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Intermolecular Heck Coupling with Hindered Alkenes Directed by Potassium Carboxylates

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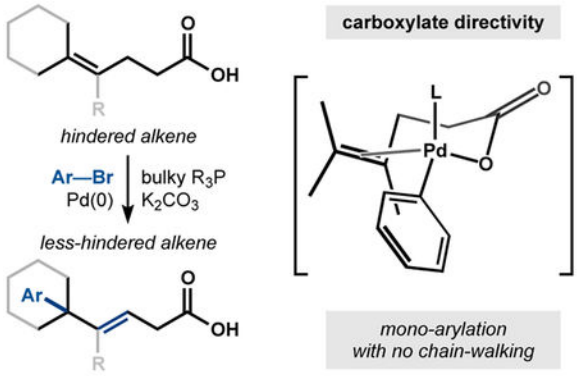
Abstract

Pd(0)-catalyzed Mizoroki-Heck reactions traditionally exhibit poor reactivity with polysubstituted, unbiased alkenes. Intermolecular reactions with simple, all-carbon tetrasubstituted alkenes are unprecedented. Here we report that pendant carboxylic acids, combined with bulky monophospine ligands on palladium, can direct the arylation of tri- and tetrasubstituted olefins. Quaternary carbons are established at high Fsp3 attached-ring junctures and the carboxylate directing group can be removed after coupling. Carboxylate directivity prevents over-arylation of the new, less substituted alkene, which can be diversified in subsequent reactions.

Graphical Abstract



Keywords

Mizoroki-Heck; cross-coupling; carboxylic acid; directing group effects

The Mizoroki-Heck reaction[1] has become a staple of cross coupling and has transformed how molecules are synthesized. A large volume of research in the decades since its discovery has identified some limitations in its scope.[2] For example, electronically unbiased, cyclic and sterically hindered olefins remain challenging substrates with low inherent reactivity and selectivity[3] in traditional Heck arylations.[4] Intermolecular Heck reactions are

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unprecedented with all-carbon tetrasubstituted olefins, with the exception of strained hydrocarbons[5] like bicyclopropylidene.[6] Here we show that potassium carboxylates serve as directing groups to enable single Heck reactions of triand tetrasubstituted alkenes, including hindered cyclic motifs. Products avoid polyarylation and include sp^2-sp^3 attached-ring motifs and diversifiable unsaturated building blocks, otherwise inaccessible by cross-coupling methods.

Many different approaches have been applied to extend the classical Heck reaction to more traditionally challenging substrates (Figure 1a). Early work by Grigg[7] and Overman[8] demonstrated the utility of intramolecular Heck reactions to overcome the reactivity barrier for highly substituted substrates, with their groups and others forging various spiro- and polycyclic systems from tri- and some tetrasubstiuted olefins. The reactivity enhancement from intramolecular delivery of the PdII-Ar species was leveraged in several directed Heck reactions.[9] Notably, the groundbreaking work of Hallberg[10] and Carretero[11] used tethered functional groups bearing basic nitrogens to alter arylation regiochemistry and relay stereochemical information, with the former able to form quaternary centers from a fully-substituted, albeit polarized substrate. A seminal report from White and coworkers in 2008 established that oxidative Heck conditions could engage unbiased terminal olefins using weakly directing functional groups to yield terminally arylated products,[12] and Sigman in 2014 extended the asymmetric redox-relay Heck reaction to trisubstituted olefins with oxidative conditions.[13,14] With the exception of enelactams, redox-relay Heck reactions do not tolerate cyclic substrates, which tend to yield mixtures of regioisomers.[15]

Heck reactions with sterically hindered and unbiased olefins remain non-trivial in many cases, evidenced by recent syntheses of κ-opioid receptor agonists 20-nor-SalA[16] and O6C-20-nor-SalA.[17] A late-stage Heck arylation on a hindered, unbiased olefin could not be achieved using traditional or oxidative Heck conditions. However, incorporation of a carboxylic acid close to the alkene significantly accelerated arylation relative to deactivation of the palladium catalyst or decomposition of the aryl halide, 3-bromofuran (Figure 1c).[16] Reactivity enhancement from the direction of carboxylic acids had been observed in the C-H activation literature, but until now has not been established in Heck arylation.[18] We wondered if carboxylate-directivity could be applied to traditionally unreactive Heck substrates.[19] Here we report that carboxylic acids accelerate and direct the intermolecular Heck reaction of tri- and tetrasubstituted olefins (Figure 1d) in substrate types (unbiased, cyclic, hindered) that are unrepresented in the Heck literature, directed or undirected. The reactivity enhancement of the *potassium* carboxylate allows the formation of quaternary centers from linear, cyclic, bicyclic, aliphatic, and hindered styrenyl substrates. Carboxylate-directivity seems to inhabit a ‘goldilocks region’ among Mizoroki-Heck regimes: cationic-Pd conditions favor chain-walking into a terminating group[13,14] and chelating directing groups prevent β-hydride elimination altogether.[19] In addition, previously-established directing groups like amines and esters are ineffective in promoting the coupling. Carboxylate-directivity promotes regioselective engagement of hindered alkenes yet allows regio- and stereoselective β-hydride elimination without iterative arylation of the new, less hindered alkene.

We identified tetrasubstituted alkene **1a** as a model substrate to explore and optimize carboxylate directivity (for a full table of optimization, see the Supporting Information). Type of base significantly influenced yield: lithium, sodium and cesium cations were inferior to potassium, and ammonium cation was ineffective. A strong influence of cation has previously been observed in carboxylate-directed C-H insertion chemistry, where a proposed κ^2 binding of alkali cation is suggested to induce a κ^1 Pd-carboxylate binding mode.[18] The effect here can alternatively be explained by altered aggregation states of different alkali cations,[20] or perturbed Lewis basicity of the alkali carboxylates. Choice of phosphine proved crucial for efficiency and breadth of scope. Bisphosphines were ineffective, likely due to occupancy of the Pd valence necessary for carboxylate coordination (entries 4–5). Rapidly dissociating, larger bite-angle bisphosphines delivered small amounts of product (entry 6). A bulky mono-phosphine proved optimal for the reaction, either favoring an L1Pd-Ar species with open binding sites for both carboxylate and alkene, or dissociating from Pd to promote a cationic pathway.[21] Interestingly, XPhos performed poorly, although it offered the highest yields in 20-nor-SalA.[16] While simple triphenylphosphine was capable of promoting the reaction, it was outcompeted by the bulkier TrixiePhos, especially with electron rich arenes (entry 9 vs. 10). Interestingly, iodoarenes reacted to low conversion despite their greater propensity towards oxidative addition. No reaction was observed in the absence of palladium.

The arylation exhibits high regio- and stereoselectivity, delivering the ***E***-alkene and the arene distal to the directing group, which is consistent with a 6-membered chelate of the carboxylate to the Pd^{II}-alkyl intermediate (see Scheme 2, below). In contrast to redox-relay Heck reactions of trisubstituted olefins, the unsaturation does not migrate into conjugation[22] with the carboxylic acid but remains adjacent to the newly formed quaternary center. Additionally, the alkene isomer preferentially formed is internal and trisubstituted rather than terminal and disubstituted.[23] The carboxylic acid was essential for reaction: substrates containing weakly Lewis basic esters, alcohols, and amides were completely unreacted under the optimized conditions after 16 hours. Tertiary amine **7** reacted to low conversion and gave a complex mixture of arylated materials.

The carboxylate-directed Heck was successfully applied to a wide range of tri- and tetrasubstituted olefins in modest to good yields after a second esterification step (Table 2). Unless otherwise noted, stereoselectivity was excellent (>20:1 E/Z by ^{1}H NMR) and regiocontrol was excellent in all cases except a cyclopentane substrate (**3t-w**). Only olefins proximal to the carboxylic acid underwent reaction; the distal olefin of **3d** was unreactive. In addition to simple linear aliphatic substrates, cyclic and styrenyl tri- and tetrasubstituted olefins were competent Heck partners. The intrinsic electronic bias of the styrene was completely overridden in the cases of **3e**, **3f**, and **3m**, giving valuable diarylated quaternary centers. Rearrangement of the styrene substitution did not change delivery of the arene electrophile (see **3s**). The use of carbo- and heterocyclic olefins produced challenging all-carbon quaternary centers at Csp^3-Csp^2 attached-ring motifs, including the bicycle **3n** and cyclododecane **3o**. These motifs represent high fraction-sp^3 (Fsp^3) equivalents of biaryls and valuable scaffolds for medicinal chemistry.[24] For example, phenyl substituted cyclohexane **8**, an intermediate in the synthesis of S1P1 agonists, could be prepared in a concise and

higher-yielding 3 step route as compared to the reported 6 step sequence.[25] Electron-rich bromoarenes performed best, in contrast to nickel-catalyzed hydroarylations,[26] which also form quaternary carbons at attached-ring bridgeheads, but usually prefer electron-deficient haloarenes.[27] Diastereoselectivity in the Heck reaction could be effected by: substitution α to the directing carboxylic acid, (**3w**), existing stereocenters on cyclic substrates (**3k**), or bridging-ring topology (**3n**). While most reactions in Table 2 were performed on small scale (0.1 mmol), scale-up proved uneventful and allowed over 500 mg of **3u** to be prepared in one batch from the tetrasubstituted cyclopentene.[28]

Aryl scope is explored in Table 3 using tetrasubstituted substrate **1a**. *Para*- and *meta*-substitution is well tolerated, and mono-, di-, and trisubstituted arenes could be installed with similar ease. Electron rich and electron neutral arenes outperform electron poor, with electron rich aryl bromides noted to complete fastest. Even highly electron-rich trimethoxyphenyl **3ag** was delivered in good yield. Aryl bromides with strongly electron-withdrawing groups in the *para* position were found to stall at low conversion from apparent catalyst deactivation (see Scheme 2 and Supporting Information). Heterocycles were acceptable coupling partners in this chemistry, exemplified by benzodioxole **3ah** and protected indole **3aj**.

The products of carboxylate-directed Heck reaction exhibit high synthetic utility by virtue of the olefin and carboxylic acid functional groups, both of which are versatile synthetic handles. To demonstrate this versatility, we diversified **3u** to form the densely functionalized products of Scheme 1. The olefin was capable of functionalization by Drago-Mukaiyama hydration,[29] epoxidation, and dihydroxylation, and treatment of the dihydroxylation product with oxalyl chloride in methanol furnished 5-membered lactone **12**. Formation of redox active ester in place of the methyl ester allowed straightforward decarboxylation or decarboxylative arylation.[30] As a result, motifs that were previously inaccessible by Mizoroki-Heck chemistry can now be unmasked and retrosynthetically transformed to unsaturated carboxylates.

Several interesting mechanistic features are also worth noting. Although less-substituted olefins were generated, over-arylation of products in Table 2 only occurred rarely and only in small quantities. The adjacent quaternary carbons were not solely responsible for enforcing single arylation: a homologated analog of the products in Tables 2 and 3 underwent facile carboxylate-directed Heck reaction (**14→15**, Scheme 2a) but the less hindered β,γ-unsaturated product (**15**) did not undergo arylation. Therefore, transition state geometry may play a role in effecting monoarylation. A low-energy, pseudo-chair conformation might be involved, which fits the relative regiochemistry of arylation and stereochemistry generated in **3w** (Scheme 2b). This assembly would be geometrically unfavorable for β,γ-unsaturated products (**15** and Tables 2 and 3) and distant alkenes (**3d**). Additionally, β-hydride elimination generates an olefin out of conjugation with the carboxylic acid, which suggests that chain-walking processes cannot occur. The preference for tetrasubstituted substrates to form the internal, trisubstituted olefin over the terminal 1,1-disubstituted olefin (see Table 3, *ca.* 10:1 on average)[23,31] is striking given that statistics should favor β-hydride elimination to the terminal position.[32,33] That the observed alkene isomer avoids the thermodynamic sink of conjugation and the statistically favored product

suggests that the carboxylate directing group has a role enforcing β-hydride elimination, kinetically or thermodynamically, in addition to directing the regiochemistry of arene insertion. The superiority of TrixiePhos to engage hindered olefins was unexpected given its large size among monodentate phosphine ligands and may suggest that dissociation occurs prior to alkene coordination. Alternatively, the monoligated palladium L_1Pd-Ar favored by bulky phosphines[34] may be necessary to allow coordination of both the carboxylate and the alkene. Another surprising feature was the poor performance of both aryl iodides and electron deficient aryl bromides, which typically couple well in Heck reactions but in our system led to catalyst deactivation. Analysis of the crude reaction mixture in reactions of electron poor arenes revealed formation of biaryls and LCMS peaks corresponding to substrate dehydrogenation. Catalyst deactivation possibly occurs downstream of reductive homocoupling to generate biaryls and inactive Pd^{II} salts,[35] a process that is bimolecular in XPd^{II}-Ar and would be disproportionality favored by rapid oxidative addition compared to the productive reaction pathway (Scheme 2c). This hypothesis also accounts for the superiority of sterically bulky ligands, which may prevent Pd^{II}-Ar association leading to deactivation — an observation made previously in styrenyl Heck reactions.[36]

In conclusion, carboxylate-directivity advances the Heck reaction to a new milestone: the intermolecular coupling of tetrasubstituted alkenes. In addition to providing products of high synthetic value, the success of this strategy underscores the profound rate enhancement imparted by carboxylate directing groups.[18] The reactivity trend in counter-cation is noteworthy and distinguishes the carboxylate from neutral protecting groups like amines or esters, which are ineffective to promote the reaction. The absence of chain walking and the regioselectivity of β-hydride elimination may also point to a role of the carboxylate downstream of arene insertion.[37,38] The observations here invite further mechanistic inquiry and the insights gained from this work may be translatable to other modes of olefin cross-coupling.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Novak AJE, Zhong JZ, Mills RB, Yan M, Yuan C, Eastgate MD, Baran PS, Angew. Chem. Int. Ed 2017, 56, 260.

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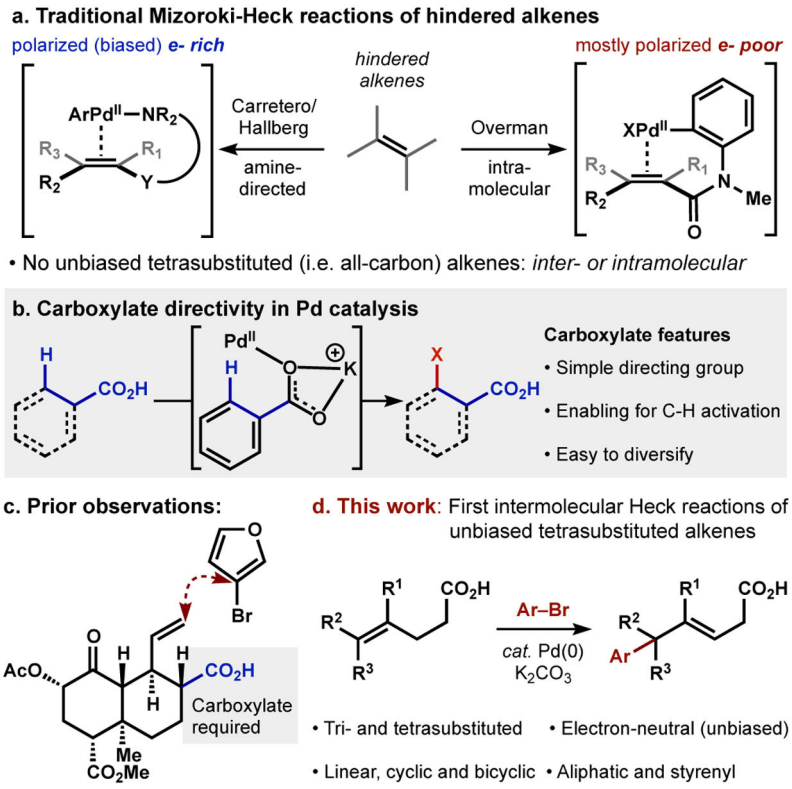
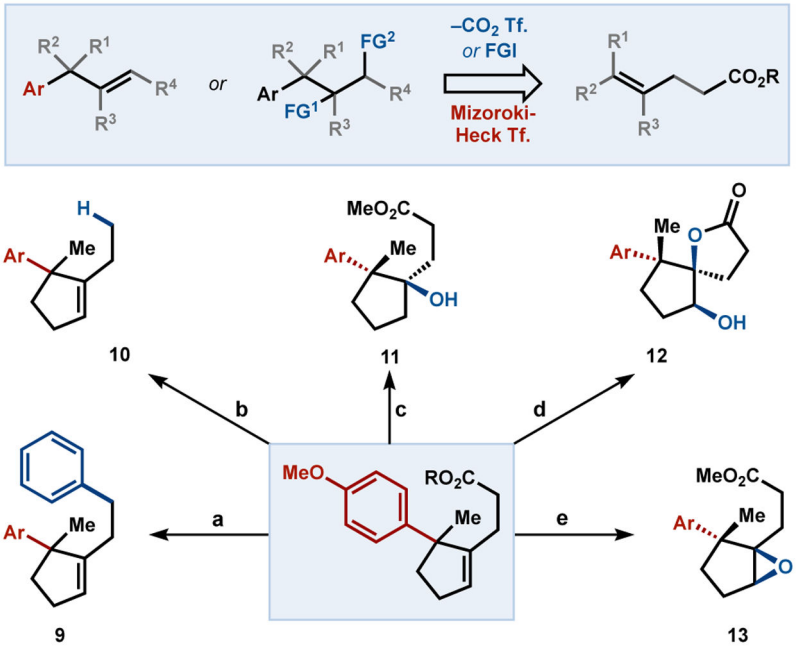


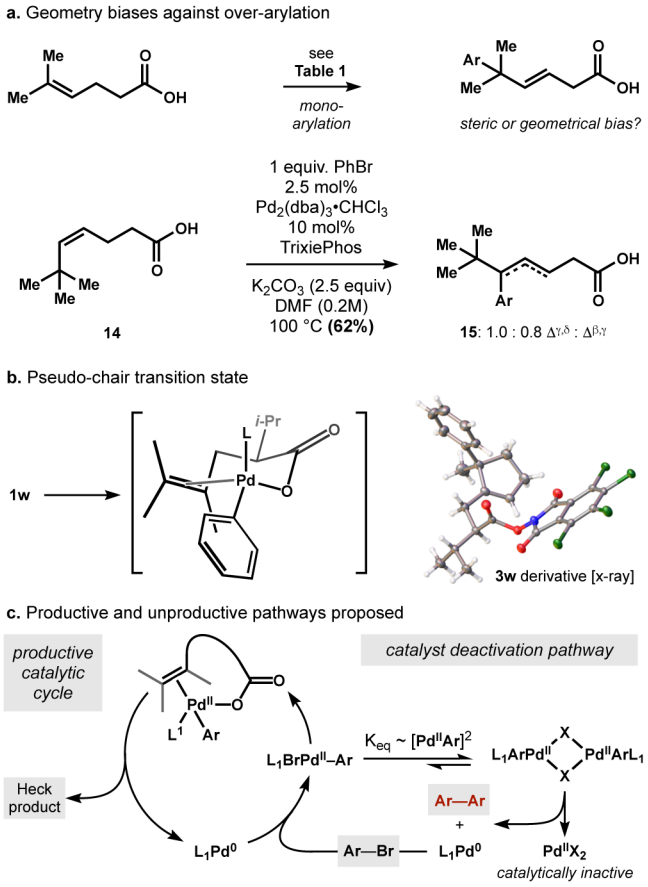
Figure 1:
Approaches to the Heck reaction on challenging substrates.



Scheme 1.

Product Diversification[a]

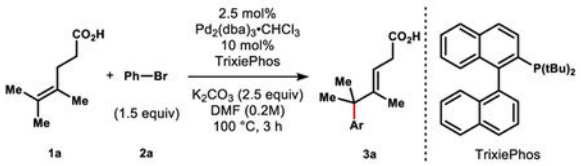
[a] Conditions: a) **R** = **NHPI**, Ph_2Zn, $Fe(acac)_2$, dppBz (34%); b) **R** = **NHPI**, Zn^0, $PhSiH_3$, $NiCl_2{\cdot}6H_2O$ (39%; c) **R** = **Me**, $Mn(acac)_2$, $PhSiH_3$, PPh_3, O_2 (64%, 2:1 dr); d) **R** = **Me**, i. NMO, OsO_4; ii. $(COCl)_2$, MeOH (65%, 6:1 dr); e) **R** = **Me**, *m*-CPBA (100%, 2:1 dr)



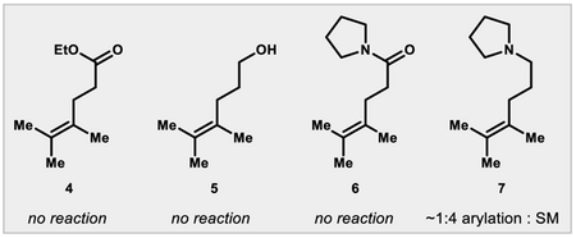
Scheme 2.
Mechanistic model for regio- and stereochemistry.

Table 1.

Reaction Optimization



Entry	Variations from above	% yield[a]
1	none	80
2	Li_2CO_3 / Na_2CO_3 / Cs_2CO_3 *vs* K_2CO_3	0 / 37 / 53
3	Et_3N *vs* K_2CO_3	0
4	BINAP *vs* TrixiePhos	0
5	dppe *vs* TrixiePhos	0
6	dppf *vs* TrixiePhos	17
7	XPhos *vs* TrixiePhos	0
8	PPh_3 *vs* TrixiePhos	67
9	4-OMe-PhBr *vs* PhBr	85[b]
10	4-OMe-PhBr *vs* PhBr, PPh3 *vs* TrixiePhos	22[b]
11	PhI *vs* PhBr	18
12	no Pd	0

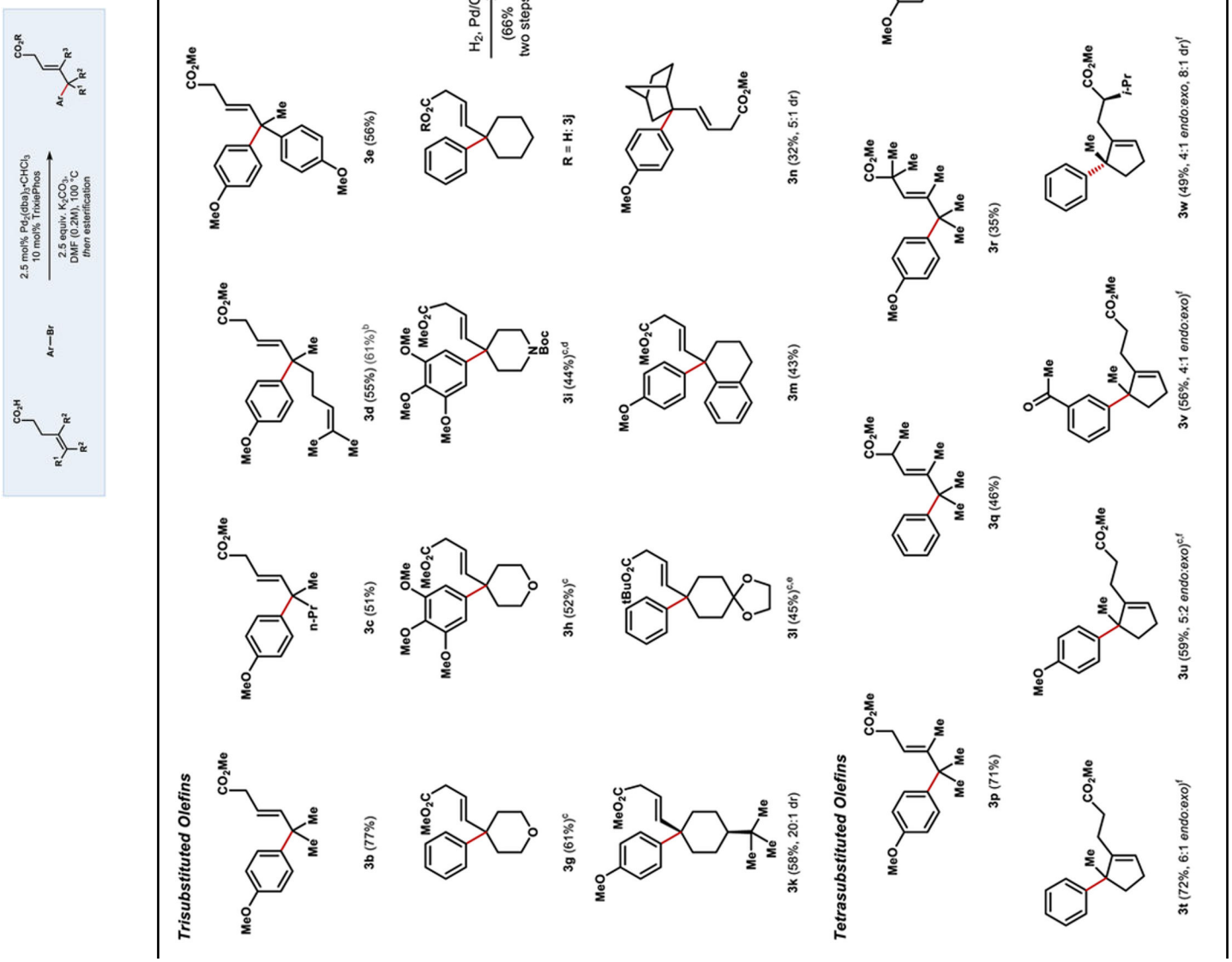


[a]0.1 mmol scale, yield determined by quantitative LCMS.

[b]Ar = 4-OMe-Ph, ^{1}H NMR yield after 1 h.

Table 2.

Olefin Scope



[a] 0.1 mmol scale, isolated yield over 2 steps, reaction time 16 h. Esterification conditions unless otherwise noted: $(COCl)_2$ (2 eq), DCM (0.1M); MeOH (excess).

[b] ^{1}H NMR Yield of crude material.

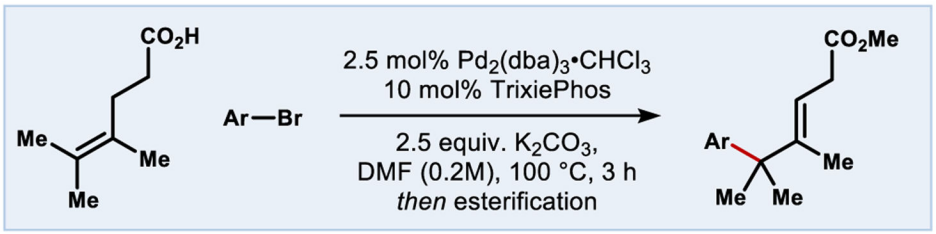
[c] 1 eqivalent of ArBr used.

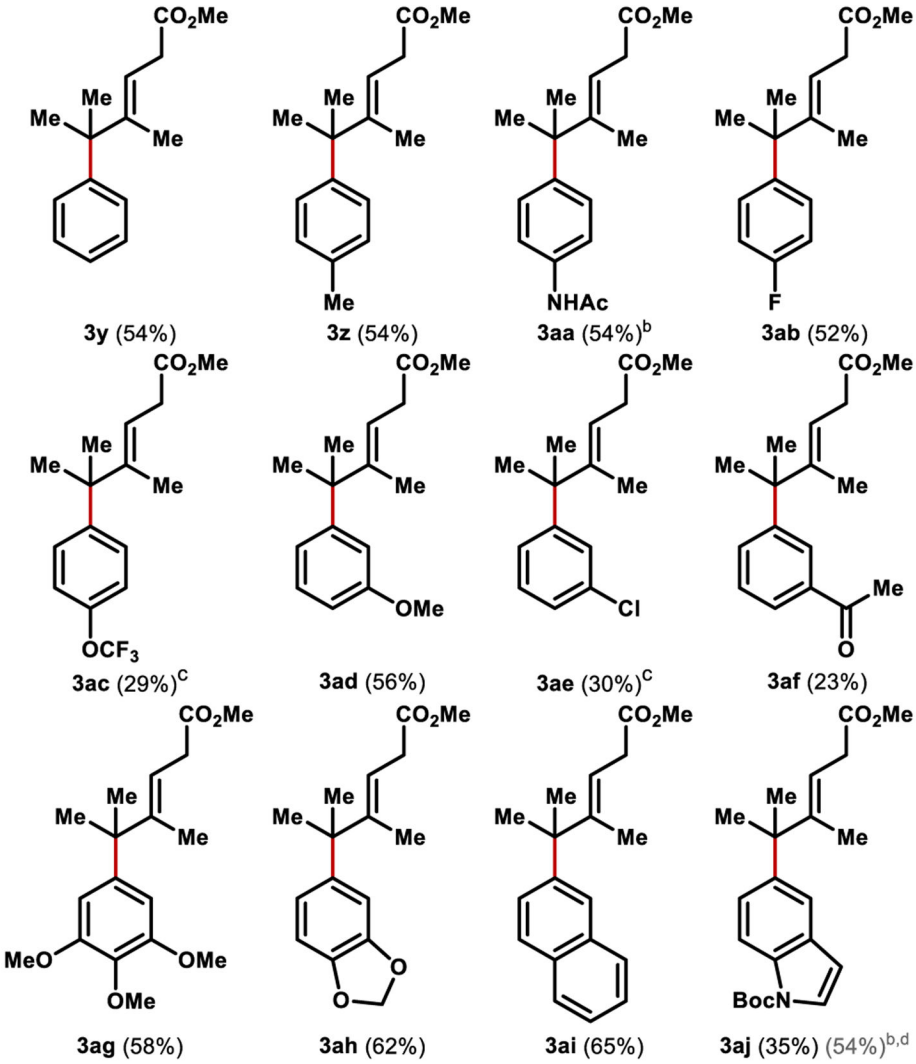
[d] Esterification: DIC, DMAP, MeOH, DCM.

[e] Esterification: *N,N'*-di-^{i}Pr-O-^{t}Bu isourea, DCM. [f] Ratio of endocyclic to exocyclic olefin products.

Table 3.

Aryl halide scope with a tetrasubstituted alkene.





[a] 0.1 mmol scale, isolated yield over 2 steps, reaction time 16 h. Esterification conditions unless otherwise noted: $(COCl)_2$ (2 eq), DCM (0.1M); MeOH (excess)

[b] Esterification conditions: DIC, DMAP, MeOH, DCM

[c]12:1 ratio of isomers favoring the internal [d] Combined yield including deprotected product.