Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

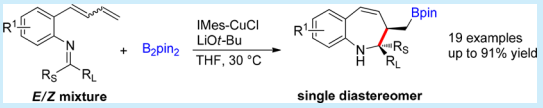
Copper-Catalyzed Regioselective and Diastereoselective Synthesis of Borylated 1-Benzo[*b*]azepines

DingXi Li, Yeji Park, and Jaesook Yun*

Department of Chemistry and Institute of Basic Science, Sungkyunkwan University, Suwon 440-746, Korea

Supporting Information

ABSTRACT: A practical regioselective and diastereoselective synthesis of functionalized 1-benzo[*b*]azepines by copper-catalyzed intramolecular cyclization has been developed. The reaction involves borylcupration of a mixture of (*E*/*Z*)-1,3-dienes, followed by capture of the generated (*Z*)-allylcopper species with an imine to produce 7-membered *N*-heterocycles as single diastereomers. The reaction is applicable to various (*E*/*Z*)-dienyl arenes with an imine moiety at the *ortho*-position, including aryl, alkyl, and heterocyclic aldimines, and ketimines, affording borylated 2,3-*cis*-substituted 1-benzo[*b*]azepines in good yields.



Benzannulated nitrogen heterocycles are key structural elements, frequently appearing in biologically active molecules, synthetic drugs, and drug candidates.[1] In particular, compounds bearing a 7-membered ring skeleton have been incorporated into many commercial pharmaceuticals, such as a drug against Gram-positive and Gram-negative bacteria (ACHN-245),[2] an anti-HIV-1 agent (orally active CCR5 antagonist),[3] and a potential drug for the treatment of pathological diseases related to hydroelectrolyte imbalances (C9) (see Figure 1).[4] As such, growing efforts have been

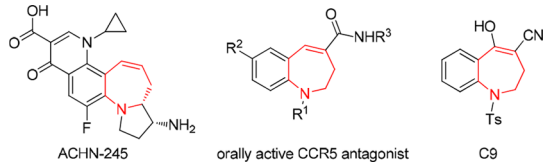
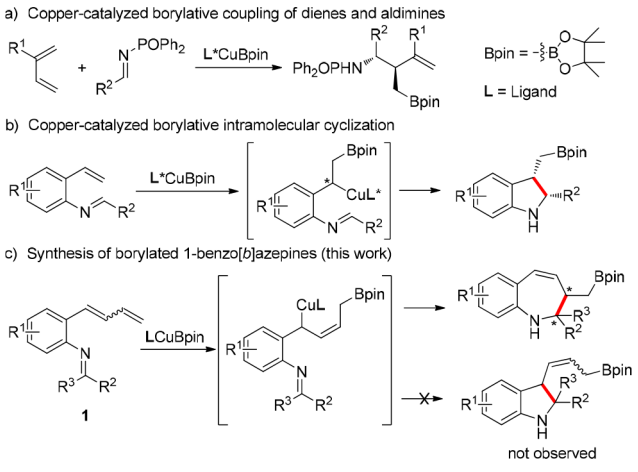


Figure 1. Bioactive compounds containing 1-benzo[*b*]azepine skeletons.

directed toward efficient preparation of the 1-benzo[*b*]azepine backbone. Newly developed methods, including catalytic RCM reactions,[5] radical cyclization reactions,[6] and catalytic [5 + 2] cycloadditions,[7] have worked well in the preparation of valuable scaffolds, but the construction of two adjacent stereocenters on the 1-benzp[*b*]azepine ring with high stereoselectivity remains difficult. Other methods, such as Ir-catalyzed allylic substitution via nucleophilic addition of amine,[8] carbene C−H or C−C insertions,[9] ring expansion by Beckmann rearrangement[10a] and Schmidt reaction,[10b] and others,[11] generally require specially functionalized substrates or expensive catalysts and give low stereoselectivity. Therefore, the development of reliable methods to construct the 1-benzo[*b*]azepine backbones from readily available starting materials is a highly desirable, yet challenging objective.

Over the past decades, the copper-catalyzed allylation of imines has received much attention, as it is an efficient route to homoallylic amines.[12] Recently, Liao and co-workers have developed an asymmetric allylation of imines by copper-catalyzed borylative coupling of pure 1,3-dienes and aldimines in an intermolecular process (Scheme 1a).[12g] More recently,

Scheme 1. Cu-Catalyzed Regioselective and Diastereoselective Borylative Coupling of Dienyl Arenes and Imines



our group and others have introduced copper-catalyzed asymmetric borylative intramolecular cyclization of vinyl arenes with tethered aldimines to produce *cis*-indolines, 5-membered *N*-heterocycles (Scheme 1b).[13,14] Based on this success, we turned our attention to dienyl arenes (**1**) containing tethered imines. When we applied Cu−Bpin catalyst to **1**, we found that a 7-membered ring unexpectedly formed, instead of the vinyl indolines (Scheme 1c). Herein, we report new developments in the copper-catalyzed borylative

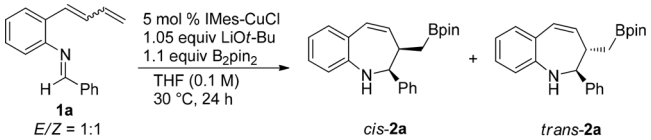
Received: October 15, 2018

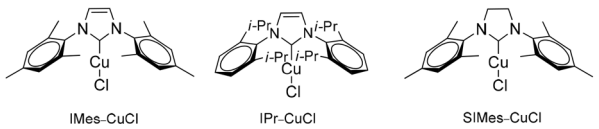
DOI: 10.1021/acs.orglett.8b03286
Org. Lett. XXXX, XXX, XXX−XXX

coupling, whereby an NHC−Cu−Bpin complex added to a mixture of (*E*/*Z*)-diene substrates combined with a tethered imine in an intramolecular process to afford 2,3-substituted 1-benzo[*b*]azepines with high efficiency and diastereoselectivity.

We used a mixture of (*E*/*Z*)-dienyl arenes **1a** as our model substrate without isolation of each individual isomer in the presence of catalytic copper chloride, LiO*t*-Bu, B_2pin_2, and various ligands (Table 1). Complete regioselectivity and

Table 1. Optimization of Copper-Catalyzed Borylative Cyclization[a]





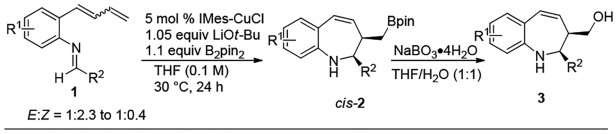
entry	condition change	conversion (%)[b]	Yield (%)[b] *cis*-**2a**	Yield (%)[b] *trans*-**2a**
1[c]	CuCl, PPh_3	100	64	–[d]
2[c]	CuCl, *rac*-Binap	93	74	17
3[c]	CuCl, dppb	100	69	5
4	none	100	85 (78)	–
5	IPr−CuCl	100	82	–
6	SIMes−CuCl	100	54	–
7	0.2 equiv LiO*t*-Bu	54	38	–

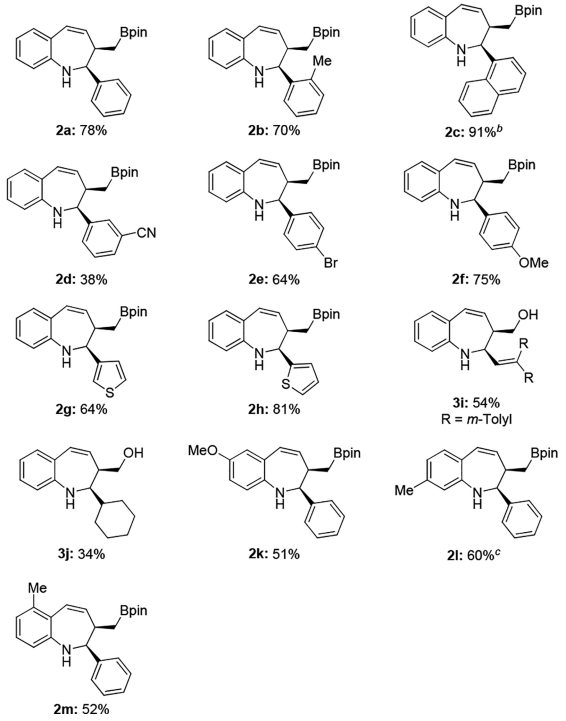
[a]Reactions were conducted on a 0.2 mmol scale. [b]Conversions and yields were determined by ^{1}H NMR analysis of the crude reaction mixture, using dimethylformamide (DMF) as an internal standard. Isolated yield of **2a** is shown in parentheses. [c]5 mol % of copper salt and ligand were used. [d]Not detected.

stereoselectivity were observed with the triphenylphosphine ligand (Table 1, entry 1). Unfortunately, the bisphosphine *rac*-binap ligand gave low diastereoselectivity (Table 1, entry 2) compared to the flexible bisphosphine ligand, dppb (Table 1, entry 3). Gratifyingly, *N*-heterocyclic carbene copper(I) complexes, IMesCuCl and bulky IPrCuCl were highly active, giving full conversion and high yield of *cis*-**2a**[15] with perfect diastereoselectivity (Table 1, entries 4 and 5), while SIMesCuCl resulted in an appreciably lower yield (Table 1, entry 6). In particular, a decrease in the amount of base from a stoichiometric quantity to a substoichiometric amount considerably decreased the conversion and yield (Table 1, entry 7), indicating a stoichiometric amount of base was necessary for the catalytic cycle.

With the optimized conditions in hand, we examined the substrate scope of this method using various dienyl arenes (see Scheme 2). First, substituent effects on the aryl ring (R^2) of the imine moiety were investigated. Sterically bulky groups, such as *ortho*-methyl (**2b**) and naphthyl (**2c**), were compatible with this catalytic system and resulted in good to high yields, even on a gram scale. However, an electron-withdrawing substituent on the aromatic ring such as −CN at the *meta*-position (**2d**) and −Br at the *para*-position (**2e**) resulted in slightly decreased yields of the desired 1-benzo[*b*]azepines. The substrate with an electron-donating methoxy group at the *para*-position of the imine moiety gave the corresponding borylated 1-benzo[*b*]-

Scheme 2. Substrate Scope of the Copper-Catalyzed Borylative Cyclization[a]





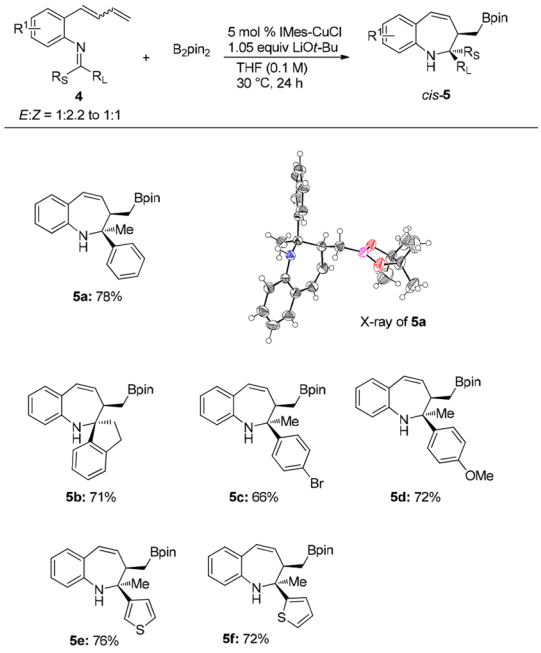
[a]Reactions were conducted on a 0.2 mmol scale. Yields of isolated products are shown. [b]Gram scale (2.9 mmol) reaction of **1c** was performed to obtain 1.1 g of **2c**; B_2pin_2 (1.65 equiv), IMesCuCl (2 mol %), and LiO*t*-Bu (1.6 equiv) were used. [c]Pure (*E*)-isomer was used.

azepine (**2f**) in good yield. The reaction of imines containing 3-thiophene and 2-thiophene afforded the corresponding *cis*-1-benzo[*b*]azepines (**2g** and **2h**) in moderate to good yield. In addition, the unstable 1-benzo[*b*]azepines (**2i** and **2j**) containing a vinyl and an alkyl substituent were oxidized to the isolable corresponding alcohols with $NaBO_3$·$4H_2O$ (**3i** and **3j**) in moderate yield. Next, different substituents (R^1) on the phenyl ring of the dienyl arene were examined. Substrates with an electron-donating substituent at the *para*-position, relative to the imine moiety, produced **2k** in moderate yield. A methyl substituent at the *para*-position (**1l**) or *ortho*-position (**1m**) to the dienyl group resulted in moderate yields as well. Unfortunately, substrates with either a strong electron-donating methoxy substituent or strong electron-withdrawing fluorine atom at the *para*-position to the dienyl group exhibited poor reactivity.[16]

In addition, less-reactive aryl ketimines were examined and were found to produce trisubstituted 1-benzo[*b*]azepines in good yields as single diastereoisomers under the optimized catalytic conditions (see Scheme 3). Methyl phenyl ketimine (**4a**), cyclic ketimine (**4b**), and ketimines containing an electron-withdrawing (**4c**) or electron-donating substituent (**4d**) resulted in moderate to good yields and excellent diastereoselectivity. The reaction of ketimines containing 3-thiophene and 2-thiophene afforded the corresponding 1-

DOI: 10.1021/acs.orglett.8b03286
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Substrate Scope of the Copper-Catalyzed Borylative Cyclization[a]

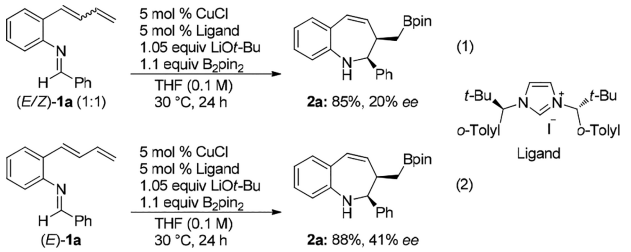


[a]Reactions were conducted on a 0.2 mmol scale. Yields of isolated products are shown.

benzo[*b*]azepines (**5e** and **5f**) in good yields. The relative configuration of **5a** was ascertained by X-ray crystallographic analysis and NOE analysis.

Finally, asymmetric reactions were briefly investigated using the Kündig-type NHC ligand, which previously has been reported to show high efficiency in copper-catalyzed intermolecular allylations of imines (see Scheme 4).[12d] A 1:1

Scheme 4. Asymmetric Copper-Catalyzed Borylative Cyclization[a]

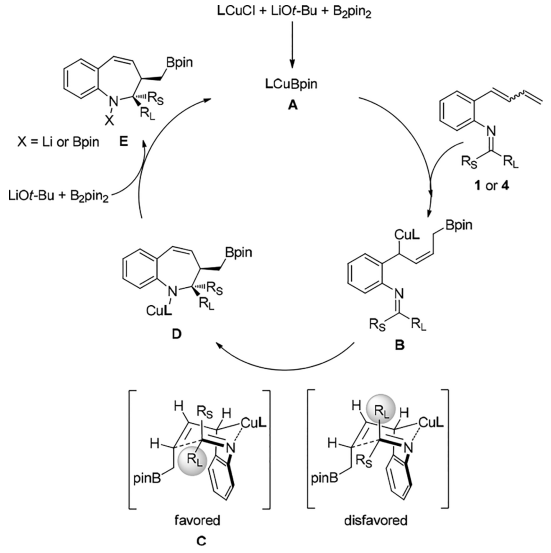


[a]Reactions were conducted on a 0.2 mmol scale. Yields of isolated products are shown. The *ee* values were determined by HPLC analysis.

mixture of (*E*/*Z*)-**1a** was converted to **2a** in 85% yield and 20% ee[17] (eq 1 in Scheme 4). With pure (*E*)-**1a**, a similar yield was obtained, but with an increased ee value (eq 2 in Scheme 4), which indicated that the asymmetric cyclization was affected by the *E*/*Z* ratio of dienyl arene, and the pure isomer could be used for better chiral induction.

The proposed catalytic cycle is shown in Scheme 5. The LCu−Bpin species (**A**) is generated from the reaction of IMes−CuCl, base, and B_2pin_2. This species then undergoes 1,4-borylcupration with the mixture of (*E*/*Z*)-1,3-dienes **1** to produce (*Z*)-σ-allylcopper intermediate **B**.[18] The allylcopper **B**

Scheme 5. Proposed Catalytic Cycle



adds as a nucleophile to the imine intramolecularly to form a cyclized 1-benzo[*b*]azepine **D** through a 6-membered ring transition state **C** with its R_L substituent in the favored equatorial position. Finally, the catalytic cycle is completed by ligand exchange with LiO*t*-Bu and B_2pin_2. The complexation of copper to the imine in the allylcopper intermediate appears to be responsible for 7-membered ring formation via a chairlike transition state.[12c,e,14]

In summary, we have developed a mild and general copper-catalyzed process for the facile construction of 2,3-substituted *cis*-1-benzo[*b*]azepines with excellent diastereoselectivity via NHC−Cu-catalyzed intramolecular borylative cyclization. This process tolerates a broad range of functionalized aryl, alkyl, heterocyclic aldimines, and various ketimines, providing rapid access to 2,3-substituted *cis*-1-benzo[*b*]azepines. In this diastereoselective protocol, a mixture of (*E*/*Z*)-dienyl arenes, instead of pure dienyl arene could be used to deliver high diastereoselectivity. Investigation of the asymmetric intramolecular cyclization is currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03286.

Experimental procedures, characterization of products, and copies of ^{1}H and ^{13}C NMR (PDF)

Accession Codes

CCDC 1863923 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jaesook@skku.edu.

DOI: 10.1021/acs.orglett.8b03286
Org. Lett. XXXX, XXX, XXX−XXX

ORCID

Jaesook Yun: 0000-0003-4380-7878

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by National Research Foundation of Korea (NRF) grants (Nos. NRF-2016R1A2B4011719 and NRF-2016R1A4A1011451), funded by the Korean government (MEST). D.L. thanks the China Scholarship Council (No. 201508260066).

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(15) The relative configuration of **2a** was determined by NOE analysis, see the Supporting Information for details.

(16) Either borylcupration or cyclization step might be affected by the electronic factors of the substituent. See Scheme 5 and the Supporting Information for data: Lee, J.; Radomkit, S.; Torker, S.; DelPozo, J.; Hoveyda, A. H. *Nat. Chem.* **2017**, *10*, 99.

(17) The absolute configuration of *cis*-**2a** is tentatively assigned.

(18) It has been reported that the (*Z*)-σ-allylcopper species is produced by 1,4-borylcupration or 1,4-silylcupration of pure (*E*)-dienes, see: (a) Sardini, S. R.; Brown, M. K. *J. Am. Chem. Soc.* **2017**, *139*, 9823. (b) Liepins, V.; Bäckvall, J.-E. *Eur. J. Org. Chem.* **2002**, *2002*, 3527. The formation of (*Z*)-σ-allylcopper species from (*Z*)-diene was also observed by us. See the Supporting Information for details.

DOI: 10.1021/acs.orglett.8b03286
Org. Lett. XXXX, XXX, XXX−XXX