



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



Sanjay Jadhav<sup>a</sup>, Gajanan Rashinkar<sup>a</sup>, Rajashri Salunkhe<sup>a,\*</sup>, Arjun Kumbhar<sup>b,\*</sup>

<sup>a</sup> Department of Chemistry, Shivaji University, Kolhapur 416004, M.S., India

<sup>b</sup> Department of Chemistry, P.D.V.P. College, Tasgaon (Sangli) 416312, M.S., India

### ARTICLE INFO

#### Article history:

Received 24 January 2017

Revised 13 June 2017

Accepted 14 June 2017

Available online 16 June 2017

#### Keywords:

Metal-free coupling

Base

Dissymmetric ketones

Suzuki reaction

### ABSTRACT

A simple, efficient and metal-free route for the synthesis of dissymmetric ketones through Suzuki type cross-coupling reaction has been established. This strategy signifies an attractive, cost-effective and operationally convenient tool for the 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 a reaction with moderate functional group tolerance. The procedure is operationally convenient and shows broad substrate scope with good to excellent product yields.

© 2017 Elsevier Ltd. All rights reserved.

In the last few decades, a massive effort has been devoted to the advancement of transition metal catalyzed cross-coupling reactions for the synthesis of many important bioactive compounds using a diverse range of electrophiles and nucleophiles.<sup>1</sup> Such a transition metal catalyzed cross-coupling reactions have 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.<sup>2</sup> These reactions are considered as the most reliable, reproducible, and straight forward synthetic tool that enables a wide number of applications in chemical industries. Recently, different research groups circumvent the transition metal catalysts from many organic transformations,<sup>3</sup> as most of the transition metal catalysts are expensive, require ligands and are toxic. Additionally, removal of even a 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 compounds<sup>4</sup> and have been synthesized from various routes (Fig. 1). Friedel-Crafts acylation reaction (Fig. 1, pathway 1) is one of the fundamental methods used for the synthesis of such dissymmetric ketones,<sup>5</sup> 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 dicarbonates<sup>6</sup> have been reported as one of the alternatives 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.<sup>7</sup> Recently, transition-metal-catalyzed *ortho* C–H acylation has been performed as an efficient and direct method for synthesis of aryl ketones.<sup>8</sup>

In continuation of our interest in the development of environmentally benign reaction conditions for organic transformation,<sup>9</sup> we report here metal-free synthesis of dissymmetric ketones through Suzuki type cross-coupling reaction. Our goal was to carry out the 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 permits 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, 4-nitrobenzoyl 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.

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

\* Corresponding authors.

E-mail address: [arjun22win@rediffmail.com](mailto:arjun22win@rediffmail.com) (A. Kumbhar).

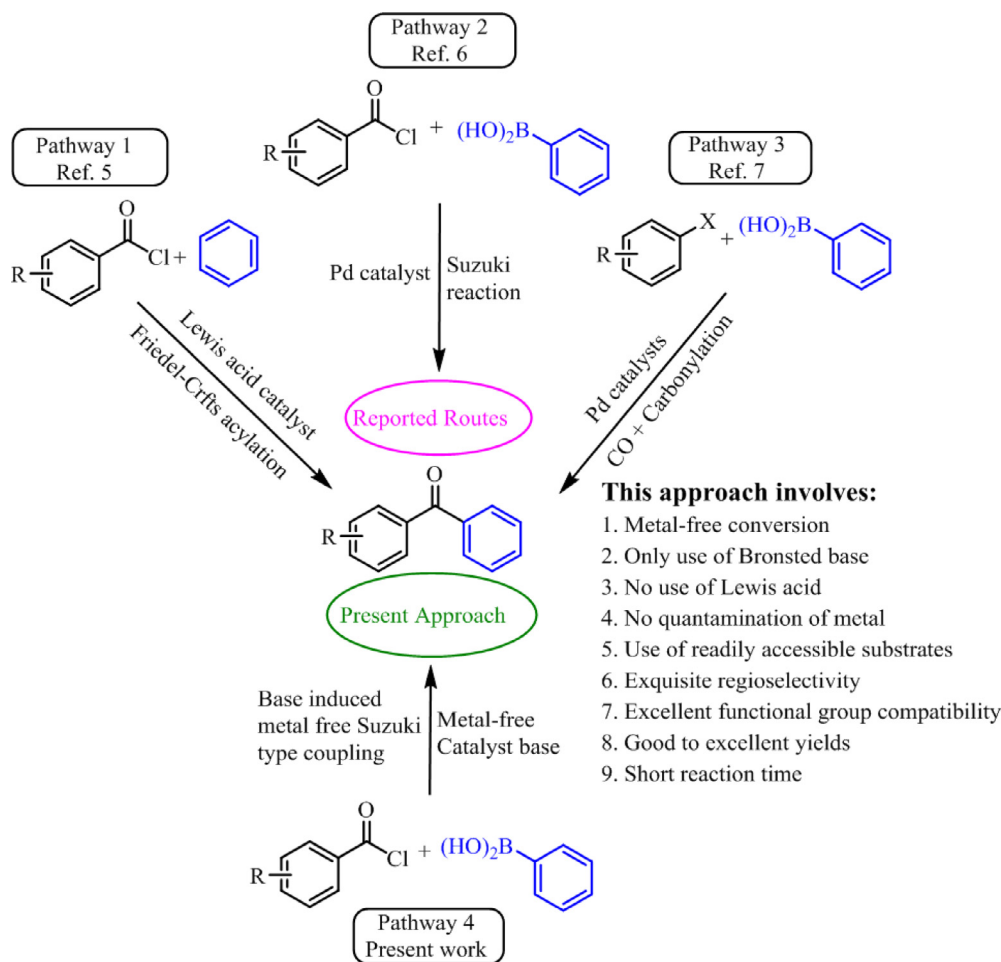
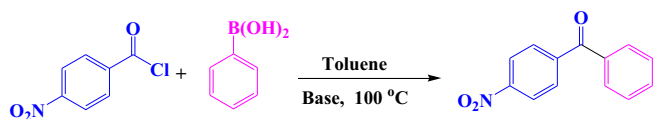


Fig. 1. Various reported and the present pathways for the synthesis of dissymmetric ketones.

**Table 1**  
Optimization of bases for the transition metal-free Suzuki type cross-coupling reaction for the synthesis of dissymmetric ketone.<sup>a</sup>

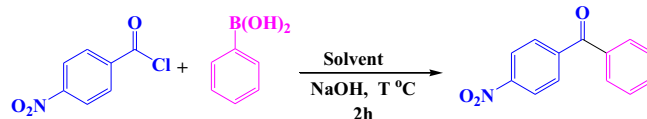


Entry	Base (mmol)	Time (h)	Yield (%) <sup>b</sup>
1	Base Free	6	no reaction
2	K <sub>2</sub> CO <sub>3</sub> (4.0)	6	70
3	Na <sub>2</sub> CO <sub>3</sub> (4.0)	6	50
4	CS <sub>2</sub> CO <sub>3</sub> (4.0)	6	84
5	Li <sub>2</sub> CO <sub>3</sub> (4.0)	6	no reaction
6	NaOAc (4.0)	6	no reaction
7	Pyridine (4.0)	6	65
8	Ethanolamine (4.0)	6	85
9	KOH (4.0)	2	90
10	NaOH (4.0)	2	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

<sup>a</sup> Reaction 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.

<sup>b</sup> Isolated yields after column chromatography.

**Table 2**  
Optimization of solvents and effect of temperature on the transition metal-free Suzuki type cross-coupling reaction for the synthesis of dissymmetric ketone.<sup>a</sup>



Entry	Solvent	T (°C)	Yield (%) <sup>b</sup>
1	EtOH	reflux	10
2	CH <sub>3</sub> CN	reflux	5
3	DMF	100	15
4	DMAc	100	10
5	MeOH	reflux	20
6	CHCl <sub>3</sub>	reflux	30
7	CCl <sub>4</sub>	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

<sup>a</sup> Reaction conditions: 4-nitrobenzoyl chloride (1.0 mmol), phenylboronic acid (1.0 mmol), NaOH (4.0 mmol), solvent (5.0 mL).

<sup>b</sup> Isolated yields after column chromatography.

Download English Version:

<https://daneshyari.com/en/article/5264605>

Download Persian Version:

<https://daneshyari.com/article/5264605>

[Daneshyari.com](https://daneshyari.com)