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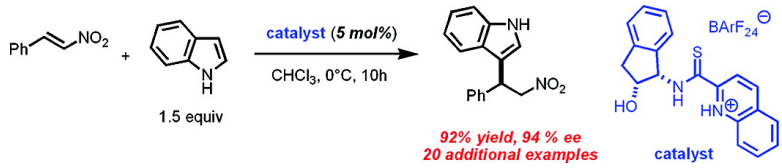

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Catalytic Enantioselective Additions of Indoles to Nitroalkenes

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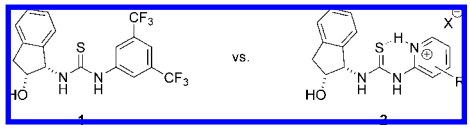
Small molecules capable of activating substrates through hydrogen bonding (HB) interactions have become a focal point of attention in the area of enantioselective catalysis.[1] Urea and thiourea containing compounds (e.g., **1**) are among the most prominent HB catalysts and have been used successfully in a remarkable variety of reactions. A factor that is impacting the development of new transformations is the activity of these HB catalysts, ultimately affecting parameters such as catalyst loading, reaction time, and the substrate scope for a given reaction. Previous efforts in preparing more active (acidic) (thio)urea catalysts have focused on *N*-tosyl[2] and *N*-sulfinyl[3] (thio)urea variants. Other approaches have centered around protonated catalysts[4] such as amidinium,[5] ammonium,[6] guanidinium,[7] quinolinium,[8] and pyridinium[9] species.[10] Here we report newly designed protonated catalysts and their application to highly enantioselective additions of indoles to nitroalkenes.[11,12]

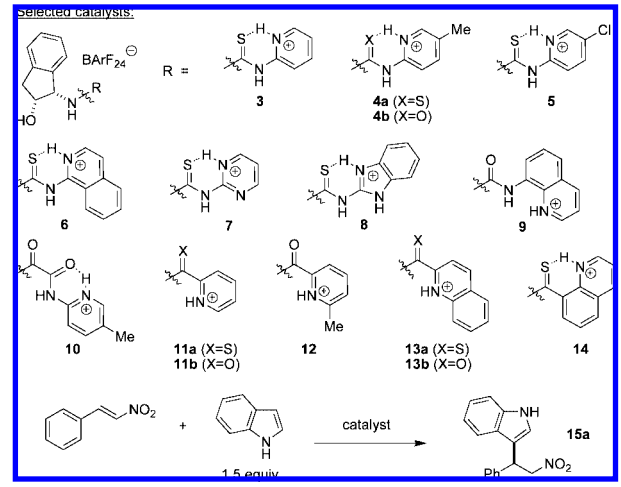


The impetus for this study was to identify new catalysts that are significantly more active than those previously reported and to do so with minimal perturbation of the overall catalyst structure. To this end, we evaluated structural modifications of **1**, a catalyst that has previously been used for enantioselective additions of indoles to nitroalkenes[11a] as well as for other transformations.[13] We hypothesized that a more active (acidic)[14] catalyst may be generated by replacing the commonly used 3,5-bis-trifluoromethylphenyl group with a protonated 2-pyridine substituent (e.g., **2**). The pyridinium subunit is expected to engage in an intramolecular N−H--S HB interaction,[15] analogously to the C−H--S HB interaction involving the 3,5-bis-trifluoromethylphenyl group,[16] resulting in structurally similar catalysts.

Indeed, significant rate acceleration and slight improvement in enantioselectivity were observed for the addition of indole to *β*-nitrostyrene when using catalyst **3** in place of **1** (Table 1, entries 1 and 2).[17] Electronic and structural variations of the pyridine subunit revealed the more acidic thiourea **5** as a more active and selective catalyst.[14] Pyrimidine and benzimidazole containing catalysts **7** and **8** proved to be inferior. Chloroform provided the highest level of enantioselectivity for catalyst **5** among the solvents tested.[18]

In an effort to develop a more enantioselective process, we subsequently explored alternative catalyst modifications. Catalyst **9**, in which intramolecular HB to the urea subunit would require a seven-membered ring, provided product with the same level of enantioselectivity as compared to **3**. "Insertion" of an additional carbonyl group resulted in the unselective catalyst **10**, whereas "removal" of the NH moiety adjacent to the pyridine ring provided a much more selective catalyst (**11a**). We speculated that this latter modification would result in direct participation of the pyridinium moiety into substrate binding.[19] Variation of this structural motif led to the identification of the highly efficient quinolinium thioamide catalyst **13a**. Its constitutional isomer **14**, in which an intramolecular N−H--S HB interaction is likely, proved to be completely ineffective. In all cases studied, substitution of sulfur for oxygen resulted in less active and/or selective catalysts. Using the optimal catalyst **13a**,[20] an effective rate acceleration of more than 280-fold as compared to catalyst **1** was achieved through variation of reaction molarity and catalyst loading (compare entries 23 and 24).

Table 1. Optimization of Reaction Parameters[a]



entry	catalyst (mol %)	solvent	concn [M]	time [h]	ee [%]
1	**1** (20)	CH_2Cl_2	0.25	192	36
2	**3** (20)	CH_2Cl_2	0.25	3	46
3	**4a** (20)	CH_2Cl_2	0.25	4	46
4	**4b** (20)	CH_2Cl_2	0.25	5	46
5	**5** (20)	CH_2Cl_2	0.25	2	56
6	**6** (20)	CH_2Cl_2	0.25	6	43
7	**7** (20)	CH_2Cl_2	0.25	26	25
8	**8** (20)	CH_2Cl_2	0.25	5	40
9	**5** (20)	PhMe	0.25	2	58
10	**5** (20)	$PhCF_3$	0.25	3	56
11	**5** (20)	$CHCl_3$	0.25	3	60
12	**5** (20)	THF	0.25	96[b]	5
13	**5** (20)	EtOAc	0.25	96[c]	5
14	**9** (20)	$CHCl_3$	0.25	8	46
15	**10** (20)	$CHCl_3$	0.25	9	0
16	**11a** (20)	$CHCl_3$	0.25	5	80
17	**11b** (20)	$CHCl_3$	0.25	6	72
18	**12** (20)	$CHCl_3$	0.25	12	50
19	**13a** (20)	$CHCl_3$	0.25	1	90
20	**13b** (20)	$CHCl_3$	0.25	2	84
21	**14** (20)	$CHCl_3$	0.25	50	9
22	**13a** (10)	$CHCl_3$	0.5	2	90
23	**13a** (5)	$CHCl_3$	1	2	86
24	**1** (20)	$CHCl_3$	1	144	35

[a] Reactions were performed at rt on a 0.25 mmol scale and were run to full conversion as judged by TLC analysis. The enantiomeric excess was determined by HPLC analysis. The active catalysts were prepared in situ; see Supporting Information for details. [b] 55% conversion. [c] 80% conversion.

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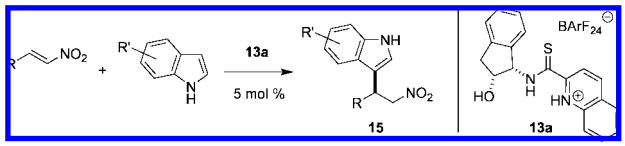
Table 2. Scope of the Reaction[a]

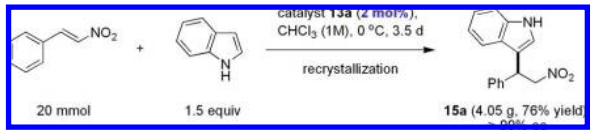


entry	R	R′	product	time [h]	yield [%]	ee [%]
1	Ph	H	**15a**	10	92	94
2[b]	Ph	5-MeO	**15b**	36	84	98
3	Ph	5-Br	**15c**	16	96	95
4	Ph	6-Cl	**15d**	30	90	91
5	4-MeO-C_6H_4	H	**15e**	22	94	90
6	4-Me-C_6H_4	H	**15f**	10	95	91
7	4-Cl-C_6H_4	H	**15g**	8	96	93
8	4-Br-C_6H_4	H	**15h**	6	91	93
9	3-Br-C_6H_4	H	**15i**	5	90	93
10	3-MeO-C_6H_4	H	**15j**	16	94	92
11[b]	2-Cl-C_6H_4	H	**15k**	12	90	94
12	2,3-$(MeO)_2$-C_6H_3	H	**15l**	20	90	90
13	3,4-OCH_2O-C_6H_3	H	**15m**	19	90	90
14[b]	1-naphtyl	H	**15n**	36	88	90
15	2-naphtyl	H	**15o**	8	91	97
16	2-furyl	H	**15p**	2	88	91
17	2-thienyl	H	**15q**	7	82	90
18[c]	*n*-C_5H_{11}	H	**15r**	40	86	91
19[c]	$CH_2CH(Me)_2$	H	**15s**	90	90	90
20[c]	$CH(Me)_2$	H	**15t**	90	92	94
21[d]	CO_2Et	H	**15u**	16	80	95

[a] Reactions were performed on a 1 mmol scale using 1.5 equiv of indole and 5 mol% of preformed catalyst **13a** in $CHCl_3$ (1 M) at 0 °C. The enantiomeric excess was determined by HPLC analysis. [b] Reactions were performed at −30 °C. [c] Reactions were performed with 10 mol% of preformed catalyst **13a** in $CHCl_3$ (0.5 M) at −30 °C. [d] Reaction was performed at −60 °C.

The scope of the reaction is summarized in Table 2. A range of substrates gave rise to the formation of products **15** in high yields and ee's when performing the reaction under the previously optimized conditions and slightly lower temperature (0 °C). Various substituted indoles, differently substituted electron-rich and electron-poor aromatic nitroalkenes, and heteroaromatic nitroalkenes were readily accommodated. Some substrates required the reactions to be performed at −30 °C to yield products with >90% ee (entries 2, 11, and 14). Aliphatic nitroalkenes were less reactive and gave products with reduced ee's under standard conditions. However, using 10 mol% of catalyst at −30 °C allowed for converting these more challenging substrates to products with high levels of enantioselectivity. The highly reactive ethyl 3-nitroacrylate gave rise to product **15u** in excellent enantioselectivity for a reaction performed at −60 °C.

Scheme 1



A large scale experiment with 2 mol% of **13a** was performed to test the utility of the new catalyst (Scheme 1). While a somewhat prolonged reaction time was required, product **15a** was isolated in good yield and with excellent enantioselectivity following a single recrystallization.

In summary, we have introduced a new design principle that provides access to more active thiourea catalysts. Highly enantioselective additions of indoles to nitroalkenes were achieved with the new quinolinium thioamide catalyst **13a**. The new catalysts are currently being evaluated in a number of other transformations.

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Supporting Information Available: Additional discussion, experimental procedures, and characterization data for all new compounds including X-ray structures of **15h**, the precatalyst of **13a**, and a model catalyst. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) $BArF_{24}^-$ = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate. The use of other counteranions such as trifluoroacetate, chloride, triflate, tetrafluoroborate, and hexafluoroantimonate resulted in catalysts of significantly lower activities.

(18) Catalysts derived from a number of other readily available aminoalcohols gave rise to lower enantioselectivities.

(19) See Supporting Information for additional discussion and X-ray crystal structure of a model catalyst.

(20) Similar to what was observed for **5**, catalyst **13a** performed best in $CHCl_3$ as compared to CH_2Cl_2, PhMe, $PhCF_3$, THF, and EtOAc.

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