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Catalytic α-Arylation of Ketones with Heteroaromatic Esters

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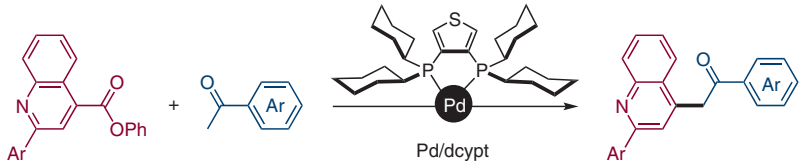

α-Arylation of Ketones with Aromatic Esters

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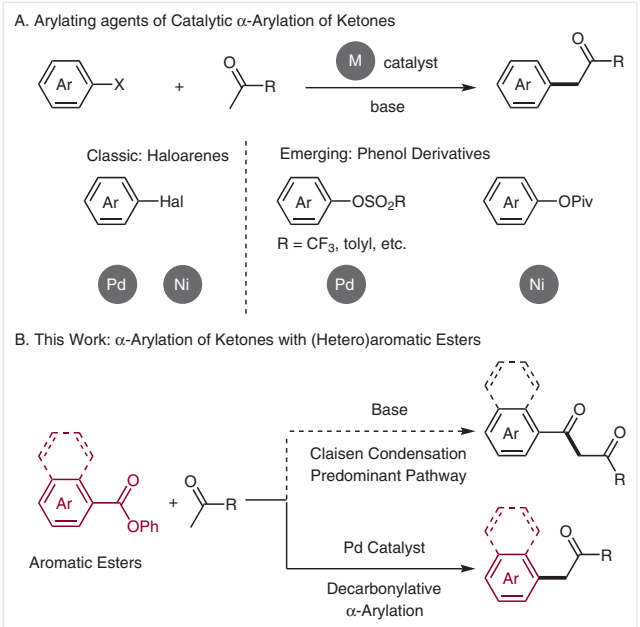
Abstract Heteroaromatic esters were found to be applicable as an arylating agent for the Pd-catalyzed α-arylation of ketones in a decarbonylative fashion. The use of our in-house ligand, dcypt, enabled this unique bond formation. Considering the ubiquity and low cost of aromatic esters, the present work will allow for rapid access to valuable α-aryl carbonyl compounds.

Key words α-arylation, aromatic esters, decarbonylative coupling, palladium, heteroarenes, ketones

α-Aryl carbonyls are fundamental building blocks because they can be transformed into a range of pharmaceuticals, agrochemicals, and π-conjugated materials. To access these compounds, transition-metal-catalyzed α-arylation of carbonyls with haloarenes is one of the most powerful and straightforward methods (Scheme 1, A).[1] Inspired by pioneering developments by Miura,[2] Buchwald,[3] and Hartwig,[4] catalytic α-arylations have resulted in a rapid development of new catalysts and ligands. Due to these efforts, α-arylations of esters, amides, and aldehydes, as well as enantioselective reactions are now feasible. Furthermore, recent research has enabled the use of alternative arylating agents such as aryl triflates[5] and tosylates[6]. Our group has also contributed to this area by developing a reaction using aryl pivalates or carbamates under the influence of an original nickel catalyst, Ni-dcypt (dcypt: 3,4-bis(dicyclohexylphosphino)thiophene).[7–9] Shortly thereafter, the Martin group reported an elegant enantioselective α-arylation of ketones with aryl pivalates by using a Ni-BINAP catalytic system.[10]

Meanwhile, our group[11] and others[12] have extensively studied the development of catalytic coupling reaction using aromatic esters and amides, which led to the realization of a variety of unique bond formations.[13,14] Arenecarboxylates are present in a wide range of commercially available building blocks and synthetic intermediates, thus, their use in coupling can give rise to new opportunities involving unconventional synthetic strategies. However, the use of esters for α-arylation is anticipated to be challenging because, the predominant reactivity of esters, led to a Claisen condensation to give diketones, particularly in the presence of a strong base (Scheme 1, B). Thus, development of an efficient catalyst is essential to conduct the reaction under mild basic conditions. Herein, we report our efforts to



Scheme 1 Catalytic α-arylation of ketones using a variety of arylating agents

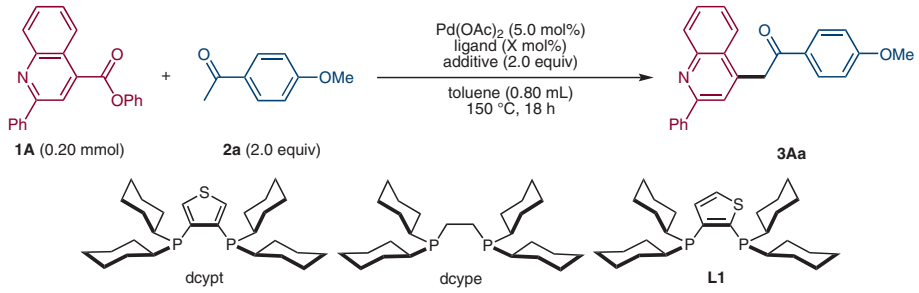
develop a catalytic α-arylation of ketones with aromatic esters.

Our study began with the optimization of reaction conditions using **1A** and **2a** as coupling partners (Table 1). To our delight, the desired α-arylation occurred smoothly using catalytic $Pd(OAc)_2$/dcypt in the presence of CsF (Table 1, entry 1). Similar ligands such as dcype and **L1** were found to be effective for this reaction, albeit generating **3Aa** in lower yields (Table 1, entries 2 and 3). P(*n*-Bu)$_3$ and *N*-heterocyclic carbenes (NHCs), which are effective ligands for a decarbonylative biaryl coupling[11c] as well as the functionalization of inert C–heteroatom bonds,[12r,15] only resulted in recovered starting materials (Table 1, entries 5 and 6). The effect of CsF was intriguingly significant, as poor yields of product were obtained when no additives or other alkali fluorides were used (Table 1, entries 6–8; see Supporting Information for details). The use of K_2CO_3 delivered the desired product **3Aa** in moderate yield, however, the decomposition of **1A** to the corresponding carboxylic acid and Claisen condensation product was also accelerated, probably due to its higher basicity compared to CsF (Table 1, entry 9). With these results, we identified our 'standard' reaction conditions: $Pd(OAc)_2$/dcypt/CsF in toluene at 150 °C.

With these optimized conditions in hand, we examined the scope of ketones for this reaction (Scheme 2). Simple aromatic ketones such as acetophenone (**2b**) and 2-acetonaphthone (**2c**) reacted well, furnishing the corresponding products **3Ab** and **3Ac**. Both *o*-methyl- and *p*-methyl-substituted acetophenones **2d** and **2e** were converted into α-arylated ketones **3Ad** and **3Ae** in 59% and 47% yields, respectively. For reasons that are currently unclear, the addition of a catalytic amount of MeOH slightly increased the reaction yields of **3Ad**, **3Ae**, and **3Af**. Substrates **2g–i** bearing electron-donating groups were capable of coupling with **1A**. Electron-poor aromatics tended to diminish the reaction efficiency as showcased in **3Aj**.[16] Ketones with an amino group (**2k**) as well as a heteroarene (**2l**) were compatible with the transformation. Although the yield is not satisfactory, the reaction of 2-acetyl fluorene (**2m**) provided the α-arylated product **3Am** without arylation at the C9 position of fluorene. This result indicated that deprotonation by a base is unlikely to be involved in the reaction mechanism because fluorenes have more acidic C–H (pK_a = 22.6 in DMSO) than the α-C–H of ketones (cf. acetophenone, pK_a = 24.7 in DMSO).[17,18] An aliphatic ketone, pinacolone (**2n**) was also reactive under the present conditions to afford **3An** in acceptable yield. Possibly due to the mild nature of the present catalytic system, Claisen condensation products were not observed in any of these reactions.

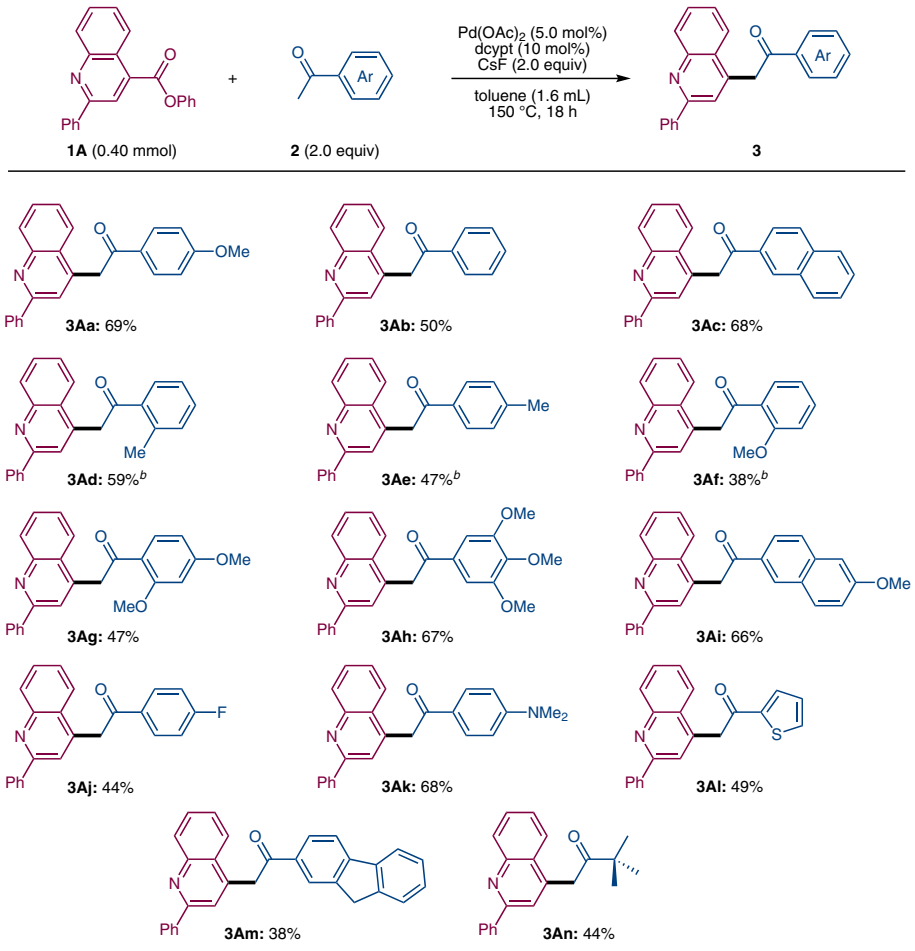
Next, the scope of aromatic esters is summarized in Scheme 3. The electronic properties of the aryl moiety at the C2 position of the quinoline were not influential. A fluorine atom on the quinoline was tolerated in the reaction. Unfortunately, this reaction was found to be specific to 2-phenyl-

Table 1 Optimization of Reaction Conditions[a]



Entry	Ligand (X mol%)	Additive	GC yield (%)[b]
1	dcypt (10)	CsF	69
2	dcype (10)	CsF	44
3	**L1**(10)	CsF	56
4	P(*n*-Bu)$_3$ (20)	CsF	0
5[c]	ICy·HBF$_4$(10)	CsF	0
6	dcypt (10)	none	trace
7	dcypt (10)	KF	11
8	dcypt (10)	NaF	1
9	dcypt (10)	K_2CO_3	41

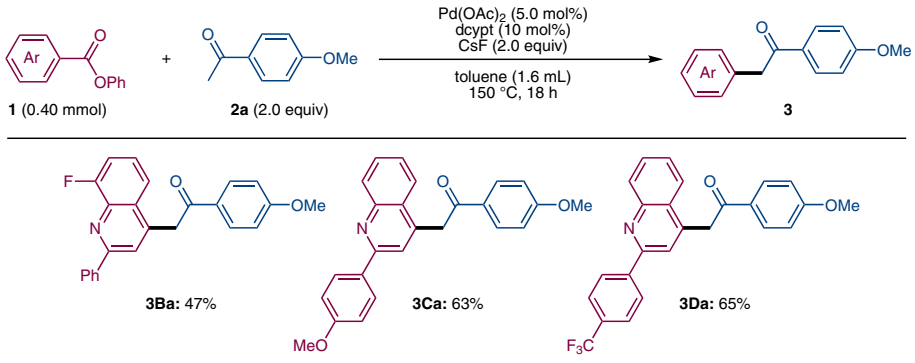
[a] Conditions: **1A** (0.20 mmol), **2** (2.0 equiv), $Pd(OAc)_2$ (5.0 mol%), dcypt (10 mol%), CsF (2.0 equiv), toluene (0.80 mL), 150 °C, 18 h.
[b] GC yield was determined by using *n*-decane as an internal standard.
[c] NaO*t*-Bu (25 mol%) was added.



Scheme 2 Scope of ketones. [a] *Reagents and conditions*: **1A** (0.40 mmol), **2** (2.0 equiv), $Pd(OAc)_2$ (5.0 mol%), dcypt (10 mol%), CsF (2.0 equiv), toluene (1.6 mL), 150 °C, 18 h. [b] MeOH (30 mol%) was added.

4-quinoline carboxylates, and other related (hetero)aromatic esters resulted in poor reaction yields (see Supporting Information).

In conclusion, we have developed a Pd-catalyzed decarbonylative α-arylation of (hetero)aromatic esters with acetophenones.[19] A ligand effect for this reaction was observed, wherein our in-house diphosphine ligands could deliver the



Scheme 3 Scope of aromatic esters. *Reagents and conditions*: **1** (0.40 mmol), **2a** (2.0 equiv), $Pd(OAc)_2$ (5.0 mol%), dcypt (10 mol%), CsF (2.0 equiv), toluene (1.6 mL), 150 °C, 18 h.

desired coupling product. Although this is the first example of catalytic α-arylation using aromatic esters in a decarbonylative manner, there is obviously room for improvement, particularly regarding the scope of the ester. Further methodology and a mechanistic study toward the development of synthetically valuable ester-based coupling reaction are ongoing in our laboratory.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1589120.

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(19) **Representative Experimental Procedure for Catalytic Decarbonylative α-Arylation of Ketones with Aromatic Esters**
A 20 mL glass vessel equipped with J. Young® O-ring tap containing a magnetic stirring bar and CsF (121.5 mg, 0.80 mmol, 2.0 equiv) was dried with a heatgun *in vacuo* and filled with N_2 gas after cooling to room temperature. To this vessel were added aromatic phenyl ester **1A** (130.2 mg, 0.40 mmol, 1.0 equiv), aryl ketones **2** (120.1 mg, 0.80 mmol, 2.0 equiv), $Pd(OAc)_2$ (4.49 mg, 0.020 mmol, 5.0 mol%), and dcypt (19.1 mg, 0.040 mmol, 10 mol%). The vessel was vacuumed and refilled N_2 gas three times. To this was added toluene (1.6 mL). The vessel was sealed with O-ring tap and then heated at 150 °C for 18 h in a 9-well aluminum reaction block with stirring. After cooling

the reaction mixture to room temperature, the mixture was passed through a short silica gel pad with EtOAc as an eluent. The filtrate was concentrated and the residue was purified by Isolera® (hexane/EtOAc = 5:1) afforded **3Aa** as a white solid (97.5 mg, 69% yield).

Compound **3Aa**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 8.8 Hz, 1 H), 8.11 (d, *J* = 8.8 Hz, 2 H), 8.04 (d, *J* = 8.8 Hz, 2 H), 7.86 (d, *J* = 8.8 Hz, 1 H), 7.73–7.67 (m, 2 H), 7.53–7.41 (m, 4 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 4.71 (s, 2 H), 3.86 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 194.7, 163.9, 157.0, 148.5, 142.0, 139.5, 130.8, 130.5, 129.4, 129.3, 129.2, 128.7, 127.5, 126.7, 126.5, 123.5, 120.7, 114.0, 55.5, 42.1. ESI-HRMS: *m*/*z* calcd for $C_{24}H_{20}NO_2$ $[M + H]^+$: 354.1489; found: 354.1487.