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A highly efficient thiourea catalyzed dehydrative nucleophilic substitution reaction of 3-substituted oxindoles with xanthydrols†

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We report a highly efficient thiourea catalyzed dehydrative nucleophilic substitution reaction. The Schreiner's thiourea catalyst A_1 catalyzed the alkylation of 3-substituted oxindoles with xanthydrols well, to furnish quaternary oxindoles in high yield. The ESI-MS analysis confirms the interaction of 3-substituted oxindole 1 with the thiourea, which might facilitate the oxindole–hydroxindole tautomerization for the alkylation.

Since Hine and co-workers discovered that biphenylenediol can catalyze the epoxide-opening reaction,[1] hydrogen-bonding donor catalysts have found widespread applications in organic synthesis.[2] In particular, (thio)urea derivatives, a type of dual hydrogen-bond donors, proved to be very useful.[3] In 1994, Curran and Kuo reported for the first time that ureas could serve as catalysts for some organic reactions.[4] Schreiner *et al.* further developed a remarkable array of thiourea catalysts, and *N*,*N*′-bis-[3,5-bis-(trifluoromethyl)phenyl]-thiourea $\mathbf{A_1}$ proved to be a powerful organocatalyst.[5] The most important advances in this field were made by the Jacobsen laboratory,[6] whose studies fueled the development of asymmetric chiral (thio)urea catalysis.[3] Later, inspired by Takemoto's work,[7] bifunctional (thio) urea-tertiary amine catalysts opened up new synthetic opportunities of urea catalysis. Despite significant achievements, it is still highly desirable to extend urea catalysis to new types of reactions.[5–7]

The dehydrative nucleophilic substitution of alcohols is an important atom economical C–C bond forming reaction.[8] Apart from electron-rich aromatics and heteroatom based nucleophiles, active methylene compounds such as malonates, β-ketoesters and 2,4-diketones are also viable substrates for this reaction. During the past decade, much progress has been made in improving its efficiency by using catalytic amount of acids.[8] Noticeably, the combination of a chiral amine catalyst with an acid co-catalyst emerges as a powerful strategy for the development of asymmetric version of this reaction,[9] since Cozzi's pioneering work.[9a] Nevertheless, there still has ample room for further studies: (1) identify new catalysts for this green methodology. Generally, the use of a Lewis acid or a specific Brønsted acid catalyst is necessary.[8,9] To the best of our knowledge, the general acid catalyzed variant is largely unexplored, although recently Cozzi reported a remarkable catalyst-free "on water" nucleophilic substitution of alcohols at 80 °C.[10a] In the studies of trifluoroacetic acid (TFA) catalyzed alkylation of oxazolones using Michler's hydrols, Rios *et al.* found that thiourea could also work, but the yield of the desired product was not given.[10b] The potential and the advantages of (thio)urea catalysis have not been explored in this important C–C bond forming reaction. (2) Enable the construction of quaternary carbons. While the arylation of tertiary alcohols has been studied,[8f–l] few attention is paid to the alternative strategy which relies on the alkylation at the tertiary carbon of nucleophiles.[8f,9e,10b] Herein, we wish to report a highly efficient thiourea-catalyzed dehydrative nucleophilic substitution of unprotected both 3-aryl and 3-alkyl oxindoles using xanthydrols.

Recently, there is an ever-increasing interest in the diverse synthesis of 3,3-disubstituted oxindoles,[11] a type of privileged scaffolds in natural products and pharmaceutically active compounds, as the substituents at the C3 position of oxindole framework greatly influenced their bioactivity. Of all the methods available, the direct functionalization of 3-substituted oxindoles proves to be very useful, and *N*-Boc protected 3-substituted oxindoles, which are so reactive that could even be elaborated under base-free phase transfer condition,[12] are the most popular substrates for reaction design. Unfortunately, their synthesis needs three steps from isatins, with the sacrifice of one more equivalent of $(Boc)_2O$.[13] Therefore, the use of less reactive but easily accessible unprotected 3-substituted oxindoles **1** for reaction design is challenging but worth of exploration.[14]

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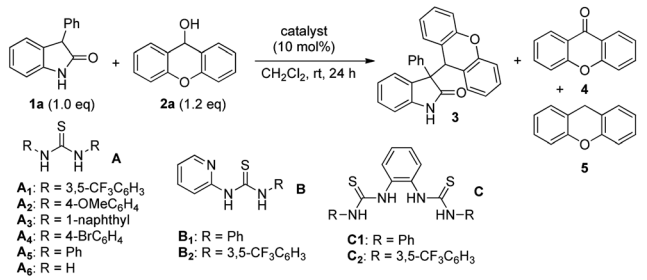
In this context, we have reported that bifunctional (thio)urea derivatives could catalyze the direct amination[15a] and Michael addition[15b] using unprotected oxindole **1**.[15] To increase the structural diversity of quaternary oxindoles, we considered the direct coupling of oxindole **1** with xanthydrols. Accordingly, the reaction of unprotected 3-phenyl oxindole **1a** and **2a** was chosen for condition optimization, and some typical results were shown in Table 1. Based on our previous studies in the acid catalyzed functionalization of tertiary alcohols,[16] various Lewis acids were first evaluated. Very surprisingly, the use of Lewis acids generally led to the deterioration of **2a**. For example, in the presence of 10 mol% of $In(OTf)_3$, no desired product **3a** was obtained, but **4** and **5** were isolated in 73% and 21% yield,[17] respectively (entry 1). While Xiao reported that the use of CuCl benefited the α-alkylation of aldehydes using **2**, it mediated the reaction to give **3a** in only 14% yield, with 56% of **4** (entry 2). Brønsted acids were then tried. Unexpectedly, when HOTf or *p*-TsOH was used, no product **3a** was obtained (entries 3 and 4), but benzoic acid as the catalyst afforded **3a** in 36% yield (entry 5). These results suggested that strong acids might result in the deterioration of **2a**, which encouraged us to try H-bonding donor catalysts. Indeed, better yield for **3a** was obtained when 1,1′-binaphthyl-2,2′-diol (BINOL) or urea $\mathbf{A_1}$ was used (entries 6 and 7). Particularly, $\mathbf{A_1}$ provided **3a** in 59% yield. These results encouraged us to optimize other thioureas $\mathbf{A_2}$–$\mathbf{A_6}$, pyridine based thioureas $\mathbf{B_1}$–$\mathbf{B_2}$ and bisthioureas $\mathbf{C_1}$–$\mathbf{C_2}$, but no further improvement was observed (entries 8–16).

In the following, other reaction parameters were studied by using 10 mol% of urea $\mathbf{A_1}$ as the catalyst at 50 °C. The study of solvent effects revealed that CH_3CN was the best, which could improve the yield of product **3a** to 77% (entries 1 to 8, Table 2). Raising the reaction temperature to 70 °C resulted in the decreased yield for **3a** (entry 9). When the reaction was run under nitrogen, the yield of **3a** could be improved to 81% (entry 10), and further to 88% by increasing the usage of **2a** from 1.2 to 2.0 equivs (entry 12). Based on these studies, the optimal condition was determined to run the reaction at 50 °C using CH_3CN as the solvent, in the presence of 10 mol% of urea $\mathbf{A_1}$ as the catalyst.

Under the optimized condition, the scope of the reaction with respect to different substituted oxindoles was examined (Table 3). The effects of substituent on the phenyl ring of oxindoles were first examined (entries 1–4), and it turned out that the electron-withdrawing substituents slowed down the reaction, but the corresponding products **3b–c** were still obtained in high yield (entries 2 and 3). 3-Monosubstituted oxindoles **1e–j** with different aromatic substituents at C3 position all worked well to give the desired products in high to excellent yield (entries 5–10). To our delight, unprotected 3-alkyl oxindoles **1k–l** were also viable substrates, giving products **3k–l** in good yield (entries 11 and 12). The 9*H*-thioxanthen-9-ol **2b** could readily react with both 3-aryl and alkyl oxindoles to give the desired products **3m–o** in good yield (entries 13–15).

It should be noted that although Rios *et al.* reported the TFA catalyzed alkylation of 3-alkyl oxindoles using Michler's hydrols, and Liu *et al.* reported a nice asymmetric reaction of *N*-Boc 3-alkyl oxindoles and Michler's hydrols catalyzed by the combination of a bis-cinchona alkaloid and methylsulfonic acid (1 : 1), our protocol was distinct from their research in that it enabled both unprotected 3-aryl and 3-alkyl oxindoles to be alkylated by xanthydrols, and most importantly, H-bonding donor catalysts such as thiourea $\mathbf{A_1}$ turned out to be more efficient in this reaction than Lewis acids and commonly used strong Brønsted acids for this S_N1 type reaction. The result prompted us to study the corresponding catalytic asymmetric

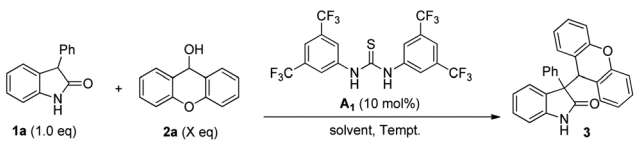
Table 1 Catalyst screening



Entry[a]	Catalyst	Yield[b] (%)	Entry[a]	Catalyst	Yield[b] (%)
1[c]	$In(OTf)_3$	Trace	9	$\mathbf{A_3}$	31
2[d]	CuCl	14	10	$\mathbf{A_4}$	44
3	HOTf	Trace	11	$\mathbf{A_5}$	45
4	*p*-TsOH	Trace	12	$\mathbf{A_6}$	33
5	$PhCO_2H$	36	13	$\mathbf{B_1}$	50
6	BINOL	52	14	$\mathbf{B_2}$	50
7	$\mathbf{A_1}$	59	15	$\mathbf{C_1}$	31
8	$\mathbf{A_2}$	23	16	$\mathbf{C_2}$	49

[a] On a 0.1 mmol scale. [b] Isolated yield. [c] **4** and **5** were obtained in 73% and 21% yield, respectively. [d] 56% of **4** and trace amount of **5**.

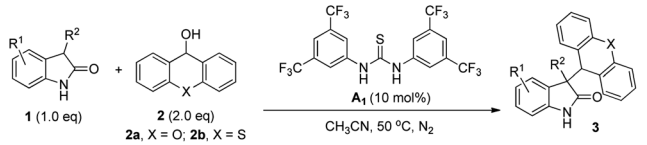
Table 2 Solvent screening and condition optimization



Entry[a]	Solvent	*X*	Temp. (°C)	Time (h)	Yield[b] (%)
1	$ClCH_2CH_2Cl$	1.2	50	15	65
2	THF	1.2	50	15	63
3	Toluene	1.2	50	15	65
4	DMF	1.2	50	15	11
5	CH_3CO_2Et	1.2	50	15	78
6	Acetone	1.2	50	15	66
7	CH_3NO_2	1.2	50	2	68
8	CH_3CN	1.2	50	6	77
9	CH_3CN	1.2	70	4	70
10[c]	CH_3CN	1.2	50	6	81
11[c]	CH_3CN	1.5	50	5	85
12[c]	CH_3CN	2.0	50	5	88

[a] On a 0.1 mmol scale. [b] Isolated yield. [c] Under N_2 atmosphere.

Table 3 Substrate scope



Entry[a]	1	2	Time (h)	3	Yield[b] (%)
1	**1a**: R^1 = H, R^2 = Ph	**2a**	5	**3a**	81
2	**1b**: R^1 = 5-F, R^2 = Ph	**2a**	22	**3b**	76
3	**1c**: R^1 = 5,7-Br, R^2 = Ph	**2a**	22	**3c**	83
4	**1d**: R^1 = 5,7-methyl, R^2 = Ph	**2a**	12	**3d**	80
5	**1e**: R^1 = H, R^2 = 4-FC_6H_4	**2a**	18	**3e**	89
6	**1f**: R^1 = H, R^2 = 4-BrC_6H_4	**2a**	18	**3f**	75
7	**1g**: R^1 = H, R^2 = 4-MeC_6H_4	**2a**	18	**3g**	86
8	**1h**: R^1 = H, R^2 = 4-$CF_3C_6H_4$	**2a**	9	**3h**	91
9	**1i**: R^1 = H, R^2 = 2-thiophenyl	**2a**	24	**3i**	65
10	**1j**: R^1 = 5-Br, R^2 = 2-naphthyl	**2a**	12	**3j**	82
11	**1k**: R^1 = H, R^2 = Bn	**2a**	22	**3k**	65
12	**1l**: R^1 = 5-Br, R^2 = Me	**2a**	24	**3l**	85
13	**1a**: R^1 = H, R^2 = Ph	**2b**	18	**3m**	79
14	**1k**: R^1 = H, R^2 = Bn	**2b**	24	**3n**	63
15	**1l**:R^1 = 5-Br, R^2 = Me	**2b**	24	**3o**	79

[a] On a 0.25 mmol scale. [b] Isolated yield.

process by using some typical chiral thiourea catalysts, but no enantiomeric excess was observed.[18]

To investigate the role of thioureas to catalyze this reaction, the ESI-MS analysis of the reaction process was undertaken.[19] Interestingly, the interaction of thioureas with 3-phenyl oxindole **1a** was confirmed by ESI-MS/MS analysis. For example, a characteristic signal $[\mathbf{1a} + \mathbf{A_5} + Na]^+$ consistent with the complex of oxindole **1a** and thiourea $\mathbf{A_5}$ was observed at *m*/*z* 460 (A, Fig. 1), which was further confirmed by the CID fragmentation pattern of the ion *m*/*z* 460 obtained from an ESI-MS/MS (positive mode) experiment (B, Fig. 1). The high resolution mass data of the detected complex was as follows: calculated for $C_{27}H_{23}N_3Na_1O_1S_1$ 460.1454; found 460.1439; with an error of 3.25 ppm. Considering the role of thiourea catalysts is generally believed to activate the electrophilic reaction partners through the hydrogen-bonding interaction, this finding is very interesting, suggesting that the thiourea might activate the nucleophile for the reaction, which is rarely reported.[3]

Based on this information, we initially proposed a dual role of the thiourea catalyst to promote this reaction, as shown in Scheme 1. The interaction of 3-substituted oxindole **1** with thiourea $\mathbf{A_5}$ lead to the oxindole–hydroxindole tautomerization, which might form a reactive intermediate (i); on the other hand, the interaction of the thiourea and xanthydrols might facilitate the formation of carbocation intermediate (ii). Accordingly, both intermediates (i) and (ii) readily reacted with each other to give the desired product **3** and regenerate the thiourea catalyst.

In conclusion, we have reported a highly efficient thiourea catalyzed alkylation of both unprotected 3-aryl and 3-alkyl oxindoles using xanthydrols. Initial investigation of the reaction mechanism by ESI-MS analysis reveals the interaction of the

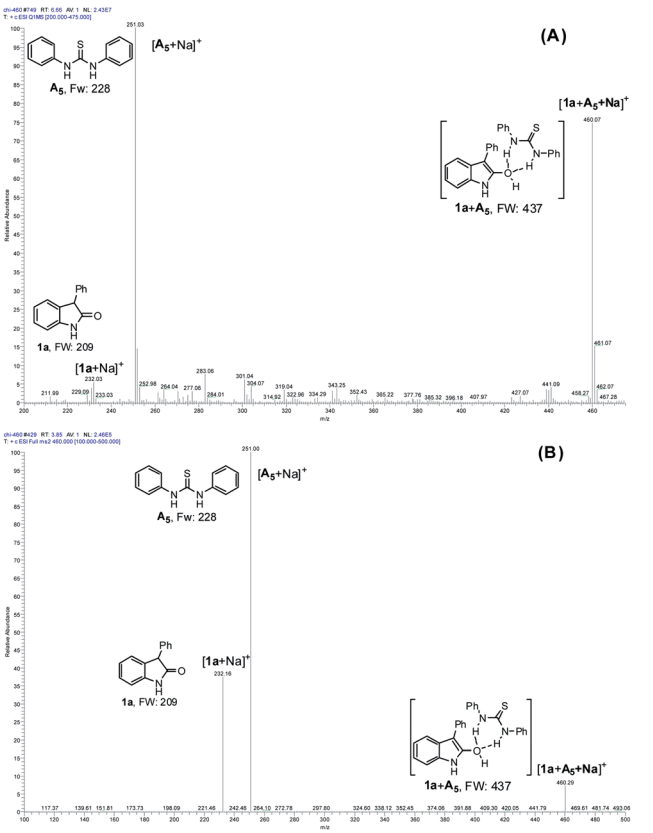


Fig. 1 (A) ESI-MS spectrum (positive mode) of the interaction between 3-phenyl oxindole **1a** and thiourea $\mathbf{A_5}$. (B) ESI-MS/MS spectrum for CID of $[\mathbf{1a} + \mathbf{A_5} + Na]^+$ at *m*/*z* 460 with a collision energy of 10 eV.

thiourea with 3-substituted oxindole, which might facilitate the oxindole–hydroxindole tautomerization for the alkylation. The scope and limitation of this methodology, the mechanism study and the development of asymmetric version is now in progress in our laboratory.

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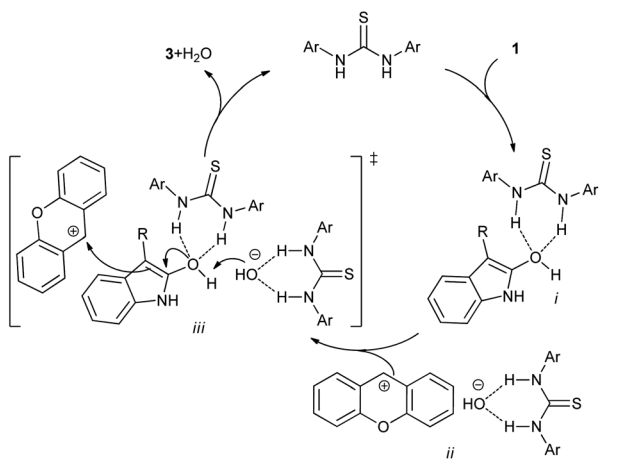

Scheme 1 Proposed reaction mechanism.

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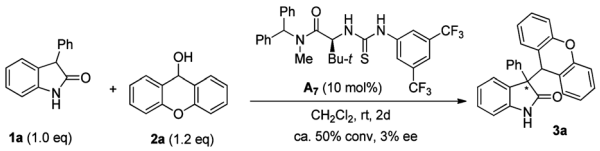

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