A Journal of the Gesellschaft Deutscher Chemiker

Angewandte Chemie

GDCh

International Edition

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Accepted Article

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Authors: Joseph Derosa, Taeho Kang, Van T. Tran, Steven Wisniewski, Malkanthi K. Karunananda, Tanner C. Jankins, Kane L. Xu, and Keary Mark Engle

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201913062
Angew. Chem. 10.1002/ange.201913062

Link to VoR: http://dx.doi.org/10.1002/anie.201913062
http://dx.doi.org/10.1002/ange.201913062

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10.1002/anie.201913062

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Nickel-Catalyzed 1,2-Diarylation of Alkenyl Carboxylates: A Gateway to 1,2,3-Trifunctionalized Building Blocks

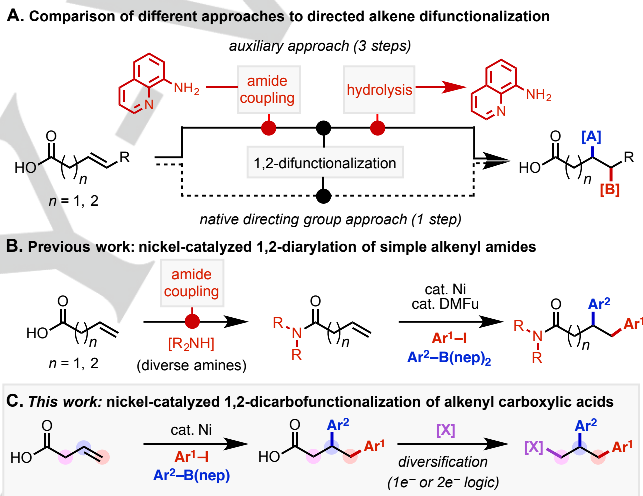
Joseph Derosa†[a], Taeho Kang†[a], Van T. Tran[a], Steven R. Wisniewski[b], Malkanthi K. Karunananda[a], Tanner C. Jankins[a], Kane L. Xu[a], and Keary M. Engle[a]*

Abstract: A nickel-catalyzed conjunctive cross-coupling of alkenyl carboxylic acids, aryl iodides, and aryl/alkenyl boronic esters is reported. The reaction delivers the desired 1,2-diarylated and 1,2-arylalkenylated products with excellent regiocontrol. To demonstrate the synthetic utility of the method, a representative product is prepared on gram scale and then diversified to eight 1,2,3-trifunctionalized building blocks using two-electron and one-electron logic. Using this method, three routes toward bioactive molecules are improved in terms of yield and/or step count. This method represents the first example of catalytic 1,2-diarylation of an alkene directed by a native carboxylate group.

Alkene starting materials serve as ubiquitous chemical feedstocks that can be readily transformed in a variety of ways to build complex molecules.[1] Transition-metal-catalyzed conjunctive cross-coupling has garnered widespread interest in recent years as a powerful tool for installing two different groups across a C–C π-bond.[2] Traditionally, 1,2-diarylation methods have been largely limited to conjugated alkene substrates; in this case, after the key 1,2-migratory insertion event, the an electronically stabilized allyl or benzyl metal species is formed, from which β-H elimination is sluggish.[3] In an effort to expand this mode of reactivity to unactivated, nonconjugated alkenes, our lab and other groups have employed an auxiliary-based chelation control strategy to stabilize the analogous alkyl metal intermediate as a metalacycle.[4] Specifically, our laboratory has developed a suite of modular nickel-catalyzed alkene 1,2-difunctionalization reactions, in which reactivity and selectivity are facilitated by an 8-aminoquinoline (AQ) amide-based bidentate auxiliary[5] through the presumed intermediacy of 5- and 6-membered nickelacycles.[4a,6] Practically speaking, the necessity for installation and removal of the AQ-directing group greatly diminishes the synthetic utility of such methods, requiring at least two concession steps (Scheme 1A).

Recently, we developed a nickel-catalyzed 1,2-diarylation reaction with a diverse array of simple alkenyl amides using dimethyl fumarate (DMFu) as ligand, which obviates the need for strong directing group and enables native amide groups to serve as efficient directors in conjunctive cross-coupling (Scheme 1B).[7] We reasoned that the utility of this chemistry could be enhanced if other functional groups commonly encountered in synthesis could serve as directing groups.[8] Given the versatility of carboxylic acids as diversifiable starting materials and their abundance as chemical feedstocks,[9,10] we envisioned that the development of a carboxylate-directed[11] 1,2-diarylation of alkenes would be synthetically enabling. Hence, the goal of the present study was to demonstrate the feasibility of using free alkenyl carboxylic acid starting materials in nickel-catalyzed conjunctive cross-coupling (Scheme 1C).

Scheme 1. Background and Synopsis of Current Work



To initiate our investigation, we elected to use 3-butenoic acid **1a** as our standard substrate, with 4-iodotoluene and phenylboronic acid neopentyl glycol ester (PhB(nep)) as coupling partners, and Ni(cod)$_2$ as the precatalyst (Table 1). After extensive optimization, we were able to identify “ligand-free” conditions that delivered the desired product in 77% isolated yield (entry 1). Key findings were that sterically bulky secondary and tertiary alcohol solvents were beneficial, metal hydroxide bases (particularly with sodium as the countercation) led to enhanced reactivity, and neopentyl glycol boronic esters outperformed other organoboron nucleophiles. Under our previously published reaction conditions for simple alkenyl amide substrates, the desired product could be detected in only 15% yield with ~20% Mizoroki–Heck product and ~10% hydroarylation product (entry 2). Interestingly, the use of commonly employed ancillary ligands such as bipyridine and triphenylphosphine resulted in only Mizoroki–Heck byproducts and Suzuki–Miyaura biaryl formation with trace amount of desired product (entries 3 and 4). Aryl bromides were found to be incompetent coupling partners (entry 5). The corresponding free boronic acid gave the product in low yield, while the pinacol boronic ester reacted in moderate yield (entries 6 and 7).[16] Various Ni(II) precatalysts were ineffective (entry 10).

[a] J. Derosa, T. Kang, V. T. Tran, Dr. M. K. Karunananda, T. C. Jankins, K. L. Xu, Dr. K. M. Engle
Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States
E-mail: keary@scripps.edu
[b] Dr. S. R. Wisniewski
Chemical & Synthetic Development, Bristol-Myers Squibb, 1 Squibb Drive, New Brunswick, New Jersey 08903, United States

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10.1002/anie.201913062

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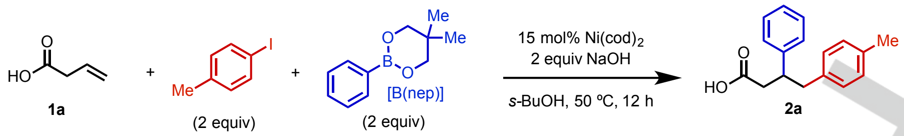
Table 1. Optimization of Reaction[a]

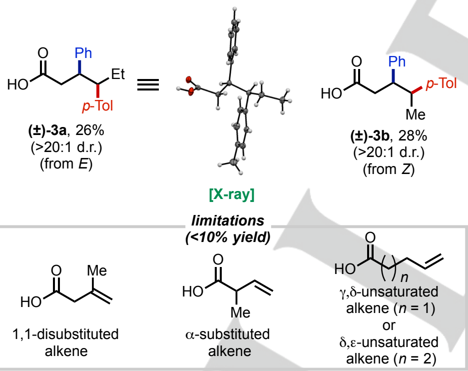


Entry	variation from standard conditions	% Yield **2a**^{b}
1	none	81 (77)^{c}
2	conditions for diarylation of alkenyl amides (Ref. 6)^{d}	15
3	with 15 mol% bipyridine	n.d.
4	with 30 mol% PPh_3	< 5%
5	bromobenzene instead of iodobenzene	n.d.
6	$PhB(OH)_2$ instead of PhB(nep)	16
7	PhBpin instead of PhB(nep)	51
8	dioxane instead of *s*-BuOH	30
9	KOH instead of NaOH	38
10	$NiCl_2$, $NiBr_2$, $Ni(acac)_2$, or NiI_2 instead of $Ni(cod)_2$	n.d.
11	r.t. instead of 50 °C	29

[a] Reaction conditions: **1a** (0.1 mmol), 0.1 M *s*-BuOH. ^{b}Percentages represent ^{1}H NMR yields using CH_2Br_2 as internal standard; n.d. = not detected. ^{c}Values in parentheses are isolated yields. ^{d} Reaction conditions: 15 mol% $Ni(cod)_2$, 15 mol% dimethylfumarate, 1.5 equiv ArI, 1.5 equiv ArB(nep), 2 equiv NaOH, 0.1 M *i*-BuOH at r.t.

Having identified optimized reaction conditions, we next explored the scope and limitations of this methodology by testing other representative alkenyl carboxylates (Scheme 2). Given that previous methods in the literature employing monodentate N(sp^2)- or O(sp^2)-based directing groups are incompatible with internal alkenes, we were delighted to find that the present 1,2-diarylation reaction took place with both *E*- and *Z*-configured alkenes, giving the final products **3a** and **3b** as single regio- and diastereoisomers, albeit in low yields. The reaction is highly sensitive to the alkene substitution pattern and the distance between the carboxylate and the alkene, as 1,1-disubstituted, α-substituted, and γ,δ- or δ,ε-unsaturated alkenes did not react well.[17]

Scheme 2. Preliminary Alkene Scope[a]



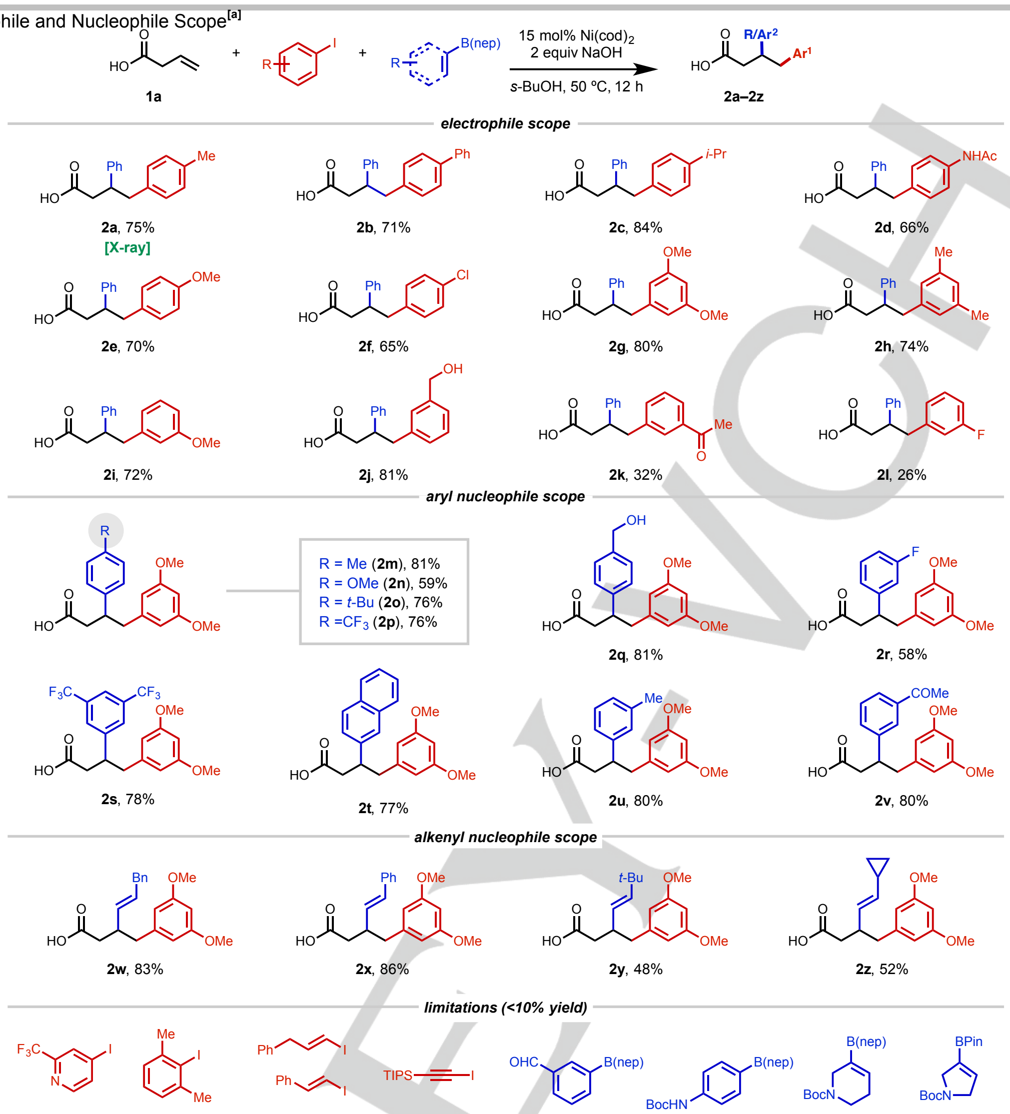
[a] Reactions performed on 0.1 mmol scale. Percentages represent isolated yields.

We moved on to examine the electrophile scope of the reaction using PhB(nep) as the nucleophilic coupling partner (Table 2). Aryl iodides bearing electron-donating substituents in the *para*- and *meta*-positions reacted in good to excellent yields to deliver the desired products (**2a–2j**). Notably, aryl iodides containing –Cl and –NHAc groups were compatible in this reaction, allowing for potential downstream modification (**2d** and **2f**). Electron-withdrawing substituents resulted in diminished reactivity, but still delivered the desired products in moderate yields (**2k** and **2l**). In general, heterocycle-containing and sterically hindered aryl iodides, alkenyl iodide, and alkynyl iodide coupling partners were incompatible under the optimized reaction conditions.

Next, we investigated the nucleophile scope of the reaction using 1-iodo-3,5-dimethoxybenzene as the electrophilic component. In general, a wide range of electron-rich and electron-poor ArB(nep) coupling partners performed well under optimized conditions, giving the desired products in good to excellent yield (**2m–2v**). Tethered alcohols and ketones could be tolerated in excellent yields (**2p** and **2v**). In order to expand the utility of this reaction platform, we wondered whether alkenyl B(nep) nucleophiles would be compatible toward 1,2-alkenylarylation. Gratifyingly, several alkenyl coupling partners were competent, delivering the corresponding 1,2-difunctionalized products in good to excellent yields (**2w–2z**). Notably, this reactivity allowed for the installation of styrenyl fragments that could be diversified downstream (**2x**), along with a vinyl cyclopropane motif (**2z**). Similar to the trend observed with aryl iodide coupling partners, heterocycle-containing B(nep) coupling partners were found to be incompatible at this stage of development.

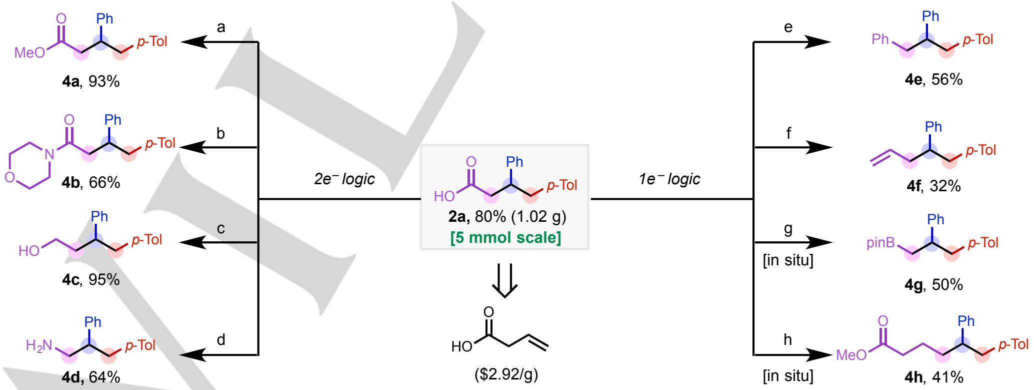
In an effort to showcase the synthetic versatility of carboxylic acid directing group, we conducted a series of diversifications on standard product **2a** (Scheme 3), which could be readily prepared on gram scale. Using the classical two-electron reactivity associated with carboxylic acid starting materials, we converted the difunctionalized products into the corresponding ester, amide, alcohol, and amine (**4a–4d**), enabling access to valuable bioactive substructures (vide infra). Additionally, viewing the carboxylic acid through the lens of one-electron synthetic logic,[9,10] we examined several decarboxylative cross-coupling methods through the intermediacy of a redox-active ester. Indeed, decarboxylative arylation provided modular entry into 1,2,3-triarylpropane motifs (**4e**). Moreover, decarboxylative vinylation and borylation gave the corresponding products in moderate yield, effectively introducing functional handles for further modification (**4f** and **4g**). Finally, decarboxylative Giese addition provided δ,ε-diarylated compound **4h**, the product of a formal double homologation.

Table 2. Electrophile and Nucleophile Scope[a]



[a] Reactions performed on 0.1 mmol scale. Percentages represent isolated yields.

Scheme 3. Product Diversification



[a] 12M HCl (aq.), MeOH, reflux. [b] Morpholine, HATU, pyridine, DCM, 25 °C. [c] $LiAlH_4$, anhydrous THF, 0 °C to 25 °C. [d] (i) DPPA, Et_3N, *t*-BuOH, 100 °C; (ii) 6 M HCl. [e] (i) TCNHPI, DIC, 10 mol% DMAP, 1,4-dioxane, 75 °C; (ii) 20 mol% $NiCl_2$•$6H_2O$, 20 mol% bathophen, $PhB(OH)_2$, Et_3N, 1,4-dioxane/DMF, 75 ºC. [f] (i) TCNHPI, DIC, 10 mol% DMAP, DCM, 25 °C; (ii) 10 mol% $Ni(acac)_2$•xH_2O, 10 mol% bipy, alkenyl zinc reagent, DMF, 25 °C. [g] (i) NHPI, DIC, 10 mol% DMAP, DCM, 25 °C; (ii) 30 mol% $Cu(acac)_2$, B_2Pin_2, LiOH•H_2O, $MgCl_2$, 1,4-dioxane/DMF, 25 °C. [h] (i) NHPI, DIC, 10 mol% DMAP, DCM, 25 °C; (ii) 20 mol% $Ni(ClO_4)_2$ •$6H_2O$, Zn, LiCl, methyl acrylate, MeCN, 25 °C.

To illustrate the utility of this carboxylate-directed alkene 1,2-diarylation in synthesis, we tested the method in several real-world scenarios involving biologically active target compounds containing a 1,2-diaryl motif (Scheme 4). Indeed, in the case of the IPR series of anti-tumor agents in breast cancer treatments, we could access the desired carboxylic acid intermediate **2aa** in a single step in 71% yield compared to four steps in 33% yield.[12] Similarly, carboxylic acid intermediate **2ab** relevant to a family of

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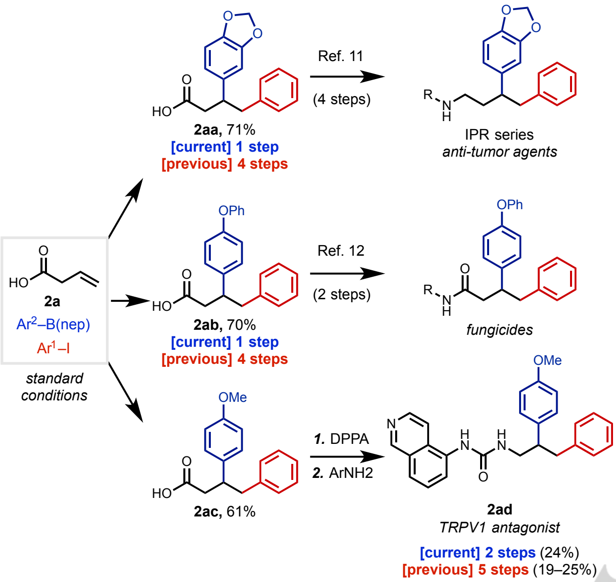
fungicides was acquired in 70% in a single step.[13] A third target, TRPV1 antagonist **2ad** was synthesized in a 2-step sequence involving our developed reaction and an interrupted Curtius rearrangement.[14] In addition to reducing the step count, our method offers a new divergent platform for probing structure–activity relationships in future industrial campaigns.

Scheme 4. Applications of 1,2-Diarylation Reaction[a]



[a] Reactions performed on 0.1 mmol scale. Percentages represent isolated yields.

To gain insight into the reaction mechanism, we carried out a series of preliminary kinetic experiments. First, we compared the initial reaction rates of a series of arylboronates and aryl iodides with systematically varied electronic characteristics. In our earlier work with monodentate amide directing groups,[7] we found that electron-rich aryl iodides led to faster reaction rates and there was no influence of aryl boronate electronic properties on rate. In contrast, in the present system we observed no clear initial rate trends across either the aryl boronate or aryl iodide series (Figure 1).[15]

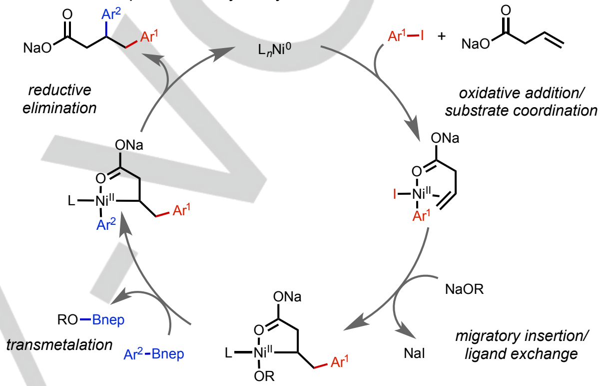
Figure 1. Hammett analysis of coupling partners in 1,2-Diarylation Reaction

	p-OMe	*p*-Me	*p*-H	*p*-Cl	*p*-CF_3
σ value	–0.27	–0.17	0.00	0.23	0.54
Ar–B(nep) (k_{rel})	1.3	1.3	1.0	0.8	1.9
Ar–I (k_{rel})	2.4	0.5	1.0	1.5	1.1

The lack of clear electronic influence of both coupling partners eliminates many possibilities regarding the identity of the turnover-limiting step. One possibility is that the turnover-limiting step changes as a function of the aryl group electronics. Alternatively, a step not involving either of the two aryl groups could be turnover-limiting, such as substrate binding or product dissociation. Additional details on this and other aspects of the reaction mechanism are currently under investigation in our lab.

A plausible catalytic cycle[18] for this nickel-catalyzed 1,2-diarylation of alkenyl carboxylates is shown in Scheme 5.[7a]. Under the basic conditions, the substrate is expected to exist primarily as the corresponding sodium carboxylate salt, which could potentially coordinate to the nickel catalyst in either an L-type[11a,e,f] or X-type fashion[11b,c,d,g], and the coordination mode could be dynamic throughout the catalytic cycle. For simplicity the L-type binding mode is shown in Scheme 5 in analogy to our earlier amide-directed system.[7a] First, nickel(0) oxidatively adds to the aryl iodide, and coordinates the alkene substrate. Next, 1,2-migratory insertion takes place to give carboxlate-bound alkyl-nickelacycle. The involvement of closed-shell intermediates is supported by the observation of a single diastereomer in the case of *syn*-1,2-diarylated product with an internal alkene starting material. Subsequent transmetalation followed by reductive elimination yields the desired product. The competitive formation of γ-arylated Heck-type byproducts in our early optimization efforts is consistent with the intermediacy of the proposed alkyl-nickelacycle.

Scheme 5. Proposed Catalytic Cycle



In conclusion, we have demonstrated that a simple carboxylate group can be used to direct nickel-catalyzed 1,2-diarylation of nonconjugated alkenes using aryl iodides and aryl boronates in the absence of an ancillary ligand. These products can be further manipulated to yield a wide range of valuable building blocks that would be difficult to synthesize using existing methods.

Experimental Section

General Procedure: To an oven-dried 8-mL scintillation vial equipped with a Teflon-coated magnetic stir bar were added the alkene substrate (0.1 mmol), the appropriate aryl iodide electrophile (0.2 mmol), and the appropriate aryl boronic acid neopentylglycol ester (0.2 mmol). The vial was then equipped with a septum cap, which was pierced by a 20-gauge needle and introduced into an argon-filled glovebox antechamber. Once transferred inside the glovebox, $Ni(cod)_2$ (15 mol%), anhydrous NaOH (0.2 mmol), and anhydrous sec-butanol (1 mL) were added. The vial was sealed with a screw-top septum cap, removed from the glovebox, and left to stir at 50 ºC for 12 h. After this time, the reaction mixture was diluted with 1M HCl (15 mL) and extracted with EtOAc (5 × 10 mL). The organic layers were combined, and the solvent was removed *in vacuo* to leave a yellow residue, which afforded pure product after silica gel column chromatography or preparative thin-layer chromatography (PTLC).

Acknowledgements

This work was financially supported by Bristol-Myers Squibb (Unrestricted Grant), the National Science

Foundation (CHE-1800280), the Alfred P. Sloan Fellowship Program, and the Camille Dreyfus Teacher-Scholar Program. We further acknowledge the NSF for a Graduate Research Fellowship (DGE-1346837, J.D.), the Kwanjeong Educational Foundation for a Graduate Fellowship (T.K.), and Dr. Art Olson and Shirley King for funding a high school internship (K.L.X.). We thank Professor Phil S. Baran for helpful discussions. We further thank Prof. Arnold L. Rheingold and Dr. Milan Gembicky (UCSD) for X-ray crystallographic analysis.

Keywords: nickel • diarylation • carboxylic acid • trifunctionalization

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[15] Though electron-rich aryl iodides typically provide higher yields, electron-poor aryl iodides react with similar rates. Low yield in these cases is attributed to increased formation of uncharacterized byproducts.

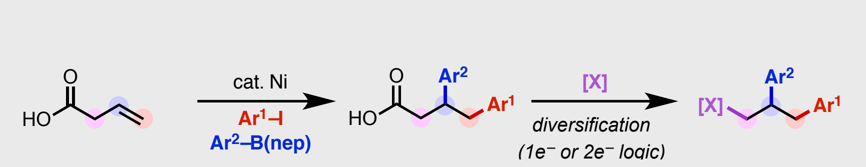
[16] Aryl boronates containing the Bnep group have been previously found to be superior to those with Bpin in nickel-catalyzed cross-coupling reactions. For examples, see Refs. 3e, 7a and the following: (a) J. Hu, Y. Zhao, J. Liu, Y. Zhang, Z. Shi, *Angew. Chem. Int. Ed.* **2016**, *55*, 8718–8722; *Angew. Chem.* **2016**, *128*, 8860–8864; (b) R. Martin-Montero, T. Krolikowski, C. Zarate, R. Manzano, R. Martin, *Synlett* **2017**, *28*, 2604–2608; (c) T. Shimasaki, Y. Konno, M. Tobisu, N. Chatani, *Org. Lett.* **2009**, *11*, 4890–4892.

[17] In the case of these longer chain alkenyl carboxylic acids, only unreacted starting material remained.

[18] When the reaction was performed in the presence of a drop of mercury, we observed 60% ^{1}H NMR yield of the desired product **2a**, ruling out the possibility of heterogeneous catalysis.

10.1002/anie.201913062

COMMUNICATION



Easy as 1, 2, 3: Under nickel catalysis, alkenyl carboxylic acids undergo selective 1,2-diarylation. The resulting products can then be readily converted into diverse 1,2,3-trifunctionalized motifs via classical carboxylic acid interconversions and modern decarboxylative cross-couplings.

*J. Derosa†, T. Kang†, V. T. Tran, S. R. Wisniewski, M. K. Karunananda, T. C. Jankins, K. L. Xu, K. M. Engle**

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Nickel-Catalyzed 1,2-Diarylation of Alkenyl Carboxylates: A Gateway to 1,2,3-Trifunctionalized Building Blocks