Palladium-Catalyzed Intermolecular Alkene Carboacylation via Ester C-O Bond Activation

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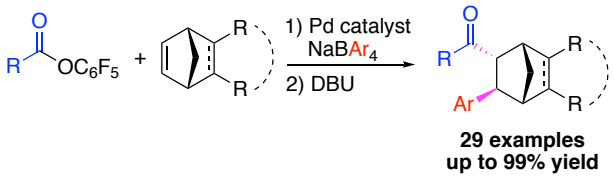
Supporting Information Placeholder



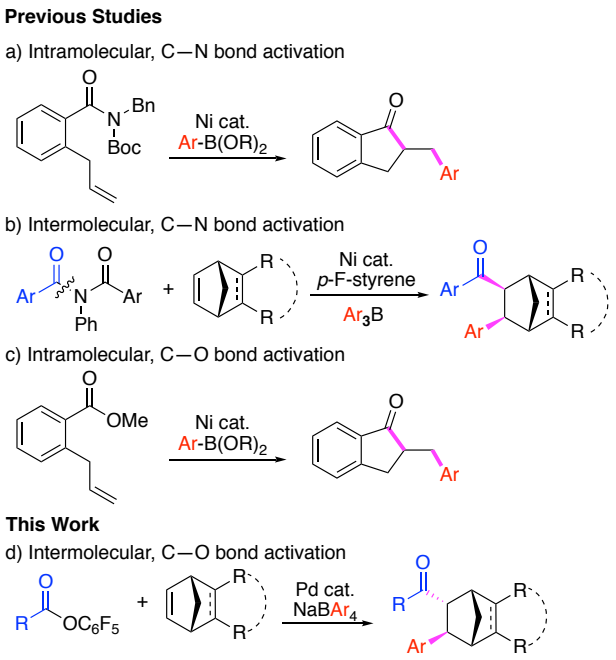
ABSTRACT: We report palladium-catalyzed intermolecular carboacylation of alkenes with ester electrophiles and tetraarylborate nucleophiles. Bicyclic alkenes react with a variety of pentafluorophenyl benzoate and alkanoate esters and sodium tetraarylborates to form ketone products in up to 99% yield. These reactions occur in the absence of a directing group and demonstrate esters as competent acyl electrophiles for intermolecular alkene carboacylation reactions.

Transition metal-catalyzed carboacylation of alkenes is a process that enables the difunctionalization of an alkene[1] to form two new C-C σ bonds. Early approaches to alkene carboacylation focus on facilitating oxidative addition into a C-C σ bond of a ketone, either by the use of strained cyclic ketones[2] or directing groups.[3] However, both of these strategies require highly specialized starting materials, which limits the synthetic utility of these approaches. A more universal electrophile in alkene carboacylation reactions, such as carboxylic acid derivatives, would allow the development of new reactions of this type from easily accessible starting materials.[4-6]

Recently, studies by a variety of groups have demonstrated a range of carboxylic acid derivatives as electrophiles in transition metal-catalyzed cross-coupling reactions, including acid halides,[7] anhydrides,[8] amides,[9] and esters.[10,11] These reactions involve the generation of acyl-metal-aryl and acyl-metal-alkyl intermediates that undergo reductive elimination to form ketone products.[12] Our group has leveraged the ability to intercept these key acyl-metal intermediates in the development of new alkene carboacylation reactions.

Our group reported the first examples of alkene carboacylation utilizing amides as the electrophilic coupling partner.[13] Intramolecular carboacylation of *o*-allylbenzamides with arylboronate esters occurs to generate indanone products in high yields in the presence of a nickel catalyst (Scheme 1a). We later reported nickel-catalyzed intermolecular alkene carboacylation that enables the three-component coupling of imide electrophiles, alkenes, and arylboron nucleophiles (Scheme 1b).[14] These developments provide a practical entry into alkene carboacylation with carboxylic acid derivatives, but the reactions proceed by oxidative addition into relatively activated amide or imide bonds. The ability to incorporate less activated carboxylic acid derivatives, such as esters, as electrophiles in these types of alkene carbodifunctionalization

Scheme 1. Current Strategies for Transition Metal-Catalyzed Synthesis of Ketones via C-X Bond Activation



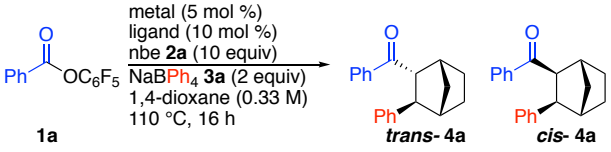
reactions remains underdeveloped. Esters are especially attractive when compared to activated amide or imide electrophiles due to their straightforward synthesis and potential for improved atom economy.

In our initial studies on intramolecular alkene carboacylation, we reported a single example of alkene carboacylation of a methyl *o*-allylbenzoate.[13] Recently, Newman and co-workers reported a robust platform for intramolecular carboacylation of

methyl *o*-allylbenzoates to generate indanone products in the presence of a nickel complex of an *N*-heterocyclic carbene ligand (Scheme 1c).[15] However, intermolecular alkene carboacylation reactions involving ester electrophiles have not been reported. Herein, we report palladium-catalyzed intermolecular carboacylation of alkenes triggered by activation of benzoate and alkanoate esters (Scheme 1d).

Our initial studies toward the development of intermolecular alkene carboacylation focused on reactions of norbornene (nbe) with a variety of benzoate ester electrophiles and sodium tetraphenylborate. Based on our previously reported studies on nickel-catalyzed alkene carboacylation initiated by amide or imide C-N bond activation, we attempted to identify nickel catalysts capable of activating ester C-O bonds and promoting the desired alkene carboacylation reaction. Unfortunately, the reaction conditions we identified led to formation of the alkene carboacylation product in only 19% yield as a 1.1:1 diastereomeric mixture and required the inclusion of multiple additives in the reaction (see Supporting Information, eq S1).

Table 1. Identification of Reaction Conditions for Pd-Catalyzed Intermolecular Alkene Carboacylation [a]

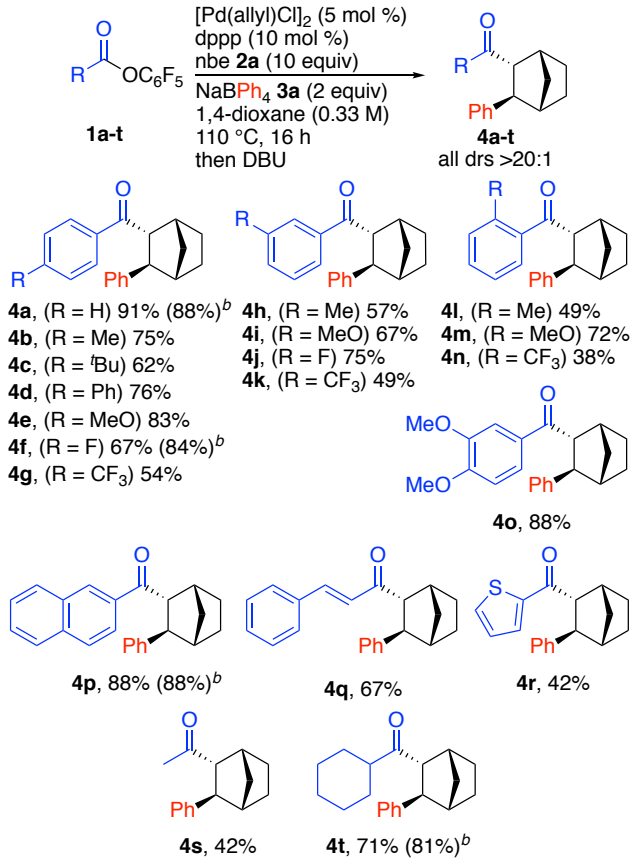


entry	precatalyst	ligand	yield **4a** (%)[b]	dr (trans:cis)
1	Pd_2dba_3	DPEPhos	54	0.80:1
2	$[Pd(allyl)Cl]_2$	DPEPhos	84	0.79:1
3	$[Pd(allyl)Cl]_2$	dppm	7	1:1
4	$[Pd(allyl)Cl]_2$	dppe	27	0.69:1
5	$[Pd(allyl)Cl]_2$	dppp	99	0.87:1
6	$[Pd(allyl)Cl]_2$	dppb	88	0.86:1
7[c]	$[Pd(allyl)Cl]_2$	dppp	99	>20:1

[a]Ester **1a** (0.10 mmol), precatalyst (0.005 mmol), ligand (0.01 mmol), nbe (1 mmol), $NaBPh_4$ (0.20 mmol), 1,4-dioxane (0.30 mL), 110 °C, 16 h. [b]Yield determined by ^1H NMR spectroscopy with dibromomethane as the internal standard. [c]1 equiv of DBU added to crude reaction mixture after 16 h, stirred for 30 minutes at 110 °C, and filtered through silica.

Given the complexity of the nickel-catalyzed reaction conditions and the low yield and selectivity, we chose to evaluate other transition-metal catalysts that have been shown to activate ester electrophiles. Palladium complexes of bisphosphine ligands were identified as promising catalysts of the target alkene carboacylation reaction.[16] We initially identified a palladium complex of DPEPhos as a promising catalyst for the carboacylation of norbornene with pentafluorophenyl benzoate and sodium tetraphenylborate (Table 1). The model reaction formed alkene carboacylation product **4a** in 54% yield as a 0.80:1 mixture of diastereomers (entry 1). Methyl benzoate and a variety of aryl benzoates did not lead to the formation of the alkene carboacylation product under analogous reaction conditions (see Supporting Information, Table S1). The yield of the model reaction increased to 84% when $[Pd(allyl)Cl]_2$ was used as the metal precatalyst (entry 2). We conducted reactions in the presence of catalysts prepared from a series of bisphosphine ligands to evaluate the impact of ligand bite angle (entries 3-6). A catalyst generated from $[Pd(allyl)Cl]_2$ and dppp led to the formation of product **4a** in nearly quantitative yield, but with poor diastereoselectivity. The poor diastereoselectivity results from epimerization of *cis*-**4a** with pentafluorophenoxide to the more thermodynamically stabile *trans*-**4a**. Epimerization of the reaction mixture with DBU after completion of the alkene carboacylation reaction formed *trans*-**4a** in 99% yield with >20:1 dr (entry 7).

Scheme 2. Carboacylation of Esters 4a-t [a]

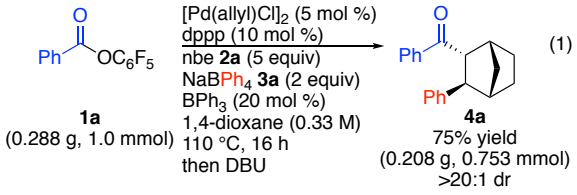


[a]Ester (0.10 mmol), $[Pd(allyl)Cl]_2$ (0.005 mmol), dppp (0.01 mmol), nbe (1 mmol), $NaBPh_4$ (0.20 mmol), 1,4-dioxane (0.30 mL), 110 °C, 16 h, then 1 equiv of DBU added to crude reaction mixture, stirred for 30 minutes at 110 °C, and filtered through silica. Yields of **4a-t** are isolated yields after column chromatography. [b]Reaction run with 20 mol % BPh_3 and 3 equiv nbe.

With a practical catalyst system identified for the model reaction, we evaluated the carboacylation of norbornene with a variety of substituted benzoate esters and sodium tetraphenylborate (Scheme 2). Benzoate esters containing electron-neutral, electron-donating, and electron-withdrawing *para*-substituted aryl groups led to the formation of products **4b-g** in moderate to good yields (54-83%). Reactions of benzoate esters containing electron-donating and electron-withdrawing *meta*-substituted aryl groups were also well tolerated, generating products **4h-k** in moderate to good yields (49-75%). The reaction of an *ortho*-methoxy benzoate ester formed carboacylation product **4m** in 72% yield. However, reactions of benzoate esters containing methyl or trifluoromethyl substituents at the *ortho* position led to the formation of alkene carboacylation products **4l** and **4n** in 49% and 38% yield.

This alkene carboacylation is not limited to simple monosubstituted benzoate esters. The reaction encompasses pol-

ysubstituted aromatic esters, α,β-unsaturated esters, heteroaromatic esters, and aliphatic esters. The reactions of a 3,4-$(MeO)_2$-substituted benzoate ester and a naphthoate ester formed products **4o** and **4p** in 88% yields. A cinnamyl ester formed the corresponding carboacylation product **4q** in 67% yield, while the reaction of a heteroaromatic ester led to formation of **4r** in 42% yield. However, reactions with pyridine- and indole-derived esters did not lead to the formation of the corresponding alkene carboacylation products. In addition, aliphatic esters led to the formation of alkene carboacylation products **4s** and **4t** in moderate to good yields (42-71%). Products of decarbonylative coupling or reductive decarbonylation were not observed in these alkene carboacylation reactions.



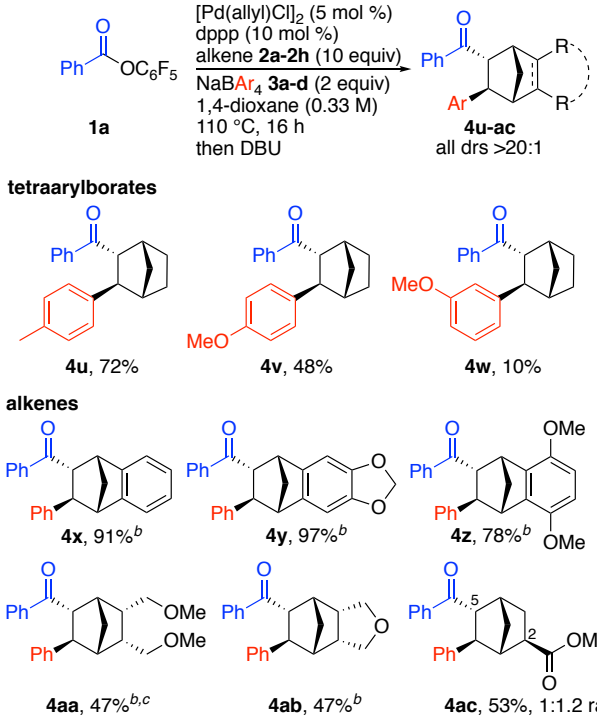
(1)

In the course of our studies, we found that the addition of catalytic BPh_3 to the reaction mixture improved the reproducibility of the catalytic reactions and allowed us to the lower the alkene loading in the reaction. For example, reactions of benzoate esters, a naphthoate ester, and an aliphatic ester occur in similar or higher yields when they are conducted in the presence of 20 mol % BPh_3 and 3 equiv of norbornene (Scheme 2, compounds **4a**, **4f**, **4p**, and **4t**). The parent reaction occurs on a 1.0 mmol scale to form ketone **4a** in 75% yield (eq 1).

We then sought to establish the scope of the alkene carboacylation with respect to arylboronate nucleophiles in reactions of norbornene and pentafluorophenyl benzoate **1a** (Scheme 3). The reaction of sodium tetrakis(4-tolylphenyl)borate with ester **1a** formed carboacylation product **4u** in 72% yield. However, perturbation of the electronic nature of the parent sodium tetraphenylborate significantly impacted product yields. The reactions of sodium tetrakis(4-methoxyphenyl)borate and sodium tetrakis(3-methoxyphenyl)borate generated carboacylation products **4v** and **4w** in 48% and 10% yield. Tetraarylborates containing electron-deficient aryl groups, such as sodium tetrakis(4-trifluoromethylphenyl)borate and sodium tetrakis(4-fluorophenyl)borate, only led to trace yields of the carboacylation products. These observations suggest that the efficiency of the catalytic alkene carboacyltion reaction is correlated with the rate of transmetalation of the arylboron nucleophile.

We then evaluated palladium-catalyzed carboacylation of a range of bicyclic alkenes with pentafluorophenyl benzoate **1a** and sodium tetraphenylborate. In the absence of triphenylborane, palladium-catalyzed carboacylation of additional alkenes does not occur in >5% yield. However, the addition of 20 mol % triphenylborane led to formation of the alkene carboacylation products in modest-to-good yields and enabled the loading of the alkene substrate to be lowered. Carboacylations of benzonorbornadienes **2b-2d** with ester **1a** and sodium tetraphenylborate **3a** generated ketone products **4x-4z** in 78-97% yields. Reactions of norbornenes containing ether and ester substituents formed products **4aa-4ac** in 47-53% yields. Epimerization of the stereocenter at C2 led to isolation of ketone **4ac** as a 1:1.2 ratio of diastereomers. Unfortunately, reactions of alkenes such as styrene, simple cycloalkenes, and vinyltrimethylsilane did not lead to the formation of alkene carboacylation products in appreciable yields.

Scheme 3. Scope of Tetraarylborates and Alkenes 4u-ac [a]

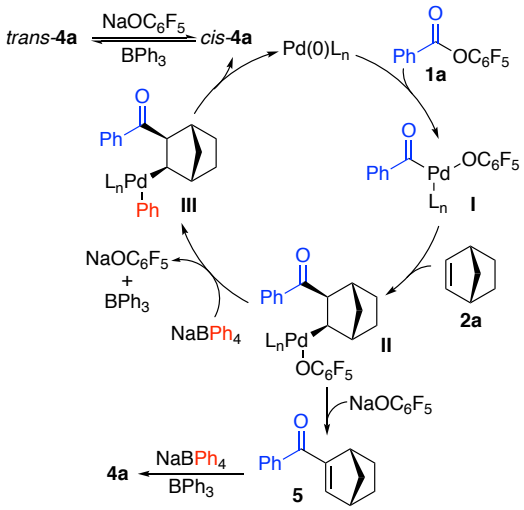


[a]Ester **1a** (0.10 mmol), $[Pd(allyl)Cl]_2$ (0.005 mmol), dppp (0.01 mmol), alkene **2a-2h** (1 mmol), $NaBAr_4$ (0.20 mmol), 1,4-dioxane (0.30 mL), 110 °C, 16 h, then 1 equiv of DBU added to crude reaction mixture, stirred for 30 minutes at 110 °C, and filtered through silica. Yields of **4u-ac** are isolated yields after column chromatography. [b]Reaction run with 20 mol % BPh_3 and 3 equiv alkene. [c]Reaction run for 24 h.

We propose the catalytic cycle shown in Scheme 4 as a plausible reaction pathway. Oxidative addition of the active Pd(0) catalyst into the ester C-O bond of **1a** affords acyl-Pd(II)-alkoxide intermediate **I**. Migratory insertion of norbornene into the Pd-(C)acyl bond of intermediate **I** generates the alkyl-Pd(II) intermediate **II**. Transmetalation with sodium tetraphenylborate forms the alkyl-Pd(II)-aryl intermediate **III**, sodium pentafluorophenoxide, and triphenylborane. Reductive elimination of the alkyl and aryl ligands from intermediate **III** leads to carboacylation product ***cis*-4a** and regenerates the Pd(0) catalyst. Ketone ***cis*-4a** can be epimerized to ***trans*-4a** in the presence of sodium pentafluorophenoxide and triphenylborane. However, a second mechanistic pathway is possible to generate **4a**. Base-assisted beta-hydride elimination of intermediate **II** could form enone **5**. Subsequent, 1,4-addition of an organoboron nucleophile to enone **5** would generate **4a**.

We have obtained data that suggests a Heck reaction/1,4-addition sequence to generate ketone **4a** is feasible under our reaction conditions. The Pd-catalyzed carboacylation of norbornene with pentafluorophenyl benzoate and sodium tetraphenylborate forms **4a** in 14% yield as a 2.5:1 ratio of *cis*:*trans* diastereomers and a 9% yield of enone **5** early in the course of the reaction (see Supporting Information, Table S2). The presence of enone **5** suggests the Heck reaction can occur, at minimum in a stoichiometric fashion, under these reaction conditions. To determine whether 1,4-addition of sodium

Scheme 4. Proposed Catalytic Cycle



tetraphenylborate to generate ketone **4a** is feasible under our reaction conditions, we reacted enone **5** with 2 equiv of sodium tetraphenylborate in the presence of 20 mol% triphenylboron. This reaction formed ketone **4a** in 40% yield with a 3.3:1 ratio of *trans*:*cis* diastereomers (see Supporting Information, eq S2). However, the diastereoselectivity of the 1,4-addition contrasts that observed in our Pd-catalyzed alkene carboacylation reactions. Although we cannot rule out a Heck reaction/1,4-addition sequence as a contributor to the formation of ketone **4a**, the contrasting diastereoselectivities of the 1,4-addition reaction versus the Pd-catalyzed alkene carboacylation suggest the alkene carboacylation pathway is likely the major pathway to form ketone product **4a**.

In summary, we have developed the first palladium-catalyzed intermolecular alkene carboacylation reaction via activation of an ester C-O bond. This palladium-catalyzed process enables the coupling of a variety of bicyclic alkenes, pentafluorophenyl benzoate and alkanoate esters, and sodium tetraarylborates to form two new C-C σ bonds and highly functionalized ketone products in up to 99% yield with excellent diastereoselectivities. Moreover, the development of this approach to alkene carboacylation expands the types electrophiles that can be harnessed in alkene carboacylation reactions to encompass readily accessible starting materials. Studies to establish the mechanism of these carboacylation reactions are ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data, and spectral data (file type, i.e., PDF)

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Notes

The authors declare no competing financial interest.

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