Asymmetric Catalysis

DOI: 10.1002/anie.201404286

Direct Asymmetric Dearomatization of Pyridines and Pyrazines by Iridium-Catalyzed Allylic Amination Reactions**

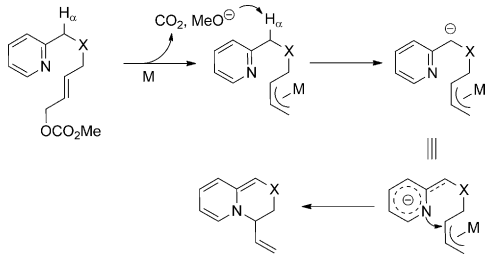
*Ze-Peng Yang, Qing-Feng Wu, and Shu-Li You**

Dedicated to Professor Changtao Qian on the occasion of his 80th birthday

Abstract: *The first iridium-catalyzed intramolecular asymmetric allylic dearomatization reaction of pyridines and pyrazines has been realized. 2,3-Dihydroindolizine and 6,7-dihydropyrrolo[1,2-a]pyrazine derivatives were obtained with excellent yields and enantioselectivity. This methodology features dearomatization by direct N-allylic alkylation of pyridines or pyrazines under mild reaction conditions.*

Aromatic compounds have found wide application as basic chemical feedstocks in polymers, paints, cosmetics, pharmaceuticals, and many others. Dearomatization reactions of these readily available and cheap starting materials could produce a variety of fused, bridged, and spiro ring structures in a very straightforward manner.[1] Therefore the dearomatization process is now one of the most important transformations of aromatic compounds and widely applied in the synthesis of functional molecules. Despite significant efforts devoted to the development of dearomatization reactions and their subsequent transformations, it has only been recently that direct catalytic asymmetric dearomatization reactions have been achieved.[1b,c] We recently found that transition-metal-catalyzed allylic substitution reactions were compatible with asymmetric dearomatization processes for various aromatics such as indoles, pyrroles, and phenols.[2,3] However, suitable aromatic compounds are limited to electron-rich nucleophiles, and electron-deficient aromatic compounds, such as pyridines and pyrazines, have not been explored yet.

To date, asymmetric dearomatization reactions of pyridine derivatives have focused on asymmetric hydrogenations,[4] transfer hydrogenations,[5] and Reissert-type reactions.[6] In most cases, preactivation by N-acylation or alkylation to generate highly electrophilic pyridinium intermediates is required. The removal of the protecting group from the nitrogen atom is always essential at a later stage. In the course of our research program on the development of catalytic asymmetric dearomatization reactions,[7] we became interested in exploring pyridine derivatives as an N nucleophile in allylic substitution reactions, thus providing the corresponding dearomatized products, which are usually found as a core structure in numerous alkaloids and biologically active compounds.[8,9] As shown in Scheme 1, the acidic H_α could be easily deprotonated, thus affording an electron-rich intermediate. The intramolecular design would favor the N atom as a nucleophile in the allylic substitution reaction, thus leading to the dearomatized product. This approach was found to work well under iridium catalysis, and we herein report such a direct asymmetric allylic dearomatization reaction of pyridines and pyrazines.



Scheme 1. Proposed allylic dearomatization reaction of pyridine.

At the outset, we utilized a well-developed catalytic iridium system including $[\{Ir(cod)Cl\}_2]$ and the phosphoramidite **L1** (Table 1) as the catalyst.[10] In the presence of 2 mol% of $[\{Ir(cod)Cl\}_2]$ and 4 mol% of **L1**, reaction of **1a** in THF at room temperature for 6 hours gave the dearomatized product **2a** in 90% yield with 96% *ee* (entry 1). Several chiral ligands were then examined, and the Alexakis ligand **L2**[11] was found to be the optimal ligand, thus affording **2a** in 99% yield and 98% *ee* (entry 2). Other screened ligands (**L3**, **L4** and **L5**) could also catalyze the reaction with excellent enantioselectivity, but in decreased yields (entries 3–5). Varying the solvents (1,4-dioxane, CH_2Cl_2, Et_2O and cyclohexane) influenced the outcome considerably. The reaction in THF gave the best result, thus affording **2a** in 99% yield and 98% *ee* (entry 2).

Under the optimized reaction conditions with the iridium catalyst, formed in situ from $[\{Ir(cod)Cl\}_2]$ and **L2**, various 2-pyridyl allylic carbonates were tested to examine the generality of the reaction. The results are summarized in Table 2. Reactions of the allylic carbonate substrates bearing a CO_2Me or CO_2Et group on the linking atom both gave the dearomatized products, thus forming the indolizines **2** in good yields with excellent *ee* values (entries 1 and 2).

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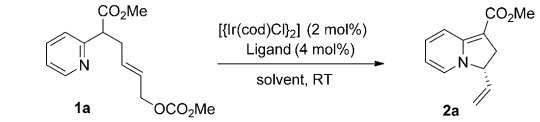
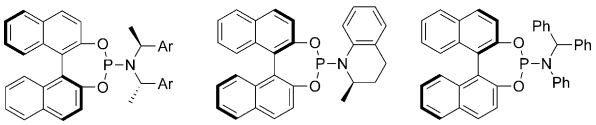
[**] We thank the National Basic Research Program of China (973 Program 2010CB833300), NSFC (21025209, 21121062, 21332009), and the Chinese Academy of Sciences for generous financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201404286.

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





L1 (S,S,S_a), Ar = Ph
L2 (S,S,S_a), Ar = 2-MeO-C_6H_4
L3 (S,S,S_a), Ar = 2-naphthyl

L4 (R,R_a)

L5 (R_a)

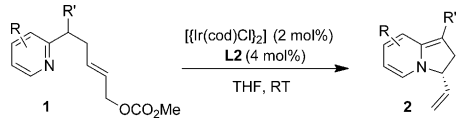
Entry	Ligand	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**L1**	THF	6	90	96
2	**L2**	THF	4	99	98
3	**L3**	THF	6	88	93
4	**L4**	THF	12	81	96
5	**L5**	THF	12	88	95
6	**L2**	1,4-dioxane	5	78	98
7	**L2**	CH_2Cl_2	12	82	83
8	**L2**	Et_2O	12	44	91
9	**L2**	cyclohexane	12	52	89

[a] Reaction conditions: $[\{Ir(cod)Cl\}_2]$/**L**/**1a** = 0.02:0.04:1.0; 0.2 mmol of **1a** in solvent (2.0 mL), RT. Catalyst was prepared by *n*$PrNH_2$ activation. [b] Yield of isolated product. [c] Determined by HPLC analysis. cod = 1,5-cyclooctadiene, THF = tetrahydrofuran.

Substrates bearing either an electron-donating group (5-MeO, 4-Me, 5-Me, 5-Ph; entries 3–6) or electron-withdrawing group (5-Cl, 5-Br; entries 7 and 8) on the pyridine core all led to the corresponding products in excellent yields and *ee* values. When the substrates **1i** and **1j**, bearing 4-Cl and 4-Br, respectively, were tested, the reaction proceeded smoothly to afford the dearomatized products with full conversion. However, the products were not stable during the purification process. After a Diels–Alder reaction (see below) with diethyl acetylenedicarboxylate in situ, the enantioselectivity of the products was determined to be 99% *ee* (entries 9 and 10).[12] The structure of the product was confirmed unambiguously by an X-ray crystallographic analysis of a single crystal of **2f**.[12] Next, various groups (R′) on the linking atom were tested. Substrates bearing an Ac (entry 11), Bz (entry 12), and *p*-Br-C_6H_4CO (entry 13) groups all gave the desired amination products in good to excellent yields and excellent enantioselectivity (82–94% yield, 91–99% *ee*). The substrate **1n**, having a $PhSO_2CH$ linker, was also tolerated and afforded the corresponding product in 82% yield and 83% *ee* (entry 14). Notably, when the dimethyl malonate substrate **1o** was used, the desired product **2o** was unstable during the purification. Therefore Pt/C-mediated hydrogenation was carried out after the dearomatization reaction, and **2o′** was obtained in 92% yield and 89% *ee* (entry 15).

Interestingly, under slightly modified reaction conditions, as shown in Table 3, pyrazine derivatives were also found to be suitable for allylic dearomatization reactions. Various substituted pyrazine-linked allylic carbonates were tested to examine the substrate scope. The results are summarized in Table 3. To our delight, all the substrates, having either various electron-withdrawing groups on the linking carbon atom or substituents on the pyrazine core, underwent the asymmetric allylic dearomatization reaction smoothly. Their

Table 2: The reaction substrate scope of pyridine derivatives.[a]



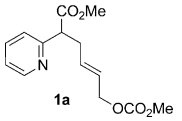
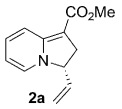
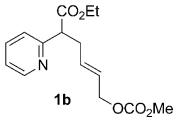
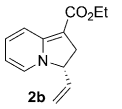
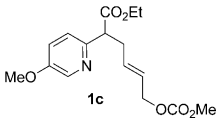
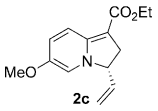
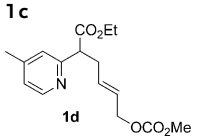
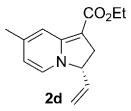
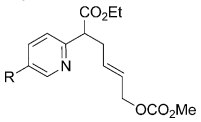
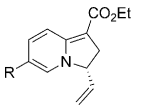
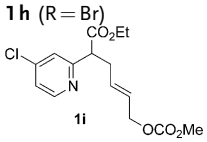
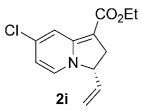
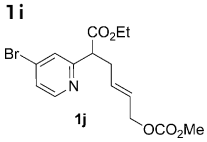
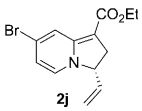
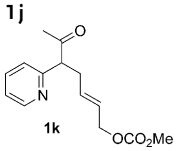
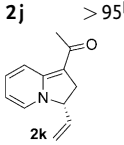
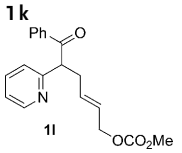
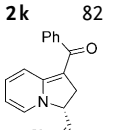
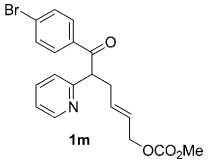
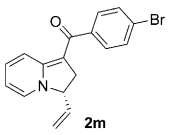
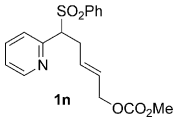
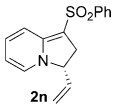
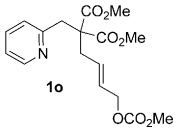
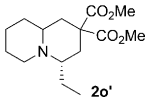
Entry	**1**	*t* [h]	**2**	Yield [%][b]	*ee* [%][c]
					
1	**1a**	4	**2a**	99	98
					
2	**1b**	4	**2b**	93	97
					
3	**1c**	2	**2c**	95	95
					
4	**1d**	4	**2d**	93	95
					
5	**1e** (R = Me)	4	**2e**	90	96
6	**1f** (R = Ph)	4	**2f**	99	98
7	**1g** (R = Cl)	4	**2g**	94	98
8	**1h** (R = Br)	3	**2h**	98	96
					
9	**1i**	4	**2i**	> 95[d]	99[e]
					
10	**1j**	4	**2j**	> 95[d]	99[e]
					
11[f]	**1k**	12	**2k**	82	93
					
12[f]	**1l**	3	**2l**	94	99

Table 2: (Continued)

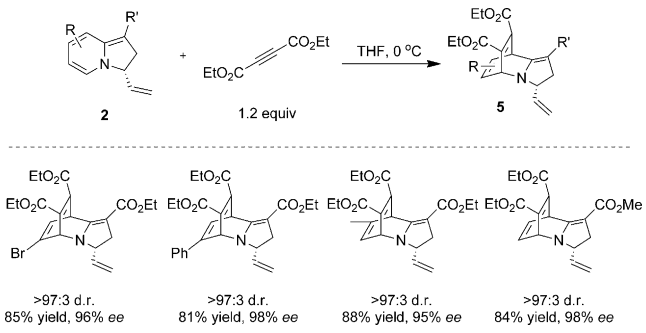
Entry	1	t [h]	2	Yield [%][b]	ee [%][c]
					
	1m		2m		
13	1m	5	2m	90	91
					
	1n		2n		
14[f]	1n	12	2n	82	83
					
	1o		2o'		
15[g]	1o	0.2	2o′	92[h]	89

[a] Reaction conditions: [{Ir(cod)Cl}$_2$]/**L2**/**1** = 0.02:0.04:1.0; 0.2 mmol of **1** in THF (2.0 mL), RT. Catalyst was prepared by *n*PrNH$_2$ activation. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] Conversion determined by ^{1}H NMR analysis of the crude reaction mixture. [e] Determined after Diels–Alder reaction with diethyl acetylenedicarboxylate.[12] [f] Reaction conducted at 50 °C. [g] Used 0.2 equiv of DABCO as the base and hydrogenation was carried out after dearomatization reaction.[12] [h] The d.r. value of **2o′** is 5:1.

corresponding 6,7-dihydropyrrolo[1,2-*a*]pyrazine derivatives were obtained in 64–95% yield and 86–97% *ee*. These results show that the dearomatization strategy by direct N-allylic alkylation is general for nitrogen-containing heteroarenes.

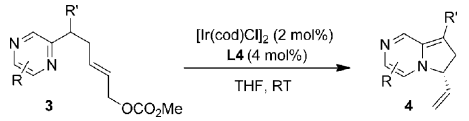
Furthermore, the dearomatized products obtained here could be applied to the Diels–Alder reaction for the synthesis of the multifunctionalized bridged ring compounds. As shown in Scheme 2, in the presence of 1.2 equivalents of diethyl acetylenedicarboxylate as the dienophile, various Diels–Alder products (**5**) could be obtained in good yields with excellent d.r. values. In all cases, the products were obtained without the loss of the enantiomeric purity.

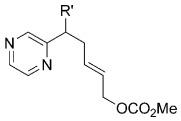
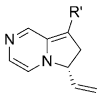
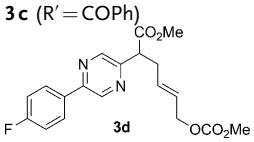
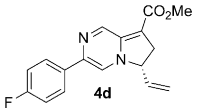
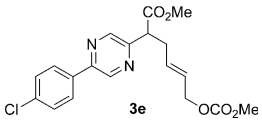
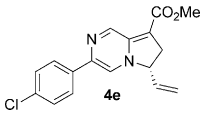
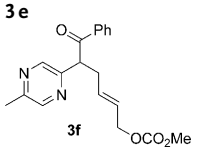
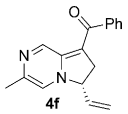
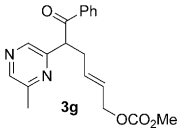
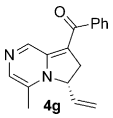
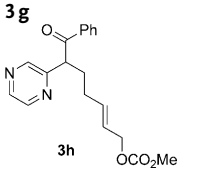
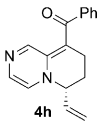
In summary, the first iridium-catalyzed intramolecular asymmetric allylic dearomatization reaction of pyridines and pyrazines has been realized. Under extremely mild reaction conditions, the dearomatized 2,3-dihydroindolizine and 6,7-dihydropyrrolo[1,2-*a*]pyrazine derivatives were obtained in excellent yields and enantioselectivity. The enantioenriched dihydroindolizine products could be subjected to Diels–Alder reactions with diethyl acetylenedicarboxylate as the dienophile. Another feature of the current dearomatization reaction is the fact that the dearomatization reaction proceeds by the direct N-allylic alkylation of pyridines and pyrazines. Work on the extension of the reaction scope and development of more efficient catalytic systems are currently underway in our laboratory.



Scheme 2. Diels–Alder reactions with diethyl acetylenedicarboxylate.

Table 3: The reaction substrate scope of pyrazine derivatives.[a]



Entry	3	t [h]	4	Yield [%][b]	ee [%][c]
					
1	3a (R′ = CO_2Et)	18	4a	88	94
2	3b (R′ = CO_2tBu)	17	4b	68	92
3	3c (R′ = COPh)	12	4c	95	97
					
	3d		4d		
4	3d	36	4d	75	96
					
	3e		4e		
5	3e	40	4e	75	97
					
	3f		4f		
6	3f	1.5	4f	64	91
					
	3g		4g		
7	3g	40	4g	71	86
					
	3h		4h		
8	3h	36	4h	91	92

[a] Reaction conditions: [{Ir(cod)Cl}$_2$]/**L4**/**3** = 0.02:0.04:1.0; 0.2 mmol of **3** in THF (2.0 mL), RT. Catalyst was prepared by *n*PrNH$_2$ activation. [b] Yield of the isolated product. [c] Determined by HPLC analysis.

Received: April 14, 2014
Published online: May 26, 2014

Keywords: allylic compounds · asymmetric catalysis · cyclization · heterocycles · iridium

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[12] See the Supporting Information for details. CCDC 985966 (**2 f**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

