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Enantioselective Ni−Al Bimetallic Catalyzed *exo*-Selective C−H Cyclization of Imidazoles with Alkenes

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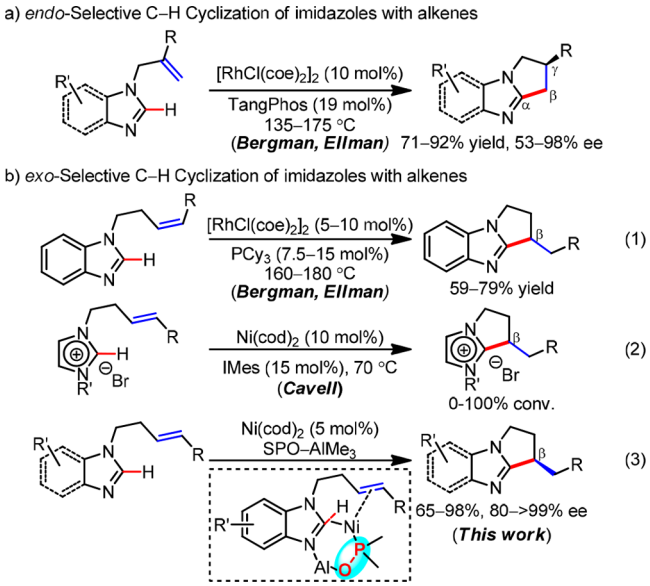
Supporting Information

ABSTRACT: A Ni−Al bimetallic catalyzed enantioselective C−H *exo*-selective cyclization of imidazoles with alkenes has been developed. A series of bi- or polycyclic imidazoles with *β*-stereocenter were obtained in up to 98% yield and >99% ee. The bifunctional SPO ligand-promoted bimetallic catalysis proved to be critical to this challenging stereocontrol.

Bi- or polycyclic imidazole moiety with a stereocenter at the *β*-position to the heteroatom N has been found in a wide range of bioactive molecules and chiral nucleophilic catalysts (see the Supporting Information).[1] However, traditional synthetic methods relying on either condensation reactions or multiple-step ring elaborations rarely provide an efficient stereocontrol for *β*-stereocenter, so that chiral starting materials or chiral resolution technique has to be used in most cases.[1] In 2001, Bergman and Ellman group gave a pioneering report on Rh-catalyzed intramolecular C−H alkylation of imidazole with alkene, providing an elegant method for the synthesis of polycyclic imidazoles with either *β*- or *γ*-stereocenter.[2] Subsequently, they succeeded in achieving an enantioselective control for the *γ*-stereocenter construction by using a unique chiral TangPhos ligand (Scheme 1a).[3−6] However, this asymmetric method is not applicable for the construction of more sterically hindered *β*-stereocenter (Scheme 1b, eq 1), probably because harsher conditions is required, leading to a more challenging stereocontrol.[2,3] Inspired by Cavell's work in which a mild *exo*-selective cyclization was obtained by using imidazole salts as substrate and nickel(0) as catalyst (eq 2),[7] we envisioned that a Lewis acid-activated imidazole could be used as a substrate for developing a mild Ni-catalyzed enantioselective *exo*-selective C−H cyclization to create the challenging *β*-stereocenter in the presence of chiral ligand.

However, although nickel metal has been widely used in numerous coupling reactions during recent years owing to its being an inexpensive, low-toxic and versatile metal catalyst,[8] the efficiency of nickel catalyst is pretty sensitive to ligand structure, often leading to a very limited selection of both nonchiral and chiral ligands.[9] Recently, an air-stable secondary phosphine oxide (SPO) has attracted intensive attention because it not only can be easily prepared from known chiral backbones but also plays a powerful phosphine ligand role in the reaction through in situ tautomerism between its pentavalent and trivalent tautomer especially in the presence of Lewis acid.[10]

Scheme 1. Selective C−H Cyclization of Imidazoles with Alkenes



After the seminal work on Ni−Al bimetallic catalysis by Hiyama and Nakao,[11−13] Cramer and co-workers made an important breakthrough in this field to find that a diamine-derived secondary phosphine oxide (SPO) ligand could act as a bifunctional ligand to combine Ni and Al for a highly efficient asymmetric control in the hydrocarbamoylation of alkenes.[14] Very recently, our group also found that a naphthyl-containing Taddol-derived SPO ligand greatly facilitated a Ni−Al catalyzed enantioselective cycloaddition of cyclopropyl amide with alkyne.[15] To continue exploring SPO-bimetallic catalysis, herein we report the first example of enantioselective *exo*-selective C−H cyclization of imidazole with alkenes, in which a proposed bis(*t*-butyl)phenyl-containing Taddol-SPO ligand promoted Ni−Al bimetallic catalysis could enable this excellent enantioselective control of *β*-stereocenter (eq 3).

We commenced our studies by treatment of homoallylic tethered benzoimidazole **1a** with 10 mol % of $Ni(cod)_2$ and various Lewis acid promoters (Table 1 and also see the Supporting Information). Commonly used $AlMe_3$ was found to

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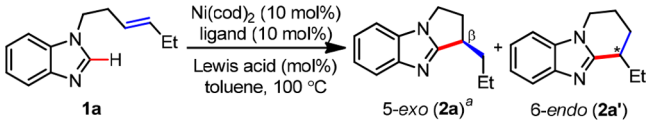
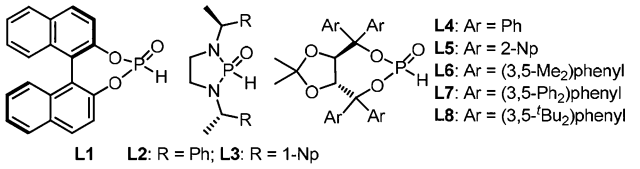
Table 1. Conditions Optimization



entry	L.A. (mol%)	ligand	yield (%, **2a**)[b]	ee (%, **2a**)[c]	yield (%, **2a'**)[b]
1	$AlMe_3$ (100)	N/A	19		0
2	$AlMe_3$ (40)	N/A	22		0
3	$AlMe_3$ (20)	N/A	10		0
4	$AlMe_3$ (40)	PCy_3	15		0
5	$AlMe_3$ (40)	PPh_3	7		0
6	$AlMe_3$ (40)	IPr	45		23
7	$AlMe_3$ (40)	IMes	17		9
8	$AlMe_3$ (40)	$Ph_2P(O)H$	51		0
9	$AlMe_3$ (40)	$Cy_2P(O)H$	46		0
10	$AlMe_3$ (40)	**L1**	7		0
11	$AlMe_3$ (40)	**L2**	78	12	0
12	$AlMe_3$ (40)	**L3**	88	16	0
13	$AlMe_3$ (40)	**L4**	87	5	0
14	$AlMe_3$ (40)	**L5**	58	66	0
15	$AlMe_3$ (40)	**L6**	89	12	0
16	$AlMe_3$ (40)	**L7**	99	90	0
17	$AlMe_3$ (40)	**L8**	92	97	0
18[d]	$AlMe_3$ (40)	**L8**	90	97	0
19[d]	$AlMe_3$ (20)	**L8**	92	97	0
20[d]	$AlMe_3$ (10)	**L8**	86	97	0

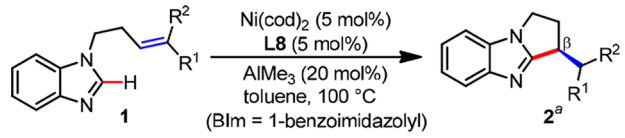


[a]Reaction conditions: **1a** (0.2 mmol), toluene (2 mL), under N_2 for 1 h. [b]Yield was determined by ^1H NMR using CH_2Br_2 as the internal standard. [c]Determined by chiral HPLC. [d]$Ni(cod)_2$ (5 mol %) and L8 (5 mol %).

be a better one and the desired product **2a** was indeed observed in 19% yield with exclusively *exo*-selectivity (entry 1). Decreasing the loading of $AlMe_3$ to 40 mol % did not have a big influence on the reaction, whereas less than 40 mol % led to a relatively low yield (entries 2 and 3). Neither trialkylphosphine nor triarylphospine ligand promoted this reaction (entries 4 and 5), whereas IPr gave a significant elevation of yield, albeit with a low selectivity between *exo*- and *endo*-cyclization (entries 6 and 7). Surprisingly, SPO ligands such as $Ph_2P(O)H$ and $Cy_2P(O)H$ greatly improved the selectivity, providing the product in 51% and 46%, respectively, with complete *exo*-selectivity (entries 8 and 9). Encouraged by this result, a variety of chiral SPO ligands were further investigated (entries 10–17). BINOL-derived SPO (**L1**) proved ineffective, whereas chiral diamine-derived SPOs (**L2** and **L3**) gave better yields but with low enantiomeric excess (ee). Taddol-derived SPO ligands provided more promising results in both yield and ee (**L4**–**L8**). However, the reaction result was also highly sensitive to the ligand structure, 3,5-bis(*tert*-butyl)phenyl-containing SPO ligand (**L8**) proved to be the optimal one, providing the product in 92% yield and 97% ee. Using **L8** as the ligand, we can further reduce the loading of $Ni(cod)_2$ and $AlMe_3$ to 5 and 20 mol %, respectively, with almost undetectable change in both yield and ee (entries 18–20).

With the above optimized reaction conditions in hand, we first explored an array of tethered alkenes bearing various substituents to test the generality of the reaction (Table 2).

Table 2. Scope of Alkenes



substrate	cyclized product	substrate	cyclized product
E–**1a**	**2a**, 88%, 97% ee	**1f**[c]	**2f**, 70%, 89% ee
Z–**1a**	**2a**, 92%, 97% ee		
1b	**2b**, 87%, 97% ee	**1g**[c]	**2g**, 65%, 94% ee
1c[b]	**2c**, 92%, 92% ee	**1h**	**2h**, 84%, >99% ee
1d	**2d**, 90%, 98% ee	**1i**	**2i**, 90%, >99% ee
1e[b]	**2e**, 86%, 87% ee	**1j**	**2j**-*cis*, 43%, 93% ee **2j**-*trans*, 48%, >99% ee

[a]Reaction conditions: **1** (0.2 mmol), toluene (2 mL), under N_2 for 1 h; isolated yield and ee was determined by chiral HPLC. [b]Using $Ni(cod)_2$ (10 mol %) and additional IPr·HCl (5 mol %) for 5 h. [c]Using $Ni(cod)_2$ (10 mol %) at 130 °C for 5 h.

Both (*E*)- and (*Z*)-alkenes offered the desired product **2a** with the same stereo configuration (Table 2). When the terminal substituent group of alkene varied from *n*-pentyl (**1b**), benzyl (**1c**), benzyloxyethyl (**1d**) and phenyl (**1e**) to bulkier isopropyl (**1f**), the yield changed from 92% to 70%, whereas ee still remained at high level (87–98%). And in some cases, using higher loadings of $Ni(cod)_2$ along with additional ligand (**1c** and **1e**)[16] or higher temperature (**1f** and **1g**) may be required for better results. Impressively, a sterically hindered trisubstituted alkene still reacted well under the modified conditions, providing the corresponding product **2g** in 65% yield and 94% ee. All monosubstituted alkenes proved to be good substrates for this reaction and excellent ees were obtained (up to >99% ee, **2h**–**2j**). The absolute configuration of major enantiomer of the product was assigned to be (*R*) by single crystal X-ray diffraction (see the Supporting Information).

We then proceeded to investigate the substituent effect of monoalkene-tethered imidazoles (Table 3). Various substituents including either electron-donating groups (**4a**–**4e**) or electron-withdrawing groups (**4f**–**4l**) on the phenyl ring of benzoimidazole had little influence on the yield or enantioselectivity of the reaction, providing the corresponding product in 68–98% yield and 84–98% ee. To our delight, Br-containing substrate still survived in this Ni(0)-catalyzed reaction, providing the readily elaborated bromo-polycyclic

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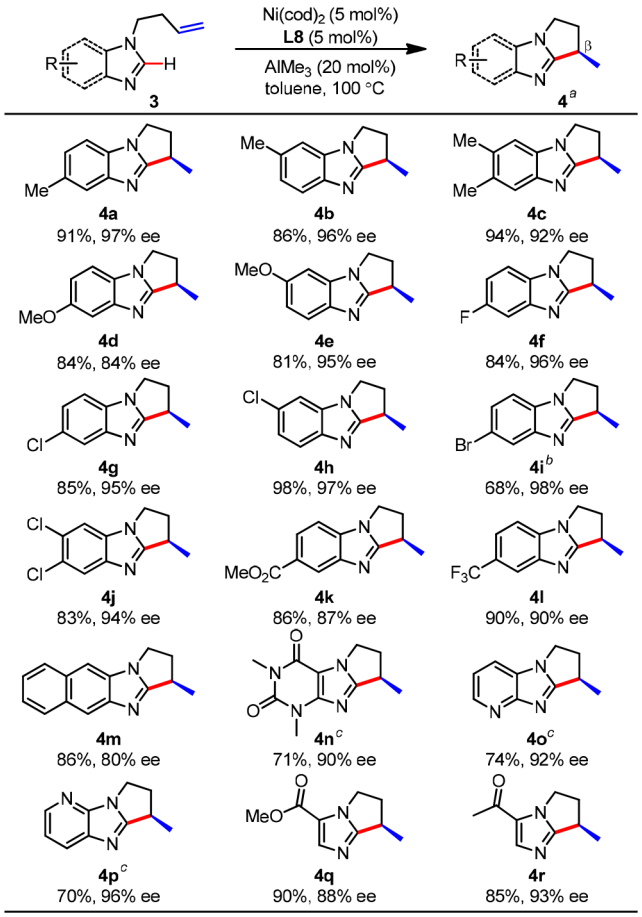
Table 3. Scope of Imidazoles

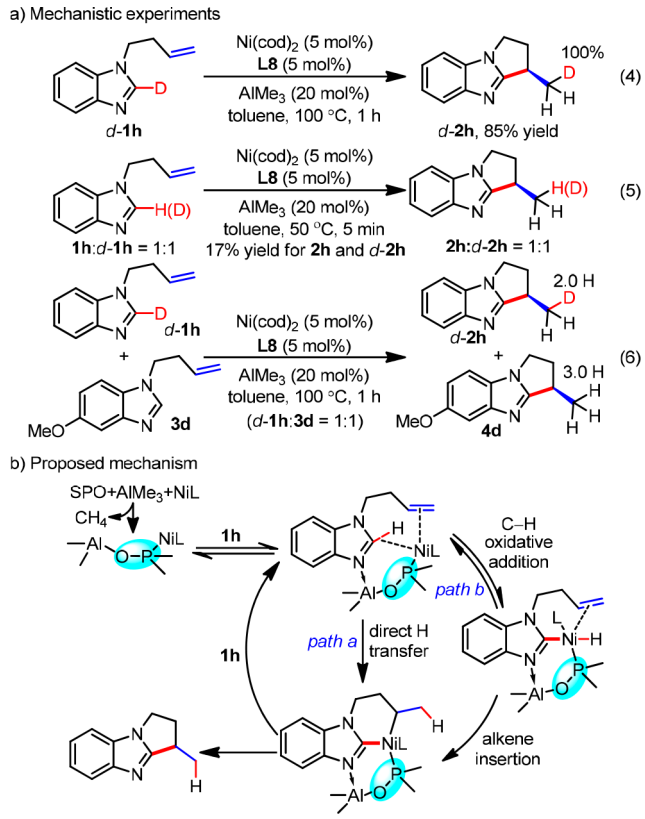


[a]Reaction conditions: **3** (0.2 mmol), toluene (2.0 mL), under N_2 for 1 h; isolated yield and ee was determined by Chiral HPLC. [b]Using $Ni(cod)_2$ (10 mol %) and additional IPr·HCl (5 mol %) for 5 h. [c]Using $Ni(cod)_2$ (10 mol %) and additional Ph_3P (15 mol %) for 5 h.

imidazole (**4i**). Good yield was obtained for naphthyl-derived imidazole (**4m**) but with relatively low ee. We reasoned that possible π–π stacking between the substrate and the ligand resulted into the diminished selectivity. Other N-containing heterocycles were also compatible with the current reaction (**4n**–**4p**), providing good yields and high ees under the assistance of additional Ph_3P ligand.[16] Notably, simple imidazole-derived substrate was completely ineffective for this reaction, only leading to partial alkene isomerization. However, imidazole bearing an electron-withdrawing substituent greatly facilitated this reaction (**4q** and **4r**), affording synthetically useful bicyclic imidazoles with a β-stereocenter.

To understand the mechanism, some additional experiments were conducted. Different from the Rh-catalyzed system,[2] the current Ni-catalyzed reaction showed a complete deuterium transfer from the deuterated imidazole (*d*-**1h**) to the terminal carbon of the product (*d*-**2h**) (Scheme 2a, eq 4). However, no significant kinetic isotope effect was observed in the competitive experiment (KIE = 1.0, eq 5). In addition, a competitive experiment between two different substrates revealed that there was no deuterium scrambling distribution (eq 6). These results suggest that the direct ligand-to-ligand H transfer from the imidazole to the alkene could be the favored pathway (Scheme 2b, path a).[17] However, the pathway involving oxidative addition of Ni(0) to the C–H cannot be

Scheme 2. Plausible Mechanism



ruled out at this current stage (path b). However, to probe the role of SPO ligand, we also performed some ^1H and ^{13}P NMR-tracing experiments (see the Supporting Information). The result showed that imidazole can easily form a complex with $AlMe_3$. When the formed complex was mixed with stoichiometric amount of $Ph_2P(O)H$, the doublet peak of H adjacent to P of $Ph_2P(O)H$ disappeared very quickly and new peaks appeared in the corresponding ^1H and ^{31}P NMR spectra, suggesting a new complex could be formed. When the resulting new complex was subjected to $Ni(cod)_2$, a quantitative yield of the product was afforded. These results suggested that SPO ligand could simultaneously bind two metals (Ni and Al) and the substrate. In addition, the complexed aluminum species can be used as a catalyst for the reaction, suggesting that aluminum species does move from one substrate benzimidazole to another (see the Supporting Information).

In summary, we have developed the first example of nickel-catalyzed enantioselective *exo*-selective C–H cyclization of imidazole with alkene. The cooperation of SPO ligands with Ni and Al provides an efficient tool for the enantioselective control, affording a series of bi- and polycyclic imidazoles with β-stereocenters in 65–98% yield and 80–>99% ee. Wider applications based on this bimetallic catalysis system are being explored in our lab.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b02547.

Experimental procedures, characterization data, and spectra of new compounds (PDF)

Data for $C_{18}H_{18}N_2$ (CIF)

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Notes

The authors declare no competing financial interest.

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