OL Organic Letters

pubs.acs.org/OrgLett Letter

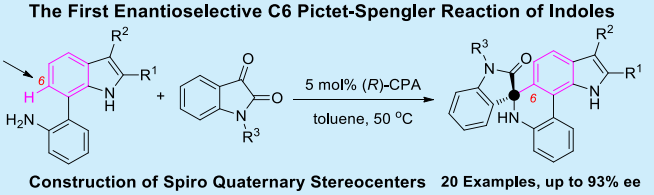
Chiral-Phosphoric-Acid-Catalyzed C6-Selective Pictet–Spengler Reactions for Construction of Polycyclic Indoles Containing Spiro Quaternary Stereocenters

Xin-Wei Wang, Wen-Jun Huang, Han Wang, Bo Wu, and Yong-Gui Zhou*

Cite This: *Org. Lett.* 2022, 24, 1727–1731 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Compared with the well-established asymmetric Pictet–Spengler reactions on the pyrrole ring of indoles, the catalytic asymmetric Pictet–Spengler reaction on the benzene ring of indoles has been rarely studied. Herein the C6-selective Pictet–Spengler reactions of indoles have been realized by employing 2-(1*H*-indol-7-yl)anilines and isatins in the presence of chiral phosphoric acid, affording novel polycyclic indole derivatives bearing spiro quaternary stereocenters in excellent yields with excellent enantioselectivities. This reaction could be conducted on the gram scale without any loss of activity or enantioselectivity.

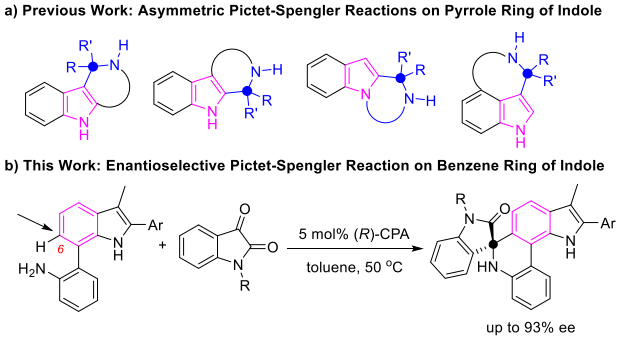


Indole polycyclic skeletons are attractive synthetic targets because they are ubiquitous in many alkaloids and synthetic organic compounds.[1] Therefore, various tactics have been developed for the synthesis of such indole polycyclic systems.[2,3] Among these methods, the catalytic asymmetric Pictet–Spengler reactions are one of the most straightforward and facile approaches to these enantioenriched molecules.[2a,c,e] Pioneering research on enantioselective Pictet–Spengler reactions has been carried out by Jacobsen,[4] List,[5] Hiemstra,[6] and other groups.[7−9] In these studies, reactions occurred selectively at the C2 or C3 position of indoles due to the inherent strong nucleophilicity of the pyrrole ring (Scheme 1a).

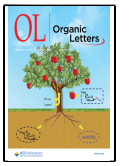
Compared with the high reactivity of the pyrrole ring, the nucleophilicity of the benzene ring of indoles was much lower. However, the asymmetric Pictet–Spengler reaction on the benzene of indoles is very valuable. For instance, a diastereoselective Pictet–Spengler reaction at the C4 position of the indole could be applied to the first syntheses of (−)-hyrtioreticulin C and (+)-hyrtioreticulin D by Yamada' group.[10] Hence it is a highly desirable challenge to explore catalytic asymmetric Pictet–Spengler reactions on the benzene of indoles.

In recent years, the direct C6 functionalization of 2,3-disubstituted indoles has been studied by several groups.[11−13] However, the direct asymmetric C6 functionalizations of 2,3-disubstituted indoles has remained a challenge and was only realized by Zhang[12] and our group[13] via chiral phosphoric acid catalysis. Very recently, we reported chiral-phosphoric-acid-catalyzed regioselective and enantioselective reactions of 2-(1*H*-indolyl)aniline derivatives and ketones for the synthesis of indole *N*-alkylated aminals[14a,b] and C3-alkylated spiro-indolin-2-ones.[14c] In consideration of the fact that catalytic asymmetric Pictet–Spengler reactions on the benzene ring of indoles have not been documented, we envisioned the design and synthesis of 2-(1*H*-indol-7-yl)anilines to facilitate the C6-selective enantioselective reaction. Herein we report the first Pictet–Spengler reaction of 2-(1*H*-indol-7-yl)anilines and isatins, affording novel C6-functionalized indole polycyclic compounds in high yields with high enantioselectivities (Scheme 1b).

Scheme 1. Catalytic Asymmetric Pictet–Spengler Reactions of Indoles



Received: February 1, 2022
Published: February 24, 2022

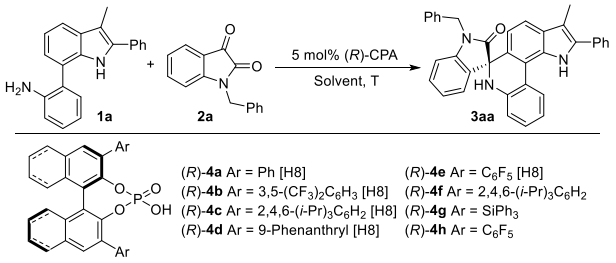


https://doi.org/10.1021/acs.orglett.2c00368
Org. Lett. 2022, 24, 1727–1731

Initially, the model substrate 2-(1*H*-indol-7-yl)anilines **1** could be conveniently prepared from 7-bromoindoles and (2-aminophenyl)boronic acid via Suzuki coupling in good yields.

Subsequently, 2-(3-methyl-2-phenyl-1*H*-indol-7-yl)aniline **1a** and *N*-benzyl-protected isatin **2a** were chosen as model substrates (Table 1). Various chiral phosphoric acids were first

Table 1. Optimization of the Reaction Conditions



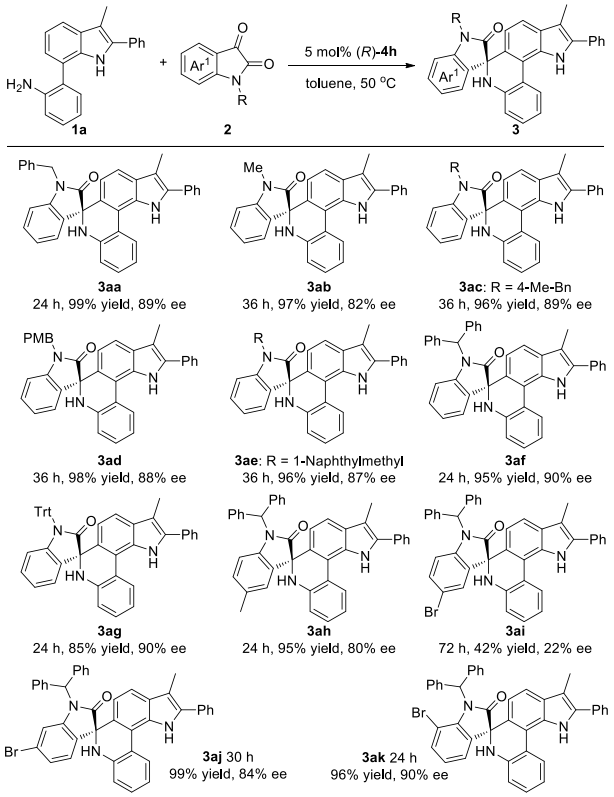
entry[a]	CPA	solvent	T (°C)	t (h)	yield (%)[b]	ee (%)[c]
1	(*R*)-**4a**	toluene	40	48	<5	
2	(*R*)-**4b**	toluene	40	48	28	11
3	(*R*)-**4c**	toluene	40	48	8	6
4	(*R*)-**4d**	toluene	40	48		
5	(*R*)-**4e**	toluene	40	48	30	77
6	(*R*)-**4f**	toluene	40	48	<5	
7	(*R*)-**4g**	toluene	40	48	<5	
8	(*R*)-**4h**	toluene	40	48	>95	89
9	(*R*)-**4h**	DCM	40	24	>95	59
10	(*R*)-**4h**	dioxane	40	48	77	81
11	(*R*)-**4h**	MeCN	40	24	>95	9
12	(*R*)-**4h**	EtOAc	40	48	>95	81
13	(*R*)-**4h**	*o*-xylene	40	48	>95	88
14	(*R*)-**4h**	mesitylene	40	48	>95	88
15	(*R*)-**4h**	toluene	30	96	90	90
16	(*R*)-**4h**	toluene	50	24	>95	89
17	(*R*)-**4h**	toluene	60	12	>95	87
18[d]	(*R*)-**4h**	toluene	50	20	>95	89

[a]Reactions were performed with **1a** (0.10 mmol) and **2a** (0.11 mmol) in toluene (1.0 mL) using 5 mol % (*R*)-CPA as catalyst. [b]NMR yield using 1,3,5-trimethoxybenzene as an internal standard. [c]Determined by HPLC. [d]50 mg of Na_2SO_4 was used.

tested for the enantioselective Pictet−Spengler reaction using toluene as the reaction medium at 50 °C (entries 1−8). Unfortunately, most of the catalysts showed poor activity. With the H8-BINOL-derived pentafluorophenyl-substituted chiral phosphoric acid (*R*)-**4e** examined, the desired C6-functionalizated adduct **3aa** could be obtained in 30% yield with moderate 77% ee (entry 5). To our delight, the use of catalyst (*R*)-**4h** straightforwardly led to the spiro target molecule in >95% yield with 89% ee (entry 8). The solvent effect was studied using (*R*)-**4h** as the optimal catalyst, and the results demonstrated that the solvents played a crucial role in the reactivity and enantioselectivity (entries 9−14). When dichloromethane and acetonitrile were used, the transformation could be completed in 24 h, albeit with low enantioselectivities (entries 9 and 11). Aromatic solvents were suitable for the reaction, and toluene gave the best result (entry 8). To further improve the reactivity, we also investigated the influence of the reaction temperature (entries 15−17). When the temperature was increased, the reactivity was remarkable improved, but the enantioselectivity slightly decreased. 50 °C was chosen as the best reaction temperature. In the presence of 50 mg of anhydrous sodium sulfate as the dehydrating reagent, the reaction time could be slightly diminished, whereas the enantioselectivity of the Pictet−Spengler reaction could not be improved. Finally, the optimized reaction conditions were established: 5 mol % (*R*)-**4h** as the catalyst, 1.1 equiv of **2a** to **1a**, in toluene at 50 °C.

With the optimal reaction conditions in hand, we examined the substrate scope of isatins (Scheme 2). When the model

Scheme 2. Substrate Scope of Isatins 2[a]



[a]Conditions: indole **1a** (0.20 mmol) and isatins **2** (0.22 mmol) in toluene (2.0 mL) using 5 mol % (*R*)-**4h** as a catalyst at 50 °C.

reaction was carried out on a 0.20 mmol scale under the optimal conditions, **3aa** could be obtained in 99% isolated yield with 89% ee. The steric hindrance of the substituted groups on the N atoms of isatins had a significant influence on the enantioselectivity of the reaction (**3aa**−**3ag**). Isatin **2a** bearing a small methyl group led to the formation of **3ab** in 97% yield but with 82% ee. A series of aromatic methyl-substituted isatins **2** reacted smoothly with indole **1a**, affording the corresponding products **3** in excellent yields with excellent enantioselectivities (**3ac**−**3ae**). Isatins with more bulky substituents such as benzhydryl or triphenylmethyl (Trt) delivered the desired adducts with 90% ee (**3af**, **3ag**). The benzhydryl substituent was identified as the optimal protecting group for the following research (**3ah**−**3ak**). A variety of isatins bearing groups at different positions on benzene ring were tested, and most of them were well tolerated in this catalysis system. The corresponding annulated products were obtained in excellent yields with high enantioselectivities. To our surprise, when 6-bromoisatin **2g** was employed, the reaction became sluggish and gave only poor 22% ee (**3ai**). When 7-bromoisatin **2k** was used, **3ak** could be achieved in 96% yield with 90% ee.

https://doi.org/10.1021/acs.orglett.2c00368
Org. Lett. 2022, 24, 1727−1731

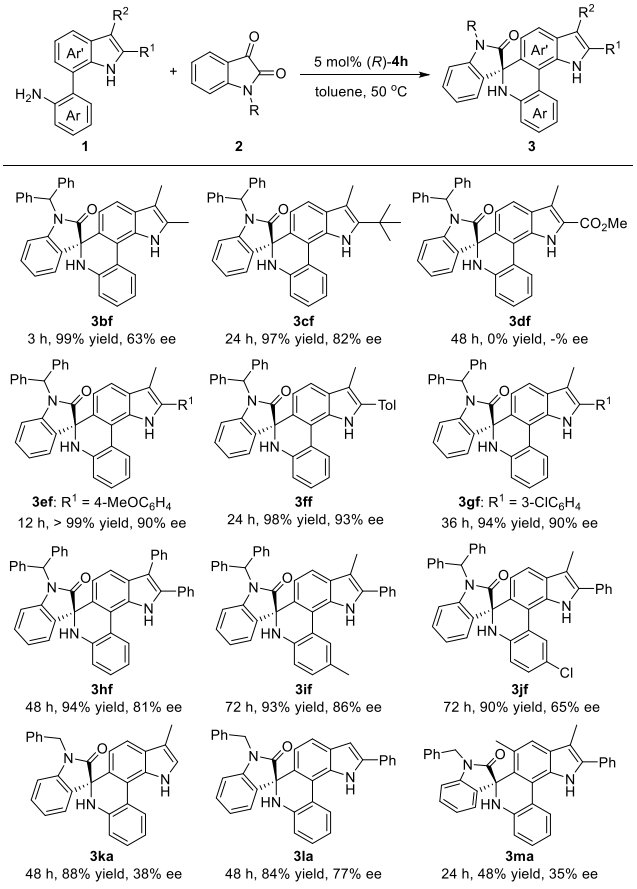
Next, the substrate scope for the enantioselective Pictet–Spengler reaction of various 2-(1*H*-indol-7-yl)anilines **1** with isatin **2** was explored under the standard conditions (Scheme 3). A range of indoles bearing different substituents on the pyrrole ring, including an alkyl substituent, ester group, and aryl substituent, were investigated, and dramatic effects were observed (**3bf**–**3hf**). 2-Methylindole **1b** offered spiro adduct **3bf** in 99% yield, albeit with a moderate 63% ee, which might be ascribed to the small steric hindrance at the C2 position of indole. Indole **1c** with a bulky *t*-butyl was well tolerated, and product **3cf** was isolated in 97% yield with 82% ee. With the electron-withdrawing CO_2Me, the C6 nucleophilicity of indole **1d** decreased, and the desired annulation could not occur. To our delight, 2-aryl-substituted 2-(1*H*-indol-7-yl)anilines **3e**–**3g** with various electron-donating or electron-withdrawing substituents underwent the reaction smoothly with isatin **2f** to afford the corresponding adducts **3ef**–**3gf** in excellent yields with excellent enantioselectivities. Diphenyl-substituted indole **1h** was also tested, and the spiroindolin-2-one **3hf** could be obtained in 94% yield with 81% ee. The substituents at the para position of the aniline moiety reduced the reactivity (**3if**, **3jf**). With an electron-donating group, 2-(1*H*-indol-7-yl)-aniline **1i** gave **3if** in 93% yield with 86% ee with a prolonged reaction time. However, when 2-(1*H*-indol-7-yl)aniline **1j** bearing an electron-withdrawing chloro group was used, product **3jf** was achieved with a moderate 65% enantioselectivity. In the absence of a substituent at the two- or three-position of the indoles, the C6-functionalized polycyclic products could be achieved in high yields, albeit with low enantioselectivities (**3ka**, **3la**). Indole **1m** with a methyl substituent in the benzene ring furnished the reaction in 48% yield with poor enantioselectivity, which may be ascribed to the steric hindrance (**3ma**).

To demonstrate the practicality of this chiral-phosphoric-acid-catalyzed C6-selective Pictet–Spengler reaction, we carried out a gram-scale experiment of 2-(1*H*-indol-7-yl)aniline **1a** and isatin **2f** (Scheme 4). Satisfyingly, the transformation proceeded smoothly, affording the desired product **3af** in 97% yield with 91% ee using only 2.0% catalyst loading without any erosion of yield or enantioselectivity.

To determine the absolute configuration of the products, we conducted the synthetic transformation reaction (Scheme 5). Treatment of (+)-**3aa** with iodomethane under basic conditions and *N*-methylation of both the indole and analine moieties provided (−)-**4** in 96% yield with 87% ee. The absolute configuration of (−)-**4** was confirmed as S by X-ray diffraction analysis after recrystallization. (See the Supporting Information.) Therefore, the absolute configuration of product (+)-**3aa** was unambiguously assigned as (*S*)-(+)-**3aa**.

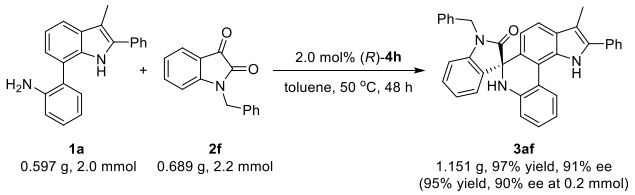
To probe the mechanism of the C6-selective Pictet–Spengler reaction, we performed a control experiment (Scheme 6). When *N*-methyl-protected indole **1n** was subjected to the optimal reaction conditions, no annulated product **3na** was observed. The result clearly indicates that the *N*-H of the indole moiety played a crucial role in both the

Scheme 3. Substrate Scope of 2-(1*H*-indol-7-yl)anilines 1[a]

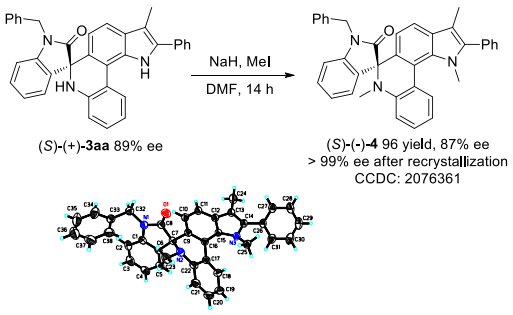


[a]Conditions: indoles **1** (0.20 mmol) and isatin **2f** (0.22 mmol) in toluene (2.0 mL) using 5 mol % (*R*)-**4h** as a catalyst at 50 °C.

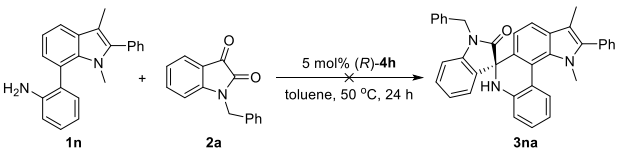
Scheme 4. Gram-Scale Experiment



Scheme 5. Synthetic Transformation and Determination of Absolute Configuration



Scheme 6. Control Experiment



https://doi.org/10.1021/acs.orglett.2c00368
Org. Lett. 2022, 24, 1727−1731

reactivity and the enantioselectivity, which is distinct from our previously reported C3-selective Pictet–Spengler reaction.[14c]

On the basis of the above experimental results, we propose a plausible reaction model to illustrate the stereochemistry of catalytic products (Figure 1). In the presence of chiral phosphoric acid (*R*)-**4h**, ketimine is generated from 2-(1*H*-indol-7-yl)aniline **1a** and isatin **2a** *via* dehydration. The chiral phosphoric acid serves as a bifunctional catalyst to activate both the indole and ketimine moieties through hydrogen-bonding interactions. The indole attacks preferentially from the *Re*-face of the C=N bond in the chiral environment to afford the S-configured adduct.

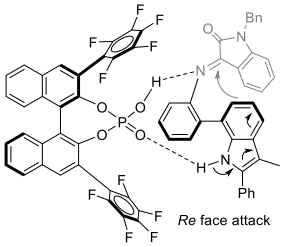


Figure 1. Proposed reaction model.

In summary, the highly enantioselective Pictet–Spengler reactions of 2-(1*H*-indol-7-yl)anilines and isatins for the synthesis of novel C6-functionalized indole polycyclic compounds have been demonstrated using chiral phosphoric acid as a catalyst. This is the first catalytic asymmetric Pictet–Spengler reaction on the benzene ring of indoles. The reaction can proceed on the gram scale without any loss of yield or enantioselectivity. Moreover, a plausible transition state was proposed to explain the enantioselectivity control. Further studies on the detailed reaction mechanism and the development of new Pictet–Spengler reactions on the benzene of indoles are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c00368.

General information, optimization results, general procedures, characterization data, spectra, and X-ray data (PDF)

Accession Codes

CCDC 2076361 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Yong-Gui Zhou − *State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, Liaoning 116023, P. R. China; Zhang Dayu School of Chemistry, Dalian University of Technology, Dalian 116024, P. R. China;* orcid.org/0000-0002-3321-5521; Email: ygzhou@dicp.ac.cn

Authors

Xin-Wei Wang − *State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, Liaoning 116023, P. R. China; Zhang Dayu School of Chemistry, Dalian University of Technology, Dalian 116024, P. R. China;* orcid.org/0000-0002-0347-2690

Wen-Jun Huang − *State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, Liaoning 116023, P. R. China;* orcid.org/0000-0001-8120-6286

Han Wang − *State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, Liaoning 116023, P. R. China*

Bo Wu − *State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, Liaoning 116023, P. R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.2c00368

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge financial support from the National Natural Science Foundation of China (21901239 and 21690074).

■ REFERENCES

(1) (a) *The Alkaloids, Chemistry, and Physiology*; Manske, R. H. F., Ed.; Academic Press: New York, 1981. (b) Somei, M.; Yamada, F. Simple Indole Alkaloids and those with a Nonrearranged Monoterpenoid Unit. *Nat. Prod. Rep.* **2004**, *21*, 278–311. (c) Kawasaki, T.; Higuchi, K. Simple Indole Alkaloids and those with a Nonrearranged Monoter-penoid Unit. *Nat. Prod. Rep.* **2005**, *22*, 761–793. (d) O'Connor, S. E.; Maresh, J. Chemistry and Biology of Monoter-peneindole Alkaloid Biosynthesis. *J. Nat. Prod. Rep.* **2006**, *23*, 532–547. (e) Cao, R.; Peng, W.; Wang, Z.; Xu, A. *β*-Carboline Alkaloids: Biochemical and Pharmacological Functions. *Curr. Med. Chem.* **2007**, *14*, 479–500. (f) Laine, A. E.; Lood, C.; Koskinen, A. M. P. Pharmacological Impor-tance of Optically Active Tetrahydro-*β*-carbolines and Synthetic Approaches to Create the C1 Stereocenter. *Molecules* **2014**, *19*, 1544–1567. (g) Homer, J. A.; Sperry, J. Mushroom-Derived Indole Alkaloids. *J. Nat. Prod.* **2017**, *80*, 2178–2187.

(2) For selective reviews, see: (a) Lorenz, M.; Van Linn, M. L.; Cook, J. M. The Asymmetric Pictet-Spengler Reaction. *Curr. Org. Synth.* **2010**, *7*, 189–223. (b) Moyano, A.; Rios, R. Asymmetric Organocatalytic Cyclization and Cycloaddition Reactions. *Chem. Rev.* **2011**, *111*, 4703–4832. (c) Stöckigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, H. The Pictet-Spengler Reaction in Nature and in Organic Chemistry. *Angew. Chem., Int. Ed.* **2011**, *50*, 8538–8564. (d) Glinsky-Olivier, N.; Guinchard, X. Enantioselective Catalytic Methods for the Elaboration of Chiral Tetrahydro-*β*-carbolines and Related Sscaffolds. *Synthesis* **2017**, *49*, 2605–2620. (e) Rao, R. N.; Maiti, B.; Chanda, K. Application of Pictet-Spengler Reaction to Indole-based Alkaloids Containing Tetrahydro-*β*-carboline Scaffold in Combinatorial Chemistry. *ACS Comb. Sci.* **2017**, *19*, 199–228.

(3) For selective publications, see: (a) Bandini, M.; Eichholzer, A.; Tragni, M.; Umani-Ronchi, A. Enantioselective Phase-transfer-catalyzed Intramolecular Aza-Michael Reaction: Effective Route to Pyrazino-indole Compounds. *Angew. Chem., Int. Ed.* **2008**, *47*, 3238–3241. (b) Cheng, H.-G.; Lu, L.-Q.; Wang, T.; Yang, Q.-Q.; Liu, X.-P.; Li, Y.; Deng, Q.-H.; Chen, J.-R.; Xiao, W.-J. Highly Enantioselective Friedel-Crafts Alkylation/*N*-hemi-acetalization Cascade Reaction with Indoles. *Angew. Chem., Int. Ed.* **2013**, *52*, 3250–3254. (c) Li, C.-F.; Liu, H.; Liao, J.; Cao, Y.-J.; Liu, X.-P.; Xiao, W.-J. Enantioselec-tive

Organocatalytic Intramolecular Ring-closing Friedel-Crafts-type Alkylation of Indoles. *Org. Lett.* **2007**, *9*, 1847−1850. (d) Bandini, M.; Melloni, A.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. Highly Enantioselective Synthesis of Tetrahydro-β-carbolines and Tetrahydro-γ-carbolines *via* Pd-catalyzed Intramo-lecular Allylic Alkylation. *J. Am. Chem. Soc.* **2006**, *128*, 1424−1425. (e) Han, X.; Widenhoefer, R. A. Platinum-catalyzed Intramolecular Asymmetric Hydroarylation of Unactivated Alkenes with Indoles. *Org. Lett.* **2006**, *8*, 3801−3804.

(4) (a) Taylor, M. S.; Jacobsen, E. N. Highly Enantioselective Catalytic Acyl-Pictet-Spengler Reactions. *J. Am. Chem. Soc.* **2004**, *126*, 10558−10559. (b) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. Enantioselective Pictet-Spengler-Type Cyclizations of Hydroxylactams: H-Bond Donor Catalysis by Anion Binding. *J. Am. Chem. Soc.* **2007**, *129*, 13404−13405.

(5) Seayad, J.; Seayad, A. M.; List, B. Catalytic Asymmetric Pictet-Spengler Reaction. *J. Am. Chem. Soc.* **2006**, *128*, 1086−1087.

(6) Wanner, M. J.; van der Haas, R. N. S.; de Cuba, K. R.; van Maarseveen, J. H.; Hiemstra, H. Catalytic Asymmetric Pictet-Spengler Reactions *via* Sulfenyliminium Ions. *Angew. Chem., Int. Ed.* **2007**, *46*, 7485−7487.

(7) For pioneering studies, see: (a) Sewgobind, N. V.; Wanner, M. J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. Enantioselective BINOL-Phosphoric Acid Catalyzed Pictet-Spengler Reactions of *N*-Benzyltryptamine. *J. Org. Chem.* **2008**, *73*, 6405−6408. (b) Bou-Hamdan, F. R.; Leighton, J. L. Highly Enantioselective Pictet-Spengler Reactions with α-Ketoamide-Derived Ketimines: Access to an Unusual Class of Quaternary α-Amino Amides. *Angew. Chem., Int. Ed.* **2009**, *48*, 2403−2406. (c) Klausen, R. S.; Jacobsen, E. N. Weak Brønsted Acid-Thiourea Co-catalysis: Enantioselective, Catalytic Protio-Pictet-Spengler Reactions. *Org. Lett.* **2009**, *11*, 887−890. (d) Holloway, C. A.; Muratore, M. E.; Storer, R. L.; Dixon, D. J. Direct Enantioselective Brønsted Acid Catalyzed *N*-Acyliminium Cyclization Cascades of Tryptamines and Ketoacids. *Org. Lett.* **2010**, *12*, 4720−4723. (e) Duce, S.; Pesciaioli, F.; Gramigna, L.; Bernardi, L.; Mazzanti, A.; Ricci, A.; Bartoli, G.; Bencivenni, G. An Easy Entry to Optically Active Spiroindolinones: Chiral Brønsted Acid-Catalysed Pictet-Spengler Reactions of Isatins. *Adv. Synth. Catal.* **2011**, *353*, 860−864.

(8) For selected recent examples, see: (a) Wang, S.-G.; Xia, Z.-L.; Xu, R.-Q.; Liu, X.-J.; Zheng, C.; You, S.-L. Construction of Chiral Tetrahydro-β-Carbolines: Asymmetric Pictet-Spengler Reaction of Indolyl Dihydropyridines. *Angew. Chem., Int. Ed.* **2017**, *56*, 7440−7443. (b) Klausen, R. S.; Kennedy, C. R.; Hyde, A. M.; Jacobsen, E. N. Chiral Thioureas Promote Enantioselective Pictet-Spengler Cyclization by Stabilizing Every Intermediate and Transition State in the Carboxylic Acid-Catalyzed Reaction. *J. Am. Chem. Soc.* **2017**, *139*, 12299−12309. (c) Glinsky-Olivier, N.; Yang, S.; Retailleau, P.; Gandon, V.; Guinchard, X. Enantioselective Gold-Catalyzed Pictet-Spengler Reaction. *Org. Lett.* **2019**, *21*, 9446−9451. (d) Andres, R.; Wang, Q.; Zhu, J. Asymmetric Total Synthesis of (−)-Arborisidine and (−)-19-epi-Arborisidine Enabled by a Catalytic Enantioselective Pictet-Spengler Reaction. *J. Am. Chem. Soc.* **2020**, *142*, 14276−14285. (e) Kim, A.; Kim, A.; Park, S.; Kim, S.; Jo, H.; Ok, K. M.; Lee, S. K.; Song, J.; Kwon, Y. Catalytic and Enantioselective Control of the C-N Stereogenic Axis *via* the Pictet-Spengler Reaction. *Angew. Chem., Int. Ed.* **2021**, *60*, 12279−12283.

(9) For a mechanistic study on the asymmetric Pictet−Spengler reaction, see: Zheng, C.; Xia, Z.-L.; You, S.-L. Unified Mechanistic Understandings of Pictet-Spengler Reactions. *Chem.* **2018**, *4*, 1952−1966.

(10) Abe, T.; Yamada, K. Concise Syntheses of Hyrtioreticulins C and D *via* a C-4 Pictet-Spengler Reaction: Revised Signs of Specific Rotations. *J. Nat. Prod.* **2017**, *80*, 241−245.

(11) (a) Liu, H.; Zheng, C.; You, S.-L. Catalytic C6 Functionalization of 2,3-Disubstituted Indoles by Scandium Triflate. *J. Org. Chem.* **2014**, *79*, 1047−1054. (b) Zhou, L.-J.; Zhang, Y.-C.; Zhao, J.-J.; Shi, F.; Tu, S.-J. Organocatalytic Arylation of 3-Indolylmethanols *via* Chemo- and Regiospecific C6-Functionalization of Indoles. *J. Org. Chem.* **2014**, *79*, 10390−10398. (c) Wu, Q.; Li, G.-L.; Yang, S.; Shi, X.-Q.; Huang, T.-A.; Du, X.-H.; Chen, Y. A Chemo- and Regioselective C6-Functionalization of 2,3-Disubstituted Indoles: Highly Efficient Synthesis of Diarylindol-6-ylmethanes. *Org. Biomol. Chem.* **2019**, *17*, 3462−3470. (d) Ling, Y.; An, D.; Zhou, Y.; Rao, W. $Ga(OTf)_3$-Catalyzed Temperature-Controlled Regioselective Friedel-Crafts Alkylation of Trifluoromethylated 3-Indolylmethanols with 2-Substituted Indoles: Divergent Synthesis of Trifluoromethylated Unsymmetrical 3,3′-and 3,6′-Bis(indolyl)methanes. *Org. Lett.* **2019**, *21*, 3396−3401. (e) Yan, J.; Zhang, Z.; Chen, M.; Lin, Z.; Sun, J. A Study of the Reactivity of (Aza-)Quinone Methides in Selective C6-Alkylations of Indoles. *ChemCatChem.* **2020**, *12*, 5053−5057.

(12) Zhou, J.; Zhu, G.-D.; Wang, L.; Tan, F.-X.; Jiang, W.; Ma, Z.-G.; Kang, J.-C.; Hou, S.-H.; Zhang, S.-Y. Remote C6-Enantio-selective C-H Functionalization of 2,3-Disubstituted Indoles through the Dual H-Bonds and π-π Interaction Strategy Enabled by CPAs. *Org. Lett.* **2019**, *21*, 8662−8666.

(13) Huang, W.-J.; Ma, Y.-Y.; Liu, L.-X.; Wu, B.; Jiang, G.-F.; Zhou, Y.-G. Chiral Phosphoric Acid-Catalyzed C6 Functionalization of 2,3-Disubstituted Indoles for Synthesis of Hetero-triarylmethanes. *Org. Lett.* **2021**, *23*, 2393−2398.

(14) (a) Wang, X.-W.; Chen, M.-W.; Wu, B.; Wang, B.; Zhou, Y.-G. Chiral Phosphoric Acid-Catalyzed Synthesis of Fluorinated 5,6-Dihydroindolo[1,2-c]quinazo-lines with Quaternary Stereocenters. *J. Org. Chem.* **2019**, *84*, 8300−8308. (b) Wang, X.-W.; Chen, M.-W.; Wu, B.; Wang, B.; Wan, B.; Zhou, Y.-G. Chiral Phosphoric Acid-Catalyzed Regioselective Synthesis of SpiroAminals with Quarter-nary Stereocenters. *Tetrahedron Lett.* **2021**, *65*, 152793. (c) Wang, X.-W.; Li, X.; Chen, M.-W.; Wu, B.; Zhou, Y.-G. Chiral Phosphoric Acid-Catalyzed Pictet-Spengler Reactions for Synthesis of 5′,11′-Dihydrospiro[indoline-3,6′-indolo[3,2-c]quinolin]-2-ones Containing Quaternary Stereocenters. *J. Org. Chem.* **2021**, *86*, 6897−6906.

https://doi.org/10.1021/acs.orglett.2c00368
Org. Lett. 2022, 24, 1727−1731