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Iridium-Catalyzed Enantioselective and Diastereoselective Hydrogenation of 1,3-Disubstituted Isoquinolines

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ABSTRACT: The development of a general method utilizing a hydroxymethyl directing group for asymmetric hydrogenation of 1,3-disubstituted isoquinolines to provide chiral 1,2,3,4-tetrahydroisoquinolines is reported. The reaction, which utilizes $[\text{Ir}(\text{cod})\text{Cl}]_2$ and a commercially available chiral xylylphos ligand, proceeds in good yield with high levels of enantioselectivity and diastereo-selectivity (up to 95% ee and >20:1 dr) on a range of differentially substituted isoquinolines. Directing group studies demonstrate that the hydroxymethyl functional group at the C1-position is more efficient at enabling hydrogenation than other substituents, although high levels of enantioselectivity were conserved across a variety of polar and non-polar functional groups. By utilizing the generated chiral β -amino alcohol as a functional handle, the synthetic utility is further highlighted via the synthesis of 1,2-fused oxazolidine, oxazolidinone, and morpholinone tetrahydroisoquinolines in one step. Additionally, a non-natural analog of the tetrahydroprotoberberine alkaloids was successfully synthesized.

INTRODUCTION

The stereocontrolled synthesis of nitrogen-containing heterocycles remains a challenge of great importance, as it provides direct access to chiral compounds that are prevalent structural motifs in many biologically active molecules.¹ As a result, the asymmetric hydrogenation of various hetero-aromatic compounds has been extensively explored as a direct, efficient synthesis of enantiopure cyclic amines.² Despite recent progress made toward the asymmetric hydrogenation of *N*-heterocycles such as quinolines, quinoxalines, and pyridines, the synthesis of 1,2,3,4-tetrahydroisoquinolines (THIQs) from isoquinolines remains significantly underdeveloped (Figure 1A).² This is due in part to the stronger basicity and coordinating ability of the THIQ products compared to those of other heterocycles (e.g., quinolines), leading to catalyst deactivation, as well as the overall lower reactivity of isoquinoline substrates.³ Although a few effective strategies toward the asymmetric hydrogenation of substituted isoquinolines have been reported, these typically require preparation of the isoquinolinium salt, substrate activation with halogenides, and harsher hydrogenation reaction conditions (Figure 1B).⁴ Furthermore, previous to our research, there were only 2 catalytic systems describing efficient methods to access chiral 1,3-disubstituted tetrahydroisoquinolines,^{4c,e,g} a more complex and sterically challenging system that generates two stereogenic centers. In addition, the limited substrate scope from these reports demonstrates the low tolerance of additional Lewis basic functionalities, such as alcohols or heteroaryl-substituted isoquinolines, which limit the applicability of these methodologies in synthesis. Since

A. Asymmetric Hydrogenation of *N*-Heterocycles:

Substrates:

B. Prior Art in Ir-Catalyzed Asymmetric Hydrogenation of Isoquinolines:

a) Substrate Activation via Isoquinolinium Salts

- 4 reports with only 1 report describing 1,3-disubstituted isoquinolines
- Requires prior formation of the salt for activation
- No example of substrate with additional Lewis basic functionalities

b) in situ and Transient Activation

- 3 reports with only 1 report describing 1,3-disubstituted isoquinolines
- Requires high temperature & pressure
- No example of substrate with additional Lewis basic functionalities

Figure 1. (a) Limitations in enantioselective hydrogenation of *N*-heterocycles. (b) Previous examples of iridium-catalyzed enantioselective and diastereoselective hydrogenation of mono-, and di-substituted isoquinolines.

1,3-disubstituted tetrahydroisoquinolines with Lewis basic moieties are ubiquitous motifs present in a wide range of natural products, such as the saframycin, naphthyridinomycin, and quinocarcin families,⁵ a general method for highly enantioselective and diastereoselective hydrogenation of neutral disubstituted isoquinolines under mild reaction conditions would be a significant advancement toward the preparation of chiral amine-containing cyclic molecules.

Recently, our group has successfully completed the total synthesis of jorumycin and jorunnamycin A, two bis-tetrahydroisoquinoline natural products that exhibit potent antiproliferative activity, as well as strong Gram-positive and Gram-negative antibiotic character.⁶ Through an unprecedented, nonbiomimetic synthetic route, we were successful in harnessing catalysis to allow expedient access to these natural products, as well as a diverse range of non-natural analogs that are otherwise inaccessible using prior biomimetic synthetic approaches. One of the key steps of this synthesis involves a catalytic enantioselective hydrogenation of bis-isoquinoline **1** to afford the THIQ motif, a crucial intermediate that forms the pentacyclic carbon skeleton **2** in one step by further hydrogenation of the second isoquinoline and eventual amide ring closure (Figure 2). Considering the ubiquity of the hydroxymethyl group at the C1 position, and the amino alcohol functionality in a large number of natural products, we envision that this synthetic method could access a wide variety of THIQs as well as chiral amino alcohols, both highly valuable pharmacophores. Following the successful development of our asymmetric hydrogenation technology for bis-isoquinolines, herein we disclose a mild, general method for the enantioselective and diastereoselective hydrogenation of 1,3-disubstituted isoquinolines.

Figure 2. Our research on iridium-catalyzed enantioselective and diastereoselective hydrogenation of 1,3-disubstituted isoquinolines.

RESULTS AND DISCUSSION

Substrate Syntheses. Due to a limited number of methods for the syntheses of 1,3-disubstituted isoquinolines,⁷ we first established a simple and divergent sequence to access a wide variety of 1-(hydroxymethyl)-3-arylisoquinoline substrates (i.e., **7**, Scheme 1). Utilizing Pd-catalyzed arylation of ester enolates reported by Donohoe and coworkers,⁸ monoarylated *tert*-butyl acetate **4** was isolated in an excellent 92% yield. Cyclization to isoquinoline triflate **5** was then achieved via hydrolysis of the ketal, followed by isoquinoline annulation with aqueous ammonium hydroxide, and alcohol triflation.⁹ At this stage, different aryl or heteroaryl groups could be coupled with intermediate **5** using Suzuki coupling conditions to deliver a wide range of 1,3-disubstituted isoquinolines (i.e., **6**), highlighting the divergent synthesis of our synthetic route. Finally, SeO₂ oxidation to the aldehyde and subsequent NaBH₄ reduction provided our desired isoquinoline starting materials **7a–r**. It is worth noting that this sequence allows for an introduction of various aryl and heteroaryl groups at the C3-position of isoquinolines, as well as different substituents with varied electronics on the isoquinoline carbocycle (e.g., **9a–f**, *vide infra*, Scheme 4). Currently in the literature, the 1,3-disubstituted isoquinoline motif is typically accessed via transition-metal-catalyzed tandem C–H activation/annulation of arenes with alkynes.¹⁰ These methods have shown limited success in producing C3-heteroaryl isoquinolines.¹¹

Scheme 1. Syntheses of 1-(hydroxymethyl)-3-aryl Isoquinoline Substrates^a

^aConditions: (a) *t*-butyl acetate (2 equiv), LiHMDS (2.5 equiv), Pd₂(dba)₃ (5 mol %), P(*t*-Bu)₃•HBF₄ (10 mol %), toluene, 23 °C, 18 h, 92% yield. (b) 33% TFA in CH₂Cl₂, 23 °C, 2 h; then aq. NH₄OH, MeCN, 70 °C, 12 h; then Tf₂O (2 equiv), pyridine, CH₂Cl₂, 0 °C, 1 h, 38% yield over 3 steps. (c) aryl/heteroaryl boronic acid (1.5 equiv), XPhos Pd G3 (2 mol %), 2:1 K₃PO₄:THF, 40 °C, 2 h, 77–95% yield. (d) SeO₂ (2 equiv), 1,4-dioxane, 110 °C, 2 h; then NaBH₄ (1 equiv), 4:1 CH₂Cl₂:MeOH, 10 min, 25–97% yield.

Reaction Optimization. With a divergent sequence to access 1,3-disubstituted isoquinolines, we began our hydrogenation studies with 1-(hydroxymethyl)-3-phenylisoquinoline (**7a**) as our model substrate, using slightly modified conditions from our previously reported hydrogenation on the bis-isoquinoline system (Table 1). An initial experiment,

employing 1.25 mol % $[\text{Ir}(\text{cod})\text{Cl}]_2$ and 3 mol % of the BTfM-xylylphos ligand (**L1**), gave high conversion of the substrate but surprisingly modest enantioselectivity (49% ee, entry 1). Seeking to improve the ee, we surveyed a wide variety of chiral ligand scaffolds (see Supporting Information) and found the xylylphos ligand framework to be optimal. By exploring different electronics of this ligand scaffold, we observed that replacing the 3,5-bis(trifluoromethyl)phenyl (BTfM) with more electron-rich aryl groups provided the product with both excellent conversion and higher enantioselectivity (entries 1–5). Ligand **L5**, which features 4-methoxy-3,5-dimethylphenyl (DMM) substituted phosphine delivers the product with the highest ee of 89%, albeit with a low 2:1 diastereoselectivity (entry 5). Interestingly, a background reaction was observed in the absence of the chiral ligand, providing the product in excellent conversion and diastereoselectivity (entry 6). From this finding, we obtained all racemic hydrogenated products by simply performing the hydrogenation in the absence of ligand, affording the *cis*-product as a single diastereomer.

Table 1. Optimization of the Enantioselective Hydrogenation of Isoquinolines to afford THIQs^a

entry	ligand	Solvent	% conversion ^b	cis:trans ^b	% ee of cis ^c
1	L1	PhMe:AcOH	>95	>20:1	~49 ^d
2	L2	PhMe:AcOH	>95	3.2:1	84
3	L3	PhMe:AcOH	66	4.5:1	63
4	L4	PhMe:AcOH	92	4.9:1	3
5	L5	PhMe:AcOH	>95	2.0:1	89
6	-	PhMe:AcOH	>95	>20:1	0
7	L5	CH ₂ Cl ₂ :AcOH	>95	1.5:1	84
8	L5	dioxane:AcOH	66	5.5:1	87
9	L5	THF:AcOH	>95	9.7:1	90
10	L5	CPME:AcOH	38	>20:1	88
11	L5	2-MeTHF:AcOH	>95	9.5:1	90
12 ^e	L5	THF:AcOH	>95	15.7:1	92

^aConditions: 0.04 mmol **7a**, 1.25 mol % $[\text{Ir}(\text{cod})\text{Cl}]_2$, 3 mol % ligand, 7.5 mol % TBAI, 60 bar H₂ in 2.0 mL 9:1 solvent:AcOH. ^bDetermined from crude ¹H NMR using 1,3,5-trimethoxybenzene as standard. ^cDetermined by chiral SFC analysis of Cbz-protected product. ^dOpposite enantiomer of ligand used. ^eReaction performed on a 0.2 mmol scale at 23 °C, 20 bar H₂, and 0.1 M concentration of **7a**.

Investigation of different solvents with **L5** as the optimal ligand reveals that while the use of CH₂Cl₂ provided similar results to toluene (entry 7), the diastereoselectivity could be improved with the use of ethereal solvents (entries 8–11). Although bulkier ethereal solvents proved to worsen conversion (entries 8 and 10), we were delighted to find that THF and the more sustainable solvent 2-MeTHF delivered the product in excellent conversion with high levels of

diastereoselectivity and enantioselectivity (entries 9 and 11). The absence of AcOH resulted in low conversion,¹² while further exploration of different additives (e.g., LiI, NaI, KI, etc.) demonstrated that TBAI is the optimal additive (see Supporting Information). Finally, we were excited to observe that lowering the temperature to 23 °C and H₂ pressure to 20 bar maintained excellent levels of conversion, diastereoselectivity, and enantioselectivity (entry 12). To the best of our knowledge, these are the mildest reaction conditions reported for isoquinoline hydrogenation to afford chiral THIQs to date.⁴

Scheme 2. Substrate Scope of Different Aryl Substituents^a

7a-m **8a-m**

Product	R	%yield	dr	%ee
8a	H	95	15.7:1	92
8b	<i>t</i> -Bu	87	13.3:1	91
8c	Ph	79	9.0:1	92
8d	OMe	75	13.3:1	92
8e	F	99	10.1:1	93
8f	CF ₃	81	4.6:1	92
8g^b	CN	83	2.4:1	82

<p>8h 78% yield 3.2:1 dr, 86% ee</p>	<p>8i 94% yield 3.5:1 dr, 89% ee</p>	<p>8j 87% yield >20:1 dr, 95% ee</p>
<p>8k 95% yield >20:1 dr, 92% ee</p>	<p>8l^c 98% yield >20:1 dr, 88% ee</p>	<p>8m 64% yield 10.1:1 dr, 49% ee</p>

^aReactions performed on a 0.2 mmol scale. ^bReaction performed at 60 °C and 60 bar H₂. ^cCH₂Cl₂ cosolvent used to improve substrate solubility.

Substrate Scope. With optimized reaction conditions identified, we explored the general substrate scope for this transformation (Scheme 2). Gratifyingly, a wide variety of aryl substituents at the 3-position of the isoquinoline are well tolerated under the mild reaction conditions of 20 bar H₂ at ambient temperature. Substitution at the *para*-position of the 3-aryl ring delivered the hydrogenated products **8a–g** in consistently high yields and enantioselectivity. Electron-rich substrates such as the 3-(*p*-*tert*-butylphenyl)isoquinoline (**7b**) and the *p*-methoxyphenyl (**7d**) afforded chiral THIQs with excellent yields, diastereoselectivity, and enantioselectivity, similar to **7a**. Interestingly, however, a general trend of lower diastereoselectivity was observed with electron-withdrawing substituents both at the *para*- and *meta*- positions (**8f–i**). We envision that the observed lower diastereoselectivity arises from the weaker coordinating ability of the nitrogen to the

iridium catalyst in electron-poor substrates, discouraging coordination to the catalyst in a bidentate fashion,¹³ and thus resulting in poorer facial selectivity in the second hydride addition step. However, at this time, we still cannot rule out the possibility that epimerization in situ also influences the trend seen in diastereoselectivity.¹⁴ Investigation of steric effects revealed that more sterically encumbered isoquinolines such as the 3-naphthyl and 3-xylyl substrates furnished the products (**8j–k**) in excellent isolated yields with similarly high enantioselectivity (95% and 92% ee, respectively) as a single diastereomer. The most sterically demanding substrate **7m**, bearing an *ortho*-tolyl substituent, provided product **8m** in a modest 64% yield with lower enantioselectivity (49% ee), albeit still with a high 10.1:1 diastereoselectivity. Additionally, we were pleased to find that the nitrile and nitro functional groups as well as the naphthyl substituent were not reduced (**8g**, **8h**, and **8j**), highlighting the chemoselectivity of this catalytic process.

Pleased to find the reaction tolerable to a range of 3-aryl substituted isoquinolines, we sought to further extend the scope of the transformation by exploring heteroaryl-substituted isoquinolines (Scheme 3). Although performing the hydrogenation at 23 °C and 20 bar H₂ resulted in lower conversion, partially due to solubility issues, we found that heterocyclic substituents including furan, thiophene, pyrazole, and pyridine were well tolerated at 60 °C and under higher pressure of 60 bar H₂, producing THIQs **8n–r**. We also observed that the substitution pattern on the heteroaryl groups strongly affects the reaction conversion. For instance, an isoquinoline with a 3-substituted thiophene proceeded with a significantly lower conversion than the 2-thiophene substrate (**8o** and **8p**). Similarly, no conversion was observed with 3- and 4-pyridyl substrates, whereas 2-pyridyl THIQ **8r** was isolated in 48% yield under the same reaction conditions. We speculate that this may be due to the competitive binding of the catalyst by the more distal heteroatom of 3- and 4-substituted heterocycles that inhibits directed hydrogenation of the isoquinoline ring. From product **8p** we were successful in obtaining an X-ray crystal structure to confirm the relative and absolute stereochemistry of our hydrogenation product.

Scheme 3. Substrate Scope of Heterocyclic Substituents^a

^aReactions performed on a 0.2 mmol scale.

Furthermore, we were interested in exploring the substrate scope of isoquinolines with different electronics and substitution patterns on the isoquinoline carbocycle (Scheme 4). Electron-poor fluorinated isoquinolines with varied electronics at the 3-position provided THIQs in high yields (77–94%) with high diastereoselectivity and enantioselectivity under our standard conditions (**10a–c**). It should be noted that these electron-poor THIQs would be difficult to access utilizing electrophilic aromatic substitution strategies, a classical method for the syntheses of THIQs. On the other hand, the electron-rich dioxolane-appended isoquinolines (**9d–e**) afforded lowered conversion under the same reaction conditions, due in part to the poor solubility of the substrates in THF. Nevertheless, executing the reaction at 60 °C and 60 bar H₂ with CH₂Cl₂ as cosolvent improved the solubility and conversion to yield products **10d–e** with high diastereoselectivity.¹⁵ Interestingly, we observed significantly lower enantioselectivity for the dioxolane THIQs, which is observed in other reports as well.^{4a,g} Finally, the naphthyl-fused THIQ **10f** was obtained with high diastereoselectivity and enantioselectivity, despite its extended aromatic system and larger steric hindrance. Although we observed modest conversion for these highly decorated isoquinolines, we were pleased to see that we were able to isolate unreacted starting material after column chromatography to obtain 80%, 99%, and 79% yield, respectively, of **10d–f** based on recovered starting material. Consistent with our results for THIQs **8j** and **8r**, we observed that only the ring with the least degree of aromatic stabilization was reduced for **10f**.

Scheme 4. Substrate Scope of IQ Backbone Substituents^a

^aReactions performed on a 0.2 mmol scale. ^bReaction performed at 60 °C and 60 bar H₂. ^cCH₂Cl₂ cosolvent used to improve substrate solubility.

Directing Group Studies. Having demonstrated that this transformation is general for a wide variety of 1,3-disubstituted isoquinolines, we then turned our attention to investigate the effects of different “directing” groups at the C1-position (Scheme 5). Isoquinolines bearing other polar groups such as an ester (**12a**), ethers (**12b–c**), and a Boc-protected amine (**12d**) delivered the products in lower yields than the hydroxy-directed substrate at 23 °C and 20 bar H₂. However, to our delight, by increasing the temperature and H₂ pressure, these yields could be improved with no erosion of enantioselectivity and diastereoselectivity.

Additionally, we found that aldehyde **11f** was reduced to the alcohol in situ, affording the hydroxymethyl THIQ **8a** in comparable yield, enantioselectivity, and diastereoselectivity to that of the hydroxy-directing substrate **7a** (*vide supra*). Interestingly, an isoquinoline lacking a potential directing group (**12e**) also afforded chiral THIQTs with no erosion of enantioselectivity (90% ee),¹⁶ although elevated temperature and pressure are needed to obtain a synthetically useful yield (64%). While the hydroxy-directing aspect is the enabling feature in the context of our total synthesis of jorumycin, we are pleased to find that we can obviate this requirement in our developed hydrogenation technology. Nevertheless, surveying a variety of different directing groups demonstrates the importance of a functional group for directed hydrogenation, with the hydroxy functionality acting as the best directing group for mild and efficient asymmetric hydrogenation. Notably, this is the first asymmetric hydrogenation method of isoquinolines in which additional Lewis basic functionalities are tolerated. It is also the first report investigating the effects of different directing groups in enantioselective hydrogenation of isoquinolines.

Scheme 5. Substrate Scope of Different Directing Groups^a

^aReactions performed on a 0.2 mmol scale. ^bReaction performed at 60 °C and 60 bar H₂. ^cRelative and absolute stereochemistry determined by experimental and computed VCD and optical rotation, see Supporting Information.16

Synthetic Utility of the Hydrogenated Products. Overall, the broad application of our hydrogenation technology to afford chiral THIQTs provides access to a range of decorated analogs that are difficult to synthesize via biomimetic approaches (e.g., Pictet-Spengler, Bischler-Napieralski). These often require electron-rich substrates to undergo cyclization (eq 1).¹⁷

With the scope of the transformation established, we sought to demonstrate the synthetic utility of the produced chiral THIQTs toward more complex scaffolds that could be applicable to natural products. Additionally, we envisioned taking advantage of the chiral β-amino alcohol that is generated in our product as a building block to forge more complex enantioenriched heterocyclic scaffolds (Scheme 6).¹⁸

Scheme 6. Derivatization of a Hydrogenated Product^a

^aConditions: (a) 37% aq. CH₂O (1.85 equiv), DCE, 23 °C, 15 min, 93% yield. (b) CDI (4 equiv), THF, 50 °C, 15 h, 84% yield. (c) 40% aq. glyoxal (20 equiv), DCE, 23 °C, 18 h, 41% yield. (d) 60% aq. 2,2-dimethoxyacetaldehyde (1.85 equiv), DCE, 23 °C, 18 h; then Eaton's Reagent (4 equiv), CH₂Cl₂, 23 °C, 3 h, 38% yield.

Prior to our investigation into the synthetic utility of THIQ products, we performed the hydrogenation of isoquinoline **7I** on a larger scale (1 mmol). We were pleased to find that the hydrogenated product **8I** was still obtained in good yield (91% isolated yield) with excellent selectivity (>20:1 dr, 88% ee). With an ample amount of **8I** in hand, we subjected THIQ **8I** to aqueous formaldehyde solution and found that the tricyclic 1,2-fused oxazolidine THIQ **13** was formed rapidly via the cyclization of the alcohol onto the iminium generated in situ. Furthermore, the reaction of amino alcohol **8I** with carbonyldiimidazole (CDI) afforded oxazolidinone-fused THIQ **14** in 84% yield.¹⁹ To our delight, we found that these 6,6,5-tricyclic systems are conserved structural motifs in a number of natural products such as quinocarcin, tetrazomine, and bioxalomycin.⁵ Lastly, a different tricyclic scaffold containing fused morpholinone (**15**) can be isolated in 41% yield by the addition of excess glyoxal to **8I** at room temperature.²⁰ Being able to access a variety of complex heterocyclic scaffolds in one step from our hydrogenated THIQs further highlights the advantages of the hydroxymethyl functionality at the C1 position, beyond directing hydrogenation.

In addition to the tricyclic scaffold, we were pleased to find that an analog of tetrahydropyprotoberberine alkaloids, a family of natural products with a tetracyclic bis-THIQ core,²¹ can be synthesized via a 2-step sequence. First, reaction of **8I** with glyoxal dimethyl acetal delivered the oxazolidine-fused intermediate with a dimethoxy acetal substituent at the carbinol-amine carbon. Subsequently, exploration of both Brønsted and Lewis acid-mediated Pomeranz-Fritsch reaction revealed that the use of Eaton's reagent²² delivered pentacyclic THIQ **16** in 38% yield as a single diastereomer. This complex scaffold could be of medicinal interest, as previous studies have shown that tetrahydropyprotoberberine derivatives possess a wide array of interesting biological activities.^{17,23}

CONCLUSIONS

We have developed a general, efficient enantioselective hydrogenation reaction of 1,3-disubstituted isoquinolines toward the syntheses of chiral THIQs. Key to the success of this reaction is the installation of a directing group at the C1-position that facilitates hydrogenation to reduce a variety of isoquinolines under mild reaction conditions. The developed method affords chiral THIQs in good yields, with

high levels of diastereoselectivity and enantioselectivity. The reaction conditions tolerate a wide range of substitution on the 1-, 3-, 6-, 7-, and 8-position of the isoquinoline core. To date, this report represents the broadest scope and highest tolerance of Lewis-basic functionality of any asymmetric isoquinoline reduction technology currently known. Furthermore, this method is amenable to the production of electron-deficient THIQs that are difficult to obtain through the classical Pictet-Spengler approach. In order to demonstrate the synthetic utility of the hydrogenated products, we utilize the hydroxyl directing group as a functional handle for further synthetic manipulations. As a result, we have completed the syntheses of various tricyclic and pentacyclic skeletons that are of potential medicinal interest. Further exploration of the mechanism, and other applications of this technology are currently underway.

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ASSOCIATED CONTENT

Supporting Information Available. Detailed experimental procedures, compound characterization data, and computational analysis. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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ABBREVIATIONS

ee, enantiomeric excess; dr, diastereomeric ratio; THIQ, 1,2,3,4-tetrahydroisoquinoline; BTfM, 3,5-bis(trifluoromethyl)phenyl; DMM, 4-methoxy-3,5-dimethylphenyl; TBAI, tetrabutylammonium iodide; CPME, cyclopentyl methyl ether; Boc, *tert*-butoxycarbonyl; DCE, 1,2-dichloroethane; CDI, carbonyldiimidazole; VCD, vibrational circular dichroism.

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SYNOPSIS TOC

Asymmetric Hydrogenation of 1,3-Disubstituted Isoquinolines

- General method for a variety of substitution patterns
- 30 examples: up to 99% yield, up to >20:1 dr, and up to 95% ee
- Additional Lewis basic functionalities tolerated

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