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Highly Enantioselective Cross-Electrophile Aryl-Alkenylation of Unactivated Alkenes

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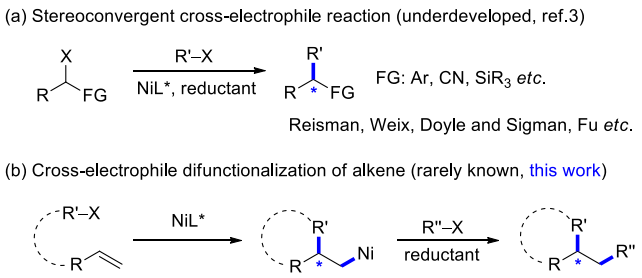
KEYWORDS. Asymmetric Catalysis, Cross-Electrophile Reaction, Difunctionalization, Alkenes, Nickel

ABSTRACT: Enantioselective cross-electrophile reactions remain challenging subject in metal catalysis, and, to data, studies have mainly focused on stereoconvergent reactions of racemic alkyl electrophiles. Here, we report an enantioselective cross-electrophile aryl-alkenylation reaction of unactivated alkenes. This method provides access to a number of biologically important chiral molecules such as dihydrobenzofurans, indolines and indanes. The incorporated alkenyl group is suitable for further reactions that can lead to an increase in molecular diversity and complexity. The reaction proceeds under mild conditions at room temperature, and easily accessible chiral pyrox ligand is used to afford products with high enantioselectivity. The synthetic utility of this method is demonstrated by enabling the modification of complex molecules such as peptides, indometacin and steroids.

1. INTRODUCTION

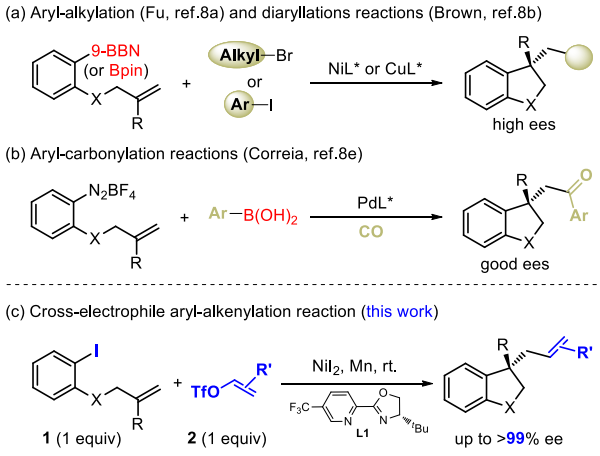
Scheme 1. Strategies for enantioselective cross-electrophile reactions



The cross-electrophile reaction has recently emerged as a powerful tool with which to forge C–C bonds. The approach has high step economy, excellent functional group compatibility, and allows unique selectivity that is orthogonal to conventional electrophile-nucleophile reactions.[1] Despite formidable advances, highly enantioselective catalytic variants of these processes are rare.[2] Most progress has been achieved on stereoconvergent cross-electrophile reactions, which have enabled efficient access to enantioenriched compounds from racemic secondary alkyl electrophiles (Scheme 1a).[3] Alternatively, the cross-electrophile difunctionalizaton of alkene can afford chiral molecules with rapid increase in molecular diversity and complexity by constructing two vicinal C–C bonds in a single step (Scheme 1b).[4] Unfortunately, partly because of the comprehensive chemo-, regio-, and stereoselectivity challenges encountered in this process,[1d] the potential of this strategy remains largely unexplored,[5] although there have been several reports in recent years on racemic reactions.[4]

In contrast, dicarbofunctionalization of alkenes has recently received considerable attention.[6] Among various studies, the cyclization/cross-coupling reaction is particularly attractive, because it provides facile access to a wide range of cyclic frameworks that constitute key moieties of many bioactive natural products and pharmaceuticals.[7] Progress in this field has led to

Scheme 2. Enantioselective dicarbofunctionalization of unactivated alkenes



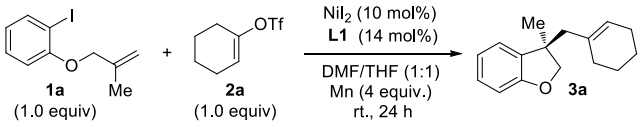
numerous important synthetic methods, including a few enantioselective reactions.[5, 8] For instance, Fu and Brown demonstrated highly enantioselective aryl-alkylation[8a] and diarylation reactions[8b] of unactivated alkenes (Scheme 2a). Very recently, Correia reported an aryl-carbonylation reaction of unactivated alkenes that proceeds with good enantioselectivity (Scheme 2b).[8e] Despite these advances, to our knowledge, there have been no studies on highly enantioselective carbo-alkenylation reactions. Such a reaction would be especially important to increase molecular complexity,[6e,f] because the incorporated alkenyl group can be transformed into a wide range of functionalities. We envisioned that a cross-electrophile strategy could provide access to a complementary scope of synthetically useful products.

Herein, we report a nickel-catalyzed enantioselective cross-electrophile aryl-alkenylation reaction of unactivated alkene (Scheme 2c). This reaction proceeds under mild conditions at room temperature, and the use of easily accessible chiral pyrox ligand affords products containing an enantioenriched quaternary stereocenter[9] with high chemo-, regio-, and stereoselectivity. The reaction represents one of rare examples of cross-electrophile reactions that use equimolar amounts of coupling fragments.[1] Moreover, this method is amenable to the functionalization of complex molecules.

2. RESULTS AND DISCUSSION

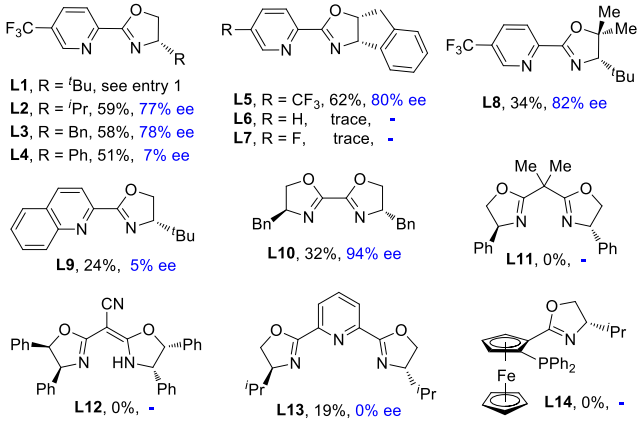
2.1 Reaction Optimization. We began our investigation by exploring the reaction of alkene **1a** with alkenyl triflate **2a** (Table 1). As expected, our initial studies revealed that the selectivity for **3a** is challenged by a number of side reactions, such as the direct coupling of Ar–I with alkenyl triflate, the protonation and homocoupling of **1a**, **2a**, or cyclized intermediate. Further studies established that performing the reaction at room temperature with chiral 5-CF_3-Pyrox-^{t}Bu(**L1**)[10] as ligand gave the best result, affording **3a** with 77% isolated yield and 98% ee (entry 1).[11] A comparable result was observed when $Ni(cod)_2$ was used, whereas the reaction with $NiCl_2$ afforded **3a** with low yield and decreased ee (entries 2 and 3). The use of THF as cosolvent inhibited the homocoupling of cyclized intermediate (entries 1 vs. 4). The reaction in THF is less effective, affording alkenyl dimer from **2a** and leaving most of **1a** intact (entry 5). Traces of **3a** were observed when Zn was used instead of Mn (entry 6). The investigation of ligands revealed that the 5-CF_3-Pyrox ligands were more effective at promoting this cyclization/cross-coupling process (**L1–L14**). We noted that (*S,S*)-Bn-Box (**L10**) and (*S,S*)-Ph-Box (**L11**), the ligands used by Correia, Weix and Reisman,[2, 8e] performed poorly under our conditions. The reaction with (*S,S*$_p$)-^{i}Pr-Phosferrox **L14**, a ligand that is used in reductive diarylation of activated alkene,[5] did not give any desired product.

Table 1. Optimization of the reaction conditions[a]



entry	change of conditions	yield (%)	ee (%)
1	none	79 (77)[b]	98
2	$Ni(cod)_2$ instead of NiI_2	68	95
3	$NiCl_2$ instead of NiI_2	30	91
4	DMF instead of DMF/THF	61	97
5	THF instead of DMF/THF	12	80
6	Zn instead of Mn	trace	-

Effect of ligands:



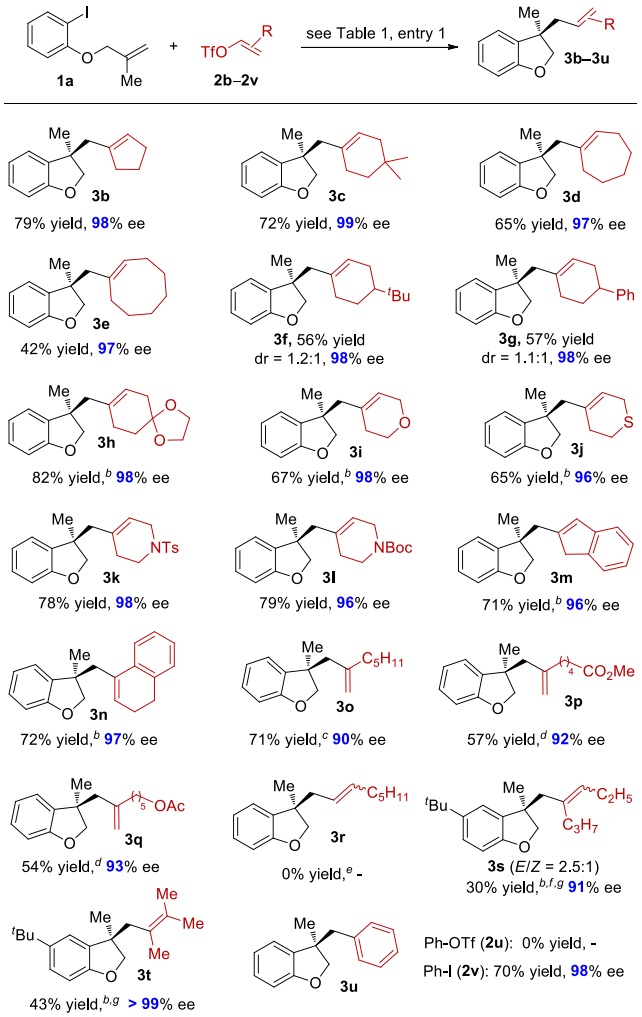
[a] **1a** (0.1 mmol) and **2a** (0.1 mmol) were used. The yields were determined by GC analysis with dodecane as an internal standard. [b] Isolated yield.

2.2 Reactions for the Synthesis of Dihydrobenzofurans. With optimized reaction conditions in hand, we evaluated the scope of the reaction with respect to alkenyl triflates (Table 2). Cyclic alkenyl triflates ranging from five- to eight-membered rings coupled efficiently to give enantioenriched products with moderate to good yields and 97–99% ee (**3b–g**). Incorporation of the functionalized alkenyl group is important to increase molecular diversity. In this respect, the reaction of **1a** with carbonyl derivative affords **3h** with 82% yield and 98% ee. Nonaromatic heterocycles are prevalent in a wide range of pharmaceuticals, but incorporation of them through C–C bond formation represents a challenge.[12] Under our conditions, dihydrobenzofurans hybridized with 3,6-dihydro-2H-pyran (**3i**), 3,6-dihydro-2H-thiopyran (**3j**), and 3-piperideine (**3k**, **3l**) were produced with high enantioselectivity. The reactions of indenyl and 3,4-dihydro-1-naphthyl triflates performed well (**3m**, **3n**). The reactions of **1a** with 1-substituted alkenyl triflates afforded functionalized products with moderate to good yields and high ee (**3o–q**). Unfortunately, the reaction with 2-substituted alkenyl triflate did not give any desired

product (**3r**). The use of 1,2-disubstituted alkenyl triflate (*E*:*Z* = 2.8:1) gave a product with a ratio of *E*/*Z* = 2.5:1, indicating the alkene geometry might be retained in this process (**3s**). When a fully substituted alkenyl triflate was employed, product **3t** was obtained with 43% yield and more than 99% ee. While the reaction of **1a** with Ph–OTf gave no desired product, the use of Ph–I afforded **3u** with 70% yield and 98% ee.

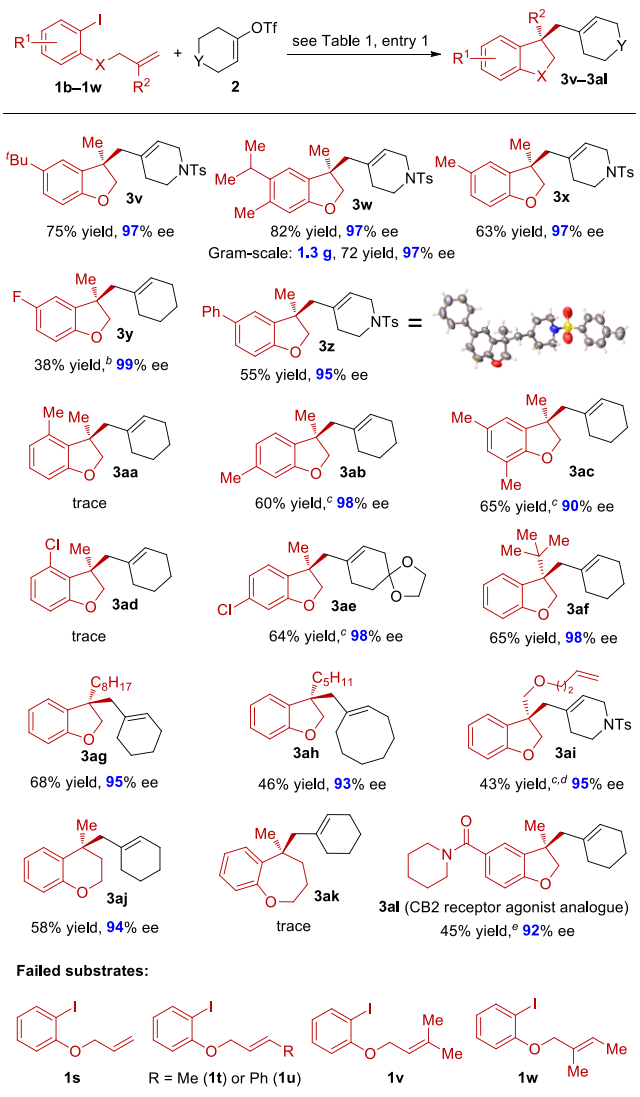
We then studied the substrate scope of the reaction with respect to aryl iodide-tethered alkenes (Table 3). Substrates with electron-donating, electron-withdrawing, or sterically hindered substituents at the aromatic ring were tolerated (**3v**–**3ae**). Furthermore, the reaction could be scaled up to gram-scale, and afforded **3w** with 72% yield and 97% ee. The absolute configuration of **3z** was determined by X-ray analysis, and that of all other

Table 2. Scope of alkenyl triflates[a]



[a]**1a** (0.2 mmol) and **2** (0.2 mmol) were used. Isolated yields. [b]Reactions in DMF. [c]Alkene **1a** (2.0 equiv) was used, reaction in THF. [d]Alkene **1a** (3.0 equiv) was used. [e]Alkenyl triflate **2r** (*Z*/*E* = 7:1) was used. [f]Alkenyl triflate **2s** (*E*/*Z* = 2.8:1) was used. [g]4-(tert-butyl)-2-iodo-1-((2-methylallyl)oxy)benzene **1b** was used.

Table 3. Scope of the reaction with respect to alkene[a]



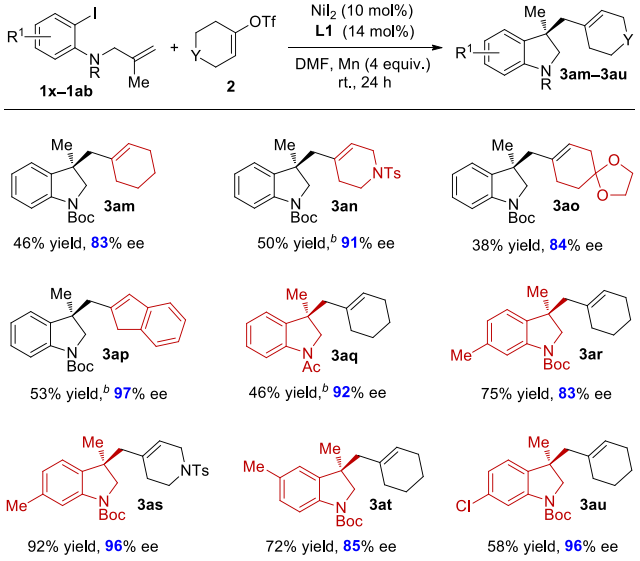
[a]**1** (0.2 mmol) and **2** (0.2 mmol) were used. Isolated yields. [b]Alkene **1e** (1.8 equiv), Ni catalyst (15%) was used. [c]Reaction in DMF. [d]Reaction at 60 °C. [e]Alkene **1r** (1.8 equiv) was used.

products was assigned accordingly.[13] The reactions of substrates bearing a substituent at the ortho-position of iodide only gave trace of **3aa** and **3ad** with most of aryl iodides protonated. In contrast, the reactions of substrates bearing a substituent at the para- or meta-position of the iodide afforded the cyclization-coupling products with moderate yields and high enantioselectivity (**3x**, **3ab**, **3ac**, **3ae**). This substitution influence is consistent with the previous reports.[5,8a-b,e] The presence of a ^{t}Bu group, alkyl long chain, or functionalized alkyl group at the quaternary carbon center was tolerated (**3af**–**3ai**). The reaction was effective for the synthesis of six-membered O-heterocycle (**3aj**), but was failed to produce seven-membered ring product (**3ak**). Optically active 2,3-dihydrobenzofurans exhibit interesting biological activity, and they have potential use as CB2 receptor agonists.[14] Our method provides facile access to this type of analogue (**3al**). At the current stage, the reactions of monosubstituted, 1,2-disubstituted or trisubstituted

alkenes were unsuccessful (**1s–1w**). In these cases, the reactions typically afforded the direct aryl-alkenyl coupling products.

2.3 Reactions for the Synthesis of Indolines. 3,3-Disubstituted indolines are ubiquitous structural motifs in many biologically active compounds and natural products, and their synthesis has attracted intense attention.[15] While a number of cyclization approaches to enantioenriched 2-oxindoles have been reported, the asymmetric synthesis of 3,3-disubstituted indolines has been less developed.[5,7b] We therefore studied the possibility of constructing these valuable targets through the cross-electrophile method. Under slightly modified standard conditions,[16] a number of N-tether alkenes were cyclized and coupled with alkenyl triflates selectively (Table 4). The reactions of substrate **1x** with cyclohexenyl-, tetrahydropyridinyl, functionalized cycloalkenyl, and indenyl triflates afforded the desired products in synthetically useful yields and good to high enantioselectivity (**3am–3ap**). The enantioselectivity was improved when the N-Ac-protected substrate was used instead of the N-Boc-protected one (**3am**, **3aq**). In some cases, the use of modified ligand **L8** was required to achieve high ee values (**3an**, **3ap**, and **3aq**). The use of electron-rich aryl iodides significantly improved the reaction efficiency, affording the products with good to high yields (**3ar–3at**). The reaction of 4-chloro-aryl substrate gave **3au** with 58% yield and 96% ee.

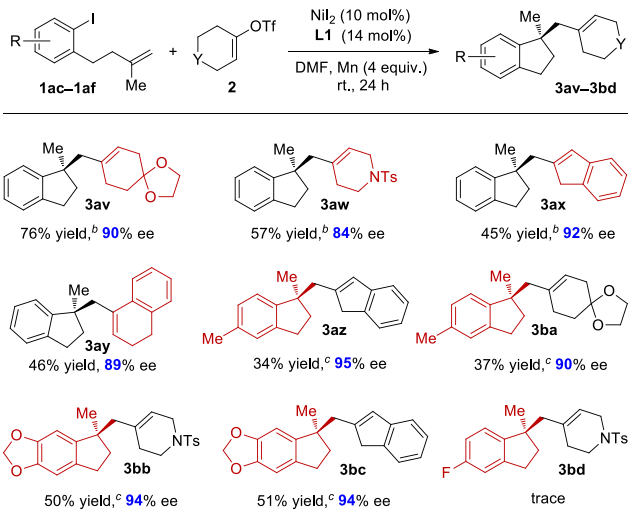
Table 4. The reactions of N-tethered alkenes with alkenyl triflates[a]



[a]**1** (0.2 mmol) and **2** (0.2 mmol) were used. Isolated yields. [b]**L8** was used.

2.4 Reactions for the Synthesis of Indanes. Indanes are substructures present in a large number of naturally occurring products and pharmaceutical compounds.[17] The potential of this method for the synthesis of these unique structures was then evaluated (Table 5). Under our conditions, enantioenriched indanes hybridized with functionalized cyclohexene, 3-piperideine, indene, and

Table 5. The reactions of C-tethered alkenes with alkenyl triflates[a]

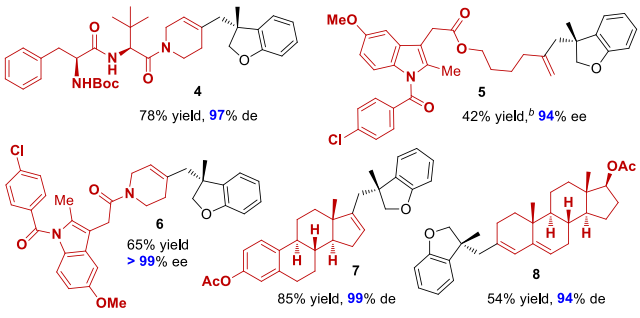


[a]**1** (0.2 mmol) and **2** (0.2 mmol) were used. Isolated yields. [b]Reaction in DMF/THF (1:1). [c]**L8** was used.

dihydronaphthalene were produced with moderate to good yields and usually high enantioselectivity (**3av–3ay**). While inferior results were obtained when a methyl substituted aryl iodide was employed (**3az**, **3ba**), the use of more electron-rich substrate afforded the products with moderate yields and 94% ee (**3bb**, **3bc**). Unfortunately, at present, the reaction of tethered aryl iodide bearing an electron-withdrawing group was inefficient, and only gave trace of **3bd** with most of aryl iodide protonated.

2.5 Application. To further demonstrate the synthetic utility of this method, we investigated its potential in the functionalization of molecules derived from complex biologically active compounds (Scheme 3). Substrates derived from peptides, which have always been problematic in transition-metal catalysis,[18] are tolerated under our conditions, and enantioenriched 2,3-dihydrobenzofuran was incorporated with 78% yield and 97% de (**4**). Indometacin is a prescription medication used to reduce fever, pain, and stiffness from

Scheme 3. Catalytic functionalization of complex molecules[a]

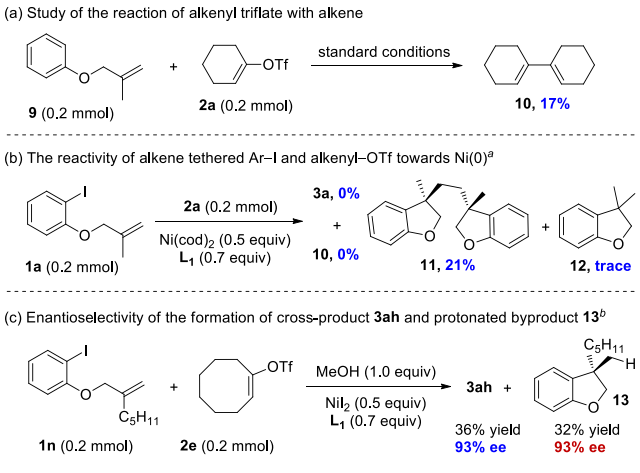


[a]See conditions in Table 1, entry 1, but **1a** (1.8 equiv) was used. [b]**1a** (3.0 equiv) was used.

inflammation.[19] The reactions of indometacin derivatives with **1a** gave enantioenriched products **5** and **6** with excellent enantioselectivity. The reactions of triflated steroids also proceeded well (**7**, **8**).

2.6 Mechanistic Investigation and Proposed Mechanism. Alkenyl–OTf was reported to be more reactive than Ar–I toward oxidative addition to Pd(0).[20] To establish whether the reaction starts with the activation of alkenyl–OTf or Ar–I in our reaction, a number of control experiments were conducted. The reaction of **9** with **2a** gave no cross-product, along with 17% of alkenyl dimer **10**, suggesting that an intermolecular migratory insertion of unactivated alkene into the alkenyl–Ni bond is not favored under our conditions (Scheme 4a). In the absence of Mn, the reaction of **1a** and **2a** with Ni(0) (0.5 equiv) afforded dimer **11** with 21% yield, leaving alkenyl–OTf intact (Scheme 4b). Moreover, the reaction of **1n** with **2e** gave the desired product **3ah** and protonated byproduct **13** with the same enantioselectivity (Scheme 4c). These results support the reaction pathway that involves activation of Ar–I with Ni(0), intramolecular migratory insertion, and reductive coupling with alkenyl–OTf.

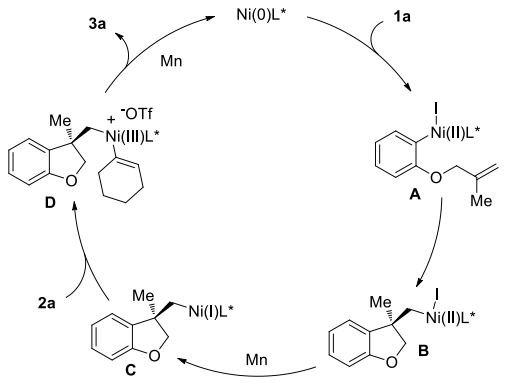
Scheme 4. Mechanistic investigation



[a]Standard conditions, but $Ni(cod)_2$ (0.5 equiv) and **L1** (0.7 equiv) were used and no Mn. [b]Standard conditions, but NiI_2 (0.5 equiv), **L1** (0.7 equiv), and MeOH (1.0 equiv) were used.

Although a detailed mechanism for this reaction is yet to be established, based on the above results and reported work, we tentatively suggest the catalytic cycle shown in Scheme 5. The reaction of Ar–I with Ni(0) might give intermediate **A**, which undergoes an enantioselective migratory insertion process to afford complex **B**. Reduction of **B** with Mn, followed by oxidative addition with **2a** and reductive elimination, would afford the cross-product **3a**.[21]

Scheme 5. Proposed mechanism



3. CONCLUSION

In summary, we have developed the first catalytic asymmetric aryl-alkenylation reaction of unactivated alkenes by using a cross-electrophile method. This reaction proceeds under mild conditions at room temperature using equimolar amounts of coupling fragments, and easily accessible chiral pyrox ligand was used to obtain products with enantioselectivity up to more than 99% ee. The synthetic utility of this method has been demonstrated by enabling the modification of biologically active complex molecules such as peptides, indomethacin, and steroids. This method showcases the potential of using cross-electrophile strategies to access complex chiral structures, wherein the incorporated alkene group will be useful to further increase molecular complexity. Further expansion of the scope of the asymmetric cross-electrophile difunctionalization reaction is ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

General information, experimental procedures, new compound characterization, crystallographic data (CIF), spectroscopic data, HPLC chromatograms and NMR spectra are provided in the Supporting Information. This material is available free of charge on the ACS Publication website.

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Notes

The authors declare no competing financial interests.

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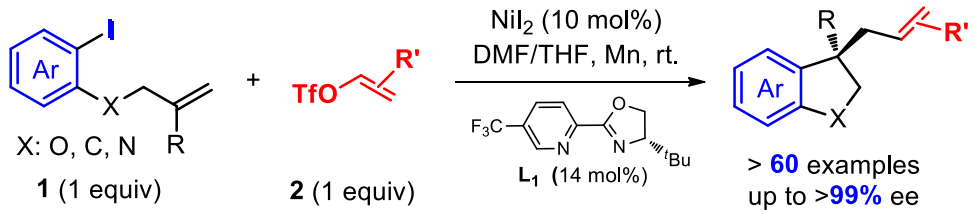

- enantioselective cross-electrophile addition
- easily accessible chiral ligand
- carbo-alkenylation
- equal amount of electrophiles
- gram-scale reaction