Asymmetric Synthesis

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Catalytic Enantioselective Friedel–Crafts Alkylation of Indoles with Nitroalkenes by Using a Simple Thiourea Organocatalyst**

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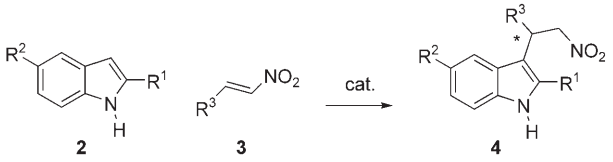
The addition of aromatic substrates to electron-deficient alkenes, which in many respects may be considered a Friedel–Crafts type alkylation, is a key reaction in synthetic organic chemistry for the formation of new C–C bonds.[1] Catalytic, enantioselective versions of this fundamental transformation have been reported,[2] which use metal-based chiral complex catalysts[3] or an imidazolidinone organocatalyst.[4] Both catalysts are capable of activating α,β-unsaturated carbonyl compounds, through a Lewis acid/Lewis base interaction with the carbonyl moiety in the former case, or through the formation of an iminium ion intermediate in the latter case. In sharp contrast with these remarkable achievements in the enantioselective Friedel–Crafts alkylation of aromatic substrates with α,β-unsaturated carbonyl compounds, to the best of our knowledge there are no reports in which nitroalkenes are employed. Nevertheless nitroalkenes are very attractive Michael acceptors,[5] since the nitro moiety is a strong electron-withdrawing group[6] that can be readily transformed into a range of different functionalities.[7]

The double hydrogen-bonding motif is becoming a powerful tool in organocatalysis for the activation of carbonyl groups and related compounds through weak hydrogen-bond interactions.[8] Considering the various molecular scaffolds that have proved effective as bidentate hydrogen-bond donors, urea- and thiourea-derived catalysts are certainly amongst the most competent structures,[9] and these are useful for many enantioselective transformations.[10] Accordingly, we have recently reported[11] the Friedel–Crafts alkylation of aromatic and heteroaromatic compounds with nitroalkenes, which are activated by the bidentate hydrogen-bonding motif present in the bis[3,5-bis(trifluoromethyl)phenyl]thiourea first developed by Schreiner for the Diels–Alder reaction.[9b,c]

Herein we present our results on the use of simply obtainable thiourea organocatalysts for the first catalytic enantioselective Friedel–Crafts alkylation of indoles **2** with nitroalkenes **3** (Scheme 1). The indole skeleton is considered

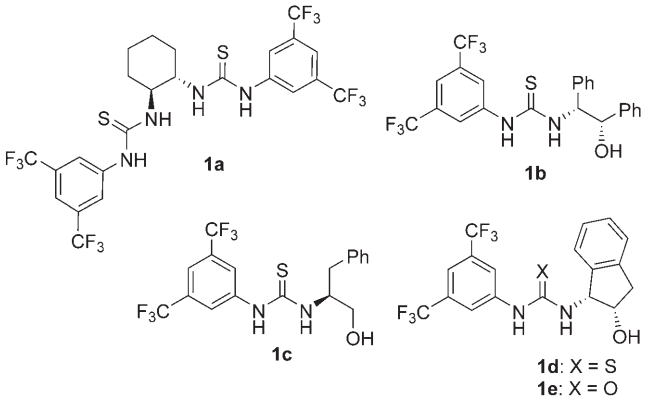


2 3 4

Scheme 1. Addition of indole **2** to *trans*-β-nitrostyrene **3** to give access to optically active 2-indolyl-1-nitro derivatives **4**.

to be one of the "privileged" structures in pharmaceutical chemistry,[4b,12] and the present method provides an easy and practical access to optically active 2-indolyl-1-nitro derivatives **4**. Taking into consideration the synthetic versatility of the nitro group, these compounds are useful intermediates for the synthesis of molecules of biological interest, such as tryptamines[13] and 1,2,3,4-tetrahydro-β-carbolines,[14] containing the indole framework in their structures.

The addition of indole **2a** to *trans*-β-nitrostyrene **3a** was used as the test reaction to explore the feasibility of the enantioselective Friedel–Crafts alkylation of indoles with nitroalkenes catalyzed by chiral thiourea- and urea-based derivatives. Besides the known C_2-symmetric bis-thiourea **1a**,[10c] we prepared and screened catalysts **1b–e**, which were easily obtained in one step and in nearly quantitative yields from the coupling reaction between 3,5-bis(trifluoromethyl)-phenyl isothiocyanate or isocyanate and the corresponding amino alcohols, both of which are commercially available. All



four thiourea-based organocatalysts **1a–d** were able to increase the reactivity of *trans*-β-nitrostyrene **3a** in the Friedel–Crafts alkylation reaction with indole **2a**, performed at room temperature in toluene (Table 1, entries 2–5), with

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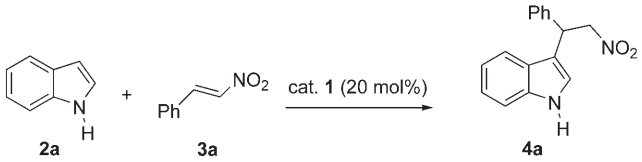
Table 1: Catalytic enantioselective Friedel–Crafts reaction of indole **2a** with *trans*-β-nitrostyrene **3a** in the presence of catalysts **1a–e** under different reaction conditions.[a]



Entry	Catalyst	Solvent	T [°C]	t [h]	Conversion [%][b]	*ee* [%][c]
1	–	toluene	20	65	17	–
2	**1a**	toluene	20	64	40	7
3	**1b**	toluene	20	64	63	13
4	**1c**	toluene	20	45	41	13
5	**1d**	toluene	20	60	>95	35
6	**1e**	toluene	20	118	23	25
7	**1d**	THF	20	110	74	27
8	**1d**	CH_2Cl_2	20	66	>95	48
9	**1d**	CH_2Cl_2	−24	72	92	85

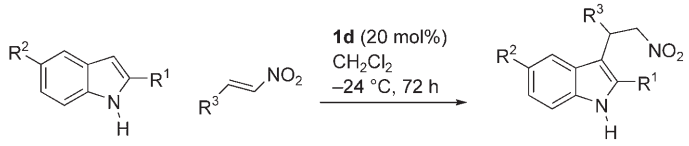
[a] Experimental conditions: to a solution of *trans*-β-nitrostyrene **3a** (0.1 mmol) and catalyst **1** (0.02 mmol) in a solvent (100 μL), indole **2a** (0.15 mmol) was added. After the stated reaction time, the product was purified by preparative TLC. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Determined by chiral stationary phase HPLC (See Supporting Information).

respect to the noncatalyzed reaction (Table 1, entry 1). However, only catalyst **1d**, obtained from 3,5-bis(trifluoromethyl)-phenyl isothiocyanate and (1*R*,2*S*)-*cis*-1-amino-2-indanol, showed a moderate yet promising asymmetric induction, as the product **4a** was produced in 35% *ee* (Table 1, entry 5). Catalyst **1d** was also the most active in terms of conversion, the reaction being complete in less than 60 h; as predicted,[9c] the corresponding urea derivative **1e** gave much poorer conversion and lower enantioselectivity (Table 1, entry 6). We found that ethereal solvents such as THF had a negative influence on the activity of the catalyst **1d** (Table 1, entry 7), whereas the use of CH_2Cl_2 led to a slight improvement in the enantioselectivity, giving **4a** in 48% *ee* (Table 1, entry 8). Finally, we were pleased to find that cooling the reaction mixture to −24°C had a remarkable positive effect on the enantioselectivity; the product **4a** was obtained in 85% *ee* while good levels of conversion were maintained (Table 1, entry 9).

We next explored the scope of this new enantioselective Friedel–Crafts alkylation of indoles with nitroalkenes, under the optimized reaction conditions (Table 2). We first tested a few indoles **2a–d** bearing different substituents in the reaction with *trans*-β-nitrostyrene **3a** catalyzed by **1d**.[15] Whereas the reaction of indole **2a** afforded the corresponding product **4a** in good yield and optical purity (Table 2, entry 1), when performed at −24°C, the Friedel–Crafts alkylation of electron-rich 2-methylindole **2b** and 5-methoxyindole **2c** proceeded at a reasonable reaction rate even at lower temperatures, furnishing the corresponding derivatives **4b** and **4c** in satisfactory yields and enantioselectivities at −45°C (Table 2, entries 2 and 3). Unfortunately, an electron-withdrawing substituent such as chlorine in the 5-position of the indole ring in **3d** caused a considerable decrease in the yield of **4d**, though the enantioselectivity was only moderately lowered (Table 2, entry 4). The generality of the reaction was further demonstrated by variation of the nitroalkene partner. Nitroalkenes **3b** and **3c**, bearing heteroaromatic groups, reacted smoothly with indole **2a** affording the corresponding products **4e** and **4f** in good yields and moderate enantioselectivities (Table 2, entries 5 and 6). Finally we tested nitroalkenes bearing aliphatic side chains such as **3d** and **3e**, and both gave good results in terms of enantioselectivity as the expected 2-indolyl-1-nitro derivatives **4g** and **4h** were produced in 83% and 81% *ee*, respectively (Table 2, entries 7 and 8), although the yield of the reaction turned out to be rather poor in the case of the more hindered isopropyl-substituted nitroalkene **3e**.[16]

The high synthetic potential of the present asymmetric transformation was then demonstrated by the straightforward conversion of the optically active product **4a** into highly valuable compounds such as tryptamine **5** and 1,2,3,4-tetrahydro-β-carboline **7**. As shown in Scheme 2, reduction

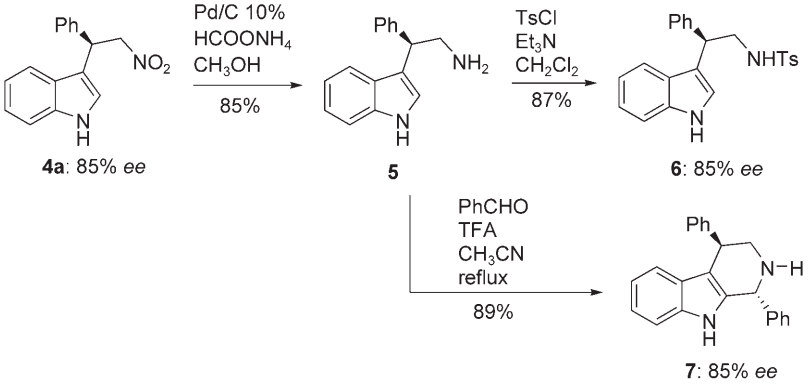
Table 2: Friedel–Crafts alkylation of indoles **2a–d** with nitroalkenes **3a–d** catalyzed by thiourea **1d**.[a]



Entry	Indole	R^1	R^2	Nitroalkene	R^3	Product	Yield [%][b]	*ee* [%][c]
1	**2a**	H	H	**3a**	Ph	**4a**	78	85
2	**2b**	Me	H	**3a**	Ph	**4b**	82[d]	74[d]
3	**2c**	H	OMe	**3a**	Ph	**4c**	86[d]	89[d]
4	**2d**	H	Cl	**3a**	Ph	**4d**	35[e]	71[e]
5	**2a**	H	H	**3b**	2-furyl	**4e**	88	73
6	**2a**	H	H	**3c**	2-thienyl	**4f**	70	73
7	**2a**	H	H	**3d**	*n*-pentyl	**4g**	76	83
8	**2a**	H	H	**3e**	*i*Pr	**4h**	37[f]	81[f]

[a] Experimental conditions: Indole **2** (0.15 mmol) was added to a solution of nitroalkene **3** (0.1 mmol) and catalyst **1d** (0.02 mmol) in CH_2Cl_2 (100 μL), cooled to −24°C. After 72 h, the product was isolated by flash chromatography. [b] Yield of isolated product. [c] Determined by chiral stationary phase HPLC (see Supporting Information). [d] Reaction performed at −45°C. [e] Reaction time: 142 h. [f] Reaction time: 96 h.

of the nitro group of **4a** proceeded under mild reaction conditions[17] giving tryptamine **5**, which could be isolated in good yield as the corresponding sulfonamide derivative **6**. Alternatively, crude **5** could be directly subjected to Pictet–Spengler cyclization[18] with benzaldehyde to furnish a previously unreported 1,4-diphenyl-substituted 1,2,3,4-tetrahydro-β-carboline as a 91:9 mixture of diastereoisomers. The highly prevailing 1,4-*trans* isomer **7** was isolated in good yield and in diastereomerically pure form after chromatography on silica gel (Scheme 2). All reactions occurred without any loss in the enantiomeric enrichment of the products, and the relative stereochemistry of **7** was tentatively assigned as 1,4-

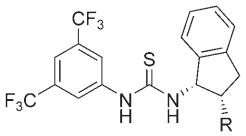


Scheme 2. Conversion of the optically active product **4a** into valuable products such as tryptamine **5** and 1,2,3,4,-tetrahydro-β-carboline **7**. Ts = toluene-4-sulfonyl, TFA = trifluoroacetic acid.

trans by means of NOE experiments. Furthermore, the formation of the sulfonamide derivative **6** allowed the assignment of the absolute configuration of the catalytic product **4a** as 2*R*, from the comparison of its optical rotation and HPLC retention time with those of an authentic sample of *ent*-**6** (in 94% *ee*), which was synthesized by the ring-opening at the benzylic position of (2*S*)-2-phenyl-1-*p*-toluenesulfonyl aziridine[19] with indole **2a** promoted by $LiClO_4$.[20]

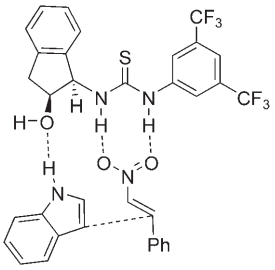
The ability of thiourea **1d** to promote the Friedel–Crafts additions of indoles **2** to nitroalkenes **3** may be interpreted on the basis of the reversible formation of a complex involving a double hydrogen bond between the thiourea hydrogen atoms and the two oxygen atoms of the nitroalkene. The recognition of the nitro group by urea moieties in solution as well as in the solid phase, leads to crystal structures that clearly present this type of interaction.[21] To gain some insight into the substrate–catalyst interactions that lead to the observed stereoselectivity, we prepared catalyst **1f**, in which the hydroxy group was protected by a sterically hindering trimethylsilyl group, and thiourea **1g**, which lacks the alcoholic function. Surprisingly, both catalysts showed poor performances in the reaction between indole **2a** and *trans*-β-nitrostyrene **3a**, not only with regard to the enantioselectivity but also in terms of the catalyst activity (Scheme 3).

On these grounds, but considering also the poor asymmetric induction observed in the reaction of *N*-methyl indole,[15] we envisioned that catalyst **1d** would act in a bifunctional fashion. Therefore, whereas the two thiourea hydrogen atoms activate the nitroalkene, the free alcoholic function will interact with the indolic proton through a weak hydrogen bond, directing the attack of the incoming nucleophile on the *Si* face of the nitroolefin as depicted in Scheme 4.



	Yield **4a**	*ee*
1d: R = OH	78%	85%
1f: R = $OSi(CH_3)_3$	18%	39%
1g: R = H	15%	0%

Scheme 3. The hydroxy-protected catalyst **1f** and the thiourea **1g** lacking the alcoholic function and their performance in the Friedel–Crafts alkylation of **2a** with **3a** to give **4a**.



Scheme 4. Possible bifunctional mode of action of the catalyst **1d**.

In conclusion, we have developed the first catalytic, enantioselective Friedel–Crafts alkylation of indoles **2** with nitroalkenes **3**, which provides optically active 2-indolyl-1-nitro derivatives **4** in fairly good yields and enantioselectivities. The reaction is efficiently catalyzed by the simple thiourea-based organocatalyst **1d**, which can be easily accessed in both enantiomeric forms from commercially available materials. The extremely simple operational procedure and the high synthetic versatility of the products render this new approach highly appealing for the synthesis of optically active target compounds such as tryptamines and 1,2,3,4-tetrahydro-β-carbolines.

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[16] The yield of the Friedel–Crafts alkylation of **2a** with **3e** could be considerably increased by simply performing the reaction at higher temperatures, and only a moderate loss of enantioselectivity in the product **4h** occurs (0°C, 76% yield, 72% *ee*).
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