as shown. This model is consistent with the observed stereochemistry of the products.[13]

This model is also consistent with the observation that the highest levels of diastereoselectivity are observed with the substrates bearing the most basic carbonyl groups (see Schemes 1 and 2). For example, while nearly all of the substrates examined react with high levels of diastereoselectivity, substrates bearing tertiary amides are slightly more selective than those with esters. This trend correlates well with the carbonyl's ability to participate in hydrogen bonding.

In conclusion, we have demonstrated that Michael additions involving α-chiral, β-nitrocarbonyl derivatives as nucleophiles can be highly diastereoselective and efficient. This mild method works with a range of nucleophiles of this type, as well as a range of Michael acceptors. In addition, the mildness of the method allows broad functional group tolerance. The products from these reactions are highly functionalized stereodiads containing a fully substituted, nitrogen-bearing stereocenter. These products should be of significant utility as building blocks in the synthesis of more complex molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02832.

Experimental procedures, NMR studies, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Ono, N. *The Nitro Group In Organic Synthesis*; John Wiley and Sons: New York, 2001.

(2) (a) Dey, C.; Lindstedt, E.; Olofsson, B. *Org. Lett.* **2015**, *17*, 4554. (b) Vogl, E. M.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 106. (c) Walvoord, R. R.; Berritt, S.; Kozlowski, M. C. *Org. Lett.* **2012**, *14*, 4086. (d) Walvoord, R. R.; Kozlowski, M. C. *J. Org. Chem.* **2013**, *78*, 8859.

(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) Gildner, P. G.; Gietter, A. A. S.; Cui, D.; Watson, D. A. *J. Am. Chem. Soc.* **2012**, *134*, 9942.

(5) For another recent nitroalkane alkylation reaction, see: Petruzziello, D.; Gualandi, A.; Grilli, S.; Cozzi, P. G. *Eur. J. Org. Chem.* **2012**, *2012*, 6697.

(6) For early papers on nitroalkane alkylation, see: (a) Seebach, D.; Lehr, F. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 505. (b) Seebach, D.; Henning, R.; Lehr, F.; Gonnermann, J. *Tetrahedron Lett.* **1977**, *18*, 1161. (c) Katritzky, A. R.; De Ville, G.; Patel, R. C. *J. Chem. Soc., Chem. Commun.* **1979**, 602a. (d) Russell, G. A.; Hershberger, J.; Owens, K. *J. Am. Chem. Soc.* **1979**, *101*, 1312. (e) Katritzky, A. R.; Kashmiri, M. A.; De Ville, G. Z.; Patel, R. C. *J. Am. Chem. Soc.* **1983**, *105*, 90. (f) Russell, G. A.; Khanna, R. K. *Tetrahedron* **1985**, *41*, 4133. (g) Branchaud, B. P.; Yu, G.-X. *Tetrahedron Lett.* **1988**, *29*, 6545.

(7) Gietter, A. A. S.; Gildner, P. G.; Cinderella, A. P.; Watson, D. A. *Org. Lett.* **2014**, *16*, 3166.

(8) For other methods for preparing these compounds, see: (a) Kornblum, N.; Boyd, S. D. *J. Am. Chem. Soc.* **1970**, *92*, 5784. (b) Miyakoshi, T.; Saito, S.; Kumanotani, J. *Chem. Lett.* **1981**, *10*, 1677. (c) Russell, G. A.; Ros, F. *J. Am. Chem. Soc.* **1982**, *104*, 7349. (d) Kunetsky, R. A.; Dilman, A. D.; Tsvaygboym, K. P.; Ioffe, S. L.; Strelenko, Y. A.; Tartakovsky, V. A. *Synthesis* **2003**, *2003*, 1339. (e) Wilson, J. E.; Casarez, A. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 11332.

(9) For previous Micheal reactions, see: (a) Alvarez-Ibarra, C.; Csákÿ, A. G.; Gómez de la Oliva, C. *J. Org. Chem.* **2000**, *65*, 3544. (b) Han, Y.; Liu, Y.; Rockenbauer, A.; Zweier, J. L.; Durand, G. g.; Villamena, F. A. *J. Org. Chem.* **2009**, *74*, 5369.

(10) For Henry-type reactions, see: (a) Sacher, J. R.; Weinreb, S. M. *Tetrahedron* **2011**, *67*, 10203. (b) Ji, C.-B.; Liu, Y.-L.; Cao, Z.-Y.; Zhang, Y.-Y.; Zhou, J. *Tetrahedron Lett.* **2011**, *52*, 6118.

(11) In some cases, we did observe a small amount (<5%) of a byproduct that results from a complex reaction sequence that includes denitration, Dieckmann condensation, and multiple alkylation steps. Resubjection of isolated Michael adducts to the reaction conditions, however, did not result in this byproduct, suggesting that it is formed via a unique pathway that is independent of the Michael reaction. Details and characterization of the side product are provided in the Supporting Information.

(12) Obtained via chromatographic separation on silica gel.

(13) After the submission of this manuscript, a similar stereochemical model for a related series of Michael additions involving functionalized nitroalkanes was published. See: Wade, P. A.; Paparoidamis, N.; Liao, J.; Manor, B. C.; DeBolt, K. *Tetrahedron Lett.* **2015**, DOI: 10.1016/j.tetlet.2015.10.055.

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