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

Alexia N. Kim,[§] Aurapat Ngamnithiporn,[§] Eric R. Welin, Martin T. Daiger, Christian U. Grünanger, Michael D. Bartberger, Scott C. Virgil, and Brian M. Stoltz*

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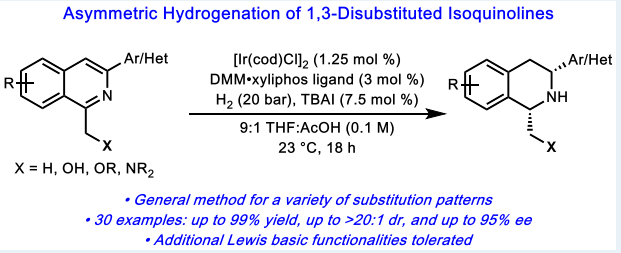
ABSTRACT: The development of a general method utilizing a hydroxymethyl directing group for asymmetric hydrogenation of 1,3-disubstituted isoquinolines to provide chiral 1,2,3,4-tetrahydroisoquinolines is reported. The reaction, which utilizes $[Ir(cod)Cl]_2$ and a commercially available chiral xyliphos ligand, proceeds in good yield with high levels of enantioselectivity and diastereoselectivity (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 in comparison to other substituents, although high levels of enantioselectivity were conserved across a variety of polar and nonpolar functional groups. By utilization of 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 analogue of the tetrahydroprotoberberine alkaloids was successfully synthesized.



KEYWORDS: *hydrogenation, asymmetric catalysis, heterocycles, isoquinolines, tetrahydroisoquinolines*

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 heteroaromatic 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 in comparison 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 two 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 and heteroaryl-substituted isoquinolines, which limits the applicability of these methodologies in synthesis. Since 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 the 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 analogues 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**

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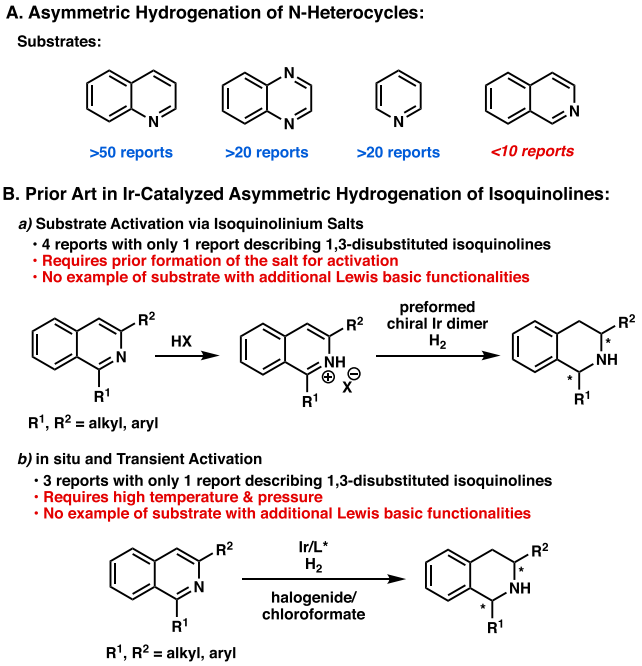


Figure 1. (A) Limitations in the enantioselective hydrogenation of N-heterocycles. (B) Previous examples of iridium-catalyzed enantioselective and diastereoselective hydrogenation of mono- and disubstituted isoquinolines.

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

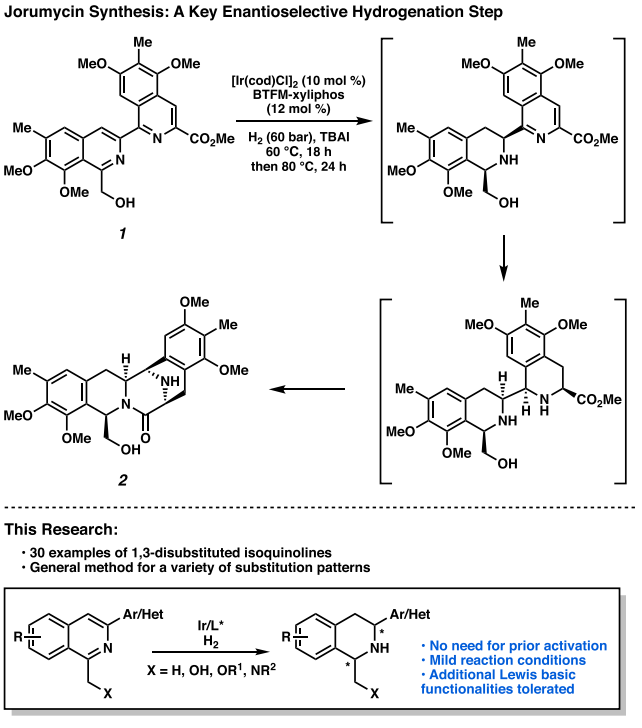


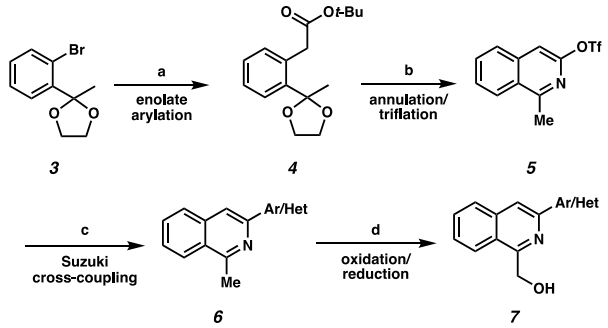
Figure 2. Our research on iridium-catalyzed enantioselective and diastereoselective hydrogenation of 1,3-disubstituted isoquinolines.

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.

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

Scheme 1. Syntheses of 1-(Hydroxymethyl)-3-aryl Isoquinoline Substrates[a]



[a]Conditions: (a) *tert*-butyl acetate (2 equiv), LiHMDS (2.5 equiv), $Pd_2(dba)_3$ (5 mol %), P(*t*-Bu_3)·HBF_4 (10 mol %), toluene, 23 °C, 18 h, 92% yield; (b) 33% TFA in CH_2Cl_2, 23 °C, 2 h, then aqueous NH_4OH, MeCN, 70 °C, 12 h, then Tf_2O (2 equiv), pyridine, CH_2Cl_2, 0 °C, 1 h, 38% yield over three steps; (c) aryl/heteroaryl boronic acid (1.5 equiv), XPhos Pd G3 (2 mol %), 2/1 K_3PO_4/THF, 40 °C, 2 h, 77−95% yield; (d) SeO_2 (2 equiv), 1,4-dioxane, 110 °C, 2 h, then $NaBH_4$ (1 equiv), 4/1 CH_2Cl_2/MeOH, 10 min, 25−97% yield.

reported by Donohoe and co-workers,[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, SeO_2 oxidation to the aldehyde and subsequent $NaBH_4$ 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]

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 conditions slightly modified from our previously reported hydrogenation on the bis-

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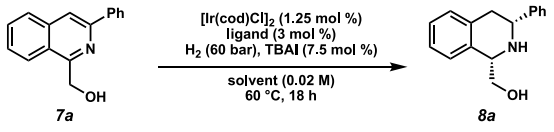
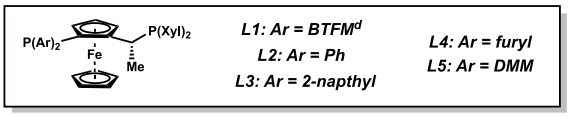
(isoquinoline) system (Table 1). An initial experiment, employing 1.25 mol % of $[Ir(cod)Cl]_2$ and 3 mol % of the

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_2Cl_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



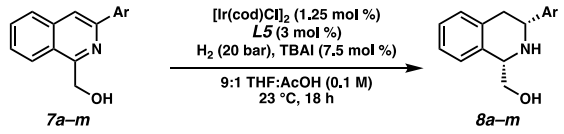
[a]Conditions: 0.04 mmol of **7a**, 1.25 mol % of $[Ir(cod)Cl]_2$, 3 mol % of ligand, 7.5 mol % of TBAI, 60 bar of H_2 in 2.0 mL of 9/1 solvent/AcOH. [b]Determined from crude ^1H NMR using 1,3,5-trimethoxybenzene as a standard. [c]Determined by chiral SFC analysis of Cbz-protected product. [d]Opposite enantiomer of ligand used. [e]Reaction performed on a 0.2 mmol scale at 23 °C, 20 bar of H_2, and 0.1 M concentration of **7a**.

BTFM-xyliphos 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 the Supporting Information) and found the xyliphos ligand framework to be optimal. By exploring different electronics of this ligand scaffold, we observed that replacing 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 a 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.

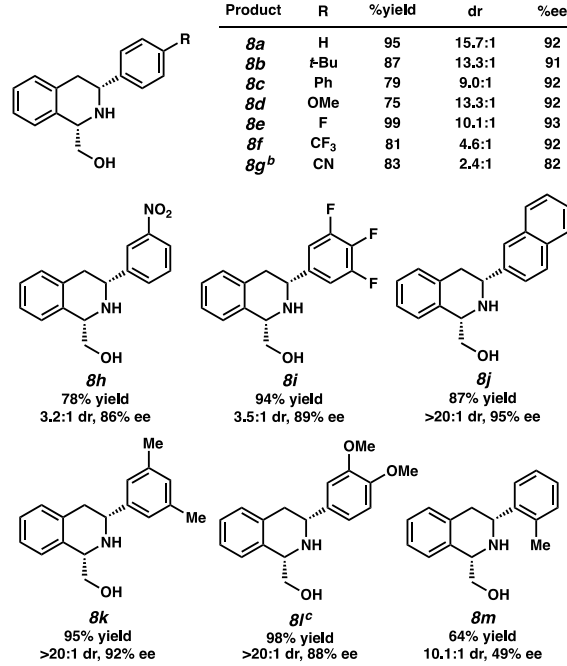
Investigation of different solvents with **L5** as the optimal ligand reveals that while the use of CH_2Cl_2 provided results similar to those for toluene (Table 1, entry 7), the diastereoselectivity could be improved with the use of ethereal solvents (entries 8−11). Although bulkier ethereal solvents 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 the Supporting Information). Finally, we were excited to observe that lowering the temperature to 23 °C and H_2 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]

Substrate Scope. With optimized reaction conditions identified, we explored the general substrate scope for this transformation (Scheme 2). Gratifyingly, a wide variety of aryl

Scheme 2. Substrate Scope of Different Aryl Substituents[a]



Product	R	%yield	dr	%ee
8a	H	95	15.7:1	92
8b	*t*-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



[a]Reactions were performed on a 0.2 mmol scale. [b]The reaction was performed at 60 °C and 60 bar of H_2. [c]CH_2Cl_2 cosolvent used to improve substrate solubility.

substituents at the 3-position of the isoquinoline are well tolerated under the mild reaction conditions of 20 bar of H_2 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)isoquinoline **7d** afforded chiral THIQs with excellent yields, diastereoselectivity, and enantioselectivity, similar to the case for **7a**. Interestingly, however, a general trend of lower diastereoselectivity was observed with electron-withdrawing substituents at both 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

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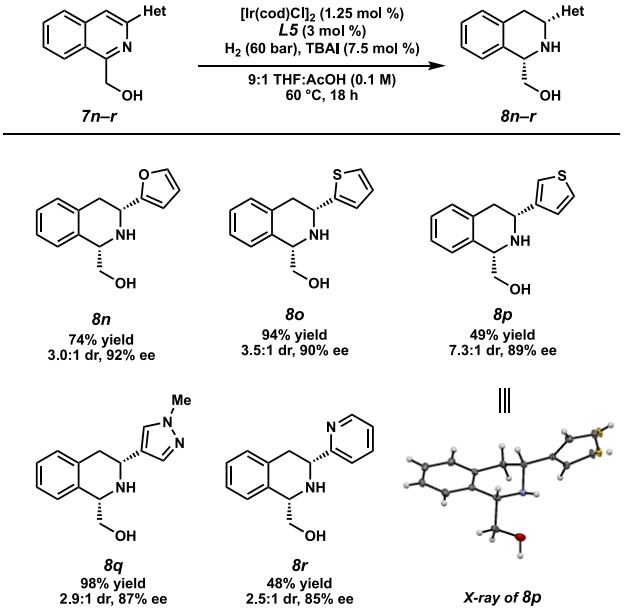
seen in diastereoselectivity.[14] An investigation of steric effects revealed that more sterically encumbered isoquinolines such as the 3-naphthyl and 3-xylyl substrates furnished the products **8j**,**k** in excellent isolated yields with similarly high enantioselectivities (95% and 92% ee, respectively) as a single diastereomer. The most sterically demanding substrate **7m**, bearing an *o*-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 and a naphthyl substituent were not reduced (**8g**,**h**,**j**), 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 of H_2 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 a higher pressure of 60 bar of H_2, 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 in comparison to the 2-thiophene substrate (**8o**,**p**). Similarly, no conversion was observed with 3- and 4-pyridyl substrates, whereas the 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.

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 of H_2 with CH_2Cl_2 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 greater 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% yields, respectively, of **10d**−**f** based on recovered starting material. Consistent with our results for THIQs **8j**,**r**, we observed that only the ring with the least degree of aromatic stabilization was reduced for **10f**.

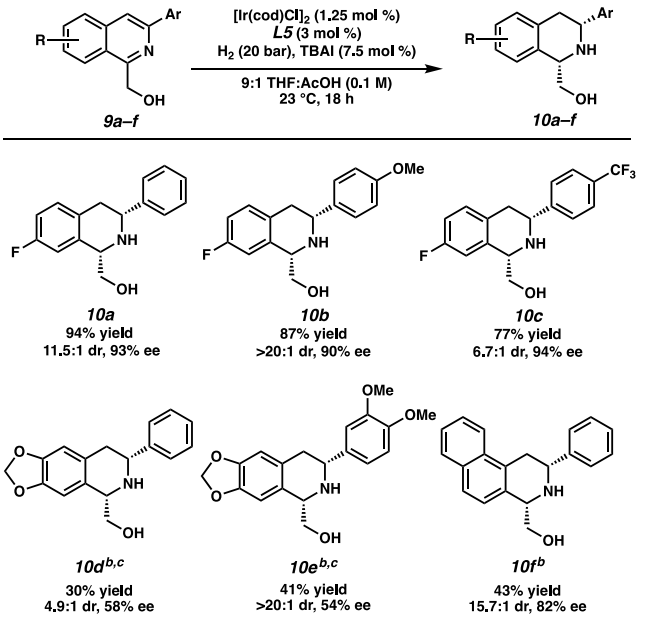
Directing-Group Studies. Having demonstrated that this transformation is general for a wide variety of 1,3-disubstituted isoquinolines, we then turned our attention to investigate the effects of different "directing" groups at the C1 position (Scheme 5). Isoquinolines bearing other polar groups such as an ester (**12a**), ethers (**12b**,**c**), and a Boc-protected amine (**12d**) delivered the products in lower yields in comparison to the hydroxy-directed substrate at 23 °C and 20 bar of H_2. However, to our delight, by increasing the temperature and H_2 pressure, these yields could be improved with no erosion of enantioselectivity and diastereoselectivity.

Scheme 3. Substrate Scope of Heterocyclic Substituents[a]



[a]Reactions were performed on a 0.2 mmol scale.

Scheme 4. Substrate Scope of IQ Backbone Substituents[a]



[a]Reactions were performed on a 0.2 mmol scale. [b]The reaction was performed at 60 °C and 60 bar H_2. [c]CH_2Cl_2 cosolvent used to improve substrate solubility.

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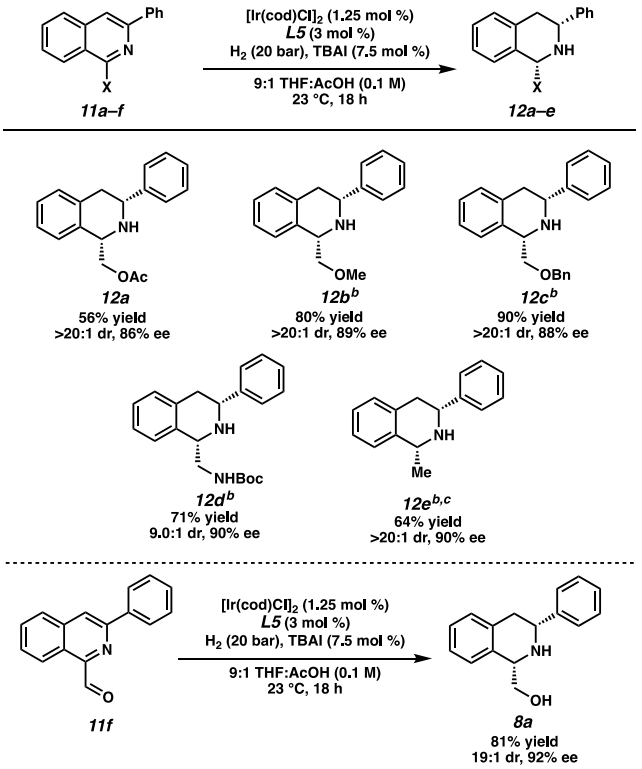
Scheme 5. Substrate Scope of Different Directing Groups[a]

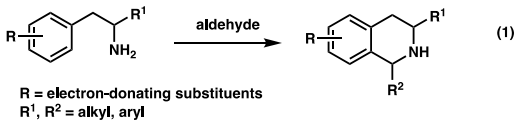


[a]Reactions were performed on a 0.2 mmol scale. [b]The reaction was performed at 60 °C and 60 bar H_2. [c]Relative and absolute stereochemistries were determined by experimental and computed VCD and optical rotation (see the Supporting Information).[15]

Additionally, we found that aldehyde **11f** was reduced to the alcohol in situ, affording the hydroxymethyl THIQ **8a** in yield, enantioselectivity, and diastereoselectivity comparable to those of the hydroxy-directing substrate **7a** (vide supra). Interestingly, an isoquinoline lacking a potential directing group (**12e**) also afforded chiral THIQs 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 the enantioselective hydrogenation of isoquinolines.

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

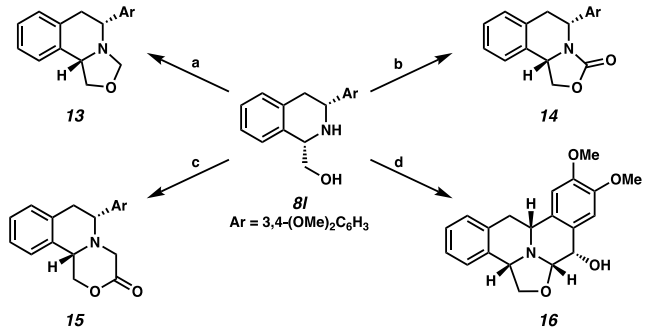
With the scope of the transformation established, we sought to demonstrate the synthetic utility of the produced chiral THIQs toward more complex scaffolds that could be applicable



(1)

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]



[a]Conditions: (a) 37% aqueous CH_2O (1.85 equiv), DCE, 23 °C, 15 min, 93% yield; (b) CDI (4 equiv), THF, 50 °C, 15 h, 84% yield; (c) 40% aqueous glyoxal (20 equiv), DCE, 23 °C, 18 h, 41% yield; (d) 60% aqueous 2,2-dimethoxyacetaldehyde (1.85 equiv), DCE, 23 °C, 18 h, then Eaton's reagent (4 equiv), CH_2Cl_2, 23 °C, 3 h, 38% yield.

Prior to our investigation into the synthetic utilitiy of THIQ products, we performed the hydrogenation of isoquinoline **7l** on a larger scale (1 mmol). We were pleased to find that the hydrogenated product **8l** was still obtained in good yield (91% isolated yield) with excellent selectivity (>20:1 dr, 88% ee). With an ample amount of **8l** in hand, we subjected THIQ **8l** to an aqueous fomaldehyde 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 **8l** 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] Finally, a different tricyclic scaffold containing fused morpholinone (**15**) can be isolated in 41% yield by the addition of excess glyoxal to **8l** at room temperature.[20] The ability 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 analogue of tetrahydroprotoberberine alkaloids, a family of natural products with a tetracyclic bis-THIQ core,[21] can be synthesized via a two-step sequence. First, the reaction of **8l** with glyoxal dimethyl acetal delivered the oxazolidine-fused intermediate with a dimethoxy acetal substituent at the carbinolamine carbon. Subsequently, exploration of both Brønsted and Lewis acid mediated Pomeranz–Fritsch reactions revealed that the use of Eaton's reagent[22] 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 tetrahydroprotobeberine derivatives possess a wide array of interesting biological activities.[16,23]

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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-positions of the isoquinoline core. To date, this report represents the broadest scope and highest tolerance of Lewis basic functionalities 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.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c00211.

Detailed experimental procedures, compound characterization data, and computational analysis (PDF)

Crystallographic data for **8p** (CIF)

Spreadsheet (XLSX)

Spreadsheet (XLSX)

AUTHOR INFORMATION

Corresponding Author

Brian M. Stoltz − *Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States;* orcid.org/0000-0001-9837-1528; Email: stoltz@caltech.edu

Authors

Alexia N. Kim − *Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States*

Aurapat Ngamnithiporn − *Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States;* orcid.org/0000-0002-5389-8171

Eric R. Welin − *Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States;* orcid.org/0000-0002-1760-4121

Martin T. Daiger − *Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States*

Christian U. Grünanger − *Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States*

Michael D. Bartberger − *1200 Pharma LLC, Pasadena, California 91101, United States;* orcid.org/0000-0002-5167-3139

Scott C. Virgil − *Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.0c00211

Author Contributions

§A.N.K. and A.N. contributed equally to this work and are listed alphabetically.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

ee, enantiomeric excess; dr, diastereomeric ratio; THIQ, 1,2,3,4-tetrahydroisoquinoline; BTFM, 3,5-bistrifluoromethylphenyl; 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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(12) See the Supporting Information for additional results using other acids. Although further studies are required to fully understand the role of acid, we speculate that the acid helps promoting (a) the tautomerization of enamine to imine prior to the second reduction and (b) the dissociation of the THIQ product from the Ir complex through protonation.

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(16) The absolute stereochemistry of product **12e** was determined via the combination of measured and computed vibrational circular dichroism (VCD) spectra and optical rotations. The configuration of **12e** (*R*,*R*) was found to be analogous to that determined for hydroxymethyl product **8a** and also observed crystallographically for **8p**. See the Supporting Information.

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(19) Alternatively, the oxazolidinone-fused product **7b** could be synthesized utilizing a two-step sequence. The first is the Boc protection of the amine. The Boc-protected product was subsequently cyclized to afford oxazolidinone-fused THIQ **7b** under the Appel reaction conditions. See the Supporting Information for experimental details.

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