Construction 7-Membered Ring via Ni-Al Bimetal-Enabled C-H Cyclization for Synthesis of Tricyclic Imidazoles

Mengchun Ye (✉ mcye@nankai.edu.cn)

Nankai University <https://orcid.org/0000-0002-2019-5365>

Jiang-Fei Li

Nankai University

Wei-Wei Xu

Nankai University

Rong-Hua Wang

Nankai University

Yue Li

Nankai University

Ge Yin

Nankai University

Article

Keywords: synthesis, catalysis, organic chemistry

Posted Date: February 9th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-198647/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Nature Communications on May 24th, 2021. See the published version at <https://doi.org/10.1038/s41467-021-23371-x>.

Abstract

The construction of 7-membered ring via direct C7–H cyclization of benzoimidazoles with alkenes would provide a more atom- and step economical route to tricyclic imidazoles and derivatives that widely exist in a broad range of bioactive molecules. However, transition metal-catalyzed C–H cyclization for medium-ring synthesis has been limited to reactive C–H bonds, instead, the activation of unreactive C–H bonds towards medium synthesis still remains an elusive challenge. Herein, we report a direct construction of 7-membered rings via Ni–Al co-catalyzed unreactive C7–H cyclization of benzoimidazoles with alkenes, providing a series of tricyclic imidazoles in 40–98% yield and with up to 95:5 er.

Introduction

Tricyclic imidazoles and derivatives bearing a 7-membered ring are an important class of structural motifs that widely exist in diverse range of bioactive and material molecules (Fig. 1a).^{1–7} However, due to the difficulty in construction of medium rings that requires overcoming unfavorable entropy and transannular strain,^{8–10} synthetic routes of such tricyclic imidazoles are quite limited. A typical method relies on Friedel-Crafts acylation for cyclization, often requiring multiple synthetic steps and stoichiometric amounts of AlCl₃ catalyst (Fig. 1b).^{11–14} Another alternative is use alkene metathesis to form 7-membered rings, generally needing lengthy routes for both starting material preparation and final product formation (Fig. 1c).¹⁵ Thereby, direct construction of 7-membered ring via C7–H cyclization of benzoimidazoles with alkenes would provide a more straightforward, atom- and step-economical access to tricyclic imidazoles from more easily-accessible substrates (Fig. 1d).

On the other hand, transition metal-catalyzed C–H cyclization for medium-ring synthesis has become an important endeavor and attracted considerable interests during the past two decades,^{16, 17} because such methods can not only allow using more readily available starting materials, but also provide more atom- and step-economical routes (Fig. 2a). Early efforts focused on the cyclization of reactive formyl C–H bonds with alkenes via rhodium catalysis.^{18–28} Until recent years, non-formyl C–H bonds were also able to be activated via nickel catalysis to form 7-membered rings (Fig. 2a).^{29–34} However, these examples were still limited to reactive C–H bonds such as heterocyclic and polyfluoro-aromatic C–H bonds, and moreover, only scattered substrates were reported with in general low to moderate yield and ee. In contrast, the activation of prevalent and unreactive aromatic C–H bonds towards 7-membered ring synthesis still remains an elusive challenge. The difficulty was ascribed to the fact that unreactive aromatic C–H bonds are often more reluctant to be activated by low-valent metals owing to their higher bond strength and weaker acidity.³⁵ To achieve unreactive C7–H bond activation, we envisioned to use a Ni–Al bimetallic synergistic catalysis instead of traditional mono-metal catalysis (Fig. 2b),^{36–44} hoping that the coordination of Al-Lewis acid to the N atom of imidazoles would contribute to decreasing electron density of the aromatic ring, thus promoting C–H bond activation, and as well as proper steric hindrance from C2 substituent of benzoimidazole could reduce unfavorable entropy effect, favoring the formation of medium rings. Herein, we report our latest result: the construction of 7-membered ring via

Ni-Al bimetal-catalyzed unreactive C7-H bond cyclization of benzoimidazoles with alkenes was achieved for the first time, providing a series of tricyclic imidazoles in 40–98% yield and with exclusively *endo* selectivity and up to 95:5 er and (Fig. 2b).

Results

Reaction optimization. We commenced our study by selecting benzoimidazole **1a** as a model substrate, nickel as a catalyst and Al-Lewis acid as a co-catalyst (Fig. 3). A systematic survey on Ni metals, Al Lewis acids, ligands, bases, and other reaction parameters led to the optimal conditions: 10 mol% of Ni(cod)₂, 10 mol% of IPr-HCl, 10 mol% of AlMe₃ and 40 mol% of *t*BuOK in toluene at 130 °C, under which an *endo* cyclization was exclusively achieved, providing tricyclic imidazole **2a** bearing a 7-membered ring in 98% yield (Fig. 3, entry 1).

Control experiments showed that the combination of Ni, IPr, AlMe₃ and *t*BuOK is critical, and the removal of any of them would greatly reduce the yield (entries 2–5). Traditional phosphine ligands such as monophosphines and bidentate phosphines were all ineffective (entries 6 and 7), whereas other N-heterocyclic carbenes were still compatible, albeit with a little lower yields (entries 8 and 9). In addition, in situ formed Ni(0) was also an effective catalyst, yet providing only 42% yield (entry 10). Base acted as another critical role in the reaction. *t*BuOLi was inefficient, whereas *t*BuONa worked well, affording a comparable result to that of *t*BuOK (entries 11 and 12). Notably, more than 10 mol% of *t*BuOK was essential to the reactivity (entries 13–15). The use of 10 mol% of *t*BuOK gave no products (entry 13), instead, leading to an imidazole with free NH group in 5% yield, which was formed from the decomposition of alkene-isomerization substrate. We reasoned that excess *t*BuOK could suppress the isomerization of the terminal alkene as the literature proposed.⁴⁵

Scope of imidazoles and alkenes. With the optimized conditions in hand, various benzoimidazole motifs bearing different substituents on the aromatic ring were investigated first (Fig. 4). Results showed that either electron-donating groups such as methyl (**2b**) and *tert*-butyl (**2c**) or electron-withdrawing groups such as CF₃O (**2d**), F (**2e** to **2h**), CF₃ (**2i**) and carboxylate (**2j**) were well compatible with the reaction, providing the corresponding products in 80–98% yield.

Notably, C2 substituents of benzoimidazoles proved critical to the reactivity. Without C2 substituents, C2-H cyclization would dominate to form a 6-membered ring as we previously reported,⁴¹ further suggesting that C7-H bond was quite unreactive towards Ni catalysis. In general, electron-deficient CF₃ group on C2 position can ensure high reactivity with using only 10 mol% of AlMe₃ co-catalyst, while CF₃ group was not indispensable, and it can be replaced by a broad range of other substituents such as alkyl (**2k** and **2l**), (hetero)aryl (**2m** and **2n**), carbamoyl (**2o** and **2p**), alkoxy (**2q**) and amino (**2r**) groups, providing the corresponding products in 40–79% yield by tuning the amount of AlMe₃. Pleasingly, imidazole-2-ones, which also widely exist in numerous bioactive compounds, were well compatible with the current reaction. When N-protecting groups varied from Me (**2s**), Bn (**2t**), PMP (**2u**) to Ph (**2v**), the

corresponding products can be smoothly obtained in 64–90% yield. In consideration of two symmetrical N atoms in the molecule, dual C–H annulation was then investigated and a tetracyclic product (**2w**) bearing two 7-membered rings can be smoothly achieved, which is not easily accessed by traditional Friedel-Crafts reaction because the second acylation would be quite difficult. Besides simple aryl and alkyl groups, carboxylate group was also tolerated, providing a translocator protein inhibitor (**2x**) in 60% yield.¹

Next, the compatibility of alkene motifs were investigated (Fig. 5). Although internal alkenes were ineffective because of big steric hindrance, various 1,1-disubstituted terminal alkenes proved to be effective. Different types of alkyls such as methyl (**3a**), linear *n*-butyl (**3b**), branched cyclohexyl (**3c**) and functionalized alkyl (**3d**) were well tolerated, delivering the corresponding products in 82–96% yield. Considering that the incorporation of aryl motifs can significantly increase the complexity of molecules, we examined various aryl substituted alkenes (**3e** to **3p**). Results showed that these aryl alkenes bearing either electron-rich groups such as methyl (**3f** to **3h**), *t*Bu (**3i**), Ph (**3j**), methoxy (**3k**), and naphthyl (**3l**) or electron-deficient groups such as CF₃O (**3m**) and F (**3n** to **3p**) at different positions of the aryl ring all proceeded smoothly, providing the corresponding products in 50–90% yield.

Enantioselective attempts. For the synthesis of medium ring, a flexible large ring transition state would be involved, rendering the enantioselective control of such a reaction quite challenging.^{29–34} By surveying a wide range of chiral carbenes, we found that bulky AnIPE was the optimal ligand (see the Supporting Information for details).^{46–48} With this ligand, a series of substrates with various alkene motifs were then tested (Fig. 6). In general, various aryl groups were well compatible with the current reaction, providing the corresponding products in good yields and with 91.5:8.5 to 95:5 er (**3e** to **3q**). However, alkyl groups, albeit still with good yields, would result in slightly decreased ee (**3a**, **3d**, **3r** and **3s**) owing to bigger structural flexibility. The absolute configuration of major enantiomer of the product was assigned to be (*R*) by single crystal X-ray diffraction.

Reaction utility and mechanistic discussion. To demonstrate the utility of the current method, a gram-scale reaction of **1a** was conducted, and a comparable yield was obtained under the standard conditions (Fig. 7a). In addition, tricyclic imidazole derivative **2s** can be easily oxidized at the benzylic position to produce an intermediate **4** in 62% yield, which can be further transformed into various bioactive molecules such as β -2-adrenergic agonists and zilpaterol (Fig. 7b).^{11–14} To gain more insights into the reaction, relevant mechanistic experiments were conducted. Deuterium-labeling experiment showed that C7-D on the aromatic ring was completely transferred to the 7-membered ring, and moreover, no deuterium scrambling was observed at other positions (Fig. 7c), which suggested that an *endo*-insertion of alkene to Ni–H bond could proceed via an irreversible step. Both competitive experiment between equivalent moles of **1a** and *d*₄**1a** and parallel reactions revealed significant kinetic isotope effect (k_H/k_D = 5.75, 4.81, respectively), indicating that the C–H cleavage could be the rate-determining step (Fig. 7d), and it could proceed via oxidative addition mechanism because direct H transfer pathway in general gives low kinetic isotope effect.³⁵ In addition, ¹⁹F NMR spectra of stoichiometric reactions suggested that

nickel could rapidly coordinate to the alkene motif of substrate **1a**, and then initiate next C–H cleavage and alkene insertion (see the Supporting Information). On the basis of these facts, a plausible mechanism was proposed as below (Fig. 7e): substrate **1a** coordinates with AlMe₃ and nickel first, and then facilitates Ni-catalyzed C7–H bond cleavage via oxidative addition process. Subsequent irreversible *endo*-type alkene migratory insertion and reductive elimination generates the Al-coordinated product, which exchanges with another substrate **1a** to initiate a next cycle.

Conclusions

In summary, we have developed a unreactive C7–H bond cyclization of benzoimidazoles with alkenes via Ni–Al bimetallic catalysis, providing a series of tricyclic imidazoles and derivatives bearing a 7-membered ring in 40–98% yield and with up to 95:5 er. The coordination of Al co-catalyst contributes to reduce the electron density of aromatic ring, favoring the activation of unreactive C7–H bond. The development of other C–H cyclization for medium ring synthesis via Ni–Al bimetallic catalysis is underway in our lab.

Methods

General Procedure for Ni-Catalyzed C7–H Cyclization. To a 15 mL oven dried tube in glove box were added Ni(cod)₂ (5.5 mg, 10 mol%), IPr•HCl (8.6 mg, 10 mol%), ^tBuOK (9 mg, 0.08 mmol, 40 mol%), benzoimidazole **1** (0.2 mmol), dry degassed toluene (2.0 mL), and AlMe₃ (1.0 M/hexane, 10 mol% or 60 mol% or 200 mol%). The tube was capped, taken outside the glove box, and stirred at 130 °C for 3 h. After that, the mixture was cooled to r.t., quenched with 2 mL of 5% EDTA disodium salt solution, and filtered through a short plug of silica gel, eluting with EtOAc. The filtration was concentrated in *vacuo* to afford the crude product, which was further purified by flash column chromatography on silica gel (EtOAc/hexanes).

Declarations

Acknowledgments

We thank the National Natural Science Foundation of China (21871145 and 91856104), the Tianjin Applied Basic Research Project and Cutting-Edge Technology Research Plan (19JCZDJC37900) and “the Fundamental Research Funds for the Central Universities” (63191601) for financial support for financial support.

Author contributions

J.-F. L. discovered and developed the reactions. W.-W. X., R.-H. W., Y. L., G. Y. performed part of synthetic experiments. M.Y. conceived, designed the investigations and wrote the manuscript. J.-F. L. wrote the Supplementary Information.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to M.Y.

Competing financial interests

The authors declare no competing financial interests.

References

1. Fukaya, T., Kodo, T., Ishiyama, T., Nishikawa, H., Baba, S., Masumoto, S. Design, synthesis and structure–activity relationship of novel tricyclic benzimidazolone derivatives as potent 18 kDa translocator protein (TSPO) ligands. *Bioorg. Med. Chem.* **21**, 1257–1267 (2013).
2. Kern, C.; Meyer, T.; Droux, S.; Schollmeyer, D.; Miculka, C. Synthesis and Pharmacological Characterization of β 2-Adrenergic Agonist Enantiomers: Zilpaterol. *J. Med. Chem.* **52**, 1773–1777. (2009).
3. Lee, G.-W.; Cho, S.-H.; Kang, H.-R.; Oh, H.-S.; Yang, J.-E. Organic electroluminescent compound and organic electroluminescent device comprising the same. PCT Int. Appl. WO 2019143184 (2019).
4. Zetterberg, F.; Leffler, H.; Nilsson, U. Preparation of triazole α -D-galactosides as inhibitors of galectins. PCT Int. Appl. WO 2018110930 (2018).
5. Casazza, U.; Pedro Ponce, G. Improved method for preparing zilpaterol. PCT Int. Appl. WO 2015174812 (2015).
6. Stoessel, P.; Joosten, D.; Breuning, E.; Kaiser, J. Metal complexes with heterocyclic ligands and their preparation and use in electronic devices. PCT Int. Appl. WO 2014008982 (2014).
7. Toyoda, T.; Tanaka, M.; Fujibayashi, N.; Maruyama, M.; Saji, I.; Antoku, F.; Muto, M.; Oda, M. Preparation of isoindole-1,3-dione derivatives as 5-HT1A receptor agonists. PCT Int. Appl. WO 2008047839 (2008).
8. Molander, G. A. Diverse Methods for Medium Ring Synthesis. *Acc. Chem. Res.* **31**, 603–609 (1998).
9. Chattopadhyay, S. K.; Karmakar, S.; Biswas, T.; Majumdar, K. C.; Rahaman, H.; Roy, B. Formation of Medium-Ring Heterocycles by Diene and Enyne Metathesis. *Tetrahedron* **63**, 3919–3952 (2007).
10. Clarke, A. K.; Unsworth, W. P. A Happy Medium: The Synthesis of Medicinally Important Medium-Sized Rings via Ring Expansion. *Chem. Sci.* **11**, 2876–2881 (2020).
11. Salaski, E. Synthesis of Imidazobenzazepinethiones: A New Series of HIV-1 Reverse Transcriptase Inhibitors. *Tetrahedron Lett.* **36**, 1387–1390 (1995).
12. Krebs, O.; Reuter, K.; Kuenti, P.; Michlig, C. Process for making a crystalline zilpaterol salt. PCT Int. Appl. WO 2010070004 (2010).
13. Boyle, J.; Fenwick, A. E.; Gethin, D. M.; Mccusker, C. F. Preparation of imidazo[4,5,1-jk][1]benzazepin-2(1H)-one derivatives as anabolic agents. PCT Int. Appl. WO 2008044127 (2008).

14. Towson, J. C.; Wong, S.-C.. An improved process for making zilpaterol. PCT Int. Appl. WO 2014095822 (2014).
15. Heald, R.; Price, S.; Safina, B.; Savy, P. P. A.; Seward, E. M.; Sutherlin, D. P.; Waszkowycz, B. U.S. Pat. Appl. Publ. US 20120202785 (2012).
16. Li, R.; Xu, X. T.; Ye, M. C. Construction of Medium Rings via Transition Metal-Catalyzed Insertion of π -Unsaturated Compounds into C–H Bonds. *Chin. J. Org. Chem.* **40**, 3196–3202 (2020).
17. Meyer, A. G.; Bissember, A. C.; Hyland, C. J. T.; Williams, C. C.; Szabo, M.; Pearsall, M. A.; Hyland, I. K.; Olivier, W. J. Seven-membered rings. *Prog. Heterocycl. Chem.* **31**, 597–647 (2020).
18. Aloise, A. D.; Layton, M. E.; Shair, M. D. Synthesis of Cyclooctenones Using Intramolecular Hydroacylation. *J. Am. Chem. Soc.* **122**, 12610–12611 (2000).
19. Sato, Y.; Oonishi, Y.; Mori, M. A New Method for the Synthesis of Cycloheptenones by Rh^{I} -Catalyzed Intramolecular Hydroacylation of 4,6-Dienals. *Angew. Chem. Int. Ed.* **41**, 1218–1221 (2002).
20. Crépin, D.; Dawick, J.; Aïssa, C. Combined rhodium-catalyzed carbon-hydrogen activation and β -carbon elimination to access eight-membered rings. *Angew. Chem. Int. Ed.* **49**, 620–623 (2010).
21. Bendorf, H. D.; Colella, C. M.; Dixon, E. C.; Marchetti, M.; Matukonis, A. N.; Musselman, J. D.; Tiley, T. A. Chelation-assisted intramolecular hydroacylation: synthesis of medium ring sulfur heterocycles. *Tetrahedron Lett.* **43**, 7031–7034 (2002).
22. Bendorf, H. D.; Ruhl, K. E.; Shurer, A. J.; Shaffer, J. B.; Duffin, T. O.; LaBarte, T. L.; Maddock, M. L.; Wheeler, O. W. Amine-directed intramolecular hydroacylation of alkenes and alkynes. *Tetrahedron Lett.* **53**, 1275–1277 (2012).
23. Shen, Z. M.; Khan, H. A.; Dong, V. M. Rhodium-catalyzed carbonyl hydroacylation: an enantioselective approach to lactones. *J. Am. Chem. Soc.* **130**, 2916–2917 (2008).
24. Shen, Z. M.; Dornan, P. K.; Khan, H. A.; Woo, T. K.; Dong, V. M. Mechanistic insights into the rhodium-catalyzed intramolecular ketone hydroacylation. *J. Am. Chem. Soc.* **131**, 1077–1091 (2009).
25. Coulter, M. M.; Dornan, P. K.; Dong, V. M. Rh-Catalyzed Intramolecular Olefin Hydroacylation: Enantioselective Synthesis of Seven- and Eight-Membered Heterocycles. *J. Am. Chem. Soc.* **131**, 6932–6933 (2009).
26. Khan, H. A.; Kou, K. G. M.; Dong, V. M. Nitrogen-directed ketone hydroacylation: Enantioselective synthesis of benzoxazecinones. *Chem. Sci.* **2**, 407–410 (2011).
27. Arnold, J. S.; Mwenda, E. T.; Nguyen, H. M. Rhodium-Catalyzed Sequential Allylic Amination and Olefin Hydroacylation Reactions: Enantioselective Synthesis of Seven-Membered Nitrogen Heterocycles. *Angew. Chem. Int. Ed.* **53**, 3688–3692 (2014).
28. Beletskiy, E. V.; Sudheer, C.; Douglas, C. J. Cooperative Catalysis Approach to Intramolecular Hydroacylation. *J. Org. Chem.* **77**, 5884–5893 (2012).
29. Shen, D.; Zhang, W. B.; Li, Z. Y.; Shi, S. L.; Xu, Y. J. Nickel/NHC-Catalyzed Enantioselective Cyclization of Pyridones and Pyrimidones with Tethered Alkenes. *Adv. Synth. Catal.* **362**, 1125–1130 (2020).

30. Cai, Y.; Ye, X. D.; Liu, S.; Shi, S. L. Nickel/NHC-Catalyzed Asymmetric C-H Alkylation of Fluoroarenes with Alkenes: Synthesis of Enantioenriched Fluorotetralins. *Angew. Chem. Int. Ed.* **58**, 13433–13437 (2019).
31. Zhang, W. B.; Yang, X. T.; Ma, J. B.; Su, Z. M.; Shi, S. L. Regio- and Enantioselective C-H Cyclization of Pyridines with Alkenes Enabled by a Nickel/N-Heterocyclic Carbene Catalysis. *J. Am. Chem. Soc.* 2019, **141**, 5628–5634 (2019).
32. Diesel, J.; Grosheva, D.; Kodama, S.; Cramer, N. A Bulky Chiral N-Heterocyclic Carbene Nickel Catalyst Enables Enantioselective C-H Functionalizations of Indoles and Pyrroles. *Angew. Chem. Int. Ed.* **58**, 11044–11048 (2019).
33. Diesel, J.; Finogenova, A. M.; Cramer, N. Nickel-Catalyzed Enantioselective Pyridone C-H Functionalizations Enabled by a Bulky N-Heterocyclic Carbene Ligand. *J. Am. Chem. Soc.* **140**, 4489–4493 (2018).
34. Donets, P. A.; Cramer, N. Ligand-Controlled Regiodivergent Nickel-Catalyzed Annulation of Pyridones. *Angew. Chem. Int. Ed.* **54**, 633–637 (2015).
35. Saper, N. I.; Ohgi, A.; Small, D. W.; Semba, K.; Nakao, Y.; Hartwig, J. F. Nickel catalysed anti-Markovnikov hydroarylation of unactivated alkenes with unactivated arenes facilitated by non-covalent interactions. *Nat. Chem.* **2020**, 12, 276–283.
36. Nakao, Y.; Kanyiva, K. S.; Hiyama, T. A Strategy for C–H Activation of Pyridines: Direct C-2 Selective Alkenylation of Pyridines by Nickel/Lewis Acid Catalysis. *J. Am. Chem. Soc.* **130**, 2448–2449 (2008).
37. Nakao, Y.; Idei, H.; Kanyiva, K. S.; Hiyama, T. Hydrocarbamylation of Unsaturated Bonds by Nickel/Lewis-Acid Catalysis. *J. Am. Chem. Soc.* **131**, 5070–5071 (2009).
38. Tsai, C. C.; Shih, W. C.; Fang, C. H.; Li, C. Y.; Ong, T. G.; Yap, G. P. A. Bimetallic Nickel Aluminum Mediated Para-Selective Alkenylation of Pyridine: Direct Observation of η^2, η^1 -Pyridine Ni(0)-Al(III) Intermediates Prior to C-H Bond Activation. *J. Am. Chem. Soc.* **132**, 11887–11889 (2010).
39. Yang, L.; Semba, K.; Nakao, Y. para-Selective C–H Borylation of (Hetero)Arenes by Cooperative Iridium/Aluminum Catalysis. *Angew. Chem., Int. Ed.* **56**, 4853–4857 (2017).
40. Liu, Q.-S.; Wang, D.-Y.; Yang, Z.-J.; Luan, Y.-X.; Yang, J.-F.; Li, J.-F.; Pu, Y.-G.; Ye, M. Ni–Al Bimetallic Catalyzed Enantioselective Cycloaddition of Cyclopropyl Carboxamide with Alkyne. *J. Am. Chem. Soc.* **139**, 18150–18153 (2017).
41. Wang, Y.-X.; Qi, S.-L.; Luan, Y.-X.; Han, X.-W.; Wang, S.; Chen, H.; Ye, M. Enantioselective Ni–Al Bimetallic Catalyzed exo-Selective C–H Cyclization of Imidazoles with Alkenes. *J. Am. Chem. Soc.* **140**, 5360–5364 (2018).
42. Chen, H.; Wang, Y.-X.; Luan, Y.-X.; Ye, M. Enantioselective Twofold C–H Annulation of Formamides and Alkynes without Built-in Chelating Groups. *Angew. Chem., Int. Ed.* **59**, 9428–9432 (2020).
43. Zhang, T.; Luan, Y.-X.; Zheng, S.-J.; Peng, Q.; Ye, M. Chiral Aluminum Complex Controls Enantioselective Nickel-Catalyzed Synthesis of Indenes: C–CN Bond Activation. *Angew. Chem., Int. Ed.* **59**, 7439–7443 (2020).

44. Wang, Y.-X.; Ye, M. Recent Advances in Ni–Al Bimetallic Catalysis for Unreactive Bond Transformation. *Sci. China: Chem.* **61**, 1004–1013 (2018).
45. Schramm, Y.; Takeuchi, M.; Semba, K.; Nakao, Y.; Hartwig, J. F. Anti-Markovnikov Hydroheteroarylation of Unactivated Alkenes with Indoles, Pyrroles, Benzofurans, and Furans Catalyzed by a Nickel–N-Heterocyclic Carbene System. *J. Am. Chem. Soc.* **137**, 12215–12218 (2015).
46. Yao, W. W.; Li, R.; Li, J. F.; Sun, J.; Ye, M. NHC ligand-enabled Ni-catalyzed reductive coupling of alkynes and imines using isopropanol as a reductant. *Green Chem.* **21**, 2240–2244 (2019).
47. Cai, Y.; Yang, X.-T.; Zhang, S.-Q.; Li, F.; Li, Y.-Q.; Ruan, L.-X.; Hong, X.; Shi, S.-L. Copper-Catalyzed Enantioselective Markovnikov Protoboration of α -Olefins Enabled by a Buttressed N-Heterocyclic Carbene Ligand. *Angew. Chem., Int. Ed.* **57**, 1376–1380 (2018).
48. Cai, Y.; Zhang, J.-W.; Li, F.; Liu, J.-M.; Shi, S.-L. Nickel/N-Heterocyclic Carbene Complex-Catalyzed Enantioselective Redox-Neutral Coupling of Benzyl Alcohols and Alkynes to Allylic Alcohols. *ACS Catal.* **9**, 1–6 (2019).

Figures

Figure 1

Synthesis of tricyclic imidazoles and derivatives bearing a 7-membered ring. a, Tricyclic imidazoles bearing a 7-member ring in bioactive molecules and materials. b, Typical method I: Friedel-Crafts reaction. c, Typical method II: alkene metathesis reaction. d, Proposed direct C-H cyclization.

Figure 2

Transition metal-catalyzed C-H cyclization for medium ring synthesis. a, Reactive C-H bond activation. b, Our proposed Ni-Al bimetallic catalysis and direct C7-H cyclization for synthesis of tricyclic imidazoles bearing a 7-membered ring (this work).

<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;"> <p>1a</p> </div> <div style="text-align: center;"> $\xrightarrow[\text{AlMe}_3 (10 \text{ mol\%}), \text{}^t\text{BuOK} (40 \text{ mol\%})]{\text{Ni(cod)}_2 (10 \text{ mol\%}), \text{IPr}\cdot\text{HCl} (10 \text{ mol\%})}$ toluene, 130 °C, N₂ "Standard conditions" </div> <div style="text-align: center;"> <p>2a</p> </div> </div>		
entry	deviation from the standard condition	yield (%)
1	none	98
2	without Ni(cod) ₂	0
3	without IPr·HCl	0
4	without ^t BuOK	0
5	without AlMe ₃	38
6	Ph ₃ P or Cy ₃ P instead of IPr·HCl	0
7	dppe or BINAP instead of IPr·HCl	0
8	IMes·HCl instead of IPr·HCl	82
9	SiPr·HCl instead of IPr·HCl	86
10	NiBr ₂ ·DME/Zn instead of Ni(cod) ₂	42
11	^t BuONa instead of ^t BuOK	98
12	^t BuOLi instead of ^t BuOK	0
13	^t BuOK (10 mol%)	0
14	^t BuOK (20 mol%)	56
15	^t BuOK (30 mol%)	86

Figure 3

Reaction optimization. Reaction conditions: 1a (0.20 mmol), toluene (1.0 mL), under N₂ for 3 h. Yield was determined by ¹H NMR analysis with CH₂Br₂ as the internal standard.

Figure 4

Scope of imidazoles. Reaction conditions: **1** (0.20 mmol), toluene (1.0 mL) under N_2 for 3 h. Yield of isolated products. * AlMe_3 (200 mol%) was used. † AlMe_3 (60 mol%) was used. ‡ AlMe_3 (100 mol%) and $t\text{BuOK}$ (80 mol%) were used.

Figure 5

Scope of alkynes. Reaction conditions: **1** (0.2 mmol), toluene (1.0 mL) under N_2 for 3 h. Yield of isolated products.

Figure 6

Enantioselective control. Reaction conditions: **1** (0.20 mmol), $\text{Ni}(\text{cod})_2$ (10 mol%), $\text{AnIPE}\cdot\text{HCl}$ (10 mol%), AlMe_3 (80 mol%), $t\text{BuOK}$ (40 mol%), toluene (1.0 mL) at 130 °C under N₂ for 3 h. Yield of isolated products. Ee was determined by chiral HPLC.

Figure 7

Synthetic utility and mechanistic experiments. a, Gram-scale reaction b, product transformation. c, Deuterium labeling experiments d, Kinetic isotope effect. e, Proposed mechanism

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Slimidazole21.pdf](#)
- [p20181121b.cif](#)
- [GraphicalAbstract.jpg](#)