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Remote Control of Axial Chirality: Synthesis of Spirooxindole−Urazoles via Desymmetrization of ATAD

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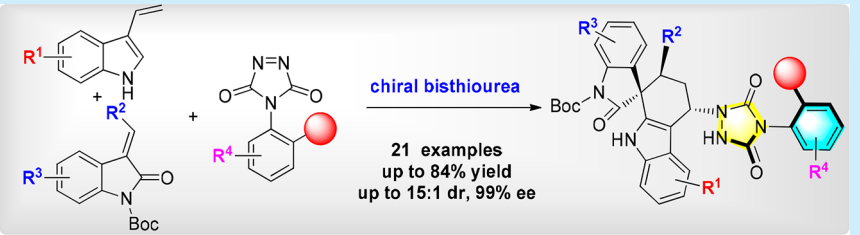
Supporting Information



ABSTRACT: For the first time, a desymmetrization strategy empowered the assembly of a class of optically pure spirooxindole−urazoles possessing an *N*-Ar stereogenic axis via remote control of axial chirality in an asymmetric three-component reaction. This transformation was realized by a tandem bisthiourea-catalyzed asymmetric Diels−Alder reaction and substrate-controlled asymmetric ene reaction. The driving force derived from aromatization and the high reactivity of 4-aryl-1,2,4-triazole-3,5-dione enophiles mediated the occurrence of the successive ene reaction under mild conditions.

The past two decades has witnessed surging interest in axially chiral frameworks by virtue of their significant applications in many fields.[1] Utmost dedication has been given to biaryl atropisomers, fostering the accomplishment of numerous elegant synthetic strategies.[1,2] The development of atropisomeric *N*-Ar skeletons, by contrast, lags behind in view of their ubiquity in natural products[3] and bioactive molecules[4] and as ligands[5] and catalysts[6] for chirality induction. The wide utilization of low-yielding optical resolution using costly chiral resolution agents or chromatography calls for novel and efficient approaches to induce axial chirality with high enantioselectivity. Of the few successful cases reported,[7] the desymmetrization strategy pioneered by Curran[8] offers an effective solution to access optically active *N*-Ar axially chiral compounds, which has engendered a suite of synthetically useful chiral C−C bond formation protocols applying maleimides as the prochiral precursors.[9] Capitalizing on their electrophilic nature, Hayashi documented the asymmetric 1,4-addition of arylboronic acids with a chiral rhodium catalyst,[9b] whereas Bencivenni devised the aminocatalytic stereoselective vinylogous Michael addition[9c] and subsequently a Diels−Alder (D−A) desymmetrization reaction with enones (Figure 1a).[9d] With our recent discovery of a new class of axially chiral urazoles containing a chiral *N*-Ar axis that are synthesized via an organocatalytic tyrosine click reaction employing 4-aryl-1,2,4-triazole-3,5-dione (ATAD) as the electrophile (Figure 1b),[10] we were inspired to cover more chemical space of *N*-Ar axially chiral compounds of synthetic origin through a desymmetrization strategy to access analogues with broader structural diversity (Figure 1c).

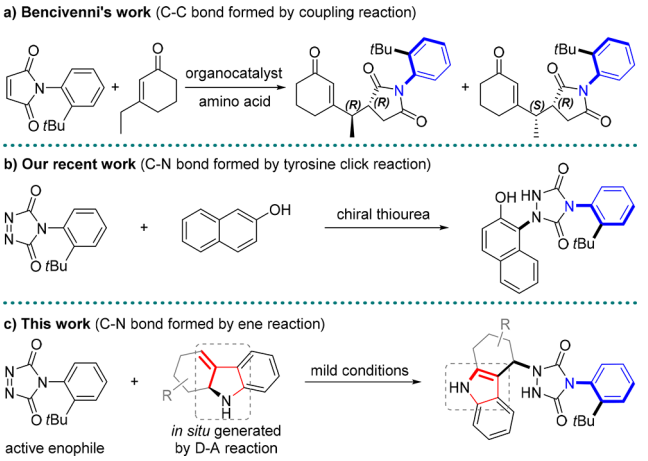


Figure 1. Desymmetrization strategy for atroposelective formation of *N*-Ar axes.

Beyond their conspicuous role as electrophiles, the enhanced electrophilicity and lower N═N π-bond dissociation energy of ATADs render them equally competent as enophiles in ene reactions.[11] While the ene reaction forges C−C and C−X bonds with high atom-economy, to the best of our knowledge it has yet to be leveraged for the enantioselective synthesis of axially chiral *N*-Ar compounds. Additionally, we surmised that

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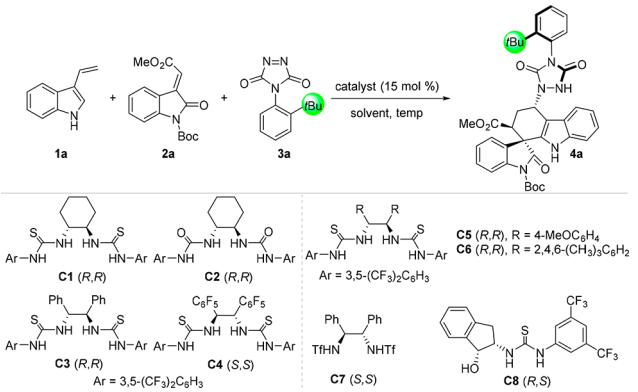
adopting a preceding D−A reaction for in situ generation of the ene partner would further impart flexibility and diversity. To this end, the spirooxindole generated from a D−A reaction between 3-vinylindole[12] and methyleneindolinone[13] could be a prime candidate given its facile conversion to indole following an aromaticity-driven [1,3]-H shift, thus releasing a ready ene partner for the ensuing ene reaction.[14] To actualize this proposition, the following challenges had to be tackled: (1) the complexity of a three-component reaction system, especially with the presence of the highly reactive ATAD reactant, and (2) exquisite stereocontrol of the ene reaction undeterred by the scarcity of reported success. Herein we report a rationally designed multicomponent reaction (MCR)[15] for the asymmetric construction of an *N*-Ar axis via desymmetrization with remote stereocontrol, furnishing complex spirooxindole−urazoles possessing multiple central or axial chiralities with good stereoselectivities.

Initial investigation of this reaction commenced with 3-vinylindole (**1a**), methyleneindolinone **2a**, and 4-(2-*tert*-butylphenyl)-3*H*-1,2,4-triazole-3,5-dione (**3a**) as model substrates, CH_2Cl_2 as the solvent, and bisthiourea **C1** as the catalyst. Not surprisingly, byproducts were predominantly formed from the competitive reactions at room temperature in only 5 min because of the high reactivity of ATAD, and only a trace amount of desired product **4a** was detected (Table 1, entry 1). To inhibit the formation of the byproducts, meticulous control of individual reaction rates became imperative. Commonly reported factors such as the solvent, catalyst, and temperature were then considered. Remarkably, the reaction solvent dramatically changed the reaction course (Table 1, entries 1−6), and it was evident that the nonpolar solvent hexane was the most conducive for this reaction among all of the tested ones, affording **4a** in 52% yield (Table 1, entry 6). Despite the much longer reaction time (48 h) for complete conversion, the product formation was accomplished with high stereocontrol (8:1 dr and 95% ee). To our delight, conducting the reaction at a lower temperature (0 °C) but with longer duration fruitfully improved the chemical yield to 80% and the ee value to 99% (Table 1, entry 7). Attempts to further improve the reaction outcome upon evaluation of various chiral catalysts met with failure (Table 1, entries 8−14). The addition of CH_2Cl_2 (10%) could shorten the reaction duration, but both the yield and enantioselectivity dropped obviously (Table 1, entry 15). Thus, the optimal reaction conditions were concluded to be the following: bisthiourea **C1** as the catalyst and hexane as the solvent at a reaction temperature of 0 °C. Under this set of reaction conditions, the desired product **4a** was isolated in 78% yield with 8:1 dr and >99% ee.

With the optimized conditions in hand, we next turned our attention to exploring the substrate scope of methyleneindolinones **2** for this three-component reaction (Scheme 1). Notwithstanding the long duration required for complete reaction (2−6 days), all of the tested substrates were well-suited for this chemistry to give axially chiral spirooxindole−urazoles **4** in moderate chemical yields with good diastereoselectivities and, gratifyingly, excellent enantiopurities. First, replacement of the methyl moiety on the ester by an ethyl group provided the desired product **4b** in 69% yield with 8:1 dr and 98% ee. Similar reaction outcomes were observed with substrates containing benzyl (**4c**) and *tert*-butyl (**4d**) esters. Apart from the ester group, ketone functionality was equally well tolerated to give the corresponding product **4e** with good stereocontrol (98% ee) in moderate yield (59%). However,

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	temp (°C)	yield (%)[b]	dr[c]	ee (%)[d]
1	**C1**	CH_2Cl_2	rt	–	–	–
2	**C1**	Et_2O	rt	–	–	–
3	**C1**	toluene	rt	–	–	–
4	**C1**	pentane	rt	41	8:1	98
5	**C1**	cyclohexane	rt	34	8:1	95
6	**C1**	hexane	rt	52	8:1	95
7	**C1**	hexane	0	80 (78)	8:1	>99
8	**C2**	hexane	0	28	6:1	20
9	**C3**	hexane	0	53	8:1	93
10	**C4**	hexane	0	69	8:1	−77
11	**C5**	hexane	0	35	7:1	69
12	**C6**	hexane	0	38	8:1	1
13	**C7**	hexane	0	46	5:1	−20
14	**C8**	hexane	0	46	6:1	−48
15[e]	**C1**	hexane/CH_2Cl_2	0	67	8:1	90

[a]Reactions were carried out with **1a** (0.15 mmol, 1.5 equiv), **2a** (0.10 mmol, 1.0 equiv), **3a** (0.15 mmol, 1.5 equiv), and 15 mol % catalyst in 4 mL of solvent. [b]Determined by ^{1}H NMR analysis using CH_2Br_2 as the internal standard. An isolated yield is given in parentheses. [c]Determined by ^{1}H NMR analysis of the crude products. [d]Determined by chiral HPLC analysis. [e]hexane/CH_2Cl_2 = 10/1.

both the dr and ee values dropped when an electron-withdrawing cyano group was employed instead (**4f**). Introduction of an electron-donating methoxy substituent on the aromatic ring led to a low yield of 49% (**4g**), while methyl substitution had a negligible impact (**4h**). Next, methyleneindolinones bearing halide substituents with varied substitution positions were examined, all of which afforded respective products with satisfactory results (**4i−l**). When the methyleneindolinone with a bromide substituent at C-4 was tested, very poor yield and stereoselectivity were observed. The absolute configuration of compound **4k** was confirmed by crystallographic analysis after recrystallization, and those of other products in this scheme were assigned by analogy.

Subsequently, we moved to extend the substrate scope of 3-vinylindoles **1**, and the results are summarized in Scheme 2. Substrates carrying an electron-donating methyl group furnished products **4m** and **4n** in very good chemical yields with excellent enantioselectivities but dissimilar diastereoselectivities arising from the distinct substitution positions. Indole-derived substrates possessing a halogen atom were also compatible, delivering the respective products with moderate results (**4o−q**).

Finally, we examined the scope of ATAD enophiles. Although inferior diastereoselectivities were observed, the

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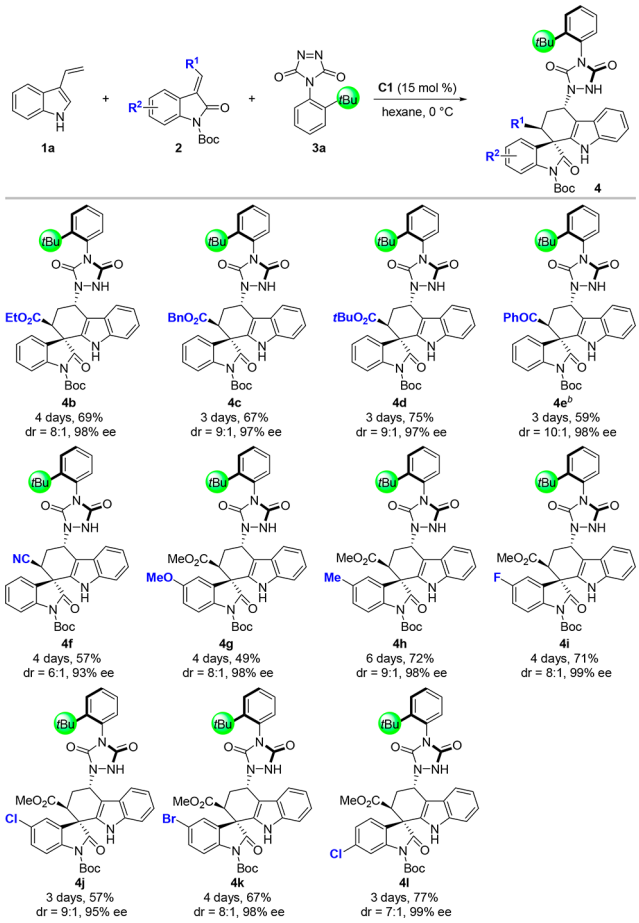
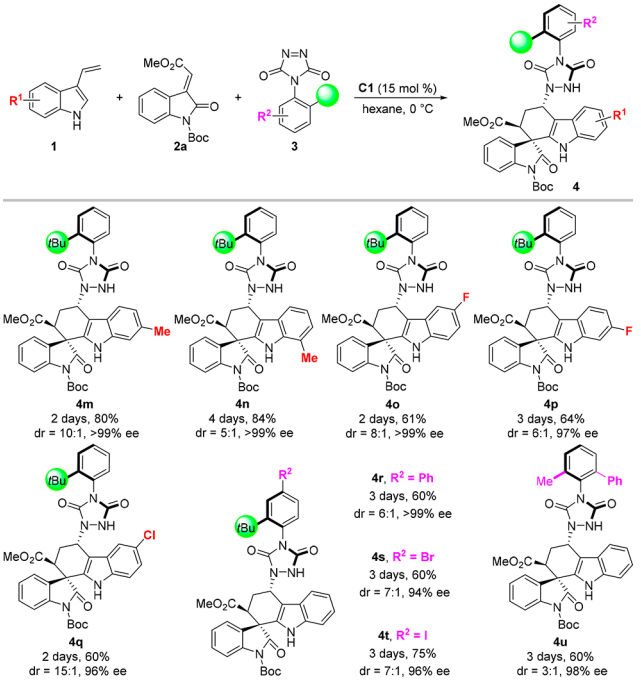
Scheme 1. Substrate Scope of Methyleneindolinones[a]



[a]Reaction conditions: **2** (0.10 mmol) and **C1** (15 mol %) in hexane (4 mL) were stirred for 15 min at 0 °C and then **1a** (0.15 mmol) and **3a** (0.15 mmol) were added, unless otherwise specified. Isolated yields of the pure major diastereomers are provided. [b]The reaction scale was doubled.

Scheme 2. Substrate Scopes of 3-Vinylindoles and ATAD Enophiles[a]



[a]Reaction conditions: **2a** (0.20 mmol) and **C1** (15 mol %) in hexane (8 mL) were stirred for 15 min at 0 °C and then **1** (0.30 mmol) and **3** (0.30 mmol) were added, unless otherwise specified. Isolated yields of the pure major diastereomers are provided.

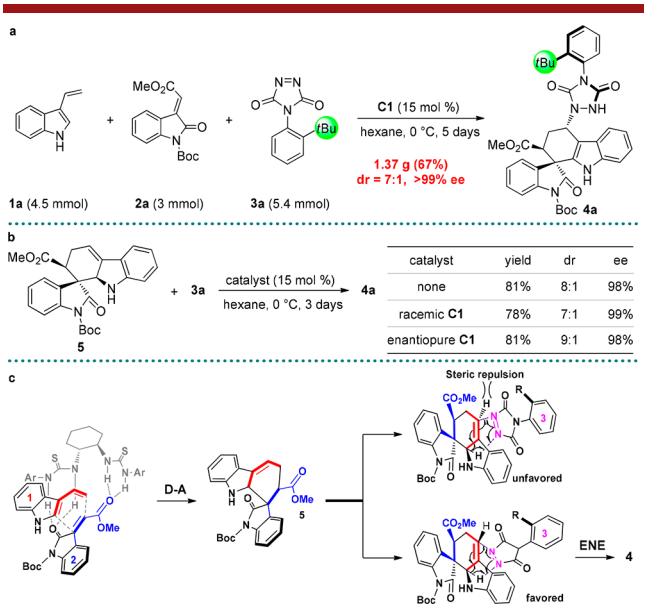


Figure 2. Gram-scale reaction, control experiments, and plausible mechanism.

chemical yields were modest, and the enantiopurities remained satisfactory (**4r–t**). An attempt to replace the *tert*-butyl group with a phenyl group for better control of the axial chirality hampered the diastereoselectivity of product **4u** significantly to 3:1 while maintaining a moderate yield of 60% with 98% ee.

To validate the utility of this catalytic enantioselective reaction, a preparative-scale synthesis of product **4a** was carried out under the optimal reaction conditions. As outlined in Figure 2a, axially chiral compound **4a** was obtained in 67% yield with excellent enantioselectivity, albeit with a moderate dr value. Compared to the small-scale synthesis, no obvious deterioration of the yield or stereochemical integrity was observed for the preparative-scale one. To verify the role of the catalyst in the ene reaction, intermediate **5** was then synthesized from **1a** and **2a** by a D–A reaction.[14] With **3a** as the enophile, no apparent differences in the stereoselectivities were detected for all of the tested conditions, including in the absence of catalyst, with racemic catalyst **C1**, and with enantiopure catalyst **C1** (Figure 2b). These results imply that the spatial configuration of intermediate **5a** is more decisive than catalyst **C1** for stereoselective formation of the C–N bond. On the basis of previous results and our investigations, a bisthiourea-catalyzed D–A reaction between **1** and **2** to afford spirooxindole derivative **5** is proposed as the first step. Subsequently, the ene reaction of the generated alkene with an allylic hydrogen and ATAD **3** affords the desired product **4**. Notably, the ATAD can approach the double bond only from the face opposite the bulky ester group and the bicyclic structure adjacent to the double bond, resulting in the excellent selectivity of the central chirality. Thus, the dr value is given in regard to the atroposelectivity. However, the remote control over the stereoselectivity of the

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axial chirality is still unclear at this stage since the *tert*-butyl group is far away from the bulky groups (Figure 2c).

In conclusion, we have developed the first asymmetric three-component reaction to construct a class of novel axially chiral spirooxindole−urazoles employing a desymmetrization strategy. An organocatalyst-controlled asymmetric D−A reaction and a substrate-controlled asymmetric ene reaction were arrayed lucidly to enable the in situ generation of complex olefinic D−A product as the ene partner for the subsequent ene reaction, thereby endowing substrate flexibility and product diversity. A gamut of 3-vinylindoles, methyleneindolinones, and ATADs were examined for modular construction of these axially chiral structures in good yields with satisfactory stereoselectivities. Several noteworthy attributes of the current methodology are recounted: (1) product diversity and chiral information is relayed between two tandem stereochemical events; (2) prudent choices of the chiral bisthiourea catalyst and the solvent inhibited the formation of byproducts from competing reactions; (3) the stereogenic axis was facilely introduced in the spirooxindole−urazole scaffold via remote control of the axial chirality; and (4) the driving force derived from the formation of an aromatic indole facilitated the occurrence of the ene reaction under mild conditions. This concise and highly efficient methodology is anticipated to offer an alternative approach to build complex axially chiral spirooxindole−urazole skeletons with multiple stereogenic elements.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications Web site. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02361.

Experimental procedures and characterization data for all new compounds (PDF)

Accession Codes

CCDC 1588495 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 e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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