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Nickel/NHC-Catalyzed Enantioselective Cyclization of Pyridones and Pyrimidones with Tethered Alkenes

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Abstract: Reported is a highly enantioselective Ni(0)-catalyzed *endo*-selective C–H annulation of 2- and 4-pyridone, and 4-pyrimidone with alkenes to provide drug-relevant bicyclic heterocycle products. The use of a readily prepared chiral bulky NHC ligand (SIPE) for Ni catalyst and commercially available $AlEt_3$ as co-catalyst enhanced the practicality of this reaction.

Keywords: asymmetric catalysis; C–H activation; Ni catalysis; chiral NHC; pyridone

Introduction

Pyridones and pyrimidones are privileged N-heterocycles prevalent in many bioactive natural products, and pharmaceuticals.[1] For example, the 2-pyridone core is the key fragment of natural products camptothecin and sophoramine, which display significant anti-tumor and cardiotonic activities, respectively.[2] Moreover, isomeric 4-pyridones are a vital structural element found in many approved drugs such as antibiotic agent levofloxacin and an antiretroviral drug dolutegravir.[3] In addition, the 4-pyrimidone and uracil scaffolds are present in bioactive agents. These include the prohibitins inhibitor aglaroxin C, the viral protease NS3 inhibitor circumdatin G, atypical antipsychotic paliperidone palmitate,[4] the myosin inhibitor mavacamten, and the phosphodiesterase inhibitor theophylline (Figure 1).[5]

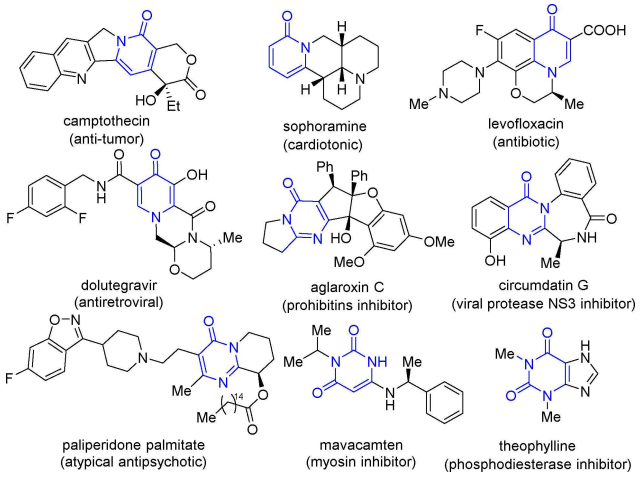

Figure 1. Examples of natural products and pharmaceuticals containing pyridone and pyrimidone scaffolds.

As a result, the development of efficient methods for the modification and construction of pyridones and pyrimidones is in high demand, and considerable effort has been devoted to this area of research.[6,7] Among these methods, the direct C–H functionalization of simple and readily available pyridone and pyrimidone cores represent the most atom- and step-economical method for the buildup of molecular complexity.[8] Moreover, progress in regiocontrolled C–H functionalization of pyridones has been made recently.[7] For example, the seminal works on C6-selective alkenylation and alkylation of pyridone core through hydroarylation of alkynes and alkene,[9] employing a powerful Ni/Al cooperative catalysis,[10,11] has been reported by Nakao, Hiyama, and co-workers (Scheme 1a). Subsequently, Cramer and co-workers developed an elegant ligand-controlled regiodivergent nickel-catalyzed C–H annulation of pyridones with alkenes

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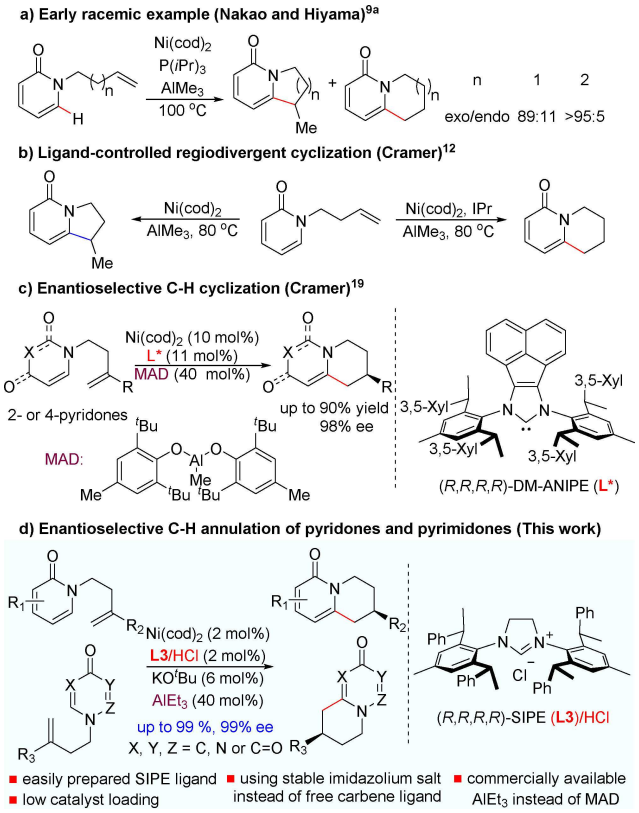

Scheme 1. C–H Cyclization of Pyridones with Alkenes.

(Scheme 1b).[12] They also reported two examples of asymmetric cyclization with modest enantioselectivity (57% ee) using an isoquinoline-based NHC ligand. Despite these advances, the highly enantioselective C–H functionalization[13] of pyridones and pyrimidones remains a challenging yet essential goal. We sought to identify a suitable type of chiral ligands for nickel catalysis that would provide a highly enantioselective method for the synthesis of chiral annulated pyridones and pyrimidones, structures widely spread in bioactive molecules and drugs (Figure 1).

We recently developed a variety of C_2 symmetric chiral NHC,[14] namely, ANIPE- and SIPE-type ligands, and successfully applied them to the first nickel-catalyzed asymmetric C–H cyclization of pyridines and polyfluoroarenes with alkenes, as well as the nickel-catalyzed enantioselective formal C–H alkenylation of alcohols with alkynes.[15,16] As our continuing exploration in this field, we report herein a Ni/NHC-catalyzed enantioselective C–H alkylation of pyridones and pyrimidones with alkenes,[17] affording an array of chiral annulated products in good to excellent levels of enantioselectivity from readily available substrates (Scheme 1d). During the course of this research, Cramer and co-workers reported a similar nickel-catalyzed method for enantioselective C–H cyclization of pyridone derivatives using DM–ANIPE as a steering ligand and bulky (2,6-*t*-Bu_2-4-Me–$C_6H_2O)_2$AlMe (MAD)[18] as co-catalyst (Scheme 1c).[19] Notably, their work represents the state-of-the-art of asymmetric synthesis of chiral annulated pyridones and is the single highly enantioselective example of C–H functionalization of pyridones. Compared with Cramer's method, practically advantageous points of our protocol include using a readily prepared[20] SIPE ligand in low catalyst loading (2 mol% in most cases), using air- and moisture- stable imidazolium salt carbene precursor in lieu of free NHC ligand, using simple and commercially available $AlEt_3$ instead of pre-synthesized MAD. Moreover, our method features a broad substrate scope and scalability to a gram-scale reaction. Besides, we present a discussion on the reaction mechanism and enantiocontrol models.

Results and Discussion

We started our studies by using alkene-tethered pyridone **1a** as the model substrate for the synthesis of chiral annulated product **2a** in the presence of Ni $(cod)_2$, chiral NHC ligands, and aluminum co-catalyst. At first, the use of the ANIPE ligand (**L1**) and 40 mol% of $AlMe_3$ gave exclusively *endo*-selective C–H annulated product (**2a**) in quantitative yield and a promising 58% ee (Table 1, entry 1). This result was different from our previous report on the annulation of pyridine substrate, where MAD was exclusively effective.[15c] Further screening of ligand using an unsaturated NHC **L2** gave similar enantioselectivity (entry 2),[16] but the use of our recently developed saturated SIPE type ligands resulted in dramatical improvements in enantioselectivity (**L3**–**4**, entries 3–4). The use of **L3** afforded **2a** in quantitative yield with 86% ee, while a bulkier ligand **L4** increased the enantioselectivity to 94%. Given that **L3** was much easier to prepare than that of **L4**,[15b] we continued using **L3** as the ligand for nickel catalyst to examine the effect of solvent (entries 5–8). Toluene was found superior to other solvents affording **2a** in 91% ee. A survey of Lewis-acids revealed that both $AlEt_3$ and MAD could increase the enantioselectivity (entries 9–12). Considering that additional chemical operations are needed to prepare bulky MAD, we thus chose the commercially available $AlEt_3$ as the Lewis acid, and the optimal results were obtained under a slightly lower reaction temperature, furnishing **2a** in quantitative yield and 97% ee (entry 14). Noteworthy, neither *exo*-cyclized products nor isomers resulting from a nickel-catalyzed alkene chain-walking process[21] was observed under the optimized conditions. We attribute the high efficiency and selectivity to steric reasons, as the large **L3**–**Ni** complex could both facilitate the *endo*-cyclization and the reductive elimination step to prevent the potential isomerization.

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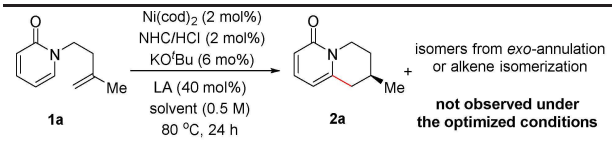
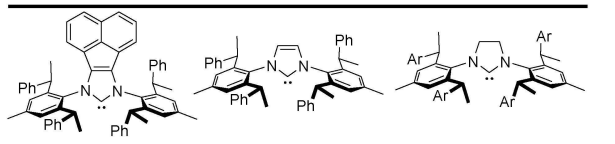
Table 1. Reaction Optimization.[a]

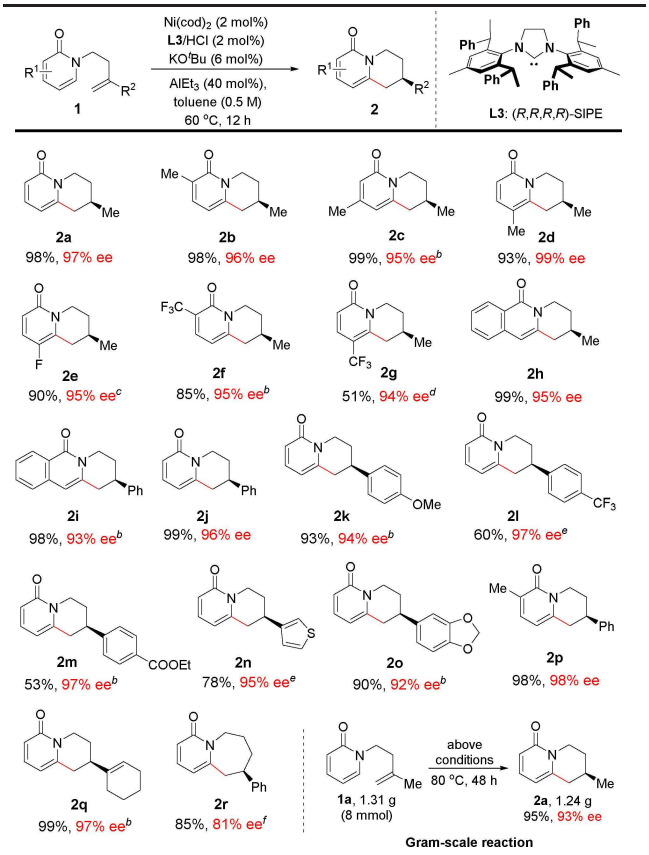


Entry	NHC	LA	Solvent	Yield [%][c]	ee [%][d]
1	**L1**	$AlMe_3$	benzene	99	58
2	**L2**	$AlMe_3$	benzene	86	61
3	**L3**	$AlMe_3$	benzene	99	86
4	**L4**	$AlMe_3$	benzene	99	94
5	**L3**	$AlMe_3$	toluene	99	91
6	**L3**	$AlMe_3$	*n*-hexane	99	86
7	**L3**	$AlMe_3$	THF	50	68
8	**L3**	$AlMe_3$	EtOAc	99	90
9	**L3**	Et_2AlCl	toluene	10	91
10	**L3**	$Al(O^iPr)_3$	toluene	0	-
11	**L3**	-	toluene	0	-
12	**L3**	MAD	toluene	99	96
13	**L3**	$AlEt_3$	toluene	99	93
14[b]	**L3**	**$AlEt_3$**	**toluene**	**99**	**97**



[a] Reactions were performed on a 0.1 mmol scale.
[b] 60 °C.
[c] Determined by GC using a crude reaction mixture.
[d] Determined by HPLC analysis with a chiral stationary phase.

Table 2. Scope for 2-pyridone.[a]



[a] Yield of the isolated product on a 0.2 mmol scale; enantioselectivities were determined by HPLC analysis with a chiral stationary phase.
[b] 80 °C.
[c] Without $AlEt_3$.
[d] Catalyst 10 mol%, 100 °C, 24 h.
[e] 80 mol% $AlEt_3$, 80 °C, 12 h.
[f] 80 mol% $AlEt_3$, 40 °C, 48 h

With the optimized reaction conditions in hand, we set out to investigate the scope of this enantioselective C–H alkylation reaction. As shown in Table 2, an array of chiral annulated pyridones was prepared in good to high yields with excellent levels of enantioselectivity (92–99% ee). Importantly, the reaction was applicable to substrates with various substituents, including methyl, fluoro-, and trifluoromethyl group at different positions of the pyridine core (**2b**–**2g**). In the case of a pyridone substrate bearing a bulky C5–CF_3 substituent (**2g**), higher catalyst loading and temperature were employed to obtain a synthetically useful yield. It bears mentioning that Cramer's method using bulky DM–ANIPE was not comparably effective for the C–H cyclization of bulky C5-substituted substrates (**2d** and **2g**).[22] Moreover, isoquinolones with alkyl and aryl substituents on alkenes served as viable substrates for this reaction, giving the tricyclic product in excellent yields and enantioselectivities (**2h**, **2i**). In addition to 1,1-dialkyl alkenes, the styrene type substrates bearing either electron-donating or electron-withdrawing substituents were all compatible. The mild reaction conditions tolerate many functional groups such as ethers (**2k**, **2o**), a fluoride (**2e**), CF_3 (**2f**, **2g**, **2l**), an ester (**2m**), a thiophene (**2n**) and an alkene (**2q**, from a 1,3-conjugated diene substrate). In addition, a seven-membered ring product could be obtained in good yield and enantioselectivity (**2r**). Notably, we successfully conducted the C–H cyclization reaction on a gram-scale (8 mmol), furnishing the product in high yield and enantioselectivity.

We next examined the possibility of employing the quinolinone and 4-pyrimidone tethered alkene substrates in this C–H cyclization reaction. As shown in Table 3, we found the use of a quinolinone substrate gave the *endo*-annulated product in excellent yield and enantioselectivity (**2s**). The absolute stereochemistry of **2s** was then determined to be (*R*)-configuration by X-ray diffraction analysis.[23] In addition, the 4-

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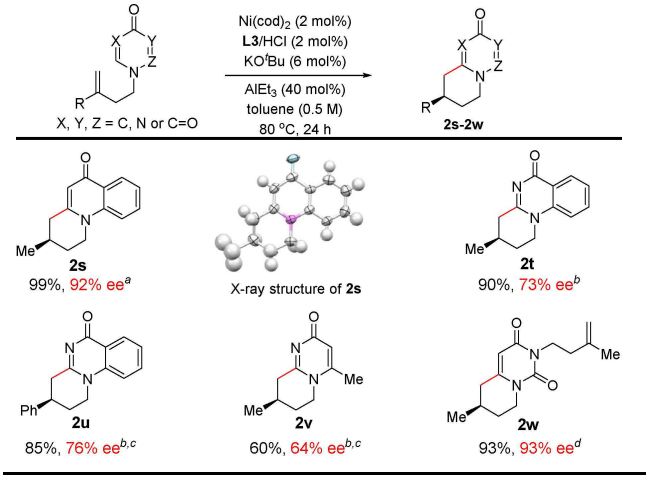
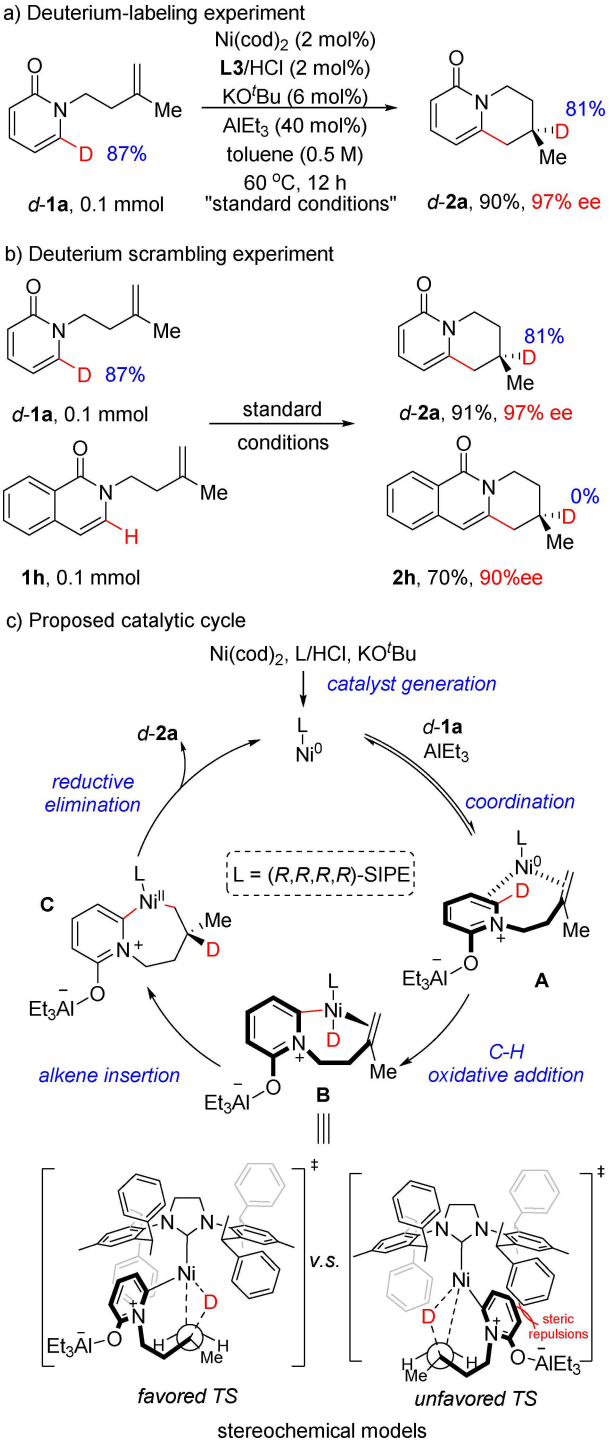
Table 3. Scope for 4-pyridone and 4-pyrimidone derivatives.



[a] 80 mol% $AlEt_3$, 40 °C, 48 h.
[b] 80 mol% $AlEt_3$, 100 °C, 24 h.
[c] 10 mol% of catalyst.
[d] 40 mol% $AlMe_3$, 36 h.



Scheme 2. Plausible mechanism.

pyrimidone substrates could undergo the desired transformation under conditions with higher catalyst loading and reaction temperature (100 °C), yielding annulated products in moderate enantioselectivities (**2t**–**2v**). Finally, the use of uracil functionalized with two alkene linkers delivered the product in high yield and excellent enantioselectivity (**2w**).

Additional experiments were performed to get preliminary mechanistic insights. First, a deuterium-labeling experiment using *d*-**1a** (87% D) under standard conditions gave the product with 81% deuterium incorporation at the internal position of the double bond (Scheme 2a). Moreover, a competitive experiment using two different substrates (*d*-**1a** and **1h**) revealed that there was no deuterium scrambling (Scheme 2b). Based on these experimental results, we proposed a plausible catalytic cycle as detailed in Scheme 2c. After in situ generations of the L–Ni(0) catalyst from the combination of imidazolium salt, Ni $(cod)_2$ and KO^{t}Bu, a Ni/Al dual coordination forms complex **A**, which undergoes a C–H bond cleavage via oxidative addition of Ni(0) to afford Ni–H species **B**. A subsequent *anti*-Markovnikov hydronickelation of the alkene gives a seven-membered ring intermediate **C**. Finally, a reductive elimination gives the annulated product and regenerates the catalyst. Based on the X-ray crystal structure of (*R*,*R*,*R*,*R*)-SIPE/Ni(0) complex,[15b] we proposed stereochemical models for this asymmetric C–H cyclization reaction (Scheme 2c). Because of the steric repulsions between the pyridone moiety and the phenyl group of the 1-phenethyl group on the ligand, the alkene insertion prefers to proceed through the transition state (left, favored TS), in which the pyridone moiety occupies the vacant space of the asymmetric environment provided by (*R*,*R*,*R*,*R*)-SIPE, thereby predominantly furnishing (*R*)-enantiomer product. We attribute the success of high levels of regio- and enantiocontrol of this nickel catalyzed C–H annulation reaction to the use of SIPE ligand. The highly electron-donating nature of SIPE is beneficial to the C–H oxidative addition of Ni, while the sterically

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demanding property of SIPE would facilitate *anti*-Markovnikov hydrometallation, the crucial reductive elimination, and the efficient enantio-discrimination.

Conclusion

In conclusion, we have developed a highly enantioselective NHC/Ni-catalyzed *endo*-selective C–H cyclization of 2-pyridone, isoquinoline, quinolinone, and 4-pyrimidone with alkenes. This protocol provides various pharmaceutically important chiral annulated *N*-heterocycles from simple and readily available starting materials. The use of easily prepared SIPE ligand for Ni catalyst and commercially available $AlEt_3$ as co-catalyst render this protocol a practical alternative to the previously reported methods. Further exploration of this NHC/metal catalysis is underway in our laboratory.

Experimental Section

In a nitrogen-filled glove box, $Ni(cod)_2$ (1.2 mg, 2.0 mol%), (*R*,*R*,*R*,*R*)-SIPE/HCl (2.8 mg, 2.0 mol%), KO^tBu (1.3 mg, 6 mol%) and toluene (0.4 mL) were charged to a 8 mL vial equipped with a magnetic stirring bar. The reaction mixture was allowed to stir at rt for 1 h, followed by the addition of **1** (0.2 mmol) and $AlEt_3$ (80 μL, 1 M in toluene, 40 mol%). The reaction vial was removed from the glove box, and the reaction mixture was stirred within the sealed vial at 60 °C for 12 h. Subsequently, the reaction mixture was cooled to ambient temperature and was quenched with 2 mL saturated sodium potassium tartrate solvent. The aqueous phase was extracted with EtOAc, and the collected organic phase filtered through a short pad of Na_2SO_4 and silica gel, eluting with EtOAc. The solvent was concentrated under reduced pressure to afford the crude product, which was purified via column chromatography to afford the products **2**.

Acknowledgements

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