Tetrahedron Letters 55 (2014) 6451-6454

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

using the corresponding aryl boronic acid and N-acyloxyphthalimide.

Pd-NHC-catalyzed synthesis of diaryl ketones

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ARTICLE INFO

ABSTRACT

Article history: Received 25 July 2014 Revised 27 September 2014 Accepted 29 September 2014 Available online 5 October 2014

Keywords: Diarvl ketones

N-Heterocyclic carbene Palladium catalysis Boronic acid N-Hydroxy phthalimide

Aryl ketones are important synthetic intermediates for organic and medicinal chemistry.¹ A classical method to synthesize aryl ketones is the Friedel–Crafts acylation using aryl acid chloride.² One may also use nucleophilic aryl metal compounds to react with aryl acid derivatives to form the desired ketone with better regional control than traditional Friedel–Crafts reactions.³ However, these synthetic approaches still suffer drawbacks such as limited compatibility of substitution groups and sometimes harsh or stringent reaction conditions. Recently, palladium catalyzed coupling between an aryl boronic acid and an aryl acid derivative such as an acid anhydride or acid chloride opened up new synthetic pathways to aromatic ketones with greater control, regioselectivity, and milder conditions.⁴

Here, we report our findings in aryl ketone synthesis using boronic acid and an activated ester in the presence of palladium catalyst and an *N*-heterocyclic carbene (NHC) ligand. Our goal was to develop an efficient procedure using more stable and easier to handle starting materials rather than aryl acid chlorides or acid anhydrides. For this purpose, we chose to investigate *N*-hydroxy phthalimide (NHP) esters as the carbonyl donor⁵ and envisioned that a proper NHC will enhance the catalytic properties of transition metals so that the desired ketone formation can be achieved.

Initial investigation started from using the NHP ester **1b** of 4-methoxybenzoic acid and phenyl boronic acid. Results are listed in Table 1. Several palladium catalysts were screened with

inorganic and organic ligands. The reactions were conducted in toluene with catalyst loading at 5% mole equivalent of the NHP ester. In these tests, palladium (II) with chloride as counter ions did not produce isolatable product (entries 1 and 2, Table 1). Other palladium (0) or (II) species could lead to moderate yields of the ketone (entries 3–6, Table 1). The best result was obtained in a one-pot reaction with palladium (II) acetate and in situ formed NHC using a triazole-based NHC precursor (reaction scheme in Table 1) and Cs₂CO₃ (entry 7, Table 1), the final yield of the reaction reached 75%.

With N-hetereocyclic carbene and palladium catalysis, diaryl ketones with a variety of functional groups

that span from electron withdrawing to electron donating substitutions can be conveniently synthesized

After this initial investigation, much wider scope of starting materials was explored using the NHC-Pd catalytic conditions. Results are summarized in Table 2.

The reactions between NHP ester **1a** or **1b** and different phenyl boronic acids bearing electron-donating or electron-withdrawing groups were investigated (entries 1-7, Table 2). Yields of these transformations were similar, with some preference of electron withdrawing groups on phenyl boronic acid indicating the good tolerance of boronic acids in general. When using the NHP ester 1c from 2-nitrobenzoic acid, the strong electron withdrawing nitro group lowered overall yields of the reaction to moderate but still acceptable levels (50-65%, entries 8-14, Table 2). For boronic acids, similar trends existed as shown in the next four examples where electron withdrawing groups such as fluoro- or trifluoromethylsubstitution enhanced the reaction yields (entries 10 and 11, Table 2), while electron donating ones such as methoxy or alkyl slightly reduced yields (entries 9, 12, and 13, Table 2). Finally, substrates with expanded conjugated system were also explored (entries 15–18, Table 2). These examples with NHP esters of either





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^a Reaction conditions: phenylboronic acid (1.6 mmol), Cs ₂ CO ₃ (1.0 mmol), and catalyst (5 mol %) in toluene (7.0 mL) were
stirred for about 20 min under nitrogen atmosphere. Then N-hydroxy phthalimide ester (1.0 mmol) was added. The mixture
was heated to 60 °C for 12 h under nitrogen atmosphere.

dppfPdCl₂ 5% Pre-NHC + Pd(OAC)₂

42

52 75

^b Isolated yield.

6 7

Table 2

Substrate scope for the synthesis of different diaryl ketones^a



Table 2 (continued)



^a Reaction conditions: arylboronic acid (1.6 mmol), Cs₂CO₃ (1.0 mmol), pre-NHC (5 mol %), and Pd(OAc)₂ (5 mol %) in toluene (7.0 mL) were stirred for about 20 min under nitrogen atmosphere. Then *N*-hydroxy phthalimide ester (1.0 mmol) was added. The mixture was heated to 60 °C for 12 h under nitrogen atmosphere. ^b Isolated yield.

4-methoxy or 4-fluoro cinnamic acid gave excellent results (75–87% yields), and the general trend for substitution effects followed previous examples: electron donating group on the aryl

ester and electron withdrawing group on the aryl boronic acid enhanced the reaction yields. Please note that while trends of electronic effects exist, many substrates contain *ortho*-substituents on both the NHP ester side and/or the boronic acid side. Steric effects may also play important roles in the overall results. Therefore, whether the trend of electronic effects can be maintained with broader substituent positions remains to be seen. We expect that the catalytic mechanism would follow conventional oxidative addition (by the NHP ester), transmetallation (by boronic acid), and reductive elimination pathways (product formation) on Pd(0)/Pd(II) species as proposed previously for similar reactions.^{4c} The NHC can be expected to act as a ligand during the process.

In summary, we reported here a simple procedure for aryl ketone formation using NHP esters of aryl acid and aryl boronic acid under catalysis by an NHC-Pd system. The wide substrate scope and mild reaction conditions should make this procedure a good complement to existing synthetic methods.

Acknowledgments

We thank Professor Erkang Fan at the University of Washington for helpful discussions. Financial support by the Shanghai Municipal Education Commission (No. 14ZZ159), Shanghai Municipal Science and Technology Commission (No. 12430501300), Shanghai University of Engineering Science (nhrc-2014-05), and the Program for Special Appointment (Eastern Scholar) at Shanghai Institutions of Higher Education are gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.09.133.

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