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Asymmetric Hydrogenation of Isoquinolines and Pyridines Using Hydrogen Halide Generated in Situ as Activator

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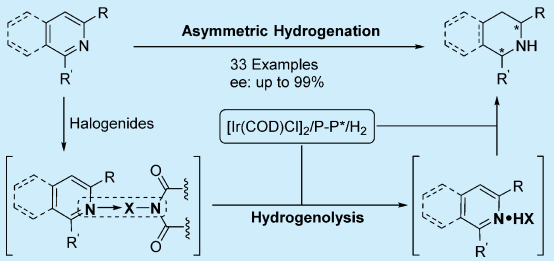
Supporting Information

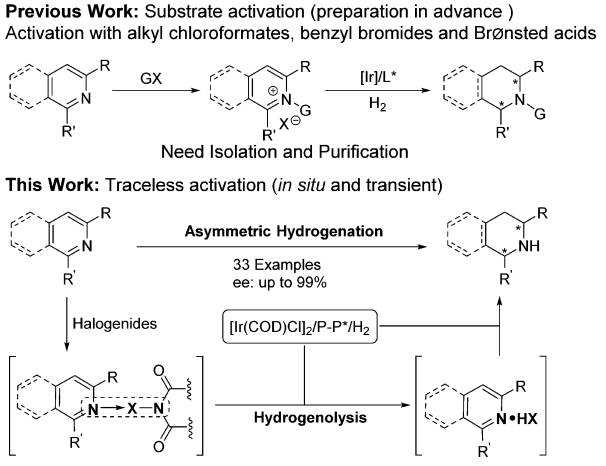
ABSTRACT: By employing halogenide trichloroisocyanuric acid as a traceless activation reagent, a general iridium-catalyzed asymmetric hydrogenation of isoquinolines and pyridines is developed with up to 99% ee. This method avoids tedious steps of installation and removal of the activating groups. The mechanism studies indicated that hydrogen halide generated in situ acted as an activator of isoquinolines and pyridines.



Chiral piperidines and tetrahydroisoquinolines are common structural motifs present in biologically active compounds,[1] and the development of efficient methods for their synthesis has attracted increasing attention.[2] One of the most straightforward and atom-economic methods is direct asymmetric hydrogenation of the corresponding pyridines[3−7] and isoquinolines.[8] However, the resonance stability and inhibiting effect of nitrogen atom on chiral catalyst impeded efficient asymmetric hydrogenation of these compounds.

In the past decades, chemists have made tireless efforts to overcome these difficulties. A number of effective strategies, including substrate activation and catalyst activation, have been developed. In 2005, an elegant asymmetric hydrogenation of the *N*-iminopyridinium ylides was reported by Charette's group.[4a] Next, the chloroformates, benzyl bromides, and Brønsted acids were successfully used as substrate activators for asymmetric hydrogenation of pyridines[4−6] and isoquinolines[8] (Scheme 1). However, installation and removal of activating groups are the major drawbacks for further synthetic applications. In addition, some activating groups cannot be installed on the substrates due to steric hindrance and electronic effects. Therefore, developing an ideal activator for the direct asymmetric hydrogenation of aromatic *N*-heterocycles is highly desirable. In this respect, an ideal activator should possess the advantages of high efficiency, simplified operation, and low cost. Furthermore, the crucial point is the circumvention of tedious steps of installation and removal without forming or breaking a covalent bond. An ideal activator with these characters can be called a traceless activator. Herein, we report a general enantioselective hydrogenation of isoquinolines and pyridines using trichloroisocyanuric acid (TCCA) as a traceless activator with excellent enantioselectivity (Scheme 1), and the salient features of this method are as follows: (1) simple operation and (2) avoidance of tedious installation and removal of activating groups.

Scheme 1. Enantioselective Hydrogenation of Isoquinolines and Pyridines via Substrate Activation



Halogenides (such as NIS and TCCA) are commercially available, stable, cheap, and low-toxic reagents, which have been widely applied in organic synthesis.[9] In 2007, a halogen-bonding interaction involving the C═N bond and NIS was reported by the Vaquero group.[10] The halogen bond, an important noncovalent interaction between an electrophilic halogen substituent X (X = Cl, Br, I) and a Lewis base, forms an interaction angle close to 180°. Over the past decades, the halogen bond has been applied to a variety of research disciplines including crystal engineering and material sciences.[11] Meanwhile, the application of the halogen bond in the field of organic synthesis and catalysis also receives important attention but is

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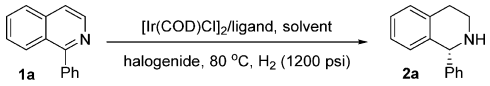
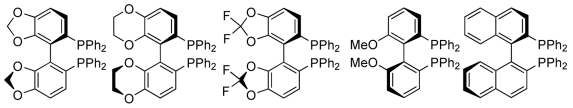
still quite rare. For example, the reduction of quinolines with Hantzsch ester using perfluorinated iodoalkanes or bis(iodoimidazolinium) compounds as halogen-bond activators was reported by the groups of Bolm and Tan,[12] respectively. In addition, halogen-bond donors could also serve as activators in the Morita–Baylis–Hillman reaction,[13a] Diels–Alder reaction,[13b,c] and so on.[13d–h] Considering that the halogenides easily form halogen-bond interactions with Lewis basic isoquinolines and pyridines, the halogenides could act as the desirable traceless activators. These activators might enhance the reactivity of pyridines and isoquinolines and provide a new opportunity for asymmetric hydrogenation of isoquinoline and pyridine derivatives.

With this hypothesis in mind, 1-phenylisoquinoline (**1a**) was chosen as a model substrate. We tested asymmetric hydrogenation of **1a** with NIS as substrate activator and [Ir(COD)Cl]$_2$/ (*R*)-SegPhos as catalyst in THF under hydrogen gas (1200 psi) at 80 °C (Table 1). Gratifyingly, the reaction proceeded

Table 1. Optimization of Reaction Conditions[a]



entry	solvent	ligand	halogenide	conv[b] (%)	ee[c] (%)
1	THF	**L1**	NIS	95	91
2	CH_2Cl_2	**L1**	NIS	40	63
3	toluene	**L1**	NIS	78	90
4	dioxane	**L1**	NIS	>95	94
5	dioxane	**L2**	NIS	75	85
6	dioxane	**L3**	NIS	>95	94
7	dioxane	**L4**	NIS	91	89
8	dioxane	**L5**	NIS	81	73
9[d]	dioxane	**L1**	NIS	17	71
10	dioxane	**L1**	NBS	>95	95
11	dioxane	**L1**	NCS	>95	94
12	dioxane	**L1**	TCCA	66	96
13	THF	**L1**	TCCA	>95	95
14[e]	THF	**L1**	TCCA	>95	95
15[e,f]	THF	**L1**	TCCA	>95	95

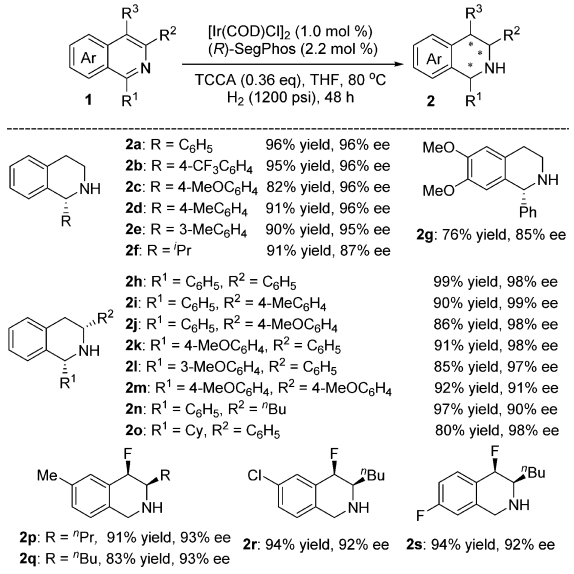


[a]Conditions: **1a** (0.125 mmol), [Ir(COD)Cl]$_2$ (2.0 mol %), ligand (4.4 mol %), H_2 (1200 psi), solvent (3.0 mL), halogenide (1.0 equiv), 48 h, 80 °C. [b]Determined by ^{1}H NMR spectroscopy. [c]Determined by HPLC analysis of the corresponding *N*-benzoyl derivatives. [d]NIS (5.0 mol %). [e]TCCA (0.36 equiv). [f]**1a** (0.25 mmol), [Ir(COD)Cl]$_2$ (1.0 mol %), (*R*)-SegPhos (2.2 mol %). NIS = *N*-iodosuccinimide, NBS = *N*-bromosuc-cinimide, NCS = *N*-chlorosuccinimide, TCCA = trichloroisocyanuric acid.

smoothly, and excellent conversion as well as enantioselectivity was obtained (entry 1). Subsequently, the solvent effects were examined (entries 1–4). It was found that solvents played a crucial role, and dioxane was more suitable than the others (entry 4). Some commercially available chiral bisphosphine ligands were also evaluated, and the best result was achieved with (*R*)-SegPhos **L1** and (*R*)-DifluorPhos **L3** (94% ee; entries 4 and 8). Notably, poor reactivity was observed without stoichiometric halogenide activator, and this result showed the halogen-bond interaction might improve reactivity (entry 9). Encouraged by the above results, some other halogenides were tested (entries 10–12). TCCA gave the most favorable 96% ee, albeit with slightly low reactivity. Fortunately, the reactivity increased obviously using THF instead of dioxane with the identical enantioselectivity (entry 13). To our delight, no loss in conversion and enantioselectivity was observed with the decreased loadings of catalyst and TCCA (entry 15). Therefore, the optimal reaction conditions were established as [Ir(COD)Cl]$_2$/(*R*)-SegPhos/TCCA/THF.

After establishing the optimal conditions, we examined the substrate scope, and the results are summarized in Scheme 2. A

Scheme 2. Substrate Scope of Isoquinolines[a–c]



[a]**2c–g**: [Ir(COD)Cl]$_2$ (2.0 mol %), (*R*)-SegPhos (4.4 mol %). [b]**2h–o**: TCCA (1.0 equiv). [c]**2p–q**: dioxane/^{i}PrOH (v/v = 5:1, 3.0 mL), H_2 (600 psi), TCCA (1.0 equiv), 20 h, 30 °C.

series of 1-aryl-substituted isoquinolines could be smoothly hydrogenated, giving the corresponding tetrahydroisoquinolines with excellent yields and enantioslectivities (**2a–d**) regardless of the electronic properties of 1-aryl substituents. Moreover, the position of substituents on 1-aryl had a marginal effect on the reactivity and enantioselectivity (**2d**, **2e**). When the aryl substituent on C1 was replaced with an alkyl substituent, good enantioselectivity and reactivity were obtained (**2f**). Introducing an electron-donating methoxy substituent on the isoquinoline core (**2g**) resulted in slightly lower enantioselectivity. Then, more challenging 1,3-disubstituted isoquinolines were tackled to deliver two stereocenters in one step. To our delight, 1,3-diaryl- (**1h–m**), 1-aryl-3-alkyl- (**1n**), and 1-alkyl-3-aryl-disubstituted isoquinolines (**1o**) can be hydrogenated with high enantioselectivities and diasteroselectivities. For example, the hydrogenation of 1,3-diphenylisoquinoline furnished the desired product **2h** in 99% yield and 98% ee. To further explore the scope of substrates, the hydrogenation of fluorinated 3,4-disubstituted isoquinolines was evaluated, providing the corresponding hydrogenation products with 92–93% ee, and no defluorination products were detected. To demonstrate the practicality of this method, the asymmetric hydrogenation of **1a** was performed on gram scale under the standard conditions with 94% yield and 94% ee without loss of reactivity and enantioselectivity.

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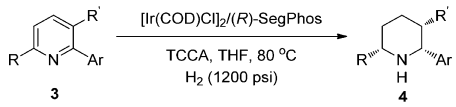
The success of asymmetric hydrogenation of isoquinolines encouraged us to apply this strategy to more challenging substrate, pyridines. Initially, we investigated the feasibility of this approach by evaluating asymmetric hydrogenation of 6-methyl-2-phenylpyridine (**3a**) under conditions of $[Ir(COD)Cl]_2$/(*R*)-SegPhos/TCCA (0.36 equiv) in THF at 80 °C. The desirable hydrogenation product **4a** could be obtained with 68% conversion, moderate 76% enantioselectivity, and excellent diastereoselectivity (>20:1). Fortunately, the 86% ee value and full conversion were obtained by adjusting the amount of activator TCCA from 0.36 to 1.0 equiv.

Having identified the optimal reaction conditions, we commenced the extension of substrate scope (Table 2). A series

Table 2. Substrate Scope of Pyridines[a]



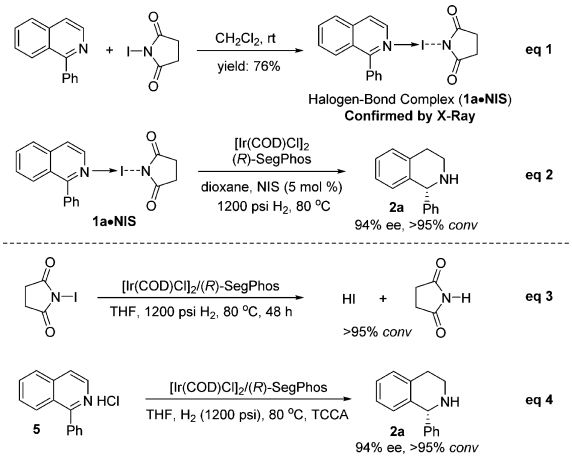
entry	R, R′	Ar	yield[b] (%)	ee[c] (%)
1	Me, H	C_6H_5	81 (**4a**)	86
2	Me, H	4-$CF_3C_6H_4$	90 (**4b**)	85
3	Me, H	3-MeC_6H_4	64 (**4c**)	85
4	Me, H	3,5-$F_2C_6H_3$	75 (**4d**)	85
5	Me, H	1-naphthyl	86 (**4e**)	73
6[d]	Me, CF_3	C_6H_5	98 (**4f**)	90
7[d]	Me, CF_3	4-MeC_6H_4	97 (**4g**)	90
8[d]	Me, CF_3	3-MeC_6H_4	96 (**4h**)	89
9[d]	Me, CF_3	4-$MeOC_6H_4$	85 (**4i**)	90
10[d]	Me, CF_3	4-$CF_3C_6H_4$	91 (**4j**)	87
11[d]	Me, CF_3	4-$C_6H_5C_6H_4$	98 (**4k**)	88
12[d]	Me, CF_3	2-naphthyl	91 (**4l**)	89
13[d]	Et, CF_3	C_6H_5	82 (**4m**)	89
14[d]	^{n}Bu, CF_3	C_6H_5	96 (**4n**)	85

[a]Conditions: **3** (0.25 mmol), $[Ir(COD)Cl]_2$ (2.0 mol %), (*R*)-SegPhos (4.4 mol %), H_2 (1200 psi), THF (3.0 mL), TCCA (1.0 equiv), 48 h, 80 °C. [b]Isolated yield. [c]Determined by HPLC analysis of the corresponding *N*-benzoyl derivatives. [d]$[Ir(COD)Cl]_2$ (2.5 mol %), (*R*)-DifluorPhos (5.5 mol %), H_2 (800 psi), DCM:^{i}PrOH (v:v = 3:1, 3.0 mL), TCCA (1.0 equiv), 36 h, rt.

of 2,6-disubstituted pyridines were successfully converted to the chiral piperidines with good to excellent enantioselectivities. The electronic properties and steric effects on the 6-arylpyridines had a marginal effect on the yields and ee values (entries 1−5). Notably, this method can provide higher enantioselectivities compared to previous method using pyridium chloride as substrates (for example, **3a**: 86% ee vs 78% ee[6b]). Furthermore, to demonstrate the versatility of this method, we turned our attention to the asymmetric hydrogenation of trifluoromethyl-substituted pyridines. After a condition reoptimization, a range of 2,3,6-trisubstituted pyridines bearing a trifluoromethyl group could be well hydrogenated with high enantioselectivities (entries 6−14). The steric and electronic nature of the aryl substituents had little influence on the outcome of the reaction, giving the corresponding products with 85−90% ees (entries 6−12). To our delight, pyridines bearing longer alkyl chain groups instead of a methyl group at the 6-position were also good partners with 85−89% ees (entries 13−14). In the previous method,[6b] we could not obtain the target product **4n** because the **3n·HCl** could not be prepared.

To gain more insight into the reaction mechanism, the following investigations were performed (Scheme 3). We began

Scheme 3. Control Experiments



our studies on the basis of the hypothesis that the asymmetric hydrogenation of isoquinolines and pyridines was activated by halogenide through halogen-bond interactions. Fortunately, the stable 1:1 halogen-bond complex was formed by mixing 1-phenylisoquinoline **1a** and NIS in CH_2Cl_2, and the structure was confirmed by single-crystal X-ray crystallography (eq 1). The angle of N(2)−I(1)−N(1) is 175.86 (9)°, almost linear disposition, and the bond length of I(1)−N(1) is 2.502(3) Å and I(1)−N(2) is 2.086(3) Å. However, the partially hidden Brønsted acid activation could not be completely ruled out in the application of halogen bond in the field of organic synthesis and catalysis.[13b,14] Furthermore, the desired product **2a** was obtained by direct asymmetric hydrogenation of **1a·NIS** complex (eq 2) under the standard conditions with identical results (Table 1, entry 4). In addition, the hydrogenolysis of NIS was conducted under the standard conditions (eq 3), giving the succinimide and hydrogen iodide with full conversion. Surprisingly, hydrogenation of 2-phenylisoquinolinium chloride **5** was conducted (eq 4), and identical reactivity and enantioselectivity were obtained under the standard conditions. The above experimental results support the asymmetric hydrogenation of isoquinolines and pyridines using hydrogen halide generated in situ as activator.

In summary, a general and highly enantioselective iridium-catalyzed asymmetric hydrogenation of isoquinolines and pyridines has been successfully developed with up to 99% ee. This work features a traceless activation strategy and circumvents the tedious steps of installation and removal of the activating reagents. This hydrogenation reaction can be easily scalable and is valuable for the preparation of chiral tetrahydroisoquinolines and piperidines with multiple stereocenters. The mechanism studies indicated that hydrogen halide generated in situ acted as the activator of isoquinolines and pyridines. Further investigation on the application of the related traceless activation strategy to other substrates and detailed mechanistic studies are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02502.

Experimental procedures, characterization data, and NMR spectra (PDF)

X-ray data for **1a·NIS** (CIF)

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Notes

The authors declare no competing financial interest.

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