Formal (4+1) Cycloaddition and Enantioselective Michael-Henry Cascade Reactions To Synthesize Spiro[4,5]decanes and Spirooxindole Polycycles

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Formal (4+1) Cycloaddition and Enantioselective Michael-Henry-Cascade Reactions to Synthesize Spiro[4,5]decanes and Spirooxindole Polycycles with Seven Stereogenic Centers

Ji-Rong Huang,[§[a]] Muhammad Sohail,[§[a]] Tohru Taniguchi,[[b]] Kenji Monde,[[b]] and Fujie Tanaka*[[a]]

Abstract: Spiro[4,5]decanes and polycyclic compounds bearing spiro[4,5]decane systems are important biofunctional molecules. We have developed diastereoselective formal (4+1) cycloaddition reactions to afford oxindole-functionalized spiro[4,5]decanes and have also developed organocatalytic enantioselective Michael-Henry-cascade reactions of the (4+1) cycloaddition products to generate spirooxindole polycyclic derivatives bearing the spiro[4,5]decane system. Spiro[4,5]decanes bearing oxindoles containing three stereogenic centers and spirooxindole polycycles having seven stereogenic centers, including two all-carbon chiral quaternary centers and one tetrasubstituted chiral carbon center, were concisely obtained with high diastereo- and enantioselectivities.

Spiro[4,5]decanes and polycyclic compounds bearing spiro[4,5]decane systems are found in bioactive natural products (Figure 1).[1-4] Functionalized molecules with these cyclic systems should be useful in drug discovery efforts. All-carbon spiro 5-membered ring systems either isolated or in the context of polycyclic systems were previously synthesized using, for example, cyclization reactions of linear carbon chains,[2] Claisen rearrangement reactions,[3] and [3+2] cycloaddition reactions.[4] Synthesis of functionalized spiro[4,5]decanes and polycyclic derivatives containing spiro[4,5]decane ring systems has not been explored, except in the synthesis of natural products and closely related molecules.[2-4] Because the oxindole moiety is present in many biofunctional molecules, we sought to combine the spiro[4,5]decane and its polycyclic ring systems with oxindole functionalities.[5,6] Here, we report the development of strategies to access to highly functionalized spiro[4,5]decanes and polycyclic compounds bearing the spiro[4,5]decane systems with oxindole functionalities (Scheme 1). We report (1) a new formal (4+1) cycloaddition[7] system involving reactions of enone derivatives with cyclic 1,3-diketones to construct spiro[4,5]decanes bearing oxindole moieties and (2) subsequent Michael-Henry-cascade transformations with nitroalkenes[8] to afford highly functionalized polycarbocyclic compounds, bearing both the spiro[4,5]decane system and the spirooxindole system, with high diastereo- and enantioselectivities.

In our formal (4+1) cycloaddition reactions, enone derivatives **1** were used as the C4 reactants. The enone derivatives were synthesized by aldol reactions of enones with isatin derivatives.[9] We hypothesized that **1** would act as a formal double Michael acceptor when appropriate conditions were used (Scheme 1).

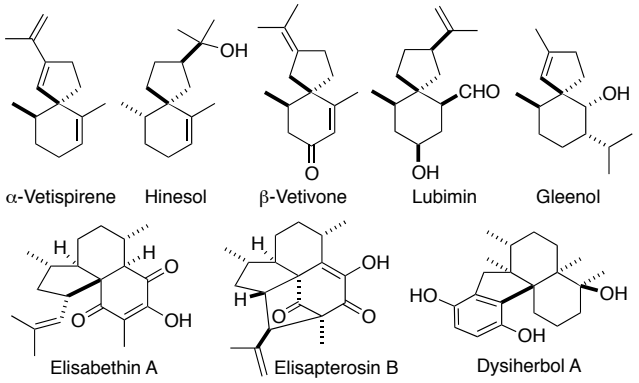
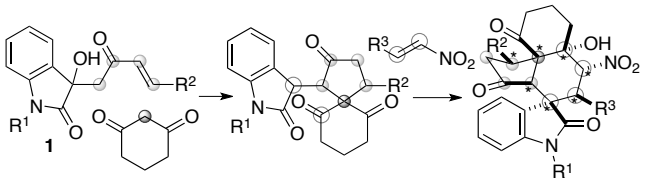


Figure 1. Spiro[4,5]decanes and polycyclic compounds bearing spiro[4,5]decanes found in bioactive natural products.



Scheme 1. Strategies described in this work for the synthesis of spiro[4,5]decanes and polycyclic compounds bearing the spiro[4,5]decane system via (1) formal (4+1) cycloaddition and (2) enantioselective Michael-Henry-cascade reactions.

First, we searched for catalysts and conditions in the reaction of **1a** with cyclohexane-1,3-dione (**2a**) to afford spiro[4,5]decane derivative **3a** or its diastereomers (such as **4a**) in high yield with high diastereoselectivity (Table 1, see also Supporting Information). We found that the reaction using CF_3SO_3H as catalyst at 60 °C efficiently gave **3a** in high yield with high diastereoselectivity in 3 h (97% and 98%, dr 16:1, Table 1, entries 9 and 12). In the formation of **3a** from **1a**, an intermediate would likely be dienone **5a**. However, when dienone **5a** was used as the C4 reactant under the same conditions used for the reaction of **1a** with **2a** (conditions in Table 1, entry 12), a long reaction time (72 h) was required to form **3a**/**4a** in high yield, and the diastereoselectivity was low (Scheme 2). Reaction of **5a** with **2a** under basic conditions did not give **3a** or **4a** in good yields in our tested conditions. Thus, to

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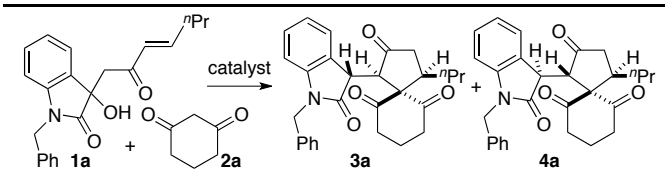
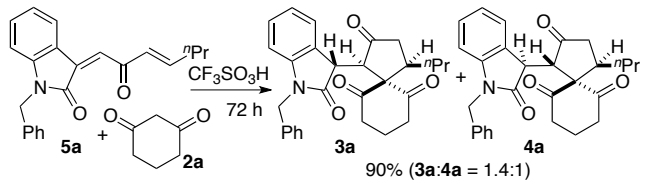
generate **3a** in high yield with high diastereoselectivity, the use of **1a** as the C4 reactant with the CF_3SO_3H catalysis was the best among conditions tested (Table 1, entry 12). Product **3a** has three stereogenic carbon centers and thus it is possible to form four diastereomers; however, only two diastereomers, **3a** and **4a**, were obtained.[10]

Table 1. Screening of catalysts and conditions in the formal (4+1) cycloaddition reaction of **1a** with **2a** to give **3a**/**4a**.[a]



entry	catalyst (equiv to **1a**)	temp (°C)	solvent	time (h)	yield (%)[b]	dr **3a**:**4a**[c]
1	*p*-TsOH (0.3)	45	DCE	40	88	4.6:1
2	$C_6F_5CO_2H$ (0.3)	45	DCE	67	20	2.0:1
3	$C_6H_5PO_3H$ (0.3)	45	DCE	68	49	2.6:1
4	CF_3SO_3H (0.3)	45	DCE	7	74	9.0:1
5	CF_3SO_3H (0.3)	25	DCE	68	76	8.3:1
6	CF_3SO_3H (0.3)	60	DCE	3	87	9.0:1
7	CF_3SO_3H (0.3)	80	DCE	3	87	7.2:1
8	CF_3SO_3H (0.3)	60	TCE	3	89	14:1
9	CF_3SO_3H (0.45)	60	TCE	2	97	16:1
10[d]	CF_3SO_3H (0.45)	60	TCE	3	89	7.7:1
11[e]	CF_3SO_3H (0.45)	60	TCE	3	96	10:1
12[f]	CF_3SO_3H (0.45)	60	TCE	3	98[g]	16:1

[a] Reaction conditions: **1a** (0.05 mmol, 1.0 equiv), **2a** (3.0 equiv), in the presence of catalyst in solvent (0.25 mL). [b] Combined yield of **3a** and **4a**, determined by ^{1}H NMR using internal standard (CH_2Br_2 or TCE). [c] Determined by ^{1}H NMR before purification. [d] **2a** (0.10 mmol). [e] Solvent (0.125 mL). [f] Solvent (0.5 mL). [g] Isolated yield. DCE = 1,2-dichloroethene; TCE = 1,1,2,2-tetrachloroethane.

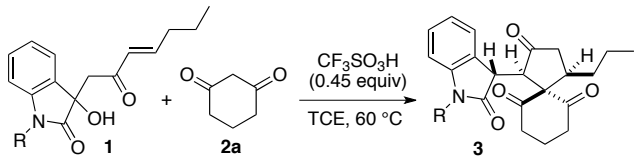


Scheme 2. Reaction of **5a** and **2a** in $CHCl_2CHCl_2$ (TCE) at 60 °C under the same conditions as Table 1, entry 12, except that **5a** was used instead of **1a**.

Next, the scope of the formal (4+1) cycloaddition reaction to synthesize spiro[4,5]decane derivatives **3** was examined using the optimum CF_3SO_3H catalysis conditions identified in the synthesis of **3a**. Various spiro[4,5]decane derivatives **3** were obtained as shown in Tables 2 and 3.

In *N*-substitutions of **1**, substituents including alkyl, allyl, aryl, acetyl, and Boc substitutions were accepted to give products **3** (Table 2, entries 1-8). The Boc-group at the nitrogen was deprotected under the reaction conditions (Table 2, entry 8). The Boc protection at the hydroxyl group of **1** did not affect the formation of **3** (Table 2, entry 10). The reaction of **1** without a substituent at the nitrogen also gave product **3** (Table 2, entry 9). For the enone substitutions, both alkyl-substituted and aryl-substituted enones **1** worked to afford **3** (Table 3). The method was further applied to the reactions with substituted cyclohexane-1,3-dione and with cyclopentane-1,3-dione (Table 3, **3t** and **3u**, respectively).

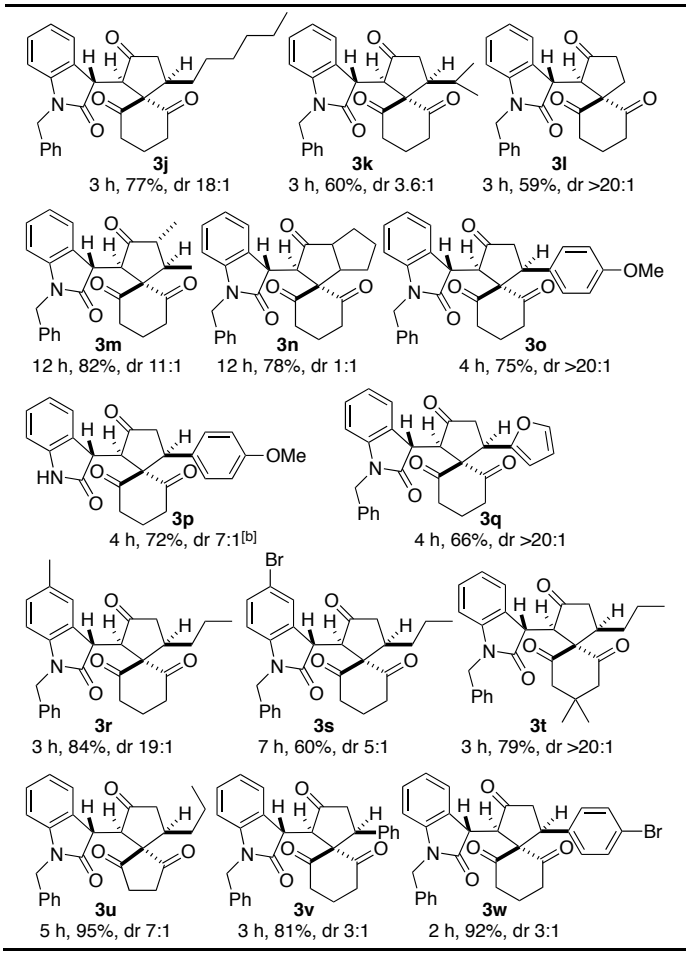
Table 2. Scope of the formal (4+1) cycloaddition; variations of the substitution at the oxindole amide nitrogen.[a]



entry	R	**1**	time (h)	product	yield (%)[b]	dr[c]
1	1-naphthylmethyl	**1b**	4	**3b**	82	12:1
2	2-naphthylmethyl	**1c**	4	**3c**	95	12:1
3	CH_3	**1d**	3	**3d**	80	17:1
4	$CH_2CH(CH_3)_2$	**1e**	4	**3e**	83	18:1
5	$CH_2CH{=}CH_2$	**1f**	3	**3f**	63	14:1
6	Ph	**1g**	3	**3g**	75	6:1
7	acetyl	**1h**	24	**3h**	75	5:1
8	Boc in **1i**; H in **3i**	**1i**	5	**3i**	44	2.8:1
9	H	**1j**	3	**3i**	75	2.6:1
10[d]	CH_2Ph	**1k**[d]	3	**3a**	56	14:1

[a] Reaction conditions: **1** (0.20 mmol, 1.0 equiv), **2a** (3.0 equiv), CF_3SO_3H (0.45 equiv) in $CHCl_2CHCl_2$ (TCE) (1.0 mL). [b] Combined yield of the diastereomers. [c] Determined by ^{1}H NMR before purification. [d] The OH group of **1** was Boc-protected.

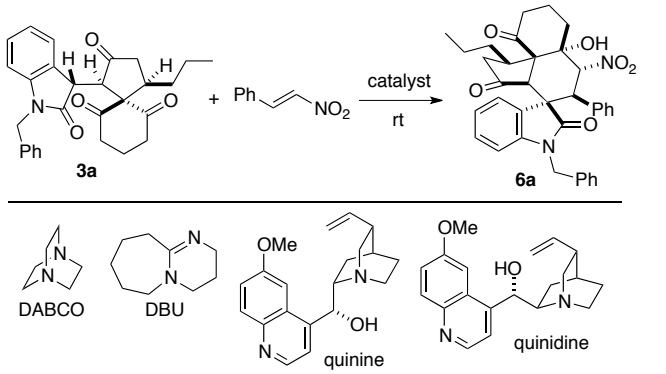
Table 3. Scope of the formal (4+1) cycloaddition; products obtained from various **1** and cyclic 1,3-diketone derivatives under the CF_3SO_3H catalysis.[a]



[a] Reaction conditions: **1** (0.20 mmol, 1.0 equiv), 1,3-diketone derivative (3.0 equiv), and CF_3SO_3H (0.45 equiv) in $CHCl_2CHCl_2$ (TCE) (1.0 mL) at 60 °C. The dr values were determined by ^1H NMR analyses before purification. [b] Ratio of isolated yields.

With the method for the synthesis of racemic **3** in hand, the construction of polycyclic systems from **3** was studied. For this aim, catalysts and conditions were screened for the transformation of racemic **3a** with nitrostyrene to afford spirooxindole polycyclic product **6a** (Table 4). When **3a** was treated with bases (such as DABCO or DBU), isomerization of **3a** to its diastereomer **4a** occurred and little **6a** was observed (Table 4, entries 1 and 2). When quinine or quinidine was used as the catalyst under appropriate conditions, the reaction of **3a** with nitrostyrene resulted in the formation of enantiomerically enriched polycyclic product **6a** (Table 4, entries 3, 4, 6-8). The formation of diastereomers of **6a** was not detected under the quinine or quinidine catalysis conditions, although **6a** has seven stereogenic centers. Of these seven stereogenic centers, two are all-carbon quaternary centers and one is tetrasubstituted carbon center. Formation of enantiomerically enriched forms of **6a** from racemic **3a** using quinine or quinidine as the catalyst occurred through a kinetic resolution mechanism. The best conditions for the synthesis of **6a** in high enantioselectivity from racemic **3a** among those tested were the use of quinine as the catalyst with 4 Å molecular sieves (Table 4, entry 8). The enantiopurity of **6a** decreased as the yield of **6a** increased and as the reaction time was prolonged (see below and Supporting Information). Isolation of **6a** from the reaction mixture within 5 h to 10 h or up to 30% yield of **6a** resulted in obtaining **6a** with high enantioselectivity (because of the kinetic resolution, the maximum yield is 50%).

Table 4. Screening of catalysts and conditions in the Michael-Henry-cascade reaction of racemic **3a** with nitrostyrene to afford **6a**.[a]



entry	catalyst (equiv to **3a**)	solvent	time (h)	ratio **6a**:**3a**:**4a**[b]	er of **6a**[c]
1	DABCO (0.1)	CH_2Cl_2	72	4:22:74	-
2	DBU (0.1)	CH_2Cl_2	72	12:52:36	-
3	quinine (0.2)	toluene	96	39:47:14	83:17
4	quinidine (0.2)	toluene	96	59:11:30	23:77
5	quinidine (0.2)	CH_2Cl_2	96	50:16:34	48:52
6[d]	quinine (0.2)	toluene	24	18:73:9	85:15
7[d]	quinine (0.05)	toluene	24	4:94:2	88:12
8[d][e]	quinine (0.05)	benzene	10	31:69:<1	96:4

[a] Reactions conditions: racemic **3a** (0.022 mmol, 1.0 equiv), nitrostyrene (3.0 equiv), and catalyst in solvent (1.0 mL) at room temperature (25 °C). [b] Determined by ^1H NMR analysis. [c] Determined by HPLC analysis. [d] 4 Å molecular sieves (50 mg) were added. [e] Nitrostyrene (0.20 mmol, 9.0 equiv) and solvent (0.25 mL) were used.

Using the quinine catalysis conditions with 4 Å molecular sieves, various polycyclic compounds **6** were obtained from racemic **3** as single diastereomers in highly enantiomerically enriched forms (Table 5). With crystallization, the enantiopurities of **6** were further improved (>99% ee).

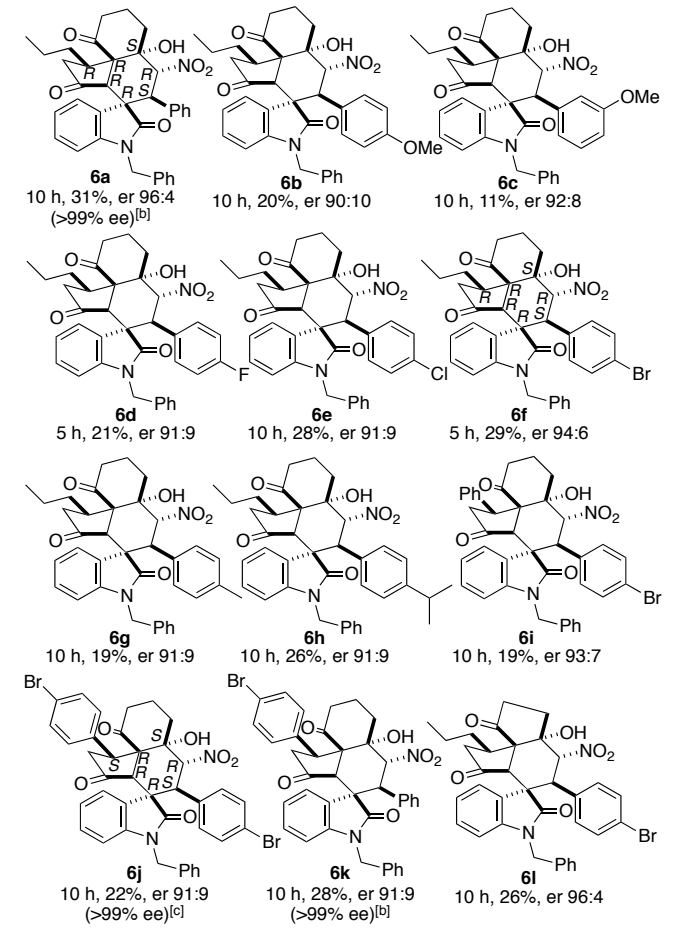
The relative stereochemistry of **6a** was determined by X-ray crystal structural analysis of the racemic crystals.[11] The absolute configuration of **6f** obtained by the quinine catalysis was determined by the VCD analysis (see Supporting Information) to be as shown in Table 5. The absolute configuration of the major enantiomer of **6j** obtained by the

quinine catalysis was also determined by X-ray crystal structural analysis to be as shown in Table 5.[11]

By tuning the reaction time, highly enantiomerically enriched forms of **3** were also obtained (i.e., unreacted enantiomers of **3** were recovered, Table 6). The absolute stereochemistries of **3a** reacted with nitrostyrene under the quinine catalysis and of the remaining enantiomer of **3a** were deduced from the configuration of **6a** and **6f**. We also demonstrated that enantioselective synthesis of **3a** was possible in the reactions of **1a** and of **5a** with **2a** in the presence of homochiral catalysts, although further development is required (see Supporting Information).

Further, the highly enantiomerically enriched form of **3a** obtained by the kinetic resolution was transformed to highly enantiomerically enriched form of **6a** in high yield (Scheme 3). This **6a** was the opposite enantiomer to the one obtained by the quinine catalysis from racemic **3a** (Scheme 3 versus Table 5).

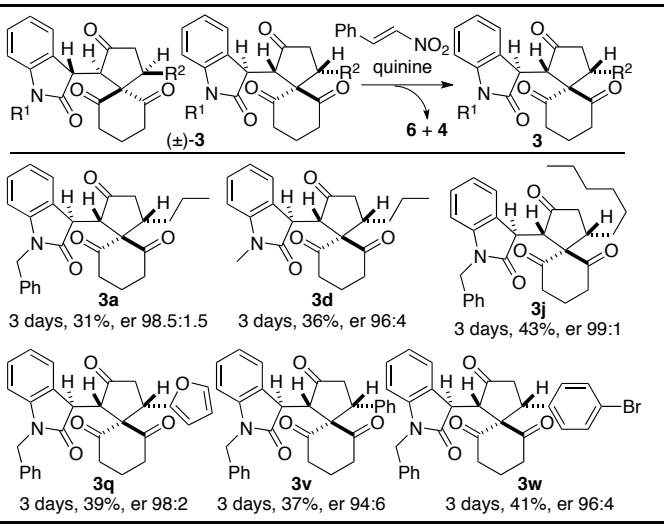
Table 5. Scope of the formation of spirooxindole polycycles **6**; products obtained from (±)-**3** with nitrostyrenes under the quinine catalysis.[a]



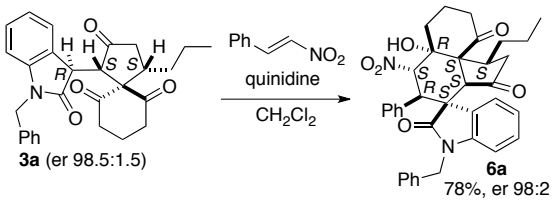
[a] Reaction conditions: (±)-**3** (0.045 mmol, 1.0 equiv), nitrostyrene (9.0 equiv), quinine (0.05 equiv), 4 Å molecular sieves (100 mg) in benzene (0.5 mL) at room temperature (25 °C). The er and ee were determined by HPLC. [b] Data after removing racemic crystals. [c] Data after crystallization (see Supporting Information).

In summary, we have developed formal (4+1) cycloaddition reactions to synthesize the spiro[4,5]decane derivatives bearing oxindole moieties and have also developed diastereo- and enantioselective Michael-Henry-cascade reactions of the (4+1) cycloaddition products to afford spirooxindole polycyclic derivatives bearing the spiro[4,5]decane system with seven stereogenic centers. The Michael-Henry-cascade reaction step occurred with kinetic resolution. Through the kinetic resolution, the spiro[4,5]decanes bearing oxindole moieties were also obtained in highly enantiomerically enriched forms. Our strategies allow access to these complex functionalized molecules in highly enantiomerically enriched forms in two steps. Further studies to elucidate the mechanisms of the reactions are underway, and the results will be reported in due course.

Table 6. Kinetic resolution of (±)-**3** to afford **3** with high enantiopurity through the reaction that forms **6** under the quinine catalysis.[a]



[a] Reaction conditions: racemic (±)-**3** (0.023 mmol, 1.0 equiv), nitrostyrene (9.0 equiv), quinine (0.05 equiv), and 4 Å molecular sieves (40 mg) in benzene (0.25 mL) at room temperature (25 °C).



Scheme 3. Transformation of an enantiomer of **3a** to **6a**.

Acknowledgements

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Keywords: asymmetric catalysis • organocatalysis • cycloaddition • Michael addition • spiro compounds

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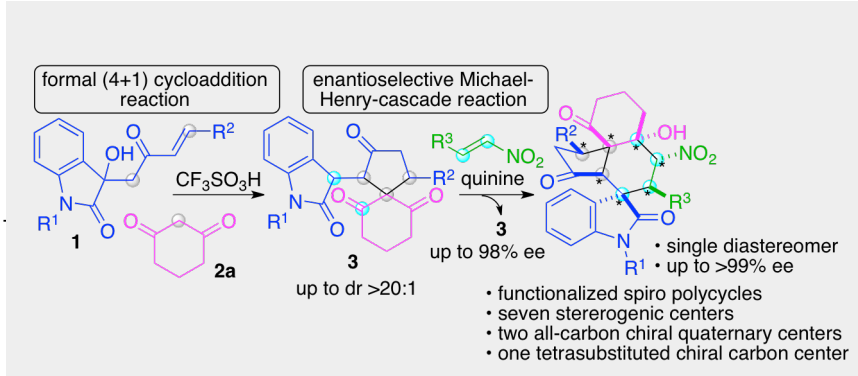
[10] Relative stereochemistries of **3a** and **4a** were determined by the X-ray crystal structural analysis of the racemic crystals of **3a** and **4a**. CCDC 1526295 for **3a** and CCDC 1526296 for **4a**.

[11] CCDC 1526298 for racemic **6a** and CCDC 1526299 for the enantiomer of **6j**.



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Formal (4+1) Cycloaddition and Enantioselective Michael-Henry-Cascade Reactions to Synthesize Spiro[4,5]decanes and Spirooxindole Polycycles with Seven Stereogenic Centers

Strategies to concisely construct oxindole-functionalized spriro[4,5]decanes and polycyclic derivatives were developed. Through formal (4+1) cycloaddition and catalytic asymmetric Michael-Henry-cascade reactions, products containing three and seven chiral centers, including two all-carbon quaternary centers and one tetrasubstituted carbon center, were obtained with high diastereo- and enantioselectivities in two steps.