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Dynamic Kinetic Asymmetric Transformation of Racemic Diastereomers: Diastereo- and Enantioconvergent Michael-Henry Reactions to Afford Spirooxindoles Bearing Furan-Fused Rings

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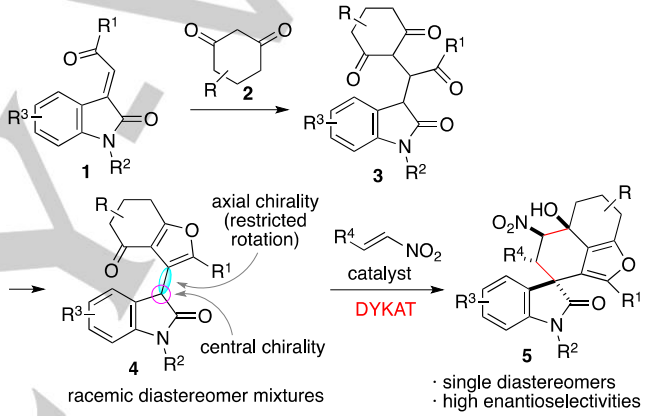
Abstract: Dynamic kinetic asymmetric transformation (DYKAT) reactions of racemic diastereomer mixtures that afford the products as essentially single diastereomers with high enantioselectivities are described. We demonstrated the DYKAT in the diastereo- and enantioselective synthesis of spirooxindoles bearing furan-fused rings. The starting materials of the DYKAT, dihydrobenzofuranone derivatives, were synthesized in racemic diastereomer mixtures, and these were transformed to the spirooxindole derivatives in high yields with high diastereo- and enantioselectivities through Michael-Henry cascade reactions with nitrostyrenes under organocatalytic conditions. In the reactions, regardless the stereochemistry of the starting materials, all the four isomers were transformed to single diastereomers with high enantioselectivities, and four new chiral centers were created.

Dynamic kinetic resolution (DKR) and dynamic kinetic asymmetric transformation (DYKAT) of racemic compounds have been used for the synthesis of enantiomerically enriched products.[1-3] Reported DKR and DYKAT of racemic starting materials have mostly been performed on compounds with a stereogenic center or axis.[1,2] There are only a few reports regarding DYKAT reactions of racemic diastereomer mixtures (i.e, compounds having more than one stereogenic center or axis as starting materials) that give single diastereomer products in high yields with high enantioselectivities.[3] Such reactions are usually considered to be difficult.[3] When racemic diastereomers having two stereogenic centers are used as starting materials of DYKAT to afford enantiomerically enriched single diastereomer products in high yields, isomerization at both the stereogenic centers must occur during the transformation to generate an actual reactant molecule used for the following selective reaction step[3a] or all four stereoisomers of the racemic diastereomers must be transformed to an achiral intermediate to be used for the enantioselective reaction step.[3b] Here we report DYKAT of racemic diastereomers with central and axial chiralities that afford essentially single diastereomers with high enantioselectivities (Scheme 1). We demonstrated the DYKAT in organocatalytic Michael-Henry cascade reactions that construct four new chiral centers for the synthesis of enantiomerically enriched spirooxindoles bearing furan-fused ring systems.



Scheme 1. Dynamic kinetic asymmetric transformation (DYKAT) for the diastereo- and enantioconvergent synthesis of spirooxindoles bearing furan-fused ring systems.

The development of methods for diastereo- and enantioselective syntheses of various types of spirooxindoles is of interest in drug discovery efforts and related research.[2a,4-6] Furan-fused ring systems, in which at least two rings are fused with the furan ring, are present in enzyme inhibitors and other biofunctional natural products.[7] Therefore, we sought strategies for the synthesis of spirooxindoles bearing furan-fused ring systems. We designed a route starting from the reaction of oxindole-derived enones **1** with 1,3-cyclohexanediones **2** to form 1,4-diketone derivatives **3** (Scheme 1). Products **3** were then transformed into oxindole-functionalized dihydrobenzofuranones **4** by the reactions of the 1,4-diketone moieties. Michael-Henry reactions of **4** with nitroolefins via DYKAT were designed to afford spirooxindoles bearing furan-fused ring systems **5**. It has been reported that dihydrobenzofuranones linked to aryl systems through a single bond are chiral.[8] We observed that **4** were diastereomers based on central chirality and axial chirality. The axial chirality present in **4** was created by the restricted rotation of the single bond between the dihydrobenzofuranones and the oxindoles.[9] Thus, the DYKAT reactions of **4** to afford **5** as single diastereomers in high yields with high enantioselectivities are distinct from the kinetic resolution reactions we previously reported that afford spirooxindole

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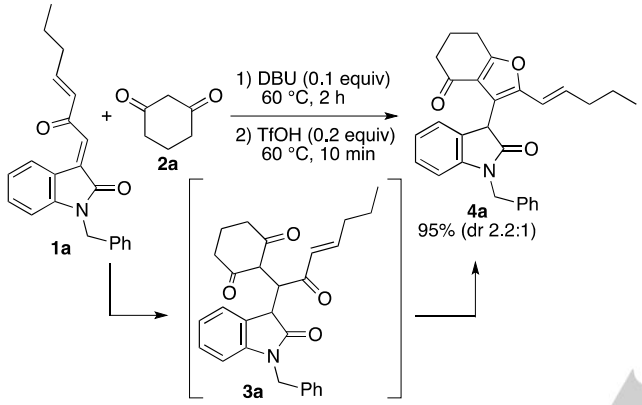
derivatives,[5g] which give the products in theoretically up to 50% yield, and also differ from the DYKAT reactions of racemic reactants that have only one chiral center or axis.[1-3]

First, conditions for the synthesis of oxindole-functionalized dihydrobenzofuranones **4a** from **1a** and **2a** were investigated. As a result, we found that the reaction in the presence of DBU followed by the reaction in the presence of TfOH in one pot led to the formation of **4a** from **1a** and **2a** (Scheme 2, see also Supporting Information). Compound **1a** has multiple electrophilic reaction sites. For the formation of **4a**, first selective formation of **3a** was necessary. Treatment of **1a** and **2a** with acids alone did not give **4a**. Under the optimized conditions, **4a** was obtained in 95% yield from **1a** in one pot, as a mixture of diastereomers due to central and axial chiralities.

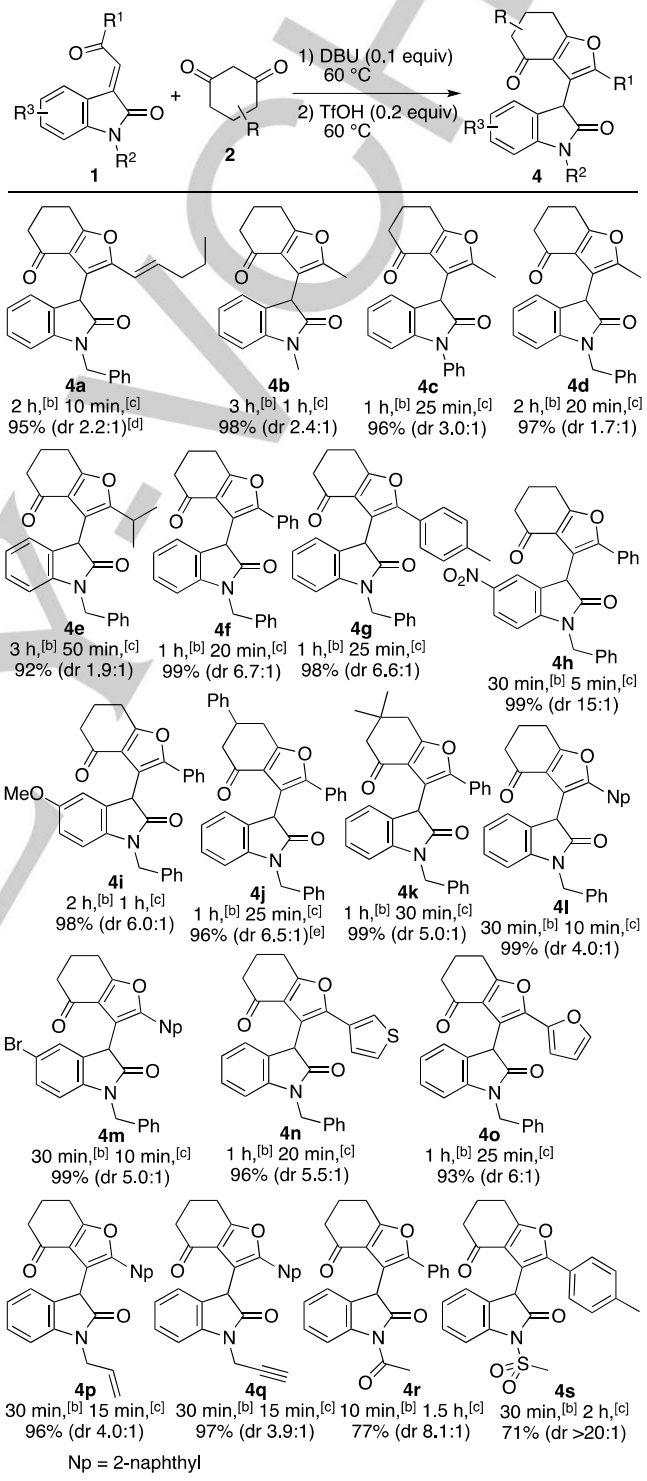


Scheme 2. Reaction of **1a** and **2a** to afford **4a** in one pot.

Using the one pot reaction method, various oxindole derivatives bearing dihydrobenzofuranones **4** were synthesized from oxindole-derived enones **1** and 1,3-cyclohexanediones **2** (Table 1). Products **4** bearing various substituents were obtained in high yields in most cases. Further, 5-substituted-1,3-cyclohexanediones were successfully used for the formation of **4j** and **4k**. In all compounds **4** synthesized, diastereomers were observed. Variable temperature ^{1}H NMR analyses[10] of selected compounds **4** in deuterated toluene showed that there was no interconversion between the diastereomers at 25 °C (Supporting Information), indicating that the rotation of the single bond between the furan ring and the oxindole moiety was restricted. For compound **4l**, the rotation of the bond involving the axial chirality was hindered even at 85 °C (Supporting Information).

For the formation of spirooxindoles bearing furan-fused ring systems **5**, catalyst systems and conditions were evaluated in the Michael-Henry reaction of (±)-**4l** with nitrostyrene[11] to afford **5a** in a high yield with high diastereo- and enantioselectivities (Table 2). The reaction in the presence of catalyst **C** in toluene at room temperature (25 °C) gave **5a** as essentially a single diastereomer (dr >97:3) with an enantiomer ratio (er) of 97:3 (Table 2, entry 11). Addition of 4 Å molecular sieves to the **C**-catalyzed reaction led the formation of **5a** with er 99:1, also as a single diastereomer, in a full conversion (100% NMR yield, Table 2, entry 14). In addition, during the formation of **5a**, the dr of unreacted **4l** was the same as that of **4l** used for the reaction (Supporting Information). Thus, the diastereo- and enantioselective formation of **5a** from **4l** in the presence of catalyst **C** occurred through a DYKAT process.[1] Under the optimized conditions but with catalyst **D** instead of catalyst **C**, the opposite enantiomer of **5a** was obtained with high enantioselectivity as a single diastereomer (Table 2, entry 15).

Table 1. Formation of **4** from **1** and **2** in one pot.[a]



[a] See Supporting Information for conditions. [b] Reaction in the presence of DBU. [c] Reaction in the presence of TfOH. [d] Data taken from Scheme 2. [e] The dr value shown is for oxindole and furan-derived moieties.

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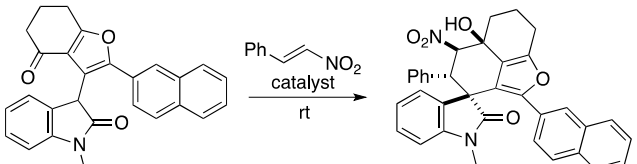
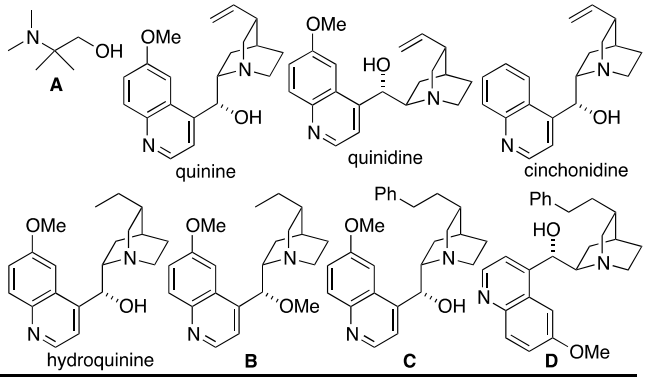
Table 2. Evaluations of catalysts and conditions for the reaction of (±)-**4l** to afford **5a**.[a]



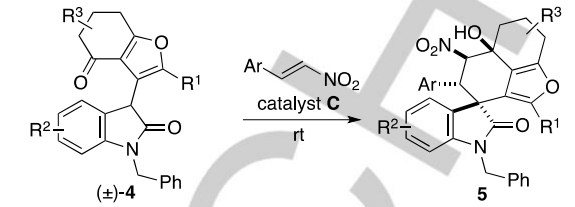


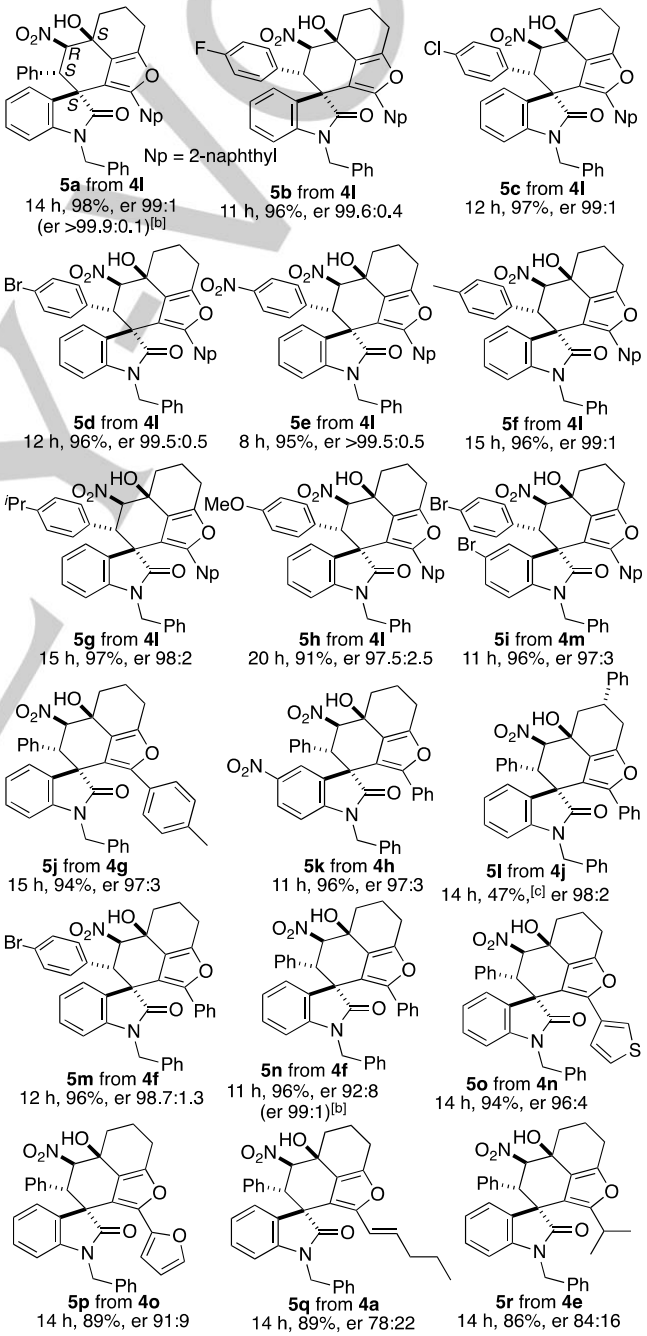
entry	catalyst	solvent	yield [%][b]	dr[b]	er[c]
1	DBU	toluene	10[d]	ND[e]	–
2	**A**	toluene	32	>97:3	–
3	quinine	toluene	28	>97:3	88:12
4	quinidine	toluene	25	>97:3	28:72
5	cinchonidine	toluene	5	ND[e]	85:15
6	hydroquinine	toluene	34	>97:3	90:10
7	hydroquinine	toluene	78	>97:3	94:6
8	hydroquinine	$CHCl_3$	12	ND[e]	88:12
9[f]	hydroquinine	toluene	58	>97:3	93:7
10	**B**	toluene	3	ND[e]	70:30
11	**C**	toluene	79	>97:3	97:3
12	**C**	*t*BuC_6H_5	75	>97:3	97:3
13	**C**	cyclohexane	46	>97:3	71:29
14[g]	**C**	toluene	100	>97:3	99:1
15[g,h]	**D**	toluene	99	>95:5	4:96

[a] Conditions: (±)-**4l** (0.041 mmol, 1.0 equiv), nitrostyrene (1.5 equiv), and catalyst (0.1 equiv) in solvent (1.0 mL for entries 1-6, 0.2 mL for entries 7-15) at rt (25 °C) for 16 h. [b] Determined by ^{1}H NMR analysis of the reaction mixture. [c] Determined by HPLC analysis after purification. [d] Isolated yield. [e] Not determined. [f] Reaction at 0 °C. [g] 4 Å molecular sieves (10 mg) were added. [h] Reaction for 12 h instead of 16 h.

Using the optimal conditions for the formation of **5a** (Table 2, entry 14), various spirooxindole furan-fused tricycles **5** were synthesized in high yields as single diastereomers with high enantioselectivities in most cases (Tables 3 and 4). In these reactions, all the four stereoisomers of **4** were transformed to **5** as single diastereomers with high enantioselectivities, and four chiral carbon centers were created. Product **5l**, which has five stereogenic centers, was also obtained with high enantioselectivity.

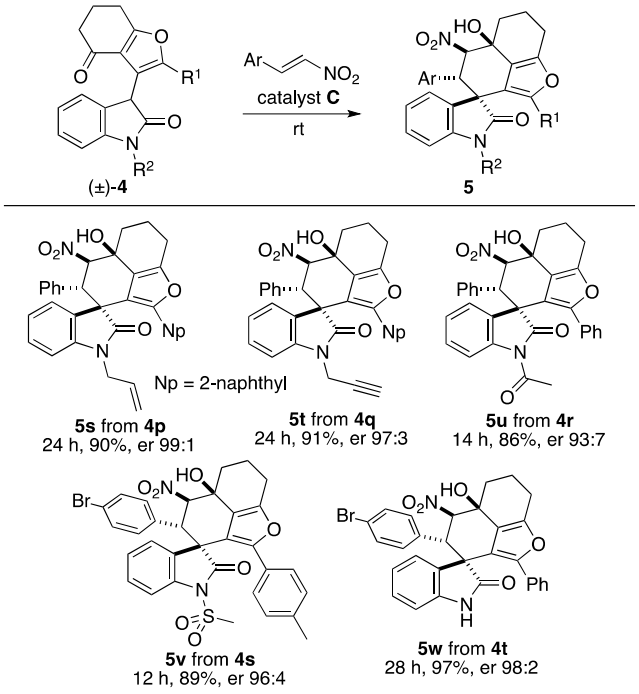
Table 3. Scope of the reaction of (±)-**4** to afford **5** in the presence of catalyst **C**.[a]





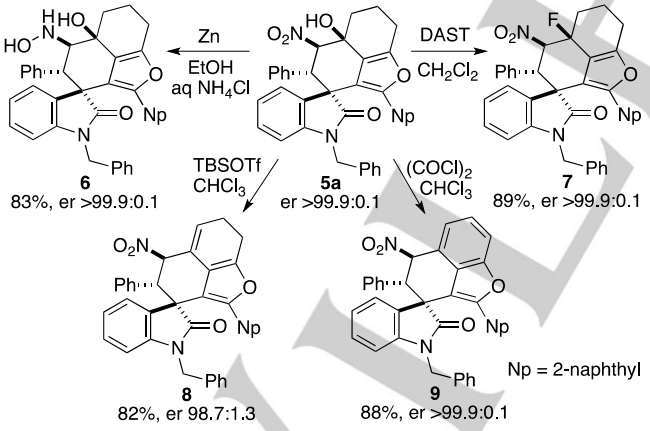
[a] See Supporting Information for conditions. [b] Data after removal of racemic precipitate. [c] The major product was isolated.

Table 4. Scope of the reaction of (±)-**4** to afford **5** in the presence of catalyst **C**.



The absolute and relative stereochemistries of the major enantiomer of **5a** obtained in the presence of catalyst **C** was determined by X-ray crystal structural analysis; the absolute configuration of **5a** is shown in Table 3.[12]

To demonstrate the utility of the reaction, product **5a** was transformed to derivatives **6**-**9**. During these reactions, the enantiopurity of **5a** was retained (Scheme 3).



Scheme 3. Transformations of **5a**.

In summary, we have developed the organocatalytic DYKAT-based diastereo- and enantioconvergent Michael-Henry reactions of racemic diastereomers that afford spirooxindoles bearing furan-fused ring systems. In the DYKAT, all the four stereoisomers originated by central and axial chiralities were transformed to the single diastereomer product in high yields with high enantioselectivities. We are investigating the detailed mechanisms of the DYKAT step. The results will be reported in due course.

Acknowledgements

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Keywords: asymmetric catalysis • dynamic kinetic asymmetric transformation • Michael addition • organocatalysis • spiro compounds

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[12] CCDC 2067701 for the major enantiomer of **5a** obtained in the presence of catalyst **C**. The data are provided free of charge by The Cambridge Crystallographic Data Centre.

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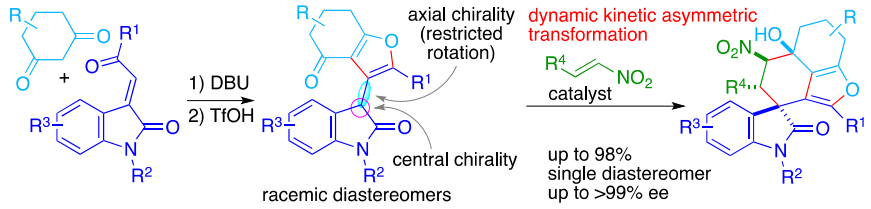

Organocatalytic Michael-Henry cascade reactions that occur through dynamic kinetic asymmetric transformations of racemic diastereomers having central and axial chiralities have been developed for the synthesis of spirooxindoles bearing furan-fused ring systems. The products, with four new chiral carbon centers, were obtained as single diastereomers in high yields with high enantioselectivities.

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