Nickel-Catalyzed 1,2-Diarylation of Simple Alkenyl Amides

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Supporting Information Placeholder

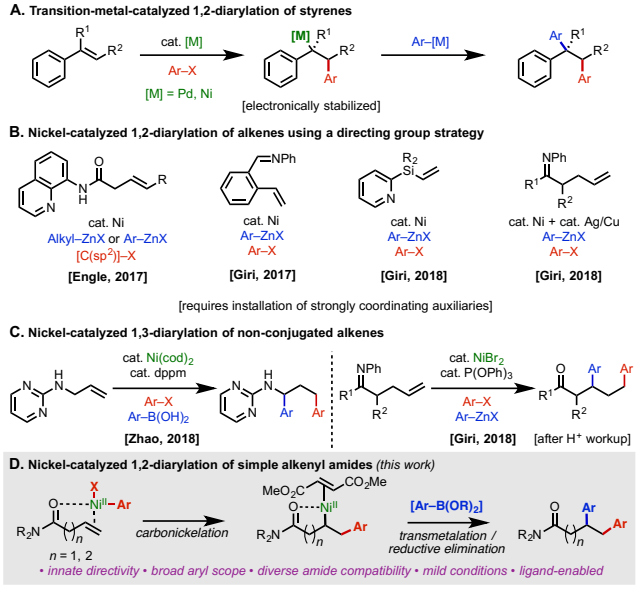
ABSTRACT: A nickel-catalyzed conjunctive cross-coupling of simple alkenyl amides with aryl iodides and aryl boronic esters is reported. The reaction is enabled by an electron-deficient olefin (EDO) ligand, dimethyl fumarate, and delivers the desired 1,2-diarylated products with excellent regiocontrol. Under optimized conditions, a wide range of amides derived from 3-butenoic acid, 4-pentenoic acid, and allyl amine are compatible substrates. This method represents the first example of regiocontrolled 1,2-diarylation directed by a native amide functional group. Computational analysis sheds light on potential substrate binding mode and the role of EDO ligand in the reductive elimination step.

Alkene starting materials serve as diversifiable chemical feedstocks for rapid build-up of molecular complexity.[1] From the perspective of synthetic chemists, the ability to regioselectively install two unique components across an alkene of interest is attractive. One approach toward alkene difunctionalization that has rapidly garnered interest in recent years is conjunctive cross-coupling, a strategy in which alkene starting materials can be used as ambiphilic reagents to unite various electrophiles and organometallic nucleophiles under transition metal catalysis.[2] In the context of regioselective 1,2-diarylation specifically, this potentially powerful synthetic strategy can be difficult to implement on electronically unactivated, non-conjugated alkenes.

Recent advances in transition-metal-catalyzed 1,2-diarylation of alkenes have generally relied on the formation of a stabilized alkylmetal intermediate after an initial migratory insertion event (Scheme 1). Due to the inherent reactivity of alkylmetal species, the alkene substrates are often limited to 1,3-dienes[3] or styrenes[4] that react to form electronically stabilized π-allyl or π-benzyl intermediates, respectively. In these cases, electronic stabilization allows for regiocontrolled addition of an aryl organometallic reagent to afford the desired 1,2-diarylated product. Several groups have made major contributions to styrene 1,2-diarylation under palladium and nickel catalysis, showcasing the ability of this method to lead to complex polyarylated alkanes (Scheme 1A).[4]

With non-conjugated alkenes it is more difficult to overcome undesired β-hydride elimination from the alkylmetal intermediates. As a consequence, the scope of non-conjugated alkenes via this mode of reactivity has been classically limited to special cases, such as norbornene-type substrates.[5] In an effort to employ more synthetically useful substrates, several research groups, including our own, have employed strongly coordinating directing groups tethered to the alkene to stabilize the putative alkylmetal species and facilitate selective 1,2-diarylation under nickel catalysis (Scheme 1B).[6] Though this approach has enabled robust 1,2-difunctionalization, the need to install and then remove the directing auxiliary detracts from the practicality of these methods. With more weakly coordinating directing groups,

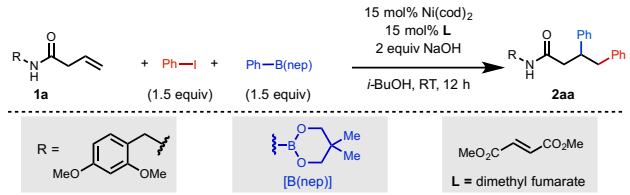
Scheme 1. Background and Synopsis of Current Work



alkylnickelacycles are prone to rapid β-hydride elimination/reinsertion, which the Zhao and Giri groups have cleverly exploited in 1,3-diarylation processes (Scheme 1C).[6c,7,8] Giri recently reported that 1,2-diarylation can be promoted in such systems through addition of copper or silver additives.[6e] It is important to note that alkyl radical addition to alkenes and interception with metalloradical species has also been shown to be a viable strategy toward 1,2-difunctionalization of non-conjugated alkenes,[14] but this strategy has not been demonstrated in the context of 1,2-diarylation. The goal of the present study was to develop an efficient alkene 1,2-diarylation directed by simple monodentate functional groups.

Our inspiration for this approach originated from a series of seminal publications by Fu and coworkers, in which simple amides and other carbonyl-containing compounds were used to effectively direct C–X oxidative addition and stabilize the resulting intermediate for a variety of enantioselective cross-coupling reactions under nickel catalysis.[9] Given our group's interest in nickel-catalyzed alkene difunctionalization,[10] we wondered if previously employed, strongly coordinating directing groups such as 8-aminoquinoline (AQ) could be replaced with simple amides. Practically speaking, this advance would be advantageous in that it would allow use of diverse amide directing groups, including those that are readily cleavable as well as those that are native to the target compound of interest. Conceptually, it would present the opportunity to engage weakly coordinating carbonyl directing groups, rather than more commonly used N(sp^2)-based directing groups, and to identify ancillary ligands that can bind to the open coordination site around nickel to facilitate key steps in catalysis.

Table 1. Variations from Standard Reaction Conditions[a]



Entry	variation from standard conditions	% Yield[b] **2aa**
1	none	92 (88)[c]
2	no ligand	n.d.
3	PPh_3 or PCy_3 instead of dimethyl fumarate	n.d.
4	bipyridine or phenathroline instead of dimethyl fumarate	n.d.
5	bromobenzene instead of iodobenzene	45
6	$PhB(OH)_2$ instead of PhB(nep)	78
7	PhBpin instead of PhB(nep)	65
8	dioxane instead of *i*-BuOH	40
9	1.0 equiv of both iodobenzene and PhB(nep) instead of 1.5 equiv	59
10	KOAc instead of NaOH	n.d.
11	10 mol% $Ni(cod)_2$	75
12	$NiCl_2$, $NiBr_2$, $Ni(acac)_2$, or NiI_2 instead of $Ni(cod)_2$	n.d.
13	$NiCl_2$, $NiBr_2$, $Ni(acac)_2$, or NiI_2 with Mn^0 instead of $Ni(cod)_2$	n.d.

[a]Reaction conditions: **1a** (0.1 mmol), 0.2 M *i*-BuOH. [b]Percentages represent ^{1}H NMR yields using CH_2Br_2 as internal standard unless noted otherwise; n.d. = not detected. [c]Parentheses represent isolated yield.

To initiate our investigation, we surveyed a range of monodentate amides and found that among many that were effective, electron-rich *N*-benzyl amides consistently gave high yields. For this reason, we elected to use 2,4-dimethoxy benzyl amide **1a** as the pilot alkene substrate, along with iodobenzene and phenylboronic acid neopentyl glycol ester (PhB(nep)) as coupling partners, and $Ni(cod)_2$ as precatalyst (Table 1). Considering the difficulty in promoting productive 1,2-diarylation with a weakly coordinating amide, we reasoned that an electron-withdrawing L-type ligand could potentially (1) prevent β-hydride elimination, (2) facilitate C–C reductive elimination, and (3) encourage substrate binding to the nickel catalyst. Electron-deficient olefins (EDOs) represent a unique class of ligands that have been demonstrated to enable various cross-coupling reactions by promoting the reductive elimination step and preventing β-hydride elimination.[11,12] To our delight, the use of dimethyl fumarate as ligand under optimized reaction conditions delivered the desired product in 88% isolated yield (Entry 1).[13] Interestingly, removal of the ligand or substitution for more commonly employed phosphine and bipyridyl-based ligands did not lead to the formation of the desired product, but instead gave ~25% of the biphenyl Suzuki–Miyaura product (Entries 2 and 3). Both free boronic acid and pinacol boronic esters also gave the corresponding product in 78% and 65% yield, respectively (Entries 5 and 6). Despite numerous attempts to use Ni(II) precatalysts, $Ni(cod)_2$ was ultimately the most competent nickel source for this reaction (Entries 11 and 12).

Having identified optimal conditions, we next sought to test the electrophile and nucleophile scope of this nickel-catalyzed 1,2-diarylation reaction (Table 2). First, we elected to evaluate the nucleophile scope using iodobenzene as the electrophile (**2a–2m**). With respect to the B(nep) component, both electron-donating and electron-withdrawing groups in the *para*-position gave the desired products in good to excellent yields (**2a–2f**). Tethered alcohol- (**2e**) and chloride-containing (**2f**) aryl fragments were also tolerated, allowing for further downstream diversification. Aryl nucleophiles with substituents at the *meta*-position (**2g–2l**) were also competent, including ketones (**2i**) and sulfones (**2k**). Given the potential sensitivity of the steric environment around the putative metalacycle, we were encouraged by the compatibility of *ortho*-Me substituted B(nep), which gave the desired product in 60% yield (**2m**).

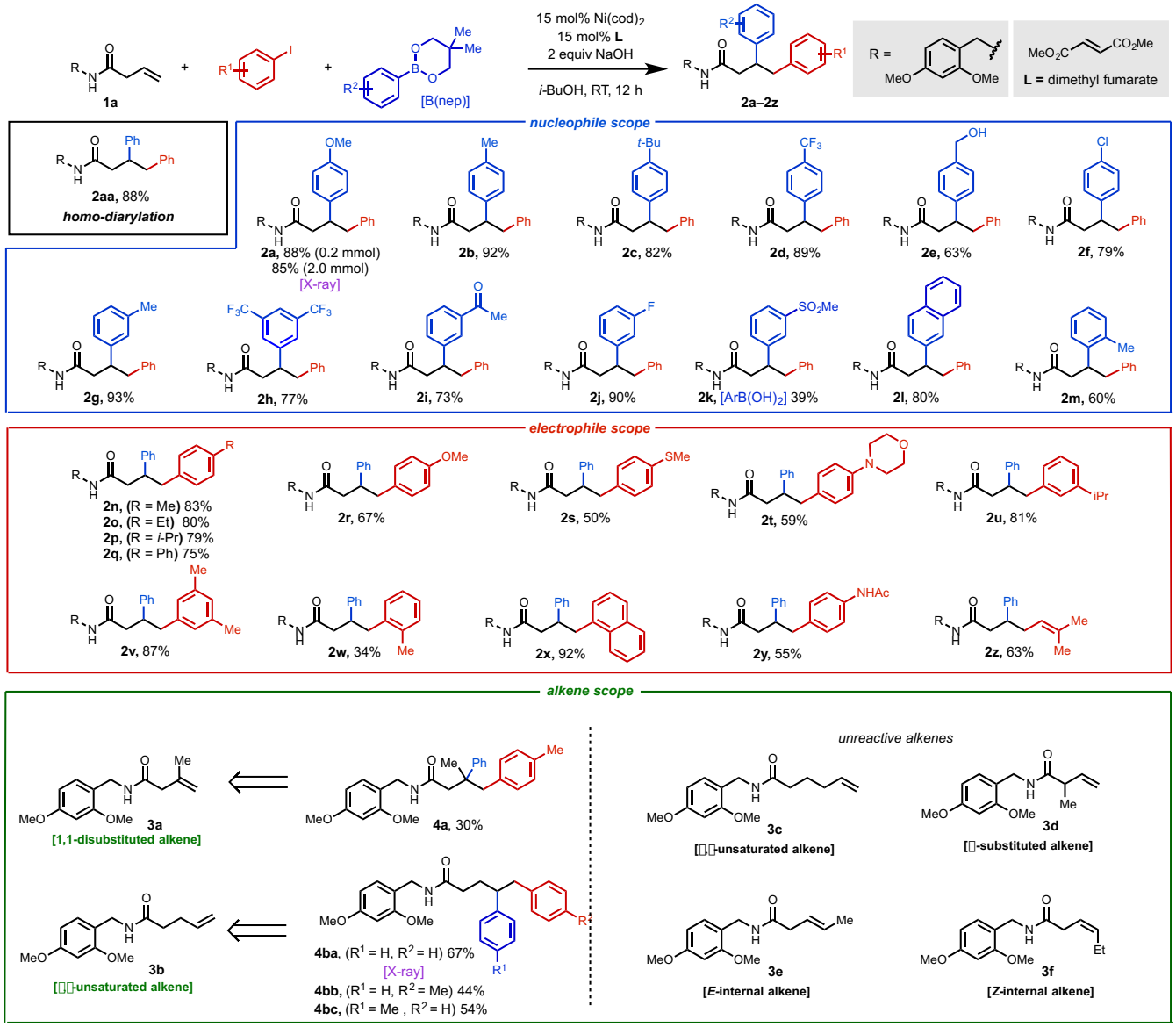
Next, we explored the electrophile scope using PhB(nep) as the nucleophile (**2n-2z**). In general, alkylated aryl iodides performed well under the optimized conditions (**2n–2q**). Electron-rich aryl iodides also gave the desired products in moderate yields, tolerating O-, S-, and N-heteroatoms (**2r–2t)**. Interestingly, the presence of a second amide on the electrophilic component could also

be accommodated (**2y**). In addition, 1,1-disubstituted vinyl iodides were reactive under optimized conditions (**2z**). Electron-poor aryl iodides were substantially less reactive, and heterocyclic aryl iodides and boronic esters were not suitable coupling partners in this reaction (see Supporting Information).

After the evaluation of our coupling partner scope, we turned our attention to other alkene substrates. Gratifyingly, 1,1-disubstituted alkenes could serve as competent substrates to set all-carbon quaternary centers, albeit in modest yield (**3a**). Upon treating γ,δ-unsaturated alkene substrate **3b** to the standard reaction conditions with iodobenzene and phenyl B(nep), we were pleased to observe the exclusive formation of 1,2-diarylation product **4ba** in 67% yield. Furthermore, hetero-diarylation could also be achieved (**4bb** and **4bc**). This method is not without its limitations. In particular, δ,ε-unsaturated alkenes, α-substituted alkenes, and internal alkenes were found to be unreactive at this stage of development (**3c–3f**). In comparison, our previously reported AQ-directed dicarbofunctionalization is compatible with the last three of those four alkenyl amide subtypes (**3d–3f**).[6a]

Gratifyingly, a wide range of *N*-substituted amides were suitable substrates under the reaction conditions previously optimized for amide **1a** (Table 3).

Table 2. Electrophile, Nucleophile, and Alkene Scope[a]

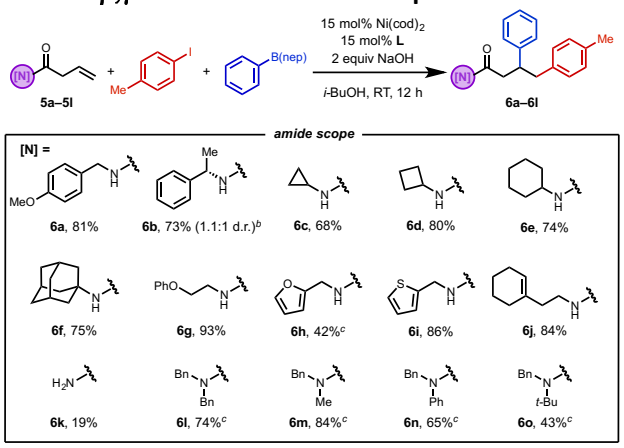


[a]Reactions performed on 0.2 mmol scale unless stated otherwise. Percentages represent isolated yields.

Removal of one methoxy group from the standard amide substrate had only a minor impact on reactivity, as 81% yield of the desired product **6a** was still obtained. Unfortunately, no stereoinduction was observed when

using chiral benzylamine substrates (**6b**). Cyclopropyl, cyclobutyl-, cyclohexyl-, and adamantyl-derived amides reacted to give desired products in good yields (**6c–6f**). Alkenyl amides with tethered heteroatoms and heterocycles also performed well (**6g–6i**). The reaction was found to be chemoselective in that in exclusively functionalized the terminal alkene over the distal trisubstituted alkene (**6i**).

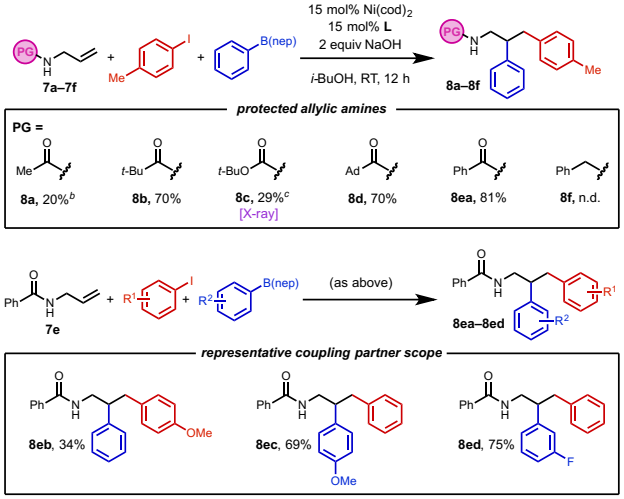
Table 3. β,γ-unsaturated Amide Scope[a]



[a]Reactions performed on 0.2 mmol scale unless stated otherwise. Percentages represent isolated yields. [b]The d.r. by crude ^{1}H NMR wass 1.0:1; d.r. of isolated compound was 1.1:1. [c] NaOH (1 equiv)

Somewhat surprisingly, *N*,*N*-dibenzyl amide still delivered the 1,2-diarylated product in good yield (**6l**). With other tertiary amides, we observed that sterically bulky groups attenuated reactivity (**6m–6o).** This observation, viewed in conjunction with the result with the chiral benzyl amine (i.e., negligible chirality transfer) led us to speculate that the reaction may be proceed via carbonyl coordination rather than nitrogen atom coordination.

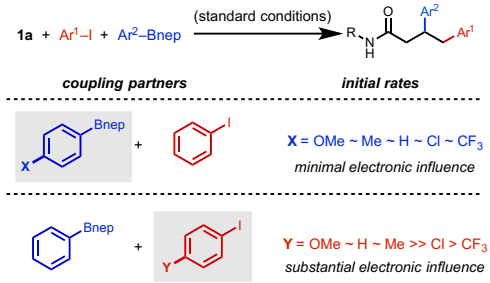
Table 4. Protected Allylic Amine Scope[a]



[a]Reactions performed on 0.2 mmol scale unless stated otherwise. Percentages represent isolated yield. [b] NaO*t*-Bu (1 equiv) used in place of NaOH. [c] NaOH (1 equiv).

In order to gain further insight into the coordination mode of the amide directing group and expand the substrate scope, we next examined substrates in which the nitrogen atom would be incorporated within the putative nickelacycle intermediate, namely protected allyl amines. Excitingly, this class of substrates also reacted under standard nickel-catalyzed 1,2-diarylation conditions in a regiocontrolled fashion (Table 4). Ac-, Piv-, and Boc-protecting groups served as competent directing groups in this reaction (**8a–8c**). With benzoyl-protected allyl amine, we tested representative coupling partner combinations and obtained similar results to the earlier system (**8ea–8ed).** Non-carbonyl-containing Bn-protected allyl amine did not react (**8f**). Based on these findings, we concluded that a carbonyl-directed model was consistent with the observed reactivity trends.

Scheme 2. Initial Rate Trends

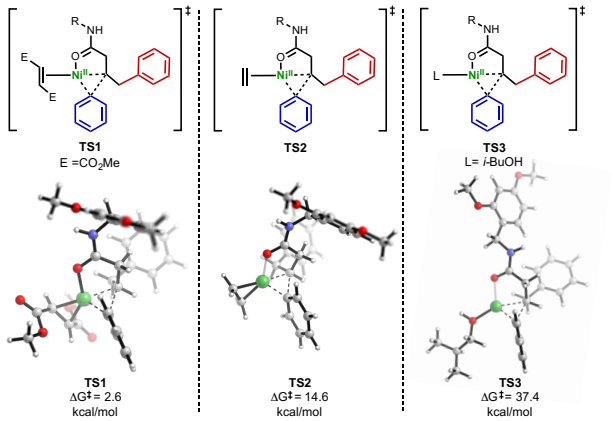


The dramatic reactivity enhancement enabled by the EDO ligand and the broad amide directing group scope prompted us to examine the reaction mechanism through kinetics and computation. First, we evaluated reaction rates with a series of electronically diverse aryl iodides and boronates (see Scheme 2 and SI). We found that the electronic properties of the aryl Bnep component had a negligible influence on rate, while electron-neutral and -rich aryl iodides reacted faster than electron-poor electrophiles. The former trend is inconsistent with a scenario in which transmetalation is rate-limiting, while the latter is inconsistent with a scenario where oxidative addition is rate limiting. One plausible explanation is that migratory insertion of the arylnickel intermediate into the alkene is the slow step in the catalytic cycle.

To shed more light on the preferred coordination mode of the substrate with nickel and the impact of the EDO ligand on the reductive elimination step (where it was expected to play a beneficial role), we performed computational analysis using density functional theory (DFT). Notably, despite a plethora of elegant experimental evidence regarding the beneficial effects of EDO ligands in promoting reductive elimination in

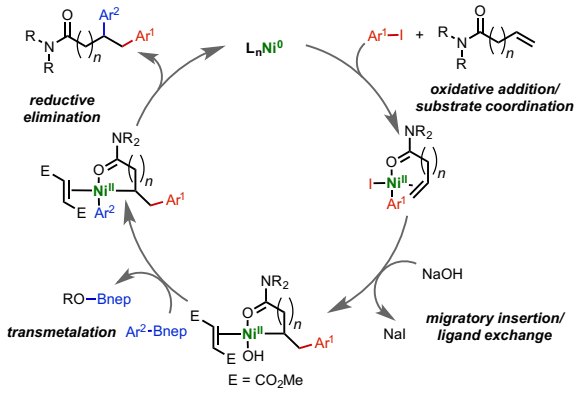
nickel-catalyzed cross-coupling, a head-to-head comparison of the effect of these ligands on reductive elimination has not been quantified from a computational perspective.[12c,15] Our calculations indicate that for each of the proposed intermediates, the corresponding carbonyl-bound nickel species are 3–8 kcal/mol lower in energy compared to their nitrogen-bound counterparts, supporting the hypothesis that the carbonyl group directs catalysis (see Supporting Information). The computed transition state for reductive elimination with dimethyl fumarate (**TS1**) has an activation energy of $\Delta G^{\ddagger}$ = 2.6 kcal/mol, significantly lower than the corresponding transition states for ethylene-bound nickel ($\Delta G^{\ddagger}$ = 14.6 kcal/mol, **TS2**)[16] and solvent-bound nickel ($\Delta G^{\ddagger}$ = 37.4 kcal/mol, **TS3**).

Figure 1. Computed Transition States for Reductive Elimination



A mechanism consistent with the observations made thus far is proposed in Scheme 3. First, the nickel catalyst oxidatively adds into the aryl iodide and coordinates with the amide and alkene moieties of the substrate. Next, the arylnickel(II) species undergoes rate-limiting 1,2-migratory insertion to yield the corresponding 5- or 6-membered nickelacycle. Transmetalation with ArB(nep) and subsequent reductive elimination, promoted by the EDO ligand, yields the desired 1,2-diarylation product and regenerates the catalyst.

Scheme 3. Proposed Catalytic Cycle



In conclusion, we have developed a regioselective, nickel-catalyzed 1,2-diarylation of simple, non-conjugated alkenyl amides using aryl iodides and aryl boronates by employing dimethyl fumarate as ligand. The reaction was found to proceed with a broad range of aryl electrophiles and aryl nucleophiles, and allows for both β,γ- and γ,δ-diarylation of carbonyl compounds. Computational analysis determined that an oxygen-bound nickelacycle is energetically preferred and that the EDO ligand dramatically lowers the activation energy of the reductive elimination step.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

Experimental details, analytical data, and ^{1}H, ^{13}C and ^{19}F NMR spectra (PDF)

X-ray data for compound **2a** (CIF)

X-ray data for compound **4ba** (CIF)

X-ray data for compound **8c** (CIF)

NMR Data (ZIP)

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Notes

The authors declare no competing financial interest.

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(14) (a) García-Dominguez, A.; Li, Z.; Nevado, C. Nickel-Catalyzed Reductive Dicarbofunctionalization of Alkenes. *J. Am. Chem. Soc*. **2017**, *139*, 6835–6838. (b) Zhao, X.; Tu, H.-Y.; Guo, L.; Zhu, S.; Qing, F.-L.; Chu, L. Intermolecular Selective Carboacylation of Alkenes via Nickel-Catalyzed Reductive Radical Relay. *Nat. Commun.* **2018**, *9*, 3488. For related examples involving conjugated alkenes, namely enamides and acrylates, respectively, see: (c) Qin, T.; Cornella, J.; Li, C.; Malins, L. R.; Edwards, J. T.; Kawamura, S.; Maxwell, B. D.; Eastgate, M. D.; Baran, P. S. A General Alkyl-Alkyl Cross-Coupling Enabled by Redox-Active Esters and Alkylzinc Reagents. *Science* **2016**, *352*, 801–805. (d) Gu, J.-W.; Min, Q.-Q.; Yu, L.-C.; Zhang, X. Tandem Difluoroalkylation-Arylation of Enamides Catalyzed by Nickel. *Angew. Chem., Int. Ed.* **2016**, *55*, 12270–12274.

(15) Skold, C.; Kleimark, J.; Trejos, A.; Odell, L. R.; Nilsson Lill, S. O.; Norrby, P.-O.; Larhed, M. Transmetallation Versus β-Hydride Elimination: the Role of 1,4-Benzoquinone in Chelation-Controlled Arylation Reactions with Arylboronic Acids. *Chem. Eur. J.* **2012**, *18*, 4714–4722.

(16) Ethylene-bound nickel was used as a model for alkene-bound nickel species that may be formed under the reaction conditions (e.g., from COD or substrate coordination)

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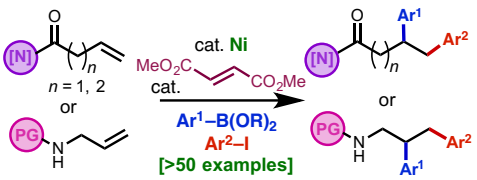

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