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Iridium-Catalyzed Intramolecular Asymmetric Allylic Alkylation of Hydroxyquinolines: Simultaneous Weakening of the Aromaticity of Two Consecutive Aromatic Rings

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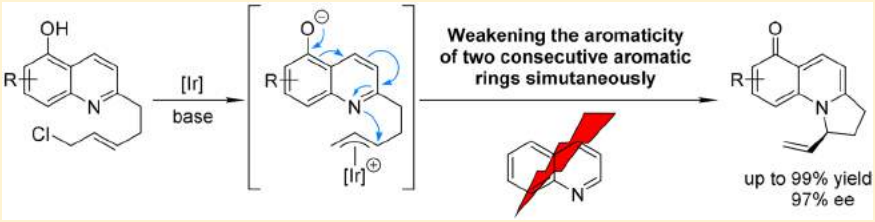
Supporting Information



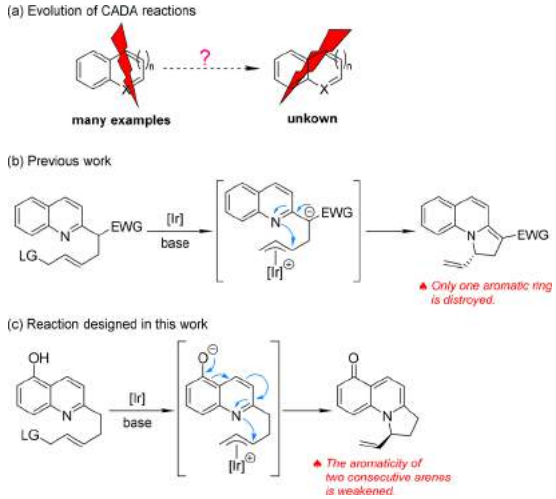
ABSTRACT: Intramolecular asymmetric allylic alkylation reactions of 5- and 7-hydroxyquinoline derivatives were realized by a chiral Ir/NHC catalyst. A series of functionalized cyclic enones were afforded in excellent yields (up to 99%) and high enantioselectivity (up to 97% ee). Theoretical computations revealed that the aromaticity of the two consecutive rings of hydroxyquinoline substrates is significantly weakened. A highly efficient formal synthesis of (−)-gephyrotoxin was accomplished based on this method.

INTRODUCTION

Aromatic compounds are fundamental building blocks of living systems as well as bulk feedstocks in chemical industry. Among the various transformations of aromatic compounds, catalytic asymmetric dearomatization (CADA) reactions serve as unique methods to functionalize planar aromatic starting materials, furnishing various valuable three-dimensional molecules.[1] The major challenge associated with CADA reactions is how to overcome the extraordinary thermodynamic stability caused by aromaticity and at the same time control the enantioselectivity. During the past several years, a large array of examples on CADA reactions of fused bicyclic (hetero)aromatic compounds, including indoles,[2] benzofurans,[3] naphthols,[4] (iso)-quinolines,[5] benzoxazoles, benzothiazoles, benzimidazoles,[6] etc., have been reported. However, in almost all cases, only one aromatic ring in these compounds is perturbed, while the other one remains intact. In fact, the restoration of the aromaticity of one aromatic ring (usually a benzene ring) in the product might be kind of compensation to the unfavorable dearomatization process. In this regard, how to extend the dearomatization reactions to (or more specifically, weakening the aromaticity of) two or more consecutive aromatic rings, emerges as an urgent and nontrivial task (Scheme 1a).[7]

As part of our ongoing program on exploring CADA reactions, we have developed Ir-catalyzed intramolecular asymmetric allylic dearomatization reactions of various electron-deficient N-heteroaromatic compounds.[6b,8] The reactions were found to be facilitated by the abstraction of an acidic proton of the 2-substituent of the quinoline ring (Scheme 1b). Prompted by this discovery, we envisioned that Ir-catalyzed intramolecular asymmetric allylation reactions of hydroxyquinolines would provide an unprecedented opportunity to achieve the simultaneous weakening of the aromaticity of the two consecutive aromatic rings of hydroxyquinolines

Scheme 1. Design Plan of This Study



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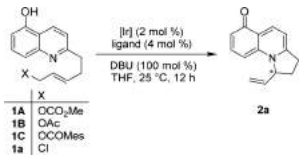
(Scheme 1c). Indeed, we recently realized this reaction by employing a catalyst of Ir/N-heterocyclic carbene (NHC) complex. The decrease of the aromaticity of the both rings during this reaction was confirmed by theoretical computations. A formal synthesis of (−)-gephyrotoxin was accomplished in a highly concise manner based on this method. Herein, we report the results of this study.

REACTION DEVELOPMENT

Our study commenced with the evaluation of the reaction conditions employing 5-hydroxyquinoline-derived allylic electrophiles **1** as the model substrates (Table 1). With the Ir-catalyst derived from $[Ir(cod)Cl]_2$ (2 mol %) and Feringa ligand **L1** (4 mol %) (Chart 1), allylic carbonate (**1A**) or other esters (**1B** and **1C**) were not reactive (entries 1−3).[9,10] Notably, when allylic chloride **1a** was subjected to the reaction, we were delighted to find that the desired product **2a** was obtained in 71% yield, albeit with almost no enantiocontrol (entry 4). To the best of our knowledge, only a few examples on Ir-catalyzed allylic substitution reactions that employ chloride as the leaving group were reported, with the highly enantioselective ones being rarer.[11] A systematic screening of chiral phosphoramidite ligands (entries 4−9) showed that the reaction of **L6** delivered **2a** in quantitative yield with significantly improved enantioselectivity (72% ee, entry 9).[12] Further evaluations on various Ir-precursors (entries 9−11) disclosed that the diene ligand beared on the Ir-catalyst has a significant effect on the enantioselectivity of the reaction.[13] $[Ir(dbcot)Cl]_2$ introduced by the Helmchen group gave better results in terms of the enantiomeric excess of **2a** (78% ee, entry 10).[13a]

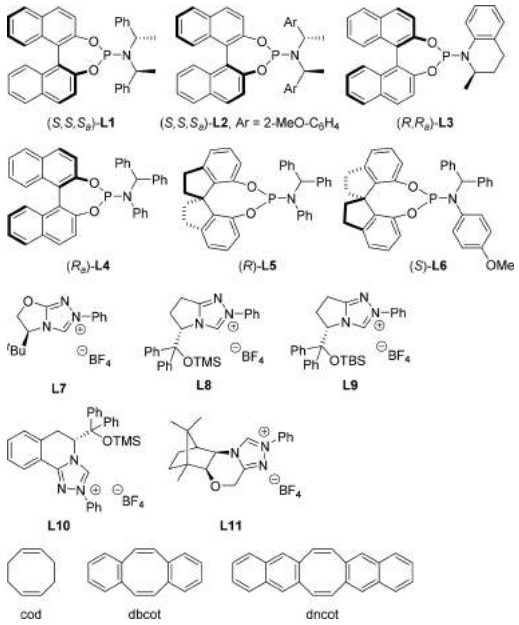
Table 1. Optimization of the Reaction Conditions[a]



entry	1	[Ir]	ligand	yield (%)[b]	ee (%)[c]
1	**1A**	$[Ir(cod)Cl]_2$	**L1**	<5	ND
2	**1B**	$[Ir(cod)Cl]_2$	**L1**	<5	ND
3	**1C**	$[Ir(cod)Cl]_2$	**L1**	<5	ND
4	**1a**	$[Ir(cod)Cl]_2$	**L1**	71	2 (−)
5	**1a**	$[Ir(cod)Cl]_2$	**L2**	77	3 (−)
6	**1a**	$[Ir(cod)Cl]_2$	**L3**	74	6 (−)
7	**1a**	$[Ir(cod)Cl]_2$	**L4**	85	52 (+)
8	**1a**	$[Ir(cod)Cl]_2$	**L5**	89	70 (−)
9	**1a**	$[Ir(cod)Cl]_2$	**L6**	99	72 (+)
10	**1a**	$[Ir(dbcot)Cl]_2$	**L6**	99	78 (+)
11	**1a**	$[Ir(dncot)Cl]_2$	**L6**	99	72 (+)
12[d]	**1a**	$[Ir(dbcot)Cl]_2$	**L7**	99	97 (−)
13[d]	**1a**	$[Ir(dbcot)Cl]_2$	**L8**	99	79 (+)
14[d]	**1a**	$[Ir(dbcot)Cl]_2$	**L9**	48	52 (+)
15[d]	**1a**	$[Ir(dbcot)Cl]_2$	**L10**	99	50 (+)
16[d]	**1a**	$[Ir(dbcot)Cl]_2$	**L11**	94	82 (+)

[a]Reaction conditions: Ir-precursor (2 mol %), ligand (4 mol %), DBU (0.2 mmol), **1a** (0.2 mmol) in THF (2.0 mL). Catalyst was prepared via $^nPrNH_2$ activation.[10k] [b]Isolated yield of **2a**. [c]Determined by HPLC analysis and the sign of optical rotation is included in the parentheses. [d]Catalyst was prepared via Et_3N activation.[15a]

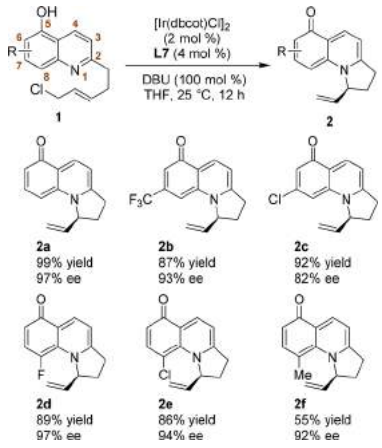
Chart 1. Chiral Ligands Screened in this Study



We postulated that the poor enantiocontrol might arise from the reversible formation of the C−N bond during the synthesis of **2a** under Ir-catalysis.[14] Recently, chiral NHCs were introduced by our group as a class of efficient ligands for Ir-catalyzed asymmetric allylic substitution reactions.[15] In general, Ir/NHC catalysts exhibit relatively lower reactivity compared with Ir/phosphoramidite catalysts, and therefore might avoid the reversible C−N bond formation process during the generation of **2a**. Hence, several chiral triazolium salts were examined as the precursors of NHC ligands (entries 12−16, Table 1). Gratifyingly, when the L-*t*-butylalaninol-derived triazolium salt **L7** was employed, the dearomatized product **2a** could be obtained in 99% yield with 97% ee (entry 12).[16]

With the optimal conditions identified, the substrate scope was then evaluated with various 5-hydroxyquinolines **1** (Table 2). Substrates bearing electron-withdrawing substituents including trifluoromethyl, chloro, and fluoro (**1b−e**) at the

Table 2. Substrate Scope: 5-Hydroxyquinolines[a]



[a]Reaction conditions: $[Ir(dbcot)Cl]_2$ (2 mol %), **L7** (4 mol %), DBU (0.2 mmol), **1** (0.2 mmol) in THF (2.0 mL). Catalyst was prepared via Et_3N activation.[15a] Isolated yields of **2** are reported. Ee values are determined by HPLC analysis.

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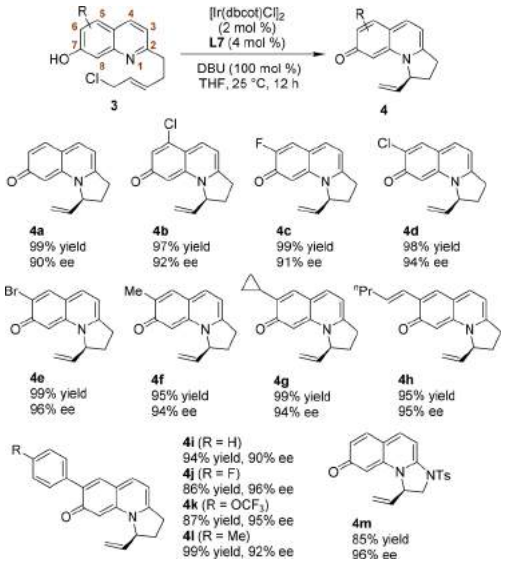
C7 or C8 position of the quinoline ring underwent the desired reactions smoothly, delivering their corresponding products (**2b**–**e**) in high yields (86–92%) with good enantioselectivity (82–97% ee). In addition, a methyl group is also well tolerated at the C8 position of the quinoline ring. The target product **2f** was obtained with high enantioselectivity (92% ee), albeit in moderate yield (55%), probably due to the steric bulkiness adjacent to the N atom.

According to our proposed mechanism, we envisioned that 7-hydroxyquinoline derived allylic chlorides **3** might also be suitable substrates. To our delight, the reactions of a range of 7-hydroxyquinolines were realized without any modification of the reaction parameters (Table 3). In general, substituents on

Table 3. Substrate Scope: 7-Hydroxyquinolines[a]



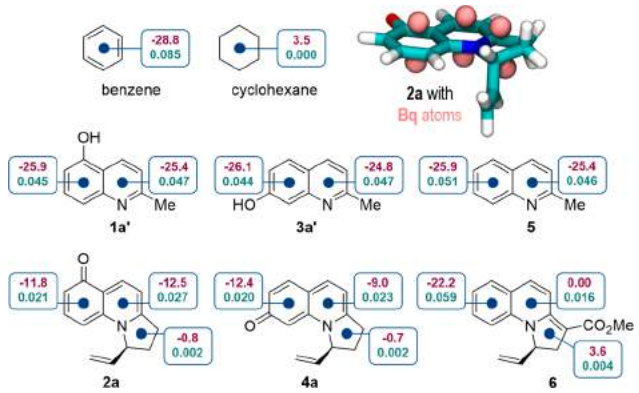
[a]Reaction conditions: $[Ir(dbcot)Cl]_2$ (2 mol %), **L7** (4 mol %), DBU (0.2 mmol), **3** (0.2 mmol) in THF (2.0 mL). Catalyst was prepared via Et_3N activation.[15a] Isolated yields of **4** are reported. Ee values are determined by HPLC analysis.

the C5, or C6 position of the quinoline core have little influence on the yield and enantioselectivity. Besides the standard product **4a**, a number of halogenated (**4b**-**e**), alkyl-substituted (**4f** and **4g**), alkenyl-substituted (**4h**) and aryl-substituted (**4i**–**l**) products were all furnished in good yields (86–99%) with high enantioselectivity (90–96% ee). Notably, an N-linkage is well tolerated between the allylic chloride and the quinoline ring of the substrate. The corresponding product **4m** was obtained in good yield (85%) with excellent enantiomeric purity (96% ee). The absolute configuration of **4d** was identified as (*S*) by electronic circular dichroism (ECD) experiments and that of other products were assigned by analogy.[12]

EVALUATIONS ON THE AROMATICITY OF THE PRODUCTS

The cyclic conjugated enone structures of **2** and **4** make it somewhat confusing when judging whether these compounds are aromatic or not at the first glance. In this regard, quantitative evaluations of the aromaticity of these compounds were performed.[12] Two widely recognized measurements of aromaticity, NICS(1)_ZZ[17] (the ZZ tensor component of the nuclear independent chemical shift values at the points 1 Å above the ring center) (B3LYP/6-31+G**) and multicenter bond indices[18] (B3LYP/6-31G**) were computed for each ring of the intramolecular N-allylation products of hydroxyquinolines (**2a** and **4a**) and quinoline (**6**), as well as their corresponding simplified parent compounds (**1a′**, **3a′** and **5**). The same calculations were also applied for benzene (typical aromatic ring) and cyclohexane (typical nonaromatic ring) as references (Chart 2). Strong aromaticity of both rings of **1a′**, **3a′** and **5** was exemplified by their significantly negative NICS(1)_ZZ values (−24.8 to −26.1) and large multicenter bond indices (0.044 to 0.051). As expected, the calculated results show that the aromaticity of the pyridine ring of the quinoline-derivative is completely destroyed after the Ir-catalyzed intramolecular asymmetric N-allylation, while that of the benzene ring of the quinoline substrate remains almost untouched. For instance, the NICS(1)_ZZ value and multicenter bond index of the six-membered N-heterocycle of **6** are 0.00 and 0.016, typical values of a nonaromatic ring. On the other hand, the corresponding values of the benzene ring of **6** remain as −22.2 and 0.059, very similar to those of **5**. Notably, the situations of **2a** and **4a** are quite different. In these two cases, the calculated NICS(1)_ZZ values (−9.0 to −12.5) and multicenter bond indices (0.020 to 0.027) of the both rings are roughly half compared with those values of **1a′** and **3a′**, indicating the aromaticity of the two rings of quinolin-5(1*H*)-one and quinolin-7(1*H*)-one are significantly weakened when compared with hydroxyquinolines. The results of NICS calculation can be visualized by the color-filled maps of the distribution of chemical shielding over the molecules[19] (Chart 3). Significant shielding areas can be found over both the benzene and the pyridine rings of **1a′**, **3a′**, and **5**, indicating their aromatic nature. For compound **6**, the shielding area is disappeared from the region over the six-membered N-heterocycle and mainly located over the benzene ring. On the other hand, it is quite obvious that the shielding areas over the both rings of **2a** and **4a** shrink significantly compared with those of **1a′** and **3a′**, indicating the weakened aromaticity of these two compounds.

Chart 2. Evaluation of the Aromaticity of Selected Compounds[a]



[a]Values in purple and blue denote the calculated NICS(1)_ZZ and multicenter bond indices. Upright corner shows the optimized structure of **2a** with six Bq atoms (pink spheres) at the positions where NICS values are calculated.

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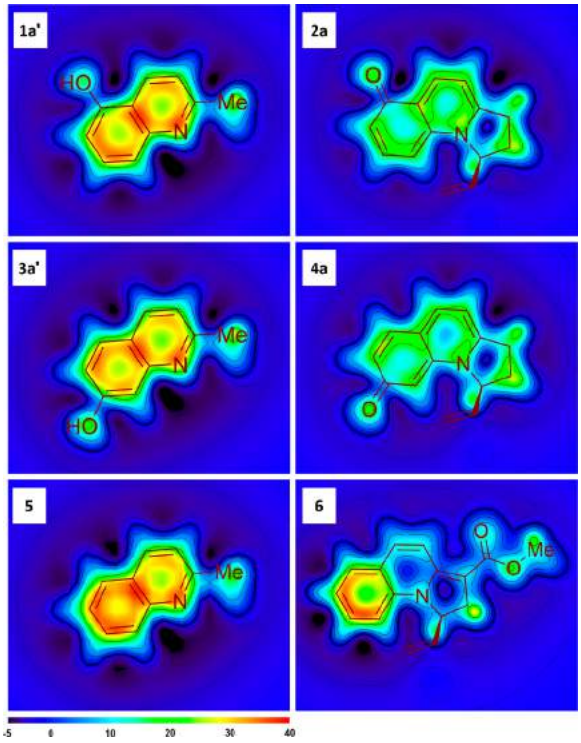
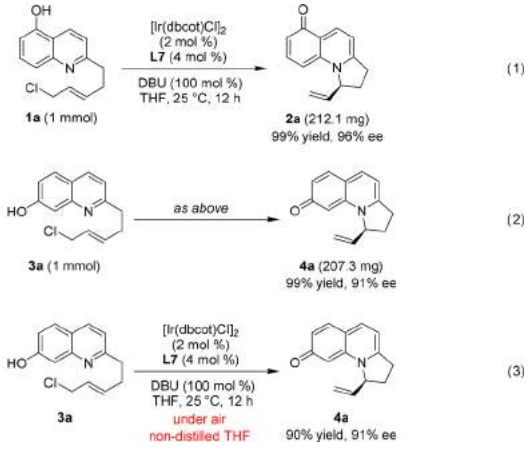
Chart 3. Color-Filled Maps of the Distribution of Chemical Shielding over the Selected Molecules[a]



[a]The negative NICS_ZZ values are scaled by the color bar.

SYNTHETIC APPLICATIONS

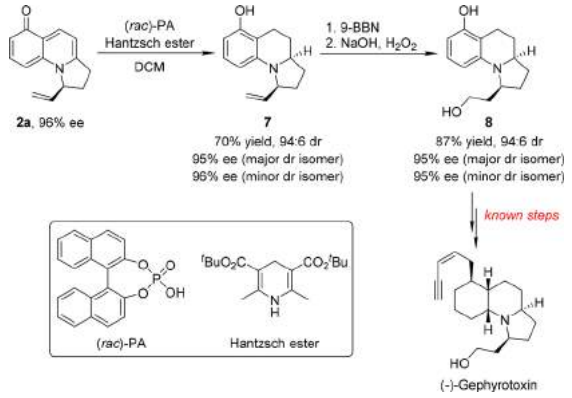
The herein disclosed Ir-catalyzed allylic alkylation reactions of hydroxyquinolines were readily amenable to be scaled-up. The reactions of **1a** and **3a** could be performed on millimole-scale under standard conditions (eqs 1 and 2). The robustness of this



methodology was further showcased by the reaction of **3a** employing nondistilled THF as the solvent under air (eq 3).[13a] No significant erosion on yield and enantiomeric purity of **4a** was observed.

To further demonstrate the potential utility of this method, we applied this process to the formal synthesis of (−)-gephyrotoxin, an alkaloid possessing muscarinic and neurological activities (Scheme 2).[20,21] The transfer hydrogenation reaction of **2a** with Hantzsch ester catalyzed by a racemic BINOL-derived phosphoric acid ((*rac*)-PA) afforded **7**

Scheme 2. Formal Synthesis of (−)-Gephyrotoxin



in 70% yield with 94:6 dr.[22] Subsequent hydroboration/oxidation process led to **8**, a known key intermediate of (−)-gephyrotoxin, in 87% yield. Compared with our previous synthesis based on the Ir-catalyzed intramolecular asymmetric allylic dearomatization reaction of quinoline derivatives,[8b] the current method provides compound **8** in a much higher yield (61%) by only two steps. Notably, taking the wide substrate scope described herein into consideration, a library of analogues of (−)-gephyrotoxin can be accomplished conveniently.

CONCLUSION

In summary, we have developed an Ir-catalyzed intramolecular asymmetric allylic alkylation of hydroxyquinolines. Computational results show that the aromaticity of two consecutive aromatic rings of hydroxyquinolines is weakened simultaneously. By employing a robust Ir-catalyst derived from $[Ir(dbcot)Cl]_2$ and chiral NHC ligand, highly functionalized products were obtained with excellent enantiopurity. The synthetic utility was showcased by an efficient formal synthesis of (−)-gephyrotoxin. The compatibility with millimole scale reaction further enhanced the synthetic practicality of this method. Meanwhile, this reaction is a valuable case for Ir-catalyzed allylic substitution reaction with allylic chlorides as the precursors.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b00136.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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