Three-Component Asymmetric Ni-Catalyzed 1,2-Dicarbofunctionalization of Unactivated Alkenes via Stereoselective Migratory Insertion

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ABSTRACT: An asymmetric 1,2-dicarbofunctionalization of unactivated alkenes with aryl iodides and aryl/alkenylboronic esters under nickel/bioxazoline catalysis is disclosed. A wide array of aryl and alkenyl nucleophiles are tolerated, furnishing the products in good yield and with high enantioselectivity. In addition to terminal alkenes, 1,2-disubstituted internal alkenes participate in the reaction, establishing two contiguous stereocenters with high diastereoselectivity and moderate enantioselectivity. A combination of experimental and computational techniques shed light on the mechanism of the catalytic transformation, pointing to a closed-shell pathway with an enantiodetermining migratory insertion step, where stereoinduction arises from synergistic interactions between the sterically bulky achiral sulfonamide directing group and the hemilabile bidentate ligand.

KEYWORDS: Enantioselective catalysis, alkene, diarylation, nickel, sulfonamide

Over the past decade, transition-metal-catalyzed 1,2-dicarbofunctionalization of alkenes (or conjunctive cross-coupling) has advanced rapidly,1a–d Nickel, a base metal, offers advantages in this reaction paradigm due to its inherent resistance to β-H elimination and ability to undergo one- or two-electronic redox processes.1e 1,2-Dicarbofunctionalization forms two adjacent C(sp³)–C bonds from an alkene, making it a potentially powerful tool in stereoselective synthesis. Nevertheless, fully intermolecular (i.e., three-component) asymmetric Ni-catalyzed dicarbofunctionalization of alkenes remains underdeveloped, with existing reports largely limited to radical processes with activated alkenes.2a-b Herein, by leveraging steric interactions between the achiral directing group and chiral hemilabile N,N-ligand during intermolecular migratory insertion, we demonstrate three-component, enantioselective 1,2-diarylation and 1,2-aryalkenylation of unactivated alkenes through a closed-shell Ni(0)/Ni(II) mechanism.

Prior work in enantioselective, nickel-catalyzed 1,2-dicarbofunctionalization has focused predominantly on intramolecular (i.e., two-component) couplings in which stereoselectivity is controlled during cyclative migratory insertion or reductive elimination (Scheme 1A and 1B).1,2b–3a In addition, Morken disclosed an intermolecular version in which acyclic secondary alcohols are accessed in high enantioselectivity (Scheme 1C).2b

![Diagram A](image1)

**A. Asymmetric Two-Component 1,2-Dicarbofunctionalization**
- Stereoselective Migratory Insertion (Cyclization)
  - [C]-M
  - [C]-X
  - [C]-[N*]
  - [C]-[C]

**B. Asymmetric Two-Component 1,2-Dicarbofunctionalization**
- Stereoselective Reductive Elimination
  - [C]-[C]
  - [C]-M
  - [C]-[N*]
  - [C]-[C]

**C. Asymmetric Three-Component 1,2-Dicarbofunctionalization**
- Stereoselective Reductive Elimination
  - [C]-[C]
  - [C]-M
  - [C]-[N*]
  - [C]-[C]

**D. This Work: Asymmetric Three-Component 1,2-Dicarbofunctionalization**
- Stereoselective Migratory Insertion
  - [C]-[C]
  - [C]-M
  - [C]-[N*]
  - [C]-[C]

L² = chiral hemilabile bidentate o-donor

![Diagram B](image2)

**Diagram B**
- DG = chiral hemilabile bidentate o-donor
- rapid construction of two stereocenters

![Diagram C](image3)

**Diagram C**
- DG = chiral hemilabile bidentate o-donor
- rapid construction of two stereocenters

![Diagram D](image4)

**Diagram D**
- DG = chiral hemilabile bidentate o-donor
- rapid construction of two stereocenters
two chiral centers in one elementary step. Our group has previously reported the use of native directing groups for 1,2-dicarbofunctionalization of unactivated alkenes via nonradical pathways. We hypothesized that the protected alkanyl amine substrates would be excellent contenders for the intermolecular asymmetric 1,2-dialylation of unactivated alkenes due to the strong σ-donating character nitrogen towards nickel and the potential for facile directing group (DG) steric tuning. To this end, we report the identification of sterically bulky aryl sulfonamides as uniquely effective directing groups in asymmetric 1,2-dialylation of alkenes under nickel/bioxazoline (biOx) ca-

Table 1. Optimization of asymmetric 1,2-dialylation reaction.

<table>
<thead>
<tr>
<th>entry</th>
<th>deviation from standard conditions (DG)</th>
<th>%Yield 2a</th>
<th>e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1 instead of L9</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>L2 instead of L9</td>
<td>30</td>
<td>52:48</td>
</tr>
<tr>
<td>3</td>
<td>L3 instead of L9</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>L4 instead of L9</td>
<td>16</td>
<td>74:26</td>
</tr>
<tr>
<td>5</td>
<td>L5 instead of L9</td>
<td>12</td>
<td>52:48</td>
</tr>
<tr>
<td>6</td>
<td>L6 instead of L9</td>
<td>40</td>
<td>12:88</td>
</tr>
<tr>
<td>7</td>
<td>L7 instead of L9</td>
<td>74</td>
<td>93:7</td>
</tr>
<tr>
<td>8</td>
<td>L8 instead of L9</td>
<td>74</td>
<td>94:6</td>
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<td>9</td>
<td>L10 instead of L9</td>
<td>74</td>
<td>94:6</td>
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<tr>
<td>10</td>
<td>L11 instead of L9</td>
<td>60</td>
<td>92:8</td>
</tr>
<tr>
<td>11</td>
<td>43 h instead of 72 h</td>
<td>63</td>
<td>95:5</td>
</tr>
<tr>
<td>12</td>
<td>no ligand</td>
<td>13</td>
<td>50:50</td>
</tr>
<tr>
<td>13</td>
<td>Ar′-B(OH)2 instead of Ph-B(nep)</td>
<td>60</td>
<td>91:9</td>
</tr>
<tr>
<td>14</td>
<td>Ar′-B(nep) instead of Ar′-B-OH2</td>
<td>n.d.</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>Ni(cod)(DMF) instead of Ni(cod)2</td>
<td>33</td>
<td>91:9</td>
</tr>
<tr>
<td>16</td>
<td>Ni(cod)TfO (without glovebox)</td>
<td>51</td>
<td>93:7</td>
</tr>
<tr>
<td>17</td>
<td>Ni(cod)(COCl, Ni(acac)2, or Ni(acac)3)</td>
<td>n.d.</td>
<td>-</td>
</tr>
<tr>
<td>18</td>
<td>10 mol% Ni(cod) instead of 20 mol%</td>
<td>66</td>
<td>95:5</td>
</tr>
<tr>
<td>19</td>
<td>1.5 equiv Ph-B(nep) instead of 3 equiv</td>
<td>n.d.</td>
<td>-</td>
</tr>
</tbody>
</table>

*Reactions performed on 0.1 mmol scale. *Reactions performed at 0 °C. *Enantiomeric ratio was not determined. *Product was synthesized from (Z)-alkene. *Product was synthesized from (E)-alkene.

Table 2. Electrophile and Nucleophile Scope.

<table>
<thead>
<tr>
<th>entry</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>X</th>
<th>%Yield 2a</th>
<th>e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>N</td>
<td>54%</td>
<td>90:10</td>
</tr>
<tr>
<td>2a</td>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>N</td>
<td>55%</td>
<td>96:4</td>
</tr>
<tr>
<td>3a</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>O</td>
<td>58%</td>
<td>90:10</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1a (0.1 mmol), i-BuOH/hexane 1:1 (0.1 M). *Values in parentheses are isolated yields. *Percentage yield by 1H NMR using CH2Br2 as the internal standard; n.d. = not detected. *nep = neopentylglycol.

There are several other examples of intermolecular, asymmetric, nickel catalyzed 1,2-dicarbofunctionalizations of alkenes via net reductive catalytic processes, which all operate through a stereoselective radical capture mechanism. The Diao, Chu, and Nevada groups have shown that styrenes, enamides, and allylic esters are competent substrates for this process (Scheme 1C). While radical-based approaches are valuable, they only allow construction of one stereocenter and are restricted to activated alkenes and reactants that benefit from radical stabilization. In contrast to a radical-based approach, we sought to develop enantioselective 1,2-diarlylation based on an enantiodetermining migratory insertion step that generates...
systematically surveyed a homoallyl amine substrate bearing a selection of different sulfonil groups at a low temperature (Table 1). The examination of the electronic series of para-substituted arylsulfonil groups DG1–4 resulted in low to excellent product yields with moderate enantioselectivities. The benzylsulfonil group DG5 gave the product with slightly higher enantioselectivity. Sterically bulky arylsulfonil groups bearing the 2,4,6-trisubstituted pattern such as mesityl DG6 demonstrated good enantioselectivity, and 2,4,6-tricyclohexylbenzene sulfonyl group DG7 gave a leap in enantioselectivity but suffered in product yield. Gratifyingly, the 2,4,6-triisopropylsulfonyl benzene sulfonyl group (Tris or Trisyl) DG8 provided 1,2-diarylated product 2a in good yield with excellent enantio- and regioselectivity, and its absolute configuration as the (S)-enantiotomer was confirmed by single-crystal X-ray diffraction. Other mono- and bisoxazoline ligands were also tested. The commonly employed Bn-BOX L1, Bn-PyBOX L2, and Bn-MOX L4 ligands all gave product in trace amounts, while Bn-PyrOX L3 ligands afforded the product in low yield as a nearly racemic mixture (Entries 1–4). The biOX ligands L5 and L6 that were previously used in asymmetric nickel catalysis by Diao2c and Nevada3d afforded product in low yields with poor enantioselectivities, highlighting the importance of the benzyl arm of the biOX ligand for this particular asymmetric reaction (Entries 5 and 6). This requirement is further exemplified with analogues of Bn-biOX L8, L10, and L11 that afforded the 1,2-diarylated product with comparable enantioselectivities; however, they gave diminished yields (Entries 8–10). It is important to note that while (S)-Bn-biOX analogue L7 gave product in moderate yield and good enantioselective ratio, the sense of stereoinduction switched to favor of the (R)-enantiotomer (Entry 7). Other Bn-biOX analogues with structurally diverse features, chiral electron-deficient olefin (EDO) ligands, and a chiral diamine ligand were all surveyed as well, but Bn-biOX L9 remained superior in both product yield and enantioselectivity.9

Performing the reaction for a shorter time resulted in a lower yield but excellent enantioselectivity (Entry 11). Exclusion of Bn-biOX ligand afforded racemic product in 13% yield indicating the presence of a modest background reaction (Entry 12). Use of arylboronic acid in place of the arylboronic ester resulted in a lower yield, while good enantioselectivity was still obtained (Entry 13). The corresponding aryl bromide electrophile 1-bromo-4-isopropoxybenzene was unreactive, and other nickel precatalysts, such as Ni[(cod)(DQ), NiCl2, Ni(acac)2, and NiBr₂·glyme, were ineffective; however, Ni[(cod)(DMFU)] afforded product in 33% with good enantioselectivity (Entries 14,15,17). One of the newly developed air-stable Ni(0) precatalysts from our group, Ni[(cod)TO₄ (TO₄ = diethyl acenaphtho[1,2-c]thiophene-7,9-dicarboxylate 8-oxide), allowed the reaction to be performed with good yield and enantioselectivity without an inert atmosphere glovebox (Entry 16).10 Lower catalyst loading resulting in a lower yield, while high enantioselectivity was maintained (Entry 18). Lowering the loading of coupling partners to 1.5 equivalents completely shut down the reaction (Entry 19).

Next, the scope of electrophile and nucleophile coupling partners was evaluated (Table 2). In terms of the electrophile scope, electron-donating groups at the para position of the aryl iodide gave the highest enantioselectivities (2b–e, 2h–j, 2p, 2q) with variable yields. (Product 2q was also obtained at 0 °C in 57% with 96:4 e.r., see Table S6 in SI.) Lower enantioselectivities and good to excellent yields were observed with electron-neutral and -donating groups at the para position of the aryl iodides (2k–o) (ρ = −0.844 at −10 °C and ρ = −0.750 at 0 °C).11 Even though aryl iodides with electron-donating groups on the meta and ortho positions of the aryl iodides (2f, 2g) gave 1,2-diarylated product in good to excellent yields, enantioselectivity was diminished. With regards to the nucleophile scope, changing the electronic properties of the para substituent on the arylboronic ester had minimal impact on the enantioselectivity (ρ = 0.012 at −10 °C).12 It is worth noting that electron-donating and -neutral or weakly electron-withdrawing substituents on the para position of the arylboronic esters (2r–v, 2x–z) afforded higher yields than the example with electron-withdrawing 4-(trifluoromethyl)phenylboronic ester (2w) as the nucleophile. Both 3-thiophenyl- and 3-furanylboronic esters

Scheme 2. Mechanistic Investigations, Proposed Catalytic Cycle and Additional Experiments. (2aa, 2ab) were tolerated in the reaction conditions giving product with good enantioselectivities albeit with low to good yields. Alkenyboronic ester nucleophiles were also surveyed because they have not previously been used in three-component asymmetric dicarbofunctionalization.2 (E)-[4-Methyl]styrylboronic acid neopentyl glycol ester afforded 1,2-aralkylenated product in excellent yield with good enantioselectivity (2ac). Other (E)-alkenyl boronic esters such as (E)-[3-phenylprop-1-en-1-yl]boronic ester and (E)-[3-(3,3-dimethylbut-1-en-1-yl)]boronic ester afforded enantioenriched products (2ad and 2ae) with good enantioselectivity and low to good yields. A 1,1-disubstituted boronic ester, namely 1-phenylvinylboronic ester, was competent in the optimized reaction giving product (2af) in moderate yield with good enantioselectivity. Finally, cyclohexenylboronic ester can be used as a coupling partner to furnish 1,2-aryalkylated product (2ag) with good enantioselectivity but low yield.
We then examined alkene substrates that are typically challenging in 1,2-diarylation. We found that (Z)- and (E)-internal alkenes with the trisyl group gave product in low yields under the optimized reaction conditions. Pleasingly, (Z)- and (E)-internal alkenes with less hindered DGG afforded products (2ah and 2ai) in moderate yields with moderate enantioselectivites and excellent diastereoselectivities. Various 1,1-disubstituted terminal alkenes were found to be ineffective. No reaction was observed with alkenyl sulfonamides with methyl substitution at the α- or β-position and methoxycarbonyl substitution at the α-position, illustrating the sensitive nature of the alkyl nickelacycle intermediate to substitution along the chain.

To probe the importance of the N–H bond of the trisyl directing group, control experiments of both trisyl sulfonate 1r and N-methylated trisyl homoallyl sulfonamide 1s were conducted, and in both cases, no reaction occurred (Scheme 2A). We were also curious about the effect of alkene distance on enantioselectivity (Scheme 2B). Either shortening of the alkyl chain to trisyl-protected allyl amine or elongating the alkyl chain to either trisyl-protected pentenyl or hexenyl amine gave no product. We hypothesize that the allyl amine substrate is not reactive because of the sterically strained 4-membered N-bound nickelacycle, whereas the bis-homoallyl and bis-homoallyl amine substrates would proceed via a less favorable 6- or 7-membered nickelacycle in comparison to the 5-membered nickelacycle with the model substrate.

To test whether the reaction proceeds via a radial intermediate, we conducted a radial clock experiment with diene 1w and obtained 1,2-diarylated product 2an in 12% yield with moderate diastereoselectivity (Scheme 2C). The cyclized diarylated product 2ao was not observed, indicating that this process is unlikely to proceed through an alkyl radical intermediate. Based on experimental and computational data, the general catalytic cycle likely follows a mechanism similar to that of our previous report (Scheme 2D).

The catalytic cycle starts with low valent Ni(n)(Bn-biOx) complex undergoing oxidative addition into the aryl iodide electrophile, followed by alkene- and N-coordination of the trisyl-protected alkyl amine. Then, a stereoselective migratory insertion follows with the formation of a 5-membered Ni(n)(Bn-biOx)(alkyl)(sulfonamide) metallacycle. Subsequent transmetalation with aryloboronic ester nucleophile affords a Ni(n)(Bn-biOx)(alkyl)aryl complex which undergoes reductive elimination to furnish the enantioenriched 1,2-diarylated product.

We next focused on establishing a method for removing the directing group to form enantioenriched 1,2-diarylated amines that would otherwise be difficult to procure. The standard product 2a was synthesized on larger scale in 73% yield (1 mmol, 0.4 g isolated) and with 95:5 e.r. (Scheme 2E). Then 2a was subjected to a trisyl deprotection method with Mg turnings, Ti(Oi-Pr)4, and TMSCI, leading to the removal of the trisyl group affording free amine 2ap in 79% yield with preservation of the enantiomeric ratio. Beyond sulfonamides, we were eager to identify a native carbonyl directing group that would participate in enantioselective diarylation. Gratifyingly, when 3-butenic acid was used, 1,2-diarylated product 2aq was obtained with good enantioselectivity, albeit low product yield (Scheme 2F).

We performed DFT calculations at the M06/SDD-6-311++G(d,p)//SMD(1-BuOH)/B3LYP-D3(BJ)/SDD-6-31+G(d,p) level of theory (see SI for Computational Methods) to investigate the reaction mechanism and the role of the Bn-biOx ligand on enantioinduction. Because of the potentially hemilabile nature of the Bn-biOx ligand and the conformational flexibility of its benzyl groups, a careful conformational analysis was performed using a workflow which consists of CREST/GFN2-xTB16 conformational sampling followed by DFT geometry optimizations of low-energy transition state conformers (see SI for details). The computed reaction energy profile is shown in Figure 1. The reaction proceeds via oxidative addition of phenyl iodide via TS1 to give Ni(n) intermediate 4, followed by ligand exchange to replace the iodide anion with the deprotonated sulfonamide substrate 1a to form a more stable Ni(n) complex 5. Upon coordination of the alkene to the nickel to form π-alkene complex 6, alkene migratory insertion via TS2a leads to the 5-membered nickelacycle 7. The reaction then proceeds via transmetalation with aryloboronic ester 8 (TS3) and reductive elimination (TS4) to give product 2n.

The computed reaction energy profile revealed several mechanistic features that would influence enantioinduction. First, although the alkene migratory insertion step has a low kinetic barrier (5.6 kcal/mol with respect to 5), it is exothermic and irreversible. Thus, this step determines the enantioselectivity. This finding is consistent with the Hammett data that suggests the aryl group from the electrophile and not the nucleophile is involved in the enantiodetermining step. Second, all Ni(n) intermediates and transition states have square-planar geometry. In these complexes, the Bn-biOx ligand binds to the Ni center with either one or two oxazoline motifs depending on the available coordination sites. This hemilabile behavior is consistent with the observation that more rigid, strongly coordinating BOX ligands are ineffective. Isomers involving dissociation of the sulfonamide directing group, rather than one of the oxazoline arms, are less favorable (see Figure S6 in SI). In the transmetalation transition state (TS3), the Bn-biOx ligand completely dissociates (see Figure S6 in SI), and then re-coordinates to the nickel center prior to the reductive elimination step (TS4). The relatively facile partial or complete dissociation of the Bn-biOx ligand kinetically promotes key elementary steps from intermediate 5 and 7.
Because of the monodentate coordination mode of the Bn-biOx ligand during the enantioselectivity-determining migratory insertion transition state, the mode of enantioinduction is distinct from common enantioselective migratory insertion processes involving C2-symmetric chiral ligands. A number of low-energy conformers of the migratory insertion transition states were located (14 within 3.0 kcal/mol of the lowest-energy TS). Among these, the most stable transition states (TS2a and TS2b) leading to the S and R enantiomers have an activation free energy of 5.6 and 6.9 kcal/mol from 5, respectively (Figure 2). The computed er from the Boltzmann averages of all migratory insertion TS conformers (see Table S8 in SI) is 87:13 favoring the S enantiomer, which is in agreement with the experimental value (88:12). In the preferred transition state TS2a, the bulky trisyl group is placed in a region less occupied by the (S)-Bn-biOx ligand, whereas greater steric repulsions between the trisyl group and the benzyl group on the associated arm of the Bn-biOx ligand was observed in the less stable transition state TS2b (see Figure S5 in SI for similar steric effects in other conformers of TS2b). In addition, the benzyl group on the dissociated arm of the Bn-biOx ligand forms favorable C–H/π interactions with the alkenyl group in TS2a, further highlighting the importance of the benzyl group in controlling the enantioselectivity.

In summary, a three-component, asymmetric, Ni-catalyzed 1,2-diarylation of trisyl-protected alkenyl amines with aryl iodides and aryl/alkenylboronic esters was developed. This method tolerates a variety of coupling partners; electron-donating electrophiles give the highest enantioselectivities while nucleophiles that contain electron-withdrawing and electron-donating substituents are well accommodated. Alkenyl nucleophiles are successful in the developed transformation, which is significant because they have not been demonstrated previously in three-component asymmetric Ni-catalyzed couplings. 1,2-Disubstituted (E)- and (Z)-alkenes are competent under the optimized conditions, affording the desired products in moderate yields and enantioselectivities. After conducting the asymmetric 1,2-diarylation, deprotection of the trisyl group can be performed to afford enantioenriched 1,2-diarylated free amines. Computational studies shed light on the mechanism of stereoinduction and the roles of the DG and ligand, establishing a conceptual framework for future development of enantioselective 1,2-diarylation as a tool in asymmetric synthesis.

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**Author Contributions**

*These authors contributed equally.*
Cyclization/Cross Coupling with Alkyl Electrophiles
Radical Relayed Reductive Coupling. We thank Dr. Jake Bailey for X-ray crystallographic analysis (USCD) and Dr. Michael A Schmidt (BMS) for helpful discussions.

REFERENCES

[(1)] For representative reviews on conjunctive cross-coupling, see:


cat. [Ni] Bn-bιOx ligand

- >30 examples
- up to 92% ee
- closed-shell mechanism

unactivated terminal and internal alkenes

stereoselective migratory insertion