

Biaryls Made Easy: PEPPSI and the Kumada–Tamao–Corriu Reaction

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Abstract: An easily employed, highly versatile Kumada–Tamao–Corriu (KTC) protocol utilizing the PEPPSI (Pyridine, Enhanced, Precatalyst, Preparation, Stabilization and Initiation) precatalysts **1** and **2** is detailed. The ease-of-use of these catalysts and the synthesis of a wide range of hindered biaryls, large coupling partners and drug-like heterocycles, in high yield, makes the PEPPSI-KTC protocol very attractive. The high reactivity of the PEPPSI system allowed a tetra-*ortho*-

substituted heterocycle, **11** to be synthesized at room temperature for the first time using any protocol. The PEPPSI protocols also tolerated the Boc protecting group and phenols required no protection in modified conditions. A relatively large scale (10 g) reaction was also performed with no loss in performance. Furthermore, PEPPSI-

Keywords: alkanes • C–C coupling • heterocycles • palladium

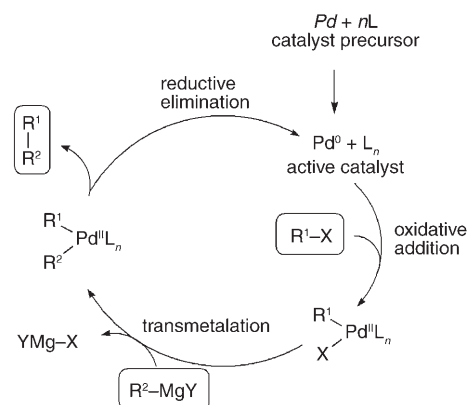
IPr, **1**, was compared to previously reported highly active phosphine ligands **42**, **43**, and **44** and was shown to result in significantly better yields under identical conditions. Finally, we demonstrated that the PEPPSI catalyst system is very adept at performing sequential KTC coupling reactions, analogous to multicomponent reactions, which allow complex polyaryl and polyheteroaryl architectures to be produced in one single operation.

Introduction

Since their discovery by Grignard,^[1] organomagnesium compounds have become fundamental reagents in synthetic organic chemistry.^[2] Their applications are numerous and many have been employed in the synthesis of complex molecules.^[3] Indeed, the first transition-metal-catalyzed cross-coupling reaction employed Grignard reagents with Ni^{II} complexes and was discovered in 1972 independently by Kumada^[4] and Corriu,^[5] who built on earlier ground-breaking work by Kharasch and Fuchs.^[6] However, it was Murahashi who was the first to report the use of catalytic palladium in the Kumada–Tamao–Corriu (KTC) reaction in 1975.^[7] The mechanism this cross-coupling reaction is believed to follow, involves oxidative addition of a Pd⁰ species into the

carbon–halide bond followed by transmetalation, and finally reductive elimination to deliver the product with regeneration of the active Pd⁰ complex (Scheme 1).^[8]

Since these pioneering coupling studies with Grignard reagents the use of organoboron^[8,9] (Suzuki–Miyaura reaction), organozinc^[8,10] (Negishi reaction) and organotin^[8,11] (Stille reaction) reagents have to a large degree replaced the use of Grignard reagents in cross-coupling reactions. This is generally due to the enhanced functional group tolerance that boron, zinc and tin organometallic species possess in



Scheme 1. Simplified Kumada–Tamao–Corriu (KTC) mechanism.

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comparison with Grignard reagents.^[2] The KTC reaction has therefore become, somewhat the poorer relation of these now well established cross-coupling protocols.^[8] Consequently, it is not surprising that only modest development of the KTC reaction has taken place in recent years.^[12] This is unfortunate as the use of Grignard reagents does have some significant advantages over organoboron and zinc reagents. Indeed, organomagnesium (or organolithium) reagents are normally employed in the synthesis of organoboron and zinc species,^[8,13] therefore their direct use in coupling reactions would reduce handling and step count. Furthermore, the synthesis of Grignard reagents and their stabilities are well known as evidenced by their extensive presence in the chemical literature,^[8a,14] their only major drawback being functional group tolerance. However, in situations where a Grignard-sensitive functionality is not present, the KTC reaction represents an exceedingly efficient method for the construction of carbon–carbon bonds, biaryl synthesis in particular. In our continuing efforts to further advance the appeal and routine use of *N*-heterocyclic carbene (NHC)-based cross-coupling methodology, we decided to investigate the use of the PEPPSI (Pyridine, Enhanced, Precatalyst, Preparation, Stabilization, and Initiation) series of complexes **1–4**^[15] (Figure 1) in this under used, yet potentially extremely valuable cross-coupling reaction.

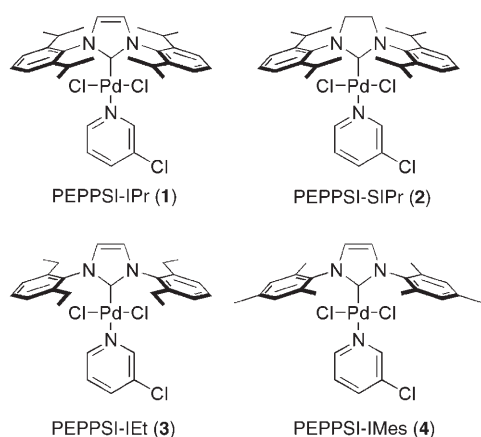


Figure 1. PEPPSI (Pyridine, Enhanced, Precatalyst, Preparation, Stabilization and Initiation) complexes.

Results and Discussion

When attempting to design any coupling protocol we believe the final process must fulfill three main criteria: 1) The protocol must be employed easily without the need for a glovebox, specialized handling of the catalyst or precatalyst or non-routine purification or handling of solvents;^[16] 2) the protocol must be amenable to a significant array of substrates and in particular heterocycles; 3) the procedure must be insensitive to change in scale, meaning that the same protocol developed to produce milligrams of product can be used with minimal, if any change to produce grams, or even

kilograms of the same target. This last point is especially important for such protocols to have any serious acceptance in industry. Working towards these objectives we chose to investigate the use of our most successful complex **1**^[15] in the KTC reaction using the conditions developed by Beller^[12e] as a starting point (Table 1). As expected we found PEPPSI-IPr, **1** to function as an excellent catalyst in a variety of conditions (Table 1, entries 1–20). Using modified Beller conditions,^[12e] THF/DME mixtures, (Table 1, entries 4 and 5) led to an acceptable yield after 24 h.

Table 1. Optimization of reaction conditions.

Entry	Additive	Solvent	<i>T</i> [°C]	Yield [%] ^[a,b]
1	–	THF	RT	7
2	–	THF/DME 1:1	RT	5
3	–	THF/DME 2:1	RT	10
4	–	THF/DME 1:1	RT	68
5	–	THF/DME 2:1	RT	74
6	–	THF	50	66 (60)
7	–	THF/DME 1:1	50	75
8	–	THF/DME 2:1	50	80
9	–	THF/DME 1:1	50	77 (74)
10	–	THF/DME 2:1	50	67
11	2 equiv LiCl	THF	RT	61 (60)
12	2 equiv LiCl	THF/DME 1:1	RT	69
13	2 equiv LiCl	THF/DME 2:1	RT	73
14	2 equiv LiCl	THF/DME 1:1	RT	71
15	2 equiv LiCl	THF/DME 2:1	RT	56
16	2 equiv LiCl	THF	50	74 (77)
17	2 equiv LiCl	THF/DME 1:1	50	67
18	2 equiv LiCl	THF/DME 2:1	50	73
19	2 equiv LiCl	THF/DME 1:1	50	46
20	2 equiv LiCl	THF/DME 2:1	50	51

[a] Reaction Conditions: PEPPSI-IPr, **1**, (2 mol %), *p*-chloroanisole (0.5 mmol), *p*-tolylmagnesium bromide (0.8 mmol), total volume of solvent 1.6 mL. Yield determined by GC/MS/MS using a calibrated internal standard (undecane) and reactions were performed in duplicate. [b] Control experiments with no catalyst showed no conversion in all cases. DME = 1,2-dimethoxyethane, DMI = 1,3-dimethylimidazolidin-2-one.

Following these encouraging results, we then investigated how solvent composition and additives affected the PEPPSI-catalyzed KTC reaction. The use of THF (Table 1, entry 1) or THF/DME mixtures (Table 1, entries 2 and 3) proved ineffective at room temperature although good results were obtained when the reactions were heated (Table 1, entries 6 to 10) or conducted in the presence of LiCl^[15a] (Table 1, entries 11 to 15).

After identifying these optimal conditions, we then submitted complexes **1–4** (Figure 2) to the test reaction shown in order to evaluate the importance of steric bulk in the vicinity of the metal center on conversion. PEPPSI-IPr, **1**, and PEPPSI-SIPr, **2**, were equally highly effective, yielding 85 and 80 % of the cross-coupled product, respectively, over a 24 h period at 50 °C. In contrast, the less sterically encum-

bered PEPPSI-IET, **3**, and PEPPSI-IMes, **4**, were substantially less effective producing only 15 and 4%, respectively (Figure 2). These results clearly demonstrate a relationship

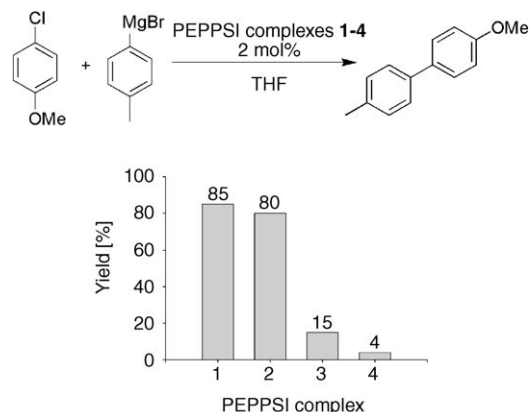


Figure 2. Evaluation of PEPPSI complexes **1–4** in KTC reaction. Sterically encumbered PEPPSI-IPr, **1**, and PEPPSI-SIPr, **2**, gave high yields 85% and 80%, respectively. However, PEPPSI-IET, **3**, and PEPPSI-IMes, **4**, gave much lower yields, 15 and 4%, respectively. These results suggest that a sterically congested palladium metal center is essential to achieve high yields in the KTC reaction. Reaction Conditions: PEPPSI complexes **1–4**, (2 mol %), *p*-chloroanisole 0.5 mmol, *p*-tolylmagnesium bromide (0.8 mmol), total volume of THF 1.6 mL, 50°C, 24 h. Yield was determined by GC/MS/MS using a calibrated internal standard (undecane); reactions were performed in duplicate and control experiments with no catalyst showed no conversion.

between a sterically constrained metal center and high cross-coupling yields. This lends support to the rational that the enhancement of reductive elimination is important. In an effort to further probe the reactivity of **1** and **2**, the cross-couplings were performed over a range of temperatures between room temperature and 80°C (Figure 3). Interestingly, we found that **2** was significantly superior to **1** at low temperatures; there was a major and dramatic increase in yield when the reaction temperature was increased from 25 to 40°C when employing **2** (Figure 3) that did not take place with **1**. However, there was a less dramatic, though pronounced, increase in yield between 40 and 60°C when utilizing **1** (Figure 3). Whether the superiority of **2** at low temperatures is due to an increase in the rate of complex activation or that **2** is simply intrinsically more active due to increased flexibility of the saturated complex is not yet understood.^[17] However the difference in activity is significant and well-defined.

Further differences in the behavior of PEPPSI complexes **1** and **2** were observed when the KTC reaction was followed over a 24 h period (Figure 4). Again, **2** outperforms the related unsaturated **1** as there was a definite increase in rate when **2** is used (Figure 4). Once more it is difficult to pinpoint the exact reasons for this increase; nevertheless we believe the enhancement of “flexible steric-bulk” in relation to the metal center’s topography is critical to the success of these PEPPSI-catalyzed KTC reactions.^[18] The effect of the metal’s steric environment was unambiguously demonstrat-

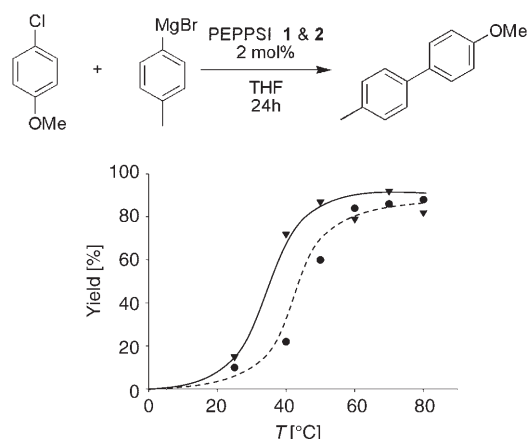


Figure 3. Effect of temperature on the KTC reaction utilizing PEPPSI complexes **1** (●) and **2** (▼). Results indicate that PEPPSI-SIPr, **2**, performs better than PEPPSI-IPr, **1**, at lower temperatures, whether this is due to easier activation of PEPPSI-SIPr, **2**, or that **2** is intrinsically more active is not yet understood. Reaction conditions: PEPPSI complexes **1** or **2**, (2 mol %), *p*-chloroanisole 0.5 mmol, *p*-tolylmagnesium bromide (0.8 mmol), total volume of THF 1.6 mL, at specified temperature, 24 h. Yield determined by GC/MS/MS using a calibrated internal standard (undecane); reactions were performed in duplicate and control experiments with no catalyst showed no conversion.

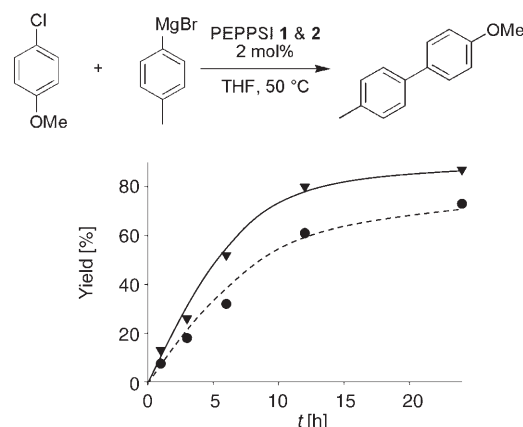


Figure 4. Effect of reaction time on the Kumada–Tamao–Corriu (KTC) reaction utilizing PEPPSI complexes **1** (●) and **2** (▼). Results indicate that PEPPSI-SIPr **2**-catalyzed reactions occur faster than those utilizing PEPPSI-IPr, **1**. This may be due to the increase flexibility of the saturated NHC ligand over the corresponding unsaturated one. Reaction conditions: PEPPSI complexes **1** or **2**, (2 mol %), *p*-chloroanisole 0.5 mmol, *p*-tolylmagnesium bromide (0.8 mmol), total volume of THF 1.6 mL, 50°C, for specified time. Yield determined by GC/MS/MS using a calibrated internal standard (undecane); reactions were performed in duplicate and control experiments with no catalyst showed no conversion.

ed (Figure 2). Therefore, it is not untenable to suggest the increased flexibility afforded to complex **2** with the saturated imidazole ring in the NHC ligand may account for the enhanced performance at low temperatures. During the various steps of the catalytic cycle the NHC ligand bound to the Pd metal center must bend and flex, the aromatic groups attached to the nitrogens rock back and forth to both accept the incoming reaction partners and expel the

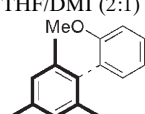
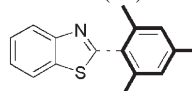
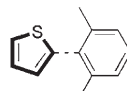
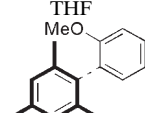
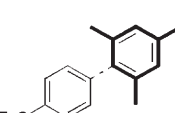
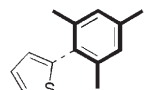
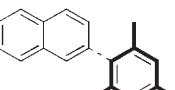
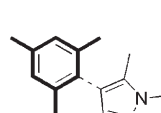
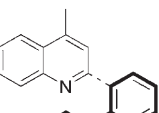
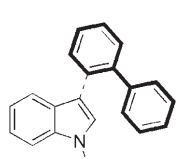
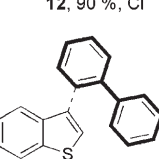
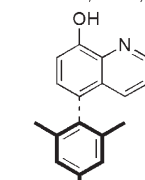
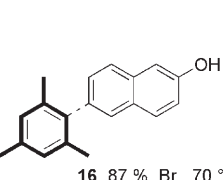
coupled product. Therefore, the increased range of movement of the saturated NHC ligand over the unsaturated NHC ligand is noteworthy.^[17]

The above optimization studies yielded a variety of effective cross-coupling protocols with the use of either PEPPSI complex **1** or **2** resulting in high yields. However, these coupling partners are not representative of substrates that would normally be of great interest and use by the wider synthetic community.

Therefore we embarked on a thorough evaluation of coupling partners utilizing the spectrum of condition outline above. Preliminary cross-couplings were performed at 50 °C (Table 2). The use of a THF/DME mixture allow the synthesis of hindered biaryl **5** (Table 2) whereas heterocycles **6** and **7** were effectively produced utilizing a THF/DME combination (Table 2). Nevertheless, the use of a single solvent would greatly simplify the protocol and pleasingly THF was found to be a very effective solvent with hindered biaryls (**5** and **10**, Table 2) and heterocyclic compounds (**11** to **14** Table 2) formed from the corresponding organo-bromides and -chlorides in reasonable to high yields. Notable results are the formation of tetrasubstituted heterocycle **11** and the tolerance of unprotected hydroxyl groups that allowed for the rapid synthesis of biaryl **15** and heterocycle **16** in high yield, with the addition of 1 equiv of NaH before Grignard addition. The synthesis of **16** was also performed on a 10 g scale with a yield of 85% demonstrating the scalability of the protocol.

Following these promising early results, **1** and in select cases **2** were evaluated in room temperature cross-couplings; it is important to note no effort was made to minimize reaction time (Table 3). Utilization of mixed solvent conditions, THF/DME or THF/DME, allowed the synthesis of a variety of heterocyclic biaryls (Table 3); again aryl bromides or chlorides were equally effective partners in the room temperature KTC reaction. Noteworthy examples are the tolerance of the Boc protecting group, **19**, and the synthesis of drug-like heterocycles **18**, **21** and **27** (THF/DME and THF/DME conditions, Table 3). Gratifyingly, the employment of THF alone led to the easy production of a considerable array of biaryls (THF conditions, Table 3). Significant results are the production of **12** to **14**, **30** and **37** in which the coupling of two large fragments and the tolerance of a Boc protecting group is achieved at room temperature. These results are important if the formation of a C–C bond is required late in synthesis, as might be the case in total synthesis or drug production. The formation of **11**, a tetra-*ortho*-substituted heterocyclic biaryl, is, to the best of our knowledge, the first time such a hindered product has been produced a room temperature with any cross-coupling protocol. The coupling of biaryl Grignard reagents to indole, benzothio-phenes and quinoline-derived halides to form **12**, **13** and **14** (THF conditions, Table 3) and the coupling of thiophene units in **31** and **34**, which are often very problematic partners for Pd-catalyzed coupling, all proceed very smoothly. Such syntheses represent a significant result for the materials area as polymeric thiophenes are currently used in con-

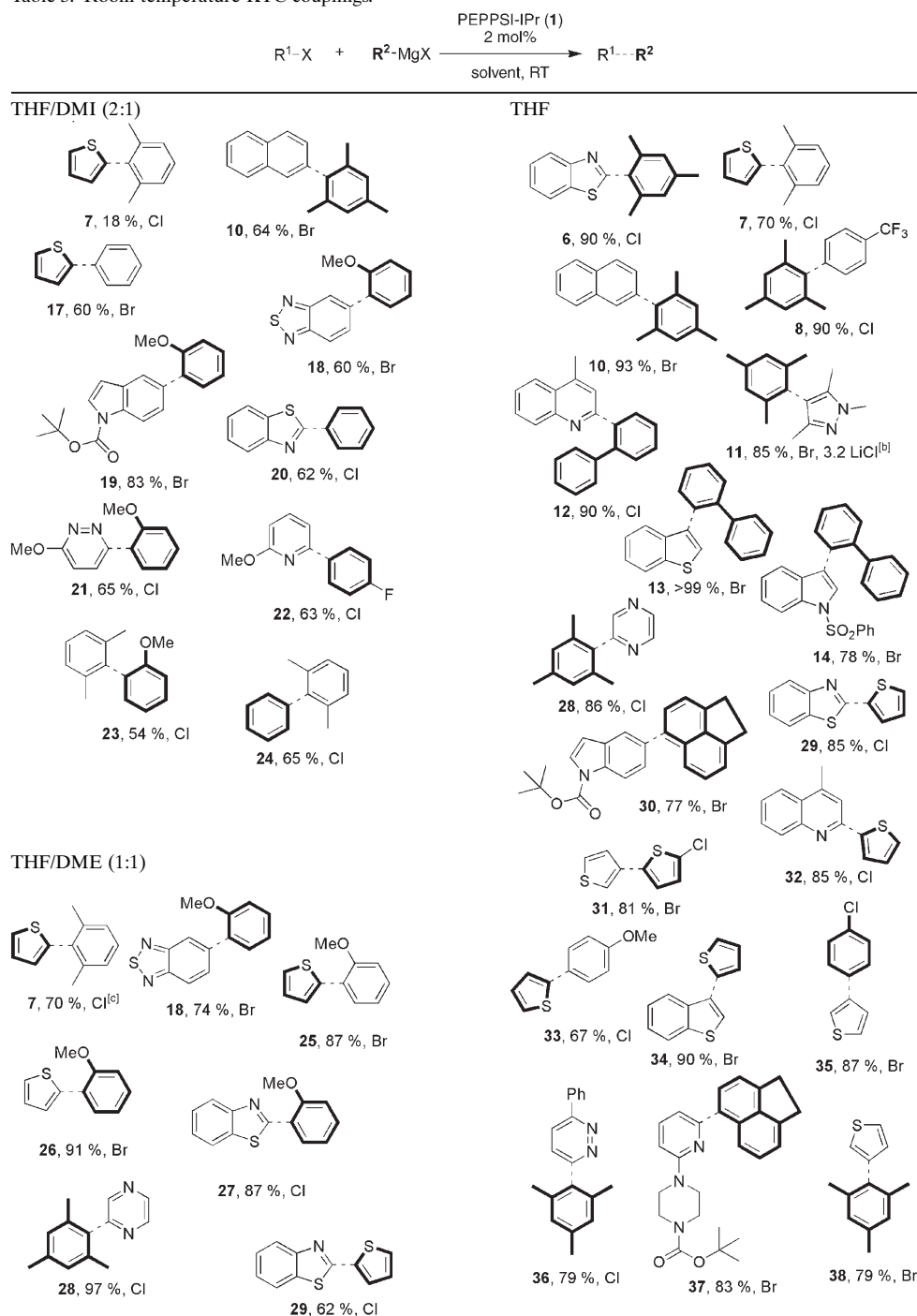
Table 2. Preliminary substrate evaluation.^[a]

$\text{R}^1\text{-X} + \text{R}^2\text{-MgX} \xrightarrow[\text{solvent, 50 } ^\circ\text{C}]{\text{PEPPSI-IPr (1) 2 mol\%}} \text{R}^1\text{---R}^2$	
 5 , 62 %, Br THF/DME (2:1)	
 6 , 90 %, Cl, 2.6 LiCl THF/DME (1:1)	 7 , 81 %, Cl, 3.2 LiCl ^[b]
 5 , 86 %, Br THF	 8 , >99 %, Cl
 9 , 80 %, Br	 10 , 92 %, Br
 11 , 70 %, Br ^[c]	 12 , 90 %, Cl
 14 , 67 %, Br	 13 , 91 %, Br
 15 , 65 %, Cl, 70 °C	 16 , 87 %, Br, 70 °C

[a] Modifications from the conditions above are outline immediately below the product. For detailed reaction procedures, see Supporting Information. [b] Yielded 99% when the reaction was performed with **2**. [c] Reaction conducted using PEPPSI-SIPr, **2** (2 mol %).

ductive polymers.^[19] The production of more routine drug-like biaryls was also readily achieved (**6**, **7**, **28**, **29**, **31**, **35** and **36**, THF conditions, Table 3). It is also worth pointing out that medicinal chemists in industry are concerned that many new catalysts and cross-coupling protocols that are claimed to be very active are only demonstrated to be effective on low molecular weight partners (e.g. simple biaryls); when

Table 3. Room temperature KTC couplings.^[a]



[a] Modifications from the conditions above are outline immediately below the product. For detailed reaction procedures, information, see Supporting Information. [b] Reaction conducted using **2** (2 mol %). [c] Yielded 90 % when the reaction was performed with **2**.

these methods are used to prepare compounds that are not only heteroatom containing, but in the range of 400–600 Da, most fail.^[20] This can be the result of poor solubility or increased bulk of the larger, more structurally complex coupling partners; the routine production of compounds such as **14**, **30** and **37**, (Tables 2 and 3) offer promise to address this concern.

Subsequent to the development of an easily-employed KTC protocol, we decided to investigate the use of **1** in sequential cross-coupling reactions (SCRs, Table 4); the use of such sequenced reactions would allow large molecular frameworks to be constructed in a single “one-pot” operation. Preliminary results (Table 4) are encouraging as the synthesis of tetracycles **39** and **40** proceeded in very good yield over the two couplings.

Interestingly, during the synthesis of **35** (Table 3) an intermediate in the synthesis of heteroaromatic **39** (Table 4) a significant exotherm was observed immediately upon mixing of **1** and the oxidative addition partner that prompted us to evaluate the use of **1** in low temperature KTC reactions (Table 5).

The synthesis of heterocycle **35** was conducted at RT, 0 and –20 °C (Table 5). A rapid and exothermic reaction resulted when the reaction was carried out at RT and 0 °C; however at –20 °C the vigorous boiling of the solvent was contained. At RT, the reaction was complete in 30 minutes, where as the –20 °C the reaction was finished in 2 h. The reactivity of the PEPPSI-IPr-NHC system opens the way for thermally unstable Grignards, and related reagents, to be utilized in the KTC reaction. Importantly, the use of [Pd(PPh₃)₄], still the most commonly-used cross-coupling catalyst, yielded no product at room temperature. However, subsequent addition of **1** to this reaction resulted in an exotherm and complete formation of product.

It is important when developing any cross-coupling protocol to place it in context with the current state-of-the-art procedures. In order to ascertain how **1** performs in relation to current highly active systems, we decided to run a comparative study with phosphines **42**,^[21] **43**^[22] and **44**^[23] as they represent the best current phosphines commercially available, with wide generality, for

Table 4. Sequential cross-coupling reactions.^[a]

SCR couplings	
39, 79 %, 50 °C	40, 62 %, RT

[a] Isolated yield.

Table 5. Low-temperature Kumada–Tamao–Corriu (KTC) reaction.^[a]

Reaction scheme showing the coupling of 2-bromothiophene with 4-chlorophenylmagnesium bromide (MgBr) catalyzed by PEPPSI-IPr (1) (2 mol%) in THF to form product 35, which is 2-(4-chlorophenyl)thiophene.

<i>T</i>	Observation	Yield [%]	<i>t</i> [h]
RT	exotherm	87	0.5 ^[b]
0 °C	exotherm	81	0.5 ^[b]
−20 °C	exotherm contained	64	2

[a] Isolated yield of duplicate reactions. [b] While the reaction was stirred for 0.5 h before being quenched, they were judge by GC/MS to be complete once the exotherm had subsided.

cross-coupling procedures when used in conjunction with a suitable palladium source (Figure 5). As mentioned $[\text{Pd}(\text{PPh}_3)_4]$, **41**, is still the most widely employed palladium catalyst, so we opted to evaluate it as well.^[24] The crude NMR spectra after workup (Figure 5) show that **1** out performs all of the current highly-active hindered phosphines and **41** as it gave the cross-coupled product cleanly in high yield (quantitative) at room-temperature; all other catalysts resulted in minimal conversion in this moderately challenging coupling reaction.

Conclusion

In summary we have developed an easily employed, highly versatile Kumada–Tamao–Corriu (KTC) protocol utilizing the PEPPSI precatalysts **1** and **2**. The ease-of-use and synthesis of a wide range of hindered biaryls, large coupling partners and drug-like heterocycles make the PEPPSI-KTC protocol highly attractive. The PEPPSI complex and oxidative addition partner can simply be weighed, the flask purged with argon the Grignard added; we believe such an easily employed protocol is ideal for medicinal chemistry and parallel synthetic applications with modern liquid handling equipment. The development of a variety of conditions allows for substantial tuning of the reaction to maximize solubility and reaction rate dependent on the reactants employed. The activity of the PEPPSI-SIPr system allowed

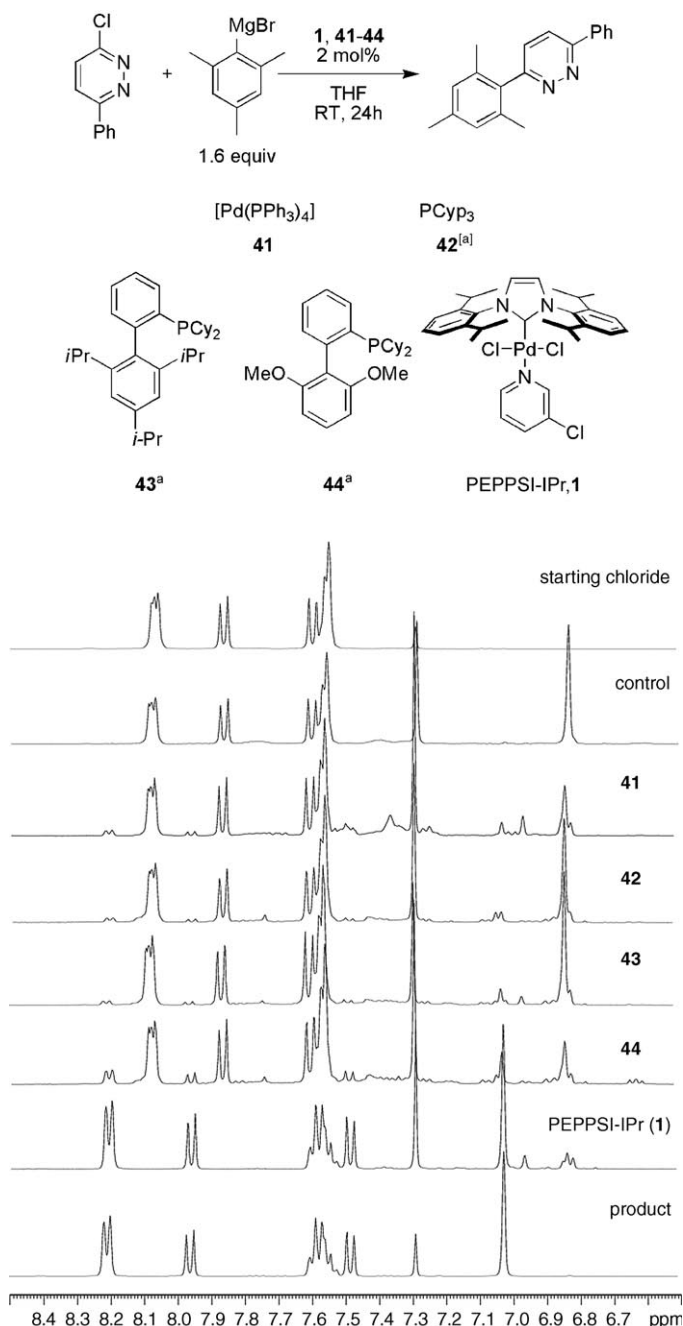


Figure 5. Comparison of PEPPSI-IPr,**1** with the current state-of-the-art phosphines and widely employed $\text{Pd}(\text{PPh}_3)_4$. The crude NMR spectra show that PEPPSI-IPr, **1** out performs the highly active phosphines **42**, **43**, and **44**, and also commonly use $[\text{Pd}(\text{PPh}_3)_4]$. Additionally, when utilizing PEPPSI-IPr, **1**, the product is formed cleanly with little byproduct formation, illustrated by the crude NMR. [a] With these ligands, 1 mol % Pd_2dba_3 was used as a palladium source.

tetra-*ortho*-substituted heterocycle **11** to be synthesized at room temperature, the first time this has been accomplished with any cross-coupling protocol. With certain substrates the reaction can be performed at −20 °C. Such low temperature conditions may allow for the coupling of Grignard reagents that decompose under previous protocols. The PEPPSI pro-

ocols also tolerated the Boc protecting group and phenols required no protection using modified conditions. Importantly, a larger-scale preparation of **16** (10 g) was also conducted with no loss in performance or yield. Furthermore, for the synthesis of heterocycle **35**, complex **1** was compared to previously reported highly-active phosphine ligands **42**, **43**, and **44** these studies showed that the use of **1** resulted in significantly better yields under identical conditions. Finally, we have also demonstrated that the PEPPSI catalyst system is very adept at performing sequential KTC coupling reactions in a manner analogous to multi-component reaction chemistry to build remarkably complex polyaryl and polyheteroaryl architectures in one single operation that can be applied readily to medicinal chemistry, natural product synthesis and material science applications.

Experimental Section

Kumada–Tamao–Corriu (KTC) cross-coupling procedures

Procedure A (THF/DMI): Under air, a vial equipped with a stir-bar was charged with complex **1** (6.8 mg, 2 mol %), sealed with a septum, and purged with argon. Distilled THF (0.26 to 0.7 mL) and dry DMI (0.53 to 0.7 mL) were added by syringe and stirred for 1–2 minutes, after which the aryl halide (0.5 mmol), and *n*-undecane (GC/MS internal standard, 50 μ L) were injected via syringe. Alternatively, if the aryl halide was solid at room temperature, it was weighed out and added to the vial in air following complex **1** addition. After 1–2 minutes of stirring, the Grignard reagent (0.65 to 0.8 mmol, 1.3 to 1.6 equiv) was added in one rapid shot by syringe. The septum was replaced with a Teflon-lined screw cap under an inert atmosphere and the reaction mixture was allowed to stir for approximately 24 h at RT/50°C prior to GC/MS and/or TLC analysis. Once product was identified, the general work-up procedure for compound isolation was followed.

Procedure B (THF/DME): Under air, a vial equipped with a stir-bar was charged with complex **1** or **2** (6.8 mg, 2 mol %), sealed with a septum, and purged with argon. Dry THF (0.35 mL) and dry DME (0.8 to 1.0 mL) was added by syringe and stirred for 1–2 minutes, after which the aryl halide (0.5 mmol), and *n*-undecane (GC/MS internal standard, 50 μ L) were injected via syringe. Alternatively, if the aryl halide was solid at room temperature, it was weighed out and added to the vial in air following complex **1** addition. After 1–2 minutes of stirring, the Grignard reagent (1.3 to 1.6 equiv) was added in one rapid shot by syringe. The septum was replaced with a Teflon-lined screw cap under an inert atmosphere and the reaction mixture was allowed to stir for approximately 24 h at RT or 50°C prior to GC/MS and/or TLC analysis. Once product was identified, the general work-up procedure for compound isolation was followed.

Procedure C (THF): Under air, a vial equipped with a stir-bar was charged with complex **1** or **2** (6.8 mg, 2 mol %), sealed with a septum, and purged with argon. The aryl halide (0.5 mmol), and *n*-undecane (only for GC/MS analysis, internal standard, 50 μ L) were injected via syringe. Alternatively, if the aryl halide was solid at room temperature, it was weighed out and added to the vial in air following PEPPSI complex **1** (or **2**) addition. The Grignard reagent (0.8 mmol, 1.6 equiv), prepared in THF, was added in one rapid shot by syringe, followed by septum replacement with a Teflon-lined screw cap under an inert atmosphere. The reaction mixture was allowed to stir for approximately 24 h at RT/50°C prior to GC/MS and/or TLC analysis. Once product was identified, the general work-up procedure for compound isolation was followed.

Sequential cross-coupling (SCR) procedure: Under air, a 10 mL round bottom flask equipped with a stir-bar was charged with complex **1** (6.8 mg, 2 mol %), sealed with a septum, and purged with argon (3 $\times$). To this was added directly the aryl halide (0.5 mmol) followed by the first

Grignard reagent (0.6 mmol, 1.2 equiv). The resulting mixture was allowed to stir at room temperature for the specified amount of time. When the reaction was deemed complete by TLC analysis, the second Grignard reagent (0.8 mmol, 1.6 equiv) was added. The resulting solution was allowed to stir at the specified temperature for the specified period of time. Once product was identified, the general work-up procedure for compound isolation was followed.

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