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Nickel-Catalyzed Enantioselective Cross-Coupling of *N*-Hydroxyphthalimide Esters with Vinyl Bromides

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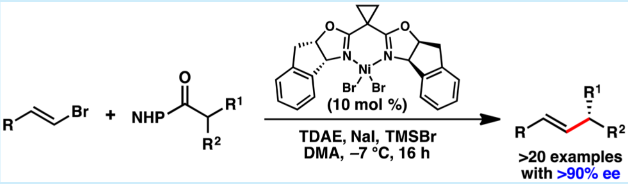
Ⓢ *Supporting Information*

ABSTRACT: An enantioselective Ni-catalyzed cross-coupling of *N*-hydroxyphthalimide esters with vinyl bromides is reported. The reaction proceeds under mild conditions and uses tetrakis(*N*,*N*-dimethylamino)ethylene as a terminal organic reductant. Good functional group tolerance is demonstrated, with over 20 examples of reactions that proceed with >90% ee.

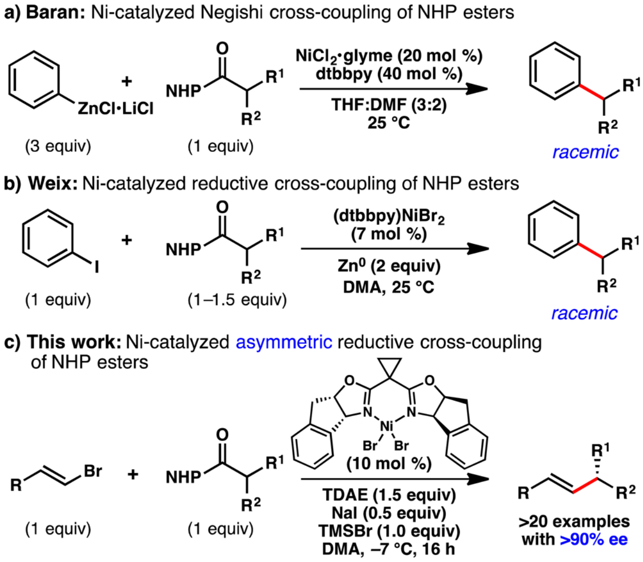


Nickel catalyzed cross-coupling reactions have emerged as powerful methods to form C(sp^3)−C(sp^2) and C(sp^3)−C(sp^3) bonds.[1] Whereas pioneering investigations focused on the canonical cross-coupling of C(sp^3) electrophiles with organometallic reagents—variants of the venerable Negishi,[2] Kumada,[3] and Suzuki[4] reactions, among others—additional modes of alkyl cross-coupling using nickel catalysis have recently been disclosed. These include cross-electrophile "reductive" couplings that use an exogenous, stoichiometric reductant to shuttle electrons to the nickel catalyst,[5] as well as cross-coupling reactions that rely on synergistic reactivity between nickel and photoredox cocatalysts.[6] Taken together, these reactions enable the cross-coupling of a broad range of C(sp^3) substrates, providing access to a variety of products.

Ni-catalyzed *reductive* cross-coupling reactions have proven particularly useful for the cross-coupling of secondary alkyl electrophiles, often providing chiral products as racemic mixtures.[5] Recognizing that the ability to render these transformations enantioselective would enhance their utility,[7] our laboratory has recently developed enantioselective Ni-catalyzed reductive cross-coupling reactions of both benzylic chlorides[8] and α-chloronitriles.[9] An important objective for further improving the synthetic usefulness of asymmetric reductive cross-coupling reactions is to develop reactions of new electrophile classes. Just as in conventional cross-coupling reactions, where different organometallic reagents (e.g., organozinc, organomagnesium, organoboron reagents, etc.) bring unique advantages to a specific synthetic scenario, the ability to cross-couple new electrophile classes broadens the tool box for strategic C−C bond formation. However, it can be challenging to apply conditions from previously developed reductive cross-coupling reactions to new electrophile classes, especially if there are changes to the mechanism by which the coupling partner undergoes oxidative addition; in particular, it can require tuning of either the ligand structure or the stoichiometric reductant (or both) in order to develop reactions that proceed in both good yield and enantioselectivity.

As part of our efforts to develop asymmetric cross-coupling reactions that employ a variety of C(sp^3) electrophiles, we became interested in the coupling of redox-active *N*-hydroxyphthalimide (NHP) esters.[10] These electrophiles are prepared from the corresponding carboxylic acids and have been recently demonstrated as C(sp^3) substrates for Ni-catalyzed Negishi,[11a,b] Suzuki,[11c] and reductive[12] cross-coupling reactions to generate racemic products (Scheme 1).[13,14] However, NHP esters have not been demonstrated as competent coupling partners in Ni-catalyzed *enantioselective* cross-coupling reactions. We recognized that the use of NHP esters might be advantageous for substrates in which the corresponding alkyl chlorides are unstable or challenging to prepare. In this letter, we report the first Ni-

Scheme 1. Ni-Catalyzed Reactions of NHP Esters



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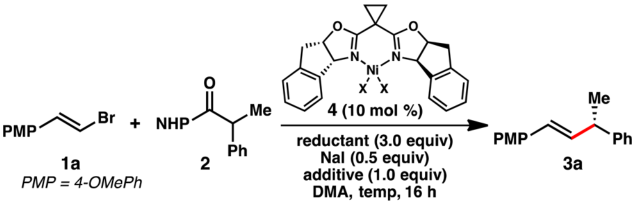
catalyzed asymmetric cross-coupling reactions of NHP esters. These reactions proceed under mild conditions using tetrakis(*N*,*N*-dimethylamino)ethylene (TDAE) as a homogeneous, stoichiometric reductant and exhibit high functional group tolerance.

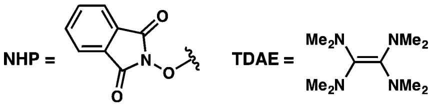
Our efforts began with ester **2**, which is prepared in one step from commercially available 2-phenylpropanoic acid. Subjection of **2** to our optimal conditions developed for the reductive cross-coupling of vinyl bromides and benzyl chlorides provided only trace quantities of product (Table 1, entry 1),[8b] highlighting the challenges presented by this new $C(sp^3)$-electrophile. Slightly improved results could be obtained under the same conditions by adding 1.0 equiv of TMSCl (entry 2). An investigation of alternative reductants revealed that TDAE substantially increased the reactivity, delivering **3a** in 61% yield and 95% ee (entries 2–4).[15]

Table 1. Reaction Optimization[a]



entry	X	reductant	additive	temp (°C)	yield (%)[b]	ee (%)[c]
1	Cl (**4a**)	Mn	none	0	trace	–
2	Cl	Mn	TMSCl	0	27	90
3	Cl	Zn	TMSCl	0	38	64
4	Cl	TDAE	TMSCl	0	61	95
5	Br (**4b**)	TDAE	TMSBr	0	75	92
6	Br	TDAE	TMSBr	−7	79	93
7[d]	Br	TDAE	TMSBr	−7	80[e]	96
8[d]	Br	TDAE	none	−7	19	88

[a] Reactions conducted on 0.2 mmol scale under N_2. [b] Determined by ^1H NMR versus an internal standard. [c] Determined by SFC using a chiral stationary phase. [d] 1.5 equiv of TDAE. [e] Isolated yield.



Monitoring the reaction progress at room temperature determined that (*E*)-1-(2-chlorovinyl)-4-methoxybenzene (**5**) was forming and accumulating under the reaction conditions, presumably through a Ni-catalyzed halide exchange process.[16] Since vinyl chloride **5** does not readily engage in the cross-coupling reaction, we hypothesized that the yield of **3a** could be improved by removing chloride from the reaction and thus preventing formation of this unproductive side product. Indeed, the use of TMSBr instead of TMSCl, and the use of $L\cdot NiBr_2$ (**4b**) as the catalyst, furnished product **3a** in 75% yield and 92% ee (entry 5). By decreasing the reaction temperature to −7 °C, and using only 1.5 equiv of TDAE, **3a** could be obtained in 80% yield and 96% ee (entry 7).[17,18] Running the reaction under the optimal conditions, but omitting TMSBr, confirms that this additive is critical for obtaining high yields of **3a** (entry 8).[19,20] We note that these optimal reaction conditions employ a 1:1 stoichiometry of the two electrophiles and only a 10 mol % catalyst loading.

To demonstrate the scope of the reaction, a series of (*E*)-vinyl bromides were cross-coupled with NHP ester **2**, providing the corresponding products (**3**) in uniformly good yield and high ee (Figure 1). The reaction exhibits good tolerance of Lewis basic functional groups: for example, anilines (**3c**), nitriles (**3e**), and esters (**3f**, **3j**) can be incorporated into the substrate without detriment to the yield or enantioselectivity. A pyridine-containing vinyl bromide also performs well, providing **3i** in 67% yield and 95% ee. In addition, alkyl-substituted vinyl bromides react smoothly, providing the corresponding products in good yield and ee (**3j**–**3o**). A vinyl bromide possessing a free alcohol couples efficiently, although silylation occurs under the reaction conditions to give silyl ether **3m**. The silyl ether can easily be cleaved with a mild acid workup; in this case it was preserved in order to facilitate purification. It is notable that alkenyl MIDA-boronate **3n** and alkenyl silane **3o** can be prepared in 97% ee from commercially available vinyl bromides. To demonstrate that this method can be used preparatively, the coupling between **1a** and **2** was conducted on 5.0 mmol scale, which delivered 918 mg (77% yield) of **3a** in 91% ee.

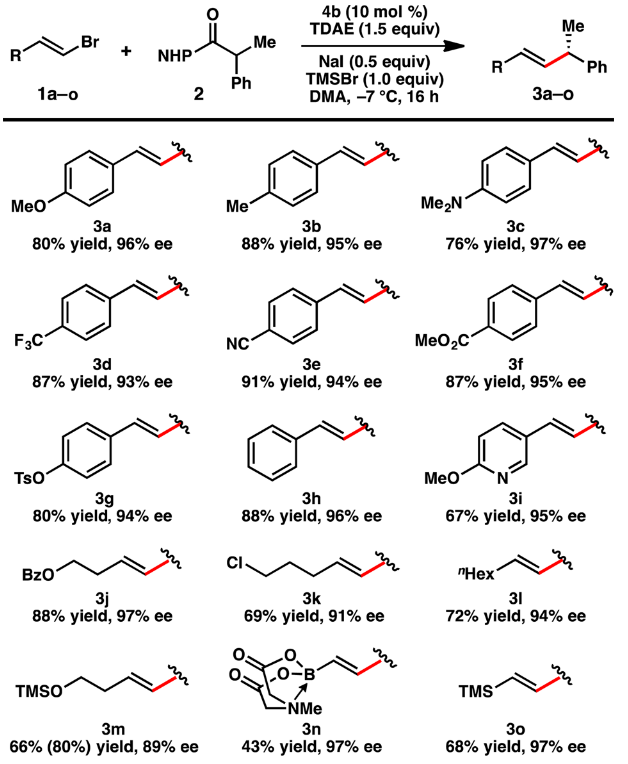


Figure 1. Scope of the vinyl bromide coupling partner. Reactions are conducted on 0.2 mmol scale under N_2. Isolated yields are provided; ee is determined by SFC using a chiral stationary phase. For **3g**, 1.5 equiv of NHP ester were used. For **3m**, 2.0 equiv of TMSBr were used; the alcohol is silylated under the reaction conditions. NMR yield of **3m** versus an internal standard is provided in parentheses.

The reaction also exhibits a broad scope for the NHP ester coupling partner, delivering good yields and high enantioselectivities for a range of substrates bearing substitution on the arene or at the benzylic position (Figure 2). In certain cases (e.g., **7a**–**7c**), the NHP esters cross-couple with improved yield relative to the corresponding benzyl chlorides (under the previously reported conditions).[8b] Moreover, aniline **7e** can be prepared in 66% yield and 94% ee; this compound could not be accessed via our previously reported benzylic chloride coupling[8b] due to challenges in preparing and handling 4-(chloro(phenyl)methyl)-*N*,*N*-dimethylaniline under standard conditions.[21] Higher substitution at the benzylic position is also tolerated (**7g**–**l**),

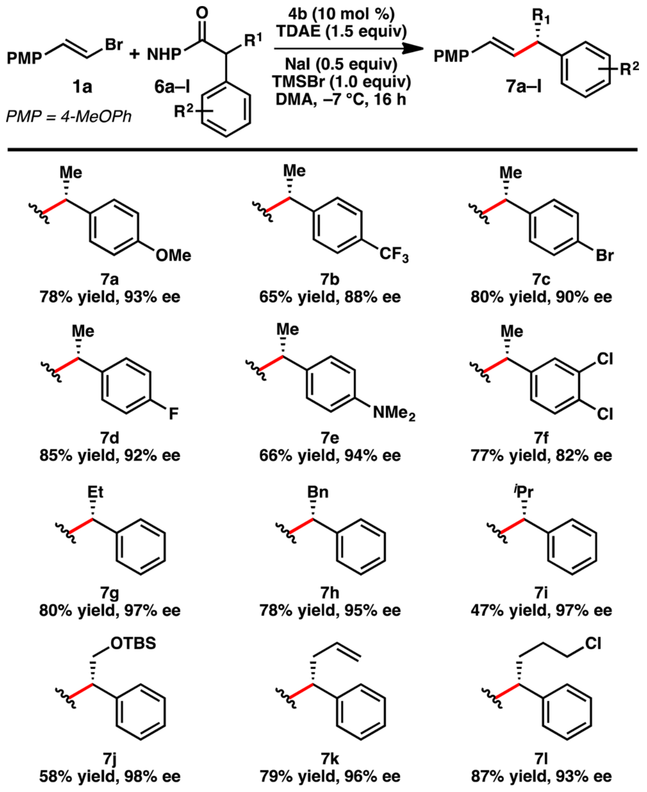


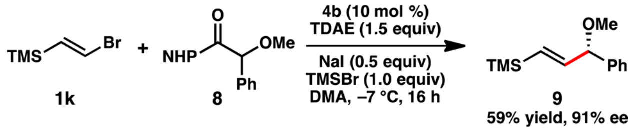
Figure 2. Scope of the NHP ester coupling partner. Reactions are conducted on 0.2 mmol scale under N_2. Isolated yields are provided; ee is determined by SFC using a chiral stationary phase.

although the yield begins to decrease with larger groups (e.g., ^{i}Pr, **7i**). Notable products include **7j**, which incorporates a siloxy group, **7k**, containing an alkene, and **7l**, which has an alkyl chloride. Perfect chemoselectivity for cross-coupling of the NHP ester over the primary alkyl chloride is observed.

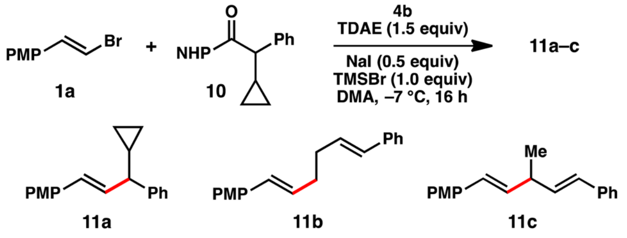
Although the primary focus of this study was the cross-coupling of NHP esters with alkyl substituents at the benzylic position, we have also have begun to investigate substrates containing heteroatom substitution (Scheme 2a). Reaction of α-methoxy ester **8** proceeds smoothly, furnishing allylic ether **9** in good yield and ee. This highlights an advantage of the NHP ester for certain C(sp^3) electrophiles, as the corresponding α-chloroether substrate is unstable and difficult to work with.

Scheme 2. Additional Experiments

(a) Reaction of an α-methoxy NHP ester:



(b) Radical clock substrate:



mol % 4b	total yield 11 (%)	ratio 11a:[11b + 11c]
5	44	1:7.5
10	42	1:5.9
20	49	1:3.9

To probe for the intermediacy of a radical species, NHP ester **10** was prepared and subjected to the standard cross-coupling conditions (Scheme 2b, 10 mol % **4b**). A 42% combined yield of the coupled products **11a–c** was obtained. It has been shown that for phenyl substituted cyclopropylcarbinyl radicals, the ring opening is reversible and that the cyclopropane species is favored at lower temperatures.[22] The fact that **11b** and **11c** predominate, even though they derive from the minor equilibrium species, perhaps indicates that the rate of radical recombination with nickel is sensitive to the steric profile of the radical. When the catalyst loading of **4b** was varied, the ratio of **11a** to total ring opened product (**11b** + **11c**) was found to increase at higher nickel concentrations. This Ni-dependent behavior suggests that the mechanism proceeds through a cage-escaped radical, which, at higher concentrations of **4b**, can competitively recombine with nickel before undergoing ring scission.[23] Further studies of the mechanism are ongoing; it is unclear at this time whether the absolute stereochemistry is set during the oxidative addition or reductive elimination steps.[24] We do note, however, that the products are formed in similar ee when using either the NHP esters under the conditions reported here or the benzylic chloride using the conditions reported previously,[8b] which suggests that the reactions proceed through the same stereochemistry-determining step.[25]

In summary, these results demonstrate that Ni-catalyzed reductive cross-coupling reactions of NHP esters can be rendered highly enantioselective, thus broadening the scope of C(sp^3) electrophiles available for asymmetric C–C bond formation. In contrast to the related reductive cross-couplings of benzyl chlorides,[8b] optimal results are obtained when TDAE is used as the terminal reductant. A preliminary result demonstrates that these conditions can be used to cross-couple α-alkoxy NHP esters and other substrates for which the corresponding benzylic chloride could be difficult to prepare or unstable. The ability to use both NHP esters (this study) and benzylic chlorides in asymmetric reductive alkenylation reactions allows users to select from either electrophile depending on factors such as commercial availability of the corresponding carboxylic acid or benzylic chloride starting material, and improves the overall scope of this transformation. The further development of asymmetric cross-electrophile coupling reactions of NHP esters and other C(sp^3) electrophiles is the focus of ongoing work in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00793.

Experimental procedures, characterization, and spectral data (PDF)
Crystallograhic data for **4b** (CIF)

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Notes

The authors declare no competing financial interest.

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(18) In the coupling of (1-chloroethyl)-benzene, TDAE provides low yield of the cross-coupled product (23% yield and 94% ee).

(19) See Supporting Information for additional control experiments.

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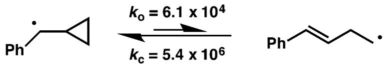

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(24) Molander and Kozlowski have calculated that the reductive elimination is the stereochemistry-determining step in a related Ni-catalyzed cross-coupling reaction of aryl halides with benzyl trifluoroborates.

(25) See Supporting Information for ee comparison data.

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