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Palladium-catalyzed cross-coupling of α-bromocarbonyls and allylic alcohols for the synthesis of α-aryl dicarbonyl compounds†

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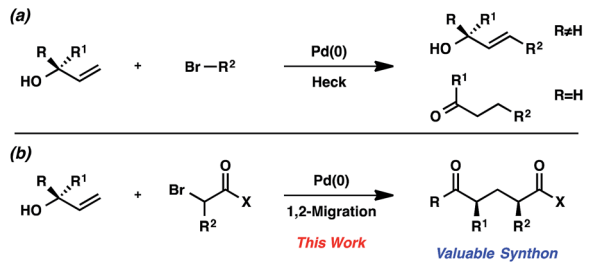
The palladium-catalyzed coupling of olefins and organohalides is a versatile approach for synthesizing complex molecules from simple starting materials. We have developed a palladium-catalyzed coupling of α-bromocarbonyl compounds with allylic alcohols for the generation of acyclic aryl-substituted dicarbonyl compounds. The reaction proceeds *via* a tandem olefin insertion of an α-acyl radical followed by a 1,2-aryl migration. In addition to providing preliminary evidence for a free radical mediated mechanism, we demonstrate unprecedented levels of 1,3-stereoinduction for the 1,2-migration step.

Introduction

Since the initial reports of the Mizoroki–Heck reaction over 40 years ago,[1] the palladium-catalyzed coupling of olefins and organohalides has become one of the most effective strategies for the generation of new carbon–carbon bonds.[2,3] The widespread use of this reaction manifold is often attributed to the functional group tolerance of palladium catalysts, along with the affordability, accessibility, and stability of olefins and organohalides.

We were interested in expanding the synthetic utility of the Mizoroki–Heck reaction by exploiting the unique reactivity of allylic alcohols. This specific class of olefin substrates reacts with organohalides under palladium catalysis to yield traditional Mizoroki–Heck products after β-hydride elimination (Scheme 1a).[4] We hypothesized that under modified conditions, the traditional β-hydride elimination pathway could be suppressed and allylic alcohols could be coupled with organohalides to undergo a 1,2-migration (Scheme 1b). Moreover, the use of bromocarbonyl compounds[5] as the organohalide would furnish acyclic substituted 1,5-dicarbonyl compounds with multiple stereocenters, which are valuable synthons for many biologically active natural products and pharmaceutical drug candidates.[6]



Scheme 1 Palladium-catalyzed coupling of allylic alcohols and organohalides.

In this communication, we describe a new strategy for synthesizing acyclic aryl dicarbonyl compounds. Bromocarbonyls and allylic alcohols are coupled in the presence of a palladium catalyst and a silver salt to furnish products with broad substrate scope. We provide evidence for the intermediacy of free radicals in this process and present preliminary data for the control of stereochemistry, with unprecedented levels of 1,3-stereoinduction in the 1,2-aryl migration.[7]

Results and discussion

Initial exploration of this new approach to aryl dicarbonyls was performed with allylic alcohol **1** and bromoester **2** in the presence of various palladium sources, phosphine ligands, and metal salts as additives (Table 1).[8] With $[PdCl_2(PhCN)_2]$ as the precatalyst and dppe as the ligand, product **3** was not formed in the presence of NaOAc or $Cu(OAc)_2$ (entries 1–2). To our delight, AgOAc furnished the desired product, albeit in low yield (entry 3), and Ag_2CO_3 proved to be a more effective additive (entry 4). The identity of the ligand also affected the efficiency of the reaction (entries 4–9), and the bidendate ligand dppe was optimal. After a survey of common organic solvents, trifluorotoluene (TFT) was identified as the reaction medium of choice (entries 10–12).

The unique reactivity of silver salts may be due to their ability to act as single electron oxidants in radical transformations.[9] In

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† Electronic supplementary information (ESI) available. CCDC 1042318. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5sc00505a

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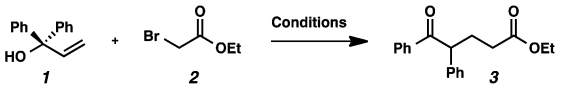
Table 1 Optimization of palladium-catalyzed synthesis of aryl dicarbonyl compounds[e]



Entry	Pd source (5 mol%)	Ligand (10 mol%)	Additive (2 equiv.)	Solvent	Temp. (°C)	Yield[a] (%)
1	$[PdCl_2(PhCN)_2]$	dppe	NaOAc	PhMe	110	0
2	$[PdCl_2(PhCN)_2]$	dppe	$Cu(OAc)_2$	PhMe	110	0
3	$[PdCl_2(PhCN)_2]$	dppe	AgOAc	PhMe	110	24
4	$[PdCl_2(PhCN)_2]$	dppe	Ag_2CO_3	PhMe	110	66
5	$[PdCl_2(PhCN)_2]$	—	Ag_2CO_3	PhMe	110	22
6	$[PdCl_2(PhCN)_2]$	PPh_3	Ag_2CO_3	PhMe	110	63
7	$[PdCl_2(PhCN)_2]$	P(*p*-Tol)$_3$	Ag_2CO_3	PhMe	110	55
8	$[PdCl_2(PhCN)_2]$	P(*o*-Tol)$_3$	Ag_2CO_3	PhMe	110	43
9	$[PdCl_2(PhCN)_2]$	PCy_3	Ag_2CO_3	PhMe	110	47
10	$[PdCl_2(PhCN)_2]$	dppe	Ag_2CO_3	DMF	120	0
11	$[PdCl_2(PhCN)_2]$	dppe	Ag_2CO_3	Dioxane	100	63
12	$[PdCl_2(PhCN)_2]$	dppe	Ag_2CO_3	$PhCF_3$	120	93(81)[b]
13	—	dppe	Ag_2CO_3	PhMe	110	0
14	*$[PdCl_2(PhCN)_2]$*	*dppe*	*Ag_2O*	*$PhCF_3$*	*120*	*94(83)[b]*
15[c]	$[PdCl_2(PhCN)_2]$	dppe	Ag_2O	$PhCF_3$	120	0
16[d]	$[PdCl_2(PhCN)_2]$	dppe	Ag_2O	$PhCF_3$	120	50

[a] HNMR yield with 1,4-dimethoxybenzene as an internal standard. [b] Isolated yield. [c] Ethyl chloroacetate (0.2 mmol) used as substrate. [d] Ethyl iodoacetate (0.2 mmol) used as substrate. [e] Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), palladium source (5 mol%), ligand (10 mol%), additive (0.2 mmol), and solvent (0.1 M), 12 h.

the absence of palladium, product **3** was not formed, which suggests that silver is not mediating this process by itself (entry 13). Another less basic silver salt, Ag_2O, proved to be an effective additive for the process (entry 14). This observation supports the role of silver salts as single electron oxidants rather than inorganic bases.

Interestingly, the corresponding chloroester did not yield the desired product (entry 15), presumably because of the greater bond dissociation energy of C–Cl than C–Br.[10] In addition, the analogous iodoester reacted with allylic alcohol **1** to furnish 1,5-dicarbonyl **3** in considerably lower yield (entry 16), which may be a result of competing reaction pathways for this more reactive α-haloester.

With optimal reaction conditions in hand (Table 1, entry 14), we examined the scope of allylic alcohols that can be coupled with bromoester **5** (Table 2). Symmetrical allylic alcohols (R = Ar) with electron-rich and electron-deficient aromatic rings yielded the aryl ketone products in synthetically useful yields (entries 1–6). The reaction was tolerant of *ortho*-, *meta*-, and *para*-substitution on the aromatic ring. Interestingly, unsymmetrical allylic alcohols coupled with bromoester **5** usually with preferential migration of the electron-deficient aromatic ring (entries 7–8), which sheds light on the mechanism of the 1,2-migration (*vide infra*). A simple aliphatic group (R = Me) resisted migration, which resulted in the formation of an acyclic unsymmetrical aryl ketone (entry 10). Accessing this ketone by many other methods would be plagued by low regioselectivity in functionalization. Alternatively, a cyclopropyl group (R = *c*-Pr) underwent 1,2-migration to yield a cyclopropyl phenylketone, albeit as the minor product (entry 11).[11] Finally, a 2-substituted allylic alcohol was a competent substrate for the coupling reaction, which furnished a quaternary carbon (entry 12).

We recognized the potential of this novel coupling reaction to generate aryl dicarbonyl compounds with multiple stereocenters (Table 3). First, we determined that substitution did not affect the efficiency of the overall process (entry 1). Next, the diastereoselectivity of product formation with methyl bromocarbonyl compounds was examined (entries 2–7). An examination of the literature reveals that the 1,4-addition of the enolate of an aryl ketone to a methacrylate derivative leads to low 1,3-stereoinduction in the formation of 1,5-dicarbonyl compounds such as **8**.[12] We therefore focused on the diastereoselective generation of product **8**. Under our palladium-catalyzed coupling conditions, methyl bromoesters generated coupling products with low diastereoselectivity regardless of the steric bulk of the ester (entries 2–4). Weinreb amides,[13] on the other hand, exhibited modest diastereoselectivity in product formation (entries 5–6). To our delight, a piperidine-substituted methyl bromoamide was converted to the aryl ketone product with a synthetically useful diastereomeric ratio of 5 : 1 (entry 7), which is the highest level of 1,3-stereoinduction in 1,2-aryl migrations reported to date.[14] The relative stereochemistry of the major diastereomer of the product was confirmed by X-ray crystallography.[15]

Initial mechanistic studies favor a free radical pathway (Scheme 2, path b) rather than organopalladium intermediates (path a). Inclusion of TEMPO in the reaction medium resulted in the formation of hydroxylamine **14**.[16] The TEMPO adduct of free radical intermediate **15** was not observed, presumably because 1,2-aryl migrations are kinetically competitive with free

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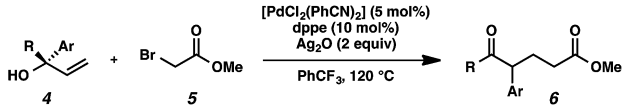
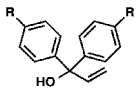
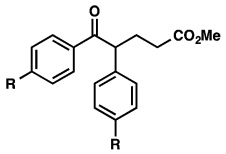
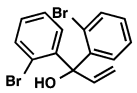
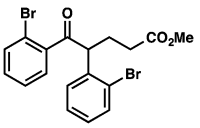
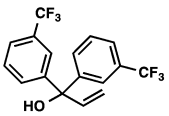
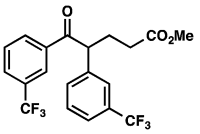
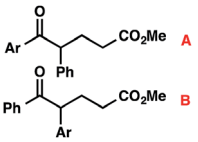
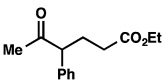
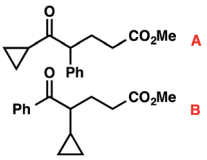
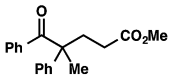
Table 2 Substrate scope of allylic alcohol[d]



Entry	Allylic alcohol		Product	Yield[a] (%)
1		R = H		84
2		R = Me		56
3		R = OMe		85
4		R = Cl		66
5				42
6				88
7		Ar = *p*-OMePh		66 (1.7 : 1)[b]
8		Ar = *p*-CF_3Ph		81 (1 : 8)[b]
9		Ar = 2-Thiophene		46 (0 : 1)[b]
10[c]				53
11				43 (2.5 : 1)[b]
12				73

[a] Isolated yield. [b] Structural isomer ratio in parentheses (A : B). Structural isomers were separable by column chromatography. [c] Ethyl bromoacetate used as substrate (0.4 mmol). [d] Reaction conditions: **4** (0.2 mmol), **5** (0.4 mmol), $[PdCl_2(PhCN)_2]$ (5 mol%), dppe (10 mol%), Ag_2O (0.4 mmol), α,α,α-trifluorotoluene (0.1 M), at 120 °C, 12 h.

radical coupling with TEMPO.[17,18] As shown previously, electron-deficient aromatic rings exhibited a greater proclivity for migration than electron-rich aromatic rings (Table 2, entries 7–8), which suggests a neophyl-type rearrangement *via* spiro[2,5]-octadienyl radical **16**.[19] The stereochemical outcome of subjecting highly enantioenriched allylic alcohols **19a** and **19b** to the reaction conditions is also consistent with a mechanism that involves acyclic free radical **15**. The loss of enantiomeric excess in the formation of aryl ketones **20a** and **20b** may be the result of 1,2-aryl migration to either stereotopic face of the radical center in intermediate **15**.[20]

Conclusions

In conclusion, we have discovered a new mode of reactivity for the palladium-catalyzed coupling of allylic alcohols with bromo carbonyl compounds to generate a broad range of aryl 1,5-dicarbonyls. Despite the intermediacy of acyclic free radicals in the proposed mechanism, we have preliminary data for the formation of acyclic 1,5-dicarbonyl products with synthetically useful levels of 1,3-stereoinduction. We are currently exploring a catalytic enantioselective version of this process and its application to the synthesis of complex natural products.

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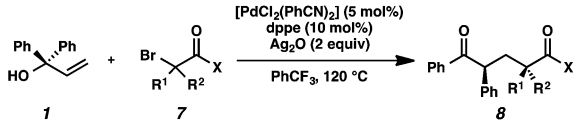
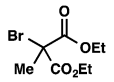
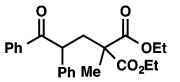
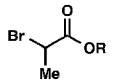
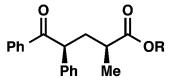
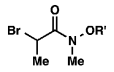
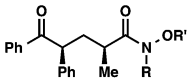
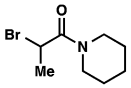
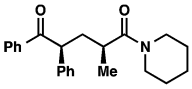
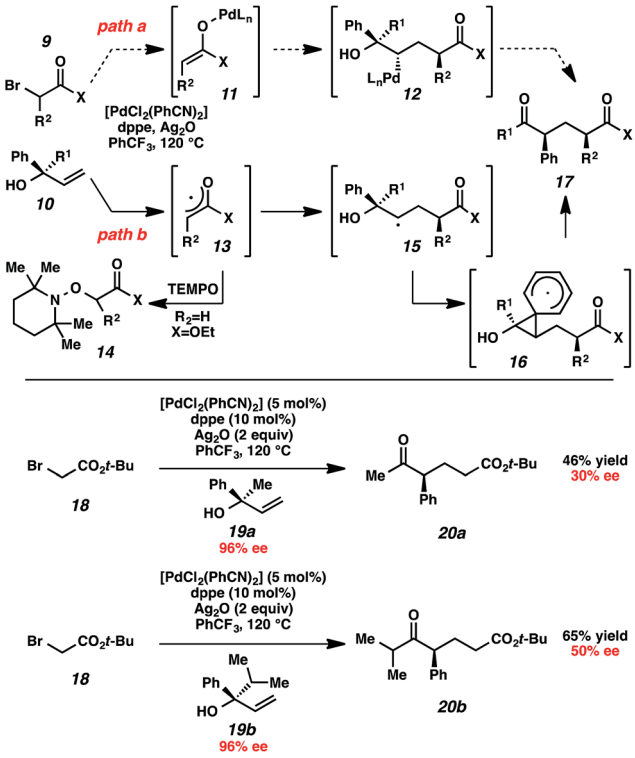
Table 3 Substrate scope of α-substituted bromocarbonyl[c]



Entry	Bromocarbonyl		Product	Yield[a] (%)
1				72
2		R = Me		98 (1.3 : 1)[b]
3		R = Et		99 (1.3 : 1)[b]
4		R = *t*-Bu		69 (1.7 : 1)[b]
5		R′ = Me		92 (3 : 1)[b]
6		R′ = *t*-Bu		75 (3.6 : 1)[b]
7				95 (5 : 1)[b]

[a] Isolated yield. [b] Diastereomeric ratio in parentheses (syn : anti). [c] Reaction conditions: **1** (0.2 mmol), **7** (0.4 mmol), $[PdCl_2(PhCN)_2]$ (5 mol%), dppe (10 mol%), Ag_2O (0.4 mmol), α,α,α-trifluorotoluene (0.1 M), at 120 °C, 12 h.



Scheme 2 Mechanistic studies.

Experimental

In an 8 mL reaction vial, a solution of 1,1-diphenylprop-2-en-1-ol **1** (0.200 mmol, 42.0 mg, 1.0 equiv.), $Pd(PhCN)_2Cl_2$ (3.80 mg, 5 mol%), dppe (8.0 mg, 10 mol%), and Ag_2O (0.400 mmol, 92.7 mg, 2.0 equiv.), in α,α,α-trifluorotoluene (1.0 mL, 0.2 M) was treated with ethyl bromoacetate **2** (0.400 mmol, 66.9 mg, 2.0 equiv.). The reaction vial was charged with nitrogen for 5 minutes and then sealed. The mixture was stirred at 120 °C for 12 h. After the reaction was finished, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was purified by silica gel flash chromatography (gradient eluent pentane/diethyl ether) to afford the desired product **3** (49.2 mg, 83% yield) as a clear oil.

Acknowledgements

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Notes and references

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