



Published in final edited form as:

J Am Chem Soc. 2019 May 29; 141(21): 8436–8440. doi:10.1021/jacs.9b04175.

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

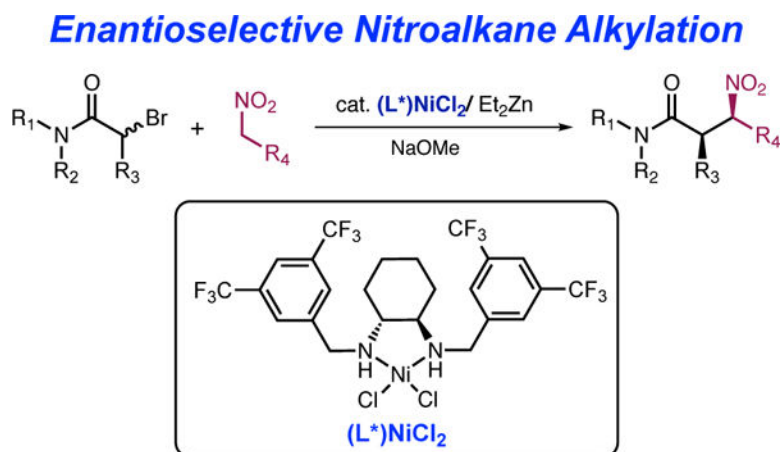
Vijayarajan Devannah, Rajgopal Sharma, and Donald A. Watson

Department of Chemistry and Biochemistry, University of Delaware, Newark, DE 19716

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.

Graphical Abstract



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

Corresponding Author dawatson@udel.edu.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

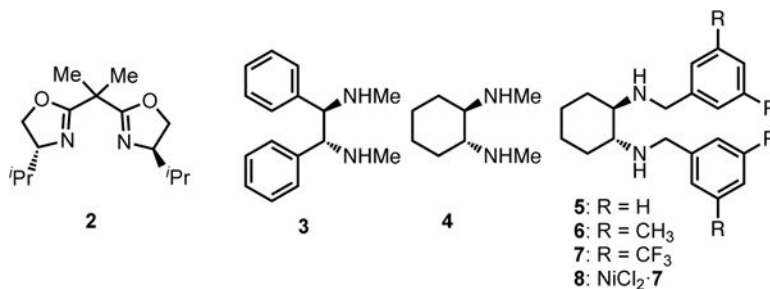
Experimental Procedures (PDF)

Crystallographic data (CIF)

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 nitrogencontaining 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 outersphere C–C bond-forming step that does not directly involve the metal catalyst or ligand.^{3a, 3c, 3d} 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 outersphere 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.

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 non-stereocontrolled 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). Eventually we found that the C₂ 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 CF₃ 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 NiCl₂ complex of this optimal ligand (complex **8**), Et₂Zn 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, unprotected and protected ketone groups, were 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 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 ¹H 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 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 non-stereoselective nitroalkane alkylation reactions, these studies indicate a mechanism involving radical intermediates. First, when the reaction was run in the presence of 1 equiv 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 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 re-isolated 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 Et₂Zn 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) compared to Et₂Zn. 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

Dr. Glenn Yap (UD) is acknowledged for assistance with X-ray crystallography.

Funding Sources

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, S10 RR026962, P20 GM104316, P30 GM110758).

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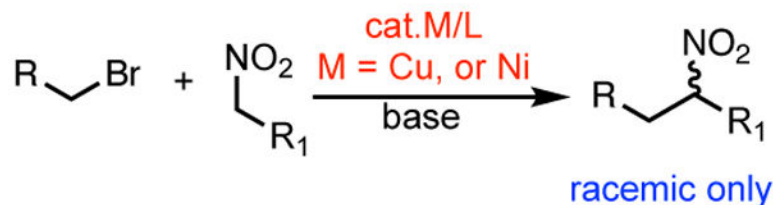
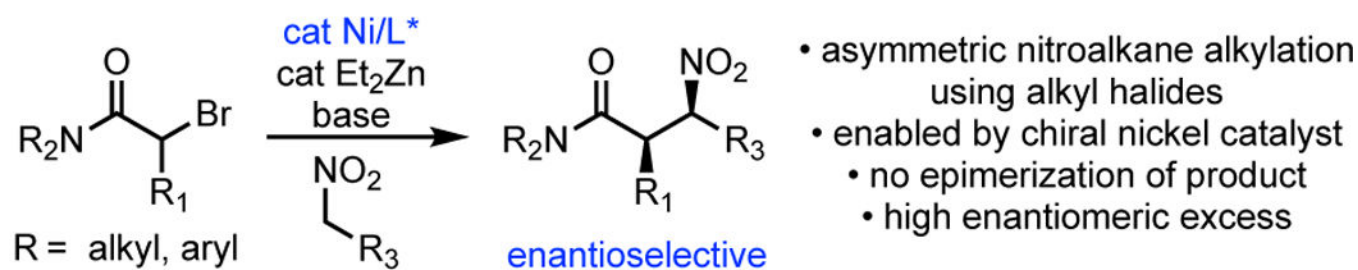
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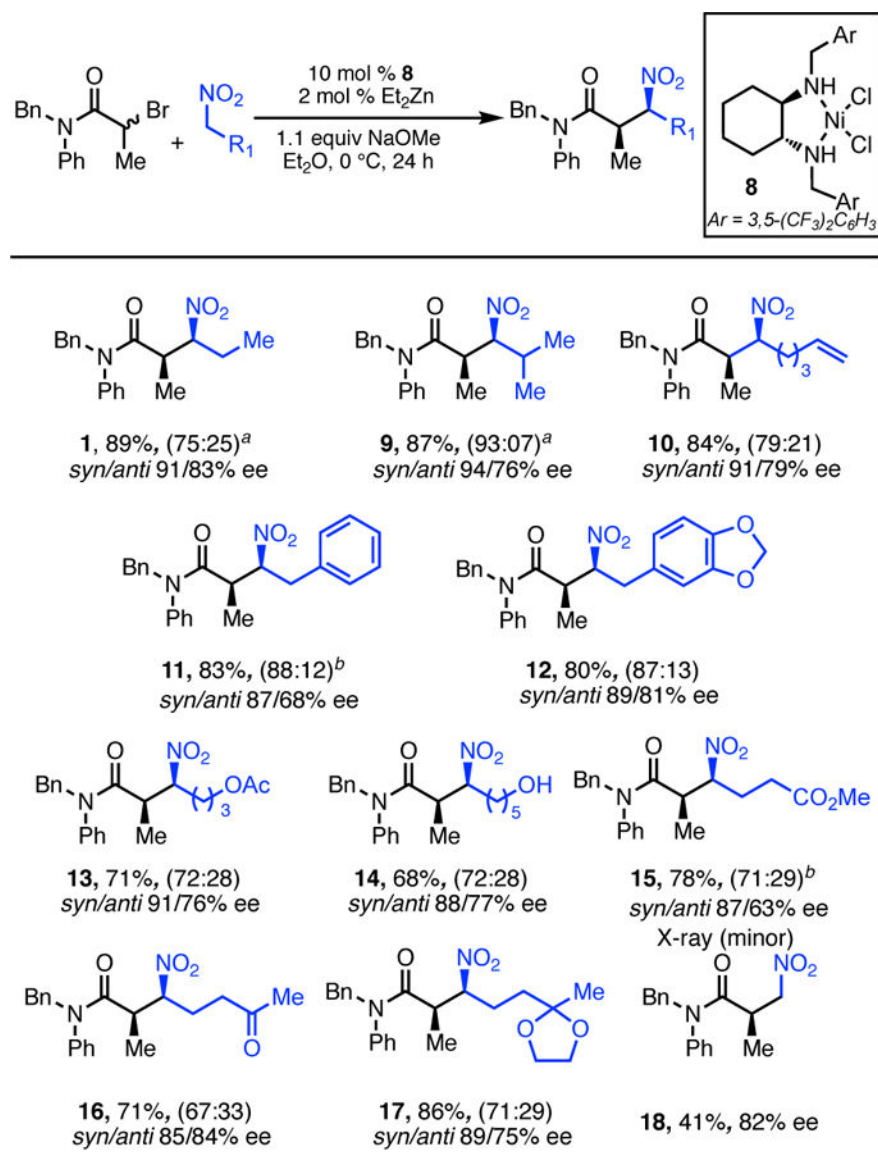
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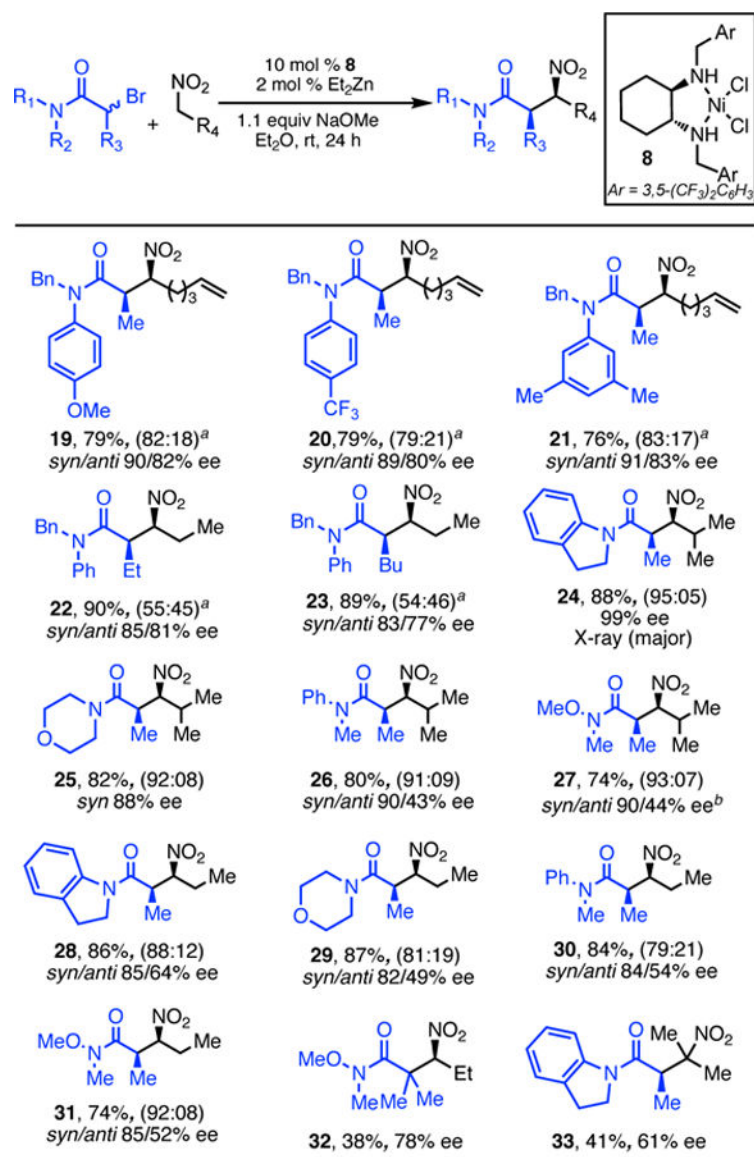
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Prior Work: Non-Selective Nitroalkane Alkylation**This Work: Enantioselective Nitroalkane Alkylation**

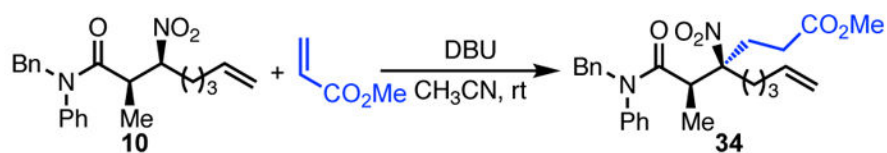
Scheme 1.
General Method for Asymmetric Nitroalkane Alkylation.



Scheme 2.
Scope of Nitroalkanes.

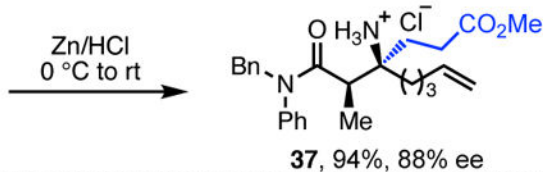


Scheme 3.
Scope of α -Bromoamides Scheme.

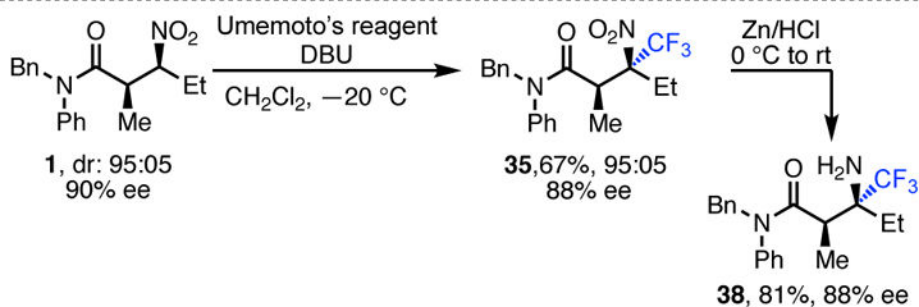


Run 1 dr: 95:05, 91% ee
Run 2 dr: 79:21, 91/82% ee

Run 1 84%, (95:05), 91% ee
Run 2 83%, (95:05), 89% ee



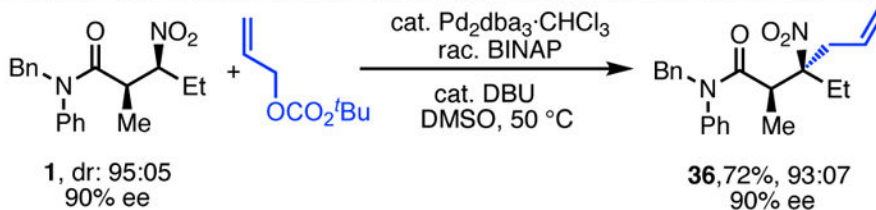
37, 94%, 88% ee



1, dr: 95:05
90% ee

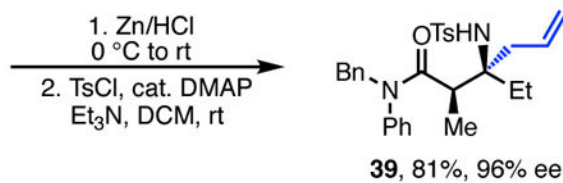
35, 67%, 95:05
88% ee

38, 81%, 88% ee



1, dr: 95:05
90% ee

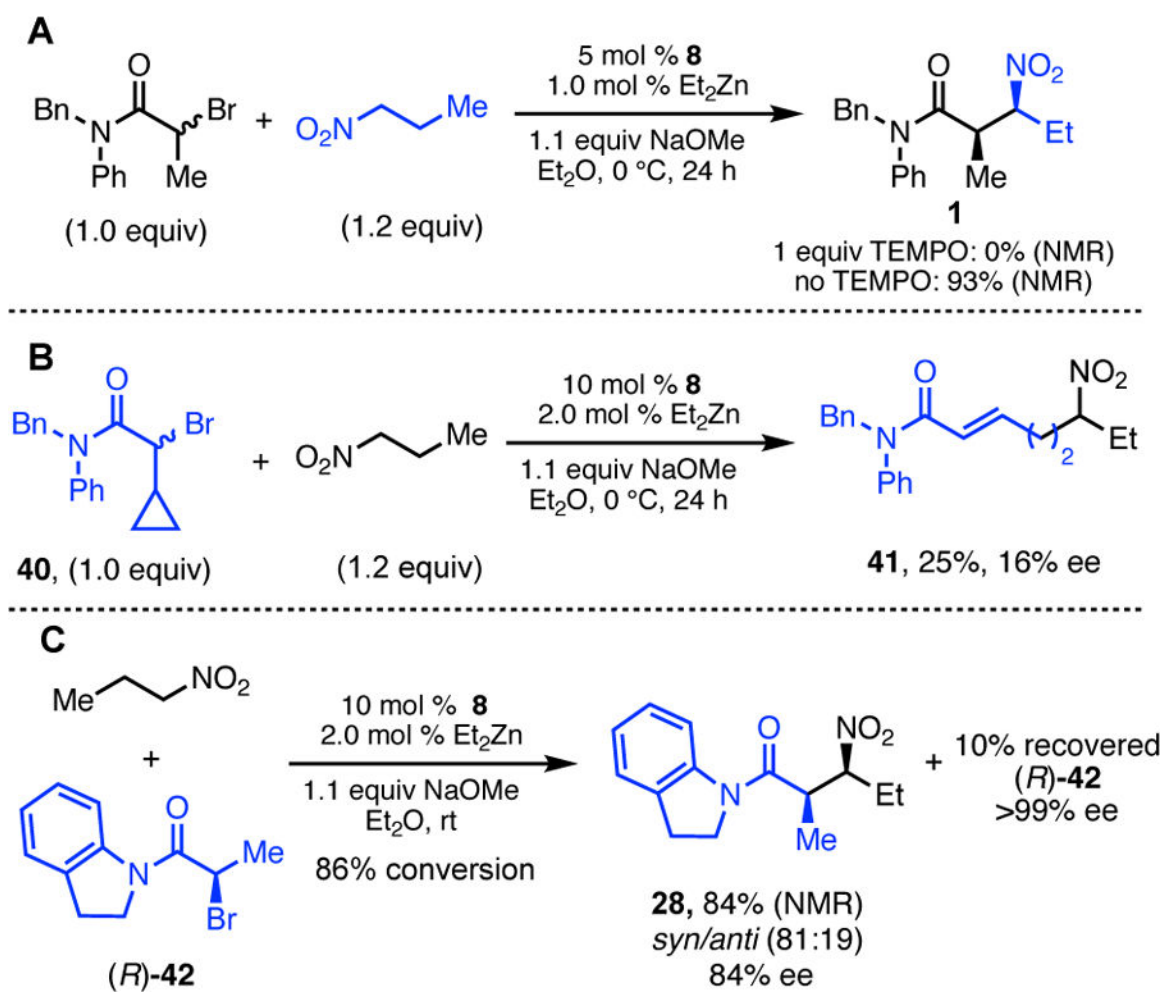
36, 72%, 93:07
90% ee



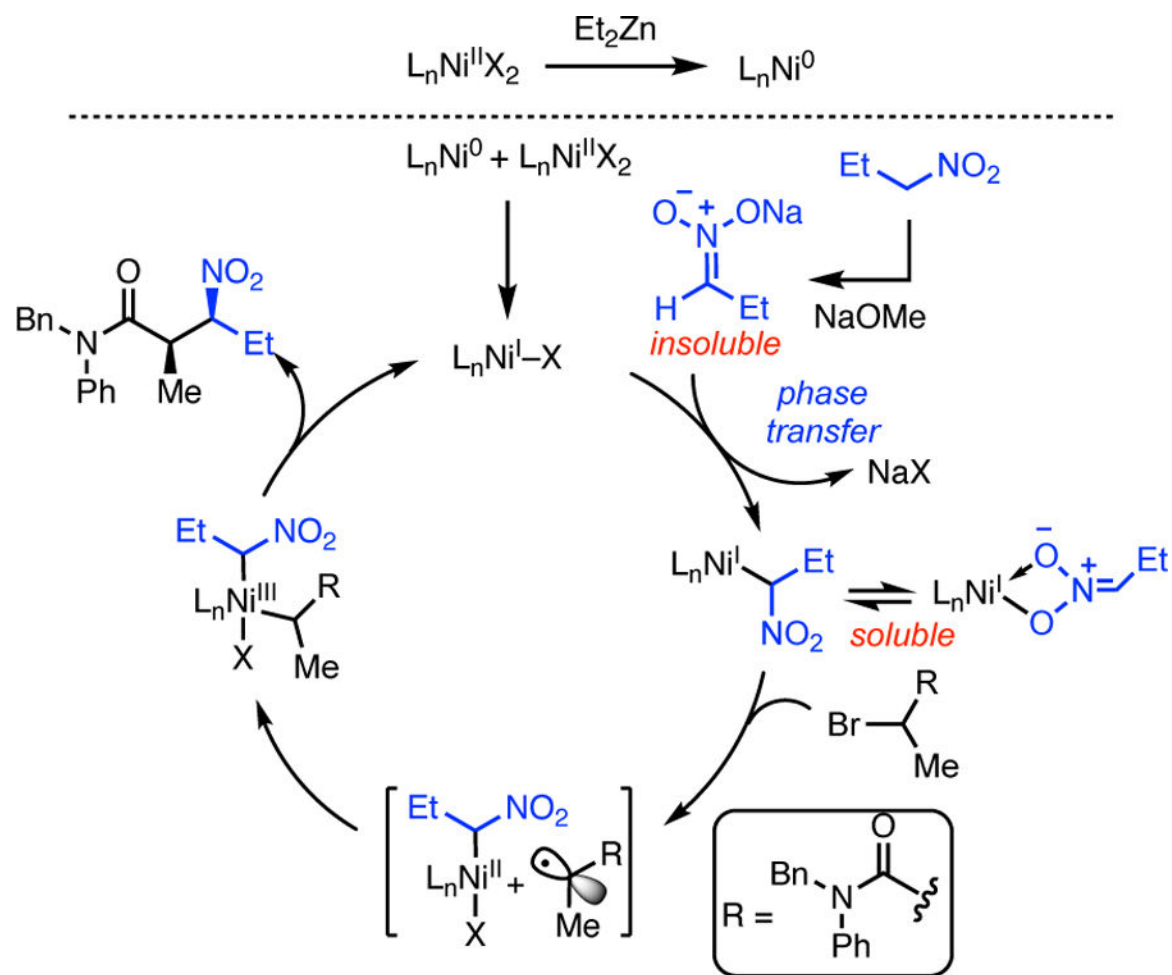
39, 81%, 96% ee

Scheme 4.

Downstream Functionalization of Alkylated Products.



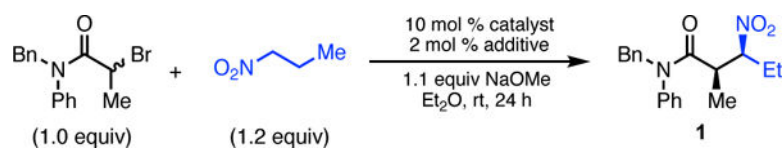
Scheme 5.
Mechanistic Probes.



Scheme 6.
Possible Mechanistic Pathway.

Table 1.

Discovery of the Catalytic System.



Entry	Catalyst	Additive	Yield of 1 ^a	d.r 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

^aDetermined via ¹H NMR against internal standard^bDetermined using chiral HPLC analysis^c0 °C.