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Organic Chemistry

One-Pot Sequential Kumada–Tamao–Corriu Couplings of (Hetero)Aryl Polyhalides in the Presence of Grignard-Sensitive Functional Groups Using Pd-PEPPSI-IPent^{Cl}**

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Abstract: We report a general and rapid chemoselective Kumada–Tamao–Corriu (KTC) cross-coupling of aryl bromides in the presence of chlorides or triflates with functionalized Grignard reagents at 0 °C in 15 min by using Pd-PEPPSI-IPent^{Cl} (**C4**). Nucleophiles and electrophiles (or both) can contain Grignard-sensitive functional groups (-CN, -COOR, etc.). Control experiments together with DFT calculations suggest that transmetallation is rate limiting for the selective cross-coupling of Br in the presence of Cl/OTf with functionalized Grignard reagents. One-pot sequential KTC/KTC cross-couplings with bromo–chloro arenes have been demonstrated for the first time. We also report the one-pot sequential KTC/Negishi cross-couplings using **C4** showcasing the versatility of this methodology.

Since the time of Kharasch,[1] the cross-coupling of Grignard reagents[2] using transition-metal catalysts has been recognized as a powerful means of making C–C bonds.[3] This is especially useful between two centers for which direct substitution is not readily possible (e.g., between two sp^2 carbon atoms). One of the historical problems associated with the use of Grignard reagents is functional-group compatibility, owing to the strong basicity and nucleophilicity of the carbanion. The high tolerance of base-sensitive functional groups is one reason why the use of organoborane derivatives (the Suzuki–Miyaura Reaction) is popular for cross-coupling.[4,5] However, (hetero)aromatic versions of these organometallics often are derived from the corresponding Grignard (or organolithium) reagent, so further developing the direct coupling of Grignards would streamline coupling, providing the compatibility issue could be overcome.

Knochel and co-workers have made significant contributions in the development of methods to prepare Grignard reagents by metal–halogen exchange with *i*PrMgCl,[6] for which the reagent can be formed at temperatures below which it will react with other functional groups, such as esters and nitriles. With such stable Grignards accessible, two strategies have been used to maintain functional-group compatibility during cross-coupling. The first is simply to maintain the cool temperatures during the coupling, which necessitates the requirement for a high reactivity catalyst.[3j,k] The second is to add the Grignard slowly to the coupling solution at a higher temperature with less reactive catalysts to allow coupling to compete with side reactions.[3b]

Another aspect of selectivity that is impacted by catalyst reactivity is chemoselectivity with oxidative addition (OA) partners bearing more than one halide/pseudohalide. The ability to couple multiple times in one single operation is generally regarded as efficient (and even "green") and is, therefore, desirable. Such approaches are also advantageous to continuous processing unit operations. The Schoenebeck group has developed a $(t\text{Bu})_3\text{P Pd}^{\text{I}}$ dimer precatalyst that is capable of coupling bromides at room temperature, but not chlorides or triflates, to provide monocoupled products.[3a] Even with a high excess of the Grignard, chlorides and triflates are untouched.

A significant step forward for this methodology would be to include base-sensitive functional groups, for example, -CN, -COOR, etc., in the aryl halide partner (Scheme 1) in which functionalized Knochel-type Grignard reagents[6] could be employed in such chemoselective cross-couplings. We envisioned that a new level in catalytic efficiency could be reached if one single, highly reactive catalyst was used to couple richly functionalized substrates, using temperature to differentially activate one OA site in the presence of a second one.

We began our investigation reacting **1** with **2** (prepared from 4-iodobenzonitrile and *i*PrMgCl·LiCl, see the Supporting Information for details) at 0 °C by using Pd-PEPPSI precatalysts.[7,8] Pd-PEPPSI-IPent^{Cl} (**C4**) in toluene was found to provide the best result, affording **3** in 91% isolated yield after just 15 min (Table 1, entry 1). Lowering the Grignard reagent (**2**) from 1.5 to 1.2 equivalents slightly decreased conversion (entry 5), whereas halving the catalyst load of **C4** had no impact (entry 6). At room temperature, the reaction sped to 70% conversion after just 5 min. (entry 7). Switching THF for

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[**] Pd-PEPPSI-IPent^{Cl} = [1,3-bis(2,6-diisopentylphenyl)-4,5-dichloroimidazol-2-ylidene](3-chloropyridyl)palladium(II)dichloride.

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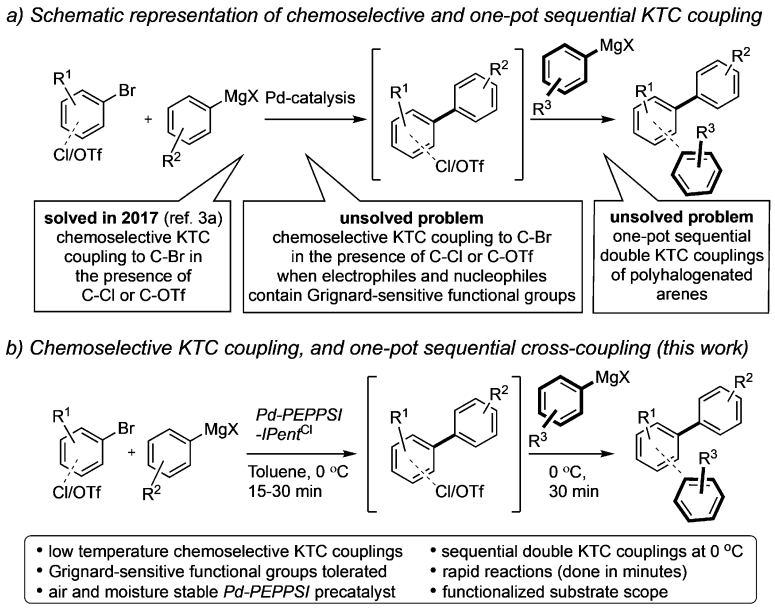
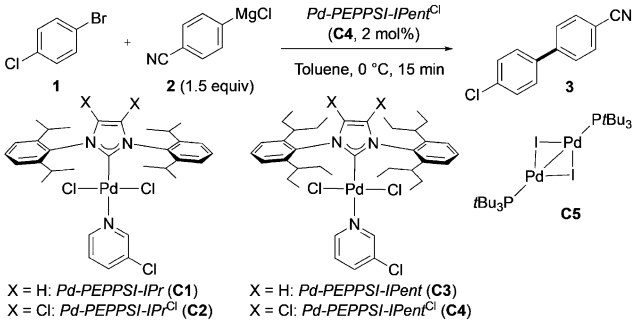


Scheme 1. Chemoselective KTC coupling of aryl halides and functionalized Grignards and one-pot sequential cross-coupling.

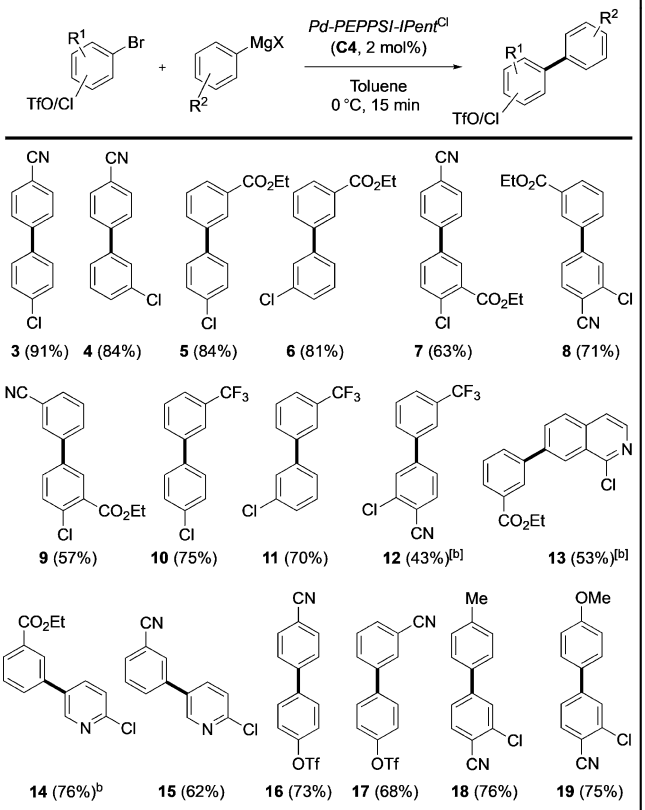
Table 1. Optimization of chemoselective KTC cross-coupling of 4-chloro-bromobenzene (**1**) with 4-cyanophenyl magnesium chloride (**2**).[a]



Entry	Deviation from standard conditions	Conv. [%][b]
1	*none*	*95 (91)*[c]
2	**C1** instead of **C4**	39
3	**C2** instead of **C4**	61
4	**C3** instead of **C4**	67
5	1.2 equiv of **2** instead of 1.5 equiv	83
6	**C4** (1 mol%)	92
7	23 °C, 5 min	73
8	THF instead of toluene	94
9	**C5** (1 mol%) instead of **C4**	27

[a] Reaction conditions: **1** (0.5 mmol), **2** (1.5 equiv), **C4** (2 mol%), toluene (1 mL), 0 °C, 15 min. [b] Percentage conversion was assessed by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c] Isolated yield (average of two runs) after purification by column chromatography.

Table 2. Scope study of chemoselective KTC cross-coupling of bromo–chloro/triflate-arenes with functionalized Grignard reagents.[a]



[a] Reaction conditions: (Het)Ar–X (0.5 mmol), ArMgX (1.5 equiv), **C4** (2 mol%), toluene (1 mL), 0 °C, 15 min. Isolated yield (average of 2 runs) after purification by column chromatography. [b] 1.2 equiv of ArMgX was used.

toluene caused no significant change (entry 8). Using Pd^I dimer **C5**[3a] led to 27% conversion of **3** (entry 9).

With robust conditions in hand, the scope of the transformation was evaluated on bromo–chloro substrates, including heterocycles (**13**–**15**) (Table 2). Base-sensitive functional groups (e.g., esters, nitriles) can be either on the OA partner (**12**, **18**, and **19**), the Grignard reagent (**3**–**6** and **13**–**17**), or both (e.g., **7**–**9**). Various aryl Grignard reagents[6] were coupled chemoselectively in good to excellent yields. The catalyst exhibits the

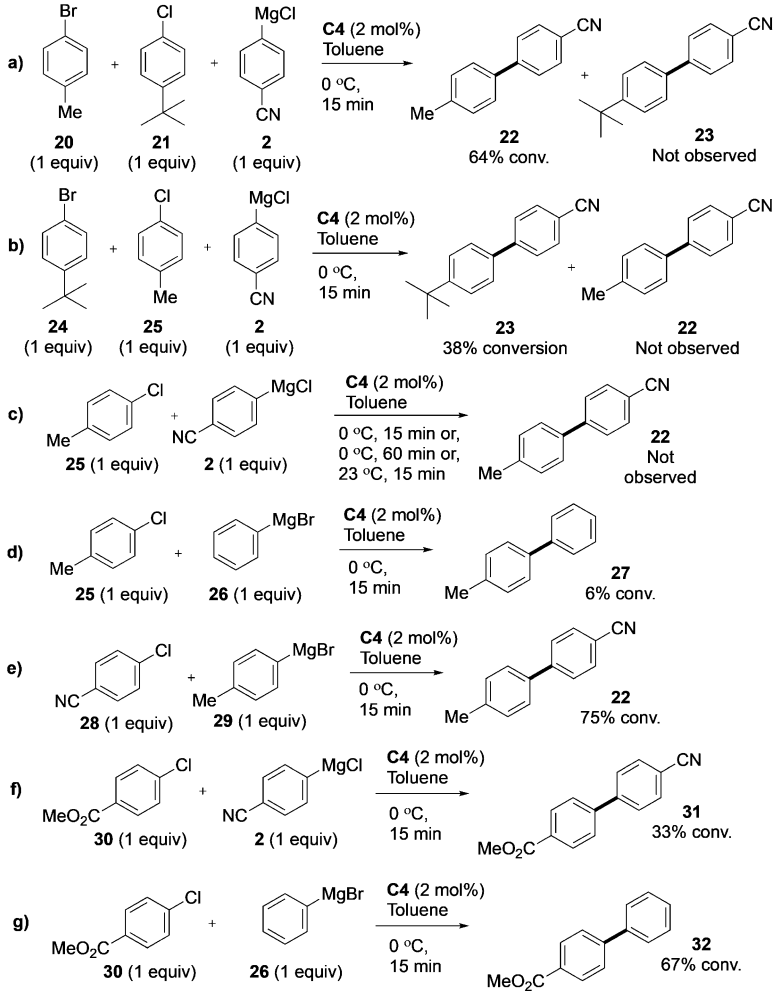
same selectivity of bromides over triflates (**16**, **17**), which vastly expands the applicability of the methodology as any bromo phenol would now become a suitable starting material.

The only side-product we observed during the reaction of **1** and **2** using our best conditions (Table 1, entry 1) resulted from trace homocoupling of the Grignard reagent. We could not find any sign of the di-coupling product, which would have resulted from OA at the C–Cl bond. To understand this remarkable chemoselectivity, we performed a series of control experiments at 0 °C (Scheme 2). When **20**, **21**, and **2** were reacted using optimized conditions, 64% conversion of **20** to **22** occurred and no chloride coupling product (**23**) was observed (Scheme 2a).

To ensure no substrate specificity, we switched the halides leading to **24** and **25** (Scheme 2b), and still the C–Br bond was the only one activated. In the absence of a competing substrate, aryl chloride **25** remained unreactive with **2**, even at room temperature (Scheme 2c). Changing the electron-deficient nucleophile (**2**) to a more electron-neutral partner (**26**) led to minor coupling (i.e., **27**, Scheme 2d). Next, an electron-poor aryl chloride (**28**) and an electron-rich Grignard reagent (**29**) were reacted together providing good conversion to **22** (Scheme 2e).

That Schemes 2c and 2e have simply flipped the reaction partners shows that reductive elimination (RE) cannot be problematic. To better understand the mechanism and to try to understand the reactivity of the Cl site, we carried out a reaction between an electron-poor (activated) aryl chloride (**30**) and an electron-poor (deactivated) nucleophile (**2**) (Scheme 2f). The result observed was 33% conversion to **31**. So, as expected, making the OA partner more electron-poor activates the sluggish C–Cl bond. Interestingly however, switching electron-poor nucleophile **2** to an electron-neutral one (**26**) doubled conversion of **30** to **32** (67%, Scheme 2g). While it is generally accepted that C–Br will oxidatively add faster than C–Cl to Pd^0, these experiments suggest transmetallation (TM) is involved in the selectivity shown by diminishing conversion at the chloride site.

To examine this reactivity pattern computationally, we studied the reaction surface of the coupling using DFT calculations (Figure 1, see the Supporting Information for full details and optimized structures). We used **1** and **2** as the model coupling partners, assuming that the active catalytic species (i.e., $IPent^{Cl}$–Pd^0) forms readily in situ by reduction of precatalyst **C4** (Figure 1). Binding of **1** to the Pd^0–NHC complex yields **33**, from which two OA transition states (TS) are available. The cal-



Scheme 2. Control experiments to examine the rate-determining step of this KTC reaction at 0 °C. Conversions were measured by ^{1}H NMR spectroscopy.

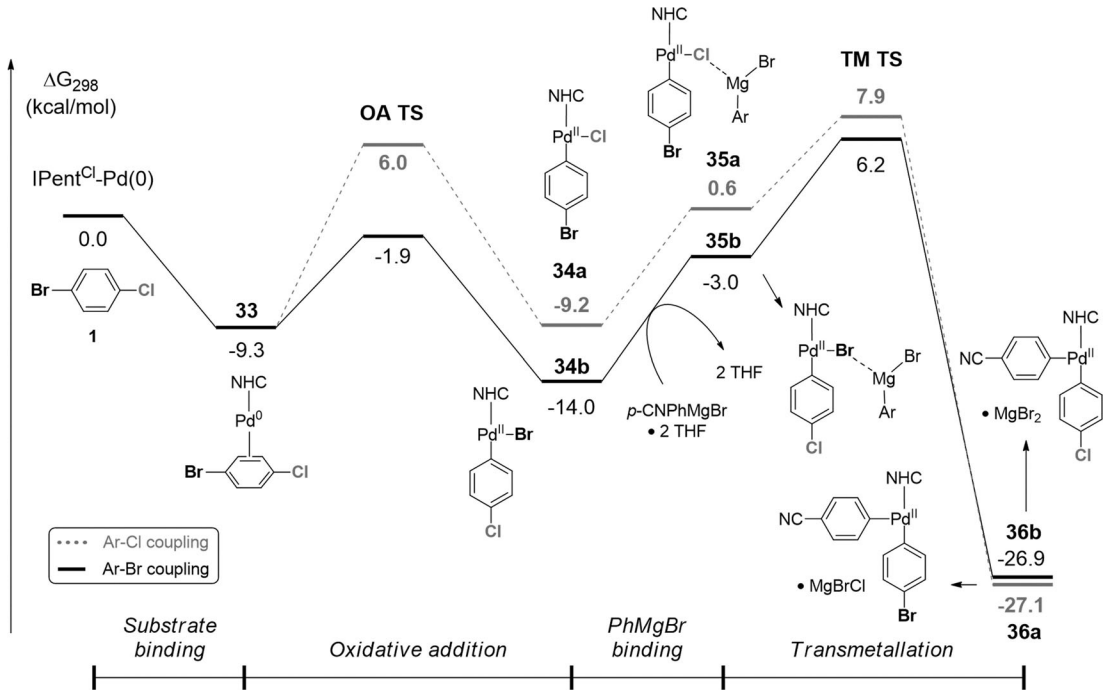


Figure 1. Free energy surface for oxidative addition and transmetallation of bromochloroarene **1** with Grignard reagent **2**, catalyzed by **C4**. DFT calculations at the ωB97X-D/Def2TZVPP/SDD(Pd)/SMD(PhMe)// ωB97X-D/Def2TZVP/LANL2DZ(Pd) level of theory.

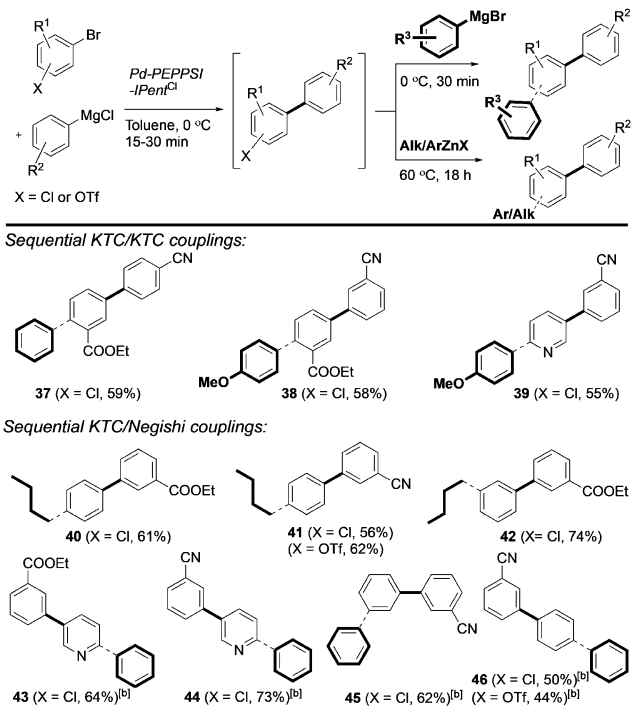
culated barrier for bromide OA is 7.4 kcal mol^{-1}, whereas that for chloride activation is 15.3 kcal mol^{-1}, which would mirror the complete selectivity observed experimentally. This preferred interaction of Pd with Br is shown again in the Pd^{II} complexes following OA, as **34 b** is 4.8 kcal mol^{-1} more stable than **34 a**. For TM, binding of *p*-CNPhMgBr (**2**) to **35 a/b** must first occur and is endergonic. From both **35 a/b**, **TM TS** is irreversible as formation of complexes **36 a/b** is greatly exergonic. Following favorable decomplexation of the MgBrX salt from **36 a/b** and facile RE, the biaryl products are obtained and the catalyst is regenerated.

For both halides, **TM TS** is higher in energy than **OA TS**, supporting the idea that TM is rate-determining in this system. However, the case of chloride activation is most interesting. First, our calculations predict that chloride OA will be reversible, as **34 a** is as stable as the pre-reaction complex **33**. This could explain why aryl chlorides only seem to react with good (electron-rich) nucleophiles for which **TM TS** will be easier to traverse. Second, although the two barriers for reaction of the chloride are very close in free energy (6.0 vs. 7.9 kcal mol^{-1}), their difference is small enough that substituents on either reagent might change which step becomes rate-determining. Indeed, on going from *p*-CNPhMgBr to *p*-MePhMgBr, the difference between the two barriers shrinks to only 0.5 kcal mol^{-1}.[11] Therefore, it is likely that with very electron-rich Grignard reagents, OA may become rate-determining, whereas for electron-poor nucleophiles, we have shown that TM is clearly the limiting step.[11]

As we have seen that activated aryl chlorides can be coupled with Grignard reagents even at 0 °C, we were interested in trying to develop a one-pot, sequential KTC/KTC couplings of bromo–chloro arenes (Table 3). To a solution of bromo–chloro arene and **C4** was added a functionalized Grignard reagent at 0 °C. After stirring for 15 min., a second Grignard reagent was added and the resulting mixture stirred for 30 min at 0 °C yielding functionalized triaryl compounds (**37**–**39**) in good yields. As Pd-PEPPSI-IPent^{Cl} (**C4**) is a highly reactive catalyst,[7] we also explored the one-pot sequential KTC/Negishi cross-couplings of bromo-chloro/triflate-arenes, first with functionalized Grignard reagents and then alkyl or aryl zinc reagents. This procedure proceeded smoothly to provide substituted biaryls (**40**–**42**) and triaryls (**43**–**46**), including heterocycles (**43**, **44**). For both sequential KTC/KTC and KTC/Negishi couplings, no additional catalyst or special handling is required as products were obtained by simply adding Grignard or alkyl/aryl zinc reagents, respectively. Such one-pot sequential KTC/KTC and KTC/Negishi cross-couplings were previously unreported.[9,10]

In summary, we have demonstrated herein a low temperature, rapid and efficient method for the chemoselective KTC cross-coupling of poly(pseudo)halogenated arenes with functionalized Grignard reagents. The functionalized Grignard reagents couple smoothly with C–Br in the presence of C–Cl or C–OTf to form functionalized biaryl chlorides/triflates. Grignard-sensitive functional groups were used both in the electrophile and in the nucleophile. A one-pot sequential KTC/KTC as well as KTC/Negishi coupling has also been developed for the first time. A single set of conditions allowed difunctionalization of (hetero)aryl polyhalides. This methodology would prove useful in applications for the divergent synthesis of molecules and to prepare building blocks for the process chemistry and medicinal chemistry in the pharmaceutical and agrochemical industries.

Table 3. One-pot, sequential KTC/KTC and KTC/Negishi cross-coupling of (hetero)aryl polyhalides with functionalized nucleophiles.[a]



[a] Reaction conditions: For the first step, arylhalides (0.5 mmol), Aryl-MgCl (1.2 equiv), Pd-PEPPSI-IPent^{Cl} (**C4**, 5 mol%), toluene (1 mL), 0 °C, 15–30 min. For the second step in the sequence, add Aryl-MgBr (1.5 equiv), 0 °C, 30 min or Alkyl/Aryl-ZnCl (2.5 equiv), 60 °C, 18 h. Isolated yield (two steps, average of two runs) following column chromatography. [b] THF was used instead of toluene.

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Conflict of interest

The authors declare the following competing financial interest(s): Catalysts used in this work are commercially available, and team members receive royalty payments from their sales.

Keywords: chemoselective coupling · cross-coupling · functionalized Grignard reagents · Pd-PEPPSI · sequential coupling

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[11] For DFT calculations using PhMgBr and *p*-MePhMgBr instead of *p*-CNPhMgBr, see the Supporting Information.

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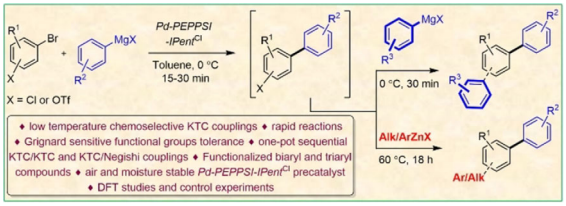

All-in-One! A general and efficient chemoselective Kumada–Tamao–Corriu (KTC) coupling of an aryl bromide in the presence of a chloride or triflate with functionalized Grignard reagents using Pd-PEPPSI-IPent^{Cl} has been described to prepare functionalized biaryl chlorides or triflates. We also demonstrated a one-pot sequential KTC/KTC and KTC/Negishi couplings using a single set of conditions (see scheme).