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Thiourea–Quaternary Ammonium Salt Catalyzed Asymmetric 1,3-Dipolar Cycloaddition of Imino Esters To Construct Spiro[pyrrolidin-3,3′-oxindoles]

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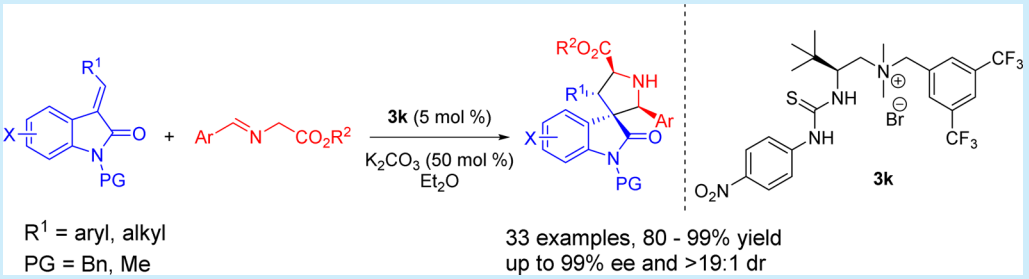
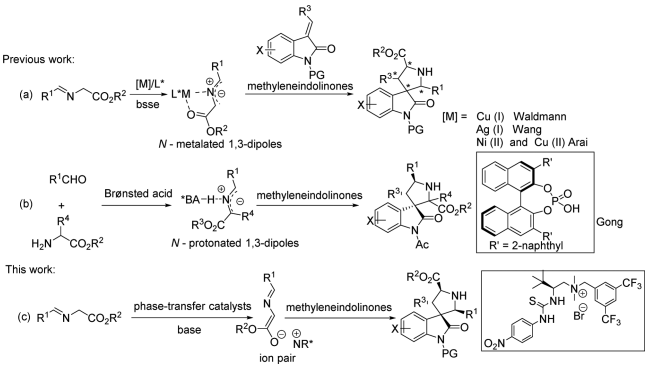
Supporting Information



ABSTRACT: A highly enantioselective 1,3-dipolar cycloaddition of imino esters with methyleneindolinones has been realized by using readily available thiourea–quaternary ammonium salts as phase-transfer catalysts, enabling efficient construction of a range of chiral spiro[pyrrolidin-3,3′-oxindoles] in good yields with excellent enantioselectivities under mild conditions.

The spiro-oxindole skeleton occurs as a key structural motif in a large number of natural and unnatural compounds, often conferring valuable bioactivity and pharmaceutical properties.[1] The structural diversity and complexity of these compounds have inspired chemists to develop numerous efficient synthetic strategies to construct these scaffolds.[2] In particular, many synthetic strategies have been developed to construct the chiral 3,3′-pyrrolidonyl spirooxindole skeletons.[3] Among them, the catalytic asymmetric 1,3-dipolar cycloaddition[4] of imino esters and methyleneindolinine derivatives has been regarded as one of the most effective methods.[5] In 2010, Waldmann and co-workers reported the 1,3-dipolar cycloaddition of methyleneindolinones with imino esters catalyzed by a Cu(I)/N,P-ferrocenyl complex,[5b] while Wang and co-workers reported the use of Ag(I)/TF-Bipham-Phos catalysts.[5c] More recently, Arai and co-workers developed Ni(II)/imidazoline–aminophenol (IAP) and the Cu(II)/bis(imidazolidine)pyridine (PyBidine) complexes for the catalysis of related 1,3-dipolar cycloadditions in 2012[5d] and 2015.[5e] These metal–chiral ligand catalyst systems have been assumed to proceed through the *N*-metalated 1,3-dipole intermediates (Scheme 1a). On the other hand, organocatalyzed asymmetric 1,3-dipolar cycloaddition was first reported by the Gong group in a three-component reaction with in situ formed azomethine ylides using a chiral Brønsted acid catalyst (Scheme 1b).[5a] Wang and co-workers also developed a tertiary amine–thiourea catalyzed 1,3-dipolar cycloaddition of cyclic imino esters with methyleneindolinones.[5f] Xiao and co-workers developed asymmetric [3 + 2] cycloaddition of chiral palladium-containing N^1-1,3-dipoles with methyleneindolinones.[5g]

Scheme 1. Asymmetric 1,3-Dipolar Cycloaddition of Imino Esters with Methyleneindolinones



In addition, the asymmetric phase-transfer catalysis has been one of the most important type of organocatalytic strategies with extensive applications in asymmetric synthesis.[8] However, the direct catalytic asymmetric 1,3-dipolar cycloaddition of

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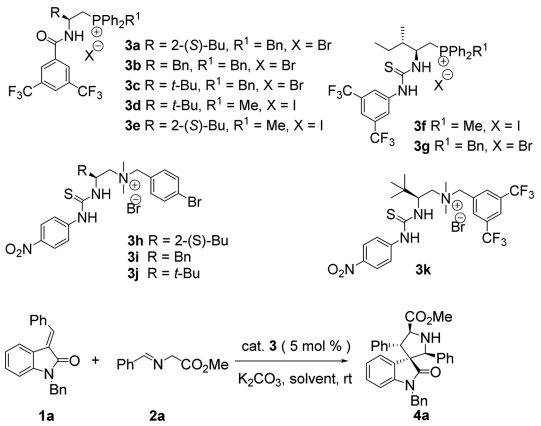
methyleneindolinones and imino esters catalyzed has not yet been reported. Our group has focused on the development of chiral organocatalysts from amino acids for a range of asymmetric reactions,[6] especially the bifunctional quaternary ammonium and phosphonium salts as chiral phase-transfer catalysts.[7] Herein, we report the application of amino acid derived quaternary ammonium salts as chiral phase-transfer catalysts for this transformation, enabling facile access to chiral spiro[pyrrolidin-3,3′-oxindoles] (Scheme 1c).

Initially, the reaction between *N*-benzyl-protected methyleneindolinone (**1a**) with imino ester (**2a**) was chosen as a model reaction to optimize the reaction conditions (Table 1). A series of bifunctional chiral quaternary phosphonium salt catalysts were first evaluated. The spirooxindole compound **4a** was obtained with moderate diastereoselectivities and enantioselectivities (entries 1−7). When L-isoleucine-derived thiourea−quaternary ammonium salt **3h** was used, we obtained the product in 99% yield with 75% ee and 91:9 dr (entry 8).

Table 1. Optimization of Reaction Conditions[a]



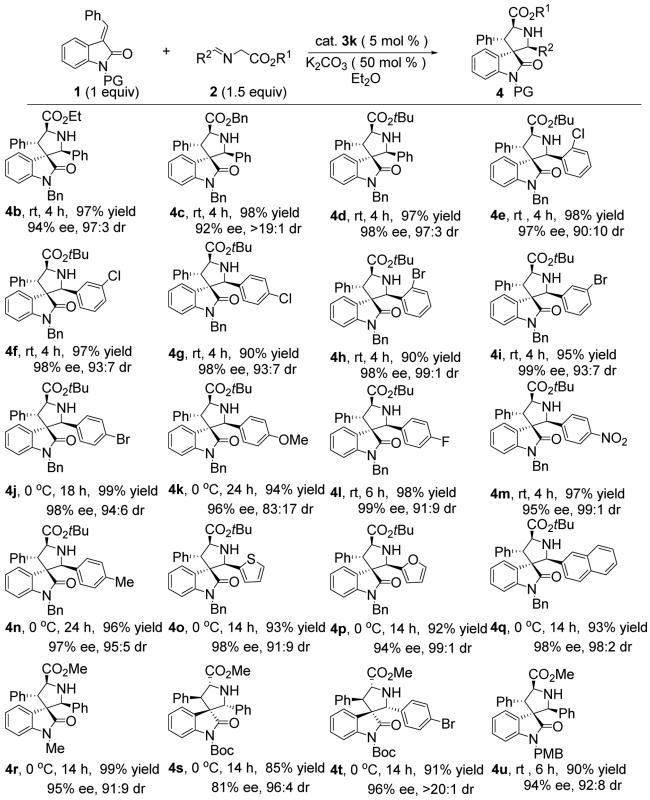
entry	cat.	solvent	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	**3a**	toluene	4	98	82:18	46
2	**3b**	toluene	3	98	71:29	51
3	**3c**	toluene	4	99	68:32	62
4	**3d**	toluene	20	80	67:33	51
5	**3e**	toluene	16	95	58:42	75
6	**3f**	toluene	20	80	65:35	59
7	**3g**	toluene	8	96	86:14	43
8	**3h**	toluene	4	99	91:9	75
9	**3i**	toluene	4	99	91:9	43
10	**3j**	toluene	4	99	88:12	91
11	**3k**	toluene	4	99	94:6	90
12	**3k**	CH_2Cl_2	12	80	86:14	85
13	**3k**	$CHCl_3$	30	85	96:4	38
14	**3k**	Et_2O	5	99	97:3	94
15	**3k**	TBME	1	99	87:13	85
16	**3k**	THF	6	86	82:18	40
17[e]	**3k**	Et_2O	1	99	94:6	72
18[f]	**3k**	Et_2O	6	92	91:9	94
19[g]	**3k**	Et_2O	12	90	84:16	92
20[h]	**3k**	Et_2O	4	95	90:10	96

[a]Unless otherwise noted, the reaction was conducted with 0.1 mmol of **1a**, 0.15 mmol of **2a**, and 1.0 equiv of base in the presence of 5 mol % of catalyst **3** at rt. [b]Isolated yield. [c]Determined by ^{1}H NMR spectroscopic analysis of the crude product. [d]Determined by HPLC using the chiral stationary phase. [e]Cs_2CO_3 was used. [f]KF was used. [g]K_2HPO_4 was used. [h]0.5 equiv of K_2CO_3 was used.

Then other amino acid derived quaternary ammonium salt catalysts with different chiral skeletons were screened, and the L-*tert*-butylleucine-derived catalyst **3j** gave the product in 99% yield with 91% ee and 88:12 dr (entry 10). Increasing the steric hindrance of the ammonium center by using a 3,5-bistrifluoromethylbenzyl group improved the diastereoselectivity of the product further to 94:6 (entry 11). The screening of several different solvents revealed that Et_2O was more suitable for the reaction, with 94% ee and 97:3 dr being achieved (entries 11−16). The use of a stronger base led to a decrease in enantioselectivity (entry 17), while the use of weaker bases resulted in longer reaction times and lower diastereoselectivities and enantioselectivities (entries 18 and 19). The use of 0.5 equiv of K_2CO_3 increased the enantioselectivity to 96% (entry 20).

Under the optimized conditions, a series of imino esters were examined, and the results are summarized in Scheme 2. Among

Scheme 2. Exploration of Imino Ester Scope



the imino esters bearing different ester groups, the *tert*-butyl imino ester gave the product **4d** with the highest enantioselectivity (98% ee). Then, a wide array of *tert*-butyl imino esters derived from various aromatic aldehydes were also examined (**4d−q**).[9] Reactions with electron-donating or electron-withdrawing substituents on the aromatic ring gave the spirooindole products with excellent enantioselectivities (96−99%) and good-to-excellent diastereoselectivities (90:10−99:1). The 2-naphthyl, 2-furyl, and 2-thienyl imino ester were well tolerated, furnishing the desired products with excellent enantioselectivities. *N*-Methyl-protected methyleneindolinone was transformed to the product **4r** in 95% ee (91:9 dr), while the N-Boc-protected methyleneindolinone gave products **4s** in 81% ee (96:4 dr) and **4t** in 96% ee (>20:1 dr).[11]

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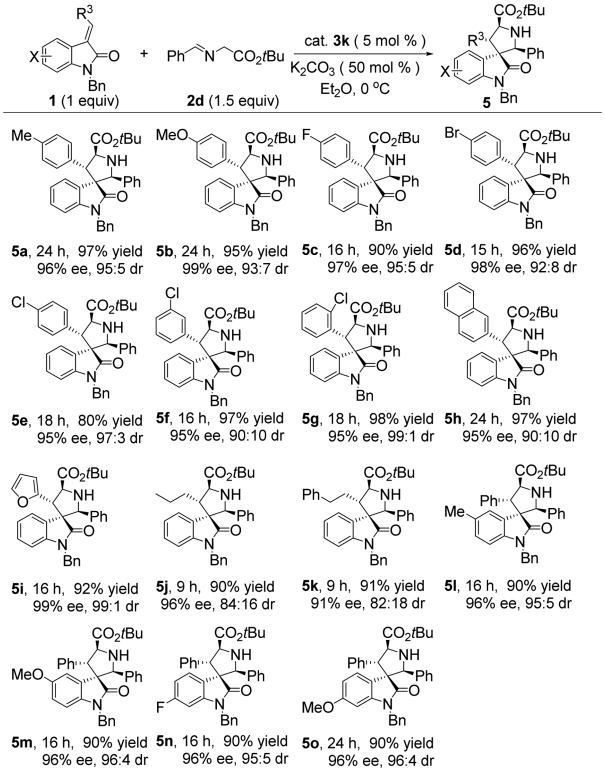
Further exploration of the reaction scope was conducted by using methyleneindolinones containing various substituents (Scheme 3). Both aromatic and aliphatic aldehydes derived

Scheme 3. Exploration of Methyleneindolinone Scope



from **1** (R^3) could be transformed to the corresponding products with excellent results. Reactions with propyl- and phenethyl-substituted methyleneindolinones, however, afforded the products **5j** and **5k** with comparatively lower diastereoselectivities (84:16 and 82:18 dr). We also investigated the substituents on the indolinone moiety of the methyleneindolinones, with good results being obtained when the substituents were at the C5 or C6 positions (**5l**–**o**). The absolute configuration of the product **5l** was was determined by X-ray cyrstallographic analysis (Figure 1), and the configurations of others were determined by analogy.[10]

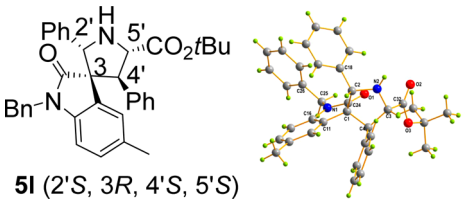


Figure 1. X-ray structure of spiro[pyrrolidin-3,3′-oxindole] **5l**.

To illustrate the utility of the transformation, the products **4t**, **4j**, and **4u** were chosen to remove the Boc group, the *tert*-butyl ester moiety, and the PMB group, which gave the corresponding products **6**,[11] **8**, and **7**,[5e] respectively, in almost quantitative yields with retention of enantioselecivity and diastereoselectivity (Figure 2a–c). When the less reactive glycinate Schiff base **2s** was subjected to the reaction with methyleneindolinone **1a**, only the Michael adduct **8** was

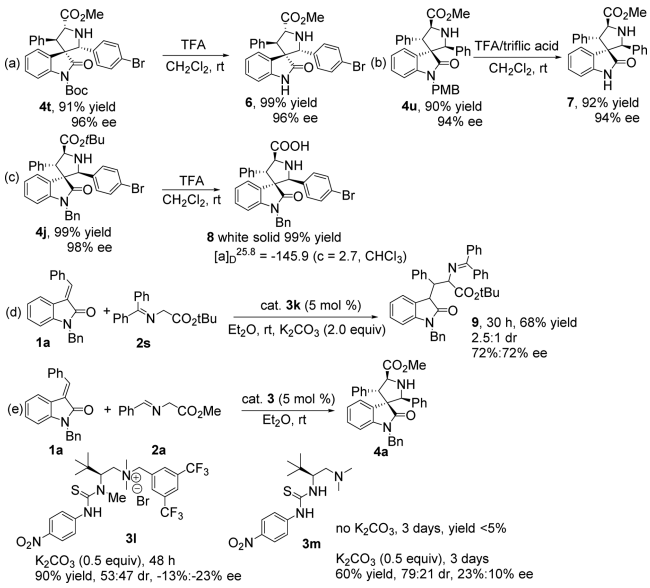


Figure 2. Product transformation and control experiments.

obtained in 68% yield with 72% ee and 2.5:1 dr (Figure 2d), which suggests the cycloaddition might proceed via a stepwise pathway. Control experiments were also performed to gain some insight into the effect of the bifunctionality of the catalyst structure on the reaction (Figure 2). Under the optimal conditions, we obtained the 1,3-dipolar cycloaddition adduct **4a** in 95% yield and 96% ee (90:10 dr) with catalyst **3k**. However, inferior results were obtained with catalyst **3l** (with a partially blocked H-bond site) and **3m** (free base instead of ammonium salt), highlighting the importance of the synergistic interaction of these functionalities in the reaction (Figure 2e).

In conclusion, we have developed a highly stereoselective 1,3-dipolar cycloaddition reaction of imino esters with 2-oxoindolin-3-ylidences by using readily available chiral thiourea–quaternary ammonium salts as phase-transfer catalysts. This transformation provides facile access to a wide range of chiral spiro[pyrrolin-3,3′-oxindole] derivatives in high yield and with excellent enantio- and diastereoselectivies under mild conditions. Efforts toward a deeper understanding of the reaction mechanism and the application of these ammonium salt catalysts to other asymmetric transformations are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02098.

X-ray crystallographic data for **5l** (CIF)
^{1}H and ^{13}C NMR spectra, HPLC traces, and crystal data for **5l** (PDF)

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Notes

The authors declare no competing financial interest.

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(9) Alkyl-substituted (R^2 = cyclohexyl, phenethyl, *tert*-butyl) imino esters derived from aliphatic aldehydes hardly underwent the reaction.

(10) Crystallographic data for **5l** have been deposited with the Cambridge Crystallographic Data Centre as deposition no. CCDC 1456687. Detailed information can be found in the Supporting Information.

(11) The absolute configuration of **6** was assigned to be (2′*R*, 3*S*, 4′*R*, 5′*R*) by comparison of the optical rotation values with the literature data (see the Supporting Information). The absolute configurations of **4s** and **4t** were determined by analogy with **6**.

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