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Rhodium(I)-Catalyzed Arylation of β-Chloro Ketones and Related Derivatives through Domino Dehydrochlorination/ Conjugate Addition

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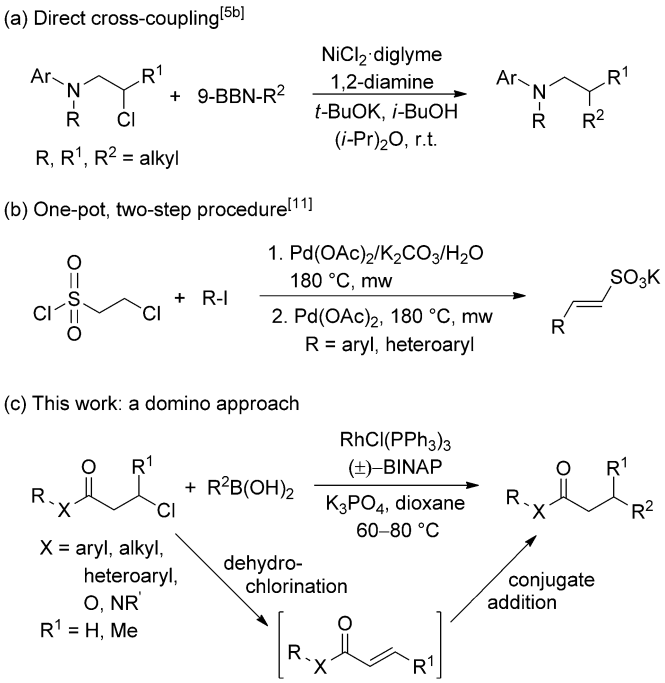
Abstract: Highly efficient arylations of β-chloro ketones and their ester and amide derivatives were achieved by means of domino dehydrochlorination/ Rh(I)-catalyzed conjugate addition. *In situ* generated vinyl ketones and their analogues were identified as the reaction intermediates. The present synthetic protocol provides a concise route to (chiral) β-aryl ketones, esters, and amides.

Keywords: arylation; β-chloro ketones; domino reactions; rhodium(I); sp^3 C–Cl bond cleavage

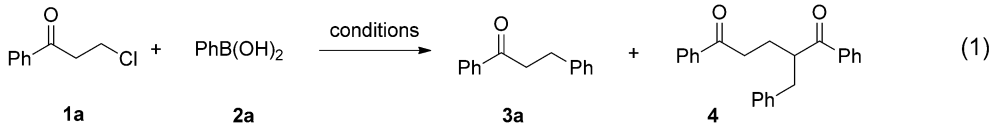
Activated alkyl chlorides have been used as electrophiles in cross-coupling processes.[1] Recently, carbon-carbon cross-couplings involving the cleavage of unactivated sp^3 C–Cl bonds have become more and more attractive.[2] Fu et al. reported nickel-catalyzed Suzuki reactions of unactivated alkyl chlorides with 9-BBN-alkyls.[3,4] Unactivated secondary alkyl chlorides also underwent the same type of reactions,[5] in which an amino-directing group was required [Scheme 1 (a)].[5b] With bimetallic nickel/copper catalysts, Hu et al. established the cross-coupling reactions of unactivated alkyl halides with terminal alkynes[6a] and heteroarenes,[6b] respectively. Chlorocycloheptane was reported to couple with lithium arylborates.[7] Unactivated chlorides have also been documented for Negishi reactions.[8] In the presence of the Grignard reagent cyclohexylmagnesiun chloride, unactivated alkyl chlorides were utilized for arene C–H functionalization.[9]

The major problem of alkyl halide-involving cross-coupling reactions is that the halide substrate or intermediate generated *in situ* undergoes β-hydride elimination to result in other undesired reactions. However, the consequence of such a β-hydride elimination process may be applied in a domino reaction sequence[10] to accomplish an indirect cross-coupling. Although nickel compounds have always been used as the effective catalysts for alkyl halide-involving cross-couplings, other transition metals have recently been reported.[7–9,11] In this aspect, a palladium-catalyzed one-pot, two-step procedure, i.e., hydrolysis/dehydrochlorination/Heck coupling of chloroethanesulfonyl chloride with iodoarenes, was realized to prepare styrene sulfonate salts [Scheme 1 (b)].[11] During



Scheme 1. sp^3 C–Cl cleavage of alkyl chlorides.

Table 1. Screening of conditions for the reaction of 3-chloropropiophenone (**1a**) and phenylboronic acid (**2a**).[a]



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

Entry	Catalyst/[mol%]	Ligand/[mol%]	Ratio **3a**:**4**	Yield of **3a** [%][b]
1[c]	$[RhCl(C_2H_4)_2]_2$/2.5	(±)-BINAP/5	>99:1	43
2	$[RhCl(C_2H_4)_2]_2$/2.5	(±)-BINAP/5	>99:1	88
3[d]	$[RhCl(C_2H_4)_2]_2$/2.5	(±)-BINAP/5	73:27	69
4	$[RhCl(COD)]_2$/2.5	(±)-BINAP/5	>99:1	69
5	$[Rh(CO)_2Cl]_2$/2.5	(±)-BINAP/5	>99:1	68
6	**$RhCl(PPh_3)_3$/5**	**(±)-BINAP/5**	**>99:1**	**97**
7	$RhCl(PPh_3)_3$/2.5	(±)-BINAP/2.5	99:1	82
8[d]	$RhCl(PPh_3)_3$/5	(±)-BINAP/5	95:5	91
9	$RhCl(PPh_3)_3$/5	PPh_3/10	93:7	75
10	$RhCl(PPh_3)_3$/5	dppe/5	93:7	69
11	$RhCl(PPh_3)_3$/5	dppp/5	93:7	80
12	$RhCl(PPh_3)_3$/5	dppb/5	99:1	83
13	$RhCl(PPh_3)_3$/5	–	99:1	88
14[e]	$RhCl(PPh_3)_3$/5	(±)-BINAP/5	96:4	85
15[f]	$RhCl(PPh_3)_3$/5	(±)-BINAP/5	92:8	86
16[g]	$RhCl(PPh_3)_3$/5	(±)-BINAP/5	92:8	82
17[h]	**$RhCl(PPh_3)_3$/5**	**(±)-BINAP/5**	**>99:1**	**99**

[a] *Reaction conditions:* **1a** (0.5 mmol), **2a** (1.0 mmol), K_3PO_4 (1.0 mmol), dioxane (2 mL), 60 °C, 20 h, 0.1 MPa N_2. The molar ratio of **3a**:**4** was determined by GC analysis.
[b] Isolated yields.
[c] **2a** (0.5 mmol).
[d] Water (0.2 mL) was added.
[e] In toluene.
[f] In THF.
[g] At 50 °C.
[h] At 80 °C.

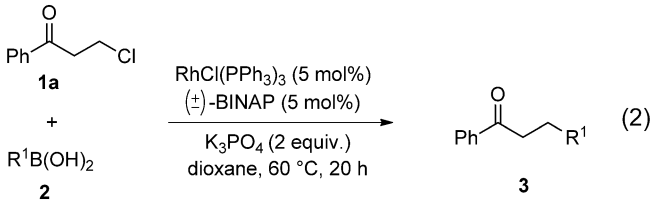
our ongoing study on sp^3 C–Cl bond activation/cleavage, we envisioned that hydrochloride might be eliminated from β-chloro ketones by a base to form the corresponding α,β-unsaturated ketones which subsequently undergo catalytic conjugate addition, affording indirect cross-coupling products. Herein, we report an efficient Rh(I)-catalyzed domino dehydrochlorination/conjugate addition process for the arylation of β-chloro ketones and their ester and amide derivatives *via* sp^3 C–Cl bond cleavage [Scheme 1 (c)].

Initially, the reaction of 3-chloropropiophenone (**1a**) and phenylboronic acid (**2a**) in a 1:1 molar ratio was carried out in dioxane at 60 °C [Eq. (1), Table 1]. In the presence of K_3PO_4 base and 2.5 mol% $[RhCl(C_2H_4)_2]_2$/(±)-BINAP (5 mol%) as catalyst, the desired product **3a** was formed in 43% yield within 20 h (Table 1, entry 1). Increasing the amount of **2a** to 2.0 equiv. led to **3a** in 88% isolated yield (Table 1, entry 2). Addition of water was detrimental to the reaction (Table 1, entry 3), while Rh(I)-catalyzed 1,4-addition reactions of enones usually require the involvement of water.[12]

$RhCl(PPh_3)_3$ was found to be the most efficient catalyst with (±)-BINAP as the suitable ligand (Table 1, entries 1–12). With 5 mol% catalyst loading, **3a** was obtained in 97% yield (Table 1, entry 6). The reaction also proceeded under ligand-free conditions (Table 1, entry 13). In toluene or THF or at 50 °C, the reaction was less efficient (Table 1, entries 14–16), whereas elevating the temperature to 80 °C resulted in the desired product in 99% yield (Table 1, entry 17). Compound **4** was detected as the minor product and its formation will be discussed in the mechanism context.

The synthetic protocol was then extended to the reactions of **1a** with various boronic acids (**2**) under the optimal conditions [Eq. (2), Table 2]. Arylboronic acids bearing an electron-donating methyl or methoxy substituent reacted with **1a** to form the desired products **3b–f** in 94–98% yields (Table 2, entries 2–6), and the steric hindrance from a 2-methoxy group on the aryl ring of **2g** lessened the reaction efficiency, producing **3g** in 73% yield (Table 2, entry 7). The reaction of **1a** with electron-withdrawing group-substituted arylboronic acids also efficiently gave the desired products, i.e., **3h–l** (91–97%) (Table 2, entries 8–12).

Table 2. Reactions of **1a** with arylboronic acids **2**.[a]



(2)

Entry	R^1 (**2**)	Product (**3**)	Yield [%][b]
1	C_6H_5 (**2a**)	**3a**	97
2	4-MeC_6H_4 (**2b**)	**3b**	95
3	3-MeC_6H_4 (**2c**)	**3c**	98
4	2-MeC_6H_4 (**2d**)	**3d**	96
5	4-$MeOC_6H_4$ (**2e**)	**3e**	94
6	3-$MeOC_6H_4$ (**2f**)	**3f**	94
7	2-$MeOC_6H_4$ (**2g**)	**3g**	73
8	4-ClC_6H_4 (**2h**)	**3h**	94
9	4-$MeO_2CC_6H_4$ (**2i**)	**3i**	91
10	4-FC_6H_4 (**2j**)	**3j**	97
11	4-$CF_3C_6H_4$ (**2k**)	**3k**	96
12	3-$CF_3C_6H_4$ (**2l**)	**3l**	94
13[c]	3-$NO_2C_6H_4$ (**2m**)	**3m**	65
14[d]	4-$OHCC_6H_4$ (**2n**)	**3n**	64
15[d]	4-*t*-BuC_6H_4 (**2o**)	**3o**	99
16	2-naphthyl (**2p**)	**3p**	87
17	1-naphthyl (**2q**)	**3q**	98
18	2-furyl (**2r**)	**3r**	69
19	3-thienyl (**2s**)	**3s**	99
20	**3-pyridyl (2t)**	**5**[e]	**53**
21	3,4-$F_2C_6H_3$ (**2u**)	**3t**	85
22	3,4,5-$F_3C_6H_2$ (**2v**)	**3u**	87

[a] *Reaction conditions:* **1a** (0.5 mmol), **2** (1.0 mmol), K_3PO_4 (1.0 mmol), dioxane (2 mL), 60 °C, 20 h, 0.1 MPa N_2.
[b] Isolated yields.
[c] At 80 °C.
[d] **2n** or **2o** (1.5 mmol), K_3PO_4 (1.5 mmol), 80 °C, 30 h.
[e] See Eq. (3).

For less reactive 3-nitro-, 4-formyl- and 4-*tert*-butylphenylboronic acids **2m**–**o**, their reactions with **1a** had to be performed at an elevated temperature, i.e., 80 °C, or at 80 °C over a longer reaction time (Table 2, entries 13–15). Naphthyl-, 2-furyl- and 3-thienylboronic acids underwent the same type of reactions, generating **3p**–**s** in 69–99% yields (Table 2, entries 16–19). 3-Pyridylboronic acid (**2t**) did not show any reactivity, and only the product **5** (53%) was collected from the reaction of **2t** with **1a** [Table 2, entry 20 and Eq. (3)]. Compound **5** is considered to be product from the domino dehydrochlorination/dimerization sequence of substrate **1a** under the stated conditions.[13,14] Di- and trisubstituted arylboronic acids **2u** and **2v** reacted with **1a** to afford **3t** and **3u** in 85% and 87% yields (Table 2, entries 21 and 22), respectively. The desired product such as **3h** could be further functionalized through a Suzuki cross-coupling protocol, providing β-carbonyl-bearing biaryl **3v** [Eq. (4)].

Next, the substrate scope was explored by using functionalized β-carbonylalkyl chlorides and various arylboronic acids as the substrates [Table 3 and Eq. (5)]. β-Carbonylalkyl chlorides are commercially available or were prepared by the Friedel–Crafts reactions of chlorides with the corresponding arenes (see the Supporting Information for details). At 80 °C, the reactions of substituted 3-chloropropiophenones efficiently proceeded to form the desired products **6a**–**n** in excellent yields (88–98%) with tolerance of methyl, methoxy, chloro and fluoro as the substituents. Only in the reactions between two 4-electron-withdrawing group-substituted substrates were the products, i.e., **6i**, **6j** and **6m**, obtained in lower yields (80–86%). Naphthyl-based 3-chloro ketone reacted with **1a** to form **6o** in 99% yield. The thienyl, furyl, pyrrolyl and indolyl derivatives of **1a** also exhibited excellent reactivity and their reactions efficiently afforded the desired products **6p**–**v**. β-Chloro ester and amide derivatives also underwent the same type of reactions, furnishing the corresponding products **6w**–**z** (68–85% from the esters) and **6z1**–**z4** (65–81% from the amides) in good to moderate yields. Aliphatic 1-chloropentan-3-one behaved very well to give the desired product **6z5** in 94% yield, whereas 3-chlorocyclohexanone only showed a poor reactivity to form **6z6** (25%). Surprisingly, 3-methyl-3-chloropropiophenone efficiently reacted with **2a**, producing **6z7** in 97% yield.

In a fashion similar to the functionalization of **3h**, product **6j** was further transformed to **6z8** [Eq. (6)],

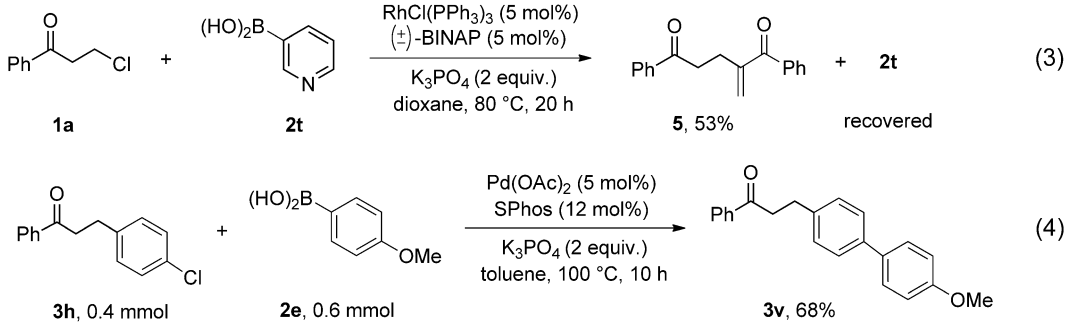
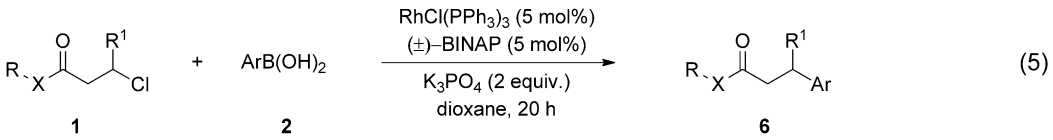
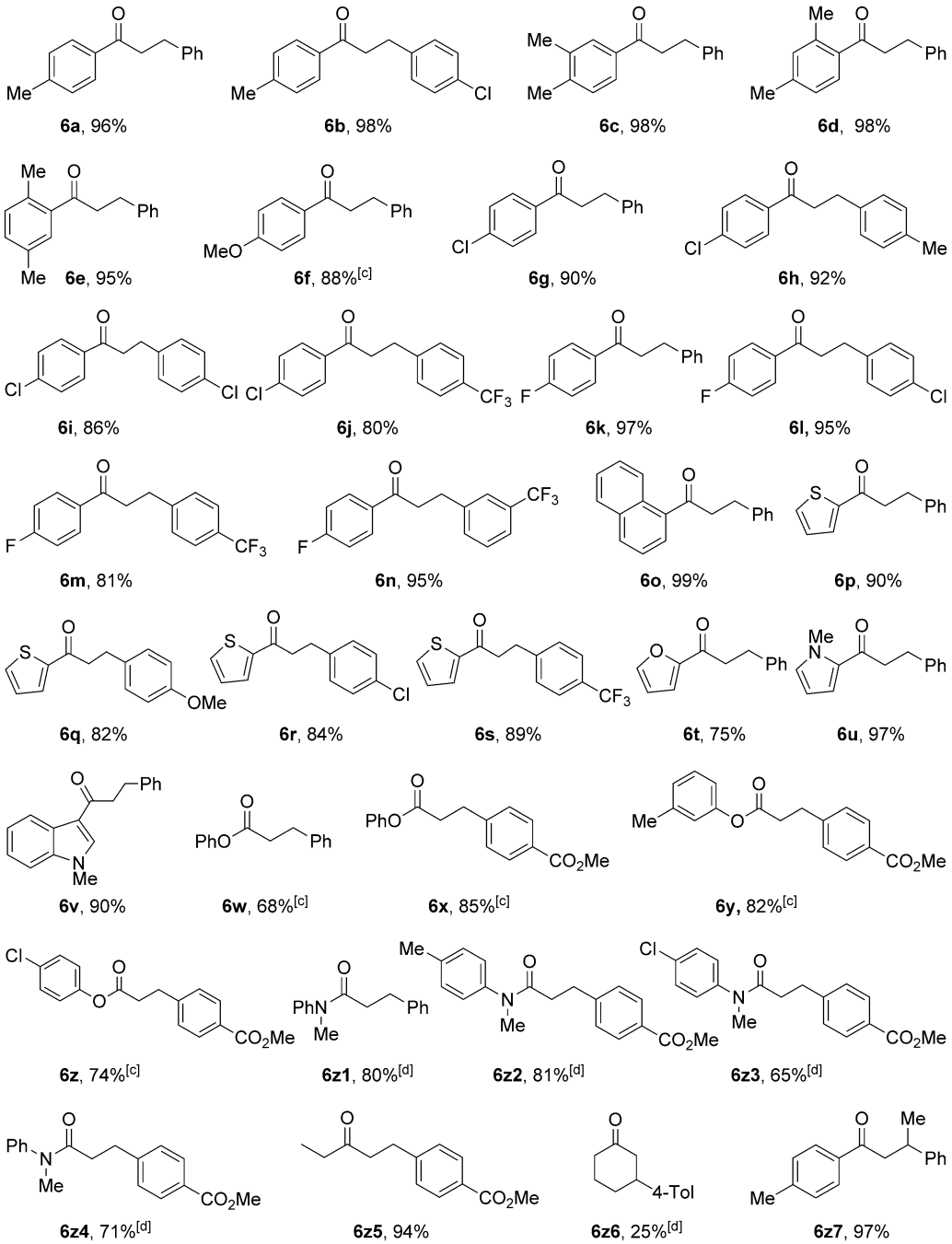
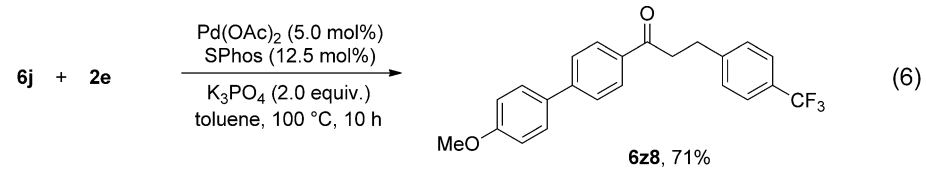


Table 3. Reactions of β-chloro ketones and their ester and amide derivatives (**1**) with arylboronic acids (**2**).[a,b]





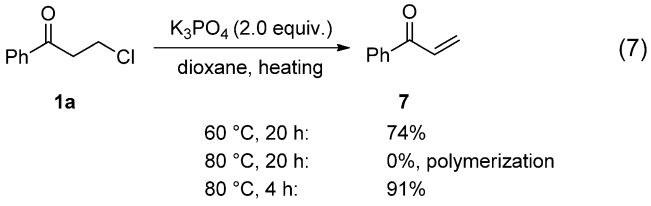
[a] *Conditions:* **1** (0.5 mmol), **2** (1.0 mmol), K_3PO_4 (1.0 mmol), dioxane (2 mL), 80 °C, 20 h, atmospheric N_2.
[b] Isolated yields.
[c] At 60 °C.
[d] At 100 °C.



(6)

demonstrating a potential application of the present synthetic methodology. The competition reactions of **1a** with **2e** and **2h** or **2a** with **1b** and **1g**, afforded **3e** and **3h** or **6a** and **6g** in a 1:3 or 1:1 molar ratio (see the Supporting Information), respectively, revealing an obvious substituent effect from substrates **2**. An electron-donating substituent on the aryl ring of an arylboronic acid decreased the efficiency of the reaction, while the substituent on the aryl ring of the alkyl chloride substrate did not obviously affect formation of the desired product. Because α,β-unsaturated carbonyls are usually susceptible to heating and air during their preparation and storage, the present work has provided a concise protocol for the *in-situ* preparation of this category of compounds.

In order to investigate the reaction pathway, control experiments were performed. Using K_3PO_4 base under heating, **1a** was dehydrochlorinated to phenyl vinyl ketone (**7**)[15] [Eq. (7)]. At 80 °C over a period of 20 h compound **7** could not remain unchanged due to its polymerization. Under the catalytic conditions **5** was only formed in 24% yield from dimerization of the *in-situ* generated **7** [Eq. (8)], also revealing self-polymerization of **7** during the reaction.



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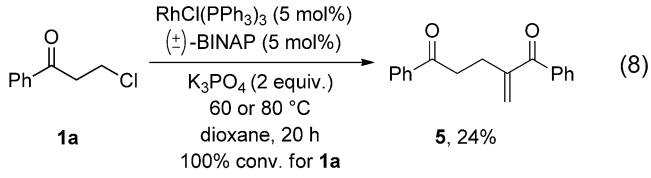
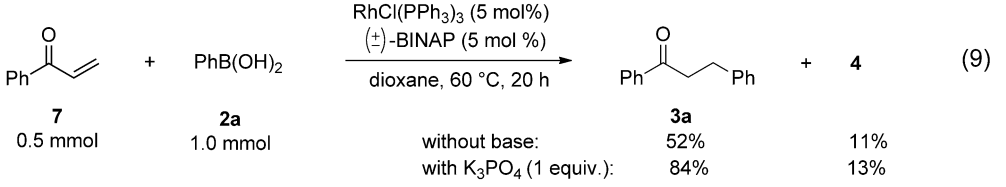


(8)

Treatment of **7** with **2a** formed **3a** as the major product and **4** as the minor product [Eq. (9)]. Formation of **4** was confirmed by the controlled reaction of **5** with **2a** [Eq. (10)], in which a base played a crucial role in the product yield. These results reveal that intermediate **7** is more reactive than **5**, and such a reactivity difference of the reaction intermediates controlled the product selectivity.

By lowering the catalyst loading to 1 mol% and shortening the reaction time to 1 h to achieve an incomplete conversion of **1a** (70%), the intermediate species, i.e., **7**, was detected to be formed from the *in-situ* dehydrochlorination of **1a** by ^{1}H NMR analysis of the reaction mixture of **1a** with **2a** [Eq. (11)]. Water necessary for the hydrolysis step in the catalytic cycle presumably came from the interaction of boronic acids and K_3PO_4 base.[16,17] Under the same conditions, chloroethyl phenyl sulfone could only be converted to phenyl vinyl sulfone which was inert to boronic acids[18] and chloroethyl phenyl ether showed no reactivity, which suggests the directing effect of the oxo functionality in **1** on the sp^3 C–Cl bond cleavage.[19] Thus, the reaction pathway of **1** with **2** can be depicted by a domino reaction sequence involving base-mediated dehydrochlorination of **1** to form an α,β-unsaturated carbonyl intermediate/Rh(I)- catalyzed conjugate addition of boronic acid **2** to the carbonyl intermediate.

Intrigued by the successful synthesis of **6z7** from the reaction of 3-methyl-3-chloropropiophenone with **2a**, (+)-**6z7** was also prepared in 97% yield with 85%



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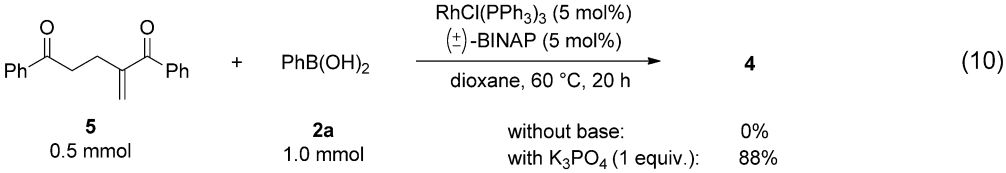
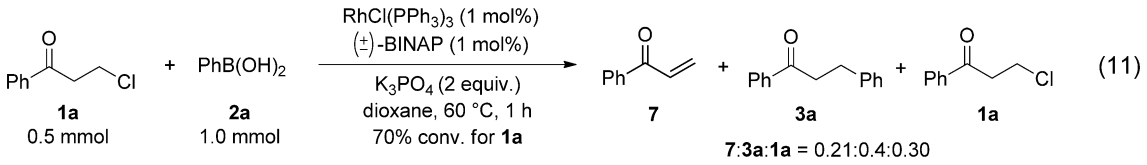


(10)



ee by using $RhCl(CO)(PPh_3)_2$ as catalyst in the presence of a chiral phosphine ligand, i.e., (*S*)-H_8-BINAP (see the Supporting Information for a screening of conditions). Under the same conditions, the substrate scope was examined and the chiral arylation products **8a**–**j** were efficiently synthesized (Table 4). β-Methyl functionality did not affect the reaction efficiency and in most of the cases, the desired chiral products were obtained in >93% yields with up to 92% enantioselectivity. The *ortho* substituent on the aryl moiety of boronic acids **2** improved the enantiopurity of chiral products (+)-**8d** and (+)-**8j**.

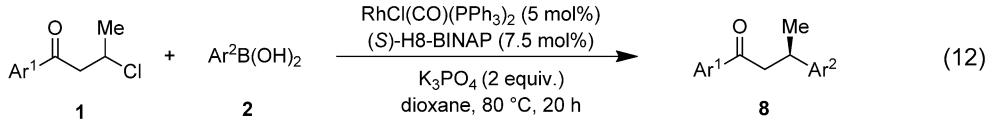
In conclusion, the highly efficient arylation of β-chloro ketones and their ester and amide derivatives was realized by means of domino dehydrochlorination/Rh(I)-catalyzed conjugate addition. This synthetic protocol has exhibited its potential application in carbon-carbon cross-coupling involving *in-situ* generated α,β-unsaturated carbonyls through β-sp^3 C–Cl bond cleavage.

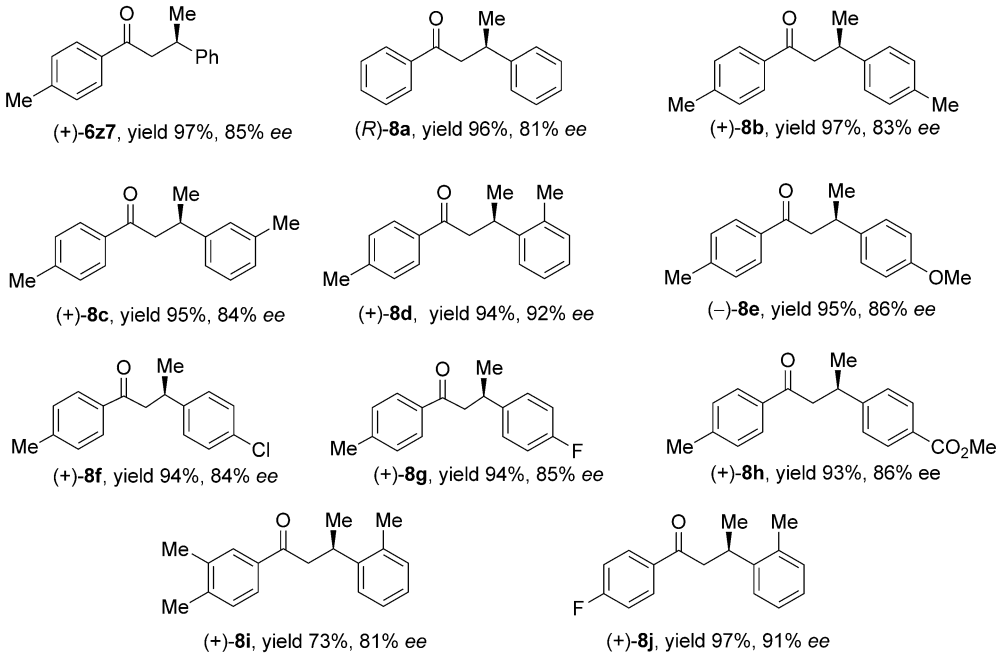
Experimental Section

Typical Procedure for the Reactions of β-Carbonylalkyl Chlorides (1) with Arylboronic Acids (2): Synthesis of 3a

Under a nitrogen atmosphere, a mixture of $RhCl(PPh_3)_3$ (23 mg, 0.025 mmol), (±)-BINAP (16 mg, 0.025 mmol), K_3PO_4 (212 mg, 1.0 mmol) in dioxane (1 mL) was stirred at room temperature for 15 min and followed by addition of phenylboronic acid (**2a**) (122 mg, 1.0 mmol), and 3-chloropropiophenone (**1a**) (84 mg, 0.5 mmol) in dioxane (1 mL). The resultant mixture was stirred at 60 °C for 20 h. After

Table 4. Asymmetric reactions of 3-chloro-1-butan-1-one (**1**) with arylboronic acids (**2**).[a–c]





[a] *Reaction conditions:* **1** (0.25 mmol), **2** (0.5 mmol), K_3PO_4 (0.5 mmol), dioxane (2 mL), 80 °C, 20 h, atmospheric N_2.
[b] Isolated yields.
[c] The *ee* values were determined by chiral HPLC using an Ad-H column.

being cooled to ambient temperature, all the volatiles were removed under reduced pressure. The resulting residue was purified by flash silica gel column chromatography (eluent: petroleum ether (60–90 °C)/Et_2O = 40:1, v/v) to afford **3a** as a white solid; yield: 102 mg (97 %).

Acknowledgements

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