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Decarboxylative Benzylations of Alkynes and Ketones

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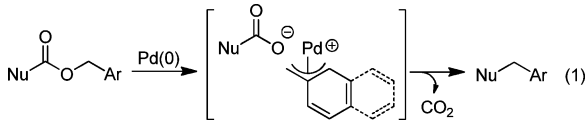
Abstract: Benzyl esters of propiolic and β-keto acids undergo catalytic decarboxylative coupling when treated with appropriate palladium catalysts. Such decarboxylative couplings allow the benzylation of alkynes without the use of strong bases and/or organometallics. This allows the synthesis of sensitive benzylic alkynes that are prone to undergo isomerizations under basic conditions. Additionally, decarboxylation facilitates the site-specific benzylation of diketones and ketoesters under mild, base-free conditions. Ultimately, the methodology described expands our ability to cross-couple medicinally relevant heterocycles.

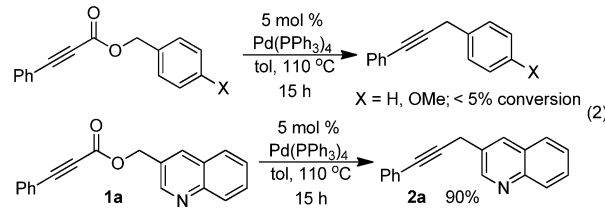
Utilization of palladium π-benzyl complexes in cross-coupling reactions is becoming increasingly important in organic synthesis.[1] However, methods for benzylic cross-couplings typically rely on the use of basic reagents or preformed organometallics. For example, Buchwald reported the cross-coupling of benzyl halides with alkynes using stoichiometric Cs_2CO_3; unfortunately, the basic reaction conditions often induce isomerization of the product benzylic alkynes to isomeric allenes.[2] Negishi reported the benzylic cross-coupling with acetylides via stoichiometric alkynyl zinc bromides that must be prepared from $ZnBr_2$.[3] Not only do these methods require stoichiometric bases or organometallics, but they also utilize benzyl halides that are expensive, hazardous, and more difficult to handle than related benzyl alcohol derivatives.

Legros, Kuwano, and others have reported catalytic benzylation of stabilized nucleophiles using activated benzylic alcohol derivatives.[4] While benzylations of highly stabilized enolates ($pK_a \approx 10-13$),[4a−d] phenols ($pK_a \approx 10$),[4e] and arene sulfinates ($pK_a \approx 7$)[4f] have been successful, the reaction of less stabilized nucleophiles has proven difficult.[5] Since we have previously developed decarboxylative coupling strategies that allow allylation of nonstabilized nucleophiles without the use of an external base or organometallic, we hypothesized that a similar strategy might allow decarboxylative coupling of benzylic esters with nonstabilized nucleophiles (eq 1).[5−7]



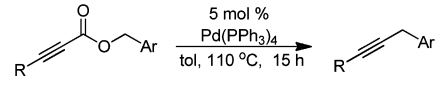
(1)

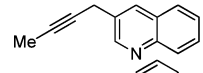
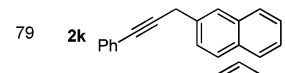
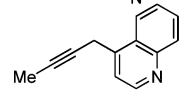
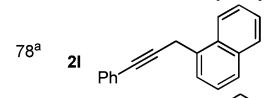
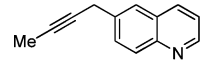
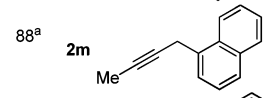
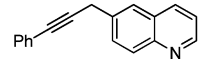
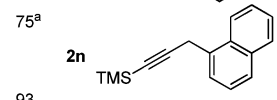
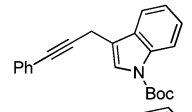
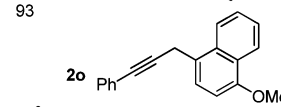
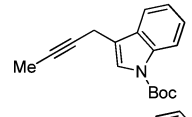
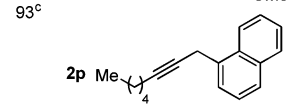
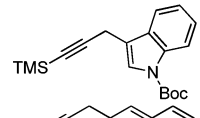
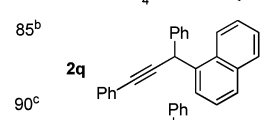
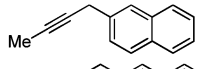
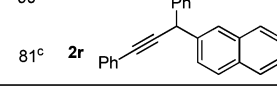
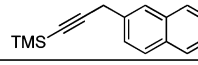
To test this hypothesis, several benzyl phenylpropiolates were synthesized and heated to 110 °C in the presence of catalytic $Pd(PPh_3)_4$ (eq 2). While the simple benzyl phenylpropiolate failed to undergo reaction under these conditions, it was gratifying to find that the heterobenzylation to form **2a** proceeded in high yield. Importantly, control reactions showed no conversion in the absence of the palladium catalyst. The much slower formation of π-benzyl palladium complexes from benzyl acetate relative to polycyclic analogs has been previously noted and ascribed to the disruption of aromaticity.[4a,8]



Having demonstrated a successful decarboxylative benzylation, we briefly examined the scope of this transformation. Doing so revealed that a variety of benzylic esters that have extended aromatic conjugation underwent smooth decarboxylative benzylation (Table 1). Heteroaromatic benzyl esters, including an array of quinolines and indoles, provide good to excellent yields of the coupled products (entries **2b**−**2h**). In addition, both 1-naphthyl- and 2-naphthylmethyl esters are compatible reaction partners (entries **2i**−**2o**). Similarly, the alkyne can bear an aliphatic or aromatic group with little effect on the yield of the reaction. This lies in contrast to decarboxylative

Table 1. Decarboxylative Benzylations of Alkynes



entry	product	yield(%)	entry	product	yield(%)
2b		79	**2k**		78[c]
2c		78[a]	**2l**		88
2d		88[a]	**2m**		88
2e		75[a]	**2n**		89[c]
2f		93	**2o**		89
2g		93[c]	**2p**		74
2h		85[b]	**2q**		30
2i		90[c]	**2r**		86[c]
2j		81[c]			

[a] Must be stored cold upon isolation. [b] 7 h reaction time. [c] 10 mol % $Pd(PPh_3)_4$.

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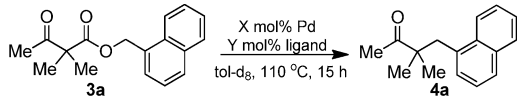
allylation of alkynes where aromatic propiolates are superior substrates.[6] Lastly, while a terminal alkyne failed to undergo any reaction, trimethylsilyl-protected alkynes could be used in lieu of a terminal alkyne (**2h**, **2j**, **2n**, Table 1).

Given the success of the benzyl alkynyl coupling, we turned our attention to developing decarboxylative benzylation of ketones. Related decarboxylative allylations have allowed allylation of ketone enolates, but these reactions have not been extended to related benzylation chemistry.[7] To begin, the 1-naphthyl-β-ketoester **3a** was treated under identical conditions to those used for benzyl alkynyl coupling (entry 1, Table 2). The reaction proceeded to 53% conversion, allowing isolation of **4a** in just 36% yield. Initial catalyst screening revealed that combination of a more electron-deficient, dba-ligated palladium precatalyst with triphenylphosphine was ineffective (entry 3, Table 2). Reasoning that a more electron-rich catalyst may facilitate the formation of the putative electron-deficient π-benzyl palladium complex, several additional Pd catalysts and ligands were explored (Table 2). While bulky, electron-rich phosphines failed to promote the reaction (entries 4 and 5), smaller electron-rich ligands provided better conversion (entries 6−8). In addition, diphenylphosphinoferrocene (dppf) provided high conversion to product when combined with a catalyst precursor that is devoid of an electron-withdrawing dba ligand (entry 10).

Table 2. Catalyst Screening



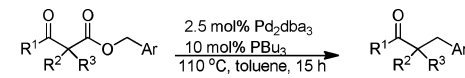
entry	X	Pd	Y	ligand	conversion (%)[a]
1	5	$Pd(PPh_3)_4$	−	none	53
2	10	$Pd(PPh_3)_4$	−	none	70
3	5	Pd_2dba_3	10	PPh_3	4
4	5	Pd_2dba_3	10	$P(t\text{-}Bu)_3$	0
5	5	Pd_2dba_3	10	PCy_3	0
6	5	Pd_2dba_3	10	PMe_3	19
7	5	Pd_2dba_3	10	PBu_3	>99
8	2.5	Pd_2dba_3	10	PBu_3	>99
9	1	Pd_2dba_3	5	PBu_3	21[a]
10	10	CpPd(allyl)	11	dppf	97

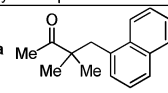
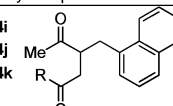
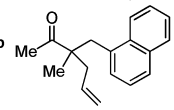
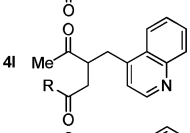
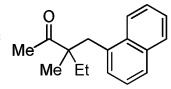
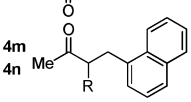
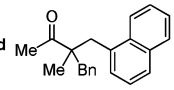
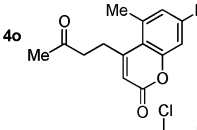
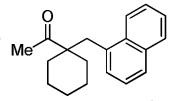
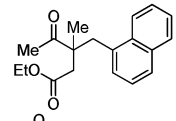
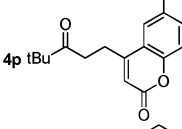
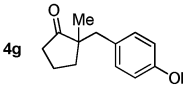
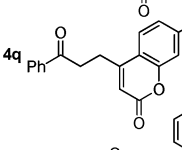
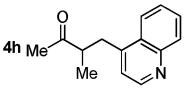
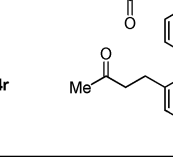
[a] Determined by ^{1}H NMR spectroscopy. [b] 97% conversion after 40 h.

Using the optimized conditions with PBu_3 as a ligand,[9] various substituted benzyl esters were converted to benzylated ketones in good to high yields (Table 3). It is noteworthy that the reaction allows C−C bond formations that give rise to hindered quaternary carbon centers. While attempted coupling of an unsubstituted benzyl electrophile failed, a *p*-methoxybenzyl electrophile was compatible with the ketone coupling (**4g**). Presumably the electron-donating methoxy substituent stabilizes the putative π-benzyl intermediate enough to facilitate the reaction. The reaction can also be extended to the formation of less substituted ketones; however $Pd(PPh_3)_4$ proved to be the best catalyst for those substrates. Importantly, the coupling is compatible with a variety of electron-rich benzyl and heterobenzylic reaction partners that are of significant interest in medicinal chemistry.

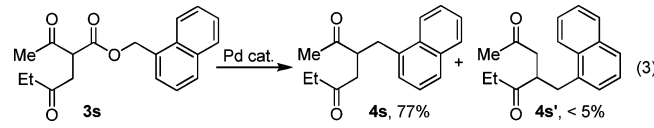
To examine the regiospecificity of benzylation, substrate **3s** was prepared via alkylation of the ketoester with 1-bromobutanone. Treatment of **3s** under our catalytic reaction conditions led to site-specific benzylation of the enolate to form **4s**; no product resulting from enolate isomerization (**4s′**) was observed. Thus, decarboxylative benzylation allows regiospecific benzylation of 1,4-diketone analogues (**4f**, **4i**−**4l**, Table 3). Such regioselectivity would be difficult, if not impossible, to achieve using standard enolate alkylation chemistry.

Table 3. Decarboxylative Benzylations of Substituted Ketones



entry	product	yield(%)	entry	product	R	yield(%)
4a		93	**4i**		OEt	75[a]
			4j		*p*-$MeOC_6H_4$	81[a]
			4k		*o*-$MeOC_6H_4$	88[a]
4b		91	**4l**		OEt	51[a,c]
4c		95[a]	**4m**		Me	87[a]
			4n		Bn	68[a]
4d		71[a]	**4o**			80[d]
4e		61				
4f		77	**4p**			90[d]
4g		67[b]	**4q**			79[d]
4h		60[a,c]	**4r**			75[d]

[a] 10 mol % $Pd(PPh_3)_4$. [b] 10 mol % CpPd(allyl), 11 mol % dppf. [c] reaction performed at 85 °C. [d] 5 mol % $Pd(PPh_3)_4$, 25 °C, MeCN.



(3)

In conclusion, we developed new catalytic decarboxylative benzylations of alkynes and ketones. Such decarboxylative couplings utilize the loss of CO_2 as a driving force in lieu of the use of external bases and/or organometallics. Furthermore, the coupling allows the site-specific benzylation of 1,4-ketone analogues to form products that would be difficult to access via traditional base-mediated enolate methodology. Ultimately, both ketones and alkynes can be coupled with a variety of medicinally relevant heterobenzylic species including quinolines, indoles, and coumarins.

Acknowledgment. We thank the National Science Foundation (CHE-0548081), the National Institutes of Health, KU Chemical Methodologies, and Library Development Center of Excellence (P50 GM069663) for support. We also thank Dr. Shelli Waetzig.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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