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Copper-Mediated Difunctionalization of Alkenylboronic Acids: Synthesis of α-Imino Ketones

Ji-Wen Jiao[†], Hong-Yan Bi[†], Pei-Sen Zou , Zhi-Xin Wang*, Cui Liang, and Dong-Liang Mo*

[a] State Key Laboratory for Chemistry and Molecular Engineering of Medicinal Resources, Ministry of Education of China; School of Chemistry and Pharmaceutical Sciences, Guangxi Normal University, 15 Yu Cai Road, Guilin 541004, China. E-mail: 862991993@qq.com; moeastlight@mailbox.gxnu.edu.cn

[†] J.-W. Jiao and H.-Y. Bi contributed equally to this work

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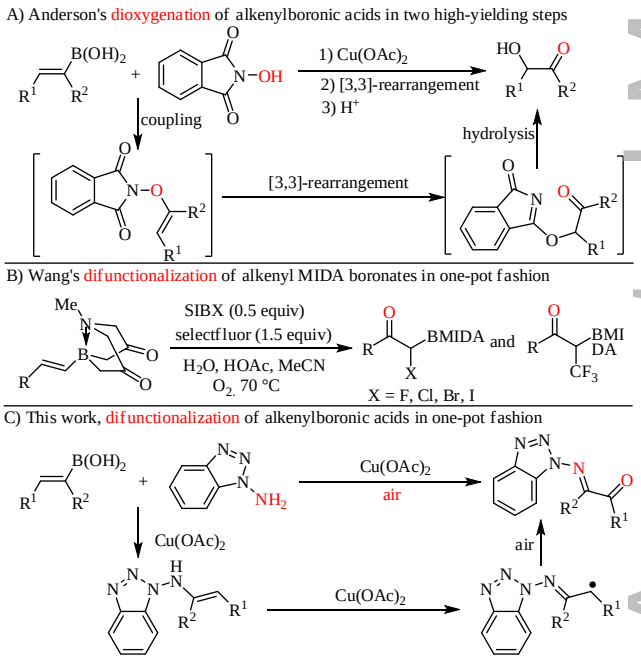
Abstract. Various α-imino ketones were prepared in good yields through a copper-mediated difunctionalization of alkenylboronic acids with benzotriazolamine in air. Mechanistic studies showed that α-imino ketones formation occurred through an initial copper-mediated coupling reaction to form an enamine, followed by homolysis of the C−Cu bond to produce an α-radical imine, and finally radical oxidation by air. The α-imino ketones were easily converted to various useful scaffolds through further transformations.

Keywords: alkenylboronic acids; benzotriazolamines; copper-catalyzed; difunctionalization; α-imino ketones

Cascade reactions, in which multistep transformations occur in one-pot to convert readily available reactants into functionalized and complex molecules, have become powerful and attractive strategies improving synthetic efficiency and simplifying operations.[1] Alkene difunctionalizations are among the most basic and efficient cascade transformations in organic synthesis.[2] Among them, aminooxygenations or oxyaminations of alkenes are important processes owing to their applications in the preparation of 1,2-amino alcohols and related derivatives.[3,4] Alkenylboronic acids have received much attention owing to their stability, easy preparation, nontoxicity, and importance in the formation of C−O, C−N and C−C bonds in cross-coupling reactions.[5] Although the use of alkenylboronic acids to construct various new bonds has been well established, the direct difunctionalization of alkenylboronic acids would be a facile route to accessing diverse functionalized molecules in a one-pot reaction. In 2012, Anderson *et al.* developed a powerful dioxygenation of alkenyl boronic acids to prepare α-oxygenated ketones using a route involving a copper-mediated etherification to form an *N*-enoxyphthalimide, a [3,3]-rearrangement, and hydrolysis of a phthalimide imidate (Scheme 1-A).[6] In 2016, Wang and co-workers reported a novel one-pot difunctionalization of alkenyl N-methyliminodiacetic acid (MIDA) boronates to synthesize halogenated and trifluoromethylated α-boryl ketones (Scheme 1-B).[7] Both these strategies are attractive, powerful, and efficient routes toward functionalized molecules.



Scheme 1. Difunctionalization of alkenylboron reagents.

During our research into copper-catalyzed selective cross-couplings of N−O bonds with aryl and alkenylboronic acids,[8] we envisioned that alkenylboronic acids might couple with benzotriazolamine to afford an enamine intermediate, followed by sequential oxidation to produce an α-

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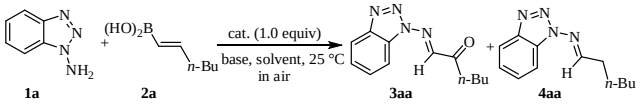
radical imine under copper(II) catalysis, with subsequent oxidation in air to afford α-imino ketones (Scheme 1-C). Many elegant examples of copper-promoted couplings of different amines with aryl- or alkenylboronic acids to construct C−N bonds have been reported.[9] However, difunctionalizations of alkenylboronic acids to afford α-imino ketones have yet to be reported. Herein, we report a copper-mediated difunctionalization of alkenylboronic acids to prepare α-imino ketones under mild conditions.

Our study began with the reaction of benzotriazolamine **1a** and alkenylboronic acid **2a** to investigate the difunctionalization process. Reaction conditions using copper salts as catalysts and pyridine (pyr) as base in DCE at room temperature under an air atmosphere were tested. α-Imino ketone **3aa** was not observed when using $CuSO_4$, but imine **4aa** was obtained in 5% yield (Table 1, entry 1). However, α-imino ketone **3aa** was obtained in 5% yield using $CuCl_2$ along with imine **4aa** in 10% yield (Table 1, entry 2). These results showed that the difunctionalization of alkenylboronic acids in a one-pot reaction under mild conditions was possible. Inspired by these results, the reaction conditions were further optimized. Using $Cu(OTf)_2$ and $Cu(OAc)_2$, the yield of **3aa** was further improved to 18% and 41%, accompanied by imine **4aa** in 11% and 15% yields, respectively (Table 1, entries 3-4). However, CuCl did not promote the reaction (Table 1, entry 5). The influence of the solvent was also investigated. Compound **3aa** was obtained as the major product in most solvents, including toluene, THF, MeOH, and DMSO, but in low yields (Table 1, entries 6-9). A 61% yield of **3aa** was obtained in MeCN (Table 1, entry 10). When the amount of $Cu(OAc)_2$ was increased to 2.0 equiv., the yield of **3aa** was increased to 66% with imine **4aa** obtained in 6% yield (Table 1, entry 11). Reducing the amount of $Cu(OAc)_2$ to 0.5 or 0.2 equiv. decreased the yield of **3aa**, but improved the yield of **4aa** (Table 1, entries 12-13). The reaction proceeded smoothly using organic and inorganic bases to afford **3aa** (Table 1, entries 14-18). Fortunately, **3aa** was obtained in good yields with inorganic bases, while **4aa** was observed in less than 5% yield (Table 1, entries 15-18). The best yield of **3aa** (86%) was obtained when $NaHCO_3$ was used as base (Table 1, entry 16). These results showed that the selectivity for α-imino ketone **3aa** and imine **4aa** formation could be controlled using copper and $NaHCO_3$. Using 0.2 equiv. of $Cu(OAc)_2$ with $NaHCO_3$ afforded **3aa** in 68% yield, but required a longer reaction time compared with entry 16 (Table 1, entry 19). Reducing the amount of alkenylboronic acid **2a** to 2.0 and 1.0 equiv. decreased the yields of **3aa** to 79% and 48%, respectively (Table 1, entries 20-21). Improving the reaction temperature to 60 °C did not afford products **3aa** and **4aa** because self-coupling byproduct of boronic acid **2a** was observed (Table 1, entry 22). When air was replaced by O_2, a 78% yield of **3aa** was obtained (Table 1, entry 23). The reactivity of boron reagents **2** was also tested. The reaction did not occur using corresponding boronate ester while a 83% yield of **3aa** was obtained using potassium trifluoroborate (Table 1, entries 24-25). Therefore, the optimal conditions for preparing α-imino ketone **3aa** were $Cu(OAc)_2$ (2.0 equiv.) with $NaHCO_3$ as base in MeCN at room temperature under an air atmosphere (Table 1, entry 16).

Table 1. Optimization of reaction conditions.[a]



1a 2a 3aa 4aa

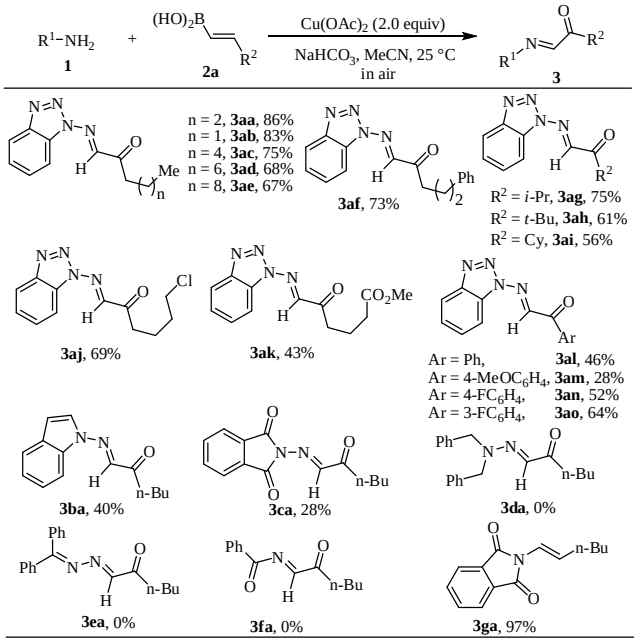
entry	cat	solvent	base	**3aa** %[b]	**4aa** %[b]
1	$CuSO_4$	DCE	pyr	-	5
2	$CuCl_2$	DCE	pyr	5	10
3	$Cu(OTf)_2$	DCE	pyr	18	11
4	$Cu(OAc)_2$	DCE	pyr	41	15
5	CuCl	DCE	pyr	5	8
6	$Cu(OAc)_2$	toluene	pyr	6	<5
7	$Cu(OAc)_2$	THF	pyr	18	10
8	$Cu(OAc)_2$	MeOH	pyr	23	9
9	$Cu(OAc)_2$	DMSO	pyr	40	11
10	$Cu(OAc)_2$	MeCN	pyr	61	9
11[c]	$Cu(OAc)_2$	MeCN	pyr	66	6
12[d]	$Cu(OAc)_2$	MeCN	pyr	36	15
13[e]	$Cu(OAc)_2$	MeCN	pyr	20	20
14[c]	$Cu(OAc)_2$	MeCN	NEt_3	73	7
15[c]	$Cu(OAc)_2$	MeCN	Cs_2CO_3	71	<5
16[c]	$Cu(OAc)_2$	MeCN	$NaHCO_3$	86	<5
17[c]	$Cu(OAc)_2$	MeCN	Na_2CO_3	80	<5
18[c]	$Cu(OAc)_2$	MeCN	NaOH	70	<5
19[e,f]	$Cu(OAc)_2$	MeCN	$NaHCO_3$	68	<5
20[c,g]	$Cu(OAc)_2$	MeCN	$NaHCO_3$	79	<5
21[c,h]	$Cu(OAc)_2$	MeCN	$NaHCO_3$	48	<5
22[c,i]	$Cu(OAc)_2$	MeCN	$NaHCO_3$	<5	<5
23[c,j]	$Cu(OAc)_2$	MeCN	$NaHCO_3$	78	<5
24[c,j]	$Cu(OAc)_2$	MeCN	$NaHCO_3$	<5	<5
25[c,l]	$Cu(OAc)_2$	MeCN	$NaHCO_3$	83	<5

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.9 mmol, 3.0 equiv.), cat (1.0 equiv.), solvent (3.0 mL), base (0.9 mmol, 3.0 equiv.), 18−24 h; [b] isolated yield; [c] $Cu(OAc)_2$ (2.0 equiv.); [d] $Cu(OAc)_2$ (0.5 equiv.); [e] $Cu(OAc)_2$ (0.2 equiv); [f] reaction time, 48 h; [g] **2a** (0.6 mmol, 2.0 equiv.); [h] **2a** (0.3 mmol, 1.0 equiv.); [i] Ran at 60 °C; [j] Air was replaced by O_2; [k] **2a** was replaced by *n*-BuCH=CHB(pin); [l] **2a** was replaced by *n*-BuCH=CHBF_3K;

With the optimized reaction conditions in hand, benzotriazolamine **1a** was reacted with a variety of monosubstituted alkenylboronic acids **2** to explore the substrate scope and reaction selectivity (Scheme 2). Alkenylboronic acids **2a-2o** containing alkyl and aryl substituents proceeded smoothly in the reaction to afford corresponding α-imino ketones **3aa-3ao** in moderate to good yields. For linear terminal alkenylboronic acids **2a-2f**, the length of the substituents had little effect on the yields of α-imino ketones (**3aa-3af**). For sterically bulky alkenylboronic acids **2g** and **2h**, both *i*-Pr and *t*-Bu

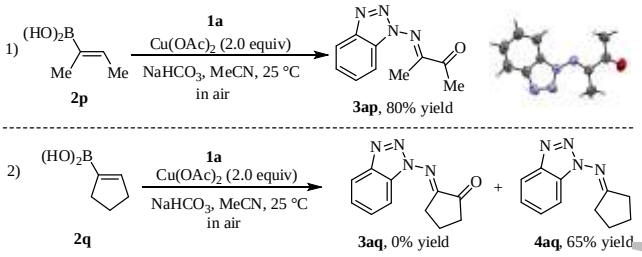
groups gave products **3ag** and **3ah** in 75% and 61% yields, respectively. Interestingly, sensitive functional substituents, such as chloro and ester groups, were well-tolerated, furnishing the desired α-imino ketones in good yields (**3aj** and **3ak**). Styrenylboronic acids **2l-2o** containing electron-donating and electron-withdrawing groups reacted smoothly with benzotriazolamine **1a** to give products **3al-3ao** in moderate yields. However, compound **3am** was obtained in only 28% yield, with a 1,3-diene byproduct isolated in high yield. The structure of α-imino ketone **3** was confirmed by X-ray diffraction analysis of compound **3ab**.[10] The structure showed that α-imino ketone **3** was an *E*-isomer with respect to the C=N bond. In all cases, imines **4** were observed in less than 5% yield. Next, various amine nucleophiles **1** were also evaluated in the reaction. Using 1-amino indole **1b**, afforded desired product α-imino ketone **3ba** in 40% yield. 2-Aminoisoindoline-1,3-dione **1c** reacted with alkenylboronic acid **2a** under the optimal conditions to give **3ca** in 28% yield only. However, other amines, such as 1,1-dibenzylhydrazine **1d**, diphenylmethylene hydrazine **1e**, benzamide **1f**, and isoindoline-1,3-dione **1g**, did not produce α-imino ketones, or imine **4**. Isoindoline-1,3-dione **1g** afforded coupling product **3ga** in 97% yield, indicating that the formation of α-imino ketone **3aa** might involve an initial coupling reaction.

Scheme 2. Reaction scope for the preparation of α-imino ketones **3**.[a,b]



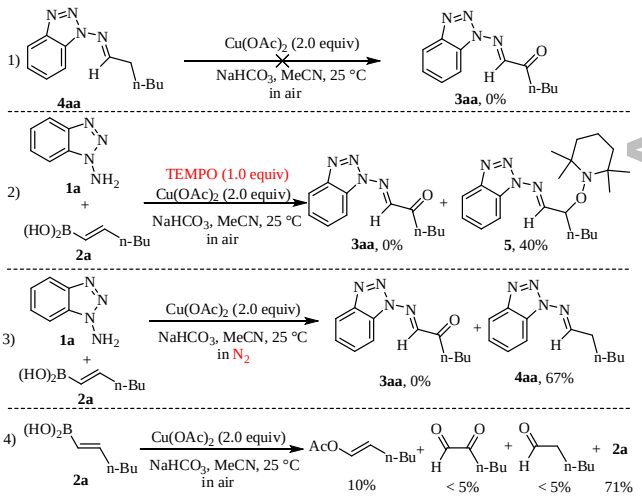
[a] Reaction conditions: **1** (0.3 mmol), **2** (0.9 mmol, 3.0 equiv.), $Cu(OAc)_2$ (2.0 equiv.), MeCN (3.0 mL), $NaHCO_3$ (0.9 mmol, 3.0 equiv.), 18−24 h; [b] isolated yield.

Z-Disubstituted alkenylboronic acids were tested in addition to monosubstituted alkenylboronic acids. As shown in Scheme 3, when *Z*-disubstituted alkenylboronic acid **2p** was subjected to the optimal conditions, desired α-imino ketone **3ap** was obtained in 80% yield (Scheme 3-1). The structure of **3ap** was confirmed by X-ray diffraction analysis.[10] When cyclic alkenylboronic acid **2q** was subjected to the optimal conditions, only imine compound **4aq** was obtained in 65% yield, while α-imino ketone **3aq** was not observed, even when the reaction time was extended to 48 h (Scheme 3-2).



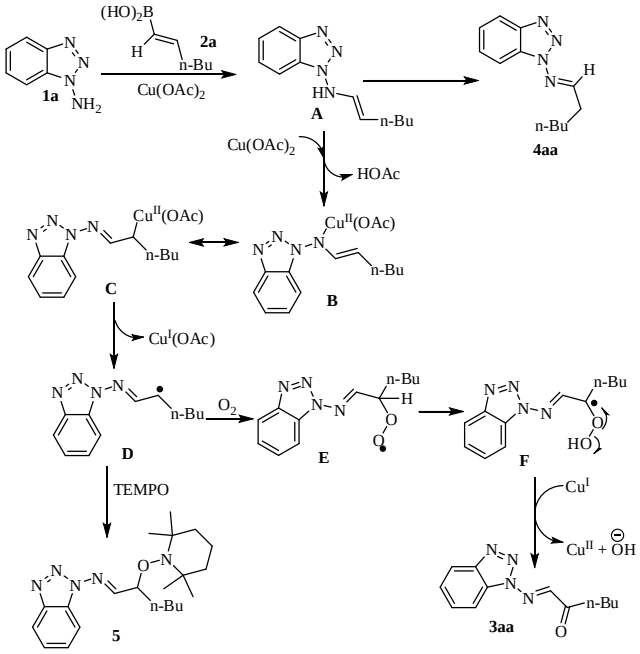
Scheme 3. Disubstituted alkenylboronic acids tested.

To better understand the formation mechanism of α-imino ketone **3aa**, control experiments were performed (Scheme 4). When imine **4aa** was subjected to the optimal conditions, **3aa** was not observed for 24 h, with only **4aa** recovered (Scheme 4-1). This result showed that **4aa** was just a competent intermediate in this reaction, not an intermediate for the formation of **3aa**. When adding radical trapping reagent (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) under the optimal conditions, **3aa** was not observed, and a TEMPO-trapped compound **5** was afforded in 40% yield (Scheme 4-2). These results showed that the reaction mechanism might involve a radical process, suggesting an α-radical imine intermediate. When the air atmosphere was replaced with N_2, only imine **4aa** was obtained in 67% yield (Scheme 4-3), suggesting that the formation of **3aa** required air. When boronic acid **2a** was reacted under the optimal conditions without **1a**, (*E*)-hex-1-enyl acetate was observed in 10% yield, hexanal was not observed, and boronic acid **2a** was recovered in 71% yield (Scheme 4-4). These results indicated that compounds **3aa** and **4aa** were not generated directly by the condensation of **1a** with the corresponding aldehydes.



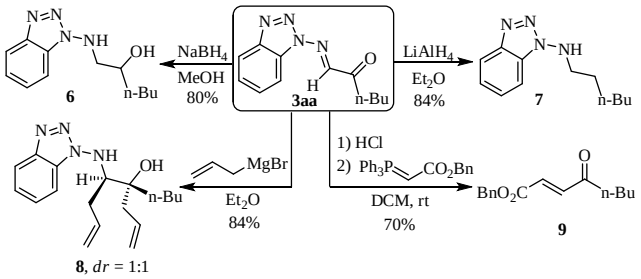
Scheme 4. Mechanistic studies.

Based on our experimental results, a possible mechanism for the formation of α-imino ketone **3aa** from benzotriazolamine **1a** and alkenylboronic acid **2a** was proposed (Scheme 5). Firstly, **1a** couples with **2a** under copper catalysis to afford enamine **A**. Tautomerization of **A** gives imine **4aa**. Otherwise, deprotonation of **A** by $Cu(OAc)_2$ affords **B** which undergoes a 1,3-migration to give an unstable organocopper(II) intermediate **C**.[4a,11] **D** then undergoes C−Cu homolysis to give radical **D**.[12] Radical **D** is then trapped by TEMPO, affording compound **5**, or alternatively, reacts with molecular oxygen to form α-imino ketone **3aa** *via* intermediates **E** and **F**. In this case, we cannot rule out the mechanism of a direct alkene oxidation under copper and air conditions.[13]



Scheme 5. Proposed mechanism.

To illustrate the superiority of these transformations, the utility of α-imino ketone **3aa** was investigated (Scheme 6). The reduction of **3aa** by $NaBH_4$ in MeOH at room temperature for 30 min afforded 1,2-amino alcohol **6** in 80% yield. Treating **3aa** with $LiAlH_4$ at 0 °C for 30 min delivered linear amine **7** in 84% yield, which showed that the carbonyl group could be reduced to a methylene group. When α-imino ketone **3aa** was reacted with allyl Grignard reagent for 30 min, amino alcohol **8**, containing two quaternary carbon centers was obtained in 84% yield with a 1:1 dr. The hydrolysis of **3aa** with HCl and addition of a phosphorus ylide afforded α,β-unsaturated-γ-keto ester **9** in 70% yield. Removing the benzotriazolamine group using this simple hydrolysis provides α-imino ketones with potential for further transformations.



Scheme 6. Application of α-iminoketone **3aa**.

In summary, we have developed a copper-mediated difunctionalization of alkenylboronic acids for the synthesis of α-imino ketones in good yields. Mechanistic studies showed that the α-radical imine produced by the copper(II) catalyst was the key intermediate in the formation of α-imino ketones. This work extends the scope of the difunctionalization of alkenylboron reagents and provides insight into further potential applications of α-radical imine intermediates.

Experimental Section

General procedure for synthesis of α-imino ketone 3aa: In a reaction flask was charged with benzotriazol-1-amine **1a** (0040 g, 0.3 mmol), alkenylboronic acid **2a** (0.115 g, 0.9 mmol, 3.0 equiv.), $Cu(OAc)_2$ (0.6 mmol, 2.0 equiv.) and $NaHCO_3$ (0.6 mmol, 2.0 equiv.) under an air atmosphere. Then, MeCN (3.0 mL) was added. The reaction mixture was stirred vigorously at 25 °C for 18−24 h until the substrate **1a** disappeared (monitored by TLC). At this time, the reaction was quenched by H_2O (10 mL) and extracted with EA (3 × 10 mL). Then, the combined organic layers were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (the crude residue was dry loaded with silica gel, 1/50 to 1/10, ethyl acetate/petroleum ether) to provide product **3aa** as a yellow solid (0.059 g, 86%). mp: 44−45 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.67−7.64 (m, 1H), 7.50−7.49 (m, 1H), 3.08 (t, J = 7.6 Hz, 2H), 1.77−1.73 (m, 2H), 1.48−1.43 (m, 2H), 1.01 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.5, 146.9, 145.8, 131.6, 129.6, 125.6, 120.6, 110.2, 37.3, 25.8, 22.4, 13.9; IR (thin film) 2958, 1695, 1616, 1448, 1271, 1046, 747 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}N_4O$ $(M+H)^+$ 231.1240, found 231.1239.

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