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Doubly Regioselective C−H Hydroarylation of Unsymmetrical Alkynes Using Carboxylates as Deciduous Directing Groups

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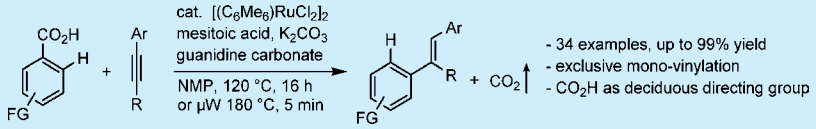
Supporting Information



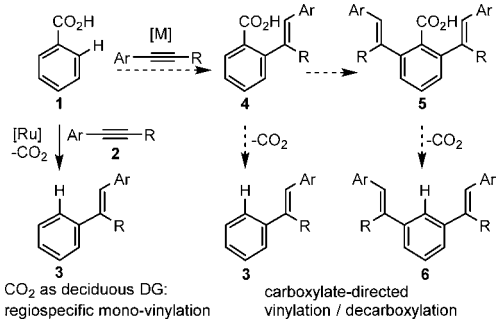
ABSTRACT: A catalyst system composed of $[(C_6Me_6)RuCl_2]_2$, potassium carbonate/guanidine carbonate, and mesitoic acid efficiently promotes the doubly regioselective C−H hydroarylation of unsymmetrical alkynes. The process involves carboxylate-directed *ortho*-C−H bond activation followed by regioselective addition to the alkyne C−C triple bond with concerted decarboxylation. This action of the carboxylate as a deciduous directing group ensures exclusive monovinylation with high selectivity for the (*E*)-1,2-diarylalkene.

Styrenes are prevalent structures often encountered in functional materials, pharmaceuticals, and natural and synthetic products.[1] Stoichiometric methods to access this structural motif, including Wittig[2] or Peterson olefinations[3] and insertions of alkynes into organometallic reagents,[4] are waste-intensive and require prefunctionalized substrates. Catalytic alternatives such as the Mizoroki−Heck reaction[5] and olefin metathesis[6] are more atom-economic but also require prefunctionalized arenes. C−H vinylations of the Fujiwara−Moritani type[7] have emerged as a powerful alternative but rely on stoichiometric oxidants.

C−H hydroarylations of alkynes compare favorably to the above concepts, especially when the regioselectivity is controlled effectively, e.g., by chelation assistance. Following early reports on ruthenium-catalyzed carbonyl-directed hydroarylations of alkynes,[8] several transition-metal catalysts, including precious[9−12] and first-row metals,[13,14] have been found to efficiently promote the insertion of alkynes into the C−H bond *ortho* to various directing groups. However, most of these directing groups, including phenol, ketone, pyridine, amide, and sulfoxide, require additional chemical steps for their synthesis, removal, or modification.

In this context, the use of carboxylates as directing groups is particularly desirable because they are easily accessible at low cost and in great structural diversity, can be transformed into a wealth of other compound classes, may serve as leaving groups in decarboxylative couplings, and are tracelessly removable by a subsequent protodecarboxylation step.[15,16] Over the years, extensive research has led to the discovery of carboxylate-directed substitutions of *ortho*-C−H atoms with (hetero)aryl, alkyl, acyl, allyl, alkoxy, olefin, amine, amide, and halogen groups.[17] The discovery that carboxylates can act as deciduous directing groups[18] that stay in place just long enough to direct one group into their *ortho*-position further improves the versatility of this group. A deciduous-type reaction pathway, in which the CO_2 is released concomitantly to C−C bond formation, intrinsically prevents unwanted double functionalization, a typical side reaction in *ortho*-C−H functionalizations (Scheme 1).[19]

Scheme 1. CO_2H as Deciduous vs Removable Directing Group (DG) in Catalytic Hydroarylations



The development of carboxylate-directed regiospecific C−H hydroarylations is challenging because of the weak coordinating ability of the carboxylate group and the known reactivity of alkynes to undergo carboxylate addition to the enol esters in the presence of Ru^{II}[20] and because carboxylate groups reduce the electron density at the arene ring, thereby lowering its reactivity.

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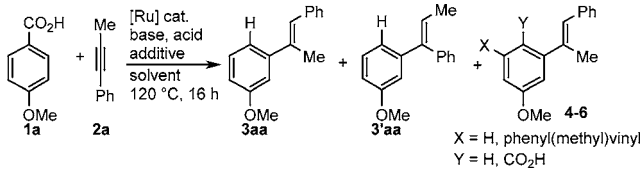
The Ackermann group, the group of Hartwig and Zhao, and our own group have independently developed Ru-catalyzed carboxylate-directed C−H hydroarylations of internal alkynes.[19a−c] All of these processes allow the decarboxylative hydroarylation of diarylalkynes in high yields. However, examples with alkylarylalkynes as coupling partners were provided only by Hartwig and Zhao, and these reactions did not proceed via a deciduous-type pathway. Selectivity for the monovinylated, decarboxylated product was achieved by using a 2-fold excess of the arenecarboxylate and a powerful copper protodecarboxylation catalyst. Satisfactory yields and selectivities were obtained merely for a few substrates.[19c]

We herein report a catalyst system that requires only low Ru loadings and no copper mediator to promote the regioselective decarboxylative monovinylation using unsymmetrical alkynes. In the search for an efficient protocol for the desired transformation, we used the reaction of *p*-methoxybenzoic acid **1a** and 1-phenyl-1-propyne **2a** as a model (Table 1).

Table 1. Optimization of the Reaction Conditions[a]



#	[Ru]	base (mol %)	acid	additive (mol %)	yield (%)		
					3aa	3'aa	4-6
1[b]	**[Ru1]**	-	-	$Cu(OAc)_2$ (20)	59	5	n.d.[19c]
2[b]	"	-	-	-	13	2	8
3[c]	**[Ru2]**	$GuanCO_3$ (20)	AcOH	2-picoline (20)	25	n.d.	21
4[c]	**[Ru3]**	"	"	"	38	"	20
5	"	"	"	"	53	3	23
6	"	"	"	-	53	3	29
8	"	K_2CO_3 (20)	"	-	31	16	8
9	"	Cs_2CO_3 (20)	"	-	23	9	8
10	"	K_2CO_3 (10)	"	-	39	3	5
11	"	$GuanCO_3$ (5) + K_2CO_3 (10)	"	-	60	9	13
12	"	"	TMBA	-	71	2	n.d.
13[d]	"	$GuanCO_3$ (10)	"	-	76	9	n.d.

[a]Method A: **1a** (0.5 mmol), **2a** (0.75 mmol), [Ru] (4 mol %), base, acid (1 equiv), additive, NMP (1 mL), 120 °C, 16 h. [b]Method A: **1a** (1 mmol), **2a** (0.5 mmol), [**Ru1**] (10 mol %) in dioxane/mesitylene/*n*-heptane (2:2:1), 80 °C, 48 h. [c]Method A: **2a** (0.5 mmol) in PhMe. [d]Method B: **1a** (1 mmol), **2a** (0.5 mmol), [Ru] (4 mol %), guanidine carbonate (10 mol %), TMBA (0.5 equiv), NMP (2 mL), 180 °C μW, 5 min. Yields were determined by GC analysis after esterification with MeI/K_2CO_3 using *n*-tetradecane as internal standard. [**Ru1**] = $(p\text{-cym})Ru(OAc)_2$, [**Ru2**] = $[(p\text{-cym})RuCl_2]_2$, [**Ru3**] = $[(C_6Me_6)RuCl_2]_2$. $GuanCO_3$ = guanidinium carbonate. TMBA = 2,4,6-trimethylbenzoic (mesitoic) acid.

When Hartwig and Zhao's conditions were used, i.e., treatment a 2-fold excess of **1a** with **2a** in the presence of [**Ru1**] and 20 mol % $Cu(OAc)_2$ in dioxane/mesitylene/*n*-heptane at 80 °C for 48 h,[19c] the desired styrene **3aa** was formed in 59% yield and a **3aa**/**3′aa** regioselectivity of 12:1 (Table 1, entry 1). Unsatisfactory results and formation of products **4**−**6** in notable amounts were observed without the copper mediator (entry 2). Our conditions previously optimized for diarylalkynes, namely **1a** (0.5 mmol), **2a** (1 equiv), $[(p\text{-cymene})RuCl_2]_2$ (4 mol %, [**Ru2**]), guanidine carbonate (20 mol %), AcOH (1 equiv), and 2-picoline (20 mol %) in toluene, provided **3aa** in 25% yield along with 21% of **4aa**−**6aa**, which are products arising from a competing nondeciduous directing mode of the carboxylate group (entry 3). Screening of various catalysts, additives, and solvents showed that the combination of a $[(C_6Me_6)RuCl_2]_2$ ([**Ru3**]) catalyst and the polar aprotic solvent NMP gave greater conversion and good regioselectivity (entry 4 and Table S1). Increasing the amount of **2a** to 1.5 equiv further improved the yield (entry 5). Interestingly, 2-picoline, which was an important component of our original conditions, did not affect the outcome here (entry 6). Higher yields were obtained when the acetic medium was buffered with 5 mol % of guanidine carbonate and 10 mol % of potassium carbonate (entries 8−11). Substituting acetic by mesitoic acid shifted the reaction completely toward the desired pathway, so that products **4**−**6** arising from competing pathways were no longer detected. Within 16 h under optimal conditions, i.e., **1a** (0.5 mmol), **2a** (0.75 mmol), $[(C_6Me_6)RuCl_2]_2$ (4 mol %), guanidine carbonate (5 mol %), K_2CO_3 (10 mol %), and mesitoic acid (1 equiv) in NMP (1 mL) at 120 °C, the monovinylated product **3aa** was obtained exclusively and with an impressive **3aa**/**3′aa** regioselectivity of 36:1 in favor of the less sterically hindered alkyl-branched product (entry 12, method A). The regiochemical preference is in agreement with findings by Fagnou, Miura, Rovis, Li, Ackermann, Larock, and others on mechanistically related oxidative annulation reactions.[21]

When a preformed *o*-vinylbenzoic acid (**4ba**) was subjected to the reaction conditions, no decarboxylation was observed (see the Supporting Information), which confirms that C−C bond formation and decarboxylation indeed occur concertedly. Further control experiments established that both base and acid additive are required (Table S1).

The only drawback of this protocol was the long reaction time. However, this can be shortened to only 5 min by employing microwave irradiation (method B) after small adjustments to the catalyst system (10 mol % of guanidine carbonate as the only base and with the amount of mesitoic acid reduced to 0.5 equiv).[22]

With two effective sets of conditions in hand, the scope and selectivity of the ruthenium-catalyzed decarboxylative C−H hydroarylation of **2a** with substituted benzoic acids **1** were evaluated (Scheme 2). The scope extends from electron-rich to electron-poor benzoic acids with various functional groups in the *ortho*, *meta*, or *para* positions, as well as heterocyclic carboxylates. Benzoic acids bearing *ortho* substituents generally gave excellent yields (**3ba**−**ka**). *Para*-substituted benzoic acids afforded monofunctionalized products (**3aa**,**la**−**oa**) exclusively and in good yields. *p*-Toluic acid (**1m**) afforded 30% of non-decarboxylated product **4ma** along with **3ma**, which presumably result from a competing nondeciduous pathway. Extending the reaction time to 48 h did not shift the product distribution further toward **3ma** (see the SI). This clearly indicates that the decarboxylated product results from a concerted C−C bond formation/decarboxylation process, and that once the non-decarboxylated product is released, it does not re-enter the catalytic cycle. The reactivity of *meta*-substituted acids was lower (**3pa**,**qa**). Deactivating substituents such as nitro groups reduced the yields (**3wa**). With 2-allyl benzoate, the side-chain double bond isomerized into conjugation under the reaction conditions (**3da**). The efficiency of the microwave method was generally

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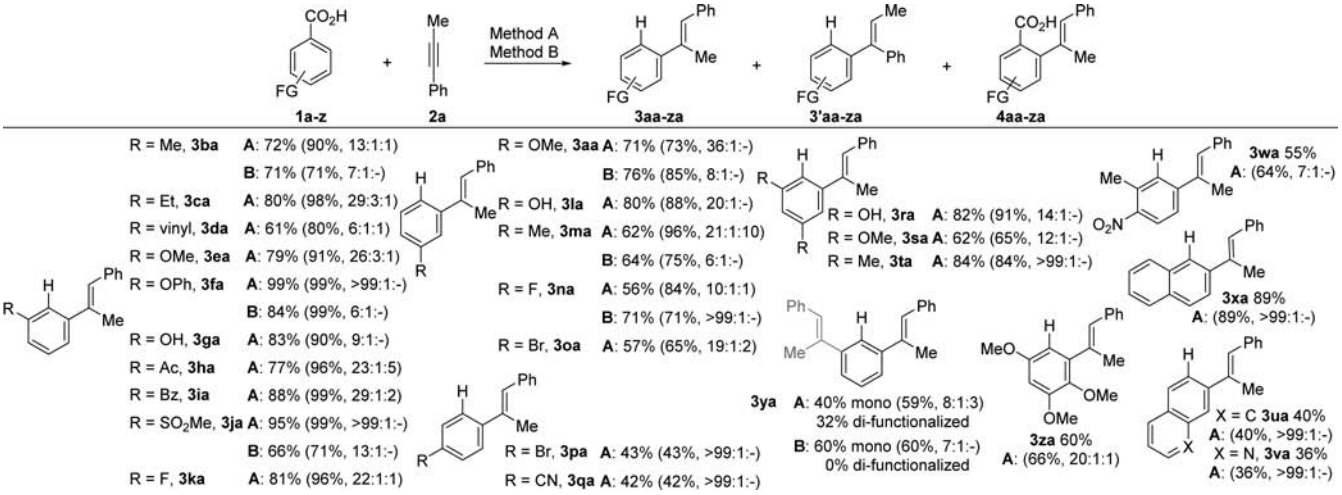
Scheme 2. Scope with Respect to the Benzoic Acids[a]

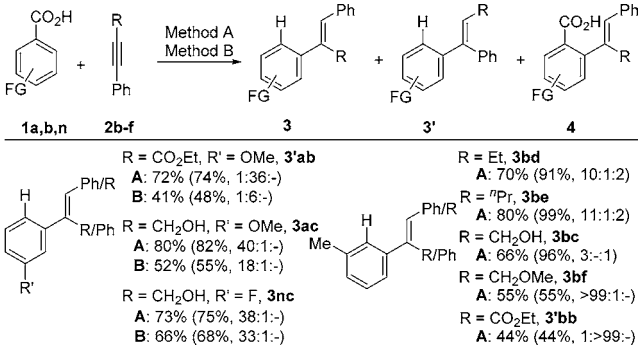


[a]Isolated yields. GC yields and product ratios of **3**:**3′**:**4**, in parentheses, after esterification using *n*-tetradecane as internal standard.

comparable, although the higher reaction temperature somewhat affected the regioselectivity. Only for unsubstituted benzoic acid (**1y**) was nondecarboxylative hydroarylation a major side reaction under thermal conditions, leading to the formation of substantial amounts of disubstituted products. However, under microwave conditions, the carboxylate acted as a deciduous directing group again, and only monovinylated product **3ya** was observed.

We next investigated the alkyne substrate scope in combination with *p*-anisic (**1a**), *p*-fluorobenzoic (**1n**), and *o*-toluic acid (**1b**) (Scheme 3). For alkylarylalkynes **2b**–**f**, high

Scheme 3. Scope with Respect to the Alkynes[a]

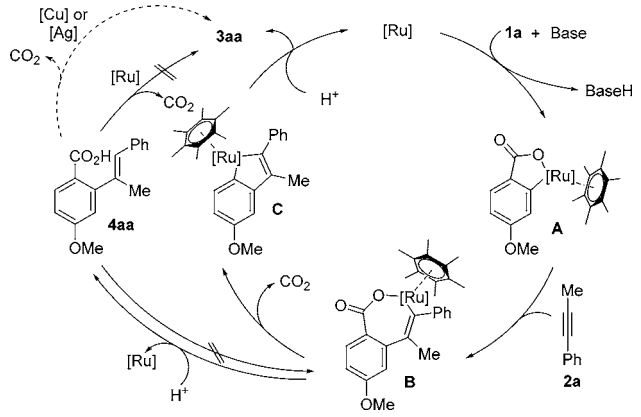


[a]Isolated yields. GC yields and product ratios of **3**:**3′**:**4**, in parentheses, after esterification using *n*-tetradecane as internal standard.

yields and excellent regioselectivities of the desired products were achieved. Electron-poor propiolates (**2b**) were successfully converted to *β*,*β*-diaryl acrylates, which are valuable synthons for further decarboxylative couplings.[18,23] Terminal alkynes did not react under the reaction conditions.

A plausible reaction pathway derived from mechanistic experiments (see the SI) is outlined in Scheme 4. Following C–H activation, the *ortho*-ruthenated complex **A** coordinates the alkyne substrate. Migratory insertion leads to the seven-membered ruthenacycle **B**. Possible next steps involve either decarboxylation to intermediate **C**, which is then protodemetalated to product **3aa**, or early protodemetalation of **B**, resulting in the nondecarboxylated compound **4aa**. Ruthenium is not

Scheme 4. Proposed Mechanism for the Ruthenium-Catalyzed Decarboxylative Hydroarylation



capable by itself of decarboxylating **4aa** under these conditions. CO_2 extrusion can occur only in the presence of copper or silver decarboxylation catalysts, as previously reported.[16]

In conclusion, an effective and broadly applicable C–H hydroarylation of unsymmetrical alkynes has been developed on the basis of the inexpensive and easy-to-handle catalyst $[(C_6Me_6)RuCl_2]_2$. The concerted C–C bond formation/CO_2 extrusion process ensures nearly exclusive formation of monovinylated products and obviates a subsequent protodecarboxylation step.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00300.

Detailed screening tables, experimental procedures, analytical data for all the products, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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