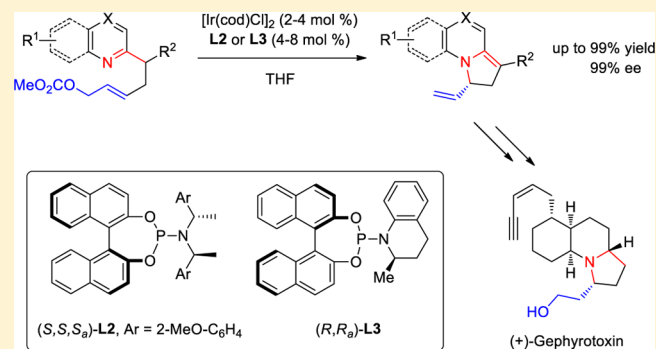# Iridium-Catalyzed Intramolecular Asymmetric Allylic Dearomatization Reaction of Pyridines, Pyrazines, Quinolines, and Isoquinolines

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Ⓢ *Supporting Information*

ABSTRACT: The first Ir-catalyzed intramolecular asymmetric allylic dearomatization reaction of pyridines, pyrazines, quinolines, and isoquinolines has been developed. Enabled by in situ formed chiral Ir-catalyst, the dearomatized products were isolated in high levels of yield (up to 99% yield) and enantioselectivity (up to 99% ee). It is worth noting that the Me-THQphos ligand is much more efficient than other tested ligands for the dearomatization of pyrazines and certain quinolines. Mechanistic studies of the dearomatization reaction were carried out, and the results suggest the feasibility of an alternative process which features the formation of a quinolinium as the key intermediate. The mechanistic findings render this reaction a yet unknown type in the chemistry of Reissert-type reactions. In addition, the utility of this method was showcased by a large-scale reaction and formal synthesis of (+)-gephyrotoxin.
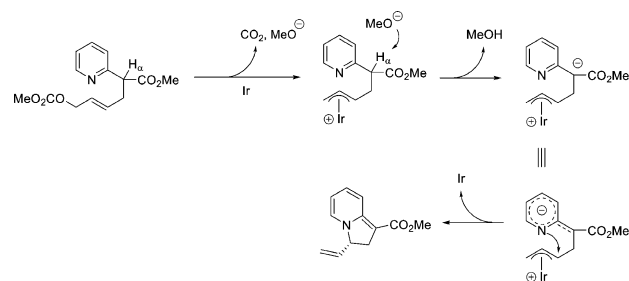
■ INTRODUCTION

Aromatic compounds are an important structural motif and widely distributed in nature. Among them, heterocyclic aromatics, especially those containing one or more nitrogen atoms, occupy a privileged position as they are found in numerous biologically active compounds and pharmaceuticals.[1] Functionalization of these compounds has witnessed significant progresses for a long time. Dearomatization reaction represents a special class of transformations, in which planar aromatics are directly converted to complex three-dimensional molecules.[2] In particular, catalytic asymmetric dearomatization (CADA) reaction has attracted enormous attention because of its potential impact on synthetic organic chemistry.[3] Over the past decade, the transition-metal-catalyzed allylic dearomatization reaction[4] has emerged as an innovative and powerful type of CADA reaction.[5] However, successful cases are limited to electron-rich aromatics, such as indoles,[5b,d,g,j,k,m,n] pyrroles,[5e,h,i] phenols,[5c,l] and naphthols,[5f] while electron-poor aromatics, such as pyridines, pyrazines, quinolines and isoquinolines, are less studied.

Direct addition of nucleophiles to preactivated electrophilic pyridinium intermediate, known as the Reissert-type reaction, is a valuable strategy for asymmetric dearomatization of pyridines.[6] Other viable methods include hydrogenation,[7] transfer hydrogenation,[8] hydrosilylation,[9] and hydroboration[10] reactions. As a step toward the dearomatization of N-heteroaromatics, we recently developed an iridium-catalyzed intramolecular asymmetric allylic dearomatization reaction of

pyridines and pyrazines.[11] By employing this method, a series of 2,3-dihydroindolizines and 6,7-dihydropyrrolo[1,2-*a*]-pyrazines were easily synthesized in high levels of yield and enantioselectivity.

This dearomatization process was originally proposed to proceed according to the mechanism shown in Scheme 1. It was speculated that the reaction is initiated by the well-established iridium-mediated oxidative addition of allylic carbonate.[12] Then the acidic Hα is deprotonated by the liberated methoxy anion, forming a relatively stable carbon anion. The conjugation effect compels the N-attack to be

Scheme 1. Originally Proposed Mechanism of the Dearomatization Reaction of Pyridine
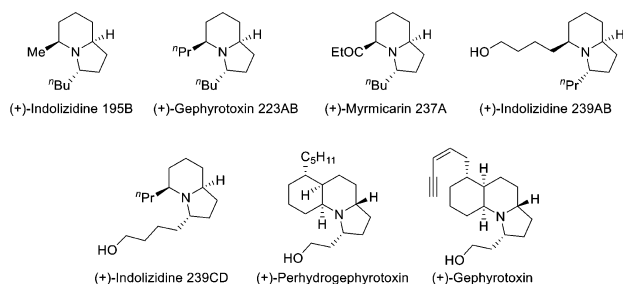
achieved, and the corresponding dearomatized product is thus obtained.

In this article, we sought to further study the scope and detailed reaction mechanism. Our research along these lines led to an alternative catalytic cycle. In addition, we exploited the synthetic utility of this method, as the core structure of the dearomatized products is found in many biologically active natural products (Chart 1).[13,14] Herein, we present a full

Chart 1. Selected Biologically Active Piperidine-Containing Natural Products

(+)-Indolizidine 195B   (+)-Gephyrotoxin 223AB   (+)-Myrmicarin 237A   (+)-Indolizidine 239AB

(+)-Indolizidine 239CD   (+)-Perhydrogephyrotoxin   (+)-Gephyrotoxin

account of our recent work on the Ir-catalyzed intramolecular asymmetric allylic dearomatization reaction of N-heteroaromatics, which mainly addresses these following aspects: (1) exploration of broader substrate scope for dearomatization reaction of pyrazines; (2) asymmetric dearomatization reaction of quinolines and isoquinolines; (3) mechanistic studies of the dearomatization reaction; and (4) formal synthesis of (+)-gephyrotoxin.

■ SUBSTRATE SCOPE AND MECHANISTIC STUDIES

Iridium-Catalyzed Intramolecular Asymmetric Allylic Dearomatization Reaction of Pyridines. First, the dearomatization of pyridines was investigated by using an in situ formed chiral Ir-complex as the catalyst. Under very mild conditions, 15 examples of intramolecular dearomatization were successfully explored (Scheme 2), and the dearomatized structure was further confirmed by X-ray analysis.[11] The corresponding 2,3-dihydroindolizine **2** was obtained in excellent yields and enantioselectivity.

Scheme 2. Ir-Catalyzed Intramolecular Asymmetric Allylic Dearomatization Reaction of Pyridines
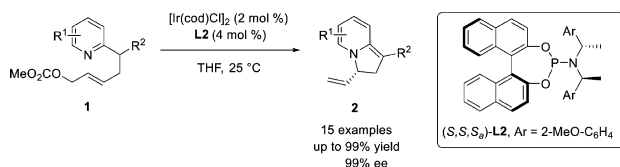
Iridium-Catalyzed Intramolecular Asymmetric Allylic Dearomatization Reaction of Pyrazines. Dearomatization of pyrazines is very important as it provides a rapid access to a variety of 6,7-dihydropyrrolo[1,2-*a*]pyrazines, which could lead to valuable piperazines after simple transformations.

Our efforts to develop the dearomatization of pyrazines began by evaluating the reaction of **3a** as the model substrate. Exposure of **3a** to chiral Ir-complex, derived from [Ir(cod)Cl]₂ and the Feringa ligand **L1**, in THF afforded the dearomatized product **4a** in 45% conversion and 85% ee (Table 1, entry 1). The low conversion might be caused by the attenuated

Table 1. Optimization of the Reaction Conditions for the Dearomatization of Pyrazines[a]
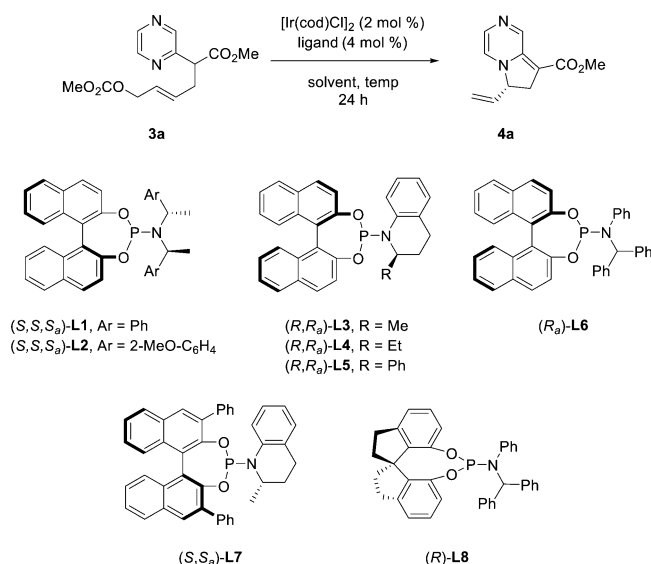
entry	ligand	T (°C)	solvent	conv. (%)[b]	ee (%)[c]
1	L1	50	THF	45	85
2	L2	50	THF	25	93
3	L3	50	THF	>95	93
4	L4	50	THF	85	94
5	L5	50	THF	33	80
6	L6	50	THF	65	93
7	L7	50	THF	80	−77
8	L8	50	THF	8	–
9	L3	25	THF	>95 (99)[d]	97
10	L3	25	CH₂Cl₂	>95	94
11	L3	25	1,4-dioxane	>95	95
12	L3	25	toluene	>95	95

[a]Reaction conditions: 2 mol % of [Ir(cod)Cl]₂, 4 mol % of ligand, and 0.2 mmol of **3a** in solvent (2.0 mL). Catalyst was prepared via ^{n}PrNH₂ activation.[12i] [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Determined by HPLC analysis. [d]Isolated yield of **4a** in parentheses.

nucleophilicity of the pyrazine core. Next, several chiral ligands were examined (Table 1, entries 2−8). To our delight, it was found that Me-THQphos **L3**, developed by our group, was effective in this reaction. Substrate **3a** was consumed completely, giving **4a** in 93% ee (Table 1, entry 3). Further screening of temperature and solvents (Table 1, entries 9−12) led to the optimal conditions: 2 mol % of [Ir(cod)Cl]₂ and 4 mol % of **L3** in THF under room temperature, and **4a** was obtained in 99% yield and 97% ee. Under these conditions, various 2-pyrazinyl allylic carbonates were examined.

As shown in Table 2, the reaction proceeded well with a range of substrates, encompassing an N-atom as terminating nucleophile and delivering a range of heterocyclic ring systems. A series of 2-pyrazinyl allylic carbonates bearing different electron-withdrawing substituents (Table 2, entries 1−9) all underwent dearomatization in good to excellent yields and enantioselectivity. For the ester group, the yield and enantioselectivity of the reaction decreased with the increase of the steric hindrance (68−99% yields, 92−97% ee; Table 2, entries 1−3). Notably, switching the ester group to cyano led to the detriment of enantioselectivity (78% yield, 61% ee; Table 2, entry 4). To our delight, aryl carbonyl-substituted allylic carbonates were suitable in this reaction, affording the

Table 2. Reaction Substrate Scope of Pyrazine Derivatives[a]

entry	3	t (h)	4	yield (%)[b]	ee (%)[c]
1	3a (R = Me)	24	4a	99	97
2	3b (R = Et)	18	4b	88	94
3	3c (R = ^{t}Bu)	17	4c	68	92
4	3d	11	4d	78	61
5	3e (Ar = Ph)	12	4e	95	97
6	3f (Ar = 4-FC$_6$H$_4$)	40	4f	66	97
7	3g (Ar = 4-ClC$_6$H$_4$)	12	4g	63	98
8	3h (Ar = 4-BrC$_6$H$_4$)	48	4h	68	96
9	3i (Ar = 4-MeC$_6$H$_4$)	12	4i	77	98
10	3j (R = 4-FC$_6$H$_4$)	36	4j	75	96
11	3k (R = 4-ClC$_6$H$_4$)	40	4k	75	97
12	3l (R = 4-MeC$_6$H$_4$)	36	4l	82	96
13	3m (R = 4-MeOC$_6$H$_4$)	21	4m	95	98
14	3n (R = 2-naphthyl)	40	4n	94	98
15	3o (R = PhS)	36	4o	82	99
16	3p	1.5	4p	64	91
17	3q	40	4q	71	86
18	3r	36	4r	91	92

[a]Reaction conditions: 2 mol % of [Ir(cod)Cl]$_2$, 4 mol % of **L3**, and 0.2 mmol of **3** in THF (2.0 mL) at 25 °C. Catalyst was prepared via ^{n}PrNH$_2$ activation. [b]Isolated yield. [c]Determined by HPLC analysis.

dearomatized products in good to excellent yields and excellent stereocontrol (63–95% yields, 96–98% ee; Table 2, entries 5–9).

To further test the potential of this Ir-catalyzed dearomatization reaction, we turned our attention toward the exploration of substrates bearing various substituents on the pyrazine core. Good to excellent yields and excellent ee values were obtained for the cyclization of **3j**–**3n**, varying aryl substituents on the 5-position of the pyrazine in the substrates (75–95% yields, 96–98% ee; Table 2, entries 10–14). It was worth noting that phenylmercapto group was also tolerated (82% yield, 99% ee; Table 2, entry 15). Furthermore, 5- or 6-methyl-substituted pyrazine derivatives proved to be good substrates for the dearomatization reaction (64–71% yields, 86–91% ee; Table 2, entries 16–17). Finally, formation of the six-membered ring also proceeded smoothly starting from substrate **3r** (91% yield, 92% ee; Table 2, entry 18).

Iridium-Catalyzed Intramolecular Asymmetric Allylic Dearomatization Reaction of Quinolines and Isoquinolines. To broaden the scope of this Ir-catalyzed dearomatization reaction, we next examined the reactions of quinolines and isoquinolines. Careful investigations of ligands revealed that Feringa ligand **L1**, Alexakis ligand **L2**, Me-THQphos **L3**, and BHPphos **L6** were all effective in this reaction, affording **6d** in good to excellent yields and excellent enantioselectivity (Table 3, entries 1–4). Especially, the Alexakis ligand **L2** and Me-

Table 3. Optimization of the Reaction Conditions for the Dearomatization of Quinolines[a]

entry	ligand	T (°C)	t (h)	solvent	yield (%)[b]	ee (%)[c]
1	L1	50	7	THF	85	94
2	L2	50	7	THF	97	98
3	L3	50	7	THF	91	97
4	L6	50	7	THF	78	98
5	L7	50	7	THF	68	−87
6	L2	25	12	THF	93	99
7	L2	25	12	CH$_2$Cl$_2$	99	78
8	L2	25	12	1,4-dioxane	87	98
9	L2	25	12	toluene	93	99
10[d]	L2	25	24	THF	88	99

[a]Reaction conditions: 4 mol % of [Ir(cod)Cl]$_2$, 8 mol % of ligand, and 0.2 mmol of **5d** in solvent (2.0 mL). [b]Isolated yield of **6d**. [c]Determined by HPLC analysis. [d]2 mol % of [Ir(cod)Cl]$_2$ and 4 mol % of **L2** were used.

THQphos **L3** offered superior results. Altering the temperature and solvents influenced the reaction considerably (Table 3, entries 6–9). Reducing the catalyst loading gave slightly decreased yield in a prolonged time (Table 3, entry 10).

During the exploration of the substrate scope, it was found that Me-THQphos **L3** could provide a better outcome for certain substrates. We attributed this fact to the delicate spatial arrangement and characteristic C(sp^2)−H bond activation of **L3** during the formation of active iridium catalyst.[15] This is also consistent with previous findings that **L3** is appropriate for reactions with bulky substrates.[15b] Hence, two conditions were employed here to investigate the substrate scope (conditions A:

4 mol % of [Ir(cod)Cl]$_2$, 8 mol % of **L2** in THF under room temperature; conditions B: 4 mol % of [Ir(cod)Cl]$_2$, 8 mol % of **L3** in THF at 50 °C), and the results are summarized in Table 4. When ester-substituted carbonates were employed, 20 mol % of DABCO was requisite to maintain the excellent enantioselectivity (87−99% yields, 98% ee; Table 4, entries 1−3). Substituents on 4-, 5-, 6-, or 7-position of the quinoline core have little influence on yield and enantioselctivity, and a number of methyl or methoxy-substituted (**5e**, **5h**, **5i**, and **5j**) and halogenated (**5f**, **5g**, **5k**, **5l**, **5m**, and **5n**) aromatics all furnished dearomatized products in excellent yields and enantioselectivity (81−99% yields, 96−99% ee; Table 4, entries 5−14). Allylic carbonates incorporating 8-halogenated arenes were found to be highly dependent on the steric effect. Switching the substituent from fluorine to chlorine resulted in a dramatic decrease in both yield and enantioselectivity (53−94% yields, 57−94% ee; Table 4, entries 15−16). The tolerance of complicated substrate was demonstrated in the successful conversion of the benzo[f]quinoline derivative **5q** (95% yield, 99% ee; Table 4, entry 17). Gratifyingly, this Ir-catalyzed dearomatization protocol was also suitable for a substrate bearing an N-linker, efficiently delivering the cyclized product **6r** (99% yield, 91% ee; Table 4, entry 18). Notably, this embedded substructure bearing an N-linker is found as a basic framework in nucleophilic acyl-transfer catalysts introduced by the Deng group.[16] Finally, when isoquinoline **5s** was used in the reaction, the dearomatized product was obtained smoothly, displaying excellent efficiency and enantiocontrol (99% yield, 96% ee; Table 4, entry 19). The structure and stereochemistry of the products were confirmed unambiguously by X-ray crystallographic analysis of a crystal of enantiopure **6h**. The absolute configuration was determined to be R, and this stereocontrol is in accord with the general rule for the Ir-catalytic system.[12c,d]

Mechanistic Studies of the Ir-Catalyzed Intramolecular Asymmetric Allylic Dearomatization Reaction. During the exploration of substrate scope of the pyridine dearomatization reaction, we tested the reaction of **1o** without electron-withdrawing substituent at the α-position under the standard conditions. As shown in Scheme 3 (top), cyclized product **2o** was obtained in excellent yield and enantioselectivity after subsequent hydrogenation reaction.[11] The previously proposed reaction mechanism (Scheme 1) could not account for the experimental observations. According to the proposed mechanism, the H$_α$ is deprotonated first by the liberated methoxy anion. However, it seems that the basicity of methoxy anion might not be enough to cleave the C−H$_α$ bond (Scheme 3, bottom). These results challenged the proposed catalytic cycle and prompted us to conduct detailed mechanistic studies on this reaction.
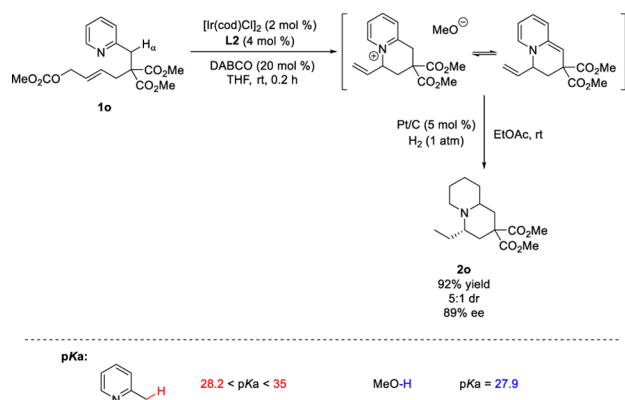
Another plausible mechanism for the dearomatization of quinolines is proposed in Scheme 4 (path b). First, oxidative addition yields the π-allyl intermediate **I**. Subsequent nucleophilic substitution by the N-atom of quinoline generates the quinolinium **IIb**, which would be deprotonated by a base to afford the dearomatized product **6a** finally. With the formation of quinolinium intermediate, the acidity of H$_α$ would increase dramatically. To some degree, the dearomatization reaction of **1o** supports the existence of path b. In addition, the fact that diminished yields and ee are observed when the steric bulkiness of the ester group increases in **3a−3c** (Table 2, entries 1−3) also supports the existence of N-allylated intermediate (pyrazinium). The bulky ester group will cause the slow

Table 4. Reaction Substrate Scope of Quinoline and Isoquinoline Derivatives


entry	5	conds.	t(h)	6	yield (%)[a]	ee (%)[b]
1[c]	5a (R = OMe)	A	4	6a	87	98
2[c]	5b (R = OEt)	A	4	6b	94	98
3[c]	5c (R = O^{n}Pr)	A	4	6c	99	98
4	5d (R = Ph)	A	12	6d	93	99
5	5e (R = OMe)	B	5	6e	91	96
6	5f (R = Cl)	B	4	6f	90	98
7	5g (R = Br)	B	4	6g	87	98
8	5h	B	4	6h	81	98
9	5i (R = Me)	A	4	6i	88	99
10	5j (R = OMe)	A	4	6j	98	99
11	5k (R = F)	A	4	6k	82	98
12	5l (R = Br)	B	5	6l	89	97
13	5m (R = F)	A	4	6m	99	98
14	5n (R = Cl)	A	4	6n	99	98
15	5o (R = F)	B	2	6o	94	94
16	5p (R = Cl)	B	24	6p	53	57
17	5q	B	10	6q	95	99
18	5r	B	1	6r	99	91
19	5s	B	7	6s	99	96

[a]Isolated yield. [b]Determined by HPLC analysis. [c]20 mol % of DABCO was used as the additive.

Scheme 3. Ir-Catalyzed Intramolecular Asymmetric Allylic Dearomatization Reaction of 1o and pKa (DMSO) Values[17] of Corresponding Compounds


Scheme 4. Plausible Mechanism of Dearomatization Reaction
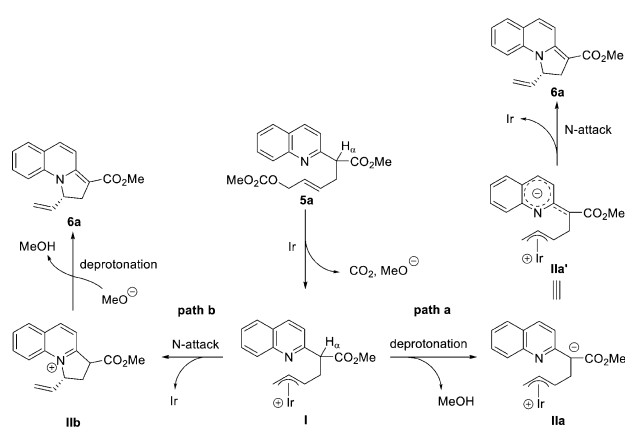
deprotonation process and therefore lead to possible C−N cleavage and other side reactions.

To further shed light on the mechanism, we synthesized substrate **5t** bearing a phosphate leaving group. Under the standard conditions, the dearomatized product **6a** was obtained in 67% yield and 42% ee (Scheme 5, top). Apparently, the observation of dearomatization of phosphate substrate **5t** seems

Scheme 5. Dearomatization of Phosphate Substrate 5t and pKa (DMSO) Values[17] of Corresponding Compounds
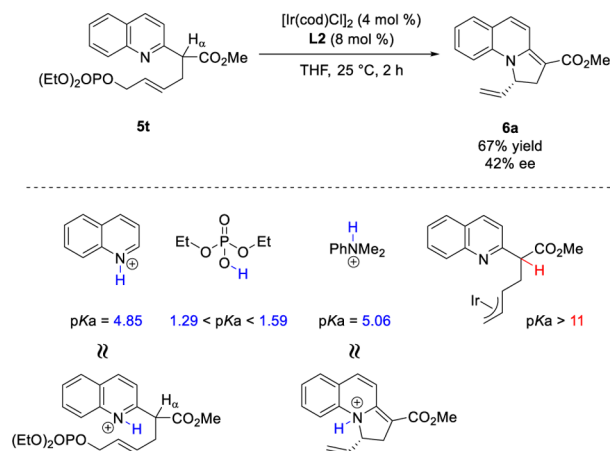
to support the existence of path b, as the base in this system (according to the pKa values, dearomatized product **6a** might be the strongest base in the system) is not strong enough to deprotonate H_α in the substrate (Scheme 5, bottom, 5.06 vs >11). The poor enantiocontrol might arise from the effect of the reversible C−N bond formation due to the slow deprotonation of quinolinium intermediate.
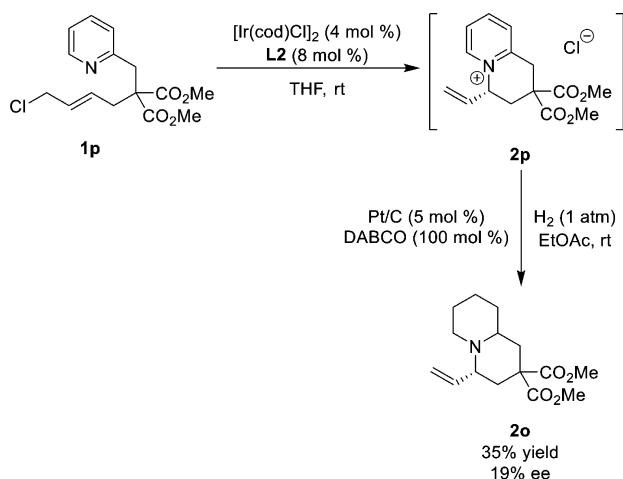
These findings encouraged us to examine whether we could observe or separate the quinolinium intermediate. However, this intermediate was difficult to be observed by in situ IR or ^{1}H NMR experiments. Thus, we prepared substrate **5u** without an electron-withdrawing group. The N-alkylation reaction could not take place under Ir-catalysis. Surprisingly, compound **6u** was obtained by employing $[Pd(PPh_3)_4]$ as the catalyst, implying the feasibility of N-attack directly (Scheme 6, top).

Scheme 6. Capture and in Situ Transformation of Quinolinium Species
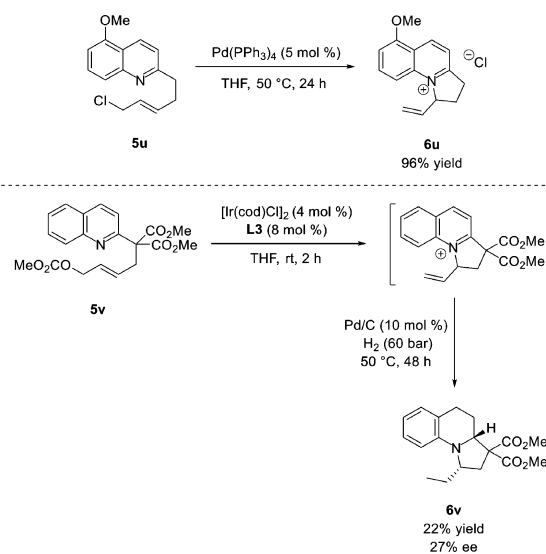
During our investigation, preliminary results showed that the reaction of allylic carbonate with a methylene linker could not afford quinolinium product, and only a small amount of hydrolysis product was obtained. At this stage, further attention was paid to the in situ transformation of the proposed quinolinium intermediate. Gratifyingly, the proposed quinolinium species can be captured by hydrogenation reaction, giving cyclized product **6v** by employing allylic carbonate **5v** as the starting material (Scheme 6, bottom). Pd-catalyzed reversible C−N cleavage during hydrogenation might account for the low ee value (27% ee).[18]
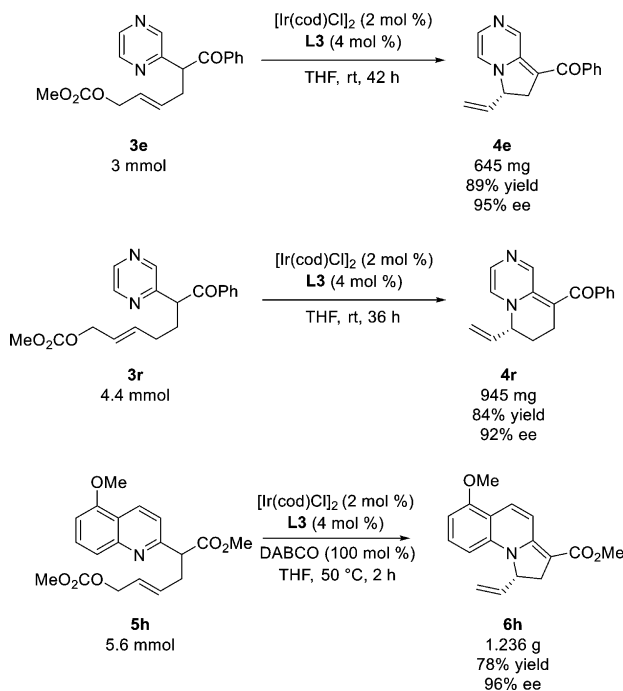
The absence of Thorpe−Ingold effect in substrate **5u** might cause the failure of its transformation under Ir-catalysis. Based on this information, it was envisaged that switching the leaving group in **1o** from carbonate to chloride will provide a chance to characterize the corresponding pyridinium intermediate with iridium complex as the catalyst. As expected, the pyridinium intermediate **2p** was obtained starting from allylic chloride substrate **1p** (Scheme 7). Subsequent hydrogenation produced **2o** with poor enantioselectivity, which was attributed to the reversible C−N bond formation. Therefore, it is strongly indicated that path b (Scheme 4) is a feasible process, albeit path a can not be ruled out.

Scheme 7. Dearomatization of Allylic Chloride Substrate 1p under Ir-Catalysis

synthetic utility of this new method, efforts have been taken toward the preparation of Ito's intermediate **12**.

As shown in Scheme 9, the synthesis commenced with the selective hydroboration/oxidation of terminal olefin in **6h**, and

Scheme 9. Formal Synthesis of (+)-Gephyrotoxin

subsequent hydrogenation furnished **8** as a single diastereoisomer in 48% yield and 92% ee. Protection of the hydroxyl group with MOMCl yielded **9** in a quantitative conversion, and its relative configuration was determined by NOE experiments.[22] Hydrolysis of the methyl ester was achieved by stirring with LiOH·H$_2$O, affording a carboxylic acid, which, after removal of aqueous MeOH, was decarboxylated smoothly under modified Barton decarboxylation conditions[23] in 64% yield over two steps. Final deprotection of the MOM group produced Ito's intermediate **12**. It is noteworthy that this route is the first asymmetric synthesis of gephyrotoxin by a catalytic method.

■ SYNTHETIC APPLICATION

Large-Scale Reaction. The robustness and practicality of current methodology could further be demonstrated by large-scale synthesis. The reaction of **3e**, **3r**, and **5h** on a gram-scale delivered the corresponding products in good yields and excellent enantioselectivity (Scheme 8).

Scheme 8. Large-Scale Reaction

■ CONCLUSION

In summary, we have developed the first Ir-catalyzed intramolecular asymmetric allylic dearomatization reaction of pyridines, pyrazines, quinolines, and isoquinolines. These reactions are enabled by in situ formed chiral Ir-catalyst. For pyrazines and certain quinolines, Me-THQphos ligand is required to obtain the best outcome. Initial mechanistic studies resulted in the discovery of an alternative reaction pathway. The new catalytic cycle features the formation of quinolinium as the key intermediate. However, the previously proposed mechanism involving the deprotonation of acidic H$_\alpha$ as the first step can not be excluded. The mechanistic findings render this reaction a yet unknown type in the chemistry of Reissert-type reaction, which is realized by an intramolecular β-H elimination protocol. Meanwhile, this is the first realization of Ir-catalyzed allylic substitution reaction by employing pyridines, pyrazines, quinolines and isoquinolines as the N-nucleophiles. The robustness and practicality of this method were demonstrated by large-scale reactions. The utility of this method was further illustrated by formal synthesis of (+)-gephyrotoxin.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b10440.

> Experimental procedures and spectral data. Single crystal X-ray diffraction data for compound **6h** (PDF)
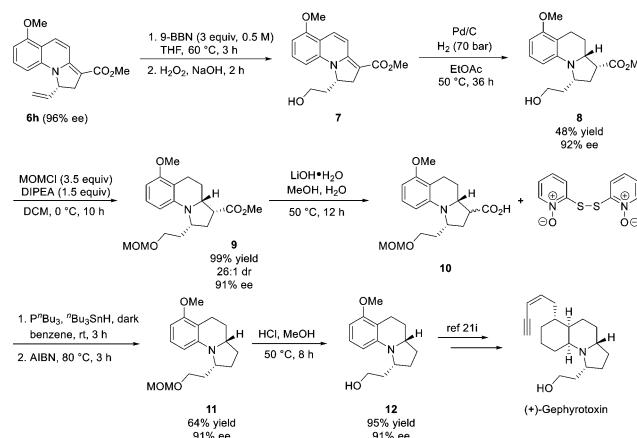
Formal Synthesis of (+)-Gephyrotoxin. Gephyrotoxin is one member of a family of alkaloids isolated from the skin extracts of the Columbian frog, *Dendrobates histrionicus*.[19] Different from other dendrobatid alkaloids, Gephyrotoxin is relatively nontoxic and possesses mild muscarinic activity and interesting neurological activities.[20] The interesting biological characteristics of gephyrotoxin have stimulated synthetic activity in many groups.[21] In 1983, Ito and co-workers synthesized hexahydropyrrolo[1,2-*a*]quinoline **12** and converted it to gephyrotoxin.[21i] To further demonstrate the

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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