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Graphical Abstract





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Transition metal-free Suzuki type cross-coupling reaction for synthesis of dissymmetric ketones

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ABSTRACT

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Keywords: Metal-free coupling Base Dissymmetric ketones Suzuki reaction A simple, efficient and metal-free route for the synthesis of dissymmetric ketones through Suzuki type reaction has been established. This strategy signifies an attractive, cost-effective and operationally convenient tool for synthesis of a wide range of dissymmetric ketones. Although conventional routes for the synthesis of ketones have been widely used, the potential challenge with these methods is functional group tolerance. The reported metal-free method represents reaction with moderate functional group tolerance. The procedure is operationally convenient and shows broad substrate scope with good to excellent product yields.

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In the last few decades, massive effort has been devoted to the advances of transition metal catalyzed cross-coupling reactions for the synthesis of many important bioactive compounds using diverse range of electrophiles and nucleophiles.¹ Such a transition metal catalyzed cross-coupling reactions has endorsed chemists to construct complex molecular frameworks containing specific functional groups covering total synthesis of natural products, active pharmaceutical ingredients as well as structurally important compounds.² These reactions are considered as the most reliable, reproducible, and straight forward synthetic tool that enables wide number of applications in chemical industries. Recently, different research groups circumvent the transition metal catalysts from many organic transformations,³ as most of the transition metal catalysts are expensive, require ligands and are toxic. Additionally, removal of even trace amount of metal from the final product is quite challenging, costly and crucial, especially in the pharmaceutical active compounds.

The dissymmetric ketones are exists as a common structural motif in many natural products and pharmaceutical important compounds⁴ and have been synthesized from various routes (Fig. 1). Friedel-Crafts acylation reaction (Fig. 1, pathway 1) is one of the fundamental method used for synthesis of such dissymmetric ketones,⁵ nevertheless this reaction have many inherent limitations. Recently, Pd catalyzed Suzuki type acylation (Fig. 1, pathway 2) of organoboranes by carboxylic acid derivatives such as acid chlorides, esters, anhydrides and dimethyl dicarbonates⁶ have been reported as one of the alternative to classical Friedel-Crafts acylation. In addition the dissymmetric ketones are also prepared by Pd catalyzed carbonylation (Fig. 1, pathway 3) of aryl halides with carbon monoxide in the presence of organometallic reagents.⁷ Recently,

transition-metal-catalyzed *ortho* C–H acylation has been performed as an efficient and direct method for synthesis of aryl ketones.⁸



Fig. 1. Various pathways for synthesis of dissymmetric ketones (reported and the present route).

In continuation of our interest in the development of environmental benign reaction conditions for organic transformation,⁹ we report here metal-free synthesis of dissymmetric ketones through Suzuki type cross-coupling

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reaction. Our goal was to carry out coupling of benzoyl chlorides with arylboronic acids by metal-free, base induced conversions, that otherwise would not be possible without Lewis acid (Fig. 1, pathway 4). By using this method we can totally bypass the transition metals as well as Lewis acids. An additional feature of this methodology is, it permit to prepare ketones which contains acid sensitive functional groups, which otherwise not conceivable by Friedel-Crafts reaction conditions.

For the development of metal-free acetylation, 4nitrobenzoyl chloride and phenylboronic acid were used as a model reaction partners. Initially, the effect of nature and the amount of bases were studied in toluene under heating (100°C) and the results are shown in Table 1.

Table 1

Optimization of bases for the transition metal-free Suzuki type cross-coupling reaction for synthesis of dissymmetric ketone.^a

O ₂ N	Cl + BioH)2 Base, 10	ne)0 °C O₂N	
Entry	Base (mmol)	Time (h)	Yield $(\%)^{b}$
1	Base Free	6	no reaction
2	K ₂ CO ₃ (4.0)	6	70
3	Na ₂ CO ₃ (4.0)	6	50
4	Cs ₂ CO ₃ (4.0)	6	84
5	Li ₂ CO ₃ (4.0)	6	no reaction
6	NaOAc (4.0)	6	no reaction
7	Pyridine (4.0)	6	65
8	Ethanolamine (4.0)	6	85
9	KOH (4.0)	2	90
10	NaOH (4.0)	1	95
11	NaOH (3.0)	2	95
12	NaOH (2.0)	4	60
13	NaOH (1.0)	6	40
14	NaOH (0.5)	6	30

^aReaction conditions: 4-nitrobenzoyl chloride (1.0 mmol), phenylboronic acid (1.0 mmol), base (0.5-4.0 mmol), toluene (5.0 mL) at 100°C.

^bIsolated yields after column chromatography.

Initially, when the model reaction was carried out without base, no product was detected even after extended reaction time to 6 h, indicating that role of base is vital (Table 1, entry 1). The base plays crucial role in activation of phenyl boronic acid similar to that in Pd catalyzed Suzuki-Miyaura cross coupling reaction.¹⁰ As Leadbeater^{3c,11} used 3.8 equivalent base for transition metal-free Suzuki-Miyaura reaction, we carried out model reaction using 4 equivalent carbonate bases. Though carbonates are commonly used and highly active bases for activating boronic acids in cross-coupling reactions, they proved to be less active for present coupling reaction. The carbonate

bases such as Na₂CO₃, K₂CO₃ and Cs₂CO₃ gave moderate yields of the desired product (Table 1, entries 2-4), while Li_2CO_3 as well as NaOAc were completely inactive and no coupling product was observed (Table 1, entries 5 and 6). Organic bases such as pyridine and ethanolamine were subsequently less effective in terms of the reaction time (Table 1, entries 7 and 8). Both NaOH and KOH proved to be most efficient bases as the model reaction afforded excellent yield of corresponding product in a short reaction time (Table 1, entries 9 and 10). Thus the scrutiny of bases revealed NaOH as the most effective base for the present protocol. It is noteworthy to mention that decreasing the quantity of NaOH from 4 equivalents to 0.5 equivalents significantly decreased the yield of reaction with increased reaction time (Table 1, entries 11-14) indicating that the 4 equivalent is optimum quantity of base for the effective acylation.

Next, the solvent screen was carried out on the model reaction (Table 2). Screening of different solvents indicated that the non-polar solvent toluene (Table 2, entry 10) is the best solvent as it gave maximum conversion as compared to other solvents (Table 2, entries 1-8). When water was used as the solvent, no reaction occurred at 100 °C temperature (Table 2, entry 9). During the optimization studies, effect of temperature was also examined in toluene. It was observed that with decreasing the reaction temperature the yield of reaction significantly decreases with increased reaction time (Table 2, entries 10-14).

Table 2

Optimization of solvents and effect of temperature on the transition metal-free Suzuki type cross-coupling reaction for synthesis of dissymmetric ketone.^a

O ₂ N	$Cl + \frac{B(OH)_2}{Na}$	olvent OH, T °C 2h	
Entry	Solvent	$T(^{\circ}C)$	Yield $(\%)^{b}$
1	EtOH	reflux	10
2	CH ₃ CN	reflux	5
3	DMF	100	15
4	DMAc	100	10
5	MeOH	reflux	20
6	CHCl ₃	reflux	30
7	CCl_4	reflux	10
8	THF	reflux	12
9	Water	100	no reaction
10	Toluene	100	95
11	Toluene	80	60
12	Toluene	60	30
13	Toluene	40	20
14	Toluene	RT	no reaction

^aReaction conditions: 4-nitrobenzoyl chloride (1.0 mmol), phenylboronic acid (1.0 mmol), NaOH (4.0 mmol), solvent (5.0 mL).

^bIsolated yields after column chromatography.

To explore the generality and scope of this method, a variety of benzoyl chlorides (1.0 mmol) and aryl boronic acids (1.0 mmol) were reacted in toluene (5.0 mL) by using NaOH (4.0 mmol) as a base at 100 $^{\circ}$ C. As shown in Table 3, the scope is

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very broad with regard to both reacting partners. The boronic acids containing electron donating substituent facilitates the coupling thereby furnishing the desired products in good to excellent yields. Similarly, the boronic acids with electron withdrawing groups also reacted efficiently albeit giving slightly lower yields. Easy access to halo boronic acids is worth mentioning as they furnish the products with additional synthetic handle for further synthetic manipulation. Similarly electronically and structurally diverse benzovl chlorides were form to couple with phenyl boronic acids in good to better yields. There was no appreciable change in reactivity observed in most of the cases. Boronic acid derivatives of heterocycles such as thiophene were smoothly transformed into desired product in good yields. Thus the heteroaryl boronic acid (thiophene-3boronic acid) did couple with benzoyl chloride, 4-nitro-benzoyl chloride and 4-methyl benzoyl chloride in good isolated yields (80-82 % yields). The transformation was less sensitive to steric effects as sterically hindered naphthyl boronic acid underwent this coupling to give 92 % yield with benzovl chloride, 90 % yield with 4-nitro-benzoyl chloride and 87 % yield with 4methyl-benzoyl chloride.

Table 3

The transition metal-free Suzuki type cross-coupling reaction of various acyl chlorides and arylboronic acids.^a



It has been known that the transition metal-free cross-coupling occurred through the different pathways like radical type homolytic aromatic substitution (HAS) reactions,¹² radical cation type hyperiodine-mediated oxidative coupling reactions,¹³ cationic type oxidative coupling reactions,¹⁴ electrophilic aromatic substitution,¹⁵ aryne pathway,¹⁶ and the classical

organocatalysis pathway.¹⁷ Though the metal-free Suzuki-Miyaura coupling occurs through base induced protodeborylation¹⁸ type nucleophilic aromatic substitution pathways.¹⁹ In this metal-free base induced Suzuki type crosscoupling of acyl chlorides with arylboronic acids the mechanism is unclear.

In this work, we developed an efficient, simple practical route for the synthesis of dissymmetric ketones by transition metal-free base induced cross-coupling reactions in toluene in short reaction time under air. The method allows broad reaction scope for the transformation of range of benzoyl chlorides and aryl boronic acids. The protocol uses readily available reagents and no additional ligand and additive were required with moderate functional group tolerance. Additionally, the synthesis can be performed under economically favorable conditions.

Experimental Section:

An oven-dried Schlenk flask, equipped with a magnetic stir bar, septum and a condenser was charged with acyl chloride (1.0 mmol), arylboronic acid (1.0 mmol), NaOH (4 mmol) and toluene (5.0 mL). The flask was immersed in an oil bath and stirred at 100 °C. Upon complete consumption of starting materials as determined by GC analysis, the water (10.0 mL) was added. The reaction mixture was extracted with diethyl ether (3 × 5.0 mL). The combined organic layer was collected, dried over anhydrous Na_2SO_4 and concentrated in vacuum to afford product which was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate = 9:1).

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Supplementary Material

Supplementary data associated with this article can be found, in the online version.

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Highlights

1. The procedure involve metal-free preparation of ketones

2. Only use of Brønsted bases and no use of Lewis acids

3. No quantamination of metal in the final product

Acceleration 4. Method shows exquisite regioselectivity with

excellent functional group compatibility

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Transition metal-free Suzuki type crosscoupling reaction for synthesis of dissymmetric ketones

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Graphical Abstract



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