JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Cite This: J. Am. Chem. Soc. 2019, 141, 8436−8440
Communication
pubs.acs.org/JACS

Nickel-Catalyzed Asymmetric *C*-Alkylation of Nitroalkanes: Synthesis of Enantioenriched β-Nitroamides

Vijayarajan Devannah, Rajgopal Sharma, and Donald A. Watson*

Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716, United States

Supporting Information

ABSTRACT: A general catalytic method for asymmetric *C*-alkylation of nitroalkanes using nickel catalysis is described. This method enables the formation of highly enantioenriched β-nitroamides from readily available α-bromoamides using mild reaction conditions that are compatible with a wide range of functional groups. When combined with subsequent reactions, this method allows access to highly enantioenriched products with nitrogen-bearing fully substituted carbon centers.

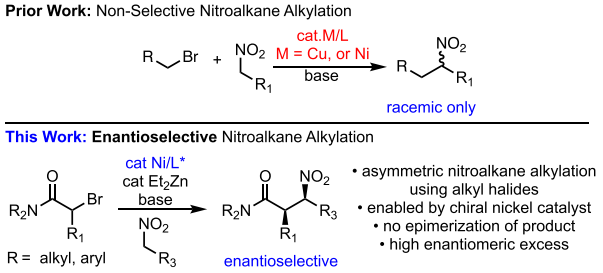
Nitroalkanes are broadly useful building blocks in organic synthesis.[1] Not only can the nitro group be converted into a range of other functional groups, but nitroalkanes also participate in a variety of C−C bond-forming reactions, including Michael, Henry, nitro-Mannich, and palladium-catalyzed allylation and arylation reactions. However, despite this great synthetic versatility, for many years the simple *C*-alkylation of nitroalkanes—a potentially important reaction for converting simple nitroalkanes into more complex nitroalkanes—remained challenging due to the dominance of *O*-alkylation, which ultimately yields aldehydes instead of the desired nitroalkane products.[2]

Over the past several years, our group has begun to address this gap by developing transition metal-catalyzed alkylation reactions of nitroalkanes.[3] By using a transition metal catalyst, we were able to change from the inherent two-electron chemistry of nitroalkanes to single-electron manifolds, thus changing the preference for *C*- vs *O*-alkylation. With these new protocols, alkylation with a variety of alkyl halides, including aliphatic alkyl halides, is now possible.

Despite these advances in the ability to control the site-selectivity of the alkylation reactions, control of stereoselectivity has remained elusive. This is particularly noteworthy because asymmetric variants of many other C−C bond-forming reactions of nitroalkanes have been described, and those reactions now constitute important ways to install nitrogen-containing stereocenters.[4] The seeming inability to render nitroalkane alkylation asymmetric stems not only from that fact that the previously identified optimal ligands are not easily rendered chiral, but more significantly from the fact that all prior mechanistic data suggested that the reactions are proceeding via a radical pathway involving an outer-sphere C−C bond-forming step that does not directly involve the metal catalyst or ligand.[3a,c,d] Thus, prior data strongly suggested that asymmetric nitroalkane alkylation would not be possible using current catalytic methods, and the asymmetric alkylation of nitroalkanes has remained an open challenge.

Recently, while exploring copper-catalyzed reactions, we observed modest, ligand-dependent changes in diastereoselection in nitroalkane alkylation.[5] Those experiments suggested a role for the ligand in C−C bond formation, prompting us to reevaluate an outer-sphere pathway and opening the possibility of asymmetric induction. Herein, we report the nickel-catalyzed asymmetric alkylation of nitroalkanes using α-bromoamides (Scheme 1),[6] which is the first example of an asymmetric nitroalkane alkylation using an alkyl halide electrophile. We show that alkylation of nitroalkanes with racemic α-bromoamides leads to highly enantioselective formation of α-substituted, β-nitroamides with good levels of diastereocontrol.[7] We demonstrate that these products can be utilized to prepare asymmetric β-aminoamides with fully substituted β-carbons with outstanding levels of enantioselectivity. Moreover, these observations also cast new light onto transition metal-catalyzed nitroalkane alkylations and suggest a more complex mechanism than previously understood.

Scheme 1. General Method for Asymmetric Nitroalkane Alkylation

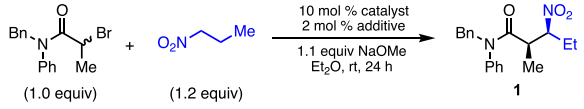


Our investigation began with reaction of commercially available racemic *N*-benzyl-2-bromo-*N*-phenylpropionamide with 1-nitropropane to make β-nitroamide **1** (Table 1). Using conditions similar to our prior nonstereocontrolled nickel-catalyzed alkylation reactions (10 mol % $Ni(COD)_2$, slight excess of NaOMe),[3d] we began to systematically investigate a variety of chiral ligands. Although many classes of ligands provided either no enantioinduction or yield of product, we were pleased to find that use of commercially available bis(oxazoline) ligand **2** provided desired product **1** with a measurable 12% ee, albeit in 30% yield and no measurable diastereoselectivity (entry 1).

Received: April 17, 2019
Published: May 13, 2019

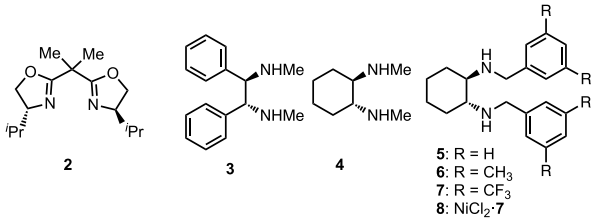
DOI: 10.1021/jacs.9b04175
J. Am. Chem. Soc. 2019, 141, 8436−8440

Table 1. Discovery of the Catalytic System



entry	catalyst	additive	yield of **1**[a]	dr syn/anti	%ee[b] syn
1	Ni(COD)$_2$/**2**		30	50:50	12
2	Ni(COD)$_2$/**3**		27	92:08	72
3	Ni(COD)$_2$/**4**		18	78:22	78
4	Ni(COD)$_2$/**5**		80	82:18	79
5	Ni(COD)$_2$/**6**		80	84:16	82
6	Ni(COD)$_2$/**7**		82	85:15	88
7	**8**[c]	Et$_2$Zn	97	79:21	90

[a]Determined via ^{1}H NMR against internal standard. [b]Determined using chiral HPLC analysis. [c]0 °C.

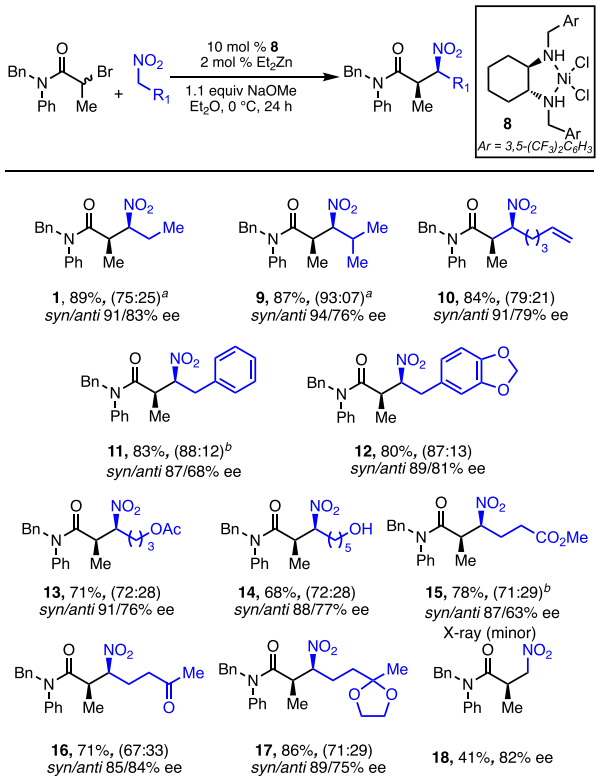


Eventually we found that the C_2 symmetric chiral 1,2-diamine **3** provided considerably higher levels of enantioselectivity (72% ee) and good diastereoselectivity (92:8, favoring the *syn*-isomer),[8] but did not improve the yield of the reaction (entry 2). *N*,*N*′-Dimethylcyclohexane-1,2-diamine (**4**) gave slightly lower dr and yield but provided better enantioselectivity (78% ee, entry 3). However, increasing the size of the amino substituents provided much higher yield, good diastereoselectivity, and retained enantioselectivity (entry 4). Although increasing the size of the aromatic groups with the use of *meta*-methyl groups (ligand **6**) did not provide substantially different results (entry 5), placing electron-withdrawing CF_3 groups at the same position (ligand **7**) provided a substantial increase in enantioselectivity and higher diastereoselectivity (entry 6). Several rounds of additional optimization led us to find that the optimal combination of enantioselectivity, diastereoselectivity, and reactivity was achieved by using the $NiCl_2$ complex of this optimal ligand (complex **8**), Et_2Zn as an *in situ* reductant, and 0 °C as the reaction temperature (entry 7).[5] These conditions resulted in high enantioselectivity, good diastereoselectivity, and outstanding yields.

With optimized conditions in hand, we investigated the scope of the nitroalkane (Scheme 2). A variety of primary nitroalkanes were subjected to the reaction using (±)-*N*-benzyl-2-bromo-*N*-phenylpropionamide as the alkylating reagent. High ee was observed for 1-nitropropane (**1**) as well as with a *β*-branched nitroalkane (**9**). A variety of functionalized nitroalkanes, including those with alkene, aryl, aryl ether, acetate, free alcohol, ester, and unprotected and protected ketone groups, was all alkylated with good to excellent ee (**10**−**17**). In all the above cases, good to excellent levels of dr were also observed. Nitromethane can also be alkylated albeit with low yield and ee (**18**).

The scope with respect to the *α*-bromoamide is also broad (Scheme 3). Good dr and high ee were observed for amides possessing electron-rich, electron-poor, and sterically encumbered groups (**19**−**21**). *α*-Bromoamides possessing *α*-alkyl substituents larger than methyl were tolerated well, albeit with

Scheme 2. Scope of Nitroalkanes



[a]5 mol % **8**, 1 mol % Et_2Zn. [b]25 °C.

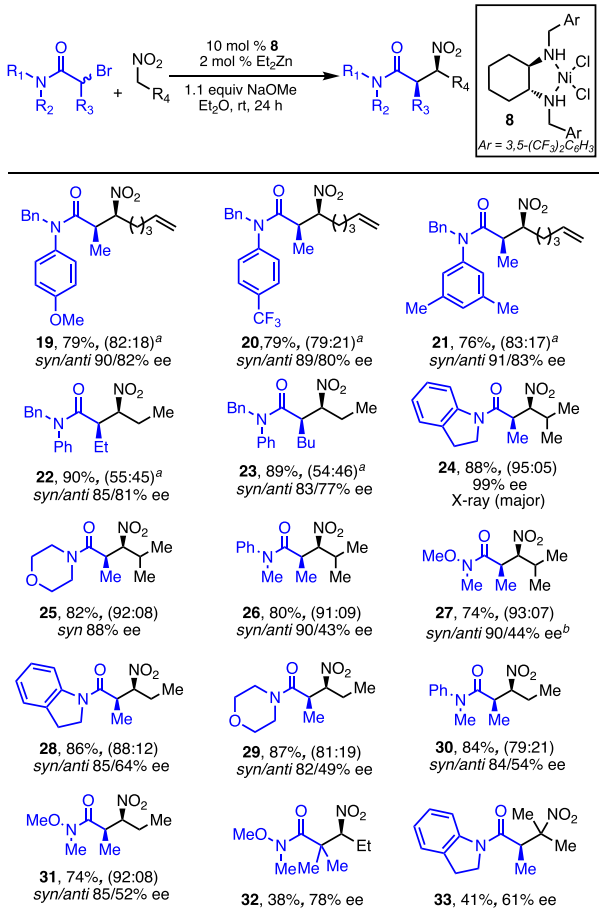
lower dr and ee (**22**, **23**). Significantly, several amide backbones, including indoline, morpholine, aryl-alkyl, and Weinreb amides, were tolerated, and all resulted in products with high dr and ee. These reactions were most effective when the nitroalkane starting material was *β*-branched (**24**−**27**), but substrates without *β*-branching also proceeded smoothly (**28**−**31**). Amides bearing tertiary bromides (**32**) and secondary nitroalkanes (**33**) could also be utilized in the alkylation reaction. In both cases, lower yields and ee were observed. However, these highly congested products would be challenging to prepare by other methods.

As shown in Schemes 2 and 3, in most cases the asymmetric nitroalkane alkylation exhibits good to excellent levels of diastereoselectivity. In all cases, the major diastereomer was formed with higher enantioselectivity, but good enantioselection was also observed for the minor isomer. In many cases, the diastereomers can be easily separated by standard flash column chromatography. In two cases (**15** and **24**), we were able to determine the relative and absolute stereochemistry of one of the diastereomers using X-ray crystallography. In both cases, the (1*R*,2*S*)-*syn*-isomer proved to be the major isomer using the *R*,*R*-catalyst.[5] Diagnostic ^{1}H NMR signals supported this relative configuration for the other entries as well.[9]

The ability to prepare enantioenriched *β*-nitroamides using this method has distinct advantages over other methods for construction of amides bearing *β*-nitrogen atoms (such as the Mannich reaction).[4h,10] Specifically, unlike Mannich products, the acidity of the proton *α* to the nitrogen atom allows *β*-nitroamides to be used in further synthetic transformations.[11] These transformations lead to highly substituted products. For example, use of the alkylation products as nucleophiles in C−C bond-forming reactions leads to *β*-nitroamides with fully substituted *β*-carbons (Scheme 4). In these reactions, the

DOI: 10.1021/jacs.9b04175
J. Am. Chem. Soc. 2019, 141, 8436−8440

Scheme 3. Scope of α-Bromoamides



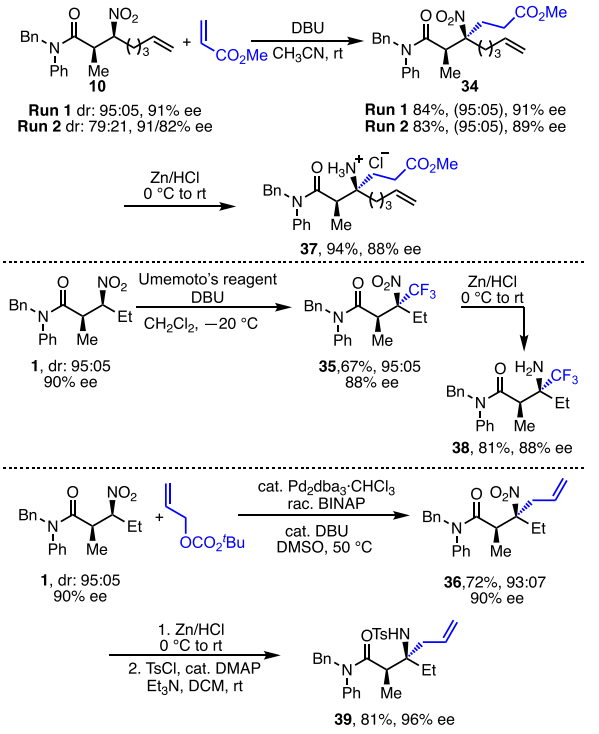
a0 °C b1.1 equiv of KO^{t}Bu.

stereocenter α to the carbonyl controls facial selection, leading to highly diastereoselective conjugate addition (top),[11] trifluoromethylation (middle),[12] and Tsuji–Trost allylation (bottom) reactions,[13] all without erosion of ee. Consistent with our earlier studies,[11,12] the *syn*-diastereomer is observed in all cases, and the nitro groups of the products are readily reduced to the corresponding amines (**37**–**39**).

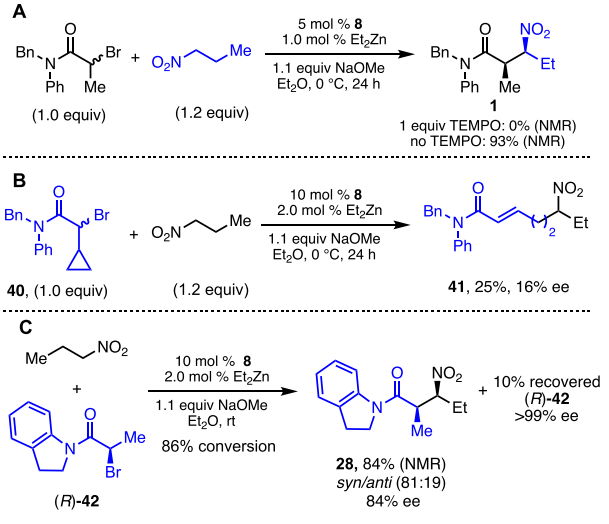
Significantly, isolation of a single diastereomer of the alkylation product is not required for use in these downstream reactions. As shown at the top of Scheme 4, the conjugate addition reaction can be conducted either with a single isolated diastereomer or with the mixture of diastereomers obtained from the nickel-catalyzed reaction. In both cases, identical diastereoselectivity and *nearly identical* enantiopurity of product are obtained. These results indicate that the diastereomers observed in the alkylation reaction are epimeric at the β-center and that the diastereomers converge upon deprotonation of the nitroalkane in the subsequent reactions.[14] From a practical standpoint, this is highly advantageous when utilizing the alkylation products in this way.

Several mechanistic experiments were carried out to probe the nature of the transformation. Consistent with our earlier nonstereoselective nitroalkane alkylation reactions, these studies indicate a mechanism involving radical intermediates. First, when the reaction was run in the presence of 1 equiv of TEMPO, a known radical scavenger,[15] no alkylation product **1** was formed (Scheme 5, top). Second, cyclopropylcarbinyl rearrangement is observed with substrate **40**, resulting exclusively in ring-opened

Scheme 4. Downstream Functionalization of Alkylated Products



Scheme 5. Mechanistic Probes

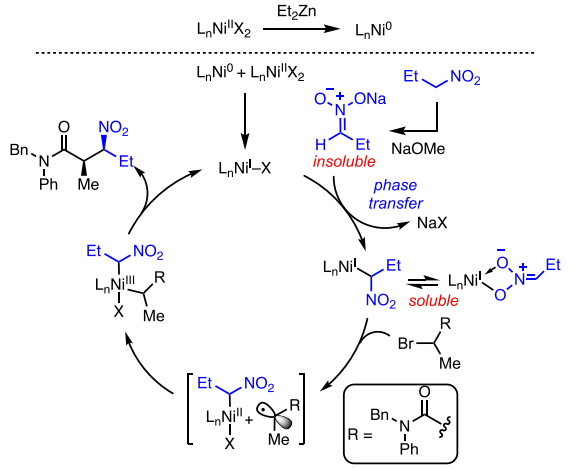


product **41** (Scheme 5, middle).[16] Finally, the enantiopurity of the starting α-bromoamide does not affect the stereoselectivity of the reaction; both enantiomers of **42** lead to identical dr and ee of products, albeit with slightly different yields. Additionally, when starting material was reisolated from reactions stopped at partial conversion, no erosion of ee of the bromoamide was observed (Scheme 5, bottom).[5] This result indicates that activation of the C–Br is irreversible.

Although further studies will be required to fully elucidate the mechanism, at present we favor the Ni^{I}/Ni^{III} catalytic cycle shown in Scheme 6.[17] Initial reduction of the Ni(II) precatalyst by Et_2Zn results in formation of a Ni(0) complex. Comproportionation with excess Ni(II) complex then results in a Ni(I) catalyst.[18] This pathway would explain the need for excess Ni(II)

DOI: 10.1021/jacs.9b04175
J. Am. Chem. Soc. 2019, 141, 8436–8440

Scheme 6. Possible Mechanistic Pathway



compared to Et_2Zn. Simultaneously, exothermic deprotonation of the acidic nitroalkane by the alkoxide base results in an insoluble (or sparingly soluble) nitronate anion, which undergoes anion exchange with the Ni(I) complex resulting in a soluble Ni(I) nitronate. This electron-rich Ni(I) complex then reacts with the alkyl bromide via a stepwise oxidative addition to form a Ni(III) alkyl nitronate. Reductive elimination then provides the observed product and regenerates the catalyst.[5]

In conclusion, the first Ni-catalyzed asymmetric *C*-alkylation of nitroalkanes using an alkyl halide has been developed. This method enables formation of highly enantioenriched β-nitroamide from readily available α-bromoamides using mild reaction conditions that are compatible with a wide range of functional groups. Significantly, due to both the acidity of the β-proton and the ability of the α stereocenter to control subsequent reactions, these products can be easily manipulated to access a range of highly substituted β-aminoamides, providing distinct advantages over competing technologies. This study also demonstrates that the mechanism of transition metal-catalyzed nitroalkane alkylation reactions are more complex than earlier believed and indicate that nickel-catalyzed nitroalkane alkylation occurs via metal-mediated C−C bond formation. Current efforts are directed at further expanding the scope of asymmetric nitroalkane alkylation reactions and better defining the mechanisms by which they proceed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b04175.

Experimental Procedures (PDF)

Crystallographic data for compounds **8** (CIF), **15** (CIF), **24** (CIF), and **39** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*dawatson@udel.edu

ORCID

Donald A. Watson: 0000-0003-4864-297X

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Dr. Glenn Yap (UD) is acknowledged for assistant with X-ray crystallography. The University of Delaware (UD), the University of Delaware Research Foundation, the Research Corp. Cottrell Scholars Program, and the NIH NIGMS (R01 GM102358) are gratefully acknowledged for support. Data was acquired at UD on instruments obtained with the assistance of NSF and NIH funding (NSF CHE0421224, CHE0840401, CHE1229234, CHE1048367; NIH S10 OD016267-01, S10 RR026962-01, P20GM104316, P30GM110758).

■ REFERENCES

(1) (a) Ono, N. *The Nitro Group In Organic Synthesis*; John Wiley And Sons: New York, 2001. (b) Ballini, R.; Palmieri, A. Synthetic Procedures for the Preparation of Nitroalkanes. *Adv. Synth. Catal.* **2018**, *360*, 2240.

(2) (a) Weisler, L.; Helmkamp, R. W. The Action of Some Benzyl Halides on Salts of Phenylnitromethane and Phenylnitro-acetonitrile. *J. Am. Chem. Soc.* **1945**, *67*, 1167. (b) Hass, H. B.; Bender, M. L. The Reaction of Benzyl Halides with the Sodium Salt of 2-Nitropropane. A General Synthesis of Substituted Benzaldehydes. *J. Am. Chem. Soc.* **1949**, *71*, 1767. (c) Kornblum, N. Substitution Reactions Which Proceed via Radical Anion Intermediates. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 734. (d) Seebach, D.; Henning, R.; Lehr, F.; Gonnermann, J. Carbon Alkylations of $\alpha.\alpha$- and $\alpha.\beta$-doubly Deprotonated Nitroalkanes. *Tetrahedron Lett.* **1977**, *18*, 1161. (e) Seebach, D.; Henning, R.; Lehr, F. Double Deprotonation of 3-Nitropropene and 4-Nitro-1-butene: Derivatives of Their Dianions as Novel Reagents for CC-Linkage. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 458. (f) Katritzky, A. R.; de Ville, G.; Patel, R. C. Carbon-Alkylation of Simple Nitronate Anions. *J. Chem. Soc., Chem. Commun.* **1979**, 602. (g) Katritzky, A. R.; Kashmiri, M. A.; De Ville, G. Z.; Patel, R. C. Kinetics and Mechanism of the C-Alkylation of Nitroalkane Anions by 1-Alkyl-2,4,6-triphenylpyridiniums: A Nonchain Reaction with Radicaloid Characteristics. *J. Am. Chem. Soc.* **1983**, *105*, 90. (h) Russell, G. A.; Khanna, R. K. The Reaction of Carbanions with tert-Butyl Radicals. *Tetrahedron* **1985**, *41*, 4133. (i) Branchaud, P. B.; Yu, G.-X. Cobaloxime-Mediated Radical Alkyl-Nitroalkylanion Cross Coupling. *Tetrahedron Lett.* **1988**, *29*, 6545.

(3) (a) Gildner, P. G.; Gietter, A. A. S.; Cui, D.; Watson, D. A. Benzylation of Nitroalkanes Using Copper-Catalyzed Thermal Redox Catalysis: Toward the Facile C-Alkylation of Nitroalkanes. *J. Am. Chem. Soc.* **2012**, *134*, 9942. (b) Gietter, A. A. S.; Gildner, P. G.; Cinderella, A. P.; Watson, D. A. General Route for Preparing β-Nitrocarbonyl Compounds Using Copper Thermal Redox Catalysis. *Org. Lett.* **2014**, *16*, 3166. (c) Shimkin, K. W.; Gildner, P. G.; Watson, D. A. Copper-Catalyzed Alkylation of Nitroalkanes with α-Bromonitriles: Synthesis of β-Cyanonitroalkanes. *Org. Lett.* **2016**, *18*, 988. (d) Rezazadeh, S.; Devannah, V.; Watson, D. A. Nickel-Catalyzed C-Alkylation of Nitroalkanes with Unactivated Alkyl Iodides. *J. Am. Chem. Soc.* **2017**, *139*, 8110.

(4) (a) Trost, B. M.; Surivet, J.-P. Diastereo- and Enantioselective Allylation of Substituted Nitroalkanes. *J. Am. Chem. Soc.* **2000**, *122*, 6291. (b) Ooi, T.; Takada, S.; Doda, K.; Maruoka, K. Highly Diastereo- and Enantioselective Formal Conjugate Addition of Nitroalkanes to Nitroalkenes by Chiral Ammonium Bifluoride Catalysis. *Angew. Chem., Int. Ed.* **2006**, *45*, 7606. (c) Palomo, C.; Oiarbide, M.; Laso, A. Recent Advances in the Catalytic Asymmetric Nitroaldol (Henry) Reaction. *Eur. J. Org. Chem.* **2007**, *2007*, 2561. (d) Dobish, M. C.; Johnston, J. N. Chiral Brønsted Base-Promoted Nitroalkane Alkylation: Enantioselective Synthesis of sec-Alkyl-3-Substituted Indoles. *Org. Lett.* **2010**, *12*, 5744. (e) Roca-Lopez, D.; Sadaba, D.; Delso, I.; Herrera, R. P.; Tejero, T.; Merino, P. Asymmetric organocatalytic synthesis of γ-nitrocarbonyl compounds through Michael and Domino reactions. *Tetrahedron: Asymmetry* **2010**, *21*, 2561. (f) Blay, G.; Hernández-Olmos, V.; Pedro, J. R. Development of New N,N-Ligands for the Enantioselective Copper(II)-Catalyzed Henry Reaction. *Synlett* **2011**, *2011*, 1195. (g) Ohmatsu, K.; Ito, M.; Kunieda, T.; Ooi, T. Ion-paired Chiral Ligands for Asymmetric Palladium Catalysis. *Nat. Chem.* **2012**, *4*, 473.

DOI: 10.1021/jacs.9b04175
J. Am. Chem. Soc. 2019, 141, 8436−8440

(h) Noble, A.; Anderson, J. C. *Chem. Rev.* **2013**, *113*, 2887. (i) Qian, H.; Yu, X.; Zhang, J.; Sun, J. Organocatalytic Enantioselective Synthesis of 2,3-Allenoates by Intermolecular Addition of Nitroalkanes to Activated Enynes. *J. Am. Chem. Soc.* **2013**, *135*, 18020. (j) Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. Bifunctional Primary Amine-Thioureas in Asymmetric Organocatalysis. *Org. Biomol. Chem.* **2013**, *11*, 7051. (k) Tsakos, M.; Kokotos, C. G. Primary and Secondary Amine-(thio)ureas and Squaramides and Their Applications in Asymmetric Organocatalysis. *Tetrahedron* **2013**, *69*, 10199. (l) Manna, M. S.; Mukherjee, S. Organocatalytic Enantioselective Formal C(sp2)−H Alkylation. *J. Am. Chem. Soc.* **2015**, *137*, 130. (m) Vara, B. A.; Johnston, J. N. Enantioselective Synthesis of β-Fluoro Amines via β-Amino α-Fluoro Nitroalkanes and a Traceless Activating Group Strategy. *J. Am. Chem. Soc.* **2016**, *138*, 13794. (n) Kawada, M.; Nakashima, K.; Hirashima, S.-i.; Yoshida, A.; Koseki, Y.; Miura, T. Asymmetric Conjugate Addition of Nitroalkanes to Enones Using a Sulfonamide−Thiourea Organocatalyst. *J. Org. Chem.* **2017**, *82*, 6986. (o) Li, Y.; Huang, Y.; Gui, Y.; Sun, J.; Li, J.; Zha, Z.; Wang, Z. Copper-Catalyzed Enantioselective Henry Reaction of β,γ-Unsaturated α-Ketoesters with Nitromethane in Water. *Org. Lett.* **2017**, *19*, 6416. (p) Lu, N.; Bai, F.; Fang, Y.; Wei, Z.; Cao, J.; Liang, D.; Lin, Y.; Duan, H. Bifunctional Phase-Transfer Catalysts Catalyzed Diastereo- and Enantioselective Aza-Henry Reaction of β,γ-Unsaturated Nitroalkenes With Amidosulfones. *Adv. Synth. Catal.* **2017**, *359*, 4111.

(5) See Supporting Information for further detail.

(6) For recent reviews of asymmetric reactions involving alkyl halides, see: (a) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. Enantioselective and Enantiospecific Transition-Metal-Catalyzed Cross-Coupling Reactions of Organometallic Reagents To Construct C−C Bonds. *Chem. Rev.* **2015**, *115*, 9587. (b) Choi, J.; Fu, G. C. Transition Metal−Catalyzed Alkyl-Alkyl Bond Formation: Another Dimension in Cross-Coupling Chemistry. *Science* **2017**, *356*, eaaf7230. (c) Bhat, V.; Welin, E. R.; Guo, X.; Stoltz, B. M. Advances in Stereoconvergent Catalysis from 2005 to 2015: Transition-Metal-Mediated Stereoablative Reactions, Dynamic Kinetic Resolutions, and Dynamic Kinetic Asymmetric Transformations. *Chem. Rev.* **2017**, *117*, 4528.

(7) Wilson, J. E.; Casarez, A. D.; MacMillan, D. W. C. Enantioselective Aldehyde α-Nitroalkylation via Oxidative Organocatalysis. *J. Am. Chem. Soc.* **2009**, *131*, 11332.

(8) Lundin, P. M.; Fu, G. C. Asymmetric Suzuki Cross-Couplings of Activated Secondary Alkyl Electrophiles: Arylations of Racemic α-Chloroamides. *J. Am. Chem. Soc.* **2010**, *132*, 11027.

(9) The absolute configuration of the other beta-nitroamide products were assigned by analogy.

(10) Arend, M.; Westermann, B.; Risch, N. Modern Variants of the Mannich Reaction. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044.

(11) Gietter-Burch, A. A. S.; Mitrut, R. E.; Watson, D. A. Highly Diastereoselective Michael Reactions Using β-Nitrocarbonyl Nucleophiles. *Org. Lett.* **2015**, *17*, 5468.

(12) Gietter-Burch, A. A. S.; Devannah, V.; Watson, D. A. Trifluoromethylation of Secondary Nitroalkanes. *Org. Lett.* **2017**, *19*, 2957.

(13) Maki, K.; Kanai, M.; Shibasaki, M. Pd-Catalyzed Allylic Alkylation of Secondary Nitroalkanes. *Tetrahedron* **2007**, *63*, 4250.

(14) Interestingly, the use of weaker bases, such as DBU leads to inconsistent stereoselection in the alkylation reaction due to epimerization of both the alpha and beta stereocenters. We attribute the stability of the product under the *tert*-butoxide conditions to be due to the solubility of the base. DBU is soluble under the reaction condition; *tert*-butoxide quantitatively deprotonates the nitronate substrate, which then precipitates from the reaction media. The fact that there is little to no free base in solution during the reaction protects the product against epimerization. See Supporting Information for more details.

(15) Bowry, V. W.; Ingold, K. U.; et al. *J. Am. Chem. Soc.* **1992**, *114*, 4992.

(16) Newcomb, M. Competition Methods and Scales for Alkyl Radical Reaction Kinetics. *Tetrahedron* **1993**, *49*, 1151.

(17) (a) Hu, X. Nickel-Catalyzed Cross Coupling of Non-Activated Alkyl Halides: A Mechanistic Perspective. *Chemical Science* **2011**, *2*, 1867. (b) Schley, N. D.; Fu, G. C. Nickel-Catalyzed Negishi Arylations of Propargylic Bromides: A Mechanistic Investigation. *J. Am. Chem. Soc.* **2014**, *136*, 16588.

(18) Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. Ligand Redox Effects in the Synthesis, Electronic Structure, and Reactivity of an Alkyl−Alkyl Cross-Coupling Catalyst. *J. Am. Chem. Soc.* **2006**, *128*, 13175.

DOI: 10.1021/jacs.9b04175
J. Am. Chem. Soc. 2019, 141, 8436−8440