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INTRAMOLECULAR OXA-MICHAEL REACTIONS OF ALDOLS GENERATED FROM ENONES AND ISATINS TO AFFORD SPIROOXINDOLE TETRAHYDROPYRANS

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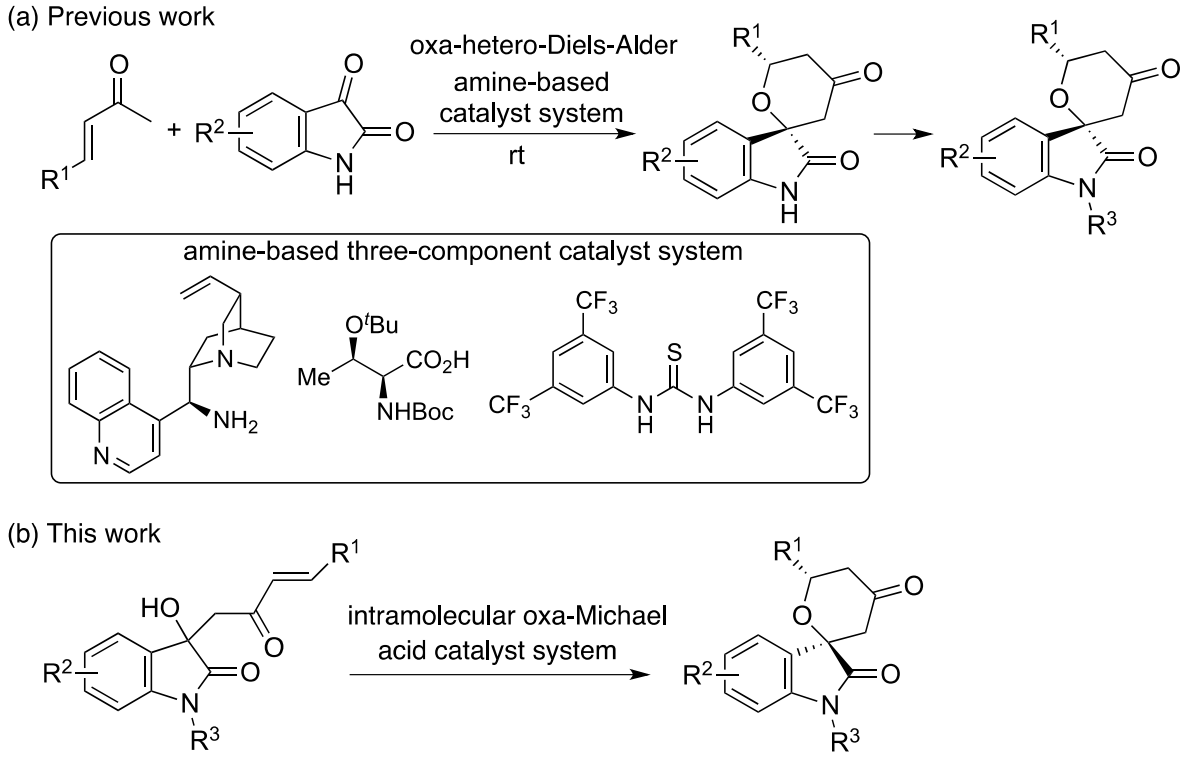
Abstract – Spirooxindole derivatives are found in bioactive natural products and are used in drug discovery and related research. Here, acid-catalyzed diastereoselective intramolecular oxa-Michael cyclization reactions of β-hydroxyenones generated from enones and isatin derivatives that afford spirooxindole tetrahydropyrans are reported. The major diastereomers of the products of these reactions were previously difficult to access by the amine-catalyzed hetero-Diels-Alder reactions of enones with isatins. With the use of enantiomerically enriched forms of the starting materials in the reactions, enantiomerically enriched spirooxindole tetrahydropyrans that retained the enantiopurities of the starting materials were obtained.

Spirooxindole derivatives are found in bioactive natural products and pharmaceuticals,[1] and the development of methods for the synthesis of spirooxindole derivatives is of interest in drug discovery efforts.[1-4] To address this demand, we have recently developed oxa-hetero-Diels-Alder reactions of enones and isatins catalyzed by amine-based catalyst systems to afford functionalized spirooxindole tetrahydropyran derivatives (Scheme 1a).[3-5] With the use of the enantioselective versions of the catalyst systems, the hetero-Diels-Alder reaction products were obtained with high diastereo- and enantioselectivities when the enones were alkyl enones or substituted-alkyl enones.[3-5] Using these reactions, however, only the spirooxindole tetrahydropyran derivatives with the same relative stereochemistries were accessible as the major products. Here we report a route to synthesize the previously minor diastereomers as the main products. We report the development of intramolecular oxa-Michael reactions of β-hydroxyenones or aldols generated from enones with isatin derivatives that

afford sprooxindole tetrahydropyrans in which the major product diastereomers have relative stereochemistries different from those of the major product diastereomers in the previously reported hetero-Diels-Alder reactions of enones with isatins[3-5] (Scheme 1b).



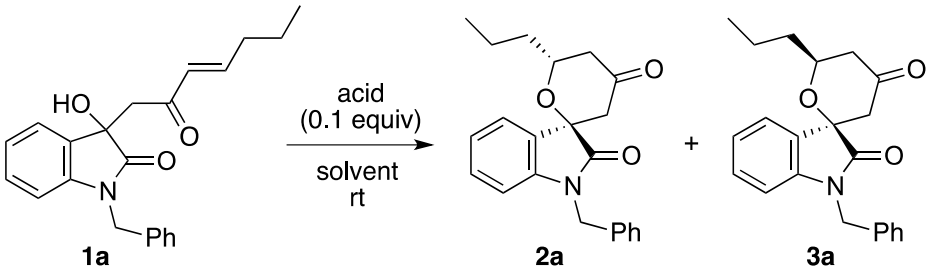
Scheme 1. (a) Previously reported oxa-hetero-Diels-Alder reactions of enones with isatins catalyzed by amine-based catalyst systems.[3-5] (b) Intramolecular oxa-Michael reactions of β-hydroxyenones or aldols generated from enones with isatin derivatives reported here.

In our previously reported oxa-hetero-Diels-Alder reactions of enones with isatins (Scheme 1a), various amine-based catalysts were tested during the development.[3-5] In these previous oxa-hetero-Diels-Alder reactions (Scheme 1a, R^1 = alkyl and substituted-alkyl groups), the diastereoselectivities were ranged from >20:1 to 1:1.[3-5] To synthesize diastereomers with relative stereochemistry different from that of the major product diastereomers of the previous oxa-hetero-Diels-Alder reactions of enones with isatins, we tested a two-step route involving an aldol reaction and an acid-catalyzed intramolecular oxa-Michael cyclization reaction.[6] Because aldol reactions of enones with isatins and with isatin derivatives have been reported,[3,7,8] including enantioselective versions,[7] we focused on the development of the intramolecular oxa-Michael reactions of the β-hydroxyenones that are obtained from aldol reactions of enones with isatin derivatives (Scheme 1b).

First, the intramolecular oxa-Michael reaction of aldol **1a** was evaluated using various acidic conditions to afford spirooxindole tetrahydropyran derivative **2a** (the desired diastereomer) and its diastereomer **3a**[3,4]

(Table 1). Previously reported catalysts used for intramolecular oxa-Michael reactions of β-hydroxyenones (non-oxindole derivatives) via 6-*endo-trig* cyclization include Pd-based catalysts, Ag-based catalysts, amberlyst, $BF_3{\cdot}Et_2O$, and $Me_3SiSO_3CF_3$.[6] We started our search for acid catalyst systems for the reaction of **1a** to give **2a** without the use of metals.

Table 1. Evaluations of the acid catalysts and conditions for the reaction of **1a** to form **2a**[a]

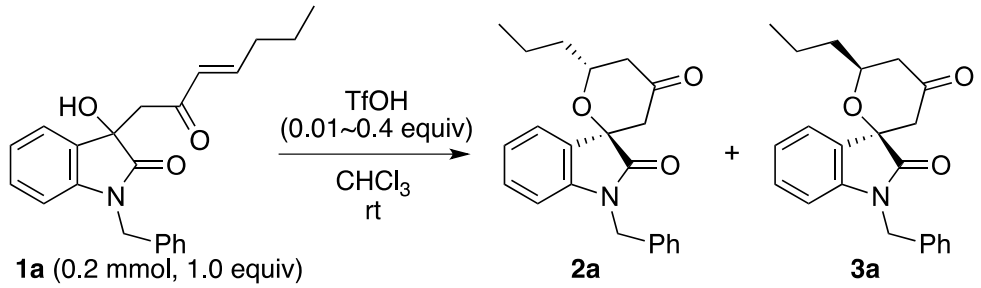


entry	acid	solvent	time (h)	conversion (%)	dr **2a**:**3a**
1	AcOH	$CHCl_3$	72	<5	-
2	*cis*-1,4-cyclohexanedicarboxylic acid	$CHCl_3$	96	<5	-
3	2-OH-$C_6H_4CO_2H$	$CHCl_3$	96	<5	-
4	CF_3CO_2H	$CHCl_3$	96	<5	-
5	$MeSO_3H$ (MsOH)	$CHCl_3$	20	50	1.5:1
6	CF_3SO_3H (TfOH)	$CHCl_3$	4	>90	3.3:1
7	4-Me-$C_6H_4SO_3H$ (TsOH)	$CHCl_3$	20	70	1.2:1
8	(+)-camphorsulfonic acid	$CHCl_3$	72	85	1.5:1
9	CF_3SO_3H (TfOH)	CH_2Cl_2	5	>90	3:1
10	CF_3SO_3H (TfOH)	MeCN	4	>90	2:1
11	CF_3SO_3H (TfOH)	toluene	3	>90	2.8:1
12	CF_3SO_3H (TfOH)	Et_2O	3	>90	2.3:1

[a] Conditions: **1a** (0.2 mmol, 1.0 equiv) and acid (0.02 mmol, 0.1 equiv) in solvent (1.0 mL) at rt (25 °C). Conversion and dr were determined by ^1H NMR analysis.

Carboxylic acid derivatives, such as acetic acid, salicylic acid, and trifluoroacetic acid, did not catalyze the formation of **2a** and/or **3a** from **1a** in $CHCl_3$ at room temperature (25 °C) (Table 1, entries 1-4). In the presence of sulfonic acid derivatives, such as methanesulfonic acid (MsOH), trifluoromethanesulfonic acid (TfOH), and *p*-toluenesulfonic acid (TsOH), **2a** was obtained as the major diastereomer (Table 1, entries 5-8). Solvents were also evaluated for the reaction (Table 1, entries 9-12). As the result, the TfOH-catalyzed reaction in $CHCl_3$ provided the best results among those tested with respect to the diastereoselectivity (dr **2a**:**3a** = 3.3:1) (Table 1, entry 6). NMR analysis of **2a** indicated that product **2a** has the same relative stereochemistry as the minor diastereomer derived from the previously reported oxa-hetero-Diels-Alder reaction of the enone and isatin.[3,4]

Table 2. Evaluations of conditions for the TfOH-catalyzed reaction of **1a** to form **2a**[a]



1a (0.2 mmol, 1.0 equiv) **2a** **3a**

entry	TfOH (equiv)	solvent (mL)	**1a** (mM)	TfOH (mM)	time (h)	dr **2a**:**3a**
1	0.005	1.0	200	1.0	48	5:1
2	0.05	1.0	200	10	8	5:1
3[b]	0.1	1.0	200	20	4	3.3:1
4	0.2	1.0	200	40	1.5	3:1
5	0.4	1.0	200	50	1.0	–[c]
6	0.05	0.5	400	20	8	3:1
7	0.05	2.0	100	5.0	8	6:1
8	**0.05**	**4.0**	**50**	**2.5**	**8**	**6.5:1**
9	**0.02**	**4.0**	**50**	**1.0**	**16**	**6.5:1**
10	**0.01**	**4.0**	**50**	**0.5**	**72**	**7:1**
11[d]	0.05	10	20	1.0	8	8:1
12	**0.05**	**20**	**10**	**0.5**	**24**	**8:1**

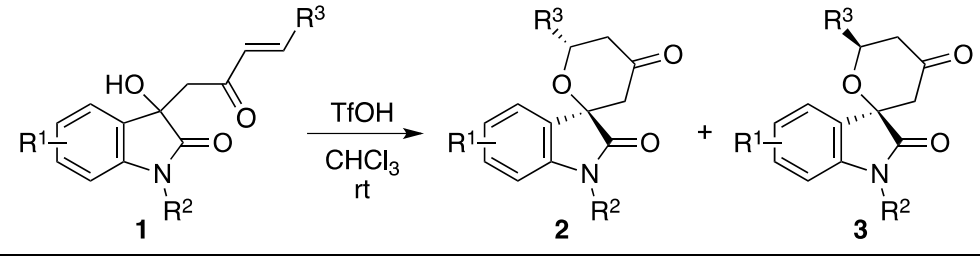
[a] Conditions: **1a** (0.2 mmol, 1.0 equiv) and TfOH in $CHCl_3$ at rt (25 °C). The reaction progress was monitored by TLC and by ^{1}H NMR analysis. The dr was determined by ^{1}H NMR analysis at the conversion was >80%, except as noted. [b] Data from Table 1, entry 6. [c] Not determined; ^{1}H NMR analysis indicated formation of byproducts. [d] Conversion 70%.

To improve the diastereoselectivity for the formation of **2a** in the reaction of **1a**, effects of loading of TfOH and of concentrations of **1a** and TfOH were evaluated (Table 2). Under the conditions with the same concentration of starting material **1a**, the reaction with higher loading (and thus higher concentration) of TfOH was faster than the reaction with lower loading (lower concentration) of TfOH; however, the reaction with lower loading of TfOH yielded the product with higher diastereoselectivity than did the reaction with higher loading of TfOH (Table 2, entries 1-5, and entries 8-10). With respect to the diastereoselectivity, reaction rate, and solvent amount, conditions used in Table 2, entries 8-10 were optimal to obtain **2a**.

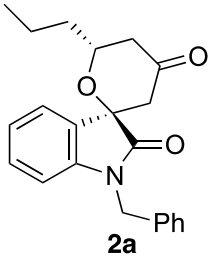
Next, the scope of the acid-catalyzed intramolecular oxa-Michael reactions of **1** to afford **2** was evaluated (Table 3). In the presence of TsOH (0.01~0.05 equiv), various spirooxindole tetrahydropyran derivatives **2** and the minor products **3** were obtained. Although the diastereoselectivity of the reaction

depended on conditions and the structure of **1**, based on the comparison of the NMR chemical shifts of the major diastereomers **2** and the minor diastereomers **3** with those of **2a** and **3a** and of **2b** and **3b**, the relative stereochemistries of major diastereomers **2c**-**2k** were assigned as shown in Table 3.

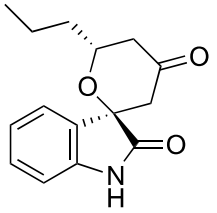
Table 3. Scope of the TfOH-catalyzed intramolecular oxa-Michael reaction of **1** to afford **2**[a]



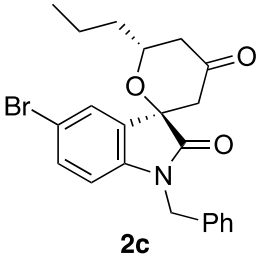
1 **2** **3**



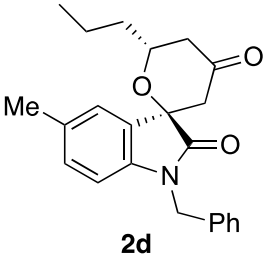
2a
72 h, 80%, dr 7:1[b]
3a 5%[b]
16 h, 79%, dr 7:1[c]



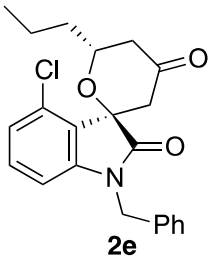
2b
96 h, 87%, dr 5:1[d]
3b 6%[d]
32 h, 79%, dr 4:1[c]



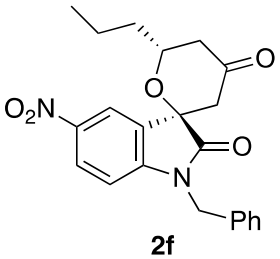
2c
72 h, 70%, dr 4:1[d]
3c 11%[d]
30 h, 66%, dr 3:1[c]
3c 23%[c]



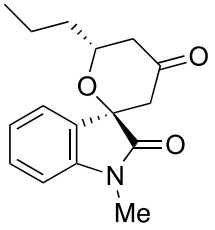
2d
72 h, 91%, dr 8:1[d]
3d 5%[d]
30 h, 80%, dr 5:1[c]
3d 15%[c]



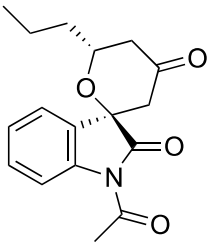
2e
120 h, 51%, dr 1.1:1[c]
3e 45%[c]
120 h, dr 1.2:1[d]



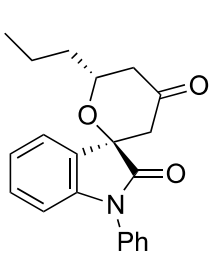
2f
96 h, 57%, dr 2:1[c]
3f 27%[c]
120 h, dr 3:1[d]



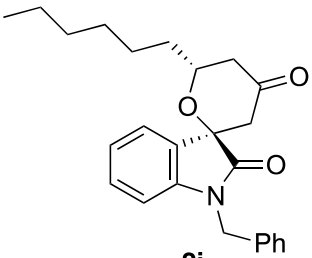
2g
48 h, 80%, dr 6:1[d]
3g 12%[d]
48 h, 79%, dr 4:1[c]
3g 18%[c]



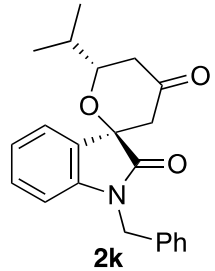
2h
72 h,
2h + **3h** 81%, dr 3:1[c]



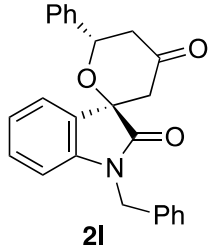
2i
24 h, 78%, dr 5:1[c]
3i 16%[c]



2j
48 h, 83%, dr 6:1[c]
3j 14%[c]



2k
144 h, 66%, dr 5:1[d,e]
96 h, 76%, dr 3:1[c]
3k 24%[c]



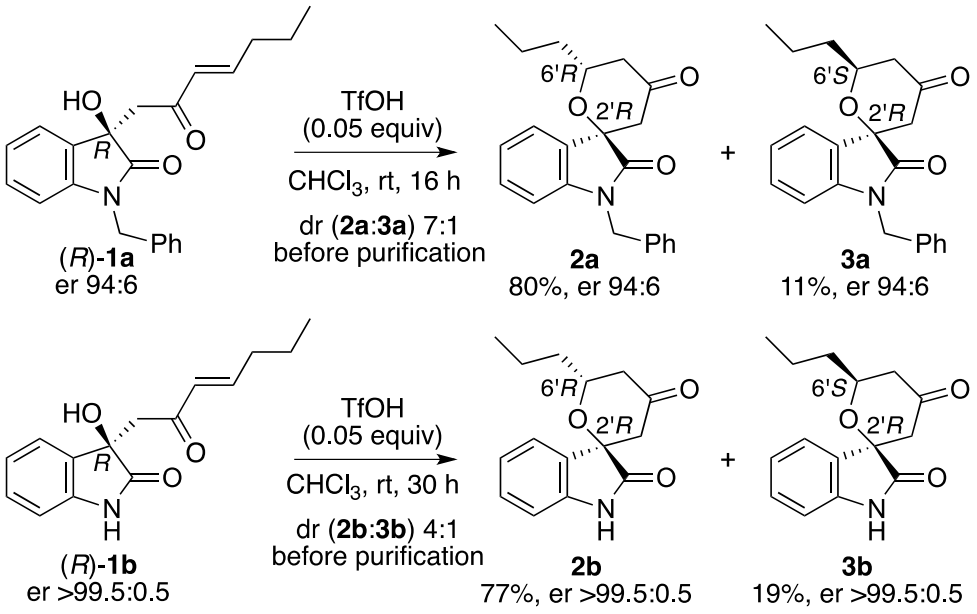
2l
192 h, 46%[c,f]

[a] Conditions: **1** (0.2 mmol) and TfOH (0.01, 0.05, or 0.02 equiv as indicated) in $CHCl_3$ (4.0 mL) at rt (25 °C); dr (**2**:**3**) was determined by ^1H NMR analysis before purification; isolated yield of **2** is shown except where noted. [b] TfOH (0.01 equiv). [c] TfOH (0.05 equiv). [d] TfOH (0.02 equiv). [e] **1** (0.1 mmol) in $CHCl_3$ (2.0 mL). [f] The dr was not determined.

A 1.0 mmol-scale reaction of **1a** in the presence of TfOH (0.01 equiv) also afforded the result (96 h, **2a** 82%, **3a** 9%) similar to that of the 0.2 mmol-scale reaction of **1a** shown in Table 3, suggestting that the reactions of **1** to afford **2** are readily scaled up.

When products **2a**, **2a**/**3a** (3:1), and **3a** were respectively treated with TfOH in $CHCl_3$ under the reaction conditions used for the formation **2a** from **1a**, no changes such as isomerization between the diastereomers, the formation of aldol **1a**, or the formation of dienone derivatives[8,9] (water-eliminated products from **1a**) were detected (see Supporting Information). These results indicate that products **2a** and **3a** are kinetically formed from **1a** in the presence of TfOH under the oxa-Michael reaction conditions and that the products are stable under the conditions.

To obtain enantiomerically enriched products **2**, reactions of enantiomerically enriched starting materials **1** were examined. When an enantiomerically enriched form of **1a** (er 94:6) was used as the starting material in the TfOH-catalyzed reaction, product **2a** was obtained with retaining the enantiopurity (er 94:6) (Scheme 2). Similarly, the reaction of **1b** (er >99.5:0.5) afforded **2b** (er >99.5:0.5) (Scheme 2). These results indicate that there is no racemization of **1** or of **2** under the TfOH-catalyzed reaction conditions. With the use of enantiomerically enriched **1**, products **2** retaining the same enantiopurity were obtained.



Scheme 2. Intramolecular oxa-Michael cyclization reactions of enantiomerically enriched forms of **1**

In summary, we have developed intramolecular oxa-Michael reactions that afford spirooxindole tetrahydropyran derivatives, in which the relative stereochemistry of the major diastereomer is different

from that of the major diastereomer accessed by previously reported amine-catalyzed oxa-hetero-Diels-Alder reactions. Enantiomerically pure forms of the products were obtained when enantiomerically pure aldol was used as the starting material. With the intramolecular oxa-Michael reactions described here and with the previously reported oxa-hetero-Diels-Alder reactions of enones and isatins, both of each diastereomer of the spirooxindole tetrahydropyran derivatives can be selectively synthesized.

EXPERIMENTAL

General procedure for the reaction of **1** to afford **2** in the presence of TfOH (0.05 equiv). To a solution of **1** (0.2 mmol) in $CHCl_3$ (4.0 mL), TfOH (0.57 M in THF, 17.6 μL, 0.01 mmol) was added at rt (25 °C), and the mixture was stirred at the same temperature until **1** was completely or almost completely consumed as monitored by TLC. A portion from the mixture was diluted with $CDCl_3$ and analyzed by ^{1}H NMR to determine the dr. The entire reaction mixture was directly purified by silica gel flash column chromatography (hexane/EtOAc) to give **2**.

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Supporting Information Available: Experimental procedures, product characterizations, NMR spectra, HPLC chromatograms.

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