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Synthesis of β , β -diaryl propiophenones via palladium-catalyzed domino

arylboronation, elimination and enone hydroarylation of enaminones

Shanshan Zhong,^a Yu Lu,^a Yan Zhang,^a Yunyun Liu^a and Jie-Ping Wan^{a,*} ^aCollege of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330022, China. Email: wanjieping@jxnu.edu.cn



The first example on the domino reactions involving the enaminone C-N conversion-based arylation has bee realized as efficient new route toward the synthesis of β , β - diaryl propiophenones.

Journal Name

ARTICLE



Page 2 of 5

Synthesis of β , β -diaryl propiophenones via palladium-catalyzed domino arylboronation, elimination and enone hydroarylation of enaminones

Received 00th January 20xx, Accepted 00th January 20xx

Shanshan Zhong,^a Yu Lu,^a Yan Zhang,^a Yunyun Liu^a and Jie-Ping Wan^{a,*}

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The synthesis of β , β -diaryl aryl propiophenones have been realized via palladium-catalyzed domino reactions of dimethyl amino functionalized enaminones and aryl boronic acids. This is the first example of transition metal-catalyzed enaminone C-N bond conversion for the generation of new C-C(aryl) structure.

As easily available, structurally diverse and highly reactive building blocks, enaminones have been well known for their universal application in both target and diversity-oriented synthesis.¹ As one of the commonsense transformations in the N,N-disubstituted enaminones, the C-N bond conversion forming new C-heteroatom bonds such as C-N, C-O and C-S bonds have been frequently employed and contributed enormously to the synthesis of functional organic molecules.² On the other hand, unlike the easy occurrence of Cheteroatom bond formation, the construction of new C-C bond by conversing the enaminone C-N bond in the presence of a Cnucleophile is hardly practical. Actually, except in the classical [2+2+2] enaminone cyclotrimerization,³ no example of other C-C bond formation via the conversion of the enaminone C-N bond has been previously known (Fig. 1). In this regard, searching for practical catalytic approaches which enable the construction of new C-C bonds by breaking the C-N bond makes up a main challenge in the present chemistry of emaninone-based organic synthesis.⁴



Figure 1. Construction of new C-heteroatom and C-C bond via enaminone C-N bond conversion

Although not an issue of long research history, the strategy of transition metal-catalyzed C-N bond activation has rapidly emerged as a powerful tool in a variety of syntheses via the construction of new chemical bonds through the C-N bond cleavage.⁵ Under the inspiration of C-N activation protocols and our longstanding efforts in exploring new synthetic applications of enaminones,⁶ we have envisioned that the conversion of the C-N bond in the enaminones might also be potentially useful as complementary route of generating new C-C bond.

Previously, Georg and co-worker have investigated and revealed that the coupling reactions between cyclic enaminones and aryl boronic acids could provide either β - or α -arylated enaminones via the cleavage of C(sp²)-H bond under the conditions of Pd-catalysis (Scheme 1).⁷ While there is presently no example on enaminone C-N bond conversionbased arylation available, discovering practical new reactions initiated by such transformation is a crucial issue in both complementing the known synthetic application of enaminones and providing efficient synthetic methods for the synthesis of diverse arylated products. After making extensive efforts in screening reaction partners and catalytic conditions, we report herein an unprecedented domino reaction pattern toward the synthesis of β , β -diaryl propiophenones via key Pd-

Georg et al: Pd-catalyzed enaminone C-H bond arylation



This work: Pd-catalyzed enaminone C-N bond arylation/hydroarylation



Scheme 1 Different enaminone C-H arylation reactions

^{a.} College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330022, P.R. China. Email: wanjieping@jxnu.edu.cn

Electronic Supplementary Information (ESI) available: [general experimental information, procedure for the synthesis of **3** and **4**, ¹H and ¹³C NMR spectra of all products and the crystallographic data of **3a**]. See DOI: 10.1039/x0xx00000x

ARTICLE

catalyzed C-N bond conversion-based arylation (Scheme 1). As useful organic molecules, the β , β -diarylated propiophenones have been predominantly synthesized by either the hydroaryaltion of enones or direct β -C-H arylation of propiophenones etc,⁸ the present method involving the Pd-catalyzed domino enaminone C=C bond aryl boronation, elimination and enone hydroarylation represents a brand new synthetic methodology toward these compounds.

Initially, the reaction of enaminone **1a** with phenylboronic acid **2a** was subjected to the condition of Pd-catalysis. It was found that the Pd(OAc)₂ could catalyze the reaction to provide β , β -diphenyl ketones **3a** in the presence of 2,2'-bipyridine (bpy) ligand with 90 °C heating (entry 1, Table 1). The employment of different Pd-catalysts indicated that Pd(OAc)₂ was a better catalyst than other palladium catalysts such as Pd(PPh₃)₄, PdCl₂ and Pd/C (entries 2-5, Table 1). Subsequently, control experiments using other ligands, such as 1,10-phenanthroline (1,10-phen), PPh₃ and L-proline suggested that bpy was the most effect ligand (entries 6-8, Table 1). Further optimization on the reaction medium utilizing solvents of different polarity

Table 1 Screening of reaction conditions



Entry	Catalyst	Ligand	Solvent	T (°C)	Yield(%) ^b
1	Pd(OAc) ₂	bpy	NMP	90	40
2	Pd(PPh ₃) ₄	bpy	NMP	90	35
3	$PdCl_2$	bpy	NMP	90	10
4	Pd/C	bpy	NMP	90	trace
5	no	bpy	NMP	90	0
6	Pd(OAc) ₂	1,10-phen	NMP	90	10
7	Pd(OAc) ₂	PPh_3	NMP	90	37
8	Pd(OAc) ₂	L-proline	NMP	90	trace
9	Pd(OAc) ₂	bpy	DMSO	90	30
10	Pd(OAc) ₂	bpy	DMF	90	62
11	Pd(OAc) ₂	bpy	1,4-dioxane	90	40
12	Pd(OAc) ₂	bpy	toluene	90	45
13	Pd(OAc) ₂	bpy	H ₂ O	90	65
14	Pd(OAc) ₂	bpy	DMF/H ₂ O(1/3)	90	73
15	Pd(OAc) ₂	bpy	DMF/H2O(1/4)	90	74
16	Pd(OAc)₂	bpy	DMF/H2O(1/5)	90	70
17	Pd(OAc)₂	bpy	DMF/H2O(1/4)	100	72
18	Pd(OAc) ₂	bpy	DMF/H ₂ O(1/4)	80	71
19 ^c	Pd(OAc) ₂	bpy	DMF/H ₂ O(1/4)	90	75
20 ^d	Pd(OAc)	hnv	$DMF/H_0(1/4)$	90	63

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led to the observation that the entry in DMF gave better yield of **3a** than other investigated solvents (entries 9345, Fable 4). In addition, the attempt on using aqueous DMF demonstrated that the mixed DMF/water (v/v = 1 : 4) was even better medium for the reaction (entries 14-16, Table 1). Varying the reaction temperature didn't afford any improvement on the product yield (entries 17-18, Table 1). Final examination on reducing the loading of Pd(OAc)₂ and ligand to 5 mol% and 10 mol% gave identically well result, and further decrease in the catalyst/ligand was not favored (entries 19-20, Table 1).

The investigation on the application scope of this synthetic method was conducted under the optimal conditions by employing various enaminones **1** and aryl boronic acids **2** for reaction. The results in providing products **3** were outlined in Table 2,⁹ according to the acquired results, this protocol is generally tolerable to the reactions of aryl functionalized enaminones and aryl boronic acids. Functional groups of different properties such as alkyl, alkoxyl, halogen and nitro etc in both substrates were all well compatible to afford target products with moderate to good yields. And no observable electronic or steric impact of the substitution to the yield or related products was observed.

Table 2 Scope for C-N arylation-based synthesis of β,β -diaryl propiophenones						
	B(OH) ₂ Pd(OAc) ₂ , b Pd(OAc) ₂ , b DMF/H ₂ O 90 ℃					
R^1	R ²	Product	¥ield (%)			
н	Н	3a	75			
н	4-Me	3b	74			
н	4-MeO	3c	72			
н	4-F	3d	71			
н	4-Cl	3e	70			
н	naphth-1-yl	3f	72			
н	2-MeO	3g	63			
4-Me	Н	3h	75			
4-Cl	Н	3 i	73			
4-MeO	Н	3j	70			
4-CF ₃	Н	3k	69			
4-NO ₂	Н	31	71			
2-NO ₂	Н	3m	65			
3-NO ₂	Н	3n	68			
3-Cl	4-Me	30	68			
4-Br	4-Me	3р	69			
naphth-2-yl	Н	3q	71			
naphth-2-yl	4-Me	3r	71			

^aYield of isolated product based on **1**.

As attempts in probing the possible reaction mechanism, some additional control experiments were designed and executed.

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Firstly, the reaction using chalcone 4 as starting material to react with phenyl boronic acid was carried out under standard reaction conditions, and it was found that product 3a was produced with excellent yield (Eq 1). On the other hand, although the reactions of enaminone with aryl boronic acids proceed quickly to provide diarylated propiophenones 3, we managed to acquire chalcone 4 in the reaction of enaminone 1a with phenyl boronic acid 2a by lowering the reaction temperature and using excess amount of enamione 1a (Eq 2). These results suggested that chalcone 4 was a key intermediate in the whole reaction process. What's more, to investigate the potential interaction of enaminone 1 with Pd(II) catalyst, a control experiment subjecting only enaminone 1a to the standard reaction was conducted, and no evident transformation of the enaminone was found. Finally, the experiment employing vinylogous ester 5 and 2a provided target product **3a** with 60% yied (Eq 3), demonstrating that the reaction might not be initiated by the interaction of palladium catalyst and the enaminone.



On the basis of the reaction results and related reports on Pdcatalyzed C-N activation, a reaction mechanism starting from the palladium catalyst insertion to the boronic acid is tentatively postulated. As showing in Scheme 3, insertion of Pd(II) catalyst to aryl boronic acid 2 provides the aryl palladium species 6. The Michael-type addition of 6 to enaminone 1 provides Pd(II) containing adduct 7, and the reductive elimination then gave intermediate 8. The subsequent extrusion of the amino and boron fragment in the fashion of



Scheme 3 The proposed reaction mechanism

elimination led to the production of chalcone 4_{vie} in all v_{vie} the products **3** is generated by palladium-catalyzed addition of the products **a** in known in literature.⁸

Conclusions

In summary, by means of pd-catalysis with the assistance of bpy ligand, the reactions of *N*,*N*-disubstituted enaminones and boronic acid have been successfully accomplished to provide β , β -diaryl aryl propiophenones. The efficient C-N bond conversion enabling new C-C bond formation has revealed new potential of enaminones as versatile building blocks in organic synthesis.

Experimental section

General procedure for the synthesis of ketones 3 and 5

To a 25 mL round-bottom flask were added enaminone **1** (0.3 mmol), aryl boronic acid **2** (0.75 mmol, or 0.3 + 0.3 mmol for heteroarylation reaction), $Pd(OAc)_2$ (0.015 mol), bpy (0.03 mmol) and DMF/water (0.4 mL/1.6 mL). Then the mixture was heated up to 90 °C, and stirred at the same temperature for 12 h under (TLC). After cooling down to room temperature, 5 mL of water was added, and the resulting mixture was extracted with ethyl acetate (3 × 8 mL). The organic phases were collected and washed with small amount of water for three times. After drying with anhydrous Na₂SO₄, the solid was filtered and the acquired solution was subjected to reduced pressure to remove the solvent. The resulting residue was subjected to flash silica gel column chromatography to provide pure products with the elution of mixed petroleum ether/ethyl acetate (v/v = 20:1).

Acknowledgments

This work is financially supported by the National Natural Science Foundation of China (21562025) and Natural Science Foundation of Jiangxi Province (20151BAB203008).

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