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Eco-friendly Suzuki-Miyaura Coupling of Arylboronic acids to Aromatic Ketones Catalyzed by Oxime-Palladacycle in Biosolvent 2-MeTHF†

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Manoj Mondal^a and Utpal Bora^{*a,b}

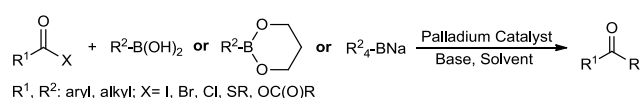
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Oxime-palladacycle catalyzed Suzuki-Miyaura cross-coupling reaction of acid chloride and arylboronic acids to yield aryl ketones was developed. The remarkable benefit of this method is the use of water immiscible (practically) 2-MeTHF as solvent, which provides easy isolation of the crude reaction mixture just by separation of 2-MeTHF-water layers, and then evaporation of 2-MeTHF. Moreover, the use of relatively equal proportion of substrates, and less generation of side products makes the method highly atom economic.

Introduction

Ketones are ubiquitous structural motifs found across various natural products, pharmaceuticals and agrochemicals.¹ They also represents a wide range of ideal starting material for the synthesis of cyanohydrins, oximes, carbazone, acetals, pinacols, etc. Conventional routes to synthesized ketone are: the Friedel-Craft acylation² and Suzuki-Miyaura cross-coupling of aryl halides with organometallic reagents under carbon monoxide atmosphere.³ However, the formation of tertiary alcohols and isomeric mixtures due to limited regioselectivity,⁴ the use of corrosive AlCl₃ and toxic carbon monoxide,⁵ are certain difficulties associated with these methods.

The palladium catalyzed Suzuki-Miyaura cross-coupling of acid derivatives with organoborons represents another powerful tool to access ketones (Scheme 1).⁶ This methodology has gained immense attention as it relies on the use of easily accessible, widely functionalized, relatively low-toxic,⁷ heat and moisture stable organoborons. Moreover, the use of active and commercially available acid derivatives presents wide scope to various ketone derivatives. In recent years, numerous significant outcomes have been achieved using diverse palladium catalysts *viz.* PdCl₂,⁸ Pd(OAc)₂,⁹ Pd/C,^[6b] Pd(dba)₂,¹⁰ Pd(PPh₃)₄,¹¹ PdCl₂(dppf),¹² POPd,¹³ Pd₂dba₃,¹⁴ imidazolium chloride tagged Pd(II) complex¹⁵ and



Scheme 1. Synthesis of ketones.

(BeDABCO)₂Pd₂Cl₆,¹⁶ under reaction systems, like toluene, THF, water, water-acetone, ionic liquid or hydrated base etc. In fact, synthetic methods based on the use of these solvents present the following disadvantages: (i) the possibility of generation of less reactive acid anhydride or carboxylic acid in aqueous system needing high substrate loading;^{6b} (ii) formation of emulsions, rag layers at the phase interface and poor extraction yields; and (iii) the long and troublesome synthetic procedures for ionic liquids.¹⁷ Overall, it is estimated that around 80 % of the chemical waste produced from a drug synthesis corresponds to the organic solvent.¹⁸ Thus, while designing the acid halide-based reactions particular care should be taken in the choice of the solvent.

Recently, Pace and co-workers reported an excellent preparation of Weinreb amides starting from acid halides under biphasic system water-2-methyltetrahydrofuran (2-MeTHF).¹⁹ Importantly, they obtained a range of pure products by simple removal of 2-MeTHF in good yields and purity, and did not use extra solvent during the work-up process. Interestingly, 2-MeTHF resembles toluene or THF in terms of physical properties, and when used in organometallic reactions it offers both economical and environmentally friendly advantages over common aprotic solvents.^{20,21} In reactions including Grignard reagent,²² organopalladium, organozinc and LiAlH₄ reductions,²³ 2-MeTHF has received wide applications. 2-MeTHF has been reported to work like THF in nickel²⁴ and copper²⁵ catalyzed couplings. Pharmaceutical process development researchers have found that the use of 2-MeTHF provides superior diastereoselectivity when compared with other solvents.²⁶

The growing interest towards 2-MeTHF is also due to its adherence with several Green Chemistry principles.²⁷ Among them, the 3rd (less hazardous chemical synthesis – *permitted daily exposure of 2-MeTHF in human is upto 6.2 mg day⁻¹*),²⁸ 5th (safer solvents and auxiliaries), 7th (use of renewable feedstocks – *it can be obtained from biomass feedstock like furfural or levulinic acid derived from corncobs and sugarcane*)^{20a} and the 10th (design for degradation – *it degrades by factors like air and sunlight, probably*

^a Department of Chemistry, Dibrugarh University, Dibrugarh 786004, Assam, India

^b Department of Chemical Sciences, Tezpur University, Tezpur 784028, Assam, India
E-mail: utbora@yahoo.co.in; ubora@tezu.ernet.in

† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/

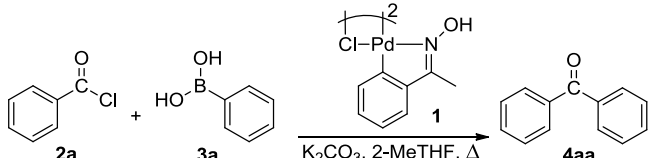
via oxidation and ring-opening)²⁹ principles refers it as a suitable green solvent for both academia and industries.

In recent years, many workers have focused their research interests on the application of oxime-palladacycles, which have exhibited high catalytic activity in various cross-coupling reactions.³⁰ They are stable to heat, air and moisture, and easily accessible from low-cost starting materials. However, to the best of our knowledge, oxime-palladacycles have never been studied for the coupling of acid chloride and arylboronic acid. As part of our ongoing efforts to develop transition-metal-catalyzed reactions,^{6b,31} we herein report the use of combination of oxime-palladacycle **1** and 2-MeTHF in the coupling of acid chlorides (Table 1). Present method provides easy isolation of reaction mixture without the use of additional organic solvent, which would enhance the application scope of the acylation coupling to a more acceptable level.

Results and Discussion

The investigation was initiated by using model reaction between benzoyl chloride **2a** and phenyl boronic acid **3a** in the presence of palladacycle **1** (1 mol%Pd) and K₂CO₃ (2 equiv.) under open air condition in 2-MeTHF at reflux condition. The results were summarized in Table 1. The desired benzophenone **4a** was formed in 97% isolated yield within 4 h (Table 1, entry 1). On optimizing the reaction conditions with different catalyst loading, best results have been obtained by using catalyst **1** (0.4 mol%Pd) in 2-MeTHF at reflux (Table 1, entry 5). Cross-coupling using commonly employed palladium source like Pd(OAc)₂, PdCl₂ and Pd/C gave comparably lower yield under present reaction condition (Table 1, entries 8-10).

Table 1. Effects of catalyst loading, temperature and time^a



Entry	Catalyst	(mol%Pd)	Temp ^r (°C)	Time (h)	Yield (%) ^b
1	1	1	80	4	98
2	1	0.5	80	4	97
3	1	0.1	80	12	43
4	1	0.25	80	12	71
5	1	0.4	80	4	97
6	1	0.4	50	12	50
7	1	0.4	27	12	32
8	Pd(OAc) ₂	0.4	80	6	42
9	PdCl ₂	0.4	80	6	39
10	Pd/C	0.4	80	6	31

^a Reaction conditions: **2a** (0.5 mmol), **3a** (0.55 mmol), 2-MeTHF (4 mL), K₂CO₃ (1 mmol). ^b Isolated yield.

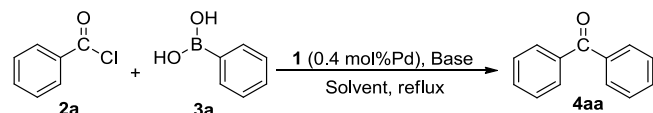
Encouraged by the highest yield in the presence of 0.4 mol% Pd catalyst **1**, we further optimized the effect of different solvents and bases (Table 2). It has been seen that the reaction proceeded with 84% isolated yield within 12 hours in acetone (Table 2, entry 1). Screening of other solvents indicated that toluene (Table 2, entry 3) was optimal; whereas DMF, acetonitrile, dichloromethane and PEG-400 gave yields lower than 87% (Table 2, entries 4, 7, 8 and 9, respectively). The use of isopropanol produces isopropyl benzoate in high amount (Table 2, entry 6). The use of co-solvent 2-MeTHF-H₂O (3:1) afforded **4a** in 65% yield (Table 2, entry 10). This may be

due to the hydrolysis of benzoyl chloride or the formation of aryloxy anion intermediate from arylboronic acid.

From these results it seems that various organic solvents could be employed for the acylation reaction with oxime-palladacycle, however, we decided to examine 2-MeTHF as the solvent for further study. The reason for our decision was that 2-MeTHF is non-carcinogenic and is practically not miscible with water (4 g/100 mL),³² which provides easy isolation during work-up step without needing to add any noxious volatile solvent [see *experimental procedure*]. Reaction under N₂ atmosphere provides slightly lower yield of coupling product (Table 2, entry 11). This suggest that the presence of dissolved air in 2-MeTHF accelerates the catalysis cycle by enhancing the rate of activation of arylboronic acid to aryl ion species, vital for catalytic-transmetalation step.

We next examined the effect of different bases, and found that the inorganic bases like Na₂CO₃, Cs₂CO₃ and Na₃PO₄·12H₂O have considerable effect on the reaction efficiency (Table 2, entries 12-14). Alkali metal hydroxides afforded the desired product within 49-58% yield (Table 2, entries 15-16). Organic base (Et₃N) gave much lower yield of the product (Table 2, entry 17). However, in the absence of any base no traceable amount of product was observed (Table 2, entry 18).

Table 2. Screening Solvents and Bases^a



Entry	Solvent	Base	Time (h)	Yield (%) ^b
1	2-MeTHF	K ₂ CO ₃	4	97
2	Acetone	K ₂ CO ₃	12	84
3	Toluene	K ₂ CO ₃	5.5	95
4	DMF	K ₂ CO ₃	8	77 ^c
5	THF	K ₂ CO ₃	6.5	88
6	<i>i</i> -PrOH	K ₂ CO ₃	4	28 ^d
7	Acetonitrile	K ₂ CO ₃	6	83
8	DCM	K ₂ CO ₃	6	73
9	PEG-400	K ₂ CO ₃	5.5	87 ^e
10	2-MeTHF-H ₂ O	K ₂ CO ₃	6	65 ^f
11	2-MeTHF	K ₂ CO ₃	6	74 ^g
12	2-MeTHF	Na ₂ CO ₃	7.5	87
13	"	Cs ₂ CO ₃	5	91
14	"	Na ₃ PO ₄ ·12H ₂ O	5	89
15	"	KOH	6	58
16	"	NaOH	6	49
17	"	Et ₃ N	6	43
18	"	-	6	trace

^a Reaction conditions: **2a** (0.5 mmol), **3a** (0.55 mmol), **1** (0.4 mol%Pd), solvent (4 mL), base (1 mmol). ^b Isolated yield. ^c Treated at 120 °C. ^d Isopropyl benzoate was formed 36% (GC yield). ^e Treated at 80 °C. ^f (3:1) ratio. ^g N₂ (1 atm).

With the standard reaction conditions, we next explored the substrate scope and limitations of the reaction by employing a variety of acid chloride **2a-d** and arylboronic acid **3a-g** (Table 3). The standard reaction condition was found to be compatible with a wide range of electronically diverse substrates. Though, slight

electronic interventions due to the substituent were also observed in certain cases. It is found that both neutral and electron rich acid chloride reacts more efficiently with both electron-rich and -poor arylboronic acids (Table 3, entries 1-6 and 10-12). It is also noteworthy that the reaction condition tolerates halogen substituent in both substrates, which are usually used in various cross-coupling reactions, and thus exhibits further synthetic utility. Unfortunately, the aliphatic acid chlorides did not respond to the present reaction condition, even after 12 h (Table 3, entries 13-14).

Table 3 Scope of acid chloride^a

Entry	R ¹ , 2	R ² , 3	4	Yield (%) ^b
1	C ₆ H ₅ , 2a	C ₆ H ₅ , 3a	4aa	97
2	C ₆ H ₅ , 2a	4-MeC ₆ H ₄ , 3b	4ab	96
3	C ₆ H ₅ , 2a	4- <i>t</i> -BuC ₆ H ₄ , 3c	4ac	93
4	C ₆ H ₅ , 2a	4-ClC ₆ H ₄ , 3d	4ad	91
5	C ₆ H ₅ , 2a	4-FC ₆ H ₄ , 3e	4ae	90
6	C ₆ H ₅ , 2a	4-CNC ₆ H ₄ , 3f	4af	94
7	4-NO ₂ C ₆ H ₄ , 2b	C ₆ H ₅ , 3a	4ba	87
8	4-ClC ₆ H ₄ , 2c	C ₆ H ₅ , 3a	4ca	91
9	4-MeOC ₆ H ₄ , 2d	C ₆ H ₅ , 3a	4da	95
10	4-MeOC ₆ H ₄ , 2d	4-ClC ₆ H ₄ , 3d	4dd	89
11	4-ClC ₆ H ₄ , 2c	4-MeOC ₆ H ₄ , 3g	4cg	91
12	4-MeOC ₆ H ₄ , 2d	4-MeOC ₆ H ₄ , 3g	4dg	94
13	CH ₃ , 2f	C ₆ H ₅ , 3a	4fa	0 ^c
14	C ₃ H ₇ , 2g	C ₆ H ₅ , 3a	4ga	0 ^c

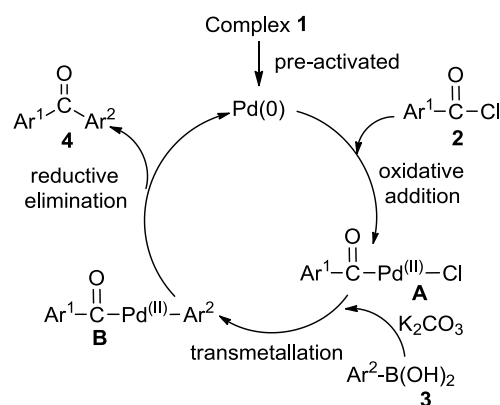
^a Reaction conditions: **2a-g** (0.5 mmol), **3a-g** (0.55 mmol), **1** (0.4 mol%Pd), K₂CO₃ (1 mmol), 2-MeTHF (4 mL) at 80 °C under air for 6 h. ^b Isolated yield. ^c treated for 12 h.

It is well established from the literature that the oxime-derived palladacycles are catalytically inactive species which supplies active Pd(0) to the reaction mixture.³⁰ Thus, they act as a reservoir of highly active Pd(0) species, which are generated by the reaction of palladacycle with one or more component of the reaction mixture and are usually released into the catalytic cycle at a slower rate than that of the catalytic reaction. This slow releasing property prevents unwanted inactivation processes such as nucleation and growth of large inactive palladium particles within the reaction system.

Catalyst poisons that could selectively stop the catalytic activity of Pd-catalysts can be used to determine the involved active catalytically species. To date, Hg(0) poisoning test is recognized as the most powerful in metal-catalyzed reactions.³³ Hg(0) amalgamates strongly with Pd(0), Rh(0) and Ni(0)-based complexes,³⁴ thereby blocking the access of the active site to the substrate. Thus, a Pd(0) species can possibly be poisoned by adding excess Hg(0) (molar ratio to [Pd] ~ 400) to the reaction mixture during the reaction. This suppression of the reaction is generally considered evidence for the presence of Pd(0) as the active species. For the Hg-poisoning test, we have performed a coupling reaction between benzoyl chloride **2a** and phenylboronic acid **3a** using catalyst **1** (0.4 mol%Pd). After 1 h of reaction (41% conversions *vide*

GC-MS) access Hg(0) was added to the reaction mixture and stirred for next 6 h. It should be noted that the catalytic activity apparently get hinder even after 6 h of constant stirring (indicated by GC-MS). This finding suggest that the true active catalyst during the reaction is Pd(0) species. The formation of palladium nanoparticles during the reaction is also demonstrated by TEM analysis (See Figure S1, supporting information).

On the basis of the literature reports,^{35,10b} the reaction mechanism of this acylation reaction was hypothesized as shown in **Scheme 2**. Initially, Pd(0) is formed by the reduction of Pd-C bond of the complex **1**, and then the oxidative addition of acid chloride **2** to Pd(0) produces the acylpalladium(II) chloride intermediate **A**. In alkaline condition, subsequent transmetalation of ArB(OH)₂ **3** to acylpalladium intermediate **A** takes place at the Pd-Cl bond to generates (acyl)(aryl)palladium(II) species **B**. Finally, the reductive elimination of species **B** delivers the oxidative coupling product **4**, regenerating the active Pd(0) species and resuming the catalytic cycle.



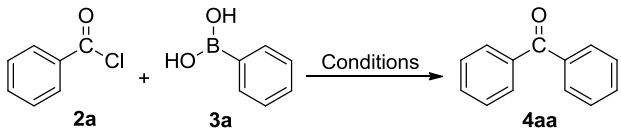
Scheme 2. Probable reaction pathways.

The cross-coupling reactions are implemented on a regular basis in large scale chemical industry due to wide accessibility and functionality of organometallic derivatives, and mild reaction conditions. Thus, we were keen to explore the scope for scale-up to prepare grams instead of milligrams of biaryl ketones. With the optimized reaction conditions and easy work-up procedure on small scale, we next investigated their performance upon scale-up. Thus, the reaction of excess benzoyl chloride **2a** (5 mmol), phenylboronic acid **3a** (5.5 mmol), K₂CO₃ (10 mmol), complex **1** (4 mol%Pd) and 2-MeTHF (20 mL) was performed at 80 °C for 4 h. We were able to isolate 0.8987 grams (98.7%) of benzophenone **4aa**.

Although, most aqueous protocols described in literature do use some amount of water as solvent, they often require excessive amounts of toxic organic solvents during product extraction from the water medium. Thus, making the total relative amount of noxious solvent in the entire process much higher, negating the main objective of green chemistry. Importantly, by using 2-MeTHF the crude mixture of cross-coupling products was simply extracted by quenching with water followed by the separation of the resulting 2-MeTHF-water phases and drying, without the need to use additional organic solvent during the entire workup procedure. Thus, present method is an excellent example of real green chemistry. Moreover, on comparing with previously reported

catalyst system, our approach shows significant advantage (Table 4).

Table 4. Comparison of Palladium Catalysts for the Suzuki-Miyaura coupling Reaction



Entry	Conditions	Catalyst (mol%)	Yield, 4aa	Reference
1	2a (1.0 mmol), 3a (1.2 mmol), Pd/C, K ₂ CO ₃ , acetone-H ₂ O, 60 °C	3	93	6b
2	2a (1.0 mmol), 3a (1.2 mmol), Pd(PPh ₃) ₄ , Cs ₂ CO ₃ , toluene, N ₂ , 100 °C, 16 h	5	80	11a
3	2a (0.75 mmol), 3a (0.5 mmol), (BeDABCO) ₂ Pd ₂ Cl ₆ , K ₂ CO ₃ , toluene, rt, 1 h	0.4	96	16
4	2a (1.5 mmol), 3a (1 mmol), PdCl ₂ , Na ₂ CO ₃ , grinding, 25-30 °C, 5 min	3.3	90	8b
5	2a (1 mmol), 3a (0.5 mmol), Pd(PPh ₃) ₄ , Cs ₂ CO ₃ , toluene, MW, 10 min	5	68	14
6	2a (0.5 mmol), 3a (0.55 mmol), Catalyst 1, K ₂ CO ₃ , 2-MeTHF, 80 °C, 4 h	0.4	97	Present Work

Conclusion

In conclusion, the oxime-palladacycle catalyzed Suzuki-type carbonylation reaction via the cleavage of the C-Cl bond of acid chloride to yield aryl ketones has been described for the first time. Overall, this protocol offers a mild and efficient alternative to the existing methods, as; (i) the oxime-palladacycle pre-catalysts are easily accessible and highly efficient, (ii) the solvent is biologically obtainable, and (iii) is immiscible in water, and this property minimizes the dissolution of moisture in the solvent surface, and avoids the need to maintain inert condition, (iv) crude reaction mixture was isolated just by separation of 2-MeTHF-water layers and then evaporation of 2-MeTHF, without the use of additional organic solvent, and (v) high atom economy (64.2 %) and E-factor (39.3) due to relatively equal proportion of substrates (2nd Green Chemistry principle).

Experimental

Typical experimental procedure for Suzuki-Miyaura Cross-Coupling of arylboronic acid

A 50 mL branched test tube was charged with a mixture of K₂CO₃ (138 mg, 1.0 mmol), complex 1 (0.4 mol% Pd), 2-MeTHF (4 mL) under open air. The solution was heated to 80 °C on a *Process Station Personal Synthesizer* with continuous stirring, and added with phenylboronic acid 3a (0.55 mmol) and benzoyl chloride 2a (0.5 mmol). The mixture was stirred at 80 °C for 4 h and progress of the reaction was monitored using TLC. After completion of the reaction, the resulting mixture was added with saturated solution of brine (4 mL). The resulting water-organic phases were separated and the organic phase (in 2-MeTHF) was dried over anhydrous

Na₂SO₄, filtered and evaporated under reduced pressure. The resultant residue was subjected to silica gel column chromatography (eluent, 10-15%: ethyl acetate/hexane) to afford the desired product.

Benzophenone (4aa):³⁶ White solid, Yield: 97%, 88.2 mg; m.p. 48-49 °C (literature,³⁷ 47-48.5 °C), ¹H NMR (CDCl₃, 400 MHz, ppm) δ: 7.81-7.79 (m, 4H), 7.57 (t, J=7.7 Hz, 2H), 7.48 (t, J=7.7 Hz, 4H); ¹³C NMR (CDCl₃, 100 MHz, ppm) δ: 196.9, 137.6, 132.5, 130.1, 128.3; FT-IR (KBr, cm⁻¹): 1659 (ν_{C=O}); GC-MS m/z: 182.1 (M⁺, 100).

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Table of Content

Eco-friendly Suzuki-Miyaura Coupling of Arylboronic acids to Aromatic Ketones Catalyzed by Oxime-Palladacycle in Biosolvent 2-MeTHF

Manoj Mondal^a and Utpal Bora^{*a,b}

Oxime-palladacycle catalyzed aerobic Suzuki-coupling of arylboronic acid and acyl chloride to yield aryl ketone was developed. The reaction proceeds efficiently in 2-MeTHF, which is biologically derived from corncobs, sugar cane, and fulfils the 3rd, 5th and 7th principles of Green Chemistry. Moreover, the water immiscible 2-MeTHF provides easy and clean phase separation during water-quenching step and avoids the use of additional organic solvent.

