

Catalytic Four-Component Assembly Based on Allenylboronate Platform: New Access to Privileged Allylic Amine Structures

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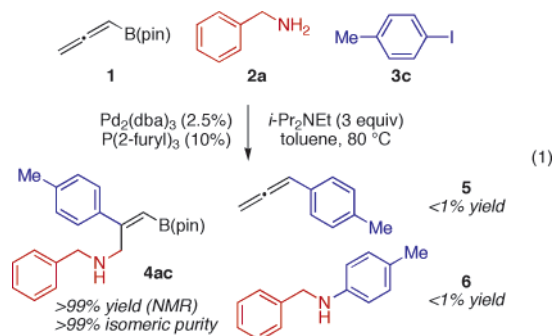
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The multicomponent assembly reaction has emerged as a powerful means for rapid generation of molecular complexity and diversity, thereby being particularly well-adapted for combinatorial chemistry and diversity-oriented synthesis.¹ In particular, multicomponent assembly based on a simple molecule bearing multiple reaction sites (platform) serves as a powerful synthetic strategy.² In such synthesis, it is extremely important to consider what kind of platform, assembling components, and reactions to use and what kind of privileged target structures to aim for.

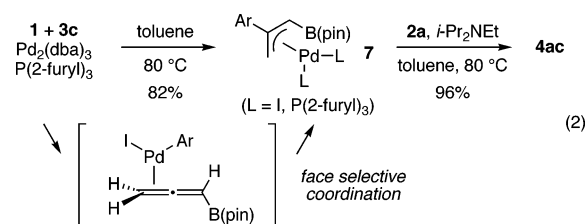
On the basis of such consideration, we recently developed vinylboronate ester as a useful platform for triarylethene-based functional π -systems.³ The synthesis began with Pd-catalyzed double C–H arylation (Mizoroki–Heck coupling) of vinylboronate, followed by Suzuki–Miyaura coupling at the remaining C–B bond. Such orthogonal and sequential assembly using an organoboron platform (reaction at the organic part followed by C–B functionalization) has attracted much interest in the context of diversity-oriented synthesis.⁴ Herein we describe a novel catalytic four-component assembly based on the allenylboronate platform, by which privileged allylic amine structures⁵ can be constructed in a regioselective, stereoselective, and diversity-oriented manner.

Allenylboronate pinacol ester (**1**: 1.2 equiv) was treated with benzylamine (**2a**: 1.2 equiv) and 4-iodotoluene (**3c**: 1.0 equiv) in the presence of Pd₂(dba)₃ (2.5 mol %), P(2-furyl)₃ (10 mol %), and *i*-Pr₂NEt (3.0 equiv) in toluene at 80 °C for 24 h. A three-component assembling reaction took place to afford allenylboronate **4ac** quantitatively with virtually complete regio- and stereoselectivity (eq 1).^{6,7} As for supporting ligands on Pd, π -acidic ligands such as P(2-furyl)₃, P(OPh)₃, and P(C₆H₄CF₃-4)₃ were found to be superior (see Supporting Information). It should be mentioned that neither the possible Suzuki–Miyaura coupling product **5** nor the Buchwald–Hartwig-type amination product **6** was formed in this reaction.



The selective production of **4ac** can be explained by assuming the following mechanism (eq 2).⁶ The terminal C=C bond of **1**

coordinates to an arylpalladium complex, formed by **3c** and Pd(0), at the face opposite to the pinacoloboryl group to avoid steric congestion. The subsequent arylpalladation across C=C bond leads to a π -allyl complex **7** with the boryl group anti to the aryl group. The stoichiometric reaction also furnished **7** in high yield. Then, amine **2a** attacks **7**, presumably at unsubstituted terminal carbon of allyl ligand, to give **4ac** with the regeneration of the Pd(0) catalyst. The *anti* stereochemistry of π -allyl intermediate **7** accounts for the *Z* stereochemistry of **4ac**. The stoichiometric reaction also furnished **4ac** quantitatively with virtually complete regio- and stereoselectivity as in the catalytic reaction.



The virtually complete stereoselectivity observed is notable. Tsuji reported in his pioneering work that the Pd-catalyzed three-component assembly of substituted allenes, organic halides, and secondary amines proceeds with low stereoselectivity (1/3 ~ 1/9).^{6a} Elsevier also reported that the stereoselectivity is highly dependent on substrates employed.^{6b} To assess the effect of the boryl group in this reaction, phenylallene, cyclohexylallene, and triisopropylsilyllallene were subjected to the conditions shown in eq 1. Surprisingly none of these substrates are comparable to **1** in terms of productivity and selectivity (see Supporting Information). Although the origin of high reactivity and selectivity is still under investigation, the boryl group clearly acts not only as a useful group that can be transformed into various functional groups afterward (vide infra) but also as a stereochemical controller in this three-component assembly.

With this extremely selective tandem three-component assembly reaction in hand, we subsequently examined catalytic four-component assembly through post C–B arylation (Suzuki–Miyaura coupling)⁸ of allenylboronates **4** formed in situ (Table 1). Thus, by simply adding second aryl iodides **8** (1.5 equiv), Cs₂CO₃ (5 equiv), and H₂O (4 equiv) into the reaction mixture of the three-component assembling reaction (**1** + **2** + **3**), multisubstituted allylic amines **9** were obtained in good to excellent yields with virtually complete isomeric purity. The reaction proceeded efficiently with electronically and structurally diverse aryl and heteroaryl iodides. Various functional groups on the aromatic ring of **3** and **8** remained unchanged in this reaction. As for amines in this coupling, secondary amines generally gave good results. Although primary amines such as **2a** can afford the three-component product **4** very

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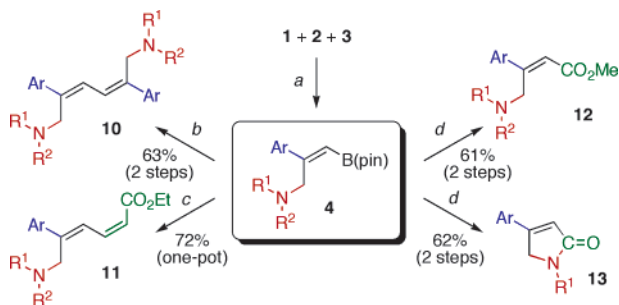
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Table 1. Synthesis of Multisubstituted Allylic Amines **9** through Catalytic Four-Component Assembly^a

run	2 ^b	Ar ¹	Ar ²	9 (yield, %) ^c
1	2b	C ₆ H ₅ (a)	4-MeCOC ₆ H ₄ (b)	9bab (73)
2	2b	4-MeC ₆ H ₄ (c)	4-MeOC ₆ H ₄ (d)	9bcd (74)
3	2b	3-thienyl (e)	4-MeC ₆ H ₄ (c)	9bec (90)
4	2b	4-CF ₃ C ₆ H ₄ (f)	C ₆ H ₅ (a)	9bfa (80)
5	2b	1-naphthyl (g)	3-MeOC ₆ H ₄ (h)	9bgh (59)
6	2c	4-MeC ₆ H ₄ (c)	C ₆ H ₅ (a)	9cca (66)
7	2c	4-MeOC ₆ H ₄ (d)	3-thienyl (e)	9cde (69)
8	2c	4-EtOCOC ₆ H ₄ (i)	2-MeC ₆ H ₄ (j)	9cij (66)
9	2d	4-MeC ₆ H ₄ (c)	4-MeOC ₆ H ₄ (d)	9dcd (52)
10	2d	C ₆ H ₅ (a)	3-pyridyl (k)	9dak (67)
11	2d	3-thienyl (e)	4-EtOCOC ₆ H ₄ (i)	9dei (82)
12	2d	4-NCC ₆ H ₄ (l)	4-ClC ₆ H ₄ (m)	9dlm (74)

^a Reaction conditions: (i) **1** (0.36 mmol), **2** (0.36 mmol), Ar¹-I (**3**: 0.30 mmol), Pd₂(dba)₃ (0.0075 mmol), P(2-furyl)₃ (0.03 mmol), *i*-Pr₂NEt (0.90 mmol), toluene (1.5 mL), 80 °C; (ii) Ar²-X (**8**: 0.45 mmol), Cs₂CO₃ (1.5 mmol), H₂O (1.2 mmol), toluene (0.5 mL), 90 °C (one-pot). ^b Morpholine (**2b**), pyrrolidine (**2c**), *N*-benzylmethylamine (**2d**). ^c Isolated yields.

Scheme 1. Synthesis of Various Allylic Amines through C–B Functionalization of **4**^a

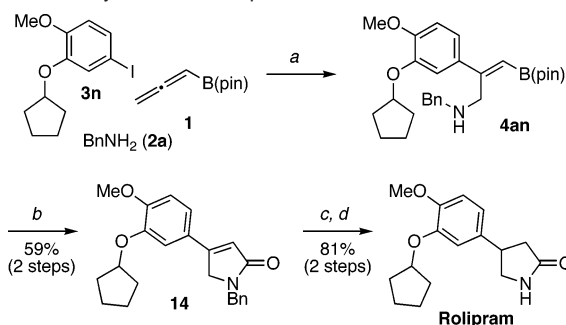
^a Conditions: (a) see eq 1 (Ar = *p*-tolyl); (b) Pd(OAc)₂, PPh₃, Cs₂CO₃, H₂O, toluene, 90 °C, under air; (c) ethyl *cis*-3-iodoacrylate, Cs₂CO₃, H₂O, 90 °C; (d) Pd(OAc)₂, PPh₃, *p*-benzoquinone, CO (1 atm), MeOH, 50 °C. **Amines:** morpholine (**2b**) for **10–12**, benzylamine (**2a**) for **13**.

efficiently as shown in eq 1, the remaining N–H functionality seems to interfere with the last C–B arylation step.

In addition to the rapid synthesis of 2,3-diarylated allylic amines **9** through post C–B arylation, other transformations of boryl groups of three-component products **4** are feasible. As demonstrated in Scheme 1, Pd-catalyzed homocoupling,⁹ Suzuki–Miyaura coupling using alkenyl halide,⁸ esterification,¹⁰ and carbonylative cyclization¹⁰ are possible to afford various potentially useful allylic amines **10–13** in good yields.

Finally, we applied our four-component assembly strategy to a short synthesis of rolipram, which is a selective inhibitor of phosphodiesterase-4 (PDE-4), an antiinflammatory agent and antidepressant (Scheme 2).¹¹ Thus, catalytic three-component assembly of **1**, benzylamine (**2a**), and aryl iodide **3n**, followed by carbonylative cyclization afforded unsaturated lactam **14** in 59% yield (two steps). Hydrogenation of C=C bond and deprotection of *N*-benzyl group with Li/NH₃ gave rolipram in 81% yield.

In summary, we have developed a novel catalytic four-component assembly based on an allenylboronate platform, by which a range of functionalized allylic amine structures can be constructed in a regioselective, stereoselective, and diversity-oriented manner. Since

Scheme 2. Synthesis of Rolipram^a

^a Conditions: (a) Pd₂(dba)₃, P(2-furyl)₃, *i*-Pr₂NEt, toluene, 80 °C; (b) Pd(OAc)₂, PPh₃, *p*-benzoquinone, CO (1 atm), MeOH, 50 °C; (c) Pd/C, H₂ (60 atm), EtOH, 60 °C; (d) Li, liq. NH₃, –40 °C.

allylic amines are ubiquitous structural constituents in pharmacologically important molecules with many interesting actions,⁵ the present diversity-oriented synthesis should find many uses in the development of new biofunctional small molecules. Investigations along this line as well as the elucidation of reaction mechanism are currently ongoing.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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