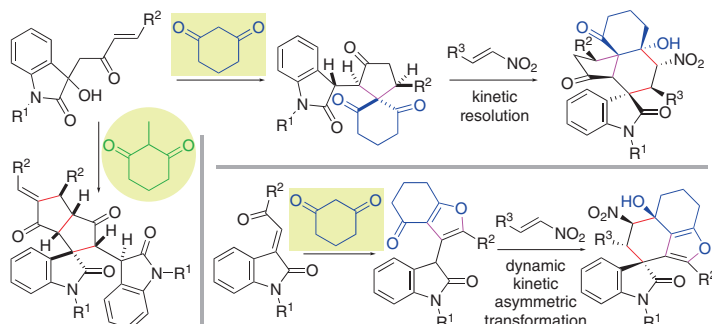


# Synthesis of Functionalized Spirooxindole Polycycles: Use of Cyclic 1,3-Diones as Reactants or as Condition-Tuning Molecules

Muhammad Sohail  
Fujie Tanaka\*

Chemistry and Chemical Bioengineering Unit, Okinawa Institute of Science and Technology Graduate University, 1919-1 Tancha, Onna, Okinawa 904-0495, Japan  
ftanaka@oist.jp

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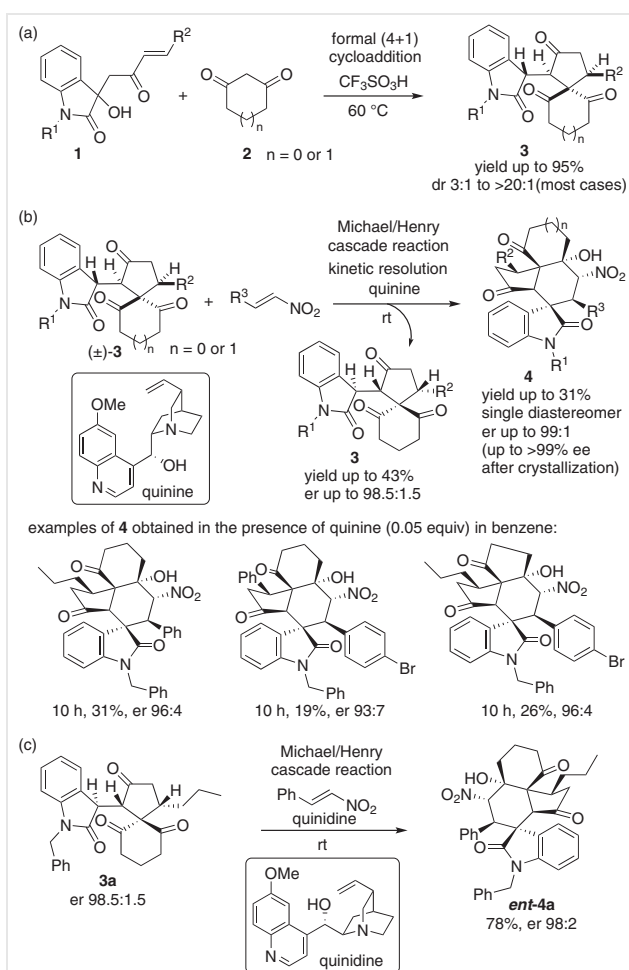
**Abstract** This account describes the strategies for the synthesis of functionalized spirooxindole polycycles, including enantiomerically enriched forms, that we have developed and reported. The syntheses of these complex molecules were accomplished in a few steps starting from relatively simple oxindole derivatives and other reactants. Organocatalytic reactions involved in kinetic resolution or in dynamic kinetic transformation led to the formation of products with high diastereo- and/or enantioselectivities. Cyclic 1,3-diones, such as 1,3-cyclohexanedione, were used as reactants to provide two reaction sites for the construction of polycyclic ring systems. To tune the reaction conditions, 2-methyl-1,3-cyclohexanedione was employed. The developed methods enabled the synthesis of complex functionalized spirooxindole polycycles bearing up to seven stereogenic centers, and will be useful for the synthesis of potentially bioactive molecules.

- 1 Introduction
- 2 Formal (4+1) Cycloaddition and Enantioselective Michael/Henry Cascade Reactions
- 3 Dynamic Stereoselective Aldol/Oxacyclization Cascade Reactions
- 4 Dynamic Kinetic Asymmetric Transformation: Diastereo- and Enantioconvergent Michael/Henry Reactions
- 5 Dimerization Reactions
- 6 Conclusion

**Key words** asymmetric catalysis, annulation, cycloadditions, enantioselectivity, Michael addition, organocatalysis

## 1 Introduction

Spirooxindole derivatives and polycyclic ring systems, such as spirodecanes, all-carbon tricycles, and pyran polycycles, are found in many bioactive natural products.<sup>1–4</sup>



**Scheme 1** Syntheses of spirooxindole tricarbaycles

Consequently, we have developed strategies for the synthesis of spirooxindole polycycles.<sup>2–5</sup> Here we describe our previously reported strategies for concise syntheses of complex functionalized spirooxindole polycyclic derivatives, including enantiomerically enriched derivatives.<sup>2–5</sup>

In one strategy for the synthesis of spiro polycyclic systems, cyclic 1,3-dione derivatives, such as 1,3-cyclohexanedione, were used as reactants.<sup>2–4</sup> These reactions are described in Sections 2–4. One or two bonds can be formed at the C(2)-position of cyclic 1,3-dione derivatives and the ketone carbonyl groups of these derivatives can also serve as reaction sites. Depending on the reactions on the cyclic 1,3-dione, chiral centers can be generated. In our second strategy, 2-methyl-1,3-cyclohexanedione was used as a molecule to tune the reaction conditions for the formation of polycyclic products:<sup>5</sup> this is described in Section 5.

## 2 Formal (4+1) Cycloaddition and Enantioselective Michael–Henry Cascade Reactions

Spirooxindole polycycles containing a spiro[4,5]decane ring systems were synthesized in two steps (Scheme 1).<sup>2</sup> The first step was a formal (4+1) cycloaddition reaction (Scheme 1a), and the second step was a Michael–Henry cascade reaction (Scheme 1b). Enone derivatives **1** were used as C4 reactants, and cyclic 1,3-diones **2** were used as C1 re-

actants to form the spiro[4,5]decane systems. Thus, derivatives **1** served as formal double Michael acceptors, and the cyclic 1,3-diones **2** served as nucleophiles to afford spiro compounds **3** in the first step (Scheme 1a). In the second step, the  $\alpha$ -position of the amide carbonyl group of the oxindole derivatives **3** serves as a nucleophile, and one of the ketone carbonyl groups of the cyclic 1,3-dione moiety serves as an electrophile (Scheme 1b).

In the first step, product **3** was obtained as the major diastereomer from the reaction of **1** with **2** in the presence of triflic acid as a catalyst (Scheme 1a). Although product **3** contains three stereogenic centers, only two diastereomers were obtained. For the second step, catalytic, highly diastereo- and enantioselective Michael–Henry cascade reactions of **3** with nitroalkenes, with quinine (0.05 equiv) as a catalyst, were achieved through kinetic resolution to afford spirooxindole polycycles **4** (Scheme 1b). The kinetic resolution was also optimized for the formation of highly enantiomerically enriched products **3**. The enantiomer of **3a** that was recovered after the formation of **4a** was transformed into *ent*-**4** in the presence of quinidine (Scheme 1c).

Notably, products **4** have seven stereogenic centers, including two all-carbon quaternary centers and one tetra-substituted carbon center. Our strategy therefore enables the diastereo- and enantioselective formation of highly complex spiro polycyclic molecules in two steps.

### Biographical Sketches



**Muhammad Sohail** received his Ph.D. in 2013 from the Beijing Institute of Technology under the direction of Fu-Xue Chen. After postdoctoral studies with Zongbao K. Zhao at the Dalian Institute of Chemical Physics (2013–2015), he joined the group of Fujie Tanaka at the

Okinawa Institute of Science Technology Graduate University (OIST) as a researcher (2015–2021). In 2021–2022, he worked as an associate professor of chemistry at the University of Education, Lahore, Pakistan. In 2022, he returned to the Tanaka group at OIST. He

is focusing on the development of catalytic asymmetric reaction methods to construct functionalized complex molecules (such as spiro or polycyclic bioactive molecules) under mild organocatalytic conditions.

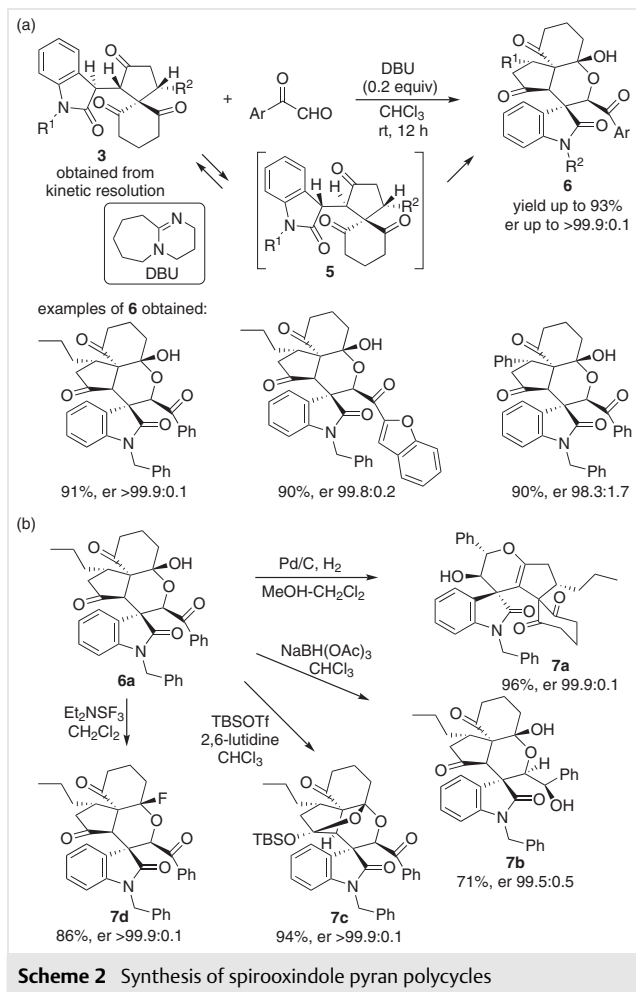


**Fujie Tanaka** received her Ph.D. from Kyoto University in 1992 under the direction of Kaoru Fuji. Then she carried out studies with Chi-Huey Wong in the Frontier Research Program, Riken; with Ikuo Fujii at the Protein Engineering Research Institute (Biomolecular Engineering

Research Institute); and with Carlos F. Barbas III and Richard A. Lerner at The Scripps Research Institute. She was appointed an assistant professor in the Department of Molecular Biology at The Scripps Research Institute, in 2000. She is currently a professor at the Okina-

wa Institute of Science and Technology Graduate University. Her research interests include synthetic organic chemistry and bioorganic chemistry, including the development and elucidation of catalytic asymmetric transformations.

### 3 Dynamic Stereoselective Aldol-Oxacyclization Cascade Reactions



Enantiomerically enriched spiro[4,5]decane derivatives **3**, obtained through the kinetic resolution described above, were used in reactions with arylglyoxals to afford spirooxindole pyran polycycles (Scheme 2a).<sup>3</sup> In these reactions, spiro compound **3** was isomerized to diastereomer **5** during the reaction in the presence of DBU (0.2 equiv), and isomers **5** reacted with the arylglyoxals to form product **6**. Product formation from **3** without isomerization did not occur. The isomerization of **3** resulted in the formation of only diastereomer **5**; no other diastereomers were detected. Subsequently, product **5** reacted with an arylglyoxal, leading to the construction of a new ring, and resulting in the formation of products **6** through a stereoselective aldol-oxacyclization cascade reaction. The use of enantiomerically enriched **3** resulted in the formation of enantiomerically enriched product **6** as single diastereomer. Products **6** have six stereogenic centers, including two all-carbon quaternary centers and one tetrasubstituted carbon center.

Whereas products **4** obtained from **3** through the Michael–Henry cascade reaction described in Section 2 had a *trans*–*cis* relationship for the formed 5–6–6 ring system, products **6** obtained from **5** had a *cis*–*cis* relationship for the 5–6–6 ring system. During the formation of **4** from **3**, two C–C bonds are formed in the cascade reaction, and a cyclohexane ring is constructed. For the formation of **6** from **5**, C–C and C–O bonds are formed, and a pyran ring is produced. The differences in the stereochemistries of the ring systems may originate from the differences in C–C and C–O bond lengths. The dynamic reaction system involved in the isomerization allows bond formation at a specific face of a specific ketone carbonyl group in the annulation step.

Compound **6a**, one of the spirooxindole pyran polycycles obtained from the aldol-oxacyclization reactions, was used for further transformations to afford various spirooxindole polycycles **7a–d** (Scheme 2b).

### 4 Dynamic Kinetic Asymmetric Transformation: Diastereo- and Enantioconvergent Michael–Henry Reactions

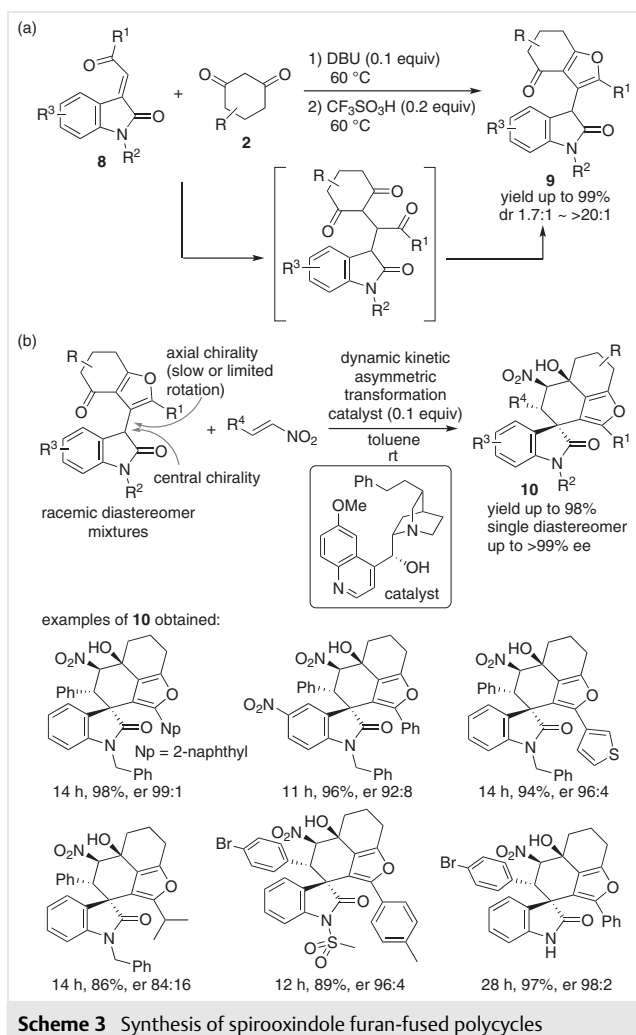
Asymmetric constructions of spirooxindoles polycycles bearing furan-fused rings were achieved through Michael–Henry reactions of oxindole-functionalized dihydrobenzofuranones with nitrostyrenes, catalyzed by a quinine-derived tertiary-amine-containing catalyst (Scheme 3).<sup>4</sup>

Reactions of oxindole-derived enones **8** with 1,3-cyclohexanediones **2** by sequential treatment with DBU and triflic acid in one pot afforded dihydrobenzofuranones **9** (Scheme 3a). The DBU-catalyzed Michael addition was followed by an acid-catalyzed furan-ring formation from the 1,4-diketone moiety. Products **9**, which have central and axial chiralities, were obtained as racemic mixtures of diastereomers.

When dihydrobenzofuranones **9** were treated with nitroalkanes in the presence of a chinchona alkaloid-derived catalyst (0.1 equiv), products **10** were obtained through a Michael–Henry cascade reactions (Scheme 3b). During the reaction, the diastereomers of **9** were isomerized and converted into products **10** as single diastereomers with high enantioselectivities. These reactions are dynamic kinetic asymmetric transformations.

### 5 Dimerization Reactions

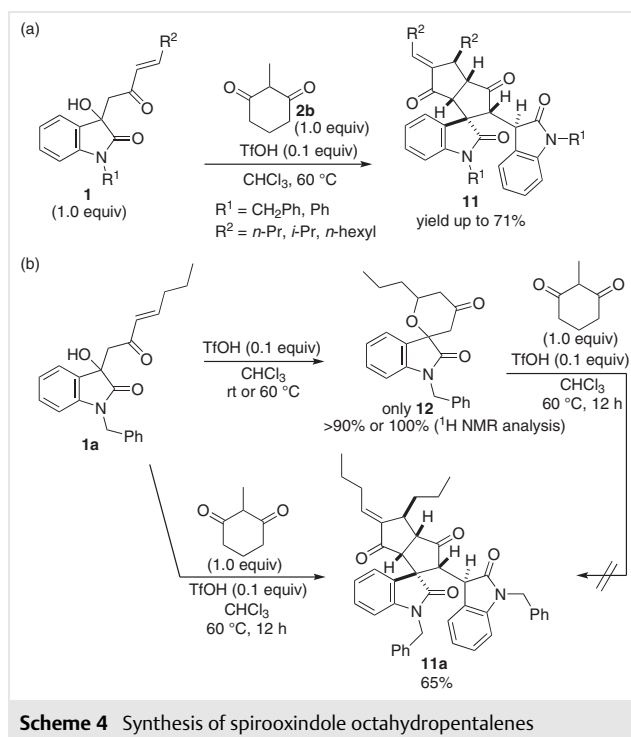
Cyclic 1,3-dione derivatives were used to tune the reaction conditions to alter the products. When compounds **1** were treated with triflic acid in the presence of 2-methyl-1,3-cyclohexanedione (**2b**), the spirooxindole octahydro-pentalene derivatives **11** were obtained (Scheme 4a).<sup>5</sup> These products were formed by dimerization of **1**. It should be noted that when **1a** alone was treated with triflic acid,



the intramolecular oxa-Michael reaction product **12** was formed (Scheme 4b).<sup>5,6</sup> Treatment of **12** with dione **2b** in the presence of triflic acid did not alter **12**, and no formation of **11** was detected (Scheme 4b).<sup>5</sup> As described in Section 2, when compounds **1** were treated with triflic acid in the presence of 1,3-cyclohexanedione (**2a**), products **3** were formed (Scheme 1a).<sup>2</sup> Thus, addition of **2b** to the reaction of **1a** in the presence of triflic acid completely altered the reaction pathway. Compound **2b** tuned the reaction conditions in these reactions, probably through its buffering function in nonaqueous solutions.<sup>5</sup>

## 6 Conclusion

We have summarized our previously reported strategies for the synthesis of complex, functionalized spirooxindole polycycles. Our methods provide spirooxindole polycycles bearing up to seven stereogenic centers as single diastereomers in highly enantiomerically enriched forms through ki-



netic resolutions or dynamic kinetic asymmetric transformations. Cyclic 1,3-dione derivatives serve as reactants to be incorporated into the products or can function as buffering molecules to tune the reaction conditions to alter the products that are formed. We are continuing to develop strategies to expand the range of the molecules that can be synthesized to contribute to the chemistry of molecular synthesis as well as to drug discovery efforts and biomedical research.

## Conflict of Interest

The authors declare no conflict of interest.

## Funding Information

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## References

- (1) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104. (b) Ye, N.; Chen, H.; Wold, E. A.; Shi, P.-Y.; Zhou, J. *ACS Infect. Dis.* **2016**, *2*, 382. (c) Han, B.; He, X.-H.; Liu, Y.-Q.; He, G.; Peng, C.; Li, J.-L. *Chem. Soc. Rev.* **2021**, *50*, 1522. (d) Cheng, D.; Ishihara, Y.; Tan,

- B.; Barbas, C. F. III. *ACS Catal.* **2014**, *4*, 743. (e) He, Z.-L.; Chen, P.; Chen, Z.-C.; Du, W.; Chen, Y.-C. *Org. Lett.* **2022**, *24*, 100. (f) Zhou, F.; Zhou, L.; Jing, P.; Sun, M.; Deng, G.; Liang, Y.; Yang, Y. *Org. Lett.* **2022**, *24*, 1400. (g) Wang, D.; Sun, J.; Han, Y.; Sun, Q.; Yan, C.-G. *Org. Lett.* **2022**, *24*, 7790. (h) You, Z.-H.; Liu, Y.-K. *Org. Lett.* **2022**, *24*, 6288. (i) Wen, Y.-H.; Yang, F.; Li, S.; Yao, X.; Song, J.; Gong, L.-Z. *J. Am. Chem. Soc.* **2023**, *145*, 4199.
- (2) Huang, J.-R.; Sohail, M.; Taniguchi, T.; Monde, K.; Tanaka, F. *Angew. Chem. Int. Ed.* **2017**, *56*, 5853.
- (3) Sohail, M.; Tanaka, F. *Commun. Chem.* **2019**, *2*, 73.
- (4) Sohail, M.; Tanaka, F. *Angew. Chem. Int. Ed.* **2021**, *60*, 21256.
- (5) Sohail, M.; Tanaka, F. *Chem. Eur. J.* **2020**, *26*, 222.
- (6) Pasha, M.; Sohail, M.; Tanaka, F. *Heterocycles* **2020**, *101*, 339.