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

Joseph Derosa[‡], Roman Kleinmans^{†‡}, Van T. Tran^{†‡}, Malkanthi K. Karunananda[‡], Steven R. Wisniewski[§], Martin D. Eastgate[§], and Keary M. Engle^{†*}

[‡]Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

[§]Chemical & Synthetic Development, Bristol-Myers Squibb, 1 Squibb Drive, New Brunswick, New Jersey 08903, United States

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 regio-control. Under optimized conditions, a wide range of amides derived from 3-butenic acid, 4-pentenic acid, and allyl amine are compatible substrates. This methodology 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 garnered rapid 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 Despite the attractiveness of this approach, competitive two-component cross-coupling and Mizoroki–Heck-type reactions often compete with the desired reactivity. 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-dienes³ or styrenes⁴ 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

A. Transition-metal-catalyzed 1,2-diarylation of styrenes

B. Transition-metal-catalyzed 1,2-diarylation of alkenes using a directing group strategy

C. Nickel-catalyzed 1,3-diarylation of non-conjugated alkenes

D. Nickel-catalyzed 1,2-diarylation of simple alkenyl amides (this 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.^{6c} 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. Given that such a reaction would necessarily proceed through a less thermodynamically stable metalacycle, we reasoned that it would be critical to identify an appropriate ligand to accelerate key elementary steps along the reaction coordinate.

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 could be replaced with simple amides.

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 phenanthroline 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>i</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.

^aReaction conditions: **1a** (0.1 mmol), 0.2 M *i*-BuOH. ^bPercentages represent ¹H NMR yields using CH₂Br₂ as internal standard unless noted otherwise; n.d. = not detected. ^cParentheses 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). A survey of other boron sources revealed promising reactivity for both free boronic acid and pinacol boronic esters, which gave the corresponding product in 78% and 65% yield, respectively (Entries 5 and 6). Notably, lowering the stoichiometry to 1.0 equivalent of each coupling partner still resulted in 59% yield, which could be useful to potential end-users who seek to employ high-value coupling partners (Entry 8). 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–2i**) 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). We hypothesize that

the intricate coordination environment of the nickel catalyst is affected in these cases, shutting down catalysis.

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**). Next, we questioned whether our new native directivity approach would allow for the functionalization of more distal alkenes, such as γ,δ -unsaturated substrates. Upon treating 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 confirmed by X-ray crystallographic analysis. Impressively, we did not observe any byproducts arising

from β -hydride elimination, such as 1,3-diarylated compounds. 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 reaction development (**3c–3f**).

As mentioned above, the goal of this study was to develop a 1,2-diarylation reaction that was compatible with a diverse array of amide substrates that could be encountered in synthesis. 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

^aReactions 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. We next

questioned whether we could achieve a diastereoselective reaction using inexpensive chiral benzyl amines, however, no stereoselection was observed (**6b**). Cyclopropyl, cy-

clobutyl-, 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, rendering this method potentially useful in medicinal chemistry campaigns (**6g–6i**). The reaction was found to be chemoselective in that it exclusively functionalized the terminal alkene over the distal trisubstituted alkene (**6i**).

Table 3. β,γ -unsaturated Amide Scope^a

^aReactions performed on 0.2 mmol scale unless stated otherwise. Percentages represent isolated yields. ^bThe d.r. by crude ¹H NMR was 1.0:1; d.r. of isolated compound was 1.1:1. ^cNaOH (1 equiv)

Somewhat surprisingly, *N,N*-dibenzyl amide still delivered the 1,2-diarylated product in good yield (**6k**). 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 proceed via carbonyl coordination rather than nitrogen atom coordination.

Table 4. Protected Allylic Amine Scope^a

^aReactions performed on 0.2 mmol scale unless stated otherwise. Percentages represent isolated yield. ^bNaOt-Bu (1 equiv) used in place of NaOH. ^cNaOH (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**). Interestingly, 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 set of data are the opposite of what one would expect if oxidative addition were 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. A wide range of amide substrates are tolerated, and this methodology can be extended to allylic amines with simple carbonyl-containing protecting groups. 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

The Supporting Information is available free of charge on the

AUTHOR INFORMATION

Corresponding Author

*keary@scripps.edu

Author Contributions

[†] R. K. and V. T. T. contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was financially supported by The Scripps Research Institute (TSRI), Pfizer, Inc., Bristol-Myers Squibb (Unrestricted Grant), and the National Science Foundation (CHE-1800280). We further acknowledge the NSF for a Graduate Research Fellowship (NSF/DGE-1346837, J.D.). We thank Dr. Jacob T. Edwards (Celgene), Tyler G. Saint-Denis (Yu lab, TSRI), and Vincent A. van der Puyl (Shenvi lab, TSRI) for helpful discussion. We further thank Prof. Arnold L. Rheingold, Dr. Milan Gembicky and Dr. Curtis E. Moore for X-ray crystallographic analysis (UCSD).

REFERENCES

- (1) For representative reviews on alkene functionalization, see: (a) Saini, V.; Stokes, B. J.; Sigman, M. S.; *Angew. Chem., Int. Ed.* **2013**, *52*, 11206–11220. (b) Coombs, J. R.; Morken, J. P. *Angew. Chem., Int. Ed.* **2016**, *55*, 2636–2649.
- (2) For representative reviews on conjunctive cross-coupling, see: (a) Derosa, J.; Tran, V. T.; van der Puyl, V. A.; Engle, K. M. *Aldrichimica Acta* **2018**, *51*, 21–32. (b) Giri, R.; KC, S. *J. Org. Chem.* **2018**, *83*, 3013–3022.
- (3) For palladium-catalyzed 1,2-diarylation of 1,3-dienes, see: Stokes, B. J.; Liao, L.; de Andrade, A. M.; Wang, Q.; Sigman, M. S. *Org. Lett.* **2014**, *16*, 4666–4669.
- (4) For transition-metal-catalyzed 1,2-diarylation of styrenes, see: (a) Urkalan, K. B.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 3146–3149. (b) Kuang, Z.; Yang, K.; Song, Q. *Org. Chem. Front.* **2017**, *4*, 1224–1228. (c) KC, S.; Dhungana, R. K.; Shrestha, B.; Thapa, S.; Khanal, N.; Basnet, P.; Lebrun, R. W.; Giri, R. *J. Am. Chem. Soc.* **2018**, *140*, 9801–9805. (d) Gao, P.; Chen, L.-A.; Brown, M. K. *J. Am. Chem. Soc.* **2018**, *140*, 10653–10657.
- (5) (a) Catellani, M.; Chiusoli, G. P.; Concar, S. *Tetrahedron* **1989**, *45*, 5263–5268. (b) Shaulis, K. M.; Hoskin, B. L.; Townsend, J. R.; Goodson, F. E.; Incarvito, C. D.; Rheingold, A. L. *J. Org. Chem.* **2002**, *67*, 5860–5863.
- (6) (a) Derosa, J.; Tran, V. T.; Boulous, M. N.; Chen, J. S.; Engle, K. M. *J. Am. Chem. Soc.* **2017**, *139*, 10657–10660. (b) Shrestha, B.; Basnet, P.; Dhungana, R. K.; KC, S.; Thapa, S.; Sears, J. M.; Giri, R. *J. Am. Chem. Soc.* **2017**, *139*, 10653–10656. (c) Li, W.; Boon, J. K.; Zhao, Y. *Chem. Sci.* **2018**, *9*, 600–607. (d) Thapa, S.; Dhungana, R. K.; Magar, R. T.; Shrestha, B.; KC, S.; Giri, R. *Chem. Sci.* **2018**, *9*, 904–909. While this manuscript was in preparation, Giri reported that copper or silver additives promote 1,2-diarylation, presumably by generating cationic organonickel intermediates via halide abstraction: (e) Basnet, P.; KC, S.; Dhungana, R. K.; Shrestha, B.; Boyle, T. J.; Giri, R. *J. Am. Chem. Soc.* **2018**, DOI: 10.1021/jacs.8b09401.
- (7) In Ref. 6c, 1,2-dicarbofunctionalization is observed when an alkenyl bromide electrophile is used, but aryl iodides lead preferentially to 1,3-diarylated products.
- (8) KC, S.; Dhungana, R. K.; Shrestha, B.; Thapa, S.; Khanal, N.; Basnet, P.; Lebrun, R. W.; Giri, R. *J. Am. Chem. Soc.* **2018**, *140*, 7782–7786.

- (9) For examples of chelating electrophiles in $C(sp^3)-C(sp^3)$ cross-coupling, see: (a) Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11908–11909. (b) Lu, Z.; Wilsily, A.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 8154–8157. (c) Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 15362–15364. (d) Wilsily, A.; Tramutola, F.; Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 5794–5797.
- (10) (a) Derosa, J.; van der Puyl, V. A.; Tran, V. T.; Liu, M.; Engle, K. M. *Chem. Sci.* **2018**, *9*, 5278–5283. (b) van der Puyl, V. A.; Derosa, J.; Engle, K. M. *Submitted*.
- (11) For a review on olefin ligands in catalysis, see: Johnson, J. B.; Rovis, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 840–871.
- (12) For representative reports on applications of electron-deficient olefin ligands in nickel-catalyzed cross-coupling, see: (a) Giovannini, R.; Stüdemann, T.; Dussin, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2387–2390. (b) Giovannini, R.; Knochel, P. *J. Am. Chem. Soc.* **1998**, *120*, 11186–11187. (c) Giovannini, R.; Stüdemann, T.; Devasagayaram, A.; Dussin, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 3544–3553. (d) Jensen, A. E.; Knochel, P. *J. Org. Chem.* **2002**, *67*, 79–85. (e) Huang, C.-Y.; Doyle, A. G. *J. Am. Chem. Soc.* **2012**, *134*, 9541–9544. (f) Nielsen, D. K.; Huang, C.-Y.; Doyle, A. G. *J. Am. Chem. Soc.* **2013**, *135*, 13605–13609. (g) Huang, C.-Y.; Doyle, A. G. *J. Am. Chem. Soc.* **2015**, *137*, 5638–5641.
- (13) Dimethyl fumarate performed the best compared to other electron-deficient olefin ligands. See Supporting Information for optimization data.
- (14) (a) García-Domínguez, A.; Li, Z.; Nevado, C. *J. Am. Chem. Soc.* **2017**, *139*, 6835–6838. (b) Zhao, X.; Tu, H.-Y.; Guo, L.; Zhu, S.; Qing, F.-L.; Chu, L. *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. *Science* **2016**, *352*, 801–805. (d) Gu, J.-W.; Min, Q.-Q.; Yu, L.-C.; Zhang, X. *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. *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)

Insert Table of Contents artwork here

• innate directivity • broad aryl scope • diverse amide compatibility • mild conditions • ligand-enabled