Enantioselective C2−H Alkylation of Pyridines with 1,3-Dienes via Ni−Al Bimetallic Catalysis

Jiang-Fei Li, Deng Pan, Hao-Rui Wang, Tao Zhang, Yi Li, Genping Huang,* and Mengchun Ye*

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ABSTRACT: A chiral phosphine oxide-ligated Ni−Al bimetallic catalyst was used to realize an enantioselective C2−H alkylation of pyridines without the need of a C2-block. A wide range of pyridines, including unsubstituted pyridine, C3, C4, and C2-substituted pyridines, and even complex pyridine-containing bioactive molecules are well compatible with the reaction, providing up to 81% yield and up to 97% ee.

Chiral C2-alkylated pyridines are important structural motifs, widely existing in pharmaceuticals, agrochemicals, and biologically active natural products, as well as catalysts (Scheme 1a).[1] The development of efficient synthetic methods to these compounds has received considerable interest in the past several decades.[2−5] Compared with either traditional

methods often requiring prefunctionalized pyridines and stoichiometric chiral reagents[2] or radical-involved Minisci reactions with the sacrifice of molecular fragments,[3] transition metal-catalyzed C−H alkylation of pyridines with π-unsaturated compounds represents a more attractive alternative owing to better atom and step economy.[4,5] However, due to the strong coordinative ability of pyridines to metals, which may inhibit the coordination of chiral ligands to metals, the development of enantioselective transition metal-catalyzed C−H alkylation of pyridines has been a formidable challenge, and successful examples are quite scarce. In 1994, a seminal study was conducted by Jordan and co-workers, in which a chiral Cp−Zr complex was used to promote C−H alkylation of 2-picoline with 1-hexene, achieving 58% ee (Scheme 1b).[6] In 2014, an important breakthrough of this field was made by Hou and co-workers, who used a cationic half-sandwich Sc complex to furnish C2−H alkylation of 2-substituted pyridines with various α-olefins, achieving up to 96% ee.[7] In 2018, Mashima and Tsurugi et al. explored C−H aminoalkylation of 2-arylpyridines with imines and found that chiral diamine-based Y or Lu complex can deliver up to 97% ee.[8] Despite big advances, all transition metal-catalyzed methods require the use of C2-blocked pyridines to hamper the deleterious coordination of pyridines to metals, leading to limited product complexity, as well as incompatibility of a wide range of non-C2-blocked pyridine-containing bioactive molecules. To address this challenge, herein we used chiral phosphine oxide (PO) ligated Ni−Al bimetallic catalyst to facilitate an enantioselective C2−H alkylation of pyridines with 1,3-dienes,[9] allowing non-C2-blocked pyridines to be enantioselectively alkylated for the first time, providing a series of C2-alkylated pyridines, including organocatalysts and complex

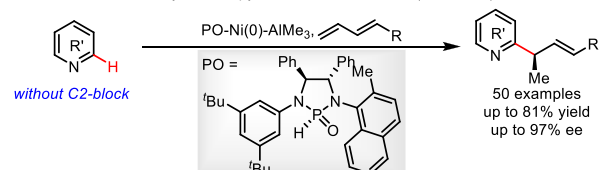## Scheme 1. Chiral C2-Alkylated Pyridines and Synthesis

a) Chiral C2-alkylated pyridines in bioactive molecules and catalysts
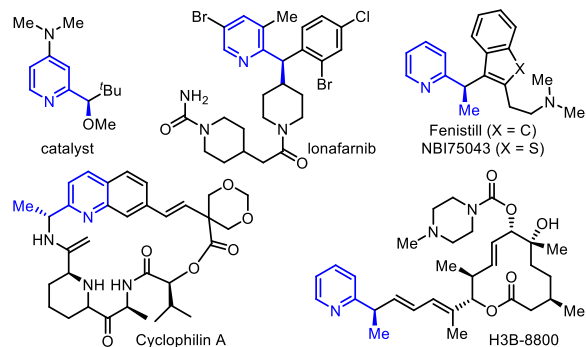
b) Enantioselective C−H alkylation of pyridines with π-unsaturated compounds
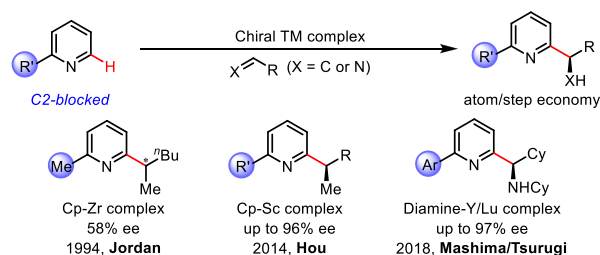
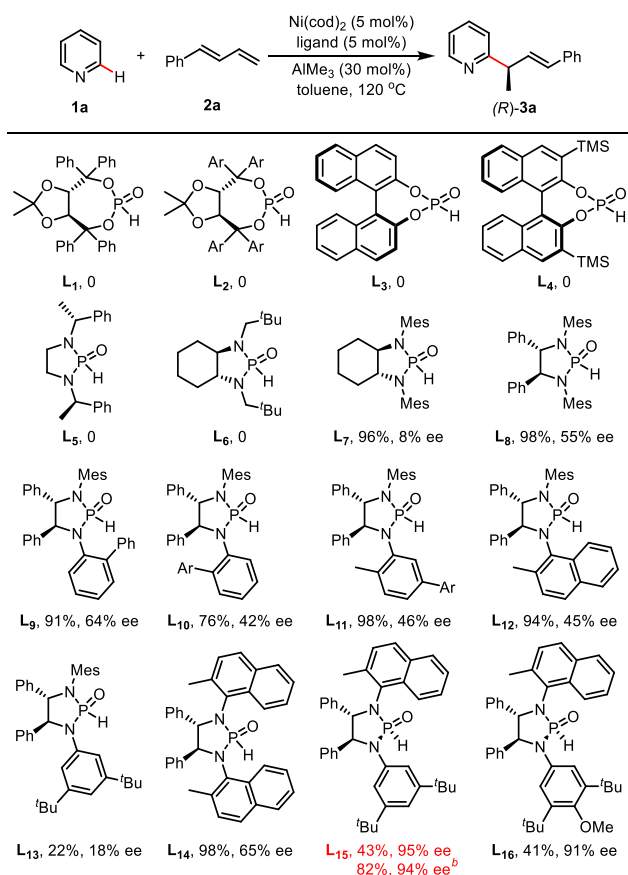c) Enantioselective C−H alkylation of pyridines with 1,3-dienes (this work)

bioactive molecules, in up to 81% yield and up to 97% ee (Scheme 1c).

Ni−Al bimetallic catalysts display excellent catalytic reactivity in a wide range of C−H activations of pyridines without the need of special modifications of pyridines.[10] However, due to the steric repulsion between Al−Lewis acid and the ligand of Ni, successful C−H alkylation was achieved only for the C4-position of pyridines with linear selectivity.[11] To reverse this selectivity into C2-selectivity with branched selectivity, we envisioned to use a ligand-ligated Ni−Al bimetal as a catalyst and 1,3-dienes as alkylating reagents, hoping that (1) when Al−Lewis acid coordinates to pyridine, the ligand linker between Ni and Al would play a directing group's role, harnessing Ni to preferentially activate the proximate C2−H bond other than remote C3−H or C4−H bonds; (2) the insertion of 1,3-dienes with Ni−H species would generate more stable allylic intermediates, delivering branched-selectivity products. Following this hypothesis, simple pyridine (1a) and phenyl 1,3-diene (2a) were selected as model substrates for the investigation. We systematically examined a broad range of chiral phosphine oxide ligands that have proved to be good linkers between Ni and Al (Table 1).[12] Chiral taddol (L₁ and L₂) and BINOL-derived phosphine oxides (L₃ and L₄) were ineffective, while diamine-derived phosphine oxides proved to be suitable ligands.

Except phosphine oxides bearing alkyl groups as side chains (L₅ and L₆), various diamine-derived phosphine oxides bearing bulky aryl groups as side chains in general displayed good to high reactivity (L₇ to L₁₆). However, the enantioselectivity was highly dependent on the chiral diamine backbone. Compared with a cyclohexane-diamine backbone bearing mesityl groups as side chains (8% ee, L₇), diphenyl-substituted diamine was a better option, providing 55% ee (L₈). With this backbone, more sterically hindered aryl groups generally led to higher reactivity with similar ee (L₉ to L₁₂) except for L₁₃. Notably, when 2-methyl naphthyl group and 3,5-di-*tert*-butyl group were incorporated as nonsymmetrical side chains, the phosphine oxide ligand existed as two separable isomers. Both of the two isomers were capable of promoting this reaction, providing similar ee (95% vs 91%) with opposite stereoconfiguration, while the mixture of them gave only 24% ee (also see Table S2), suggesting that the chiral P center of these isomers was critical to the enantioselectivity of the reaction. The optimal isomer (L₁₅), confirmed by single crystal X-ray diffraction, gave the desired product in 43% yield with 95% ee. By heating to 135 °C from 120 °C, the yield can be further elevated to 82% without significant loss of ee. Further modification of *N*-phenyl group by introducing an extra methoxy group did not give better results (L₁₆).

With the optimal ligand in hand, we proceeded to examine the scope of pyridines (Table 2). A broad range of C3-

Table 1. Ligand Identification[a]

Table 2. Scope of Pyridines[a]
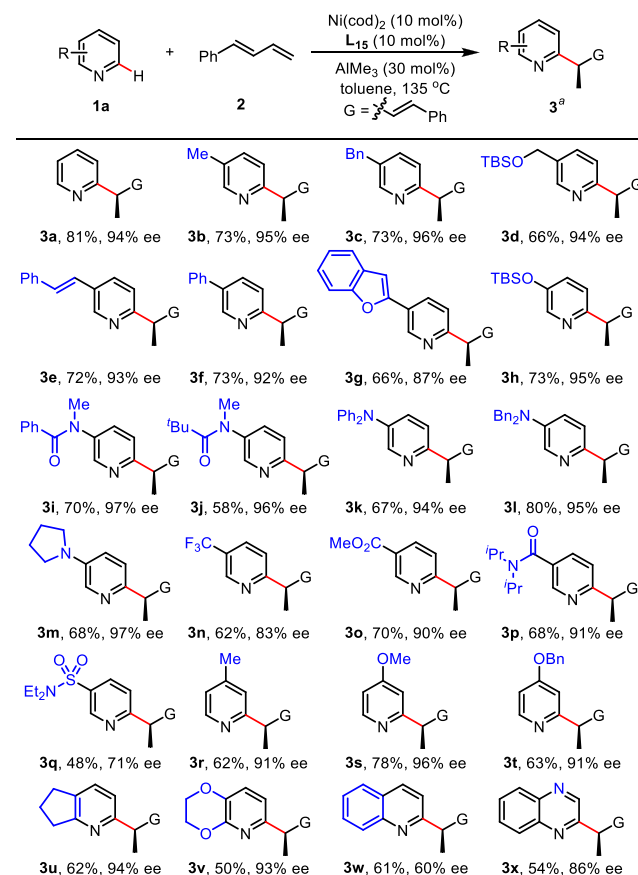
[a]Reaction conditions: 1a (0.2 mmol), 2a (0.25 mmol), toluene (1 mL) under N₂ for 8 h; yield of isolated products; ee was determined by chiral HPLC. [b]135 °C. Mes = mesityl. Ar = 3,5-ᵗBu₂C₆H₃.
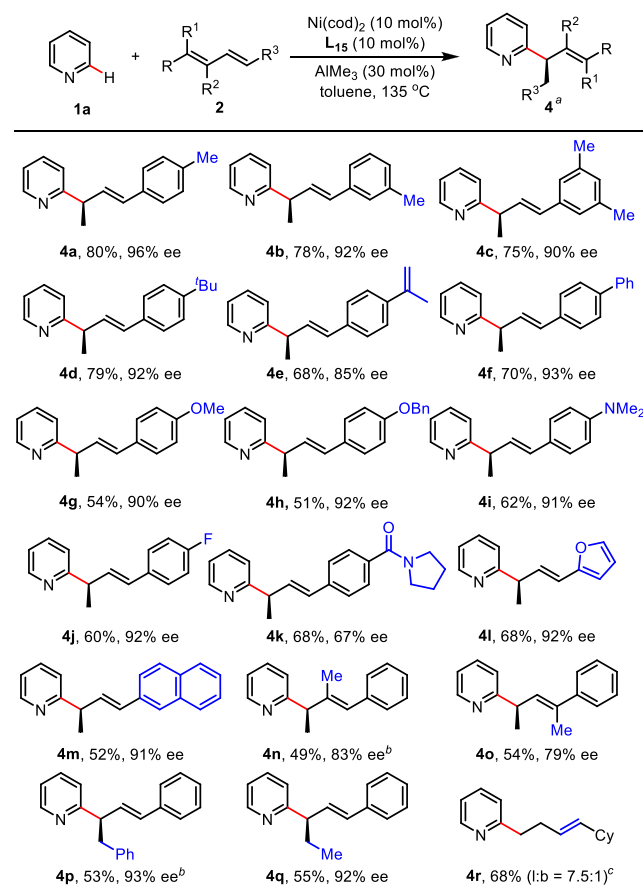
[a]Reaction conditions: 1a (0.2 mmol), 2 (0.25 mmol), toluene (1 mL) under N₂ for 8 h; yield of isolated products; ee was determined by chiral HPLC.

substituents were well compatible with the reaction, selectively delivering a branched isomer as the sole product. For example, an alkyl group (**3b**, **3c**, and **3d**), alkenyl group (**3e**), and (hetero)aryl group (**3f** and **3g**) provided the corresponding products in 66−80% yield and in 87−96% ee. More electron-donating groups such as alkoxy group (**3h**), amino group with an acyl group (**3i** and **3j**), diaryl amino group (**3k**), and dialkyl (**3l** and **3m**) amino group also worked well, affording 58−80% yield and 91−97% ee, in spite of the fact that the electron-rich pyridine ring disfavors Ni(0)-catalyzed C−H activation via the oxidative addition pathway. As expected, electron-withdrawing groups such as CF₃ (**3n**) and carboxylate groups (**3o** and **3p**) were tolerated well, offering the desired products in 62−70% yield and 83−91% ee. However, as an exception, sulfamide-substituted pyridine gave a little lower yield (48%) and ee (71%) (**3q**), probably attributed to the fact that the coordination of sulfamide with Al−Lewis acid inhibited the activation of pyridines. Similar to C3-substituents, C4-substituents such as methyl group (**3r**) and alkoxy group (**3s** and **3t**) were also well compatible with the reaction, providing 62−78% yield and 91−96% ee. In comparison with C3- or C4-substituents, C2-substituents had stronger influence on the coordination of pyridines with Al−Lewis acid. In general, bulky C2-substituents gave low yield, but pyridines with less sterically hindered C2-substituents still smoothly participated in this reaction (**3u** and **3v**), affording the corresponding products in 50−62% yields and 93−94% ee. In addition, quinoline (**3w**) and quinoxaline (**3x**) were also tolerated, giving the desired product in 61% yield with 60% ee and 54% yield with 86% ee, respectively. However, heterocycles such as bipyridines, terpyridines, pyridazines, and imidazoles are incompatible, probably owing to stronger coordination of Al with the substrates, which inhibited the regeneration of bimetallic catalyst.

Next, the scope of 1,3-dienes was investigated (Table 3). With respect to aryl dienes, either various electron-donating groups such as alkyl groups (**4a**, **4b**, **4c**, and **4d**), alkenyl group (**4e**), aryl group (**4f**), alkoxy group (**4g** and **4h**), and amino group (**4i**), or electron-withdrawing fluoro (**4j**) and carbox-amide (**4k**) at the phenyl ring were all well compatible, providing the corresponding products in 54−80% yield and 67−96% ee. In addition, 2-furyl dienes (**4l**) and naphthyl (**4m**) were also suitable substrates, giving 68% yield with 92% ee and 52% yield with 91% ee, respectively. Besides monosubstituted 1,3-dienes, disubstituted 1,3-dienes (**4n**, **4o**, **4p**, and **4q**) were also compatible with the reaction, delivering 49−55% yield and 79−93% ee. Notably, aryl group in 1,3-dienes proved to be critical to the branched selectivity. The replacement of aryl group with alkyl group (**4r**) or H (1,3-butadiene in the SI) generated linear isomers as main products. Additionally, diene structural motif was another key factor to the branched selectivity. The use of styrene instead of dienes led to a mixture of branched and linear isomers in a ratio of 1.9:1 and in 96% total yield (see page S33).
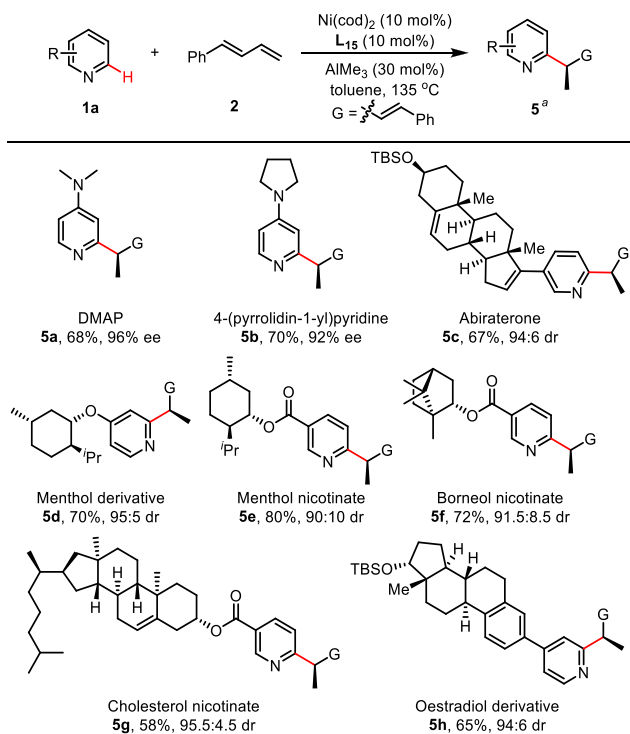
This method provides an efficient tool for the late-stage modification of non-C2-blocked pyridine-containing complex bioactive molecules and organocatalysts (Table 4). 4-(Dimethylamino)pyridine (DMAP) and 4-pyrrolidinopyridine (PPY) are particularly attractive organocatalysts for nucleophilic reactions, while the synthesis of their enantioenriched chiral counterparts are very challenging, often requiring lengthy and time-consuming processes.[13] In contrast, the current method allowed a one-step procedure for their

Table 3. Scope of 1,3-Dienes[a]

4a, 80%, 96% ee	**4b**, 78%, 92% ee	**4c**, 75%, 90% ee
4d, 79%, 92% ee	**4e**, 68%, 85% ee	**4f**, 70%, 93% ee
4g, 54%, 90% ee	**4h**, 51%, 92% ee	**4i**, 62%, 91% ee
4j, 60%, 92% ee	**4k**, 68%, 67% ee	**4l**, 68%, 92% ee
4m, 52%, 91% ee	**4n**, 49%, 83% ee[b]	**4o**, 54%, 79% ee
4p, 53%, 93% ee[b]	**4q**, 55%, 92% ee	**4r**, 68% (l:b = 7.5:1)[c]

[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.25 mmol), toluene (1 mL) under N₂ for 8 h; yield of isolated products; ee was determined by chiral HPLC. [b]Ni(cod)₂ (20 mol %), **L₁₅** (20 mol %), AlMe₃ (60 mol %). [c]b:l = branched:linear.

convenient synthesis, providing chiral DMAP (**5a**) in 68% yield and 96% ee, and chiral PPY (**5b**) in 70% yield and 92% ee. Medicinally relevant compounds were also competent in this process. For example, the abiraterone (**5c**), an anticancer drug, was alkylated at the C2-position of the pyridine motif, providing the corresponding product in 67% yield with 94:6 dr. In addition, a range of bioactive molecules, such as menthol derivative (**5d**), nicotinic acid-derived complex molecules, such as (−)-menthol (**5e**), (−)-borneol (**5f**), and cholesterol (**5g**), as well as steroid hormones estradiol (**5h**), were also found to be suitable substrates in this reaction, providing 58−80% yields and 90:10−95.5:4.5 dr. The absolute configuration of major enantiomer of the product was determined by single crystal X-ray diffraction (see the SI).
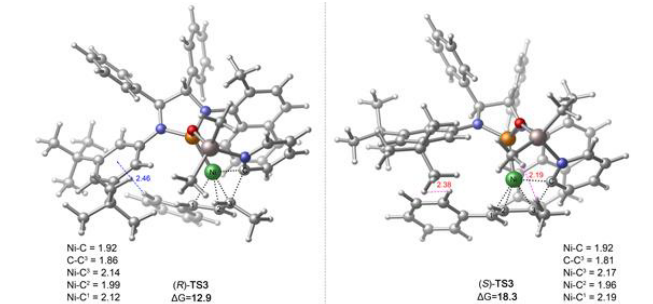
C2-alkylated pyridines bearing an olefin motif are versatile synthetic precursors (Scheme 2a). For example, the hydrogenation of **3a** provided chiral pyridine **6** in quantitative yield without significant loss of ee, and the oxidation of **3a**, followed by a reduction, generated alcohol **7** in 70% yield with the same ee. To gain more insights into the mechanism, relevant mechanistic experiments were carried out. Deuterium-labeling experiment using racemic phosphine oxide ligand (Mes-DAPO, see the SI) revealed that C2-deuterium of pyridine was distributed at two positions of the product, including the methyl group (1.21 D) and the allylic hydrogen (0.27 D). At the same time, the C5-deuterium was partially replaced by H

Table 4. C2-Alkylation of Pyridine-Containing Organocatalysts and Bioactive Molecules[a]

DMAP
5a, 68%, 96% ee

4-(pyrrolidin-1-yl)pyridine
5b, 70%, 92% ee

Abiraterone
5c, 67%, 94:6 dr

Menthol derivative
5d, 70%, 95:5 dr

Menthol nicotinate
5e, 80%, 90:10 dr

Borneol nicotinate
5f, 72%, 91.5:8.5 dr

Cholesterol nicotinate
5g, 58%, 95.5:4.5 dr

Oestradiol derivative
5h, 65%, 94:6 dr

[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.25 mmol), toluene (1 mL) under N_2 for 8 h; yield of isolated products; ee and dr were determined by chiral HPLC.

(0.48 H) (Scheme 2b). These results suggested that the formation of allyl-Ni species was a reversible process, which would lead to a scramble of C5-deuterium and methyl H. In addition, no significant kinetic isotopic effect was observed in parallel experiments (k_H/k_D = 1.04) (Scheme 2c), indicating that the cleavage of C2−H would not be involved in the rate-determining step. Beyond these experiments, stoichiometric experiments were also conducted, including preparing bimetallic catalyst by using readily available Mes-DAPO instead of chiral ligand **L₁₅** (see page S36 in the SI), achieving the complex of the catalyst with pyridine and investigating its reactivity, which further confirmed that PO−Ni−Al complex could be a vital catalyst. Density functional theory calculations were also performed (Scheme 2d and see the SI for details) and the computations showed that (1) C2−H activation proceeds via a reversible ligand-to-ligand H transfer pathway ((R)-**TS1**), which is accordance with the observed scramble of C5-deuterium and kinetic isotopic effect;[14] (2) subsequent isomerization of η^1 to η^3 allylic nickel complex leads to intermediate **IM4**, which undergoes reductive elimination to generate product **3a**; (3) the reductive elimination step is the turnover-limiting step with an overall energy barrier of 30.2 kcal/mol ((R)-**TS3** relative to (R)-**IM4**); (4) the computed energy difference between the pathways leading to two stereoisomers is 2.7 kcal/mol, which is also in accordance with the observed 94% ee value; (5) the enantioselectivity is mainly caused by the C−C reductive elimination of the S-pathway being much higher in energy than that of the R-pathway. In favorable (R)-**TS3**, the C−H−π interaction between the phenyl group of the allylic moiety and the N-phenyl group of the ligand was observed, while the steric

Scheme 2. Synthetic Utility and Mechanistic Experiments

a) Product transformation

6, 99%, 92% ee   **3a**, 94% ee   **7**, 70%, 94% ee

b) Deuterium-labeling experiment

c) Determination of kinetic isotope effect

parallel experiment: k_H/k_D = 1.04

d) DFT calculation and proposed mechanism

e) Stereochemical model ((R)-**TS3** favored)
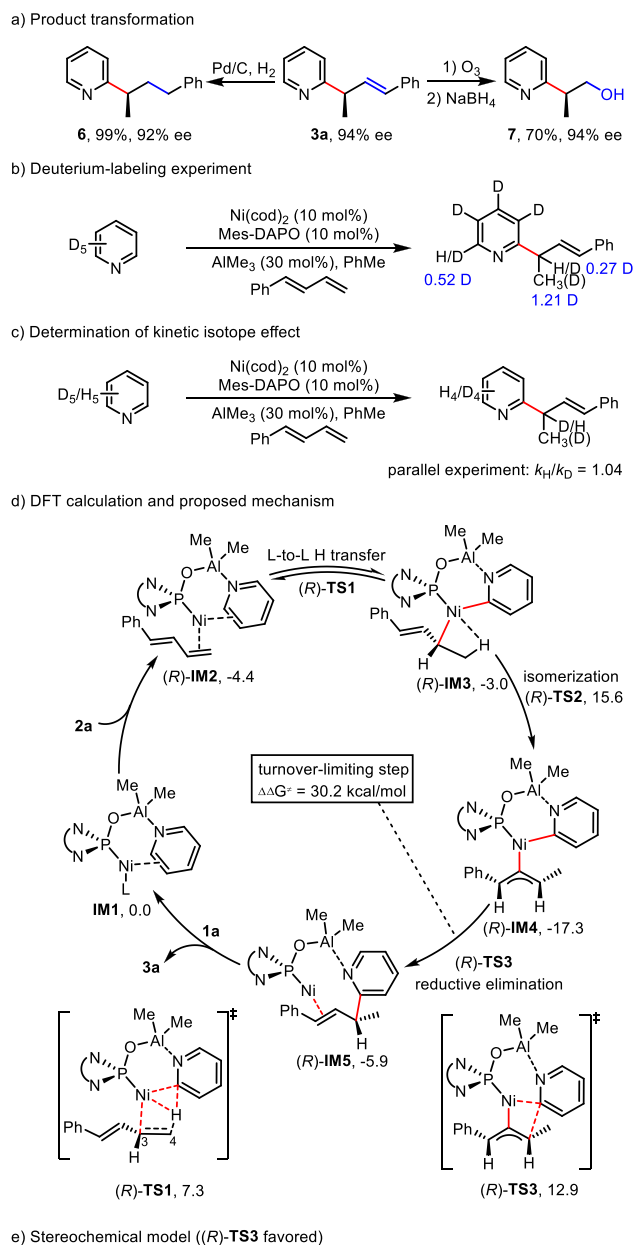
repulsion between the allylic moiety and Ni−Al catalyst was found (S)-**TS3**. These two factors would result in the experimentally observed enantioselectivity (Scheme 2e). In addition, DFT calculations also exclude C3- or C4−H activation of pyridine, and site-selectivity of 1,3-dienes.

In summary, we have developed an enantioselective Ni-catalyzed C2−H alkylation of pyridines without the need of a

C2-block, providing a series of chiral pyridine derivatives in 54−81% yield and 60−97% ee. This method enables efficient C2-alkylation of a wide range of general pyridines, including unsubstituted pyridine, C3, C4, or C2-substituted pyridines, and even complex pyridine-containing bioactive molecules. The olefin motif in products allows versatile elaborations, providing rapid and convenient access to various chiral pyridine derivatives. The phosphine oxide-ligated Ni−Al bimetallic catalyst proves to be critical in improving the reactivity and controlling the selectivity. The search for wider applications of this bimetallic catalyst is underway in the lab.

◼ ASSOCIATED CONTENT

ⓈⒾ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c09306.

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

Accession Codes

CCDC 2165167 and 2165471 contain 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.

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Notes

The authors declare no competing financial interest.

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