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An unprecedented Pd-catalyzed *trans*-addition of boronic acids to ynamides†

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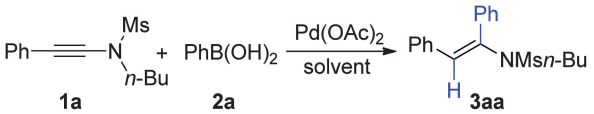
An unprecedented Pd-catalyzed *trans*-addition of boronic acids to ynamides has been reported, giving α,β-disubstituted enamides in high yields with excellent regio- and stereoselectivity. A possible mechanism involving the palladium carbene intermediate has been proposed to account for the unusual *trans*-addition.

Enamides are remarkably versatile building blocks in organic chemistry because they participate in a wide selection of chemical transformations.[1] Consequently, the interest in enamides has been long standing and the effective synthesis of these motifs, especially the stereocontrolled version, is still in urgent need. So far, enamides can be assembled by the isomerization of *N*-allylamides,[2] hydroamination of alkynes or alkenes,[3] methylenation of amides,[4] amidation of alkenyl halides or equivalents,[5] and the C–H activation strategy.[6] The functionalization of ynamides, including silaboration,[7a] hydroboration,[7b] hydrophosphorylation,[7c] hydroacyloxylation,[7d] hydroamination,[7e] hydrohalogenation,[8] carbometallation,[9] cycloaddition,[10] and other reactions,[11] stands out as an attractive alternative protocol for accessing highly substituted enamides. In continuation of our program geared towards the functionalization of ynamides,[12] we describe here a Pd-catalyzed stereospecific *trans*-addition of boronic acids to ynamides, providing stereodefined α,β-disubstituted enamides in high yields with excellent regio- and stereoselectivity. It should be noted that, although transition-metal-catalyzed addition of boronic acids to alkynes has become a powerful method for the assembly of multifunctional alkenes,[13] the Pd-catalyzed *trans*-hydroarylation of C–C triple bonds with boronic acids has not been reported before.[14]

The initial investigation began by screening the reaction conditions for hydroarylation of ynamide **1a** with $PhB(OH)_2$ (**2a**). When the reaction was conducted with 5 mol% of $Pd(OAc)_2$, 10 mol% of PPh_3, and 2 equiv. of Na_2CO_3 in dioxane at 70 °C under a nitrogen atmosphere for 5 h, a mixture of 80 : 20 *E*/*Z* isomers of **3aa** was obtained (Table 1, entry 1). Interestingly, the base was found to be unnecessary for the addition (Table 1, entries 2 and 3). A survey of solvents utilizing $P(3\text{-tol})_3$ as the ligand revealed that the readily accessible and environmentally friendly EtOH was the most effective, affording **3aa** as a single (*E*)-isomer in 93% yield (Table 1, entry 8). The regio- and stereochemistry of this reaction was unambiguously determined by the NOE and HMBC measurements (see ESI†). Other ligands such as PPh_3, PCy_3, dppe, and $P(4\text{-tol})_3$ provided inferior results (Table 1, entries 9–12). Therefore, the best reaction conditions for *trans*-addition of boronic acids to ynamides were affirmed as follows: 5 mol% of $Pd(OAc)_2$ and 10 mol% of $P(3\text{-tol})_3$ in EtOH under a nitrogen atmosphere at 70 °C for 5 h.

Table 1 Screening of the reaction conditions[a]



Entry	Ligand	Solvent	*E*/*Z*[b]	Yield[c] (%)
1[d]	PPh_3	Dioxane	80 : 20	67
2[d]	$P(3\text{-tol})_3$	Dioxane	86 : 14	71
3	$P(3\text{-tol})_3$	Dioxane	85 : 15	75
4	$P(3\text{-tol})_3$	DMF	95 : 5	82
5	$P(3\text{-tol})_3$	THF	89 : 11	78
6	$P(3\text{-tol})_3$	MeOH	95 : 5	88
7	$P(3\text{-tol})_3$	Toluene	98 : 2	91
8	$P(3\text{-tol})_3$	EtOH	>98 : 2	93
9	PPh_3	EtOH	75 : 25	62
10	PCy_3	EtOH	78 : 22	76
11	dppe	EtOH	38 : 62	56
12	$P(4\text{-tol})_3$	EtOH	96 : 4	87
13[e]	$P(3\text{-tol})_3$	EtOH	92 : 8	85

[a] Reaction conditions: **1a** (0.30 mmol), **2a** (0.45 mmol), $Pd(OAc)_2$ (5 mol%), ligand (10 mol%), under N_2, 70 °C, 5 h. [b] Determined by GC. [c] Isolated yield. [d] 2 equiv. of Na_2CO_3 was added. [e] Under an air atomosphere.

Then, the scope of this *trans*-hydroarylation reaction was investigated by using different types of organoboron reagents (Table 2). Arylboronic acids possessing both electron-withdrawing

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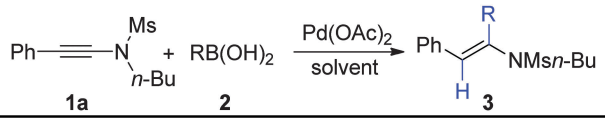
Table 2 Scope of boronic acids[a]



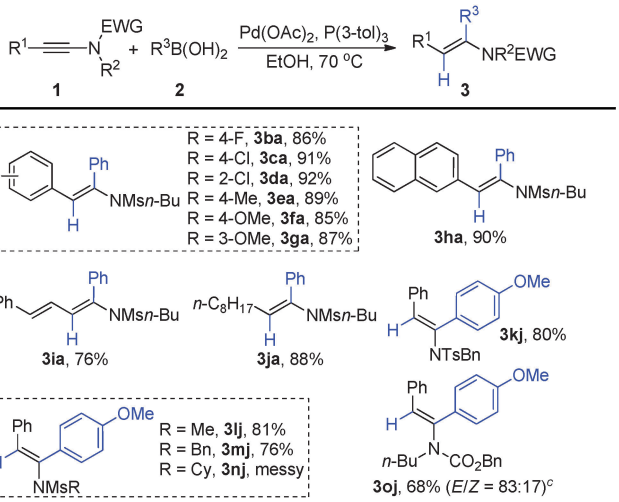
Entry	2	Yield[b] (%)
1	4-F-C_6H_4 (**2b**)	90 (**3ab**)
2	2,4-F_2-C_6H_3 (**2c**)	89 (**3ac**)
3	4-CF_3-C_6H_4 (**2d**)	84 (**3ad**)
4	3-NO_2-C_6H_4 (**2e**)	82 (**3ae**)
5	4-Cl-C_6H_4 (**2f**)	85 (**3af**)
6	4-Me-C_6H_4 (**2g**)	91 (**3ag**)
7	3-Me-C_6H_4 (**2h**)	91 (**3ah**)
8	2-Me-C_6H_4 (**2i**)	89 (**3ai**)
9	4-OMe-C_6H_4 (**2j**)	84 (**3aj**)
10	3,4-$(OMe)_2$-C_6H_3 (**2k**)	88 (**3ak**)
11	3,4-Methylenedioxyphenyl (**2l**)	92 (**3al**)
12	4-CHO-C_6H_4 (**2m**)	87 (**3am**)
13	4-MeCO-C_6H_4 (**2n**)	83 (**3an**)
14	4-CN-C_6H_4 (**2o**)	88 (**3ao**)
15	4-Ph-C_6H_4 (**2p**)	85 (**3ap**)
16	2-Naphthyl (**2q**)	86 (**3aq**)
17	(*E*)-1-Pentenyl (**2r**)	79 (**3ar**)
18	(*E*)-Styryl (**2s**)	70 (**3as**)
19	2-Thienyl (**2t**)	82 (**3at**)
20	2-Benzothiazolyl (**2u**)	77 (**3au**)
21	PhBpin (**2v**)	76 (**3aa**)
22	Me (**2w**)	NR

[a] Reaction conditions: see Table 1. [b] Isolated yield.

and electron-donating substituents served as the good coupling partners in this process. Of note, the steric hindrance of **2** seemed to have no significant influence on the yield (Table 2, entries 1, 2, and 6–8). Gratifyingly, various functional groups such as F, CF_3, NO_2, Cl, OMe, CHO, Ac, CN, alkyl and aryl substituents were found to be compatible (Table 2, entries 1–16). Alkenyl boronic acids **2r** and **2s** furnished the 1,3-dienyl amides **3ar** and **3as** in good yields with excellent regio- and stereoselectivity (Table 2, entries 17 and 18). Moreover, the reaction was applicable to heteroarylboronic acids, as demonstrated by the reaction of **2t** and **2u** (Table 2, entries 19 and 20). Reaction of PhBpin (**2v**) performed well to generate **3aa** in satisfactory yield, while $MeB(OH)_2$ (**2w**) did not yield the desired product (Table 2, entries 21 and 22).

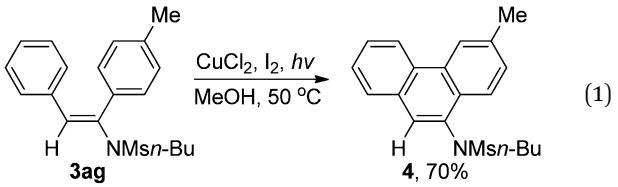
On the other hand, a variety of ynamides were successfully applied to the present *trans*-hydroarylation reaction. As shown in Table 3, both electron-poor and electron-rich ynamides **1b–g** reacted well to produce the corresponding enamides in excellent yields (Table 3, **3ba–ga**). Vinylic ynamide **1i** furnished dienyl enamide **3ia** in 76% yield, and substrate **1j**, with an alkyl chain, was also found to be well tolerated (Table 3, **3ia** and **3ja**). The *N*-Me and *N*-Bn substrates **1l** and **1m** provided **3lj** and **3mj** in high yields, while the *N*-Cy counterpart **1n** failed to produce the expected product, implying that the steric effects of *N*-substituents of ynamides had some influence on this reaction (Table 3, **3lj–nj**). In contrast, ynamide **1o** provided the *trans*-addition product **3oj** in reduced stereoselectivity (Table 3, **3oj**). Additionally, when 3-(2-phenylethynyl)-2-oxazolidinone (**1p**) was subjected to the standard reaction conditions, only low conversion (<15%) was observed.

Table 3 Scope of ynamides[a,b]

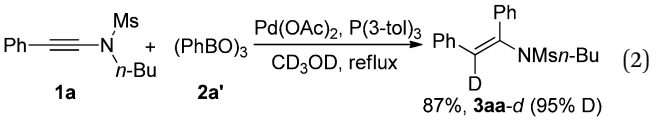


[a] Reaction conditions: see Table 1, 5–12 h. [b] Isolated yield. [c] Determined by GC.

Next, we turned our attention to explore the synthetic utility of this protocol. When compound **3ag** was treated with 1 mol% of I_2 and 5 mol% of $CuCl_2$ in MeOH at 50 °C for 24 h,[12b] a phenanthrene derivative **4** was obtained in 70% yield upon isolation (eqn (1)).



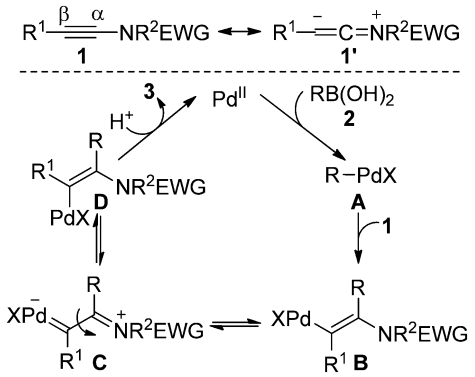
(1)



(2)

Meanwhile, the deuteration experiments were conducted by reacting **1a** with $(PhBO)_3$ in CD_3OD at reflux for 5 h, and consequently, **3aa**-*d* was isolated in 87% yield with 95% deuterium incorporation (eqn (2)). Although the detailed mechanism for this unexpected *trans*-addition of boronic acids to ynamides is still unclear at the current stage, a plausible mechanism is proposed in Scheme 1. Initially, an intermediate **A**, generated from transmetallation of Pd(II) with boronic acids **2**, undergoes the *cis*-carbopalladation with **1** to afford the species **B**. The highly polarized C–C triple bond of **1**, resulted from the electron donation by the nitrogen atom, may be responsible for controlling the regioselectivity of carbopalladation. Then, the *E*–*Z* isomerization[15,16] can take place *via* the palladium carbene species **C**, leading to the production of **D**. Finally, the protonolysis of the alkenyl C–Pd bond[17] of **D** provides **3** and regenerates the Pd(II) catalyst (Scheme 1).

In summary, we have achieved a Pd-catalyzed stereospecific *trans*-addition of boronic acids to ynamides for the first time, furnishing α,β-disubstituted enamides in high yields with excellent regio- and stereoselectivity. The reaction operates under mild



Scheme 1 A possible mechanism.

reaction conditions and a broad spectrum of functional groups are found to be well tolerated. Moreover, it allows a facile route to prepare phenanthrene derivatives *via* the photochemical transformation of generated enamides. Further investigations on the reaction mechanism of *trans*-addition of boronic acids to ynamides are currently underway.

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