

Cite this: *Chem. Sci.*, 2022, 13, 3227

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 2nd December 2021
Accepted 16th February 2022

DOI: 10.1039/d1sc06729j

rsc.li/chemical-science

Iridium-catalyzed asymmetric *trans*-selective hydrogenation of 1,3-disubstituted isoquinolines†

Alexia N. Kim,^a Aurapat Ngamnithiporn,^{ab} Michael D. Bartberger^c and Brian M. Stoltz^{*,a}

The development of the first asymmetric *trans*-selective hydrogenation of 1,3-disubstituted isoquinolines is reported. Utilizing [Ir(cod)Cl]₂ and a commercially available chiral Josiphos ligand, a variety of differentially substituted isoquinolines are hydrogenated to produce enantioenriched *trans*-tetrahydroisoquinolines in good yield with high levels of enantioselectivity. Directing group studies demonstrate that the hydroxymethyl functionality at the C1 position is critical for hydrogenation to favor the *trans*-diastereomer. Preliminary mechanistic studies reveal that non-coordinating chlorinated solvents and halide additives are crucial to enable *trans*-selectivity.

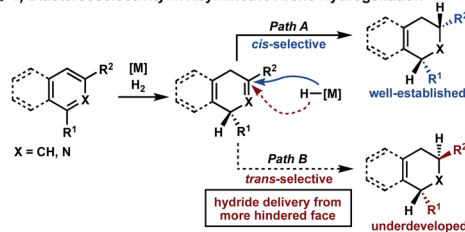
Introduction

The asymmetric hydrogenation of heteroarenes has recently emerged as a powerful strategy to directly access enantioenriched, saturated heterocycles.^{1,2} While significant progress has been made in this field, controlling selectivity in the formation of multiple stereocenters in a single reaction remains challenging. Transition metal-catalyzed hydrogenation of arenes typically proceeds through initial dearomatative reduction of the substrate and subsequent rapid hydrogenation, resulting in high *cis*-selectivity of product (Fig. 1A, path A).^{3,4} In contrast, accessing the *trans*-isomer requires a π -facial exchange of the arene to allow hydride delivery from the more sterically hindered face, rendering its synthesis significantly more difficult (Fig. 1A, path B). While several reports describe the *trans*-selective hydrogenation of arenes, most are limited in scope and not enantioselective.^{5,6} Considering the synthetic value of *trans*-substituted saturated heterocycles, a general method for an asymmetric *trans*-selective hydrogenation of heteroarenes would be a highly desirable and powerful strategy.^{7,8}

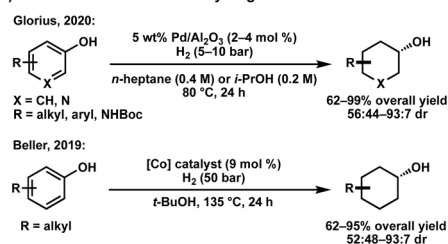
Recently, our group has reported the asymmetric hydrogenation of 1,3-disubstituted isoquinolines to access enantioenriched *cis*-1,2,3,4-tetrahydroisoquinolines (THIQs).⁹ This method enables the asymmetric hydrogenation of isoquinolines with Lewis basic functionalities, such as primary alcohols

and heteroaryl-substituted isoquinolines, that significantly expanded the scope of the transformation compared to prior reports.¹⁰ During the course of this investigation, we also observed formation of the *trans*-THIQ under certain conditions

A. 1) Diastereoselectivity in Asymmetric Arene Hydrogenation

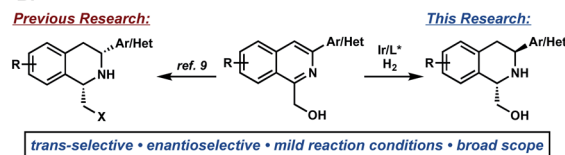


2) Prior Art in *trans*-selective Hydrogenation



No general method of a *trans*- and enantioselective hydrogenation of arenes reported

B.



^aWarren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125, USA. E-mail: stoltz@caltech.edu

^bLaboratory of Medicinal Chemistry, Chulabhorn Research Institute, 54 Kamphaeng Phet 6 Road, Bangkok, 10210, Thailand

^c1200 Pharma LLC, 844 East Green Street, Suite 204, Pasadena, CA, 91101, USA

† Electronic supplementary information (ESI) available. CCDC 2120281. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc06729j

Fig. 1 (A) Challenges in diastereoselectivity of *trans*-selective arene hydrogenation. (B) Our research on iridium-catalyzed asymmetric hydrogenation of 1,3-disubstituted isoquinolines.



in excellent enantioselectivity, albeit in small amounts. Herein, we disclose our efforts to develop the first examples of an asymmetric *trans*-selective hydrogenation of 1,3-disubstituted isoquinolines to access enantioenriched *trans*-THIQs (Fig. 1B).

Results and discussion

We began our studies with 1-(hydroxymethyl)-3-phenylisoquinoline (**1a**) as a model substrate. An initial experiment employing 1.25 mol% of $[\text{Ir}(\text{cod})\text{Cl}]_2$, 3 mol% of chiral Josiphos ligand **L1**, and 7.5 mol% of TBAI in THF delivered the THIQ product with high *cis*-selectivity (Table 1, entry 1).⁸ We observed that using CH_2Cl_2 as solvent gave higher levels of diastereoselectivity for *trans*-isomer **2a**, with excellent enantioselectivity as well (97% ee, entry 2).¹¹ Gratified by this result, we explored different additives and observed that smaller halides afforded higher levels of the desired diastereoselectivity, albeit with diminished conversions of **1a**. Overall, TBABr provided the best combination of diastereo- and enantioselectivity (Table S1[†]). Other additives such as TBAPF₆ previously investigated by Pfaltz and co-workers completely shut down the reaction, demonstrating that halide salts were crucial for this transformation (entry 5).¹²

Seeking to improve the diastereoselectivity, we surveyed a variety of chiral ligand scaffolds and found the xyliphos ligand framework to be optimal (Table S2[†]). We observed that more electron-rich aryl groups on the chiral ligand provided the *trans*-product with higher selectivity, with the DMM-substituted phosphine **L1** affording the highest diastereoselectivity of 2 : 1 *trans* : *cis* (entry 3 vs. entries 6–9). In contrast, more electron-withdrawing aryl groups such as **L5** favored the formation of the *cis*-product (entry 9).

Having identified **L1** as the optimal ligand, we briefly investigated different solvents. We observed that non-coordinating chlorinated solvents such as chloroform and 1,2-dichloroethane delivered product **2a** with the highest *trans*-selectivity (entries 12–13), while non-chlorinated solvents toluene and ethyl acetate gave nearly a 1 : 1 diastereomeric ratio (entries 10–11).¹³

We also explored different directing groups at the C1 position to probe their effects on the diastereoselectivity of this reaction. Isoquinolines bearing functionalities such as a methyl ether, benzyl ether or acetate substituent (**3a–c**) solely provided the *cis*-THIQ, suggesting that they are not functioning as directing groups in the reaction (Table 1, entries 14–16). Indeed, the hydrogenation of isoquinoline **3d** that lacks any potential directing group also afforded only the *cis*-diastereomer of

Table 1 Optimization of the asymmetric *trans*-selective hydrogenation^a

Entry	X	Ligand	Solvent	Additive	% conv. ^b	<i>trans</i> : <i>cis</i> ^b	% ee of <i>trans</i> ^c
1	OH (1a)	L1	THF	TBAI	>95	1 : 15.7	—
2	OH	L1	CH_2Cl_2	TBAI	>95	1 : 1.5	97
3	OH	L1	CH_2Cl_2	TBABr	>95	2 : 1	93
4	OH	L1	CH_2Cl_2	TBACl	75	2.3 : 1	80
5	OH	L1	CH_2Cl_2	TBAPF ₆	<10	—	—
6	OH	L2	CH_2Cl_2	TBABr	>95	1.8 : 1	94
7	OH	L3	CH_2Cl_2	TBABr	95	1.4 : 1	99
8	OH	L4	CH_2Cl_2	TBABr	45	1 : 2.3	35
9	OH	L5	CH_2Cl_2	TBABr	83	1 : 2.9	81
10	OH	L1	PhMe	TBABr	>95	1.2 : 1	91
11	OH	L1	EtOAc	TBABr	>95	1 : 1.1	89
12	OH	L1	CHCl_3	TBABr	68	2.4 : 1	93
13	OH	L1	1,2-DCE	TBABr	>95	2.4 : 1	92
14	OMe (3a)	L1	1,2-DCE	TBABr	>95	1 : 17	N.D.
15	OBn (3b)	L1	1,2-DCE	TBABr	>95	1 : >20	N.D.
16	OAc (3c)	L1	1,2-DCE	TBABr	57	1 : >20	N.D.
17	H (3d)	L1	1,2-DCE	TBABr	92	1 : >20	N.D.
18	NHBoc (3e)	L1	1,2-DCE	TBABr	>95	1.4 : 1	25
19	NH ₂ (3f)	L1	1,2-DCE	TBABr	0	—	—

L1: Ar = DMM (4-methoxy-3,5-dimethylphenyl)
L2: Ar = Ph **L3:** Ar = 2-naphthyl **L4:** Ar = 2-furyl
L5: Ar = BTFM (3,5-bistrifluoromethylphenyl)

^a Performed on a 0.04 mmol scale. ^b Determined by ¹H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as standard.

^c Determined by chiral SFC analysis of Cbz-protected *trans*-product.



product (entry 17). While Boc-protected amine **3e** provided the product in 1.4 : 1 dr favoring the *trans*-THIQ, basic amine functionalities such as primary amine **3f** gave trace product, potentially due to catalyst deactivation (entry 19). Nevertheless, the investigation of different directing groups demonstrates that the hydroxyl functionality serves as the best directing group to selectively access the *trans*-diastereomer by enabling π -facial exchange of the substrate and facilitating hydride delivery from the more sterically hindered face *via* a directed hydrogenation.

With optimized reaction conditions identified, we explored the substrate scope of this transformation (Table 2). Due to the inseparable nature of the *cis*- and *trans*-diastereomers of the hydrogenated products, the crude reaction mixture was subsequently treated with 1,1'-carbonyldiimidazole (CDI) to afford the oxazolidinone-fused THIQs that were easily separable by column chromatography. From **5a**, the relative and absolute stereochemistry of the *trans*-THIQ product was confirmed by X-ray crystallography.¹⁴

Gratifyingly, a wide variety of aryl substituents at the 3-position of the isoquinoline were well tolerated, selectively yielding the *trans*-product in moderate to excellent ee.¹⁵ Substitution at the *para*-position of the 3-aryl ring delivered hydrogenated products **5b–5g** in high selectivities, ranging from electron-rich substrates **5b–5c** to more electron-withdrawing

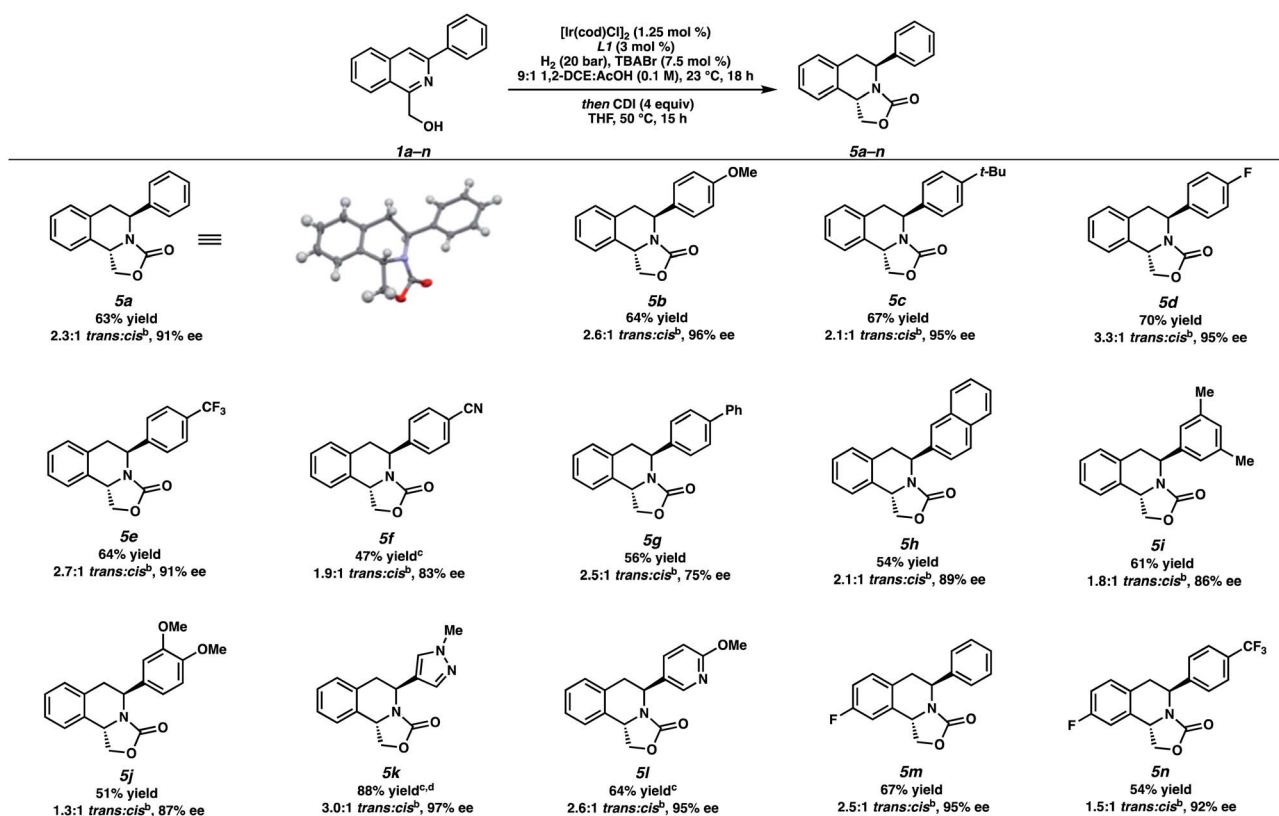
substrates **5d–5f**. Sterically encumbered substrates such as 3-naphthyl, 3-xylyl isoquinolines also afforded products **5h–5i** in good isolated yields, with slightly diminished enantioselectivity. Furthermore, the nitrile functional group in **5f** and naphthyl substituent of **5h** were not reduced in this process, highlighting the chemoselectivity of this transformation.

Additionally, we were pleased to observe that heteroaryl-substituted isoquinolines were well tolerated at 60 °C and 60 bar H₂ to produce *trans*-THIQs **5k,l** in high enantioselectivities (97% and 94% ee, respectively), and with no erosion of diastereoselectivity. Finally, different electronics of the isoquinoline carbocycle such as fluorinated isoquinolines **1m–n** were hydrogenated to afford electron-poor THIQs **5m–n** in high selectivities under our standard conditions.

Having demonstrated that this transformation is general for a wide range of 1,3-disubstituted isoquinolines, we sought to derivatize the oxazolidinone-fused THIQs (Scheme 1). We were pleased to find that the oxazolidinone functional group could be efficiently removed with Ba(OH)₂ · 8H₂O to afford THIQ **2a** in 81% yield.^{16,17} Alternatively, reduction with DIBAL afforded *N*-methyl THIQ **6a** in 73% yield, providing a facile access of our hydrogenated products to *N*-methyl protected THIQs.

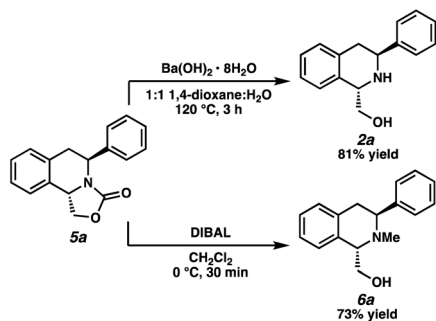
To elucidate the factors controlling the *trans*-selectivity in this transformation, several control experiments were

Table 2 Substrate scope of the *trans*-selective hydrogenation of 1,3-disubstituted isoquinolines^a



^a Isolated yields on a 0.2 mmol scale. SFC analysis was used to determine ee. ^b Determined by ¹H NMR analysis of crude reaction. ^c Performed at 60 bar H₂ and 60 °C. ^d Total isolated yield of inseparable diastereomers.

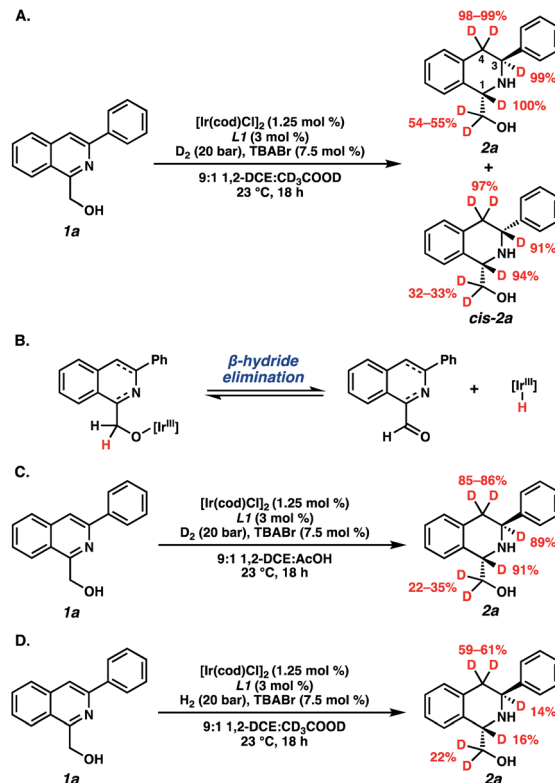




Scheme 1 Synthetic derivatizations of product 5a.

conducted to probe the reaction mechanism (Scheme 2). Substituting TBABr for TBAI as the additive gave a 1 : 1.2 dr favoring the *cis*-product, with high enantioselectivities exhibited for both products (Scheme 2A). This suggests that the bromide ligand facilitates π -facial exchange of the substrate over iodide to afford higher levels of the *trans*-diastereomer.^{18,19} Replacing 1,2-DCE solvent for THF also delivered similar results, indicating that ethereal solvents inhibit the formation of *trans*-2a through stronger coordination with iridium (Scheme 2B).²⁰ Overall, the combination of non-coordinating, chlorinated solvents and smaller halides are crucial in governing the observed *trans*-selectivity.

Deuterium experiments were also conducted to determine the degree of deuteration of our hydrogenated products (Scheme 3). Interestingly, the combination of both D₂ and CD₃COOD delivered deuterium at the C1-, C3-, and C4-positions of the THIQ, as well as at the methylene carbon of the hydroxymethyl functional group (Scheme 3A). We attribute this exocyclic deuteration to a competitive β -hydride elimination pathway that is operative *in situ* under our *trans*-hydrogenation conditions (Scheme 3B).^{21,22} However, this is likely not a critical pathway toward the *trans*-product, as deuterium incorporation in the corresponding *cis*-isomer (*cis*-2a) is also observed. Exchanging either D₂ or CD₃COOD for their protic counterparts demonstrated deuteride delivery primarily from the gas at the

Scheme 3 Deuterium experiments of (A) D₂ and CD₃COOD, (B) observed β -hydride elimination pathway, (C) D₂ and protic AcOH, and (D) H₂ and CD₃COOD.

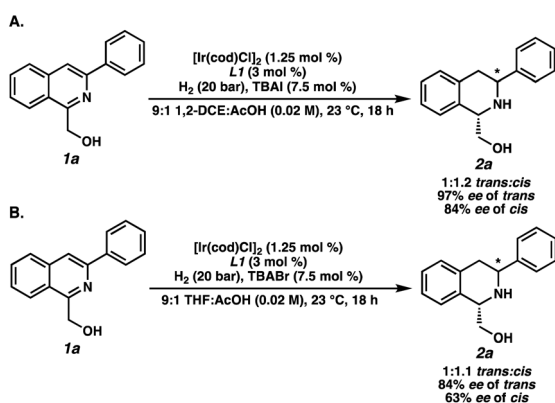
C1- and C3-positions of 2a, yet the acid also enables reduction of the isoquinoline ring. This suggests a proton-hydride exchange occurring between the acid and the iridium hydride species for hydrogenation.^{19,23} Further investigations of the mechanism²⁴ and other applications of this technology are currently underway and will be reported in due course.

Conclusions

In conclusion, we have developed an asymmetric *trans*-selective hydrogenation reaction of 1,3-disubstituted isoquinolines for the syntheses of enantioenriched *trans*-THIQs. Key to this enantio- and diastereoselective reaction is the hydroxymethyl directing group at the C1-position which enables π -facial exchange of the substrate and facilitates hydride delivery from the sterically more hindered face. This method tolerates a wide range of electronics, Lewis basic functionalities, and substitution at the C1, C3, and C8-positions of the isoquinoline core, representing one of the first examples of an asymmetric hydrogenation technology to selectively access the *trans*-diastereomer of hydrogenated aromatic compounds.

Data availability

Data for this work, including optimization tables, general experimental procedures, characterization data for all new compounds and X-ray data are provided in the ESI.†

Scheme 2 Control experiments of the asymmetric *trans*-selective hydrogenation by using (A) TBAI instead of TBABr and (B) THF instead of 1,2-DCE.

Author contributions

B. M. S. conceived and directed the project. A. N. K. and A. N. designed, performed, and analyzed the synthetic chemistry experiments. M. D. B. assisted with VCD studies of THIQ **2a**. A. N. K., A. N., M. D. B., and B. M. S. prepared the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the NIH-NIGMS (R01GM127972A) and Caltech for financial support. A. N. thanks the Royal Thai Government Scholarship Program. We thank Dr David VanderVelde for NMR expertise, Dr Scott Virgil for instrumentation, Dr Mona Shahgholi for mass spectroscopy, and Dr Michael Takase and Larry Henling for assistance with X-ray analysis.

Notes and references

- For recent reviews of asymmetric hydrogenation of heteroarenes, see: (a) D.-S. Wang, Q.-A. Chen, S.-M. Lu and Y.-G. Zhou, *Chem. Rev.*, 2012, **112**, 2557–2590; (b) Y.-G. Zhou, *Acc. Chem. Res.*, 2007, **40**, 1357–1366; (c) D. Zhao and F. Glorius, *Angew. Chem., Int. Ed.*, 2013, **52**, 9616–9618; (d) A. N. Kim and B. M. Stoltz, *ACS Catal.*, 2020, **10**, 13834–13851; (e) Y.-E. Luo, Y.-M. He and Q.-H. Fan, *Chem. Rec.*, 2016, **16**, 2697–2711; (f) N. Fleury-Brégeot, V. de la Fuente, S. Castellón and C. Claver, *ChemCatChem*, 2010, **2**, 1346–1371.
- For recent reviews of asymmetric C=N bond hydrogenation, see: (a) A. Cabré, X. Verdager and A. Riera, *Chem. Rev.*, 2022, **122**, 269–339; (b) R. Abed Ali Abdine, G. Hedouin, F. Colobert and J. Wencel-Delord, *ACS Catal.*, 2021, **11**, 215–247; (c) R. Molina Betancourt, P.-G. Echeverria, T. Ayad, P. Phansavath and V. Ratovelomanana-Vidal, *Synthesis*, 2021, **53**, 30–50; (d) J. Barrios-Rivera, Y. Xu, M. Wills and V. K. Vyas, *Org. Chem. Front.*, 2020, **7**, 3312–3342; (e) Y. Liu, X. Yue, C. Luo, L. Zhang and M. Lei, *Energy Environ. Mater.*, 2019, **2**, 292–312.
- M. P. Wiesenfeldt, Z. Nairoukh, T. Dalton and F. Glorius, *Angew. Chem., Int. Ed.*, 2019, **58**, 10460–10476.
- C. Gelis, A. Heusler, Z. Nairoukh and F. Glorius, *Chem.–Eur. J.*, 2020, **26**, 14090–14094.
- For examples of *trans*-selective arene hydrogenation, see: (a) M. Wollenburg, A. Heusler, K. Bergander and F. Glorius, *ACS Catal.*, 2020, **10**, 11365–11370; (b) K. Murugesan, T. Senthamarai, A. S. Alshammari, R. M. Altamimi, C. Kreyenschulte, M.-M. Pohl, H. Lund, R. V. Jagadeesh and M. Beller, *ACS Catal.*, 2019, **9**, 8581–8591; (c) H. Li, Y. Wang, Z. Lai and K.-W. Huang, *ACS Catal.*, 2017, **7**, 4446–4450; (d) A. Tugler and E. Szabados, *Org. Process Res. Dev.*, 2016, **20**, 1246–1251; (e) T. Maegawa, A. Akashi, K. Yaguchi, Y. Iwasaki, M. Shigetsura, Y. Monguchi and H. Sajiki, *Chem.–Eur. J.*, 2009, **15**, 6953–6963; (f) S. Jansat, D. Picurelli, K. Pelzer, K. Philippot, M. Gómez, G. Muller, P. Lecante and B. Chaudret, *New J. Chem.*, 2006, **30**, 115–122.
- For an example of a sequential enantioselective hydrogenation to access the *trans*-diastereomer of product, see: M. P. Wiesenfeldt, D. Moock, D. Paul and F. Glorius, *Chem. Sci.*, 2021, **12**, 5611–5615.
- (a) H. Matsuda, K. Ninomiya, H. Shimoda, N. Nishida and M. Yoshikawa, *Heterocycles*, 2001, **55**, 2043–2050; (b) S. J. Rochfort, L. Towerzey, A. Carroll, G. King, A. Michael, G. Pierens, T. Rali, J. Redburn, J. Whitmore and R. J. Quinn, *J. Nat. Prod.*, 2005, **68**, 1080–1082.
- For recent total syntheses of *trans*-THIQ natural products, see: (a) S. Uenishi, R. Kakigi, K. Hideshima, A. Miyawaki, J. Matsuoka, T. Ogata, K. Tomioka and Y. Yamamoto, *Tetrahedron*, 2021, **90**, 132165–132176; (b) J. Kayhan, M. J. Wanner, S. Ingemann, J. H. van Maarseveen and H. Hiemstra, *Eur. J. Org. Chem.*, 2016, 3705–3708.
- (a) A. N. Kim, A. Ngamnithiporn, E. R. Welin, M. T. Daiger, C. U. Grünanger, M. D. Bartberger, S. C. Virgil and B. M. Stoltz, *ACS Catal.*, 2020, **10**, 3241–3248; (b) E. R. Welin, A. Ngamnithiporn, M. Klatte, G. Lapointe, G. M. Pototschnig, M. S. J. McDermott, D. Conklin, C. D. Gilmore, P. M. Tadross, C. K. Haley, K. Negoro, E. Glibstrup, C. Grünanger, K. M. Allan, S. C. Virgil, D. J. Slamon and B. M. Stoltz, *Science*, 2019, **363**, 270–275.
- For recent reports of Ir-catalyzed asymmetric hydrogenation of 1,3-disubstituted isoquinolines, see: (a) M.-W. Chen, Y. Ji, J. Wang, Q.-A. Chen, L. Shi and Y.-G. Zhou, *Org. Lett.*, 2017, **19**, 4988–4991; (b) J. Wen, R. Tan, S. Liu, Q. Zhao and X. Zhang, *Chem. Sci.*, 2016, **7**, 3047–3051; (c) Y. Kita, K. Yamaji, K. Higashida, K. Sathaiyah, A. Iimuro and K. Mashima, *Chem.–Eur. J.*, 2015, **21**, 1915–1927.
- The absolute configuration of the *trans*-diastereomer was assigned as (*S,S*) by VCD, see ESI 43.†
- S. P. Smidt, N. Zimmermann, M. Studer and A. Pfaltz, *Chem.–Eur. J.*, 2004, **10**, 4685–4693.
- Attempts to further improve the diastereoselectivity were unsuccessful, see Tables S1 and S2.†
- The absolute stereochemistry for all other hydrogenated products were assigned by analogy to **5a**.
- Attempts to prepare 3-alkyl substituted isoquinolines were unsuccessful.
- C.-Y. Liu, V. Angamuthu, W.-C. Chen and D.-R. Hou, *Org. Lett.*, 2020, **22**, 2246–2250.
- Cbz-protected **2a** was obtained in 91% ee, ruling out any racemization occurring in the reaction.
- K. Fagnou and M. Lautens, *Angew. Chem., Int. Ed.*, 2002, **41**, 26–47.
- R. Dorta, D. Broggini, R. Stoop, H. Rüegger, F. Spindler and A. Togni, *Chem.–Eur. J.*, 2004, **10**, 267–278.
- R. Díaz-Torres and S. Alvarez, *Dalton Trans.*, 2011, **40**, 10742–10750.
- (a) M. V. Jiménez, J. Fernández-Tornos, F. J. Modrego, J. J. Pérez-Torrente and L. A. Oro, *Chem.–Eur. J.*, 2015, **21**, 17877–17889; (b) O. Blum and D. Milstein, *J. Am. Chem. Soc.*, 1995, **117**, 4582–4594.



- 22 The same deuterium experiment under the *cis*-selective hydrogenation conditions demonstrates no deuteration at the methylene carbon of **1a**, ruling out an alternative tautomerization mechanism.
- 23 (a) H. Liu, W.-H. Wang, H. Xiong, A. Nijamudheen, M. Z. Ertem, M. Wang and L. Duan, *Inorg. Chem.*, 2021, **60**, 3410–3417; (b) S. R. Klei, J. T. Golden, T. D. Tilley and R. G. Bergman, *J. Am. Chem. Soc.*, 2002, **124**, 2092–2093.
- 24 A proposed catalytic cycle is described in the ESI, see ESI 32.†

