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Synthesis of chalcones *via* domino dehydrochlorination/Pd(OAc)$_2$-catalyzed Heck reaction

Tenglong Guo [a], Quanbin Jiang [a], Likun Yu [b], Zhengkun Yu [a,*]

[a] *Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, Liaoning, China*

[b] *Fertilizer Analysis Station of Technology Center, SINOPEC Baling Petrochemical Company, Yueyang 414003, Hunan, China*

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ABSTRACT

A new method has been developed for the cross-coupling of aryl halides with *β*-chloroalkyl aryl ketones and their ester and amide analogs through a domino dehydrochlorination/Pd(OAc)$_2$-catalyzed Heck reaction sequence. The enone intermediates generated *in situ* reduced the occurrence of side reactions and therefore enhanced the efficiency of the reaction. This reaction exhibited good tolerance to various functional groups on both substrates and provides rapid access to a wide range of chalcone derivatives.

1. Introduction

Chalcones are an important class of biologically active compounds (Scheme 1) [1,2], which have been reported to exhibit a wide range of pharmacological properties, including anticancer, anti-inflammatory, antioxidant, antimicrobial, and antiallergic activity [3]. Compounds belonging to this structural class are also recognized as important intermediates for the synthesis of heterocyclic systems [4–6] and functional materials [7,8]. Chalcones are generally synthesized using a Claisen-Schmidt condensation [9]. However, the overall efficiency and functional group tolerance of this reaction are usually poor because of its requirement for strongly basic conditions. To overcome these limitations, several transition-mental-catalyzed cross-coupling reactions have been developed for the synthesis of chalcones, which can be conducted under relatively mild conditions [10–13].

The Pd-catalyzed Heck reaction is one of the most powerful methods for the arylation and vinylation of alkenes [14]. Although chalcones can be generated directly by the Heck-type cross-coupling of aryl halides with aryl vinyl ketones, there have been very few examples of this reaction in the literature [15,16]. The main reason for the lack of publications in this area can be attributed to the poor stability of most aryl vinyl ketones (enones), which can decompose upon exposure to heat, light and oxygen during their preparation and storage. Multi-step procedures are therefore often required for the preparation of *α,β*-unsaturated carbonyl compounds starting from the corresponding saturated carbonyl compounds [17,18]. For the synthesis of chalcones using enones as substrates, it is envisaged that a domino reaction sequence involving the *in-situ* generation of an enone followed by its cross-coupling with an aryl halide would provide facile access to a broad range of chalcones. The Pd-catalyzed cross-coupling reactions of propiophenones with aryl carboxylic acids [19] and (hetero)arenes [20] have been reported to afford chalcon-

* Corresponding author. Tel/Fax: +86-411-8437 9227; E-mail: zkyu@dicp.ac.cn
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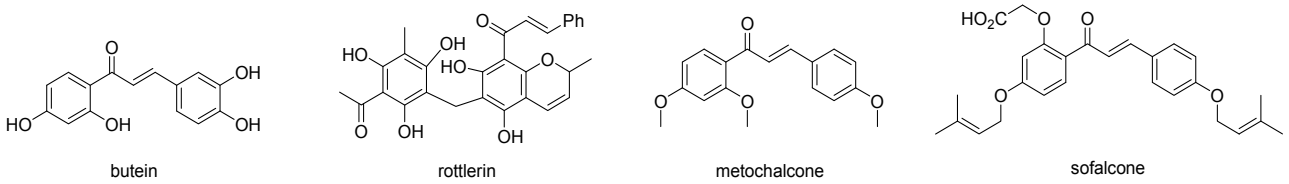


Scheme 1. Examples of bioactive chalcones.

es via the *in-situ* generation of the corresponding enones. The decarboxylative arylation of benzoylacrylic acids has also been reported to provide access to chalcones in a similar manner [21]. Although these methods represent useful strategies for the synthesis of chalcones, their overall utility has been limited by their general requirement for high loadings of the catalysts and oxidants under relatively harsh conditions. We recently found that *β*-chloroalkyl aryl ketones and their ester and amide analogs could be used as precursors to *α,β*-unsaturated carbonyls in the Rh(I)-catalyzed conjugate addition by arylboronic acids [22], as well as the Pd-catalyzed, Cu-mediated synthesis of carbazoles [23]. As part of our ongoing research into the development of new domino reactions [24], we envisioned that *in-situ* generated enones could be employed in a Heck-type cross-coupling reaction under mild conditions without the addition of an oxidant. Herein, we report the development of a new method for the synthesis of chalcones by Pd-catalyzed formal sp^2 C-X (X = I, Br) / sp^3 C-Cl cross-coupling of aryl halides with *β*-chloroalkyl aryl ketones, and their ester and amide analogs.

2. Experimental

General considerations. All the aryl halides were purchased from commercial suppliers and used as provided without further purification. The *β*-chloroalkyl carbonyl compounds were either purchased from commercial suppliers or prepared according to the literature procedures [22]. Compounds **3a**–**3c** [21], **3d** [25], **3e** and **3f** [21], **3g** [26], **3h** [21], **3i** [25], **3j** [21], **3k** [27], **3l** [27], **3m** [21], **3n** [28], **5a** and **5b** [10], **5c** [29], **5d** [30], **5e** [31], **5f** and **5g** [10], **5h** and **5i** [25], **5j** [32], **5k** [33], **5l** [34], and **5m** and **5n** [35] are known compounds and the spectroscopic features of the materials synthesized in current study were found to be in good agreement with those reported in the literature. All of the solvents used in the current study were freshly distilled prior to use. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer (Bruker, German) and all the chemical shift values were measured relative to tetramethylsilane (TMS; δ_{TMS} = 0.00) or the residual chloroform peak of $CDCl_3$ [δ(^{1}H) = 7.26; δ(^{13}C) = 77.16].

General procedure for the synthesis of chalcones – synthesis of chalcone **3a**. A mixture of $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), PPh_3 (11.2 mg, 0.04 mmol), iodobenzene (**1a**) (82 mg, 0.4 mmol), 3-chloropropiophenone (**2a**) (87 mg, 0.5 mmol), and K_2CO_3 (166 mg, 1.2 mmol) in DMF (2.5 mL) was stirred under a N_2 atmosphere at room temperature for 10 min, and then heated at 90 °C for 16 h. The reaction was then cooled to ambient temperature and diluted with CH_2Cl_2 (10 mL) before being filtered through a short pad of silica gel. The silica pad was rinsed with DCM (5 mL), and the combined filtrates were washed with brine (15 mL), dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure to give the crude product as a residue, which was purified by silica gel column chromatography eluting with a mixture of petroleum ether (60–90 °C)/EtOAc (v/v = 30:1).

(*E*)-Chalcone (3a) [21]. Yield 90%, pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 7.3 Hz, 2H, aromatic CH), 7.90 (d, *J* = 15.7 Hz, 1H, C*H*=CHCOPh), 7.72 (dd, *J* = 6.3, 2.8 Hz, 2H, aromatic CH), 7.69–7.55 (m, 4H, aromatic CH and CH=C*H*COPh), 7.52–7.46 (m, 3H, aromatic CH).

(*E*)-1-Phenyl-3-(*p*-tolyl)prop-2-en-1-one (3b) [21]. Yield 83%, pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07–7.99 (m, 2H, aromatic CH), 7.80 (d, *J* = 15.7 Hz, 1H, C*H*=CHCOPh), 7.61–7.46 (m, 6H, aromatic CH and CH=C*H*COPh), 7.24 (t, *J* = X Hz, 2H, aromatic CH), 2.40 (s, 3H, CH_3).

(*E*)-1-phenyl-3-(*m*-tolyl)prop-2-en-1-one (3c) [21]. Yield 84%, pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 7.4 Hz, 2H, aromatic CH), 7.85 (d, *J* = 15.7 Hz, 1H, C*H*=CHCOPh), 7.58 (m, 4H, aromatic CH and CH=C*H*COPh), 7.49 (d, *J* = 6.0 Hz, 2H, aromatic CH), 7.35 (t, 1H, aromatic CH), 7.28 (t, 1H, aromatic CH), 2.44 (s, 3H, CH_3).

(*E*)-1-Phenyl-3-(*o*-tolyl)prop-2-en-1-one (3d) [25]. Yield 87%, pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 15.6 Hz, 1H, C*H*=CHCOPh), 8.08 (m, 2H, aromatic CH), 7.75 (d, *J* = 7.4 Hz, 1H, aromatic CH), 7.63 (t, *J* = X Hz, 1H, aromatic CH), 7.53 (m, 3H, aromatic CH and CH=C*H*COPh), 7.35 (t, 1H, aromatic CH), 7.28 (m, 2H, aromatic CH), 2.52 (s, 3H, CH_3).

(*E*)-3-(4-Methoxyphenyl)-1-phenylprop-2-en-1-one (3e) [21]. Yield 85%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.1 Hz, 2H, aromatic CH), 7.79 (d, *J* = 15.6 Hz, 1H, C*H*=CHCOPh), 7.59 (m, 3H, aromatic CH), 7.50 (t, *J* = X Hz, 2H, aromatic CH), 7.42 (d, *J* = 15.6 Hz, 1H, CH=C*H*COPh), 6.94 (d, *J* = 8.5 Hz, 2H, aromatic CH), 3.86 (s, 3H, OCH_3).

(*E*)-3-(4-Chlorophenyl)-1-phenylprop-2-en-1-one (3f) [21]. Yield 86%, pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (m, 2H, aromatic CH), 7.74 (d, *J* = 15.7 Hz, 1H, C*H*=CHCOPh), 7.57 (m, 3H, aromatic CH), 7.49 (m, 3H, aromatic CH and CH=C*H*COPh), 7.37 (d, *J* = 8.5 Hz, 2H, aromatic CH).

(*E*)-3-(2-Chlorophenyl)-1-phenylprop-2-en-1-one (3g) [26]. Yield 81%, pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 15.8 Hz, 1H, C*H*=CHCOPh), 8.02 (d, *J* = 7.2 Hz, 2H, aromatic CH), 7.75 (dd, *J* = 7.0, 2.4 Hz, 1H, aromatic CH), 7.59 (t, *J* = X Hz, 1H, aromatic CH), 7.50 (m, 3H, aromatic CH and CH=C*H*COPh), 7.43 (m, 1H, aromatic CH), 7.32 (m, 2H, aromatic CH).

(*E*)-3-(4-fluorophenyl)-1-phenylprop-2-en-1-one (3h) [21]. Yield 91%, pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ

= 8.02 (d, *J* = 7.3 Hz, 2H, aromatic CH), 7.77 (d, *J* = 15.7 Hz, 1H, C*H*=CHCOPh), 7.66–7.56 (m, 3H, aromatic CH), 7.49 (m, 3H, aromatic CH and CH=C*H*COPh), 7.10 (t, 2H, aromatic CH).

(*E*)-1-Phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (3i) [25]. Yield 80%, pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 7.6 Hz, 2H, aromatic CH), 7.80 (d, *J* = 15.7 Hz, 1H, C*H*=CHCOPh), 7.73 (d, *J* = 8.1 Hz, 2H, aromatic CH), 7.66 (d, *J* = 8.1 Hz, 2H, aromatic CH), 7.60 (m, 2 H, aromatic CH and CH=C*H*COPh), 7.51 (t, *J* = 7.5 Hz, 2H, aromatic CH).

(*E*)-Methyl 4-(3-oxo-3-phenylprop-1-en-1-yl)benzoate (3j) [21]. Yield 79%, pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08–7.98 (m, 4 H, aromatic CH), 7.79 (d, *J* = 15.7, 1H, C*H*=CHCOPh), 7.67 (dd, *J* = 8.3, 1.8 Hz, 2H, aromatic CH), 7.62–7.55 (m, 2H, aromatic CH and CH=C*H*COPh), 7.49 (m, 2H, aromatic CH), 3.92 (s, 3H, CO_2CH_3).

(*E*)-4-(3-Oxo-3-phenylprop-1-en-1-yl)benzonitrile (3k) [27]. Yield 70%, pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 7.4 Hz, 2H, aromatic CH), 7.78–7.70 (m, 3H, aromatic CH and C*H*=CHCOPh), 7.68 (d, *J* = 8.6 Hz, 2H, aromatic CH), 7.64–7.57 (m, 2H, aromatic CH and CH=C*H*COPh), 7.51 (t, 2H, aromatic CH).

(*E*)-3-(4-Nitrophenyl)-1-phenylprop-2-en-1-one (3l) [27]. Yield 58%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 8.7 Hz, 2H, aromatic CH), 8.04 (d, *J* = 7.3 Hz, 2H, aromatic CH), 7.81 (m, 3H, aromatic CH and C*H*=CHCOPh), 7.64 (m, 2H, aromatic CH and CH=C*H*COPh), 7.53 (t, *J* = 7.6 Hz, 2H, aromatic CH).

(*E*)-3-(4-Acetylphenyl)-1-phenylprop-2-en-1-one (3m) [21]. Yield 51%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (m, 4 H, aromatic CH), 7.80 (d, *J* = 15.8 Hz, 1H, C*H*=CHCOPh), 7.71 (d, *J* = 8.4 Hz, 2H, aromatic CH), 7.64–7.56 (m, 2H, aromatic CH and CH=C*H*COPh), 7.50 (m, 2H, aromatic CH), 2.62 (s, 3H, CH_3).

(*E*)-1-Phenyl-3-(thiophen-2-yl)prop-2-en-1-one (3n) [28]. Yield 75%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 7.6 Hz, 2H, aromatic CH), 7.94 (d, *J* = 15.3 Hz, 1H, C*H*=CHCOPh), 7.57 (t, *J* = X Hz, 1H, aromatic CH), 7.49 (t, *J* = X Hz, 2H, aromatic CH), 7.41 (d, *J* = 5.0 Hz, 1H, thienyl CH), 7.37–7.30 (m, 2H, thienyl CH and CH=C*H*COPh), 7.11–7.03 (m, 1 H, thienyl CH).

(*E*)-3-Phenyl-1-(*p*-tolyl)prop-2-en-1-one (5a) [10]. Yield 83%, pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 8.2 Hz, 2H aromatic CH), 7.82 (d, *J* = 15.7 Hz, 1H, C*H*=CHCOPh), 7.64 (m, 2H, aromatic CH), 7.55 (d, *J* = 15.7 Hz, 1H, CH=C*H*COPh), 7.41 (m, 3H, aromatic CH), 7.30 (d, *J* = 8.1 Hz, 2H, aromatic CH), 2.43 (s, 3H, CH_3).

(*E*)-1-(4-Methoxyphenyl)-3-phenylprop-2-en-1-one (5b) [10]. Yield 89%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.8 Hz, 2H, aromatic CH), 7.80 (d, *J* = 15.7 Hz, 1H, C*H*=CHCOPh), 7.63 (m, 2H, aromatic CH), 7.55 (d, *J* = 15.6 Hz, 1H, CH=C*H*COPh), 7.40 (m, 3H, aromatic CH), 6.97 (d, *J* = 8.8 Hz, 2H, aromatic CH), 3.86 (s, 3H, OCH_3).

(*E*)-1-(3,4-Dimethylphenyl)-3-phenylprop-2-en-1-one (5c) [29]. Yield 83%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (m, 3H, aromatic CH and C*H*=CHCOPh), 7.65 (m, 2H, aromatic CH), 7.55 (d, *J* = 15.7 Hz, 1H, CH=C*H*COPh), 7.46–7.39 (m, 3H, aromatic CH), 7.26 (d, *J* = 7.8 Hz, 1H, aromatic CH), 2.35 (d, *J* = 3.8 Hz, 6H, 2×CH_3).

(*E*)-1-(2,4-Dimethylphenyl)-3-phenylprop-2-en-1-one (5d) [30]. Yield 84%, pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (m, 2H, aromatic CH), 7.52 (d, *J* = 16.0 Hz, 1H, C*H*=CHCOPh), 7.47 (d, *J* = 7.6 Hz, 1H, aromatic CH), 7.40 (m, 3H, aromatic CH), 7.19 (d, *J* = 16.0 Hz, 1H, CH=C*H*COPh), 7.10 (d, *J* = 9.1 Hz, 2H, aromatic CH), 2.46 (s, 3H, CH_3), 2.39 (s, 3H, CH_3).

(*E*)-1-(2,5-Dimethylphenyl)-3-phenylprop-2-en-1-one (5e) [31]. Yield 82%, pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (m, 2H, aromatic CH), 7.48 (d, *J* = 16.1 Hz, 1H, C*H*=CHCOPh), 7.40 (m, 3H, aromatic CH), 7.31 (s, 1H, aromatic CH), 7.22–7.12 (m, 3H, aromatic CH and CH=C*H*COPh), 2.41 (s, 3H, CH_3), 2.38 (s, 3H, CH_3).

(*E*)-1-(4-Chlorophenyl)-3-phenylprop-2-en-1-one (5f) [10]. Yield 86%, pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.4 Hz, 2H, aromatic CH), 7.81 (d, *J* = 15.7 Hz, 1H, C*H*=CHCOPh), 7.64 (m, 2H, aromatic CH), 7.47 (m, 3H, aromatic CH and CH=C*H*COPh), 7.41 (m, 3H, aromatic CH).

(*E*)-1-(4-Fluorophenyl)-3-phenylprop-2-en-1-one (5g) [10]. Yield 90%, pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (dd, *J* = 8.7, 5.5 Hz, 2H, aromatic CH), 7.82 (d, *J* = 15.7 Hz, 1H, C*H*=CHCOPh), 7.64 (m, 2H, aromatic CH), 7.51 (d, *J* = 15.7 Hz, 1H, CH=C*H*COPh), 7.46–7.37 (m, 3H, aromatic CH), 7.17 (t, *J* = X Hz, 2H, aromatic CH).

(*E*)-3-Phenyl-1-(thiophen-2-yl)prop-2-en-1-one (5h) [25]. Yield 80%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.81 (m, 2H, thienyl CH and C*H*=CHCOPh), 7.70–7.60 (m, 3H, thienyl CH and aromatic CH), 7.40 (m, 4H, aromatic CH and CH=C*H*COPh), 7.18 (t, *J* = 4.2 Hz, 1H, thienyl CH).

(*E*)-1-(Furan-2-yl)-3-phenylprop-2-en-1-one (5i) [25]. Yield 78%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 15.8 Hz, 1H, C*H*=CHCOPh), 7.63 (m, 3H, furyl CH and aromatic CH), 7.49–7.37 (m, 4H, aromatic CH and CH=C*H*COPh), 7.32 (d, *J* = 3.3 Hz, 1H, furyl CH), 6.57 (dd, *J* = 3.4 and 1.5 Hz, 1H, furyl CH).

(*E*)-1-(1-Methyl-1H-indol-3-yl)-3-phenylprop-2-en-1-one (5j) [32]. Yield 85%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54 (dd, *J* = 6.5, 2.3 Hz, 1H, indolyl CH), 7.80 (d, *J* = 15.6 Hz, 1H, C*H*=CHCOPh), 7.75 (d, *J* = 2.6 Hz, 1H, indolyl CH), 7.61 (d, *J* = 7.3 Hz, 2H, aromatic CH), 7.38 (m, 3H, aromatic CH), 7.34–7.25 (m, 4H, aromatic CH and CH=C*H*COPh), 3.77 (s, 3H, NCH_3).

***m*-Tolyl cinnamate (5k)** [33]. Yield 79%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 16.0 Hz, 1H, C*H*=CHCOOPh), 7.66–7.55 (m, 2H, aromatic CH), 7.44 (m, 3H, aromatic CH), 7.31 (t, *J* = 7.7 Hz, 1H, aromatic CH), 7.09 (d, *J* = 7.6 Hz, 1H, aromatic CH), 7.01 (d, *J* = 8.6 Hz, 2H, aromatic CH), 6.66 (d, *J* = 16.0 Hz, 1H, CH=C*H*COOPh), 2.40 (s, 3H, CH_3).

4-Chlorophenyl cinnamate (5l) [34]. Yield 77%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 16.0 Hz, 1H, C*H*=CHCOOPh), 7.60 (m, 2H, aromatic CH), 7.45 (m, 3H, aromatic CH), 7.38 (d, *J* = 8.8 Hz, 2H, aromatic CH), 7.14 (d, *J* = 8.8 Hz, 2H, aromatic CH), 6.63 (d, *J* = 16.0 Hz, 1H, CH=C*H*COOPh).

***N*-Methyl-*N*-(*p*-tolyl)cinnamamide (5m)** [35]. Yield 90%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 15.6 Hz, 1H, C*H*=CHCONAr), 7.29 (m, 5H), 7.22 (d, *J* = 8.0 Hz, 2H, aromatic CH), 7.10 (d, *J* = 8.1 Hz, 2H, aromatic CH), 6.39 (d, *J* = 15.6 Hz, 1H, CH=C*H*CONAr), 3.38 (s, 3H, NCH_3), 2.40 (s, 3H, CH_3).

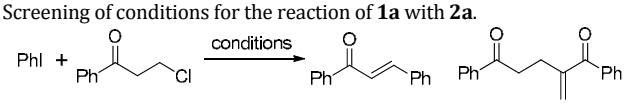
***N*-(4-Chlorophenyl)-*N*-methylcinnamamide (5n)** [35]. Yield 88%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 15.5 Hz, 1H, C*H*=CHCONAr), 7.41 (d, *J* = 7.5 Hz, 2H, aromatic CH), 7.32 (m, 5H, aromatic CH), 7.18 (d, *J* = 7.5 Hz, 2H, aromatic CH), 6.35 (d, *J* = 15.5 Hz, 1H, CH=C*H*CONAr), 3.39 (s, 3H, NCH_3).

3. Results and discussion

3.1. Optimization of the reaction conditions

The reaction of iodobenzene (**1a**) with a single equivalent of 3-chloropropiophenone (**2a**) was selected as a model reaction for the optimization of the reaction conditions. The model reaction was initially conducted in dioxane at 90 °C under a N_2 atmosphere using 5 mol% $Pd(OAc)_2$ as the catalyst, 10 mol% PPh_3 as the ligand, and K_3PO_4 as the base, which gave the desired chalcone product **3a** in a GC yield of 74% (Table 1, entry 1). Several other solvents were screened in the reaction, including MeCN, DMF, DMSO, $PhCH_3$ and H_2O, and DMF was found to provide the best results in terms of the yield of the chalcone product **3a** (Table 1, entries 2–6). It is noteworthy

Table 1
Screening of conditions for the reaction of **1a** with **2a**.

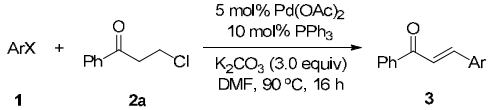


1a **2a** **3a** **4**

Entry	Solvent	Base	Yield [a] (%)
1	Dioxane	K_3PO_4	74
2	CH_3CN	K_3PO_4	83
3	DMF	K_3PO_4	90 (78) [b]
4	DMSO	K_3PO_4	65
5	$PhCH_3$	K_3PO_4	40
6	H_2O	K_3PO_4	60
7	DMF	K_2CO_3	90 [b]
8	DMF	Na_2CO_3	78
9	DMF	Cs_2CO_3	0
10 [c]	DMF	K_3PO_4	83
11 [c]	DMF	K_2CO_3	97 (90) [b]
12 [d]	DMF	K_2CO_3	95 [e]

Reaction conditions: **1a** (0.4 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), and base (1.2 mmol) in solvent (2.5 mL) at 90 °C for 16 h under 0.1 MPa of N_2. [a] GC yield using mesitylene as an internal standard. [b] Isolated yield in parentheses. [c] **2a** (0.5 mmol). [d] **1a** (0.5 mmol) and **2a** (0.4 mmol). [e] Yield based on **2a**.

Table 2
Reactions of aryl halides with **2a**.



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

Entry	Aryl Halide (**1**)	Product (**3**)	Isolated yield (%)	Entry	Aryl Halide(**1**)	Product(**3**)	Isolated yield (%)
1	**1a**	**3a**	90	9	**1i**	**3i**	80
2	**1b**	**3b**	83	10	**1j**	**3j**	79
3	**1c**	**3c**	84	11	**1k**	**3k**	70
4	**1d**	**3d**	87	12	**1l**	**3l**	58
5	**1e**	**3e**	85	13	**1m**	**3m**	51
6	**1f**	**3f**	86	14	**1n**	**3n**	75
7	**1g**	**3g**	81	15	**1o**	**3a**	33
8	**1h**	**3h**	91	16	**1p**	**3a**	0

Reaction conditions: **1** (0.4 mmol), **2a** (0.5 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), and K_2CO_3 (1.2 mmol) in DMF (2.5 mL) at 90 °C for 16 h under 0.1 MPa of N_2.

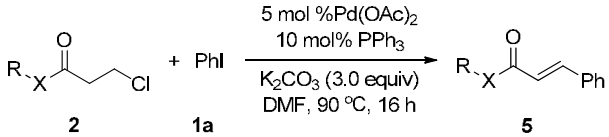
that the reaction proceeded smoothly in H_2O to form **3a** in moderate yield (Table 1, entry 6). Having identified the optimum solvent, we proceeded to screen a series of different bases, including K_2CO_3, Na_2CO_3 and Cs_2CO_3 (Table 1, entries 7–10). Interestingly, K_3PO_4 and K_2CO_3 both worked more efficiently than Na_2CO_3, whereas the use of the stronger base Cs_2CO_3 failed to provide any of the desired products (Table 1, entry 9). Increasing the loading of **2a** to 1.25 equiv. led to an increase in the isolated yield to 90% when K_2CO_3 was used as the base (Table 1, entry 11). In contrast, increasing the loading of **1a** to 1.25 equiv. led to a slight decrease in the yield (Table 1, entry 12).

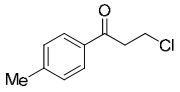
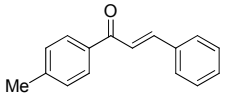
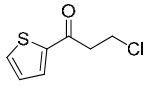
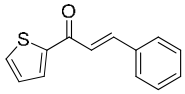
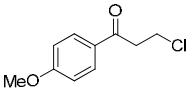
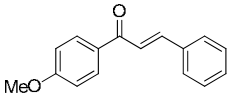
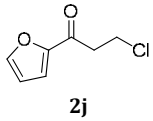
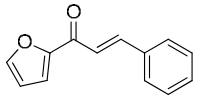
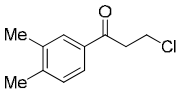
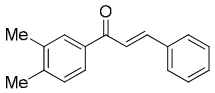
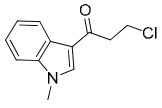
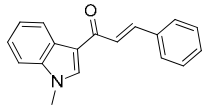
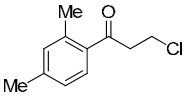
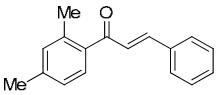
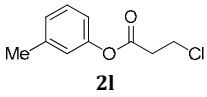
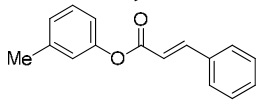
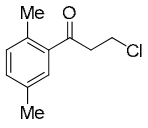
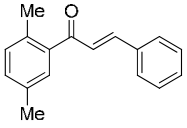
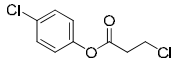
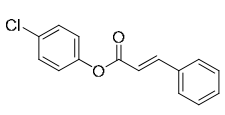
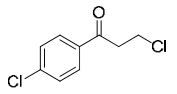
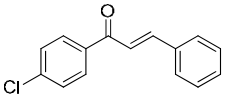
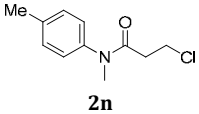
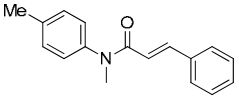
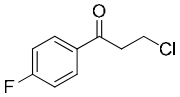
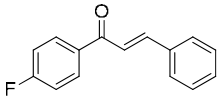
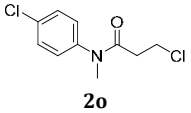
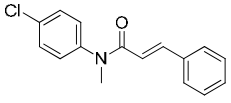
Notably, only trace amounts of **4**, formed from the dimerization of the *in-situ* generated enone—that is, the phenyl vinyl ketone from the dehydrochlorination of **2a**—were detected during the optimization of this reaction.

3.2. Substrate scope

With the optimized conditions in hand, we proceeded to evaluate the scope of the reaction using a series of aryl halides (Table 2). Pleasingly, aryl iodides bearing an electron-donating group such as a methyl or methoxy group reacted smoothly with **2a** to give the desired products **3b**–**3e** in 83%–87% yields (Table 2, entries 2–5). Furthermore, compound **2a** reacted with 4-, 3- and 2-iodotoluene to give the corresponding products in similar high yields, showing no obvious steric effect (Table 2, entries 2–4). Aryl iodides bearing weakly electron-withdrawing groups also reacted smoothly with **2a** to afford the corresponding chalcone products **3f**–**3j** in good to excellent yields (Table 2, entries 6–10). However, highly electron-deficient aryl iodides, such as **1k**–**1m**, exhibited much lower levels of reactivity to give **3k**–**3m** in moderate yields (Table 2, entries 11–13).

Table 3
Reactions of *β*-chloroalkyl carbonyl compounds with **1a**.



Entry	*β*-Chloroalkyl carbonyl (**2**)	Product (**5**)	Isolated yield (%)	Entry	*β*-Chloroalkyl carbonyl (**2**)	Product (**5**)	Isolated yield (%)
1	 **2b**	 **5a**	83	8	 **2i**	 **5h**	80
2	 **2c**	 **5b**	89	9	 **2j**	 **5i**	78
3	 **2d**	 **5c**	83	10	 **2k**	 **5j**	85
4	 **2e**	 **5d**	84	11	 **2l**	 **5k**	79
5	 **2f**	 **5e**	82	12	 **2m**	 **5l**	77
6	 **2g**	 **5f**	86	13	 **2n**	 **5m**	90
7	 **2h**	 **5g**	90	14	 **2o**	 **5n**	88

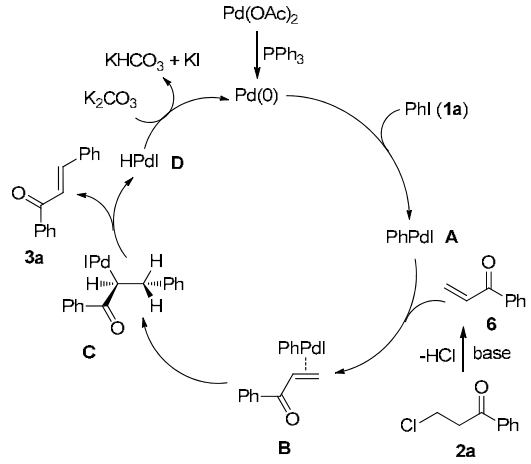
Reaction conditions: **1** (0.4 mmol), **2a** (0.5 mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), and K_2CO_3 (1.2 mmol) in DMF (2.5 mL) at 90 °C for 16 h under 0.1 MPa of N_2.

2-Iodothiophene also reacted smoothly under the optimized conditions to give **3n** in 75% yield (Table 2, entry 14). Although aryl iodides reacted efficiently with **2a** to give the corresponding chalcones, bromobenzene reacted slowly to form **3a** in 33% yield (Table 2, entry 15). Furthermore, chlorobenzene failed to provide any of the desired product under the optimized conditions (Table 2, entry 16).

The scope of the *β*-chloroalkyl carbonyl compounds was also explored by reacting a series of these compounds with iodobenzene (**1a**) under the optimized conditions (Table 3). The reactions of substituted 3-chloropropiophenones **2b**–**2h** proceeded efficiently to afford the desired products **5a**–**5g** in 82%–89% yields, with good functional group tolerance exhibited towards methyl, methoxy, chloro, and fluoro substituents on the phenyl ring (Table 3, entries 1–7). The corresponding thienyl, furyl, and indolyl derivatives of type **2** also exhibited good reactivity to give the corresponding products **5h**–**5j** in 78–85% yields (Table 3, entries 8–10). Pleasingly, the ester and amide substrates **2l**–**2o** also reacted smoothly under the optimized conditions to furnish **5k**–**5n** (77%–90%), with the esters reacting more efficiently than the amides (Table 3, entries 11–14).

Competition reactions were performed to determine the reactivity of the different substrates. An equimolar mixture of **1b** and **1f** was reacted with **2a** to give a mixture of **3b**/**3f** (mol/mol = 39:61; Eq. (1)), revealing that the presence of an electron-withdrawing substituent on the phenyl ring of the aryl iodide substrate provided a higher yield of the corresponding chalcone than the corresponding reaction with an electron-donating group. Treatment of **1a** with an equimolar mixture of **2b** and **2g** under the same conditions led to a mixture of **5a** and **5f** (mol/mo = 41:59; Eq. (2)), demonstrating that an electron-withdrawing substituent on the aryl moiety of the *β*-chloroalkyl aryl ketone provided a higher yield of the corresponding chalcone than the corresponding reaction with an electron-donating group.

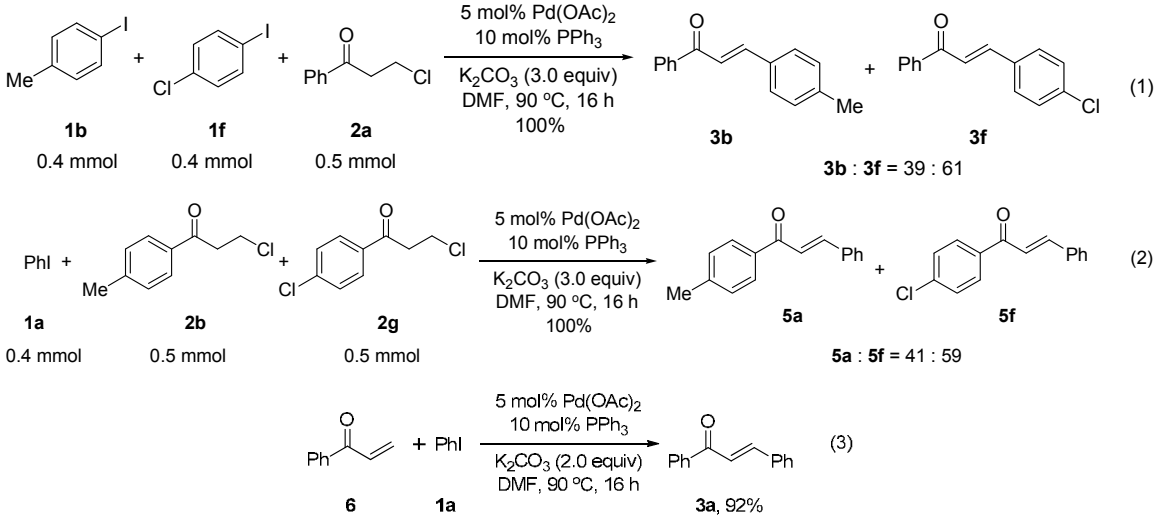
3.3. Mechanism



Scheme 2. A proposed mechanism for the reaction of **1a** with **2a**.

It has been confirmed that heating substrates such as **2** under basic conditions leads to formation of the corresponding enones [22,23]. Interestingly, the reaction of phenyl vinyl ketone (**6**) with **1a** under conditions similar to those developed in this study afforded **3a** in 92% isolated yield (Eq. (3)), which suggested that enones such as **6** were being generated *in situ* from **2**, and that enones could therefore be acting as intermediates in the current coupling reactions of **1** with **2**.

Based on the results of this study, we have proposed a mechanism for this transformation, which is depicted in Scheme 2 for the reaction of **1a** with **2a**. Briefly, $Pd(OAc)_2$ would be reduced by PPh_3 to give a Pd(0) species, which would initiate the catalytic reaction. Oxidative addition of PhI to Pd(0) would lead to the formation of species **A**, which would react with enone **6** (generated *in-situ* from **2a**) to produce π-complex **B**. Enone **6** would then undergo alkene insertion into the Pd-C bond to yield **C**, followed by *β*-hydride elimination to produce product **3a** and the Pd(II) species **D**. The Pd(0) species would then be regenerated by the reductive elimination of HI from **D** in the presence of K_2CO_3 to complete the catalytic cycle.



Graphical Abstract

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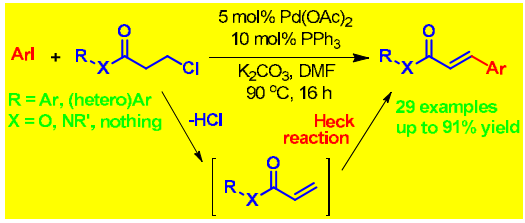
Synthesis of chalcones *via* domino dehydrochlorination/ Pd(OAc)$_2$-catalyzed Heck reaction

Tenglong Guo, Quanbin Jiang, Likun Yu, Zhengkun Yu*
Dalian Institute of Chemical Physics, Chinese Academy of Sciences; SINOPEC Baling Petrochemical Company

Efficient cross-coupling of aryl halides with β-chloroalkyl aryl ketones and their ester and amide analogs through a novel domino dehydrochlorination/Pd(OAc)$_2$-catalyzed Heck reaction has been developed. The new strategy uses *in-situ* generated enones as the reaction intermediates to reduce the occurrence of side reactions and enhance the reaction efficiency. This new protocol represents a concise method for the synthesis of chalcones.



4. Conclusions

In summary, a new reaction for the cross-coupling of aryl halides with β-chloroalkyl aryl ketones and their ester and amide analogs has been developed involving a domino dehydrochlorination/Pd(OAc)$_2$-catalyzed Heck reaction with *in-situ* generated enones acting as the reaction intermediates. This new method provides rapid access to chalcones from readily available starting materials.

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