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Asymmetric Reductive Dicarbofunctionalization of Alkenes via Nickel Catalysis

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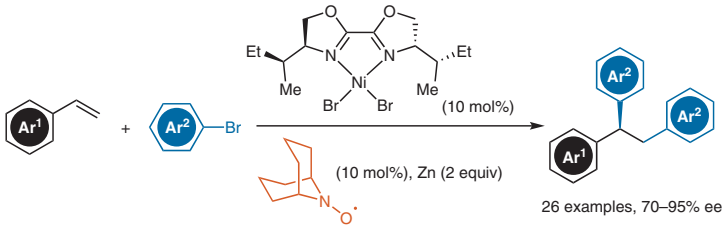

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Abstract Alkenes are an appealing functional group that can be transformed into a variety of structures. Transition-metal catalyzed dicarbofunctionalization of alkenes can efficiently afford products with complex substitution patterns from simple substrates. Under reductive conditions, this transformation can be achieved while avoiding stoichiometric organometallic reagents. Asymmetric difunctionalization of alkenes has been underdeveloped, in spite of its potential synthetic utility. Herein, we present a summary of our efforts to control enantioselectivity for alkene diarylation with a nickel catalyst. This reaction is useful for preparing triarylethanes. The selectivity is enhanced by an *N*-oxyl radical additive.

Key words asymmetric catalysis, nickel catalysis, alkene difunctionalization, reductive coupling, triarylethanes

David Anthony (left) obtained his Bachelor's degree in chemistry from Cornell University in 2014. As an undergraduate student, he performed research in organic synthesis under the supervision of Dr. Chad A. Lewis. In 2015, he began his graduate studies at New York University under the supervision of Prof. Tianning Diao. His research focuses on the development of novel chemical methods catalyzed by transition metals.

Tianning Diao (right) received her Ph.D. in chemistry from the University of Wisconsin–Madison in 2012 under the supervision of Prof. Shannon Stahl. She conducted her postdoctoral research with Prof. Paul Chirik at Princeton University. In 2014, she joined the faculty of NYU, where she is currently an Assistant Professor of Chemistry.

Introduction

Dicarbofunctionalization of alkenes represents a compelling approach to efficiently access substituted, saturated molecular scaffolds from simple, abundant starting materials.[1] Traditional methods to difunctionalize α,β-unsaturated carbonyl compounds have been achieved through a two-step process, in which a nucleophile undergoes conjugate addition with an activated alkene, the resulting enolate is then trapped with an electrophile (Scheme 1A).[2] This strategy is limited to activated alkenes in conjugation with a carbonyl group, and functional groups must be compatible with the highly reactive organometallic nucleophiles.

Transition metal catalysis has allowed for one-step difunctionalization of alkenes using a nucleophile and an electrophile (Scheme 1B).[1a] This redox-neutral strategy has employed palladium catalysts and aryl or vinyl nucleophiles and electrophiles to achieve the regioselective difunctionalization of vinylarenes,[3] dienes,[4] and, using a directing group, unactivated alkenes.[5] A few asymmetric variants have been reported, but the scope has been restricted to diene substrates[6] or intramolecular reactions.[7] Nickel catalysts have expanded the scope of nucleophiles and electrophiles to include alkyl groups,[8] but asymmetric reactions have been restricted to intramolecular examples.[9]

Reductive coupling reactions have recently emerged to eschew stoichiometric nucleophiles and thus expand the substrate scope to include moieties sensitive to organometallic nucleophiles.[10] Nevado developed a Ni-catalyzed reductive dicarbofunctionalization of alkenes using alkyl and aryl iodides in combination with tetrakis(dimethylamino)ethylene (TDAE) as a reductant (Scheme 1C).[11] In this reaction, Ni mediates the formation of an alkyl radical, which

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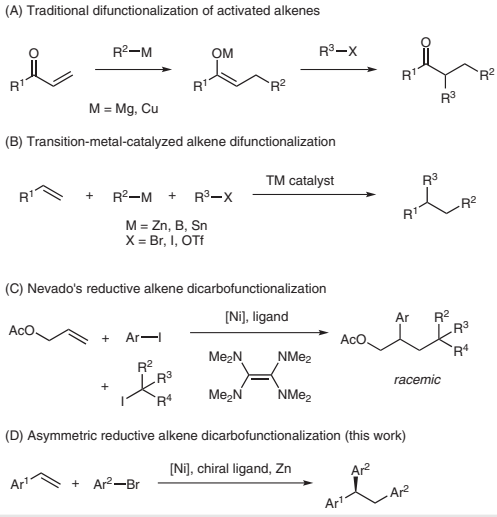
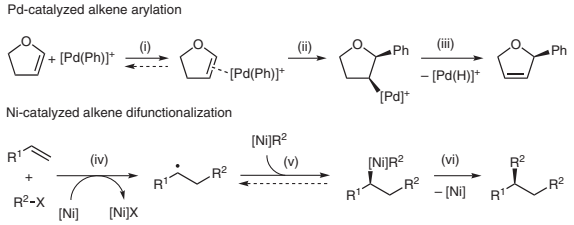


Scheme 1 Strategies for difunctionalization of alkenes

is added to the alkene. Combination of the radical and Ni forms a Ni-alkyl intermediate, which undergoes reductive elimination to afford the product. While the C(sp^3) electrophile is restricted to tertiary alkyl iodides, this method is notable for its mild conditions.

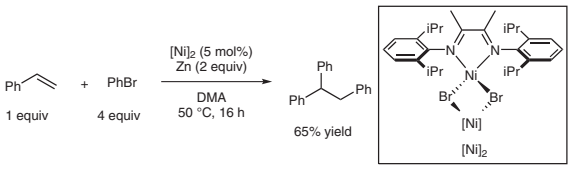
This example highlights the radical reactivity of nickel compared to its Group 10 congener palladium, which favors two-electron pathways.[12] The access to radical intermediates by nickel catalysts provides new opportunities for controlling enantioselectivity. In particular, for palladium-catalyzed arylation of alkenes, the enantioselectivity is dictated by either the alkene coordination or migratory insertion step (Scheme 2, steps *i* and *ii*),[13] while for a nickel-mediated pathway involving single-electron redox chemistry, radical capture by nickel (*v*) or reductive elimination (*vi*) could be enantio-determining.[14] We applied the radical properties of nickel catalysts to develop an intermolecular asymmetric difunctionalization of alkenes (Scheme 1D).



Scheme 2 Mechanisms of palladium- and nickel-catalyzed asymmetric alkene functionalization

Reaction Development

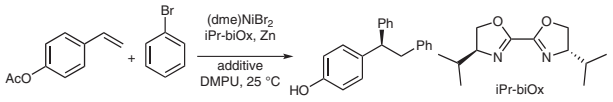
We began our investigation by developing conditions for racemic diarylation of styrene using bromobenzene. A dimeric nickel(I) catalyst has been previously shown to enable the carbofunctionalization of styrene[15] to 1,1,2-triphenylethane in good yield, so these conditions were used as a basis from which an asymmetric reaction could be evolved (Equation 1). Polar, aprotic solvents such as *N*,*N*-dimethylacetamide (DMA) or dimethylpropyleneurea (DMPU) were necessary in order to achieve high yields of the desired difunctionalization products. Heterogeneous reductants such as manganese and magnesium offered some diarylation product, while zinc powder gave the highest yield. Among various classes of chiral ligands, biOxazoline (biOx) ligands, commonly used in nickel catalysis,[16] proved to be the most effective for achieving high yield and enantioselectivity.



Equation 1 Racemic diarylation of styrene with bromobenzene

We observed a marked decrease in enantioselectivity from 38% to only 2% when the styrene substrate was distilled prior to use rather than used directly from its commercial bottle (Table 1, entries 1 and 2). Due to their propensity for auto-polymerization, styrenes are typically stabilized with radical inhibitors such as 2,6-di-*tert*-butyl-4-methylphenol (BHT). We speculated that the presence of such an additive, or the stabilized *O*-radical resultant from

Table 1 Optimization of Reaction Conditions[a]



Entry	Additive (mol%)	Yield (%)[b]	ee (%)[c]
1[d]	none	73	38
2	none	61	2
3	BHT (10%)	62	14
4	TEMPO (10%)	44	49
5	TEMPO (5%)	72	26
6	TEMPO (20%)	1	–
7	ABNO (10 mol%)	57	76
8[e]	**ABNO (8 mol%)**	**90**	**91**

[a] Reaction conditions: 4-acetoxystyrene (0.2 mmol), bromobenzene (0.8 mmol), (dme)$NiBr_2$ (10 mol%), *i*Pr-biOx (13 mol%), Zn (0.4 mmol), DMPU (0.2 mL). Reaction was performed for 16 h, then ester was hydrolyzed with aqueous NaOH prior to purification.
[b] Yields were determined by ^{1}H NMR analysis with mesitylene as internal standard.
[c] Enantiomeric excess was determined by HPLC with a chiral column after column chromatography purification.
[d] 4-Acetoxystyrene was used directly from commercial bottle without distillation.
[e] Reaction performed with (dme)$NiBr_2$ (10 mol%), *sec*-Bu-biOx (20 mol%), and DMPU/THF (0.1 mL each) at 10 °C.

quenching of a radical by BHT, could be responsible for this discrepancy. While the use of BHT did not result in higher enantioselectivity (entry 3), the addition of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) had a dramatic effect, raising the enantiomeric excess to 49% (entry 4). Furthermore, equimolar TEMPO loading with respect to nickel was paramount in order to achieve optimal results, with lower loading engendering worse enantioselectivity (entry 5), while higher loading shut down the reaction (entry 6).

These observations led us to evaluate various accessible *N*-oxyl radicals. The enantioselectivity exhibits a strong correlation with the percent buried volume ($\%V_{bur}$), a computationally derived steric descriptor,[17] of the *N*-oxyl radical. Less bulky *N*-oxyl additives gave higher enantioselectivities (Figure 1). 9-Azabicyclo[3.3.1]nonane *N*-oxyl (ABNO) delivered the difunctionalized product with the highest enantiomeric excess (Table 1, entry 7). Enantioselectivity was further improved by modifying the substituent on the biOx ligand, lowering the reaction temperature, and using a mixture of DMPU and tetrahydrofuran (THF) as the solvent (entry 8).

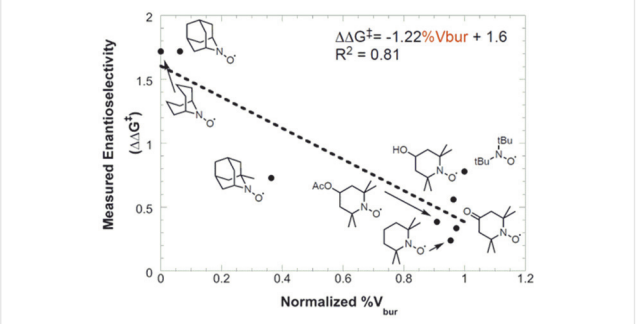
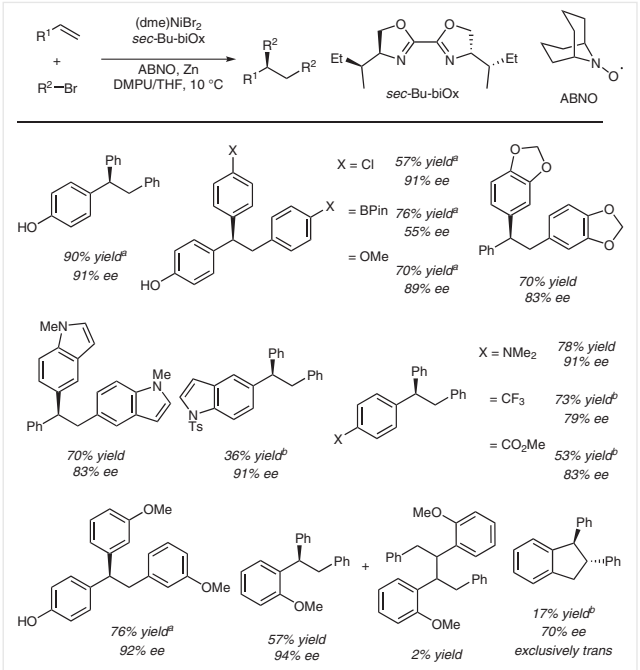


Figure 1 Steric effect of *N*-oxyl additives on enantioselectivity

With optimized conditions in hand, we explored the substrate scope of this reaction (Scheme 3).[18] Electron-donating and -withdrawing substituents had little effect on the enantioselectivity, although higher catalyst loadings were required to obtain good yields for electron-poor vinylarene substrates. Disubstituted alkenes were not well-tolerated, with 1,1-disubstituted vinylarenes showing no reactivity, although diarylation of indene gave a 17% yield of the *trans*-difunctionalized product.

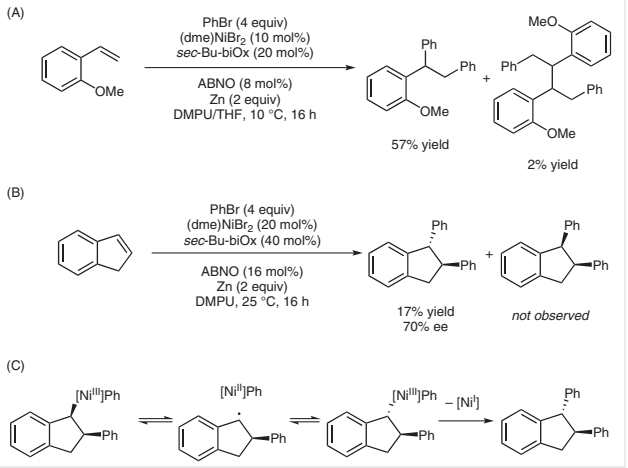
Mechanistic Investigation

We gained insight into the mechanism by considering several observations. First, formation of a dimer at the benzylic position suggests the presence of a benzylic radical (Scheme 4A). Second, the diarylation of indene resulted solely in the formation of the *trans*-diarylation product (Scheme 4B). One would expect a *syn*-addition from a typical migratory insertion, so the observed product diastereomer suggests the formation of a radical that combines with nickel on its less-hindered face (Scheme 4C). Third, the



Scheme 3 Selected asymmetric diarylation substrate scope. *Reagents and conditions*: alkene (0.2 mmol), aryl bromide (0.8 mmol), (dme)NiBr_2 (10 mol%), *sec*-Bu-biOx (20 mol%), ABNO (8 mol%), Zn (0.4 mmol), DMPU/THF (0.1 mL each). Reactions were performed for 16 h. Yields were measured by ^{1}H NMR analysis with an internal standard. [a] Product was hydrolyzed with aqueous NaOH prior to isolation. [b] 20 mol% (dme)NiBr_2, 40 mol% *sec*-Bu-biOx, and 16 mol% ABNO were used.

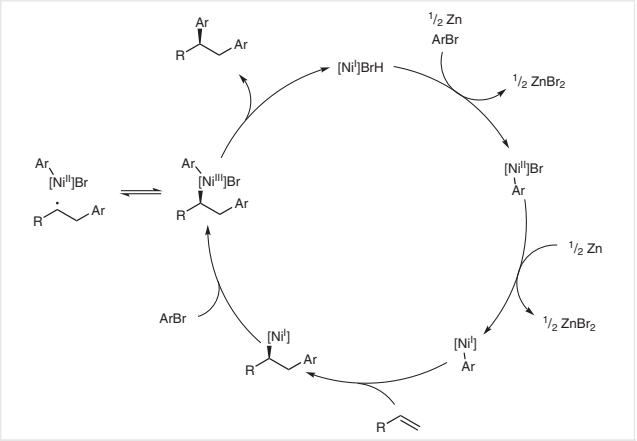
presence of excess *N*-oxyl radical with respect to nickel inhibited the reaction, mostly likely via interference of radical intermediates. Finally, no evident linear correlation was found between the observed enantiomeric ratio and the electronic effect of vinylarenes, suggesting that the enantio-determining step perhaps involves radicals.



Scheme 4 Mechanistic experiments and proposed origin of *trans*-diastereoselectivity

We performed control experiments to investigate the possible in situ generation of an organozinc reagent, which could afford the difunctionalized alkene as in redox-neutral strategies. When phenylzinc chloride was used in place of bromobenzene in the absence of zinc powder, no diarylation product was observed. This experiment suggests that direct oxidative addition of zinc to the aryl bromide does not enable the reaction.

A mechanistic hypothesis consistent with our findings is presented in Scheme 5. Oxidative addition and reduction of a nickel(I) bromide species to the aryl bromide electrophile results in an arylnickel(I) species.[19] This intermediate undergoes migratory insertion with the alkene substrate. Oxidative addition of another molecule of aryl bromide to the arylnickel(I) makes a nickel(III) species. This open-shell intermediate can eject a stabilized benzylic radical, which accounts for our observations of both the benzylic dimer byproduct and the *trans*-diastereoselectivity with indene. This reversible radical ejection is consistent with computational work performed by Kozlowski and co-workers.[16]■■*ref 14?*■■ Recombination of this radical with the chiral nickel catalyst followed by reductive elimination furnishes the diarylated product and regenerates the nickel(I) bromide.



Scheme 5 Proposed catalytic cycle

Future Outlook

We have developed the first intermolecular asymmetric diarylation of vinylarenes using a chiral biOx-nickel catalyst. The enantioselectivity is enhanced by the use of an auxiliary *N*-oxyl radical ligand, although the precise role of this radical remains obscure. However, we have shown that the radical mechanistic pathways available to nickel can be harnessed to elicit control over reaction outcomes in a different way than palladium commonly operates. We anticipate that the elucidation of the precise role of the *N*-oxyl additive could provide insight for the development of asymmetric nickel-mediated reactions with mechanisms invoking radical pathways.

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References

(1) (a) Giri, R.; KC, S. *J. Org. Chem.* **2018**, *83*, 3013. (b) Derosa, J.; Apolinar, O.; Kang, T.; Tran, V. T.; Engle, K. M. *Chem. Sci.* **2020**, *11*, 4287.
(2) (a) Chapdelaine, M. J.; Hulce, M. *Org. React.* **2004**, *38*, 225. (b) Ihara, M.; Fukumoto, K. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1010. (c) Wang, X.; An, J.; Zhang, Z.; Tan, F.; Chen, J.; Xiao, W. *Org. Lett.* **2011**, *13*, 808.
(3) Urkalan, K. B.; Sigman, M. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 3146.
(4) (a) Liao, L.; Jana, R.; Urkalan, K. B.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 5784. (b) McCammant, M. S.; Liao, L.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 4167. (c) Stokes, B. J.; Liao, L.; de Andrade, A. M.; Wang, Q.; Sigman, M. S. *Org. Lett.* **2014**, *16*, 4666.
(5) Liu, Z.; Zeng, T.; Yang, K. S.; Engle, K. M. *J. Am. Chem. Soc.* **2016**, *138*, 15122.
(6) (a) Wu, X.; Lin, H.; Li, M.; Li, L.; Han, Z.; Gong, L. *J. Am. Chem. Soc.* **2015**, *137*, 13476. (b) Stokes, B. J.; Liao, L.; de Andrade, A. M.; Wang, Q.; Sigman, M. S. *Org. Lett.* **2014**, *16*, 4666.
(7) Yasui, Y.; Kamisaki, H.; Takemoto, Y. *Org. Lett.* **2008**, *10*, 3303.
(8) (a) Qin, T.; Cornella, J.; Li, C.; Malins, L. R.; Edwards, J. T.; Kawamura, S.; Maxwell, B. D.; Eastgate, M. D.; Baran, P. S. *Science* **2016**, *352*, 801. (b) Derosa, J.; Tran, V. T.; Boulous, M. N.; Chen, J. S.; Engle, K. M. *J. Am. Chem. Soc.* **2017**, *139*, 10657. (c) Shrestha, B.; Basnet, P.; Dhungana, R. K.; Kc, S.; Thapa, S.; Sears, J. M.; Giri, R. *J. Am. Chem. Soc.* **2017**, *139*, 10653. (d) Derosa, J.; van der Puyl, V. A.; Tran, V. T.; Liu, M.; Engle, K. M. *Chem. Sci.* **2018**, *9*, 5278. (e) Huang, D.; Olivieri, D.; Sun, Y.; Zhang, P.; Newhouse, T. R. *J. Am. Chem. Soc.* **2019**, *141*, 16249. (f) Gao, P.; Chen, L. A.; Brown, M. K. *J. Am. Chem. Soc.* **2018**, *140*, 10653.
(9) (a) Cong, H.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 3788. (b) Wang, K.; Ding, Z.; Zhou, Z.; Kong, W. *J. Am. Chem. Soc.* **2018**, *140*, 12364. (c) Jin, Y.; Wang, C. *Angew. Chem. Int. Ed.* **2019**, *58*, 6722. (d) Tian, Z. X.; Qiao, J. B.; Xu, G. L.; Pang, X.; Qi, L.; Ma, W. Y.; Zhao, Z. Z.; Duan, J.; Du, Y. F.; Su, P.; Liu, X. Y.; Shu, X. Z. *J. Am. Chem. Soc.* **2019**, *141*, 7637.
(10) (a) Weix, D. J. *Acc. Chem. Res.* **2015**, *48*, 1767. (b) Wang, X.; Dai, Y.; Gong, H. *Top. Curr. Chem.* **2016**, *374*, 43.
(11) Garcia-Dominguez, A.; Li, Z.; Nevado, C. *J. Am. Chem. Soc.* **2017**, *139*, 6835.
(12) Hazari, N.; Melvin, P. R.; Beromi, M. M. *Nat. Rev. Chem.* **2017**, *1*, 0025.

(13) (a) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417. (b) Ashimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, *57*, 4571. (c) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477.
(14) Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2015**, *137*, 4896.
(15) Kuang, Y.; Anthony, D.; Katigbak, J.; Marrucci, F.; Humagain, S.; Diao, T. *Chem* **2017**, *3*, 268.
(16) Diccianni, J. B.; Diao, T. *Trends Chem.* **2019**, *1*, 830.
(17) Falivene, L.; Cao, Z.; Petta, A.; Serra, L.; Poater, A.; Oliva, R.; Scarano, V.; Cavallo, L. *Nat. Chem.* **2019**, *11*, 872.
(18) Anthony, D.; Lin, Q.; Baudet, J.; Diao, T. *Angew. Chem. Int. Ed.* **2019**, *58*, 3198.
(19) Lin, Q.; Diao, T. *J. Am. Chem. Soc.* **2019**, *141*, 17937.