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Organocatalytic Asymmetric Annulation between Hydroxymaleimides and Nitrosoarenes: Stereoselective Preparation of Chiral Quaternary *N*-Hydroxyindolines

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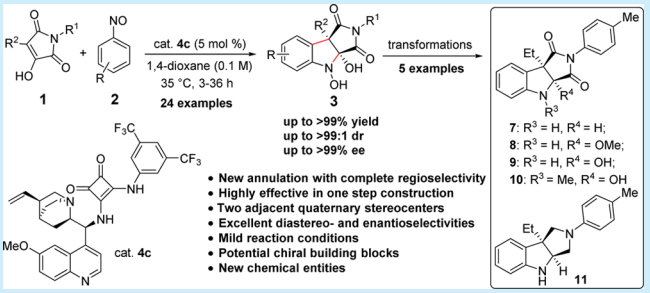
Supporting Information

ABSTRACT: An unusual and highly effective asymmetric annulation of nitrosoarenes with hydroxymaleimides catalyzed by a chiral bifunctional amine squaramide catalyst has been disclosed. A wide range of highly fused chiral *N*-hydroxyindolines with two consecutive quaternary stereocenters and multifunctional groups were directly and effectively prepared in excellent yields (up to >99%) with complete regioselective cyclization and excellent stereoselectivities (up to >99:1 dr and >99% ee). The efficiency and potentials of the new reaction and the target chiral entities were well demonstrated by delicate transformations into a series of new chiral indolines.

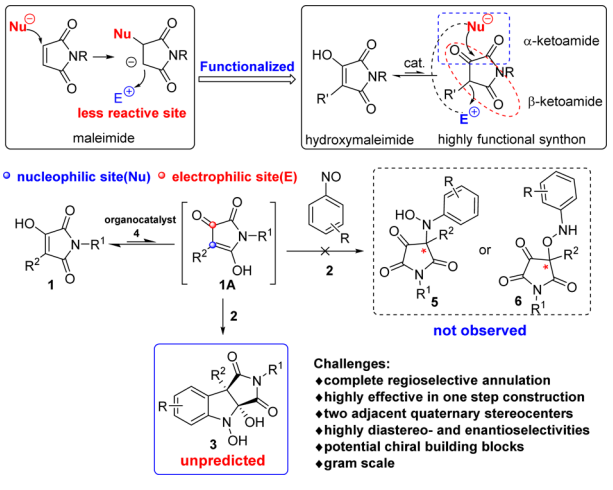


The indoline skeleton, presented as a common structural motif in numerous natural products, has aroused extensive attention from several research groups for its important role in biological and pharmaceutical activities.[1] As a result, many efficient strategies[2] for their preparation, such as asymmetric hydrogenations of indoles,[3] dearomatic cycloadditions of indoles,[4] intramolecular couplings,[5] and kinetic resolutions,[6] have been developed in recent years. Specifically, *N*-hydroxyindolines are key intermediates for the preparation of neoxaline,[7] bioactive in inhibiting cell proliferation and arresting the cell cycle during M phase.[1c] However, there are still only limited preparations[7,8] for *N*-hydroxyindolines. In 2015, the Zhou[8a] and Chang[8b] groups independently disclosed a rhodium-(III)-catalyzed C−H cyclization of nitrones with diazoesters. To date, no direct asymmetric approach for the preparation of *N*-hydroxyindolines has been reported, especially for those possessing quaternary stereocenters and highly functional groups.

Nitrosoarenes,[9] generally unstable with a highly reactive nitroso group, showed N- and O-selectivities in Diels−Alder reactions,[10] oxyaminations,[11] aminoxylations,[12] cycloadditions,[13] and other reactions.[14] Among those reactions, the control of the regioselectivity constitutes a great challenge.

On the other hand, maleimides are also important building blocks[15] as both excellent Michael acceptors[16] and good dienophiles.[17] Based on our related work in asymmetric reactions of maleimides,[16a,17c] and considering the inert reactivity of maleimide in a domino reaction after an initial nucleophilic addition[17b,d] (Scheme 1), herein we devised and introduced a hydroxyl group to the maleimide skeleton and wished it to work as a new multifunctional synthon, which possessed ketoamide and *β*-acidic C−H active groups (Scheme 1). Thus, the reactivity and the reaction modes were totally broadened, and some new domino reactions may be expected. As the beginning of a series of new reactions, a possible oxyamination or an aminoxylation of

Scheme 1. Potential Reaction Protocols of Hydroxymaleimide as a New Synthon



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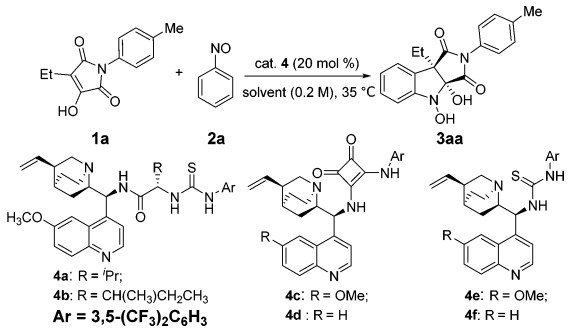
hydroxymaleimide with nitrosoarenes was also expected as we have reported for such a similar kind of reaction.[11c] However, the totally unexpected annulation products of *N*-hydroxyindolines **3** with two quaternary stereocenters rather than the expected adduct **5** or **6** were exclusively obtained in excellent diastereo- and enantioselectivities. Considering the scaffold and functional groups in the obtained chiral *N*-hydroxyindolines, they may be devised or transformed as chiral building blocks and new chemical entities with potential applications in pharmaceutical preparations. Herein, we presented the first organocatalytic unprecedented asymmetric regioselective cyclization of nitrosoarenes with hydroxymaleimides for a direct and highly effective preparation of a series of new chiral dihydropyrrolo[3,4-*b*]indole-1,3-diones in excellent yields with excellent stereoselectivities.

We began our study by testing the model reaction of 3-ethyl-4-hydroxy-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (**1a**) and nitrosobenzene (**2a**) in the presence of chiral bifunctional organocatalyst **4a** (20 mol %) in dichloromethane (DCM) at 35 °C (Table 1). The

Table 1. Optimizations of Reaction Condition[a]



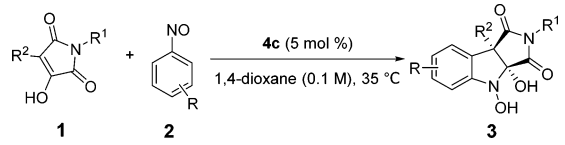
entry	cat.	solvent	time (h)	yield[b] (%)	ee[c] (%)
1	**4a**	DCM	48	65	85
2	**4b**	DCM	48	73	79
3	**4c**	DCM	12	77	92
4	**4d**	DCM	12	70	92
5	**4e**	DCM	12	85	89
6	**4f**	DCM	12	79	88
7	**4c**	$CHCl_3$	12	81	95
8	**4c**	THF	12	72	96
9	**4c**	1,4-dioxane	12	99	97
10	**4c**	toluene	12	67	87
11[d]	**4c**	1,4-dioxane	12	95	97
12[d,e]	**4c**	**1,4-dioxane**	**12**	**>99**	**98**

[a]Unless otherwise noted, the reaction was performed with **1a** (0.1 mmol), **2a** (0.12 mmol), and catalyst **4** (20 mol %) in solvent (0.2 M) at 35 °C for indicated time; >99:1 dr, determined by ^{1}H NMR. [b]Isolated yield. [c]Determined by chiral HPLC. [d]5 mol % cat. **4c** used. [e]Performed at 0.1 M.

reaction proceeded smoothly to afford the unexpected product **3aa** in 65% yield with complete regioselectivity and good stereoselectivities (>99:1 dr, 85% ee; entry 1), whereas the expected adduct **5** or **6** was not observed. To improve the enantioselectivity, chiral cinchona alkaloid squaramides **4c**,**d** and thioureas **4e**,**f** were evaluated, and the readily available **4c** gave the best results (77% yield, >99:1 dr, 92% ee; entry 3). Ethers and chloro solvents gave good to excellent yields (72−99%) and excellent stereoselectivities (>99:1 dr, 95−97% ee; entries 7−9), and 1,4-dioxane afforded the best yield and stereoselectivities (99% yield, >99:1 dr, 97% ee; entry 9). However, an inferior result was observed in toluene (67% yield, 87% ee; entry 10). Lower catalyst loading to 5 mol % still gave an excellent result within 12 h (95% yield, >99:1 dr, 97% ee; entry 11), which demonstrated the efficiency of the new reaction and the catalyst. Positively, enantioselectivity was slightly improved when lowering the reaction concentration (>99% yield, >99:1 dr, 98% ee; entry 12; for more details, see the Supporting Information, SI).

Under the optimized conditions, the generality of hydroxymaleimides **1** was studied. As shown in Table 2, a wide range of

Table 2. Substrate Scope of Hydroxymaleimides 1 with Nitrosoarenes 2[a]



entry	**1**/R^1/ R^2	**2**/R	**3**/yield[b] (%)	ee[c] (%)
1	**1a**/4-MeC_6H_4/Et	**2a**/H	**3aa**/99	98
2	**1b**/4-$MeOC_6H_4$/Et	**2a**/H	**3ba**/92	95
3	**1c**/Ph/Et	**2a**/H	**3ca**/>99	99
4	**1d**/4-FC_6H_4/Et	**2a**/H	**3da**/88	96
5	**1e**/4-ClC_6H_4/Et	**2a**/H	**3ea**/93	98
6	**1f**/4-BrC_6H_4/Et	**2a**/H	**3fa**/94	97
7	**1g**/3-$MeOC_6H_4$/Et	**2a**/H	**3ga**/70	98
8	**1h**/3-MeC_6H_4/Et	**2a**/H	**3ha**/94	97
9	**1i**/3-ClC_6H_4/Et	**2a**/H	**3ia**/84	96
10	**1j**/3-BrC_6H_4/Et	**2a**/H	**3ja**/84	96
11[d]	**1k**/2-$MeOC_6H_4$/Et	**2a**/H	**3ka**/78	*e*
12[f]	**1l**/2-ClC_6H_4/Et	**2a**/H	**3la**/86	90/91[g]
13	**1m**/3,5-$(Me)_2C_6H_3$/Et	**2a**/H	**3ma**/96	96
14	**1n**/^{n}Bu/Et	**2a**/H	**3na**/65	96
15	**1o**/4-MeC_6H_4/Me	**2a**/H	**3oa**/93	>99
16	**1p**/4-MeC_6H_4/^{n}Pr	**2a**/H	**3pa**/98	96
17	**1q**/4-MeC_6H_4/Bn	**2a**/H	**3qa**/81	91
18	**1r**/4-MeC_6H_4/Ph	**2a**/H	**3ra**/NR	
19	**1a**/4-MeC_6H_4/Et	**2b**/4-Me	**3ab**/83	92
20	**1a**/4-MeC_6H_4/Et	**2c**/3-Me	**3ac**/80	99
21	**1a**/4-MeC_6H_4/Et	**2d**/3-Cl	**3ad**/80	97
22	**1a**/4-MeC_6H_4/Et	**2e**/2-Me	**3ae**/84	95
23	**1a**/4-MeC_6H_4/Et	**2f**/2-Cl	**3af**/99	>99
24	**1a**/4-MeC_6H_4/Et	**2g**/2-Br	**3ag**/99	96
25	**1a**/4-MeC_6H_4/Et	**2h**/2,4-$(Me)_2$	**3ah**/87	84

[a]Reactions were performed with **1** (0.2 mmol), **2** (0.24 mmol), and **4c** (5 mol %) in 1,4-dioxane (0.1 M) at 35 °C for 3−36 h; >99:1 dr, determined by ^{1}H NMR. [b]Isolated yield. [c]Determined by chiral HPLC. [d]2:1 dr. [e]Enantiomers failed to be separated. [f]1:1 dr. [g]Values of ee were determined from fully reduced product **12** (SI).

1 was tolerated. The aromatic R^1 bearing *para*- or *meta*-substituents all gave good to excellent yields with excellent diastereo- and enantioselectivities (70 to >99% yields, >99:1 dr, 95−99% ee, entries 1−10), whereas *ortho*-substituents, regardless of the electronic characteristics, gave good yields and significantly decreased diastereoselectivities (78−86% yields, 1:1−2:1 dr, entries 11 and 12). The possible reason for the low diastereoselectivities may be the atropisomerism of the N−Ar single bond of maleimide.[17d] 3,5-Dimethyl phenyl group also smoothly gave excellent yield and enantioselectivity (96% yield, >99:1 dr, 96% ee, entry 13). For an alkyl-substituted group (R^1 = ^{n}Bu), **3na** was efficiently obtained in moderate yield with

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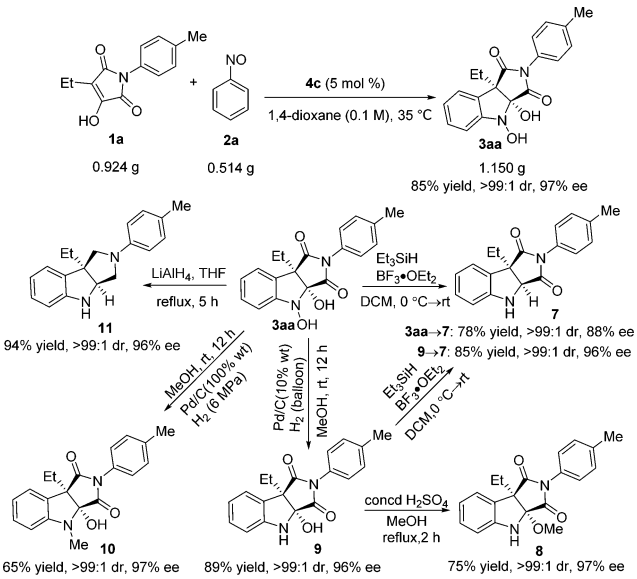
excellent diastereoselectivity and enantioselectivity (65% yield, >99:1 dr, 96% ee, entry 14). When R^2 was replaced by a methyl, *n*-propyl, or benzyl group, target products were smoothly obtained in excellent yields without loss of stereoselectivities (81−98% yields, >99:1 dr, 91 to >99% ee, entries 15−17). Unfortunately, phenyl-substituted substrate **1r** did not work with **2a**, probably due to the steric hindrance and the highly delocalized double bond enolized from the ketoaminde **1r** (Scheme 1). Further, the scope of nitrosoarenes **2** was broadened under optimized conditions. Substituted positions had a remarkable effect on the reaction. 4-Methylnitrosobenzene **2b** with **1a** gave a good outcome (83% yield, >99:1 dr, 92% ee, entry 19). However, other *para*-substituted nitrosobenzenes cannot work smoothly (SI). When 3-substituted nitrosobenzenes were used, annulations took place in the *para* position exclusively (80% yields, >99:1 dr, 97−99% ee, entries 20 and 21). Additionally, *ortho*-substituents (Me, Cl, Br) also worked well in excellent yields with excellent diastereo- and enantioselectivites (84−99% yields, >99:1 dr, 95 to >99% ee, Table 2, entries 22−24). In particular, 2-chloronitrosobenzene and 2-bromonitrosobenzene effectively furnished the products completely within 3 h. Dimethyl-substituted **2h** also efficiently gave **3ah** in 87% yield, >99:1 dr, and 84% ee. The absolute configuration of the product **3fa** was established to be (3a*R*,8b*R*) by X-ray crystallographic analysis.[18] Based on the experiments and related literature,[9a,14d,19] a plausible mechanism was suggested (SI).

Considering the great potentials of the multifunctional chiral products and for diversity of chiral indoline preparations, we further tried to perform the reaction on a larger scale of **1a** under the optimal conditions and furnished **3aa** with equally excellent results (Scheme 2). The efficiency and potentials of the new reaction and the target chiral entities were well demonstrated by delicate transformations to a series of new chiral indolines typically from **3aa**. Reduction of **3aa** with triethylsilane in the presence of $BF_3{\cdot}OEt_2$ gave the totally dehydroxylated indoline **7**, which can also be obtained from **9** under the reported conditions.[20] Hydrogenation of **3aa** in the presence of 10% Pd/C (10% loading) gave product **9** in excellent yield with excellent stereoselectivities (89% yield, >99:1 dr, 96% ee) under atmospheric hydrogen pressure with exclusive N−OH bond cleavage.[11c] Additionally, the selective reduction of the C−OH bond was studied. However, we failed to get the desired product **7** directly, and the unexpected N-methylated product **10** was obtained in good results (65% yield, >99:1 dr, 97% ee) under higher hydrogen pressure (6 MPa) in methanol. When excessive $LiAlH_4$ used, completely reduced product **11** was obtained in excellent results (94% yield, >99:1 dr, 96% ee). The reduction was also found in alternative preparations for similar racemic indolines.[21] Product **8** was easily formed from **9** in methanol in the presence of catalytic concentrated sulfuric acid.[21a] To the best of our knowledges, the total preparations of those special chiral indolines were not found in the literature, and those transformations may provide a great potential for pharmaceutically active molecules.

Scheme 2. Scale-up Experiment and Representative Transformations of the Product 3aa



In summary, hydroxymaleimide has been successfully devised as a novel synthon. An unconventional asymmetric regioselective cyclization of nitrosoarenes with hydroxymaleimides was first disclosed in the presence of a chiral bifunctional amine squaramide catalyst. A series of highly fused chiral *N*-hydroxyindolines with two adjacent quaternary stereocenters and multifunctional groups were directly and effectively prepared in excellent yields (up to >99%) with complete regioselective annulation and excellent stereoselectivities (up to >99:1 dr and >99% ee). The efficiency and potentials of the new reaction and the target chiral entities were well demonstrated by delicate transformations to a variety of new chiral indolines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00893.

X-ray data for compound **3fa** (CIF)

Experimental procedures and detailed characterization data for the new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(18) CCDC 1523309 (**3fa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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