Cross-Coupling

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Branched Arylalkenes from Cinnamates: Selectivity Inversion in Heck Reactions by Carboxylates as Deciduous Directing Groups

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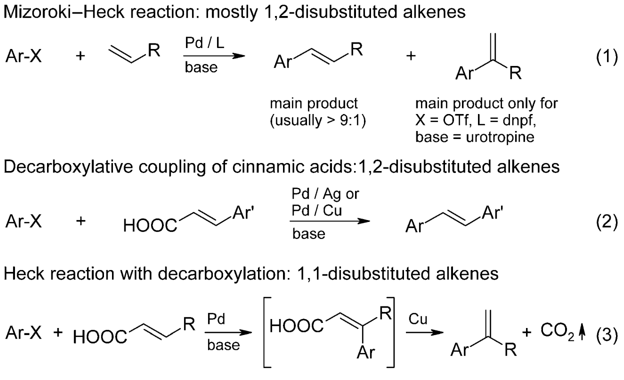
Abstract: *A decarboxylative Mizoroki–Heck coupling of aryl halides with cinnamic acids has been developed in which the carboxylate group directs the arylation into its β-position before being tracelessly removed through protodecarboxylation. In the presence of a copper/palladium catalyst, both electron-rich and electron-deficient aryl bromides and chlorides bearing numerous functionalities were successfully coupled with broadly available cinnamates, with selective formation of 1,1-disubstituted alkenes. This reaction concept, in which the carboxylate acts as a deciduous directing group, ideally complements traditional 1,2-selective Heck reactions of styrenes.*

1,1-Disubstituted alkenes are prevalent in natural[1] and synthetic products[2] with a wide spectrum of applications. Traditional syntheses of this substructure, such as Wittig or Peterson olefinations,[3] arylations of alkynes,[4] olefin metathesis,[5] and transition-metal-catalyzed cross-coupling reactions of preformed α-metalated vinylarenes[6] or 2-alkenyl electrophiles,[7] are limited in scope, waste-intensive, and/or require multistep syntheses of starting materials.

The selective synthesis of 1,1-diarylalkenes from widely available aryl (pseudo)halides by Heck-type reactions would be a welcome alternative.[8] However, electronic and steric factors usually determine the regiochemical outcome of the carbopalladation for simple hydrocarbons,[9–12] so that 1,2-diarylalkenes are obtained from styrenes [Scheme 1, Eq. (1)].[13] Only in very few cases has this selectivity been successfully shifted towards the 1,1-diarylakenes: Zou et al. reported that aryl triflates react with selected styrenes with formation of 1,1-diarylakenes when using a urotropine base and the exceptionally bulky 1,1′-bis[di(1-naphthyl)phosphino]ferrocene (dnpf) ligand.[14]

As a result of the wealth of methods for their preparation, cinnamic acids are more widely available in greater structural diversity than styrenes, and are, thus, more attractive starting materials.[15] In Heck coupling reactions with aryl halides, the carboxylate group should direct the carbopalladation into its β-position,[16] thereby leading to the intermediate formation of diarylacrylic acids. Their in situ conversion into the desired 1,1-diarylalkenes might be accomplished by an added copper or silver decarboxylation catalyst [Eq. (3)]. However, this attractive approach seemed to be out of reach, because the same catalyst combination is known to effectively promote a decarboxylative cross-coupling with formation of 1,2-diarylalkenes [Eq. (2)].[17]



Scheme 1. Synthesis of substituted alkenes.

The utility of carboxylates as directing groups that are tracelessly cleavable in situ has been demonstrated for example, for C–H hydroxylations,[18] amidations,[19] (hydro)-arylations,[20] and alkoxylations.[21] Ideally, the carboxylate will act as a deciduous rather than a removable directing group, staying in place for only just as long as it is required to direct the metal catalyst into the α-position, but is destabilized by the newly formed bond to an extent that it is shed directly afterwards.

To switch the reaction of cinnamic acids with aryl halides from a decarboxylative coupling pathway to the desired Heck pathway, with the carboxylate acting as a deciduous directing group, it is critical to identify a catalyst system that a) promotes the carbopalladation of cinnamic acids with unprecedented efficiency and b) efficiently mediates the decarboxylation of diarylacrylic acids, but c) does not promote the decarboxylation of cinnamates, thus blocking decarboxylative cross-coupling (Scheme 2).

Prerequisite (a) already represented a substantial hurdle because the reactivity of the electron-rich cinnamate salts formed under the basic conditions of a Heck process is low. The Nájera and Fujiwara research groups found that cinnamic acids gave unsatisfactory yields (42%) even under optimized conditions, whereas the corresponding alkyl cinnamates reacted quantitatively.[22] However, these literature results demonstrate that both oxidative addition and carbopalladation should take place at temperatures below those required for most decarboxylative coupling reactions.

To probe whether prerequisites (b) and (c) could be fulfilled, we performed decarboxylation studies, and were

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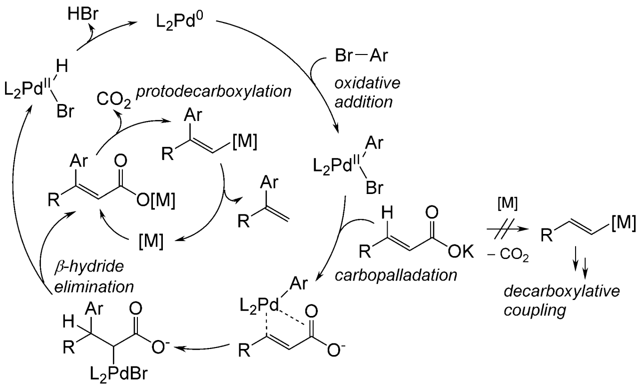


Scheme 2. Mechanistic outline for the envisioned process.

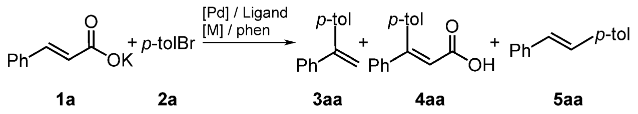
delighted to find that an additional aryl group strongly activates the substrates towards CO_2 extrusion. Thus, β-tolylcinnamic acid underwent almost quantitative protodecarboxylation at 130 °C in the presence of a Cu_2O catalyst, whereas under the same conditions, cinnamic acid showed < 5 % conversion after 16 h (see Table S1 in the Supporting Information).

These preliminary experiments served to define a starting point for the rational development of a catalyst. We chose the reaction of potassium cinnamate **1a** with 4-bromotoluene (**2a**) as a model to systematically investigate the influence of Heck and decarboxylation catalysts on the reaction outcome under various conditions (Table 1). Subjecting substrates **1a** and **2a** to classical Mizoroki–Heck conditions (Table 1, entry 1) led to only low conversion being observed, mostly to the non-decarboxylated Heck product **4aa**, along with decarboxylative cross-coupling product **5aa**. However, when copper(I) bromide was added, the selectivity for the branched product **4aa** increased sharply, which indicates that the soft Lewis acid CuBr promotes the carbometalation step more strongly than the decarboxylation (entry 2). The addition of Lewis acids, such as $Sc(OTf)_3$, facilitated the Heck coupling reaction even more strongly, but the selectivity was lower (entries 2 and 3). This finding suggests that the role of the copper is mainly that of a soft Lewis acid. Lower yields were observed starting from preformed copper cinnamate, which speaks against the intermediacy of these compounds in the transformation (entry 4). In the presence of Ag_2CO_3, **5aa** was formed as the main product (entry 5). Increasing the temperature led to preferential formation of decarboxylated product **3aa** over **4aa**, without reducing the selectivity for the branched over the linear product **5aa** (entries 6 and 7).

Systematic variation of the phosphine ligand revealed that the moderately electron-donating, sterically demanding ligand tri-*o*-tolylphosphine was most effective and gave greater than 10:1 selectivity for **3aa** at full conversion (entries 8–12). $Pd(acac)_2$ was found to be the optimal Pd precursor (entries 13–16). Among the Cu sources, copper halides and CuBr, in particular, were most effective (entries 17 and 18). A solvent mixture of NMP and quinoline gave the best results (entries 19 and 20).

The addition of potassium acetate is required when starting directly from cinnamic acid, whereas stronger bases retard the reaction (entries 21–23). Control experiments confirmed that neither the Pd nor the Cu catalyst alone are able to mediate this transformation (entries 24 and 25).

Table 1: Optimization of the reaction conditions.[a]



Entry	[Pd]	Ligand	[M]	Yield [%]		
				3 aa	**4 aa**	**5 aa**
1[b]	$Pd(acac)_2$	PPh_3	–	4	12	10
2[b]	$Pd(acac)_2$	PPh_3	CuBr	2	23	4
3[b]	$Pd(acac)_2$	PPh_3	$Sc(OTf)_3$	6	40	12
4[b,c]	$Pd(acac)_2$	PPh_3	–	5	< 1	< 1
5[b]	$Pd(acac)_2$	PPh_3	Ag_2CO_3	6	< 1	12
6[d]	$Pd(acac)_2$	PPh_3	CuBr	28	9	7
7	$Pd(acac)_2$	PPh_3	CuBr	73	< 1	12
8	$Pd(acac)_2$	Cy_3P	CuBr	76	< 1	12
9	$Pd(acac)_2$	$(p\text{-tol})_3P$	CuBr	76	< 1	14
10	$Pd(acac)_2$	BINAP	CuBr	78	< 1	13
11	$Pd(acac)_2$	Johnphos	CuBr	77	< 1	11
12	$Pd(acac)_2$	$(o\text{-tol})_3P$	CuBr	92	< 1	8
13	$PdCl_2$	$(o\text{-tol})_3P$	CuBr	83	< 1	13
14	$PdBr_2$	$(o\text{-tol})_3P$	CuBr	82	< 1	12
15	$Pd(TFA)_2$	$(o\text{-tol})_3P$	CuBr	86	< 1	14
16	$Pd(dba)_2$	$(o\text{-tol})_3P$	CuBr	88	< 1	12
17	$Pd(acac)_2$	$(o\text{-tol})_3P$	CuCl	90	< 1	10
18	$Pd(acac)_2$	$(o\text{-tol})_3P$	Cu_2O	75	< 1	10
19[e]	$Pd(acac)_2$	$(o\text{-tol})_3P$	CuBr	25	< 1	11
20[f]	$Pd(acac)_2$	$(o\text{-tol})_3P$	CuBr	42	< 1	7
21[g]	$Pd(acac)_2$	$(o\text{-tol})_3P$	CuBr/KOAc	88	< 1	12
22[g]	$Pd(acac)_2$	$(o\text{-tol})_3P$	$CuBr/K_2CO_3$	43	< 1	15
23[g]	$Pd(acac)_2$	$(o\text{-tol})_3P$	$CuBr/K_2CO_3$	< 1	< 1	< 1
24	$Pd(acac)_2$	$(o\text{-tol})_3P$	–	6	< 1	16
25	–	–	CuBr	< 1	< 1	< 1

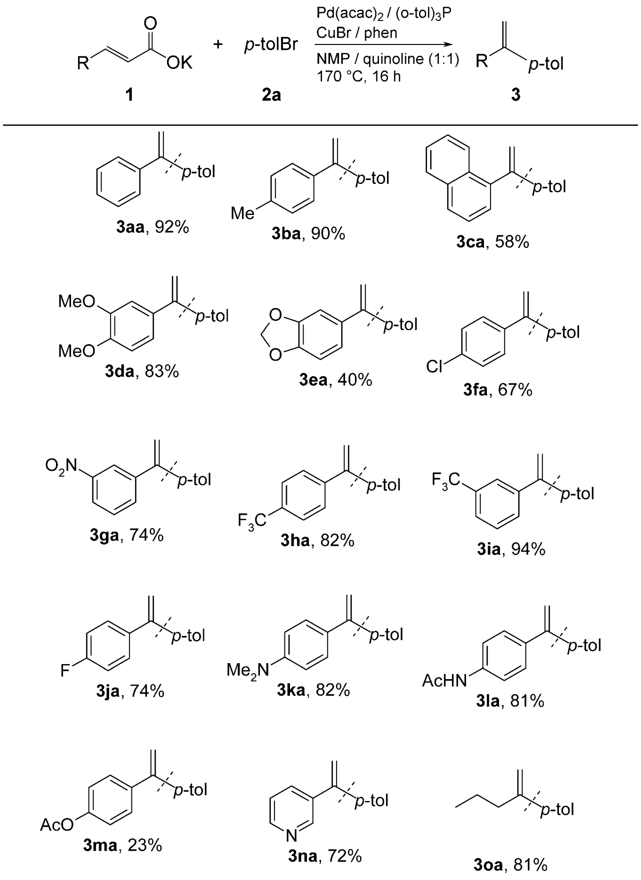
[a] Reaction conditions: **1a** (0.60 mmol), **2a** (0.5 mmol), [M] (10 mol %), 1,10-phenanthroline (10 mol %), [Pd] (2 mol %), P ligand (5 mol %), 3 mL solvent (NMP/quinoline (1:1)), 170 °C, 16 h. Yields were determined by GC analysis after esterification with MeI using *n*-tetradecane as an internal standard. For abbreviations see Ref. [23]. [b] 130 °C. [c] Copper cinnamate was used instead of **1a**. [d] 150 °C. [e] In NMP. [f] In NMP/mesitylene (1:1). [g] Starting from cinnamic acid.

We next investigated the scope of the optimized procedure (2 mol % $Pd(acac)_2$, 5 mol % $(o\text{-tol})_3P$, 5 mol % Cu_2O, 10 mol % 1,10-phenanthroline, NMP/ quinoline (1:1), 170 °C, 16 h) with regard to the α,β-unsaturated carboxylic acids.

Both electron-rich and electron-poor cinnamic acids reacted smoothly with 4-bromotoluene (**2a**; Table 2). Common functionalities, such as halo, ester, ether, carbonyl, and even nitro and amino groups, were tolerated. The reaction also proceeded well with heterocyclic and alkyl-substituted allylic acids.

The reaction is also widely applicable with regard to the electrophilic coupling partner (Table 3). *ortho*-, *meta*-, and *para*-substituted aryl bromides bearing sensitive functionalities including ether, ester, carbonyl, thioether, and tertiary amino groups were successfully converted. Besides aryl bromides, alkenyl and heteroaryl bromides were successfully converted, although in somewhat lower yields. Changing the ligand to XPhos led to less expensive, but also less reactive, aryl chlorides also being converted in high yields.

Table 2: Scope with regard to the carboxylates.[a]



3aa, 92%; **3ba**, 90%; **3ca**, 58%

3da, 83%; **3ea**, 40%; **3fa**, 67%

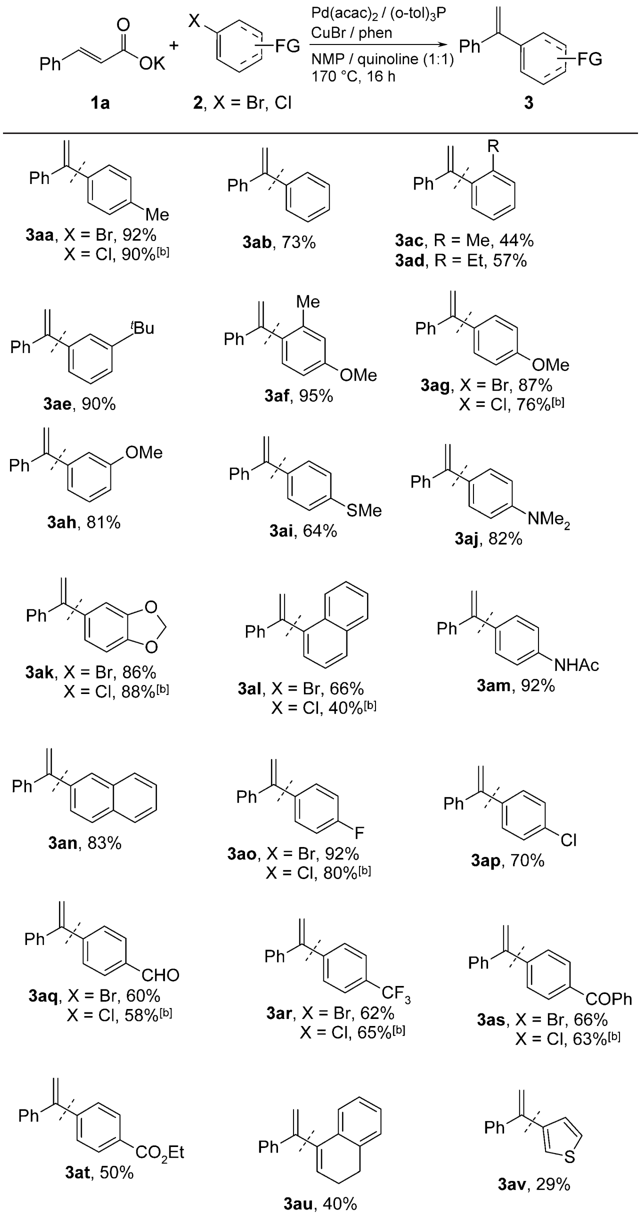
3ga, 74%; **3ha**, 82%; **3ia**, 94%

3ja, 74%; **3ka**, 82%; **3la**, 81%

3ma, 23%; **3na**, 72%; **3oa**, 81%

[a] Reaction conditions: **1** (1.20 mmol), **2a** (1.00 mmol), CuBr (10 mol%), 1,10-phenanthroline (10 mol%), Pd(acac)$_2$ (2 mol%), (*o*-tol)$_3$P (5 mol%), 3 mL of solvent (NMP/quinoline (1:1)), 170°C, 16 h. Yields of isolated products.

Table 3: Scope with regard to the electrophiles.[a]



3aa, X = Br, 92%
X = Cl, 90%[b]

3ab, 73%

3ac, R = Me, 44%
3ad, R = Et, 57%

3ae, 90%

3af, 95%

3ag, X = Br, 87%
X = Cl, 76%[b]

3ah, 81%

3ai, 64%

3aj, 82%

3ak, X = Br, 86%
X = Cl, 88%[b]

3al, X = Br, 66%
X = Cl, 40%[b]

3am, 92%

3an, 83%

3ao, X = Br, 92%
X = Cl, 80%[b]

3ap, 70%

3aq, X = Br, 60%
X = Cl, 58%[b]

3ar, X = Br, 62%
X = Cl, 65%[b]

3as, X = Br, 66%
X = Cl, 63%[b]

3at, 50%

3au, 40%

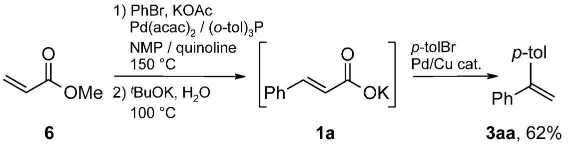
3av, 29%

[a] Reaction conditions: **1a** (1.20 mmol), **2** (1.00 mmol), CuBr (10 mol%), 1,10-phenanthroline (10 mol%), Pd(acac)$_2$ (2 mol%), (*o*-tol)$_3$P (5 mol%), 3 mL of solvent (NMP/quinoline (1:1)), 170°C, 16 h. Yields of isolated products. [b] **1a** (0.60 mmol), **2** (0.5 mmol), CuBr (10 mol%), 1,10-phenanthroline (10 mol%), Pd(acac)$_2$ (2 mol%), XPhos (5 mol%), 3 mL of solvent (NMP/quinoline (1:1)), 170°C, 16 h. Yields of isolated products. FG = functional group.

The new decarboxylative Heck process was successfully combined with a traditional Heck reaction into a convenient one-pot synthesis of unsymmetrically substituted 1,1-diarylalkenes from two different aryl bromides and methyl acrylate. In the first step, a cinnamate salt was synthesized from the corresponding aryl bromide and methyl acrylate by a Mizoroki–Heck reaction followed by hydrolysis of the methyl cinnamate. Subsequently, without solvent change or isolation of intermediates, a decarboxylative Heck coupling reaction furnishes the 1,1-diarylethylene in 62% yield (Scheme 3).

A series of experiments was performed to shed more light on the reaction mechanism (see the Supporting Information). The reaction occurred smoothly in the presence of the radical scavenger 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO), thus suggesting that neither coupling nor decarboxylation proceed through a radical pathway.[24] The reaction of styrene with 4-bromotoluene (**2a**) yielded the linear product **4aa** with high selectivity, which rules out a reaction pathway involving protodecarboxylation followed by a Heck reaction. When the reaction was performed with the deuterium-labeled starting material potassium (*E*)-3-(3,4-dimethoxyphenyl)-2-propenoate-3-*d* (D-**1d**), only 20% of the deuterium was incorporated in the original position of the carboxylate group. This indicates that the Heck coupling and decarboxylation steps occur in a separate rather than concerted fashion.

In conclusion, the decarboxylative Heck reaction disclosed herein opens up a convenient route to the synthesis of unsymmetrical 1,1-disubstituted alkenes from widely available precursors. Key advantages are the good regiochemical control, which is complementary to that of traditional Heck reactions, the use of cinnamates as the source of the vinyl group, and the excellent functional group tolerance. In this process, the carboxylate controls the regiochemistry of C−C



Scheme 3. One-pot synthesis of 1,1-diarylethylenes from methyl acrylate.

bond formation and is subsequently shed, thus acting as a deciduous directing group.

Acknowledgments

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Keywords: alkenes · carboxylic acids · copper · Heck reaction · palladium

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[23] phen = 1,10-phenanthroline; acac = acetylacetonate; BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; Johnphos = (2-biphenyl)di-*tert*-butylphosphine; TFA = trifluoroacetate; dba = dibenzylideneacetone; NMP = *N*-methyl-2-pyrrolidone.

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Communications

Cross-Coupling

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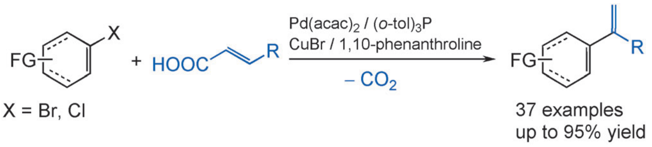
Branched Arylalkenes from Cinnamates: Selectivity Inversion in Heck Reactions by Carboxylates as Deciduous Directing Groups



Directors cut: A palladium/copper-catalyzed Mizoroki–Heck coupling of aryl halides with cinnamic acids has been developed in which the carboxylate group directs the arylation into its β-position before being tracelessly removed through protodecarboxylation. 1,1-Disubstituted alkenes are selectively obtained in this transformation, which ideally complements traditional 1,2-selective Heck reactions of styrenes.