Construction 7-membered ring via Ni–Al bimetal-enabled C–H cyclization for synthesis of tricyclic imidazoles

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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.
Tricyclic imidazoles and derivatives bearing a 7-membered ring are an important class of structural motifs that widely exit 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 AlCl\(_3\) catalyst (Fig. 1b)\(^11\)–\(^14\). Another alternative is to 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

**Fig. 1 Synthesis of tricyclic imidazoles and derivatives bearing a 7-membered ring.** a Tricyclic imidazoles bearing a 7-membered ring in bioactive molecules and materials. b Typical method I: Friedel-Crafts reaction. c Typical method II: alkene metathesis reaction. d Medium ring synthesis via transition metal-catalyzed cyclization of reactive C–H bonds. e Ni-Al bimetal-catalyzed direct C7–H cyclization for synthesis of tricyclic imidazoles bearing a 7-membered ring (this work).
a more straightforward, atom- and step-economical access to tricyclic imidazoles from more easily-accessible substrates. However, transition metal-catalyzed C–H cyclization for medium-ring synthesis has been a challenging goal during the past two decades. Early efforts focused on the cyclization of reactive formyl C–H bonds with alkenes via rhodium catalysis. Until recent years, non-formyl C–H bonds were also able to be activated via nickel catalysis to form 7-membered rings, while 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.

Here, we show that the construction of 7-membered ring via Ni–Al bimetal-catalyzed unreactive C7–H bond cyclization of benzoimidazoles with alkenes via rhodium catalysis. We commenced our study by selecting benzoimidazole 1a as a model substrate, nickel as a catalyst and Al-Lewis acid as a co-catalyst. As системatics 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 tBuOK 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 (entry 1).

Control experiments showed that the combination of Ni, IPr, AlMe3 and tBuOK is critical, and the removal of any of them would greatly reduce the yield. Traditional phosphine ligands such as monophosphines and bidentate phosphines were all ineffective, whereas other N-heterocyclic carbenes were still compatible, albeit with a little lower yields. In situ formed Ni(0) was also an effective catalyst, yet providing only 42% yield. Base acted as another critical role in the reaction. tBuOLi was inefficient, whereas tBuONa worked well, affording a comparable result to that of tBuOK. Notably, more than 10 mol% of tBuOK was essential to the reactivity. The use of 10 mol% of tBuOK gave no products, instead, leading to an imidazole with free NH group in 5% yield, which was formed from the decomposition of alkene.

**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. 2). 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 tBuOK 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 (entry 1).

Control experiments showed that the combination of Ni, IPr, AlMe3 and tBuOK 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. tBuOLi was inefficient, whereas tBuONa worked well, affording a comparable result to that of tBuOK (entries 11 and 12). Notably, more than 10 mol% of tBuOK was essential to the reactivity (entries 13–15). The use of 10 mol% of tBuOK 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.

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. 3).

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 reported41, 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% yield1.

Next, the compatibility of alkene motifs were investigated (Fig. 4). Although internal and trisubstituted 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–3p). Results showed that these aryl alkenes bearing either electron-rich groups such as methyl (3f–3h), tBu (3i), Ph (3j), methoxy (3k), and naphthyl (3l) or electron-deficient groups such as CF₃O (3m) and F (3n–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 challenging29–34. By surveying a wide range of chiral carbenes, we found that bulky ANIPE, previously developed by Shi and Cramer groups39–41, was the optimal ligand (see the Supplementary Information for details). With this ligand, a series of substrates with various alkene motifs were then tested (Fig. 5). 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 ((R)-3e to (R)-3g). However, alkyl groups, albeit still with good yields, would result in slightly decreased ee ((R)-3a, (R)-3d, (R)-3r and (R)-3s) owing to bigger structural flexibility. The (R) absolute configuration of major enantiomer of the product was determined 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. 6a). 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. 6b)\(^\text{11-14}\). In addition, bioactive molecule, translocator protein inhibitor (2x in Fig. 3), can be easily accessed from readily available imidazole-2-one through the current method.

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. 6c), 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 \( \text{1a} \) and \( \text{d}_4\text{-1a} \) and parallel reactions revealed significant kinetic isotope effect \( (k_{\text{H}}/k_{\text{D}} = 5.75, 4.81, \text{ respectively}) \), indicating that the C–H cleavage could be the rate-determining step (Fig. 6d), and it could proceed via oxidative addition mechanism because direct H transfer pathway in general gives low kinetic isotope effect\(^{35}\). In addition, \( ^{19}\text{F} \) NMR spectra of stoichiometric reactions suggested that nickel could rapidly coordinate to the alkene motif of substrate \( \text{1a} \), and then initiate next C–H cleavage and alkene insertion (see the Supplementary Information). On the basis of these facts, a plausible mechanism was proposed as below (Fig. 6e): substrate \( \text{1a} \) coordinates with AlMe\(_3\) and nickel first, and then facilitates Ni-catalyzed C7–H bond cleavage via oxidative addition process. Subsequent

**Fig. 6 Synthetic utility and mechanistic experiments.**

- **a** Gram-scale reaction.
- **b** Product transformation.
- **c** Deuterium labeling experiments.
- **d** Kinetic isotope effect.
- **e** Proposed mechanism.
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.

Methods

General procedure for Ni-catalyzed C7–H cyclization. To a 15 mL oven dried tube in glove box were added 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 rt., 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).

Data availability

The authors declare that the data supporting the findings of this study are available within the article and its Supplementary Information file. For the experimental procedures, data of NMR and HPLC analysis, see Supplementary Methods in Supplementary Information file. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition number CCDC 2009572. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures/.

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References

1. Fukaya, T. et al. Design, synthesis and structure–activity relationship of novel tricyclic benzimidazolam 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 p2-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. WO2019143184 (2019).
4. Zetterberg, F., Lefl, H. & Nilsson, U. Preparation of triazole α-D-galactosides as inhibitors of galectins. PCT Int. Appl. WO2018110930 (2018).
5. Casazza, U. & Pedro Ponce, G. Improved method for preparing zilpaterol. PCT Int. Appl. WO2015174812 (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. WO2014008982 (2014).
7. Toyoda, T. et al. Preparation of isouido-1,3-diene derivatives as 5-HT1A receptor agonists. PCT Int. Appl. WO2008087439 (2008).
8. Molander, G. A. Diverse methods for medium ring synthesis. Acc. Chem. Res. 31, 603–609 (1998).
9. Chattopadhyay, S. K. et al. Formation of medium-ring heterocycles by diene 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 imidazobenzazepinones: 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. WO2007070004 (2010).
13. Boyle, J., Fenwick, A. E., Gethin, D. M. & McCusker, C. F. Preparation of imidazo[4,5-1:4:5-k1][1]benzazepin-2(1H)-one derivatives as analagobic antibacterials. PCT Int. Appl. WO2008044127 (2008).
14. Towson, J. C. & Wong, S.-C. An improved process for making zilpaterol. PCT Int. Appl. WO2014095822 (2014).
15. Heald, R. et al. Preparation of heterocyclic compounds as selective inhibitors of the p110 delta isoform of PI3K for treating inflammation, immune diseases and cancers. U.S. Pat. Appl. Publ. US20120207275 (2012).
16. Li, R., Xu, X. T. & Ye, M. C. Construction of medium rings via transition metal-catalyzed insertion of α-unsaturated compounds into C–H bonds. Chem. J. Org. Chem. 40, 3196–3202 (2020).
17. Meyer, A. G. et al. Seven-membered rings. Prog. Heterocycl. Chem. 31, 597–647 (2020).
44. 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).
45. 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).
46. Wang, Y.-X. & Ye, M. Recent advances in Ni–Al bimetallic catalysis for unreactive bond transformation. *Sci. China. Chem.* **61**, 1004–1013 (2018).
47. Hu, Y. & Wang, C. Bimetallic C–H activation in homogeneous catalysis. *Acta Phys. Chim. Sin.* **35**, 913–922 (2019).
48. 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).
49. 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).
50. Cai, Y. et al. Copper-catalyzed enantioselective markovnikov protoboration of α-olefins enabled by a buttressed N-heterocyclic carbene ligand. *Angew. Chem. Int. Ed.* **57**, 1376–1380 (2018).
51. 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).

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**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.

**Competing interests**

The authors declare no competing interests.

**Additional information**

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