RESEARCH ARTICLE doi.org/10.1002/adsc.202100812

Advanced Synthesis & Catalysis

Divergent Access to Benzocycles through Copper-Catalyzed Borylative Cyclizations

Wan Seok Yoon,[a] Jung Tae Han,[a] and Jaesook Yun[a,*]

[a] Department of Chemistry and Institute of Basic Science, Sungkyunkwan University, Suwon, 16419, Korea
E-mail: jaesook@skku.edu

Manuscript received: June 30, 2021; Revised manuscript received: August 11, 2021;
Version of record online: ■■, ■■

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202100812

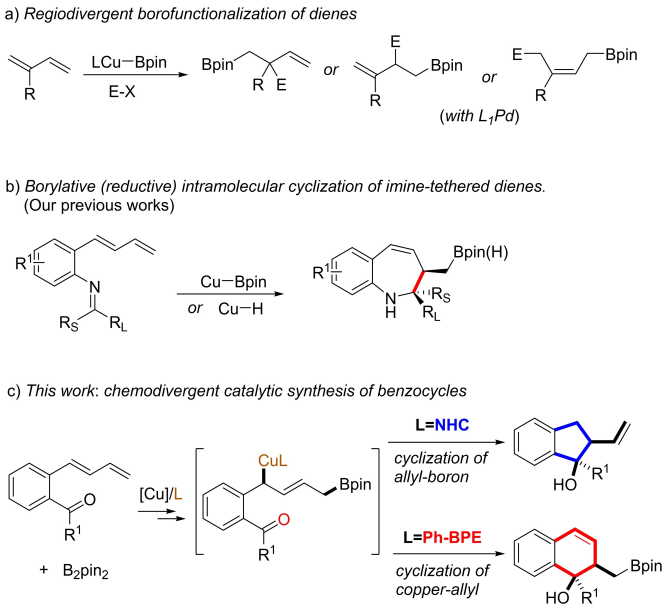
Abstract: A copper-catalyzed chemodivergent approach to five- and six-membered benzocycles from dienyl arenes tethered with a ketone has been developed. Through proper choice of coordinating ligands and catalytic conditions, copper-catalyzed borylative cyclization of a single dienyl arene can be diverted to two different pathways, leading to indanols and dihydronaphthalenols with high stereoselectivity. The chiral bidentate bisphosphine ligand (*S*,*S*)-Ph-BPE was optimal for asymmetric copper-allyl addition to a tethered ketone *via* a boat-like transition state, whereas NHC ligands led to boro-allyl addition producing indanols with high diastereoselectivity.

Keywords: Allylation; Asymmetric Cyclization; Benzocycles; Copper; Divergent Synthesis

Introduction

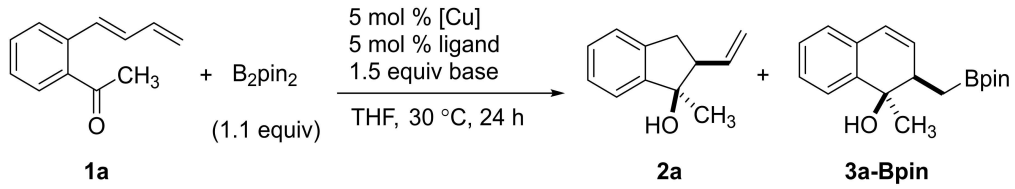
Benzocycles containing five- and six-membered carbocyclic rings are common core structures of biologically active molecules and natural products and thus, serve as attractive targets in organic synthesis and the pharmaceutical industry.[1] While many methods have been extensively practiced for their synthesis,[2] catalytic divergent approaches to variously-sized benzocycles from the same starting material with good stereocontrol are rare and challenging. Since divergent approaches provide great potential to build target molecules efficiently in a single synthetic operation with a slight modification of catalytic conditions,[3] the development of such processes is highly desirable.

Copper-catalyzed difunctionalizations of unsaturated C–C bonds have become valuable synthetic methods due to their high efficiency and synthetic versatility over the past decade.[4] In particular, conjugate dienes as π-substrates are challenging substrates, as they can produce a complex mixture of isomeric products, including (*E*)-, (*Z*)-alkenyl isomers and regioisomers. However, recent advances in copper-catalyzed functionalization of dienes delivered selective formation of a single isomeric product with good diastereo- and/or enantio-control by trapping *in-situ* generated allyl copper intermediates with various electrophiles.[5] In addition, along with the development of ligand-controlled regiodivergent borofunctionalization of terminal alkenes,[6a,b] allenes,[6c,d] and alkynes,[6e] regiodivergent borofunctionalizations of conjugate dienes disclosed by the Procter group and



Scheme 1. Catalyst Controlled Functionalization of Dienes.

Table 1. Optimization.



1a **2a** **3a-Bpin**

entry	conditions	Isolated yield (%) **2a**:**3a-Bpin**[a]	**2a**	**3a**[b]
1[c]	IPrCuCl, LiO*t*Bu	>20:1	57	–
2[c]	SiMesCuCl, LiO*t*Bu	>20:1	61	–
3[c]	IMesCuCl, LiO*t*Bu	>20:1	69	–
4	IMesCuCl, LiO*t*Bu, 1 equiv. MeOH	>20:1	57	–
5	IMesCuCl, LiOMe, 1 equiv. MeOH	>20:1	86	–
6[c]	CuCl, 2 equiv. PPh_3, LiO*t*Bu	>20:1	54	–
7	CuCl, Xantphos, NaO*t*Bu	>20:1	45	–
8	CuCl, (*S*)-BINAP, NaO*t*Bu	1:1.6	–	60 (62% ee)
9	CuCl, (*S*)-Segphos, NaO*t*Bu	1:0.9	–	43 (63% ee)
10	CuCl, (*R,S*)-Josiphos, NaO*t*Bu	1:>20	–	72 (0% ee)
11	CuCl, (*S,S*)-Ph-BPE, NaO*t*Bu	1:>20	–	76 (92% ee)

[a] Determined by crude ^{1}H NMR analysis and reaction was conducted on a 0.2 mmol scale of **1a**.
[b] The corresponding hydroxy compound (**3a**) was obtained by $NaBO_3 \cdot 4H_2O$ oxidation of **3a-Bpin** in THF/H_2O.
[c] 1.05 equiv. of base was used.

Brown group have provided ready access to functionalized regioisomeric derivatives of π-bonds in one operation[7] (Scheme 1a); e.g. borocyanation[7a,b] and boroarylation with palladium cocatalyst.[7c,d]

With our continued interests in the development of new asymmetric synthetic methods using Cu–H and Cu–B catalysts, we recently focused on intramolecular functionalization of dienes with an aryl-tethered functional group.[8] Previously, we reported copper-catalyzed intramolecular borylative[8a,9] and reductive cyclization[8b] of dienes tethered with an imine group affording 7-membered benzazepine derivatives with high diastereo- and enantioselectivity through a strained cyclic transition state (Scheme 1b). In this context, our investigation with dienyl arene compounds with a carbonyl group[8c] that can generate smaller benzocycles *via* borylative cyclization was initiated. Herein, we describe a copper-catalyzed chemodivergent approach to five- and six-membered benzocycles from the same dienyl compounds with a tethered ketone substituent with high stereoselectivity; a simple switch in readily available ligands under catalytic conditions results in a chemodivergent pathway leading to five- and six-membered carbocycles with high selectivity (Scheme 1c).

Results and Discussion

We started our investigation by examining copper-catalyzed borylative coupling of the simple 1,3-dienyl arene compound (**1a**) containing a methyl ketone moiety with bis(pinacolato)diboron (B_2pin_2) by varying ligands for copper (Table 1 and Figure 1). In our initial survey, we focused on NHC (=N-heterocyclic carbene) ligands, which previously led to highly diastereoselective azepine synthesis from imine-tethered arenyl dienes,[8a] and found that NHC ligands gave the unexpected 5-membered cyclic compound **2a** instead of the 6-membered dihydronaphthalenol derivative (**3a-Bpin**) (entry 1–3). Among the screened NHC–CuCl precursors, IMesCuCl afforded **2a** in good yield as the major diastereomer without detectable formation of **3a-Bpin** using LiO*t*Bu as the base (entry 3). We suspected that the formation of **2a** would result from proton sources in the reaction mixture such as *t*BuOH formed from the enolizable ketone moiety

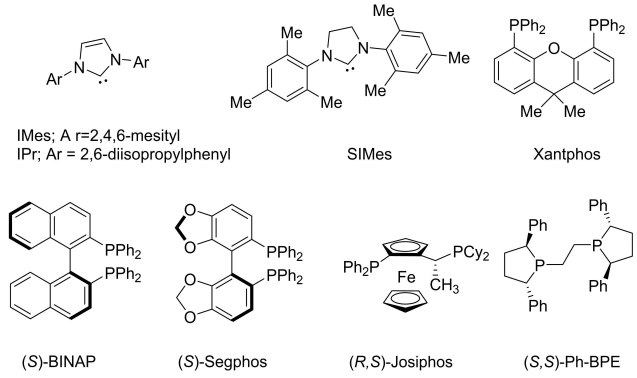


Figure 1. Structures of the Ligands.

by the alkoxide base and inadvertent water, and thus decided to include additional proton sources (entries 4 and 5). Indeed, the addition of 1 equivalent of MeOH with LiOMe as the base offered the best results, yielding **2a** in 86% yield with 96:4 diastereomeric ratio, which was chosen for the optimal conditions for synthesis of 5-membered benzocycles **2** (entry 5).

Phosphine ligands such as PPh_3 and Xantphos also produced **2a**, but in lower yields (entries 6 and 7). When the C_2 symmetric chiral bisphosphine ligands, BINAP and Segphos were used with the NaO*t*Bu base, both **2a** and **3a-Bpin** formed in a ~1:1 ratio *via* ^{1}H NMR analysis, and the corresponding hydroxy compound **3a** was isolated in moderate yield and ee after oxidation instead of unstable **3a-Bpin** (entries 8 and 9). The use of Josiphos ligand was not suitable for the formation of **3a**, yielding a racemic product (0% ee) despite its improved yield. Finally, the optimal ligand for the asymmetric formation of **3a** was found to be (*S*,*S*)-Ph-BPE ligand with a high enantioselectivity (92% ee) and with no detectable formation of **2a**. The relative configuration of **2a**[10] was determined by NOE experiments (See SI, Fig S1) and the absolute configuration of **3a** was determined by X-ray crystal analysis of the corresponding 4-bromobenzoate derivative of **3a**, which contained two molecules in a unit cell (Figure 2).[11]

Having established conditions for **2a** and **3a**, we surveyed the scope of copper-catalyzed chemodivergent intramolecular cyclization of dienyl arenes (**2**) using condition A or B (Scheme 2). First, scaled-up reactions of **1a** under both conditions were carried out and each product was formed with no significant change in yield or enantioselectivity. Dienyl arenes with an alkyl-substituted ketone moiety (R^1 = alkyl; **1b** and **1c**) were suitable for both reactions, yielding each benzocycle in good yield and with high enantioselectivity for dihydronaphthalenols (**3b** and **3c**). Substrates with an aromatic substituent (R^1 = Ar) were appropriate for the formation of corresponding indanols (**2d** and **2e**), but dihydronaphthalenol formation were less efficient, resulting in decreased yield or ee.

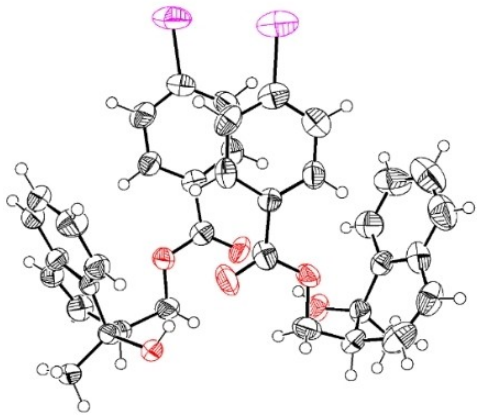
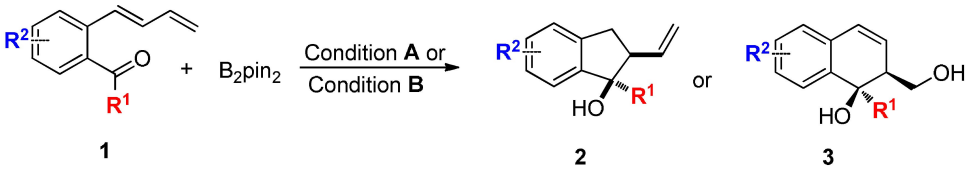


Figure 2. X-ray Structure of 4-bromobenzoate of **3a**.

The effect of different substituents (R^2) on the aromatic ring of dienyl arenes were investigated. In general, all substrates with either electron-donating (**1f–1h**) or electron-withdrawing substituents (**1i–1l**) produced the corresponding indanols (**2f–2l**) in moderate to good yield with high diastereoselectivity under condition A. However, in cases of 6-membered ring formation, substrates with an electron-donating or electron withdrawing group were slightly less efficient than neutral substrates, giving cyclized products (**3**) in moderately reduced yield or ee. Especially, in the case of the strongly electron-withdrawing CF_3-containing substrate **1i**, the intramolecular copper-allyl cyclization was not very effective, forming the indanol byproduct **2i** in a ~1:1 ratio.

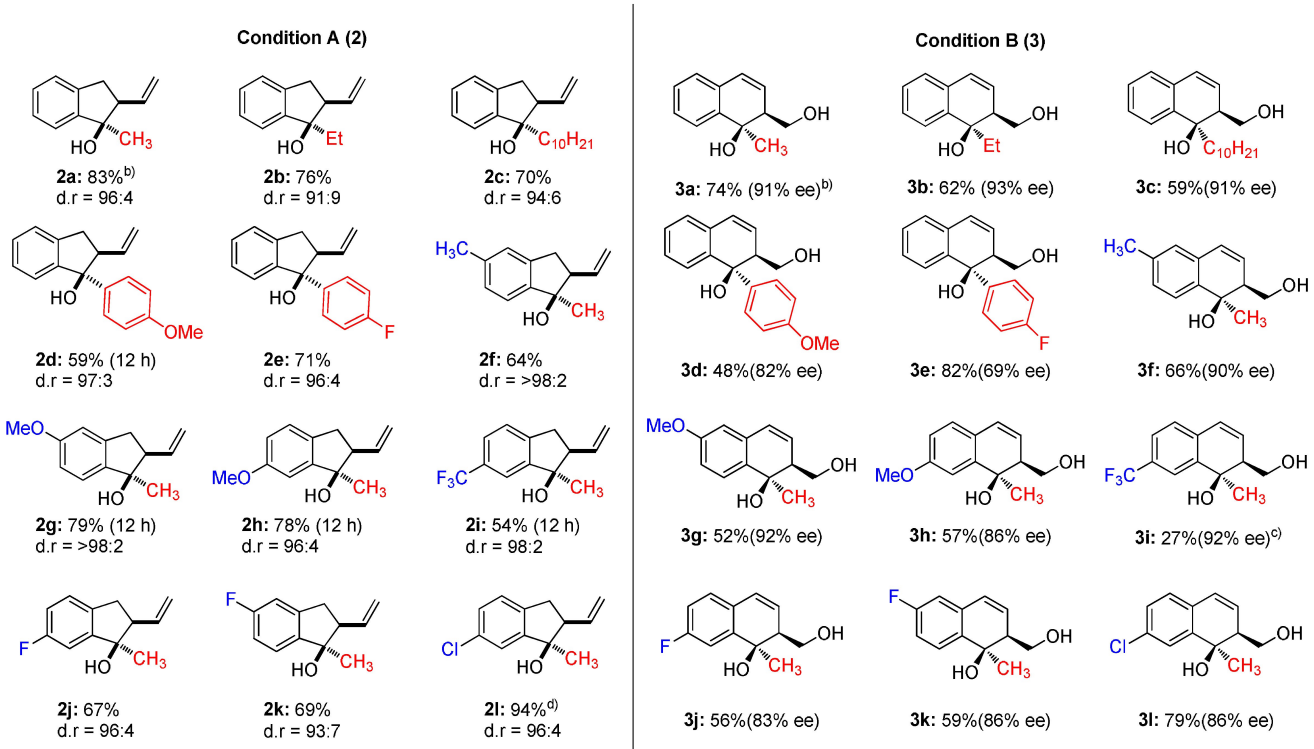
Next, we tried to explain the reaction pathways to benzocycles **2** and **3** (Scheme 3). With IMesCu catalyst, when the reaction was carried out without additional MeOH in a glovebox, a low yield of **2a** was obtained. The yield increased to 67% through the addition of 0.5 equiv. of MeOH. Moreover, the addition of 1 equiv. of MeOD resulted in 66% deuterium incorporation to the benzylic carbon of **2a**, indicating protonation of the benzylic Cu–C bond (Scheme 3a). Therefore, for IMesCu catalyst,[8a] it was proposed that copper-catalyzed intramolecular addition of IMes-copper allyl intermediate **III** was not facile,[12] undergoing protonation of the Cu–C bond by proton sources to yield (*Z*)-allylboronate **IV**.[13,14] Subsequent intramolecular cyclization of the allylboronate[15] to the carbonyl group produced racemic indanols **2** with high diastereoselectivity. Also, DFT calculations showed that IMes-copper allyl complex **III** did not allow structural rotations necessary for the copper-allyl addition, requiring high activation energy of 20.2 kcal/mol (See SI, Fig S4).

In the case of copper-BPE catalyst, copper-allyl addition to the ketone moiety[17] efficiently occurs, yielding dihydronaphthalene derivative (**3a-Bpin**) with good enantioselectivity. Detailed density functional theory (DFT) calculations were carried out (Scheme 3b). Copper-allyl intermediate **I**, a formal 1,4-borocupration product is generated by 1,2-borocupration of the diene **1a** and subsequent allylic isomerization.[8,16] Then, intermediate **I** undergoes intramolecular cyclization to produce the dihydronaphthalenol derivative (**3a**) through copper-catalyzed allylation. Although attaining a favorable transition state was expected to be difficult due to a low level of flexibility, the copper-BPE catalyst was highly efficient for preferred production of **3a** *via* a boat-like transition state with relatively low activation energy of 3.1 kcal/mol (TS-I). Overall, the proposed catalytic cycles for



1 2 3

Condition **A (2)**:
5 mol % IMesCuCl, 1.5 equiv LiOMe, 1 equiv MeOH, THF, rt, 6 h
Condition **B (3)**:
5 mol % CuCl, 5 mol % (*S*,*S*)-Ph-BPE, 1.5 equiv NaO*t*Bu, THF, rt, 24 h; then oxidation with $NaBO_3 \bullet 4H_2O$



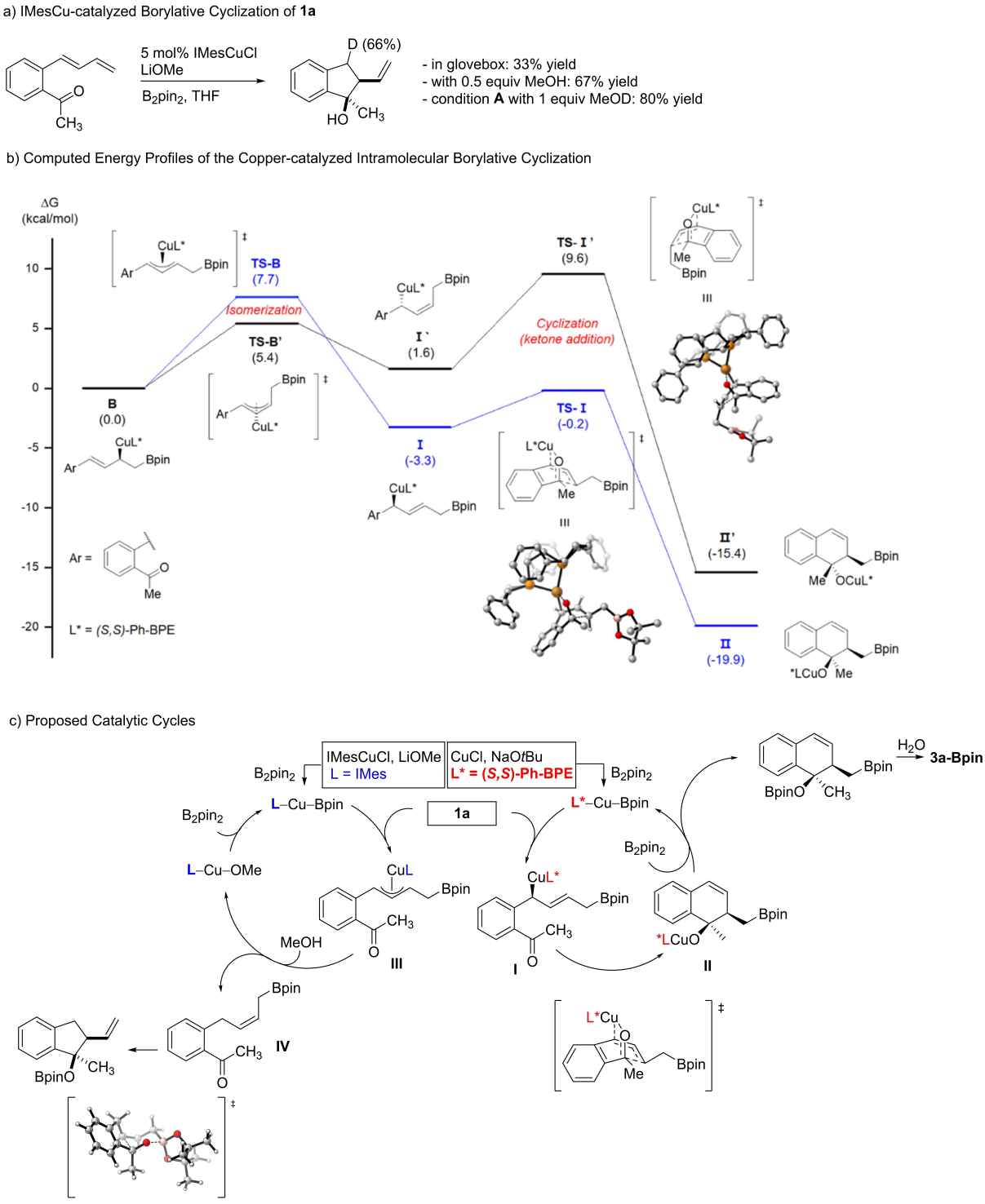
a) All reactions were carried out on a 0.2 mmol scale unless noted otherwise. Diastereomeric ratios of **2** and **3** were determined by ^{1}H NMR analysis of a crude reaction mixture and ee values were determined by chiral HPLC analysis. Diastereomeric ratios of **2** were indicated in each entry and compounds **3** were detected as a single diastereomer (d.r = >20:1) b) The reaction was run on a 2 mmol scale for 24 h. c) The 5-membered indanol **2i** was obtained in 20% yield along with **3i** under condition B. d) The conditions in entry 3 of Table 1 were used.

Scheme 2. Substrate Scope of the Intramolecular Cyclization of Dienyl Arenes (**1**).[a]

the divergent synthesis of benzocycles are summarized in Scheme 3c.

Conclusion

In conclusion, we developed copper-catalyzed chemodivergent intramolecular allyl addition of dienyl arenes with a tethered ketone group. By proper choice of coordinating ligands under catalytic conditions, allyl addition can be diverted to two different pathways, leading to five- and six-membered benzocycles with high stereoselectivity from a single substrate. The bidentate bisphosphine ligand (*S*,*S*)-Ph-BPE was suitable for copper-allyl addition to a tethered ketone to produce dihydronaphthalenol compounds, and rendered the cyclization asymmetric. With NHC ligands, such cyclization is not facile, leading to boroallylation that produces indanols with high diastereoselectivity.



Scheme 3. Mechanistic Investigations and Proposed Catalytic Cycles.

Experimental Section

General Procedure for the Synthesis of Indanol 2 (Scheme 2, Condition A)

A mixture of IMesCuCl (0.01 mmol, 4.0 mg), LiOMe (0.3 mmol, 11.4 mg) and B_2pin_2 (0.22 mmol, 55.8 mg) in anhydrous THF (1 mL) was stirred for 10 min in a Schlenk tube under an atmosphere of N_2. A dienyl arene (**1**) (0.2 mmol) dissolved in anhydrous THF (1.0 mL) was added to the reaction mixture, followed by MeOH (0.2 mmol, 8 μL) and stirred for 6–24 h. Upon completion of the reaction indicated by TLC, the reaction mixture was quenched with water. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined

organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude residue was purified by silica gel chromatography (EtOAc:Hexane = 1:10).

General Procedure for the Synthesis of Dihydronaphthalenol 3 (Scheme2, Condition B)

A mixture of CuCl (0.01 mmol, 1.0 mg), NaO*t*Bu (0.3 mmol, 28.8 mg), (*S*,*S*)-Ph-BPE (0.01 mmol, 5.1 mg) and B_2pin_2 (0.22 mmol, 55.8 mg) in anhydrous THF (1 mL) was stirred for 5 min in a Schlenk tube under an atmosphere of N_2. A dienyl arene (**1**) (0.2 mmol) dissolved in anhydrous THF (1.0 mL) was added to the reaction mixture and stirred for 24 h. And then, to the mixture was added sodium perborate tetrahydrate (3 equiv) and THF:H_2O (2 mL, 1:1). The reaction mixture was stirred for overnight at room temperature. The reaction was quenched with water and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Pinacol was removed by dissolving the crude mixture in MeOH:H_2O (1:1), followed by concentration in vacuo with 65 °C water bath (usually 2–3 cycles).[18] The crude was purified by silica gel chromatography (EtOAc:Hexane = 1:2).

Acknowledgements

This research has been supported by grants from the National Research Foundation of Korea (NRF) (2019R1A2C2005706 and 2019R1A4A2001440).

References

[1] a) A. Kleeman, J. Engel, B. Kutscher, D. Reichert, *Pharmaceutical Substances*; Thieme: New York, **2001**; b) D. J. Faulkner, *Nat. Prod. Rep.* **2002**, *19*, 1–48; c) T. K. Devon, *Handbook of Naturally Occurring Compounds V1*; Elsevier: Amsterdam, **2012**.

[2] a) I. Gallou, C. H. Senanayake, *Chem. Rev.* **2006**, *106*, 2843–2874; b) W. A. L. Otterlo, C. B. Koning, *Chem. Rev.* **2009**, *109*, 3743–3782; c) J.-R. Chen, X.-Q. Hu, L.-Q. Lu, W.-J. Xiao, *Chem. Rev.* **2015**, *115*, 5301–5365; d) E. Aguilar, R. Sanz, M. A. Fernandez-Rodriguez, P. Garcia-Garcia, *Chem. Rev.* **2016**, *116*, 8256–8311; e) X.-D. An, J. Xiao, *Org. Chem. Front.* **2021**, *8*, 1364–1383.

[3] a) B. Baskar, H. J. Bae, S. E. An, J. Y. Cheong, Y. H. Rhee, A. Duschek, S. F. Kirsch, *Org. Lett.* **2008**, *10*, 2605–2607; b) P. Sun, S. Gao, C. Yang, S. Guo, A. Lin, H. Yao, *Org. Lett.* **2016**, *18*, 6464–6467; c) D. Ji, K. Liu, J. Sun, *Org. Lett.* **2018**, *20*, 7708–7711; d) L.-C. Yang, Y.-N. Wang, R. Liu, Y. Luo, X. Q. Ng, B. Yang, Z.-Q. Rong, Y. Lan, Z. Shao, Y. Zhao, *Nat. Chem.* **2020**, *12*, 860–868.

[4] a) F. Wang, P. Chen, G. Liu, *Acc. Chem. Res.* **2018**, *51*, 2036–2046; b) D. Hemming, R. Fritzemeier, S. A. Westcott, W. L. Santos, P. G. Steel, *Chem. Soc. Rev.* **2018**, *47*, 7477–7494; c) Q. Dherbassy, S. Manna, F. J. T. Talbot, W. Prasitwatcharakorn, G. J. P. Perry, D. J. Procter, *Chem. Sci.* **2020**, *11*, 11380–11393; d) Z. Liu, Y. Gao, T. Zeng, K. M. Engle, *Isr. J. Chem.* **2020**, *60*, 219–229.

[5] For a review: a) G. J. P. Perry, T. Jia, D. J. Procter, *ACS Catal.* **2020**, *10*, 1485–1499; For selected examples:; b) Y. Sasaki, C. Zhong, M. Sawamura, H. Ito, *J. Am. Chem. Soc.* **2010**, *132*, 1226–1227; c) L. Jiang, P. Cao, M. Wang, B. Chen, B. Wang, J. Liao, *Angew. Chem. Int. Ed.* **2016**, *55*, 13854–13858; *Angew. Chem.* **2016**, *128*, 14058–14062; d) Y.-Y. Gui, N. Hu, X.-W. Chen, L.-L. Liao, T. Ju, J.-H. Ye, Z. Zhang, J. Li, D.-G. Yu, *J. Am. Chem. Soc.* **2017**, *139*, 17011–17014; e) Y. Huang, K. B. Smith, M. K. Brown, *Angew. Chem. Int. Ed.* **2017**, *56*, 13314–13318; *Angew. Chem.* **2017**, *129*, 13499–13503; f) J.-J. Feng, M. Oestreich, *Angew. Chem. Int. Ed.* **2019**, *58*, 8211–8215; *Angew. Chem.* **2019**, *131*, 8295–8299.

[6] a) R. Sakae, K. Hirano, M. Miura, *J. Am. Chem. Soc.* **2015**, *137*, 6460–6463; b) W. Su, T.-J. Gong, X. Lu, M.-Y. Xu, C.-G. Yu, Z.-Y. Xu, H.-Z. Yu, B. Xiao, Y. Fu, *Angew. Chem. Int. Ed.* **2015**, *54*, 12957–12961; *Angew. Chem.* **2015**, *127*, 13149–13153; c) W. Yuan, S. Ma, *Adv. Synth. Catal.* **2012**, *354*, 1867–1872; d) R. Y. Liu, Y. Yang, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 14077–14080; *Angew. Chem.* **2016**, *128*, 14283–14286; e) W. Su, T.-J. Gong, Q. Zhang, Q. Zhang, B. Xiao, Y. Fu, *ACS Catal.* **2016**, *6*, 6417–6421.

[7] a) T. Jia, Q. He, R. E. Ruscoe, A. P. Pulis, D. J. Procter, *Angew. Chem. Int. Ed.* **2018**, *57*, 11305–11309; *Angew. Chem.* **2018**, *130*, 11475–11479; b) T. Jia, M. J. Smith, A. P. Pulis, G. J. P. Perry, J. Procter, *ACS Catal.* **2019**, *9*, 6744–6750; c) K. B. Smith, M. K. Brown, *J. Am. Chem. Soc.* **2017**, *139*, 7721–7724; d) S. R. Sardini, M. K. Brown, *J. Am. Chem. Soc.* **2017**, *139*, 9823–9826.

[8] a) D. Li, Y. Park, J. Yun, *Org. Lett.* **2018**, *20*, 7526–7529; b) D. Li, Y. Park, W. Yoon, H. Yun, J. Yun, *Org. Lett.* **2019**, *21*, 9699–9703; c) R. K. Acharyya, S. Kim, Y. Park, J. T. Han, J. Yun, *Org. Lett.* **2020**, *22*, 7897–7902.

[9] For reviews on borylative cyclizations: a) E. Buñuel, D. J. Cárdenas, *Eur. J. Org. Chem.* **2016**, 5446–5464; b) Y. Ji, M. Zhang, M. Xing, H. Cui, Q. Zhao, C. Zhang, *Chin. J. Chem.* **2021**, *39*, 391–401.

[10] T. Mita, M. Uchiyama, Y. Sato, *Adv. Synth. Catal.* **2020**, *362*, 1275–1280.

[11] See the Supporting Information for the preparation of compound **4a**, 4-bromobenzoate of **3a**. CCDC 2085917 (**4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[12] See the Supporting Information Figure S3 for the structural optimization of IMes-copper allyl intermediate **III**.

[13] a) K. Semba, M. Shinomiya, T. Fujihara, J. Terao, Y. Tsuji, *Chem. Eur. J.* **2013**, *19*, 7125–7132; b) S. Gao, M. Wang, M. Chen, *Org. Lett.* **2018**, *20*, 7921–7925.

[14] Previously we reported that protoboration of 1-phenyl-1,3-butadiene with IMesCu-Bpin resulted in the formation of the corresponding (*Z*)-allylboronate. See ref. 8a and 8b.

[15] a) A. E. Walts, L. K. Hoong, W. R. Roush, *J. Am. Chem. Soc.* **1985**, *107*, 8186–8190; b) M. A. Adam, A. E. Walts, D. J. Harris, W. R. Roush, *J. Am. Chem. Soc.* **1986**, *108*, 3422–3434; c) S. R. Chemler, W. R. Roush, *Recent Applications of the Allylation Reaction to the Synthesis of Natural Products. In Modern Carbonyl Chemistry*; (Eds.: J. Otera), Wiley-VCH: Weinheim, Germany, **2000**; pp 403–490.

[16] a) C. Li, R. Y. Liu, L. T. Jesikiewicz, Y. Yang, P. Liu, S. L. Buchwald, *J. Am. Chem. Soc.* **2019**, *141*, 5062–5070; b) C. Li, K. Shin, R. Y. Liu, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2019**, *58*, 17074–17080; *Angew. Chem.* **2019**, *131*, 17230–17236.

[17] For intermolecular copper-allyl additions to carbonyl: a) M. Kanai, R. Wada, T. Shibuguchi, M. Shibasaki, *Pure Appl. Chem.* **2008**, *80*, 1055–1062; b) F. Meng, H. Jang, B. Jung, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2013**, *52*, 5046–5051; *Angew. Chem.* **2013**, *125*, 5150–5155; c) B. Fu, X. Yuan, Y. Li, Y. Wang, Q. Zhang, T. Xiong, Q. Zhang, *Org. Lett.* **2019**, *21*, 3576–3580; d) J.-J. Feng, Y. Xu, M. Oestreich, *Chem. Sci.* **2019**, *10*, 9679–9683; e) J. M. Zanghi, S. J. Meek, *Angew. Chem. Int. Ed.* **2020**, *59*, 8451–8455; *Angew. Chem.* **2020**, *132*, 8529–8533.

[18] M. V. Joannou, B. S. Moyer, S. J. Meek, *J. Am. Chem. Soc.* **2015**, *137*, 6176–6179.

RESEARCH ARTICLE

Divergent Access to Benzocycles through Copper-Catalyzed Borylative Cyclizations

Adv. Synth. Catal. **2021**, *363*, 1 – 8

W. S. Yoon, J. T. Han, J. Yun*