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Regio- and Enantioselective C−H Cyclization of Pyridines with Alkenes Enabled by a Nickel/N-Heterocyclic Carbene Catalysis

Wu-Bin Zhang,[†] Xin-Tuo Yang,[†] Jun-Bao Ma, Zhi-Ming Su, and Shi-Liang Shi*

State Key Laboratory of Organometallic Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, People's Republic of China

Supporting Information

ABSTRACT: Annulated pyridines are ubiquitous scaffolds in many bioactive molecules. A highly regio- and enantioselective Ni(0)-catalyzed *endo*-selective C−H cyclization of pyridines with alkenes has been developed. An unprecedented enantioselective C−H activation at pyridyl 3- or 4-positions was enabled by bulky chiral N-heterocyclic carbene ligands. This protocol provides expedient access to a series of optically active 5,6,7,8-tetrahydroquinolines and 5,6,7,8-tetrahydroisoquinolines, compounds otherwise accessed with difficulty, in moderate to high yields (up to 99% yield) and enantioselectivities (up to 99% ee). To our knowledge, this is the first example of enantioselective C−H cyclization of pyridines to chiral annulated products.

Pyridine derivatives are among the most significant heterocyclic structural units found in pharmaceuticals and bioactive natural products. In particular, the pyridine ring system is the single most commonly found aromatic nitrogen heterocycle among FDA approved medicines in the U.S.[1] Moreover, they are also widely used as versatile building blocks in organic synthesis and ligand design (Figure 1).[2] Therefore,

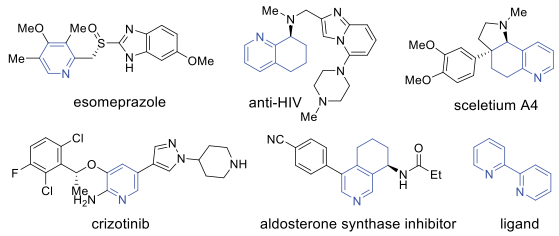
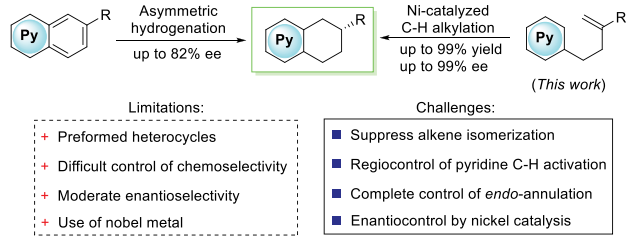


Figure 1. Examples of pharmaceuticals, natural products, and ligands possessing pyridine rings.

the construction and modification of the pyridine ring represents an important research objective. Among the many strategies that have been investigated, the direct C−H functionalization of pyridines[3] constitutes an atom- and step-economical method[4] to access pyridine derivatives, and much effort has been devoted to this approach.[5] However, despite recent advances in the C−H functionalization of pyridines to deliver racemic products, methods for the enantioselective functionalization of pyridines via a C−H activation process are very rare[6] and basically limited to functionalization at the 2-position.[7,8] Hou and co-workers developed a Sc-catalyzed enantioselective C−H alkylation at the 6-position of 2-substituted pyridines with terminal alkenes.[6a] Direct asymmetric C−H functionalization at the 3- and 4-positions of pyridines remains elusive. Importantly, the asymmetric C−H cyclization of pyridines to chiral annulated pyridines has not been reported despite the fact that chiral annulated pyridines, such as 5,6,7,8-tetrahydroquinolines (THQ) and -tetrahydroisoquinolines (THIQ), are frequently encountered in bioactive molecules and drugs (Figure 1).[9]

Although synthetic methods to access enantioenriched 1,2,3,4-THQs and -THIQs are well established,[10] approaches to chiral 5,6,7,8-THQs and -THIQs are very limited, and catalytic, enantioselective methods are especially undeveloped.[11,12] In general, catalytic asymmetric hydrogenation of quinolines and isoquinolines tends to reduce the pyridine moiety, and the selective hydrogenation of the carbocycle is challenging due to the higher level of aromatic stabilization and inefficient coordination to the metal by the carbocycle. Indeed, enantioselectivities of up to 82% ee were recently achieved by Kuwano and co-workers using ruthenium catalysis and represents the state-of-the-art of the catalytic, enantioselective synthesis of 5,6,7,8-THQs and -THIQs.[12] In this context, we envisioned that a nickel catalyzed regio- and enantioselective C−H alkylation of easily available alkene-tethered pyridines might serve as an efficient alternative approach to optically active 5,6,7,8-THQs and -THIQs (Scheme 1). We were aware, however, three formidable challenges presented in this nickel catalyzed asymmetric process. First, the competitive olefin isomerization of alkene substrates, which could easily occur in the presence of nickel catalysts under harsh conditions, has to

Scheme 1. Catalytic Asymmetric Synthesis of Chiral 5,6,7,8-THQs and 5,6,7,8-THIQs



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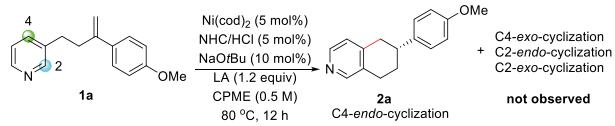
be suppressed.[13] Second, complete site control of the hydroarylation event at both the alkene and the pyridine parts is nontrivial but is critical to deliver decent isolated yields of products. Third, despite nickel being earth-abundant and wildly applied in numerous coupling reactions,[14] Ni-catalyzed asymmetric C−H functionalization reactions have rarely been reported.[15] High levels of enantiocontrol for these reactions is rather challenging to achieve because the reactivity of nickel catalysts is generally highly sensitive to ligand and substrate structure, resulting in very limited selections of viable chiral ligands and limitations in substrate scope.[16] However, we felt that if a suitable family of ligands could be identified, the above-mentioned challenges could be tackled and thus provide a straightforward approach for the enantioselective construction of chiral 5,6,7,8-THQs and -THIQs.

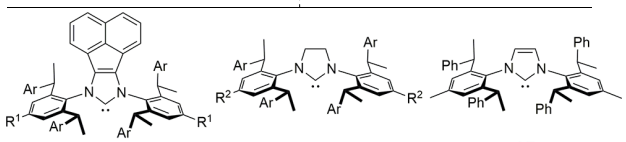
Toward this goal, we recently developed a series of bulky chiral N-heterocyclic carbenes (NHCs),[17] namely SIPE and ANIPE type ligands, and successfully applied them to the first nickel catalyzed asymmetric formal C−H alkenylation of alcohol with alkynes to form chiral allylic alcohols.[18] As a continuation of our work in this area, we report herein the first example of the enantioselective C−H activating cyclization of pyridines. In the newly developed chemistry, our recently disclosed chiral NHCs enabled the Ni-catalyzed direct asymmetric C−H alkylation at the 3- and 4-positions of pyridines with excellent levels of regio- and enantiocontrol to afford chiral 5,6,7,8-THQs and -THIQs from easily available substrates.

Inspired by the seminal work on cooperative nickel−aluminum catalysis by Nakao and Hiyama[19,20] and recent significant advances on asymmetric C−H activation of nitrogen heterocycles using this concept from the group of Cramer as well as Ye,[8h−j] we felt that aluminum-based Lewis acid additives should coordinate to the pyridine nitrogen to activate the pyridine ring and thus facilitate the pyridine C−H functionalization process. We thus commenced our study by using alkene-tethered pyridine **1a** as the model substrate for the synthesis of chiral annulated products in the presence of $Ni(cod)_2$, aluminum-based Lewis acid, and a chiral ligand. At the outset, a variety of commonly used chiral phosphines and NHC ligands were examined, none of which provided desired product **2a** (see Supporting Information (SI)). However, the use of our previously disclosed ligand **L1** in the presence of a bulky additive MAD[21] gave encouraging results, providing pyridine C4-*endo*-cyclized product **2a** exclusively in almost quantitative yield and 72% ee (Table 1, entry 1). Importantly, neither isomers from a nickel-catalyzed alkene chain walking process nor the isomeric product of 2-position annulation was observed. We reasoned that the large steric hindrance of MAD shielded the pyridyl 2-position by Al−N coordination, resulting in excellent selectivity in favor of 4-functionalization. For the alkene tether, we rationalized that a bulky ligand on nickel facilitates the *anti*-Markovnikov hydroarylation for steric reasons. We next attempted to improve enantiocontrol by employing bulkier ligands to further push the flanking groups to the nickel center. While replacing the R^1 methyl with a bulkier diphenylmethyl group (**L2**) slightly increased enantioselectivity (entry 2), the change of the phenyl groups on the 2,6-substituent to 3,5-xylyl improved the enantioselectivity to 86% ee (**L3**, entry 3). Pleasingly, the use of our recently developed SIPE type ligands resulted in further significant improvements in the enantioselectivity (entries 4−6). Among them, **L4** gave the optimal result, affording product in 93% ee

Table 1. Reaction Optimization[a]



Entry	NHC	LA	Yield (%)[b]	ee (%)[c]	Entry	NHC	LA	Yield (%)[b]	ee (%)[c]
1	**L1**	MAD	99	72	7	**L7**	MAD	77	60
2	**L2**	MAD	99	76	8	**L4**	$AlMe_3$	0	/
3	**L3**	MAD	99	86	9	**L4**	$AlEt_3$	0	/
4	**L4**	**MAD**	**99**	**93**	10	**L4**	/	0	/
5	**L5**	MAD	80	96	11	/	MAD	0	/
6	**L6**	MAD	64	90	12[d]	**L4**	MAD	0	/



[a]Reactions were performed on 0.1 mmol scale. [b]Determined by GC analysis. [c]Determined by HPLC analysis with a chiral stationary phase. [d]Without $Ni(cod)_2$.

and quantitative yield (entry 4). Bulkier ligand **L5** further improve the enantioselectivity to 96%, albeit with slightly lower reactivity (entry 5). Surprisingly, a replacement of the methyl on the R^2 position by methoxy (**L6**) reduced both yield and enantioselectivity (entry 6). In addition, the use of unsaturated NHC **L7** dramatically decreased the yield and enantioselectivity (entry 7). It seems that both steric and electronic properties of the ligand strongly effected on the outcome of this nickel catalyzed reaction. Moreover, a survey of Lewis acids suggest that MAD was superior to $AlMe_3$ and $AlEt_3$ (entries 8−9). Finally, control experiments in the absence of nickel, MAD and NHCs, respectively, gave no detectable products, supporting the critical role of each component (entries 10−12).

With the optimized reaction conditions in hand, we first explored the scope of this C−H cyclization using pyridine C3 tethered alkenes substrates as shown in Table 2. An array of 5,6,7,8-THIQs products with moderate to high yields, and excellent enantioselectivities were obtained with complete regiocontrol. Regardless of alkyl or aryl substituent on the alkenes, only *endo*-annulated products on the pyridine 4-position were obtained. The steric effect of the alkene substituent has little influence on the performance and bulky substituents such as 1-naphthyl (**2e**), 2-naphthyl (**2f**), *tert*-butyl (**2q**), and other substituents with quaternary carbons (**2c,d**) were all compatible. The styrene type substrates bearing electron-donating substituents such as ethers (**2a**, **2g**, **2i**), dimethylamine (**2j**), morpholine (**2k**), and weakly electron-withdrawing substituents such as fluorine (**2h**) underwent C−H cyclization smoothly. In some cases, the use of higher loading of nickel catalyst, switch of ligand, or higher temperature were required for better results. Remarkably, substrate possessing amide group with acidic proton afforded product in good yield and excellent enantiocontrol in the presence of additional MAD and increased catalyst loading. However, substrate containing ester gave a lower isolated yield of product, accompanied by alkene isomerization of the

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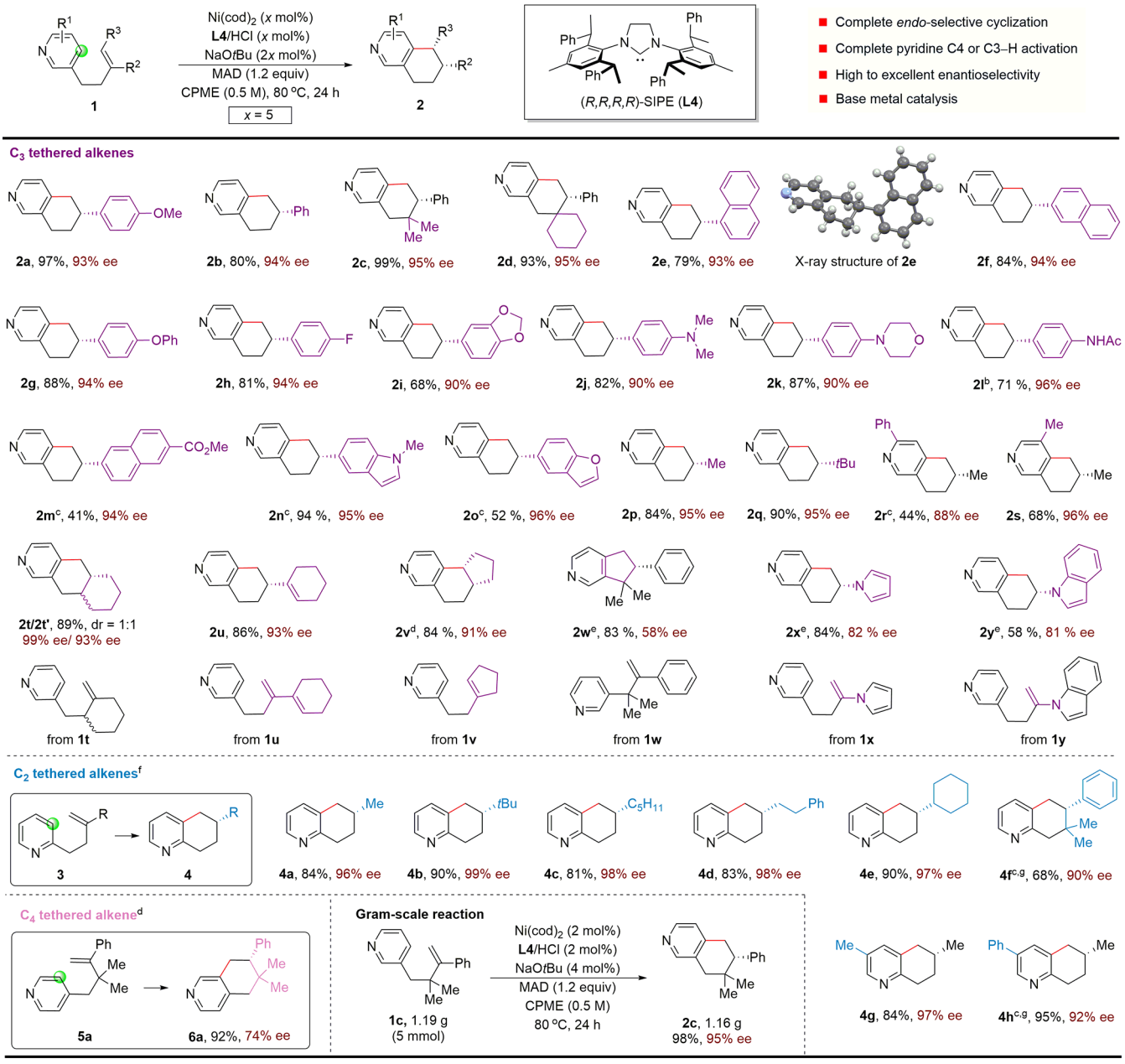
Table 2. Substrate Scope[a]



[a]Yields of isolated products on 0.2 mmol scale. [b]Using 20 mol % catalyst based on **L5** and 2.4 equiv MAD at 100 °C for 72 h (x = 20). [c]Using 10 mol % catalyst based on **L5** at 120 °C for 48 h (x = 10). [d]Using 10 mol % catalyst based on **L3** at 80 °C for 48 h (x = 10). [e]Using 10 mol % catalyst based on **L3** at 120 °C for 48 h (x = 10). [f]Using n-heptane as solvent. [g]Using $AlEt_3$ instead of MAD.

substrate under the higher temperatures needed for good reactivity (**2m**). Notably, substrate containing pharmaceutically important heterocycles, including morpholine (**2k**), benzofuran (**2n**), indole (**2o**, **2y**), and pyrrole (**2x**), were well tolerated. In addition to 1,1-disubstituted alkenes and styrenes, the use of 1,3-conjugated diene (**1u**), cyclic trisubstituted alkene (**1v**), and enamines (**1x**, **1y**) also delivered products with complete selectivity for the 4-position, with good to excellent enantioselectivity. The reactions using enamines were particularly intriguing, as it provided several chiral amine products which are nontrivial to access (**2x**, **2y**). A cyclopentapyridine (**2w**) was formed exclusively with *endo*-cyclization in high yield, albeit with moderate enantioselectivity.[22] Next, we examined the effect of the pyridine substituents on the reaction. Although a C2 substituent might be expected to block coordination of MAD and a C3 substituent could potentially suppress the C−H insertion of the bulky nickel catalyst, the corresponding cyclized products (**2r** and **2s**) were nevertheless obtained in moderate to good yields and high enantioselectivities. The connectivity and absolute stereochemistry of **2e** was determined by single crystal X-ray diffraction.

Subsequently, we surveyed the scope of pyridine C2 tethered alkenes. We were able to obtained a series of enantioenriched 5,6,7,8-THQ compounds (**4a**−**f**) in good to high yields (64−90%) and excellent level of enantiocontrol (90−99% ee) from 1,1-disubstituted alkenes. With respect to the pyridine ring, substrates with methyl (**4g**) or phenyl (**4h**)

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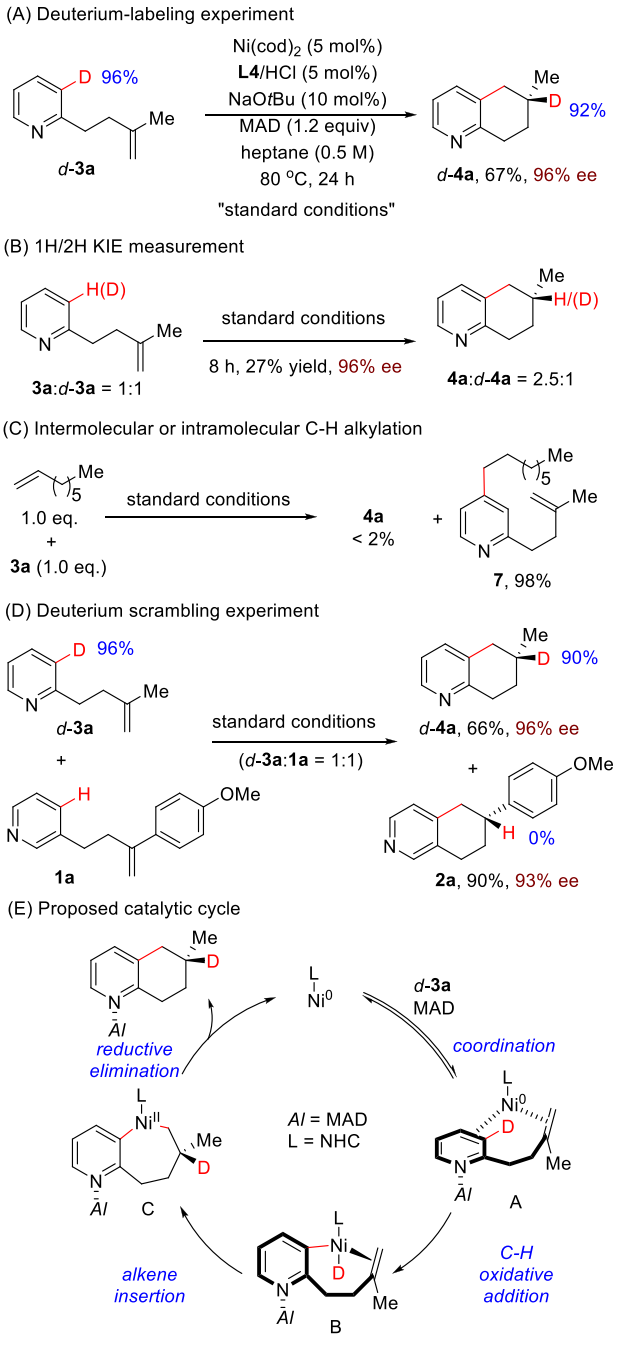
groups on the C5 position delivered products with high yields and enantioselectivities. Moreover, a pyridine C4 tethered alkene was tested (**5a**), and the *endo*-cyclized product (**6a**) was obtained with high yield and moderate enantioselectivity. Finally, we conducted the C−H cyclization reaction on a gram scale using **1c** as substrate while simultaneously decreasing catalyst loading to 2 mol %, and the cyclized product **2c** was obtained with high yield and enantioselectivity as before, highlighting the robustness of the method.

To obtain some mechanistic insight, we then conducted some additional experiments. First, a deuterium-labeling experiment using *d*-**3a** (96% D) under the standard conditions gave 92% deuterium incorporation at the internal position of the functionalized double bond (Scheme 2A). The kinetic isotope effect (KIE = 2.5) was observed in an intermolecular competition experiments, indicating the C−H cleavage step may be the rate-determining step (Scheme 2B). Interestingly, when we subjected **3a** to the standard conditions in the presence of 1-octene (1.0 equiv), the intermolecular *para*-C-H alkylated product (**7**) formed in near quantitative yield and only a trace amount of the C−H cyclization product (**4a**) was observed. This result indicated that the *para*-C-H oxidative addition is probably reversible and fast (Scheme 2C). In addition, another competition experiment using two different substrates suggested no deuterium scrambling occurred in this reaction (Scheme 2D). On the basis of these results, we proposed a possible catalytic cycle as shown in Scheme 2E: (1) Sterically bulky MAD coordinates to pyridine nitrogen, which pushes the tethered alkene close to nickel center and facilitates the formation of an η^2-alkene nickel complex A. (2) A subsequent C−D bond cleavage via oxidative addition of Ni(0) forms the Ni-D species B. (3) The *anti*-Markovnikov hydronickelation of the alkene then give a seven-membered ring intermediate C. (4) Finally, reductive elimination affords the *endo*-annulation product and regenerates the nickel catalyst. The use of SIPE and ANIPE type NHC ligands, which possess both the highly electron-donating property and highly steric hindrance nature, is apparently crucial to not only the key C−H cleavage and reductive elimination step but also the alkene insertion step, thus leading to excellent regio- and enantiocontrol of this challenging nickel catalyzed C−H alkylation.

In conclusion, we have developed the first enantioselective C−H cyclization of pyridines. An unprecedented asymmetric C−H alkylation at pyridyl 3- and 4-positions was achieved by employing bulky chiral NHC ligands for the nickel catalyst. Pyridine 2-, 3-, and 4-position tethered alkenes, including 1,1-disubstituted alkenes, styrenes, a diene, a trisubstituted alkene, and enamines, were all compatible with this completely *endo*-selective annulation method. This protocol provides an atom- and step-economical way to access a variety of chiral bi- and polycyclic pyridines, including 5,6,7,8-THQs and 5,6,7,8-THIQs, compounds otherwise difficult to access from racemic building blocks. Wider applications of this nickel-NHC catalysis are currently being explored in our laboratory.

Scheme 2. Plausible Mechanism



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b00931.

Experimental procedures, spectroscopic data, and NMR spectra of all products (PDF)

Crystallographic data for **2e** (CCDC 1902389) (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*shiliangshi@sioc.ac.cn

ORCID

Shi-Liang Shi: 0000-0002-0624-6824

Author Contributions

†W.-B.Z. and X.-T.Y. contributed equally.

Notes

The authors declare the following competing financial interest(s): A patent for some of the ligands in this Communication has been filed.

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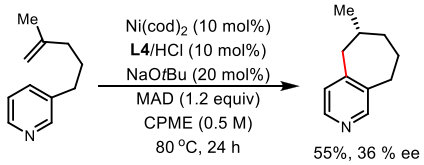

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