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Palladium-Catalyzed Heck-Type Coupling via C–N Cleavage

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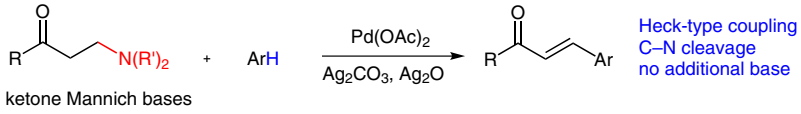

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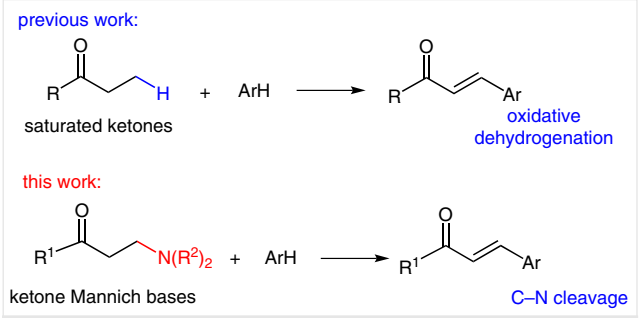
Abstract A palladium-catalyzed Heck-type coupling method between arenes and ketone Mannich bases via C–N cleavage to synthesize chalcones is reported. This protocol offers good yields and tolerates a broad range of functional groups. Based on the extensive experimental data, we propose a plausible coulping mechanism.

Key words palladium-catalyzed, Heck-type coupling, C–N cleavage, control experiment, mechanism

Chalcones and their heterocyclic analogues are prominent structural motifs of many bioactive natural products,[2] pharmaceuticals,[3] and functional materials.[4] Recently, intense efforts have focused on the development of effective methods to synthesize these compounds. Traditionally, chalcones are synthesized by the aldol condensation between aromatic aldehydes and ketones with the proper bases.[5] Because of some groups sensitive to bases, researchers developed other synthetic methods,[6,7] including palladium-catalyzed Sonogashira coupling of electron-deficient aryl halides with aryl 1-propargyl alcohols[6a,b] and palladium-catalyzed carbonylative Heck coupling of aryl halides with styrenes.[6c,d]

The direct metal-catalyzed C–H bond formation has attracted more attention in synthetic chemistry, providing an atom economical strategy and reducing the production of toxic byproducts which contributes to the growing field of reactions with decreased environmental impact.[8] Inspired by this C–H activation idea, Su[9] reported a versatile method for the facile synthesis of chalcone through palladium-catalyzed dehydrogenative cross-coupling between arenes and aryl ethyl ketones (Scheme 1). In his detailed mechanistic studies, the most important intermediate was in situ generated α,β-unsaturated ketone,[9,10] and subsequent oxidative dehydrogenation to finish the reaction.[10]

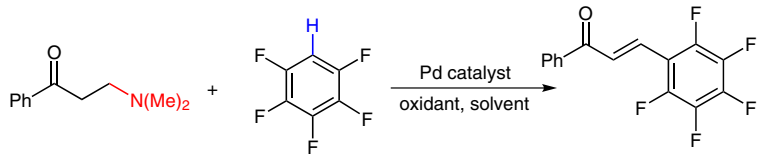


Scheme 1 Direct C–H functionalization routes for chalcone synthesis

Encouraged by this in situ generated method, ketone Mannich bases, successfully employed in Heck-type coupling,[11] were chosen as precursors to do the same reaction. Herein, a palladium-catalyzed Heck-type coupling method between arenes and ketone Mannich bases via C–N cleavage to synthesize chalcones is reported. Some control experiments suggest that this reaction proceeds through a similar olefin intermediate in situ and a subsequent oxidative coupling mechanism.[9,10]

Initially, 3-(dimethylamino)-1-phenylpropan-1-one (**1a**) and a highly electron-deficient pentafluorobenzene (**2a**)[12] were chosen as model substrates in the presence of different palladium catalysts, oxidants, and solvents to optimize the reaction conditions. To our delight, when the reaction was conducted with $Pd(OAc)_2$ (0.05 equiv) and Ag_2CO_3 (1.5 equiv) in DMSO at 120 °C, **3a** was formed in 65% yield (Table 1, entry 1). Other palladium catalysts [$PdCl_2$, $Pd(OTf)_2$, and $Pd_2(dba)_3$] showed less activity (Table 1, entries 2–4). Further reaction attempts with other oxidants

Table 1 Optimization of the Conditions[a]



1a **2a** **3a**

Entry	Pd cat. (5 mol%)	Oxidant (1.5 equiv)	Yield (%)[b]
1	$Pd(OAc)_2$	Ag_2CO_3	65
2	$PdCl_2$	Ag_2CO_3	15
3	$Pd(OTf)_2$	Ag_2CO_3	43
4	$Pd_2(dba)_3$	Ag_2CO_3	<5
5	$Pd(OAc)_2$	Ag_2O	51
6	$Pd(OAc)_2$	O_2	<5
7	$Pd(OAc)_2$	$PhI(OAc)_2$	0
8	$Pd(OAc)_2$	DDQ	0
9	$Pd(OAc)_2$	Ag_2CO_3 + Ag_2O (1:1)	81
10	no	Ag_2CO_3 + Ag_2O (1:1)	<5
11	$Pd(OAc)_2$	no	0

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), catalyst (5 mol%), oxidant (1.5 equiv), DMSO (3 mL), 120 °C, 24 h
[b] Isolated yield.

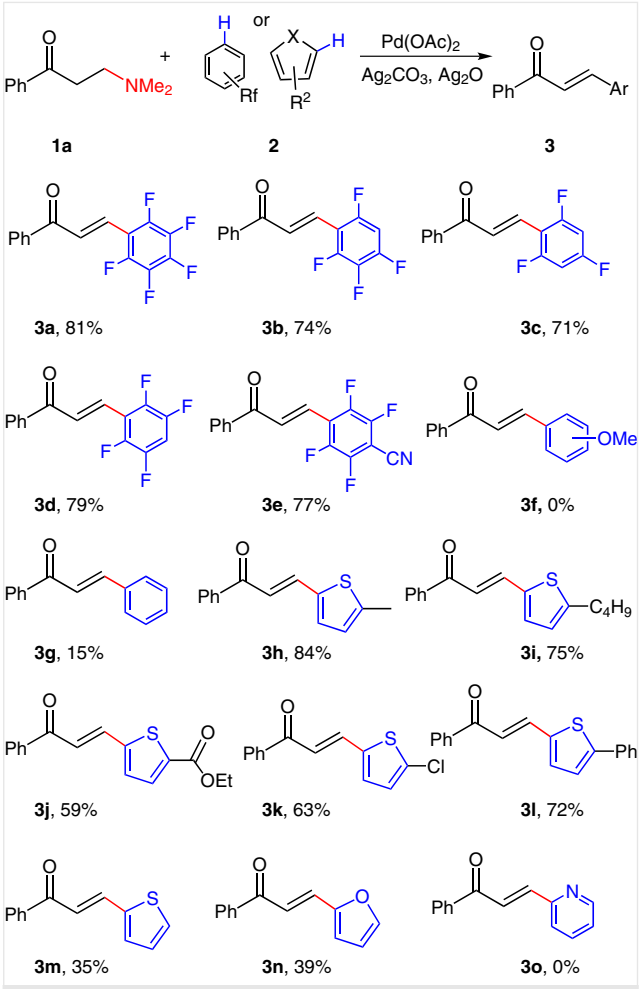
showed that a mixture of Ag_2CO_3 and Ag_2O (1:1, Table 1, entry 9) afforded the best yield of 81% (Table 1, entries 5–9). The use of other solvents, increasing the amount of loading catalyst or carrying out the standard reaction under inert argon atmosphere, led to no significant improvement on the yield (see Supporting Information, SI Tables 1). In the absence of catalysts or oxidants, it showed less or no activity (Table 1, entries 10 and 11).

With the optimized reaction conditions in hand [$Pd(OAc)_2$ (5 mol%), Ag_2CO_3 + Ag_2O (1.5 equiv, 1:1), DMSO (3.0 mL), and 120 °C], we first examined the substrate scope of this reaction (Scheme 2). Some other perfluoroarenes also showed good activity (**2a**–**e**, 71–81%), similar to Zhang's work.[12] However, electron-rich substrates (**2f**,**g**) showed less or no activity. Subsequently, the other electron-deficient heterocycles were screened. Both electron-withdrawing and electron-donating substituents on thiophene furnished good yields (**3h**–**l**, 59–84%), in which electron-withdrawing substituents show a litter lower activity. Note that **3k** containing a Cl group always got good yield (63%) without dehalogenation. In contrast, unsubstituted heteroarenes **3m** and **3n** afforded very poor yields (35% and 39%, respectively). It's a pity that we did not isolate any **3o**, which might be due to the strong coordination to palladium and poisoning the catalyst. The reaction occurred exclusively at the 5-position of monosubstituted thiophene or furan rings, which might involve an electrophilic process.

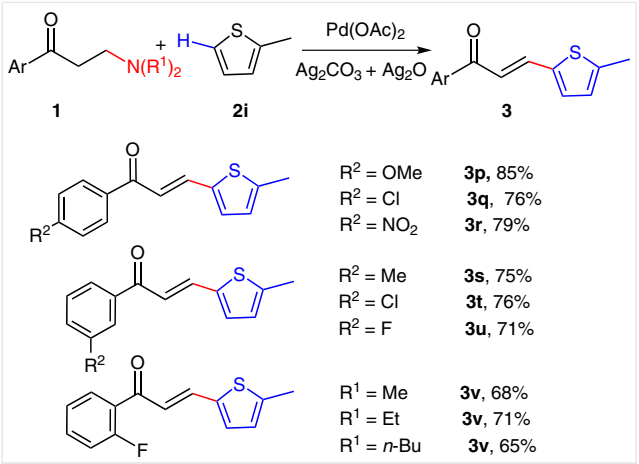
Next, we evaluated the scope of aryl ketone Mannich bases by using 2-methyl thiophene as a coupling partner (Scheme 3). Variations of substitution positions and electronic effect did not much influence the product yields, exhibiting good yields (**3p**–**v**, 65–85%). When R^1 was changed to Me, Et, or *n*-Bu, the yield of **3v** was also influenced a little. It suggests that there was no $N(R^1)_2$ group involved in the catalytic intermediates. Note that all the products **3a**–**v**[18] showed *E* regioselectivity due to the high temperature (120 °C).

To understand the role of each compound in this formation, control experiments were performed (see SI-1 in the Supporting Information). First, the reaction of **1a** was stirred under standard conditions and 78% yield of phenyl vinyl ketone (**1a'**) was detected by ^1H NMR spectroscopy in five hours. When the reaction finished, adding one equivalent of **2h** and stirring for 12 hours afforded 82% yield of **3h** (Scheme 4). Second, (*E*)-3-(5-methylthiophen-2-yl)-1-phenylprop-2-en-1-one (**3h'**)[9,15] reacting under standard conditions for 48 hours only got 15% yield of **3h**. These results agree with a β-amino elimination first and subsequent oxidative dehydrogenation mechanism (Scheme 5).[9,10,12]

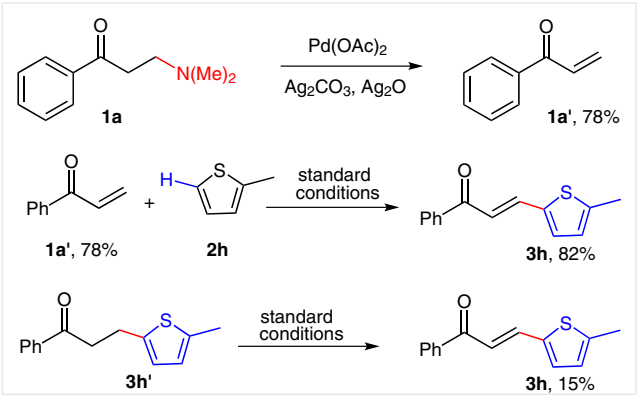
In summary, a palladium-catalyzed Heck-type coupling method between arenes and ketone Mannich bases via C–N cleavage to synthesize chalcones is reported. This protocol offers good yields and tolerates a broad range of functional groups. Based on the extensive experimental data, we pro-



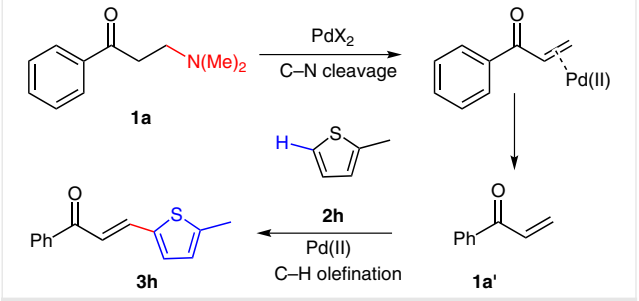
Scheme 2 The scope of the arenes and heterocycles. *Reagents and conditions*: **1** (0.2 mmol), **2** (0.6 mmol), $Pd(OAc)_2$ (5 mol%), Ag_2CO_3 + Ag_2O (1:1, 1.5 equiv), DMSO (3 mL), 120 °C, 24 h, yields are isolated yields.



Scheme 3 The scope of the aryl ketone Mannich bases. *Reagents and conditions*: **1** (0.2 mmol), **2** (0.6 mmol), $Pd(OAc)_2$ (5 mol%), Ag_2CO_3 + Ag_2O (1:1, 1.5 equiv), DMSO (3 mL), 120 °C, 24 h, yields are isolated yields.



Scheme 4 Control experiments



Scheme 5 A possible mechanism

pose a plausible coupling mechanism. Further studies concerning the detailed mechanism and the broader scope of substrates are currently in progress.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379911.

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(1) The authors contributed equally to this work.
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(18) **Synthesis of 3a–p**
A mixture of **1** (0.2 mmol), **2** (0.6 mmol), DMSO (3 mL), $Pd(OAc)_2$ (5 mol%), and Ag_2CO_3 and Ag_2O (1.5 equiv, 1:1) was stirred at 120 °C under air atmosphere for 24 h. To the reaction mixture was added H_2O and EtOAc, and the aqueous phase was extracted with EtOAc (3×). The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to give the corresponding products (**3a**,[12] **3g**,[13] **3h**,[14] **3i**–**l**,[9] **3m**,[16] **3n**,[17] **3p**,**q**,**s**–**v**[9] according to the literature).
(*E*)-3-(2,3,4,6-Tetrafluorophenyl)-1-phenylprop-2-en-1-one (3b)
Yield 74%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 7.2 Hz, 2 H), 7.78–7.50 (m, 4 H), 7.35 (d, *J* = 16.8 Hz, 1 H), 7.08 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.2, 153.0 (dm, *J* = 248.0 Hz), 149.9 (dm, *J* = 251.0 Hz), 148.5 (dm, *J* = 249.6 Hz), 139.2 (dm, *J* = 241.2 Hz), 136.8, 135.9 (m), 131.5, 128.6, 126,9, 115.8, 114.1 (m), 102.9 (m). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –118.5 (t, *J* = 9.6 Hz, 1 F), –134.9 (m, 1 F), –138.7 (dd, *J* = 19.5, 5.5 Hz, 1 F), –163.8 (m, 1 F). HRMS: *m/z* calcd for $C_{15}H_8OF_4$: 280.0511; found: 280.0517.
(*E*)-3-(2,4,6-Trifluorophenyl)-1-phenylprop-2-en-1-one (3c)
Yield 71%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 7.0 Hz, 2 H), 7.62–7.50 (m, 4 H), 7.34 (d, *J* = 16.6 Hz, 1 H), 6.96 (t, *J* = 9.0 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.8, 165.2 (dm, *J* = 248.8 Hz), 139.1, 135.8 (m), 130.5, 128.9, 127.8, 117.1, 111.9 (m), 101.9 (m). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –105.7 (m, 1 F), –113.1 (t, *J* = 8.2 Hz, 2 F). HRMS: *m/z* calcd for $C_{15}H_9OF_3$: 262.0605; found: 262.0613.
(*E*)-3-(2,3,5,6-Tetrafluorophenyl)-1-phenylprop-2-en-1-one (3d)
Yield 79%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.837–7.75 (m, 3 H), 7.68–7.59 (m, 3 H), 7.35 (d, *J* = 17.4 Hz, 1 H), 7.15 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.3, 149.5 (dm, *J* = 256.4 Hz), 145.8 (dm, *J* = 262.5 Hz), 138.7 (m), 137.1, 128.5, 127.6, 118.3 (m), 114.5, 103.6 (t, *J* = 22.8 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –139.7 (m, 2 F), –144.8 (m, 2 F). HRMS: *m/z* calcd for $C_{15}H_8OF_4$: 280.0511; found: 280.0508.

(*E*)-3-(4-Cyano-2,3,5,6-tetrafluorophenyl)-1-phenylprop-2-en-1-one (3e)

Yield 77%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.04–8.02 (m, 2 H), 7.98 (d, *J* = 16.0 Hz, 1 H), 7.78 (d, *J* = 16.0 Hz, 1 H), 7.67–7.55 (m, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.9, 148.5 (dm, *J* = 246.3 Hz), 145.3 (dm, *J* = 257.9 Hz), 138.5 (m), 135.4, 129.9, 128.3, 128.4, 127.5, 116.1 (t, *J* = 13.7 Hz), 114.7, 99.3 (m). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –132.5 (dd, *J* = 21.6, 8.0 Hz, 2 F), –138.4 (dd, *J* = 21.6, 8.2 Hz, 2 F). HRMS: *m/z* calcd for $C_{16}H_7ONF_4$: 305.0464; found: 305.0471.

***(E)*-3-(5-Methyl-2-thienyl)-1-(4-nitrophenyl)-2-propen-1-one (3r)**

Yield 79%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.0 Hz, 2 H), 7.95 (d, *J* = 15.4 Hz, 1 H), 7.68 (d, *J* = 8.0 Hz, 2 H), 7.34 (d, *J* = 3.6 Hz, 1 H), 7.25 (d, *J* = 15.4 Hz, 1 H), 6.88 (d, *J* = 3.6 Hz, 1 H), 2.62 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.8, 146.8, 140.2, 140.0, 139.3, 137.5, 134.2, 129.9, 128.5, 127.3, 118.4, 16.1. HRMS: *m/z* calcd for $C_{14}H_{11}NO_3S$: 273.0460; found: 273.0465.