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

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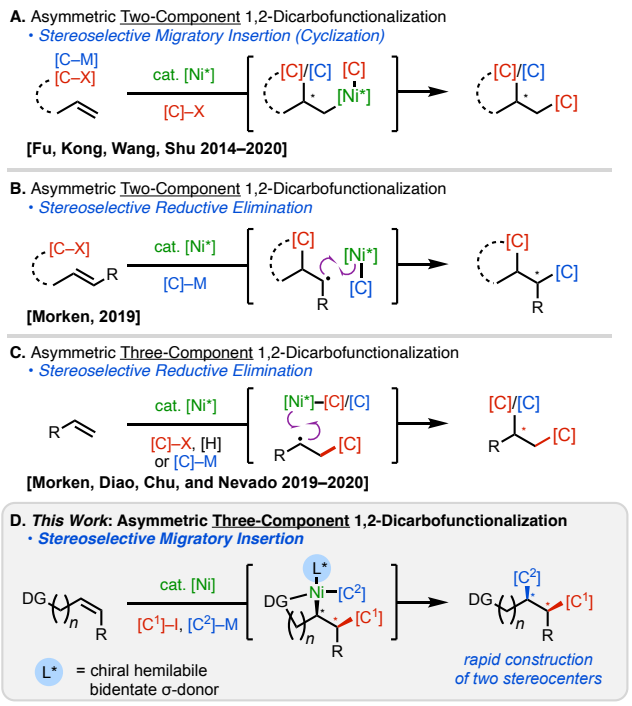
***ABSTRACT*:** An asymmetric 1,2-dicarbofunctionalization of unactivated alkenes with aryl iodides and aryl/alkenylboronic esters under nickel/bioxazoline catalysis is disclosed. A wide array of aryl and alkenyl nucleophiles are tolerated, furnishing the products in good yield and with high enantioselectivity. 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*

Introduction.

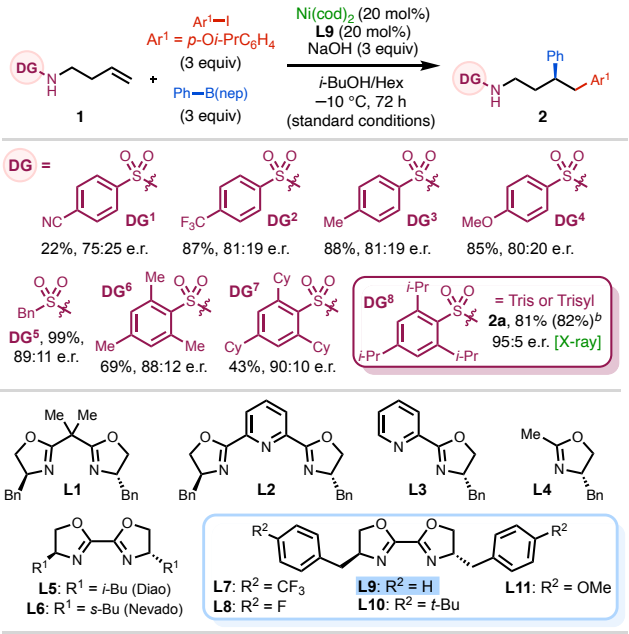
Over the past decade, transition-metal-catalyzed 1,2-dicarbofunctionalization of alkenes (or conjunctive cross-coupling) has advanced rapidly.[1a–d] Nickel, a base metal, offers advantages in this reaction paradigm due to its inherent resistence to β-H elimination and ability to undergo one- or two-electronic redox processes.[1e] 1,2-Dicarbofunctionalization forms two adjacent C(sp^3)–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] 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-arylalkenylation 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).[1f,2b,3-6] In addition, Morken disclosed an intermolecular version in which acyclic secondary alcohols are accessed in high enantioselectivity (Scheme 1C).[2b] There are several other examples of intermolecular, asymmetric, nickel catalyzed



Scheme 1. Precedents and synopsis of this work

Table 1. Optimization of asymmetric 1,2-diarylation reaction.[a]

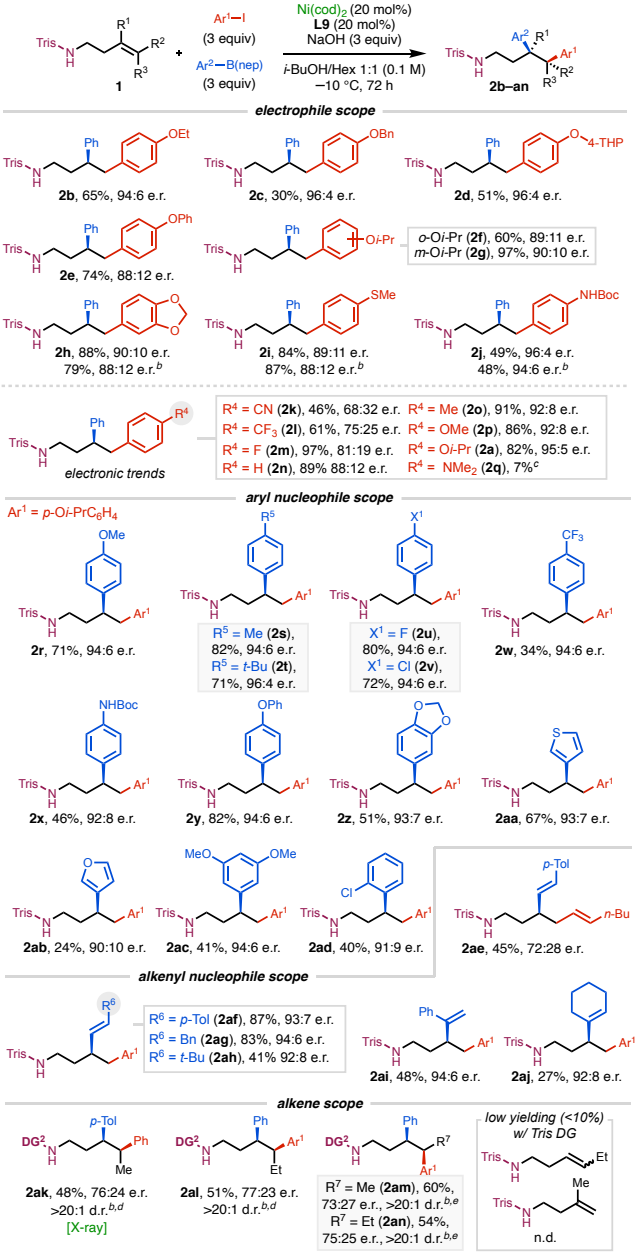


entry	deviation from standard conditions (**DG[8]**)	%Yield **2a**[c]	e.r.
1	**L1** instead of **L9**	<5	- -
2	**L2** instead of **L9**	30	52:48
3	**L3** instead of **L9**	<5	- -
4	**L4** instead of **L9**	<5	- -
5	**L5** instead of **L9**	16	74:26
6	**L6** instead of **L9**	12	52:48
7[d]	**L7** instead of **L9**	40	12:88
8	**L8** instead of **L9**	74	93:7
9	**L10** instead of **L9**	74	94:6
10	**L11** instead of **L9**	60	92:8
11	43 h instead of 72 h	63	95:5
12	no ligand	13	50:50
13	$Ph–B(OH)_2$ instead of Ph–B(nep)	60	91:9
14	Ar^1–Br instead of Ar^1–I	n.d.	- -
15	Ni(cod)(DMFU) instead of $Ni(cod)_2$	33	91:9
16	Ni(cod)TO[A] (without glovebox) instead of $Ni(cod)_2$	51	93:7
17	Ni(cod)(DQ), $NiCl_2$, $Ni(acac)_2$, or $NiBr_2$•glyme instead of $Ni(cod)_2$	n.d.	- -
18	10 mol% $Ni(cod)_2$ instead of 20 mol%	65	95:5
19	1.5 equiv Ph–B(nep), Ar^1–I and NaOH instead of 3 equiv	48	95:5

[a]Reaction conditions: **1a** (0.1 mmol), *i*-BuOH/hexane 1:1 (0.1 M)' nep = neopentylglycol. [b]Values in parentheses are isolated yields. [c]Percentage yield by ^{1}H NMR using CH_2Br_2 as the internal standard; n.d. = not detected. [d](*R*,*R*)-**L7** was used.

1,2-dicarbofuncationalizations of alkenes via net reductive catalytic processes, which all operate through a stereoselective radical capture mechanism. The Diao,[2c] Chu,[2a] and Nevado[2d] 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 nickel-catalyzed 1,2-diarylation based on an enantiodetermining migratory insertion step that generates two chiral centers in one elementary step, which would complement recent advances in palladium catalysis.[7,8] Our group has previously reported the use of native directing groups for 1,2-dicarbofunctionalization of unactivated alkenes via nonradical pathways.[9] We hypothesized that the protected alkenyl amine substrates would be excellent contenders for the intermolecular asymmetric 1,2-diarylation of unactivated alkenes due to the strong σ-donating character nitrogen towards nickel and the potential for facile directing group (DG) steric tuning.[9e] To this end, we report the identification of sterically bulky aryl sulfonamides as uniquely effective directing groups in asymmetric 1,2-diarylation of alkenes under nickel/bioxazoline (biOx) catalysis via a stereodetermining migratory insertion step (Scheme 1D).

Table 2. Electrophile and Nucleophile Scope.[a]



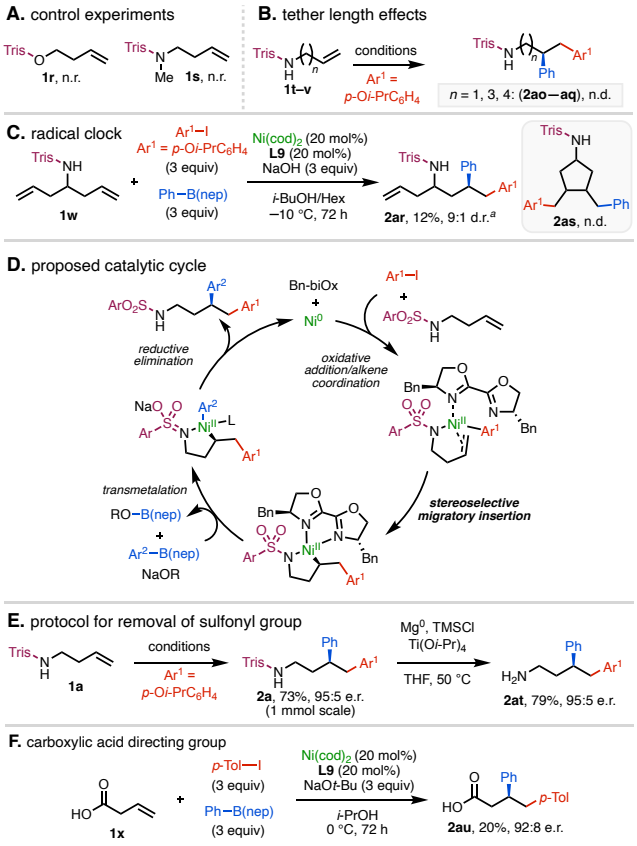
[a]Reactions performed on 0.1 mmol scale. [b]Reactions performed at 0 °C. [c]Enantiomeric ratio was not determined. [d]Product was synthesized from (*Z*)-alkene. [e]Product was synthesized from (*E*)-alkene.

Results and Discussion.

To commence the investigation, we selected 1-iodo-4-isopropoxybenzene and phenylboronic acid neopentyl glycol ester (PhB(nep)) as model coupling partners with commercially available (*S*)-benzyl biOx (Bn-biOx, **L9**) as the ligand and systematically surveyed a homoallyl amine substrate bearing a selection of different sulfonyl groups at a low temperature (Table 1). The examination of the electronic series of *para*-substituted arylsulfonyl groups **DG**[1–4] resulted in low to excellent product yields with moderate enantioselectivities. The benzylsulfonyl group **DG**[5] gave the product with slightly higher enantioselectivity. Sterically bulky arylsulfonyl groups bearing the 2,4,6-trisubstituted pattern such as mesityl **DG**[6] demonstrated good enantioselectivity, and 2,4,6-tricyclohexylbenzene sulfonyl group **DG**[7] gave a leap in enantioselectivity but suffered in product yield. Gratifyingly, the 2,4,6-triisopropylbenzene sulfonyl group (Tris or Trisyl) **DG**[8] provided 1,2-diarylated product **2a** in good yield with excellent enantio- and regioselectivity, and its absolute configuration as the (*S*)-enantiomer 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 Diao[2c] and Nevado[2d] 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 **L7**, **L8**, **L10**, and **L11** that afforded the 1,2-diarylated product with comparable enantioselectivities; however, they gave diminished yields (Entries 7–10). 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.[10]

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), $NiCl_2$, $Ni(acac)_2$, and $NiBr_2$•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)TO[A] (TO[A] = 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).[11] Lower loading of catalyst or coupling partners resulted in a lower yield, while high enantioselectivity was maintained (Entry 18, 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**) ($\rho = -0.844$ at –10 °C and $\rho = -0.750$ at 0 °C).[12] 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 ($\rho = 0.012$ at –10 °C).[13] 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 (**2aa**, **2ab**) were tolerated in the reaction conditions giving product with good enantioselectivities albeit with low to good yields. Both *meta*- and *ortho*-substituted arylboronic esters afforded 1,2-diarylated product in moderate yield with good to excellent enantioselectivities (**2ac** and **2ad**). Alkenylboronic ester nucleophiles were also surveyed because they have not previously been used in three-component asymmetric dicarbofunctionalization.[2] Use of (*E*)-(4-methyl)styrylboronic acid neopentyl glycol ester led to 1,2-dialkenylated product **2ae** in moderate yield and with comparatively low enantioselectivity and to 1,2-arylalkenylated product **2af** in excellent yield and with good enantioselectivity. Other (*E*)-alkenyl boronic esters such as (*E*)-(3-phenylprop-1-en-1-yl)boronic ester and (*E*)-(3,3-dimethylbut-1-en-1-yl)boronic ester afforded enantioenriched products (**2ag** and **2ah**) 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 (**2ai**) in moderate yield with good enantioselectivity. Finally, cyclohexenylboronic ester can be used as a coupling partner to furnish 1,2-arylalkenylated product (**2aj**) with good enantioselectivity but low yield.



Scheme 2. Mechanistic Investigations, Proposed Catalytic Cycle and Additional Experiments. [a]Unreacted starting materials remained.

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, switching to less hindered **DG**[2] enabled reactivity with both (*Z*)- and (*E*)-internal alkenes, with diarylated products **2ak**–**2an** formed as single diastereomers, albeit with moderate yields and ee values. The major enantiomer of **2ak** could be isolated using preparative chiral SFC, and its absolute stereochemistry was confirmed by single-crystal X-ray diffraction. 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.[14]

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 alkenyl chain to trisyl-protected allyl amine or elongating the alkenyl 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,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 radical intermediate, we conducted a radical clock experiment with diene **1w** and obtained 1,2-diarylated product **2ar** in 12% yield with moderate diastereoselectivity (Scheme 2C). The cyclized diarylated product **2as** 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).[9e] The catalytic cycle starts with low valent Ni^0(Bn-biOx) complex undergoing oxidative addition into the aryl iodide electrophile, followed by alkene- and *N*-coordination of the trisyl-protected alkenyl amine. Then, a stereoselective migratory insertion follows with the formation of a 5-membered Ni^{II}(Bn-biOx)(alkyl)(sulfonamido) metallacycle. Subsequent transmetalation with arylboronic ester nucleophile affords a Ni^{II}(Bn-biOx)(alkyl)(aryl) species which undergoes reductive elimination to furnish the enantioenriched 1,2-diarylated product.[9c–e]

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(O*i*-Pr)$_4$, and TMSCl, leading to the removal of the trisyl group affording free amine **2at** in 79% yield with preservation of the enantiomeric ratio.[15] Beyond sulfonamides, we were eager to identify a native carbonyl directing group that would participate in enantioselective diarylation. Gratifyingly, when 3-butenoic acid was used, 1,2-diarylated product **2au** 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(*i*-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.[16] Because of the potentially hemilabile nature of the Bn-biOx ligand[2d] and the conformational flexibility of its benzyl groups, a careful conformational analysis was performed using a workflow which consists of CREST/GFN2-xTB[17] 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^{II} intermediate **4**, followed by ligand exchange to replace the iodide anion with the deprotonated sulfonamide substrate **1a'** to form a more stable Ni^{II} 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 arylboronate 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(II) 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 S7 in SI). In the transmetalation transition state (**TS3**), the Bn-biOx ligand completely dissociates (see Figure S7 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**.

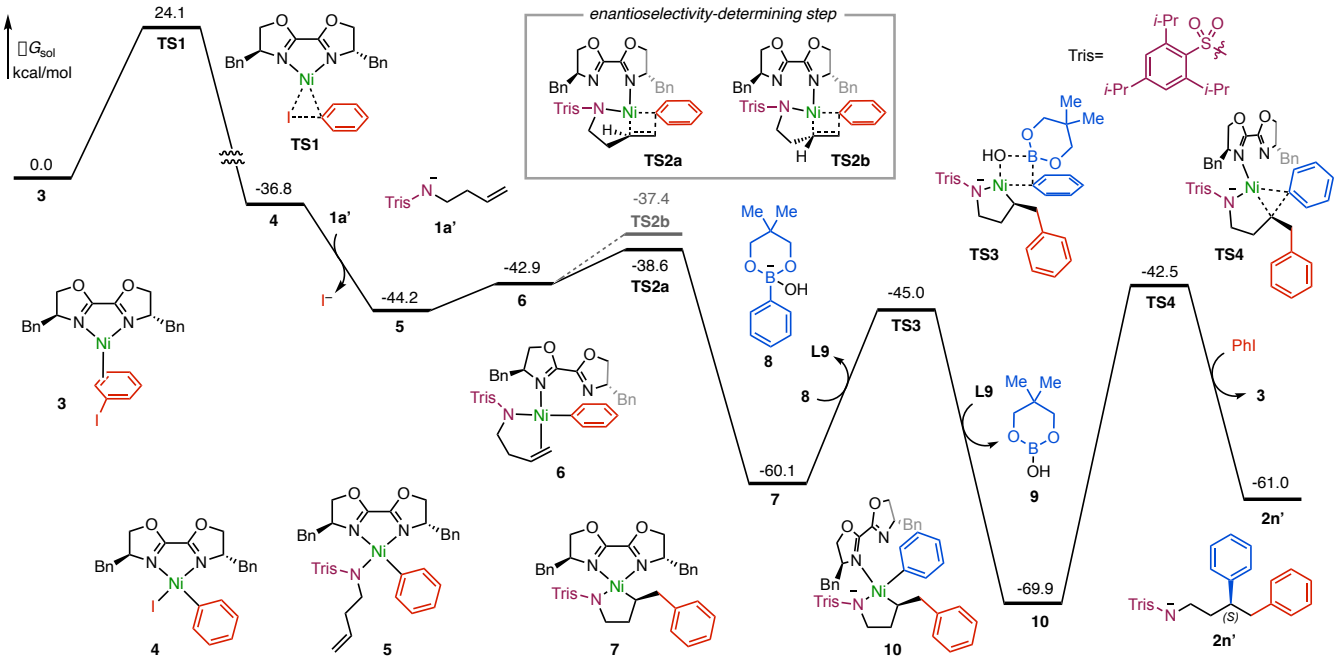


Figure 1. Computed reaction energy profile of the Ni-catalyzed 1,2-diarylation of alkene **1a**. All Gibbs free energies are with respect to the (**L9**)Ni^0(PhI) complex **3** and the deprotonated **1a'**.

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.[18] 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

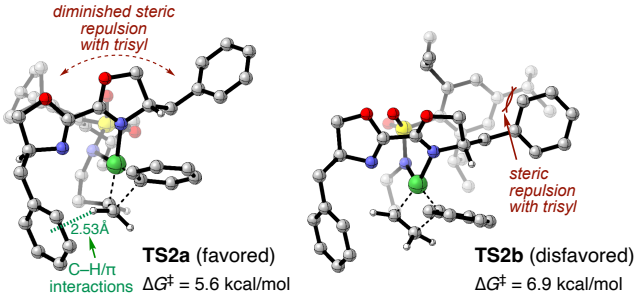


Figure 2. Enantioselectivity-determining migratory insertion transition states. Activation free energies are with respect to **5**.

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. The enantioselectivity with an electron-deficient (*p*-CN)C$_6$H$_4$I electrophile was also investigated computationally (see Figure S6 in the SI). Stronger T-shaped π/π interactions between the electron-deficient aryl group and the Bn group of the Bn-biOx ligand stabilize a low-energy TS conformer that leads to the minor enantiomeric product,[19] which slightly decreases the predicted enantioselectivity in agreement with the experimental data.

Conclusions.

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

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

Accession Codes

CCDC 2150217 and 2201810 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cam- bridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

ACKNOWLEDGMENT

This work was financially supported by the National Science Foundation (CHE-2102550) and Bristol Myers Squibb. We acknowledge the NSF for Graduate Research Fellowships (DGE-1842471, O.A. and DGE-1346837, J.D.) and the Kwanjeong Educational Foundation for a Graduate Fellowship (T.K.). We further thank Dr. Jake Bailey and Dr. Milan Gembicky for X-ray crystallographic analysis (UCSD) and Dr. Michael A. Schmidt (BMS) for helpful discussions.

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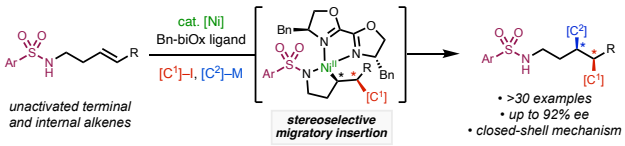
cat. [Ni]
Bn-biOx ligand
[C1]–I, [C2]–M
unactivated terminal
and internal alkenes
stereoselective
migratory insertion
• >30 examples
• up to 92% ee
• closed-shell mechanism