Asymmetric Catalysis

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Highly Regio- and Enantioselective Synthesis of N-Substituted 2-Pyridones: Iridium-Catalyzed Intermolecular Asymmetric Allylic Amination**

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Abstract: *The first iridium-catalyzed intermolecular asymmetric allylic amination reaction with 2-hydroxypyridines has been developed, thus providing a highly efficient synthesis of enantioenriched N-substituted 2-pyridone derivatives from readily available starting materials. This protocol features a good tolerance of functional groups in both the allylic carbonates and 2-hydroxypyridines, thereby delivering multifunctionalized heterocyclic products with up to 98% yield and 99% ee.*

N-substituted 2-pyridones, particularly those possessing a stereocenter α to the nitrogen atom, have emerged as important structural motifs in many natural products and medicinal targets, and they are often crucial for the expression of interesting biological and pharmacological functions (Figure 1).[1]

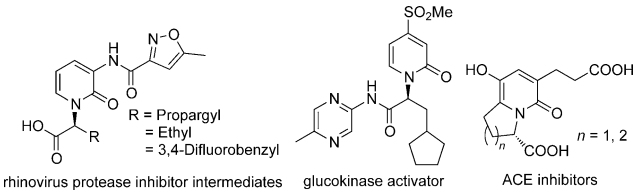
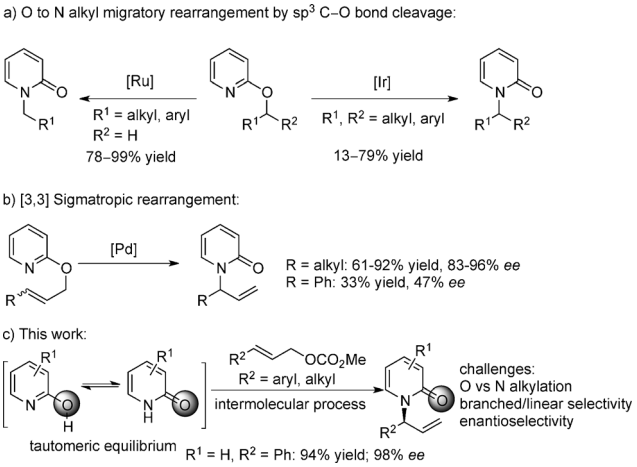


Figure 1. Examples of biologically active chiral 2-pyridones.

Accordingly, a reliable and efficient entry into such a class of compounds represents a highly important task. However, a brief survey of the literature reveals that direct approaches to the preparation of N-alkylated 2-pyridones are much less well explored,[2] likely because of the competing process between O and N alkylation given their ambivalent character.[3] In this regard, the rearrangement reactions starting from O-substituted pyridines have been developed to address this problem through O to N alkyl migration by sp^3 C–O bond cleavage[4] or Claisen rearrangement.[5] Dong et al. disclosed the first catalytic approach to an efficient O to N alkyl migration in pyridines in the presence of a ruthenium catalyst in 2011 (Scheme 1a).[4a] Shibata and co-workers reported an



Scheme 1. Synthesis of N-substituted pyridones.

elegant iridium-catalyzed migration of 2-alkoxypyridines bearing a secondary O-alkyl group (Scheme 1a).[4b] Despite the progress made in the Claisen rearrangement reactions, a catalytic asymmetric example for enantioselective synthesis of pyridones is limited to the report by Batey and co-workers who describe the palladium(II)-catalyzed [3,3] sigmatropic rearrangement of 2-allyloxy pyridines (Scheme 1b).[5g,6] This methodology features a wide substrate scope, however, the reaction of a cinnamyl-alcohol-derived substrate occurs in a moderate yield (33%) and enantioselectivity (47% *ee*).

In contrast, dearomatization reactions serve as important transformations for aromatic compounds, thus giving rise to a variety of ring systems in a very straightforward manner.[7] Despite the significant progress made with transition-metal-catalyzed allylic dearomatization reactions,[8] only recently has the strategy been found to be compatible with electron-deficient arenes.[9] The allylic dearomatization reaction of pyridine was achieved under iridium catalysis in excellent yields and enantioselectivity in an intramolecular fashion.[9a] According to the proposed mechanism, the acidic Hα is easily deprotonated, thus leading to the intermediate which favors N attack. However, the intermolecular reaction remains

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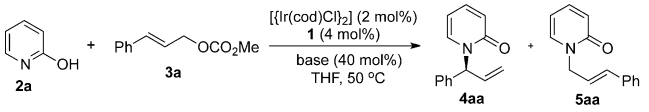
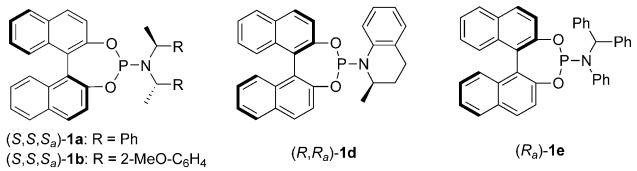
unknown. Inspired by the previous report, we envisaged that the utilization of 2-hydroxypyridine might allow entry to the intermolecular asymmetric allylic dearomatization because there exists a tautomeric equilibrium between 2-hydroxypyridine and 2-pyridone.[10] This methodology will provide a direct approach to the asymmetric synthesis of N-substituted 2-pyridones bearing a stereocenter α to N (Scheme 1c). Herein, we report our results from this study.

The initial experiment was performed with 2-hydroxypyridine (**2a**) and cinnamyl methyl carbonate (**3a**) in the presence of a well-developed iridium catalytic system[11,12] including [{Ir(cod)Cl}$_2$] (2 mol%) and the Feringa phosphoramidite (*S*,*S*,*S*$_a$)-**1a** (4 mol%) in tetrahydrofuran at 50°C. By using Cs_2CO_3 as the base, the desired N-alkylation process proceeded in 96% conversion to give the branched product **4aa** in 84% yield and 94% *ee* without observation of the O-alkylation product (entry 1, Table 1). It is likely that the corresponding η^3-allyl/Ir intermediate is a soft electrophile, which is more easily attacked by the soft 2-pyridone nitrogen nucleophile rather than the hard oxygen anion of 2-hydroxypyridine.[13] The feasibility of N attack of **2a** encouraged us to investigate other chiral phosphoramidite ligands. To our delight, the reaction proceeded much more quickly with a significant increase in yield and enantioselectivity (entry 2) when the Alexakis ligand (*S*,*S*,*S*$_a$)-**1b** was used.[14] The reaction with **1c** also led to a satisfactory result (entry 3). However, the use of (*R*,*R*$_a$)-**1d** or (*R*$_a$)-**1e** afforded the desired product (**4aa**) in moderate enantioselectivity but with disappointing yield and regioselectivity (entries 4 and 5). Next, we turned our attention to examining the effect of the base. Notably, the reaction did not occur at all in the absence of an additional base (entry 6, Table 1). Meanwhile, the use of a weak base such as Et_3N could only give trace amounts of product (entry 7). In contrast, a stronger organic base such as DBU and various inorganic bases such as *t*BuOLi, K_3PO_4, K_2CO_3, and NaH could all be tolerated, thus affording the desired products in good yields and excellent enantioselectivity (entries 8–12). Among them, Cs_2CO_3 was found to be the optimal base (entry 2). Then, varying the amount of Cs_2CO_3 indicated that increasing the loading of base to 1 equivalent led to a slightly lower yield. However, 2 equivalents of Cs_2CO_3 had a detrimental effect on both the conversion and regioselectivity (entries 13 and 14). Above all, the best conditions were obtained as the following: reaction of **3a** with 2 equivalents of **2a** in THF with 2 mol% of [{Ir(cod)Cl}$_2$], 4 mol% of (*S*,*S*,*S*$_a$)-**1b**, and 40 mol% of Cs_2CO_3 at 50°C (entry 2, Table 1).[15]

Table 1: Investigation of the reaction conditions.[a]

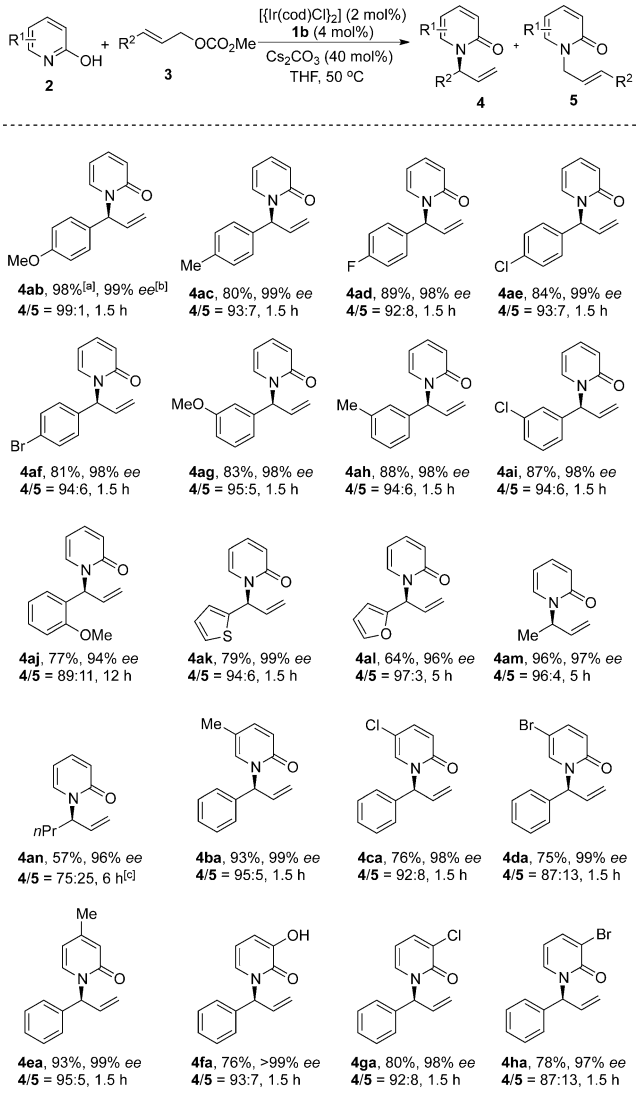




Entry	Ligand	Base	*t* [h]	Conv. [%][b]	**4aa**/**5aa**[b]	**4aa** Yield [%][c]	**4aa** *ee* [%][d]
1	**1a**	Cs_2CO_3	19	96	95:5	84	94
2	**1b**	Cs_2CO_3	1.5	>95	95:5	94	98
3	**1c**	Cs_2CO_3	6.5	>95	96:4	96	93
4	**1d**	Cs_2CO_3	19	82	48:52	26	77
5	**1e**	Cs_2CO_3	19	26	18:82	6	60
6	**1b**	–	22	<5	–	–	–
7	**1b**	Et_3N	22	16	–	14	96
8	**1b**	DBU	1.5	92	>97:3	83	98
9	**1b**	*t*BuOLi	22	85	94:6	79	99
10	**1b**	K_3PO_4	1.5	85	94:6	79	99
11	**1b**	K_2CO_3	1.5	>95	95:5	85	98
12	**1b**	NaH	1.5	>95	94:6	87	99
13[e]	**1b**	Cs_2CO_3	1.5	>95	94:6	84	99
14[f]	**1b**	Cs_2CO_3	22	89	89:11	61	98

[a] Reaction conditions: 2 mol% of [{Ir(cod)Cl}$_2$], 4 mol% of **1**, 40 mol% of base, 200 mol% of **2a** and 100 mol% of **3a** in 2.0 mL THF at 50°C. Unless noted, N/O > 95:5. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yield of isolated **4aa**. [d] The *ee* value of **4aa** was determined by HPLC analysis. [e] 100 mol% of Cs_2CO_3 was used as the base. [f] 200 mol% of Cs_2CO_3 was used as the base. cod = 1,5-cyclooctadiene, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, THF = tetrahydrofuran.

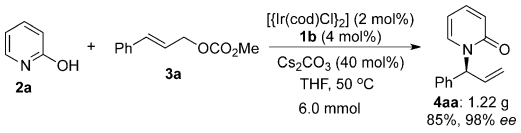
Under the optimized reaction conditions, the substrate scope of this intermolecular allylic amination with 2-hydroxypyridines was examined. Firstly, various allylic carbonates were tested using **2a** as the nucleophile. As summarized in Scheme 2, for the aryl allylic carbonates, substituents on different positions of the phenyl moiety (4-MeOC_6H_4, 4-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3-MeOC_6H_4, 3-MeC_6H_4, 3-ClC_6H_4) were well tolerated, and their corresponding products **4ab–ai** were obtained in 80–98% yields with 98–99% *ee*. Notably, the generally unfavorable *ortho*-substituted substrate was also compatible with this transformation, and **4aj** was obtained in 77% yield and 94% *ee*. To our delight, heteroaryl allylic carbonates were also suitable substrates, thus delivering the amination products **4ak** and **4al** with excellent regioselectivity and *ee* values, and good yields upon isolation. In addition to aromatic substituents, aliphatic allylic carbonates (Me, *n*Pr) were also tested. The reaction of methyl crotyl carbonate occurred smoothly, thus affording satisfactory results (**4am**/**5am**), but the reaction of *n*-propyl-substituted allylic carbonate gave rise to moderate chemoselectivity and regioselectivity, with excellent enantioselectivity (N/O = 86:14; **4an**/**5an**). No notable improvement on the chemo-, regio-, and enantioselectivity was observed using [{Ir(dbcot)Cl}$_2$][12g,16] (N/O = 82:18; **4an**/**5an**) instead of [{Ir(cod)Cl}$_2$]. Notably, the bulky *t*-butyl-substituted allylic carbonate was found to be unreactive.[17] Next, the generality of the reaction with respect to the 2-hydroxypyridine derivatives using the cinnamyl carbonate **3a** as the electrophilic counterpart was explored. We were pleased to discover that the reactions of substrates with a range of substituents on the pyridine moiety, including those bearing either an electron-donating (5-Me, 4-Me, 3-OH) or electron-withdrawing group (5-Cl, 5-Br, 3-Cl, 3-Br), were highly efficient with excellent regioselectivity (**4**/**5**: 87:13–95:5) and enantioselectivity (**4ba–4ha**). The reaction of 5-NO_2 pyridone (**2i**) and **3a**



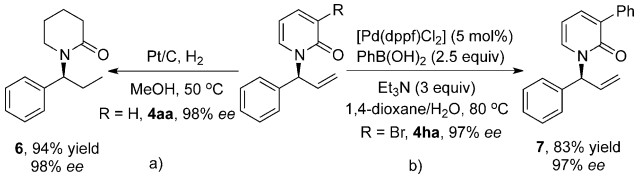
Scheme 2. Reaction substrate scope. Reaction conditions: 2 mol% of $[\{Ir(cod)Cl\}_2]$, 4 mol% of (*S*,*S*,S_a)-**1b**, 0.4 mmol of **3**, 0.8 mmol of **2**, and 0.16 mmol of Cs_2CO_3 in 4.0 mL THF at 50 °C. The ratio of **4**/**5** and N/O selectivity were determined by ^{1}H NMR analysis of the crude reaction mixture. Catalyst was prepared by nPrNH$_2$ activation. Unless noted, N/O > 95:5. [a] Yield of isolated **4**. [b] The *ee* value of **4** was determined by HPLC analysis. [c] N/O = 86:14.

was attempted. However, poor reactivity and regioselectivity were observed (**4ia**: 16%, 87% *ee*, **4**/**5**: 25:75, 19 h).[17] It is worth noting that the relatively electron-rich 2-hydroxypyridine derivatives exhibited better regioselectivity than the electron-deficient ones. The absolute configuration of the product **4aa** was assigned by comparing the sign of the optical rotation with that reported in the literature.[5g]

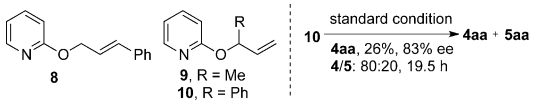
To explore the practicality of the current methodology, a gram-scale synthesis of **4aa** was carried out. The reaction of **2a** with **3a** on a 6.0 mmol scale delivered the desired product **4aa** in 85% yield and 98% *ee* (Scheme 3). Then subjecting **4aa** (98% *ee*) to a Pt/C-catalyzed hydrogenation reaction afforded the chiral amide in 94% yield and 98% *ee* (Scheme 4a). A palladium-catalyzed Suzuki coupling was conducted with the bromo-containing product **4ha** and



Scheme 3. A gram-scale synthesis of **4aa**.



Scheme 4. Transformation of the products. dppf = 1,1′-bis(diphenylphosphino)ferrocene.



Scheme 5. Conversion of O-allylation products.

$PhB(OH)_2$, furnishing **7** (97% *ee*) without any loss of the enantiomeric purity (Scheme 4b).[17]

To further shed light on the reaction mechanism, we synthesized the possible O-alkylated products (**8**, **9**, **10**; Scheme 5). Under the standard reaction conditions, the reaction did not occur at all with either 2-(cinnamyloxy)pyridine (**8**) or 2-(but-3-en-2-yloxy)pyridine (**9**). The reaction with 2-((1-phenylallyl)oxy)pyridine (**10**) took a much more prolonged reaction time (19.5 h) to give the desired 2-pyridone products (**4aa** and **5aa**) in 38% conversion and 80:20 branched to linear selectivity. **4aa** was isolated in 28% yield and 83% *ee*, which were quite different from the results obtained from **2a** and **3a** (branched/linear 95:5; **4aa**, 1.5 h, 94%, 98% *ee*). These data indicate the O allylation followed by rearrangement or rapid retroreaction of the O-allylation product is unlikely to be involved.[17]

In conclusion, the first iridium-catalyzed intermolecular regio- and enantioselective allylic amination reaction with 2-hydroxypyridines has been developed, thus providing a highly efficient synthesis of enantioenriched N-substituted 2-pyridone derivatives from readily available starting materials. This protocol features a good tolerance of functional groups in both the allylic carbonates and 2-hydroxypyridines, thus delivering multifunctionalized heterocyclic products in excellent yields and enantioselectivity. Further transformation of the products is ongoing in our laboratory.

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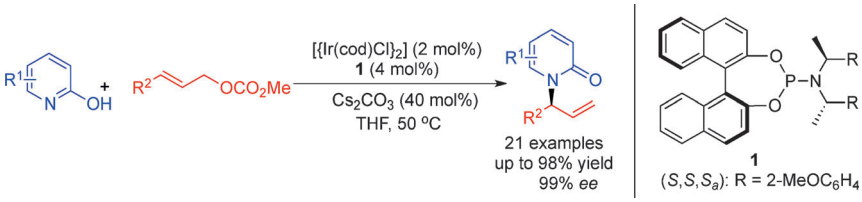
[17] See the Supporting Information for details.

Communications

Asymmetric Catalysis

X. Zhang, Z.-P. Yang, L. Huang, S.-L. You* ——— ■■■■–■■■■

Highly Regio- and Enantioselective Synthesis of N-Substituted 2-Pyridones: Iridium-Catalyzed Intermolecular Asymmetric Allylic Amination



Readily available 2-hydroxypyridines are converted into enantioenriched N-substituted 2-pyridone derivatives by means of a highly efficient protocol. The title reaction features a good tolerance of functional groups in both the allylic carbonates and 2-hydroxypyridines, thus delivering multifunctionalized heterocyclic products with up to 98% yield and 99% *ee*. cod = 1,5-cyclooctadiene.