Dianhydrohexitols: new tools for organocatalysis. Application in enantioselective Friedel-Crafts alkylation of indoles with nitroalkenes

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Abstract
A series of hydrogen bonding organocatalysts was synthesized from dianhydrohexitol and was used for the first time in organocatalysis for Friedel-Crafts alkylation of indoles with nitroalkenes. Moderate yields and enantioselectivities were achieved.

Keywords: Organocatalysis, biomass, asymmetric catalysis, isomannide, isoidide, thiourea

Introduction

The use of small and metal-free homochiral organic molecules to catalyze enantioselective transformation, named organocatalysis, is a fascinating research area in asymmetric synthesis. In the past decade, it has attracted much attention and significant development has been achieved.[1-4] Among various types of organocatalysts, hydrogen bonding catalysts[5-8] have played an extremely important role. From them, urea- and thiourea-based organocatalysts have been widely used due to their strong activation of carbonyl and nitro groups through efficient double hydrogen bonding interactions.[8-10] The most commonly used catalysts are derived from trans-cyclohexyldiamine, 2,2'-binaphthyl, amino acids, or the cinchona alkaloids.[11-14] Although carbohydrate are very attractive starting material because of their availability and well defined stereocenters, only few thiourea organocatalysts derived from saccharide were used in asymmetric organocatalytic reactions, mainly for Mannich and aza-Henry reactions.[15-18]

As a part of our ongoing program devoted to asymmetric catalysis, we were interested in the development of new chiral ligands derived from dianhydrohexitols (isomannide, isosorbide and isoidide). Ligands derived from dianhydroglycitols have already been used in organometallic

catalysis to perform asymmetric Diels-Alder reactions,[19-22] nucleophilic addition to aldehyde,[23-24] hydrogen transfer reduction of prochiral ketones[25-28] and asymmetric hydrogenation of olefins.[29-30] However, to the best of our knowledge, none of them has been used in asymmetric organocatalysis.

Herein, we report our preliminary results concerning the design and the synthesis of new chiral thioureas derived from isoidide and isomannide and their evaluation as organocatalysts in enantioselective Friedel-Crafts alkylation of indoles with nitroalkenes.[31-41] The indole skeleton is considered to be one of the most useful moieties in pharmaceutical chemistry.[42-43]

Results and Discussion

A series of novel organocatalysts **1-5** derived from isomannide and organocatalyst **6** from isoidide have been synthesized (Figure 1). A similar synthetic route could be used, with the formation of the diamines **9** and **11** as key intermediates which were then transformed into their corresponding mono or dithioureas derivatives (Scheme 1 and 2 respectively). For organocatalyst **5**, a sulfonamide function was introduced on the amino group of the monothiourea **1.**
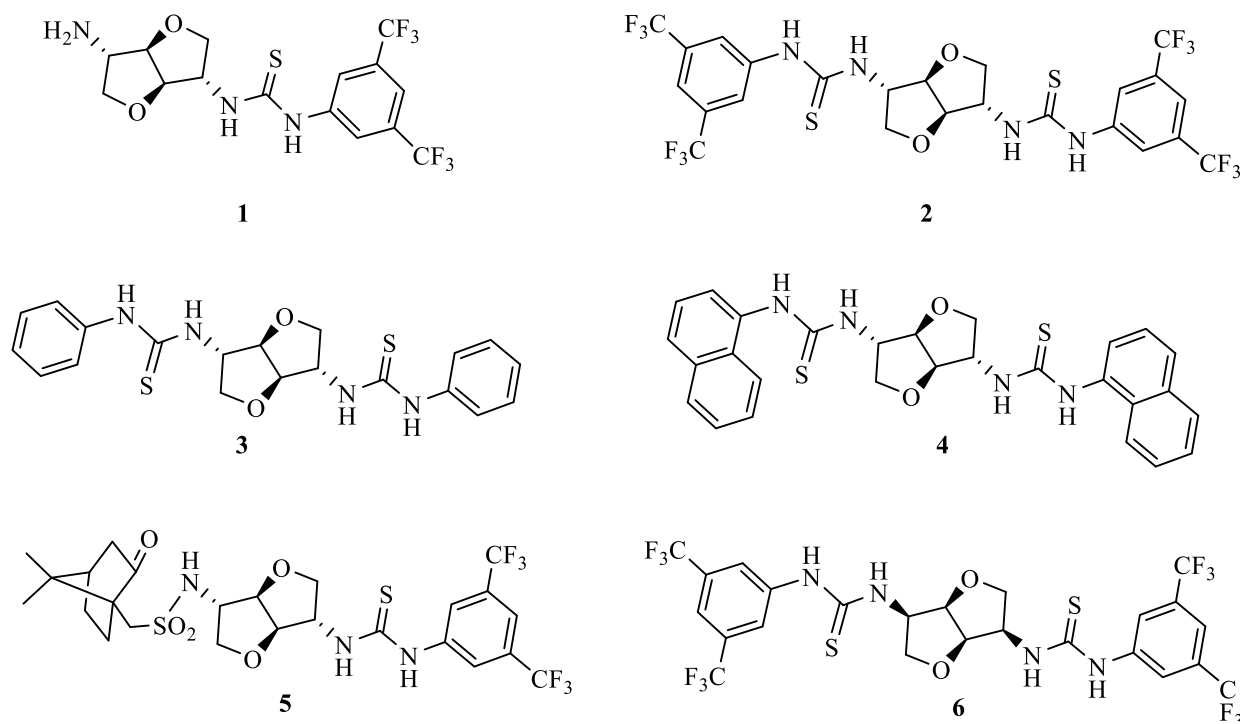

**Figure 1.** Hydrogen bonding organocatalysts.

The synthesis of diamine **9**[44] was initiated by the ditosylation of the hydroxyl groups of isomannide in the presence of a catalytic amount of DMAP leading to **7** in 91% yield.

Subsequently, the substitution of the two tosylated groups with sodium azide in DMF at 120 °C afforded diazide **8** in 77% yield which was then hydrogenated in almost quantitative yield to form the diamine **9** (Scheme 1). For the synthesis of diamine **11**, as the ditosylation of isoidide and the displacement of the two mesylated groups with sodium azide was unsuccessful,[19] the triflate was chosen as a leaving group. In the presence of Tf$_2$O, isoidide led to the corresponding triflate which was then used without further purification. The introduction of the azide groups was then performed to afford the diazide **10** in 26% yield over 2 steps (Scheme 2).

    Finally, the reaction of diamine **9** with 1 equivalent of 3,5-trifluoromethylphenyl isothiocyanate led to a mixture of the monothiourea **1** and the dithiourea **2** in 51% and 12% yield respectively. In the presence of 2 equivalents of isothiocyanate, diamine **9** was converted into the corresponding dithiourea catalysts **2**, **3**, **4** (Scheme 1) and diamine **12** into dithiourea **6** (Scheme 2) in good yield (> 80%). Catalyst **5**, presenting a thiourea and an amide function, was prepared in 64% yield, using monothiourea **1** and L-(-)-camphorsulfonyl chloride in basic conditions (Scheme 1).
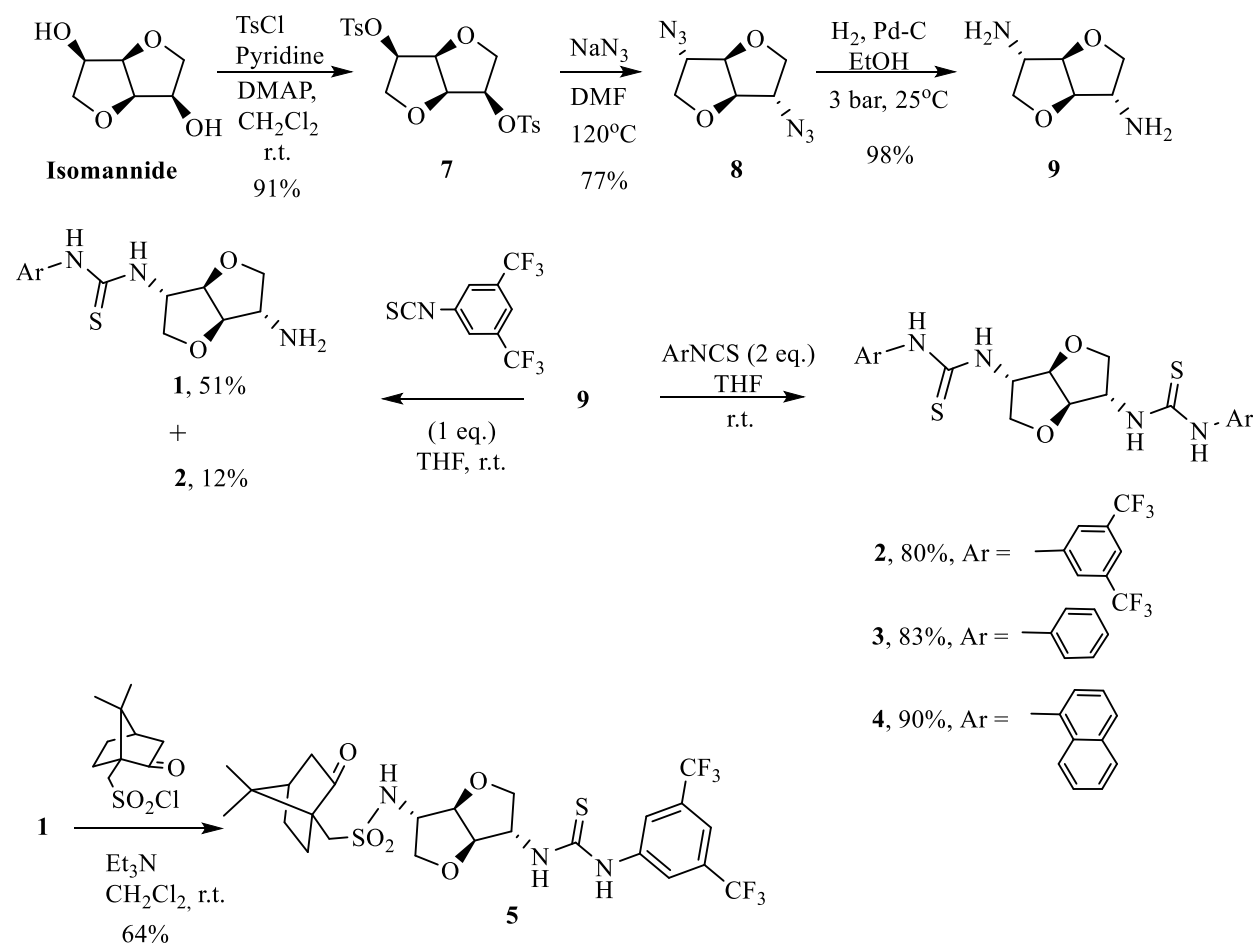
Scheme 1. Synthetic route for organocatalysts **1**-**5**.
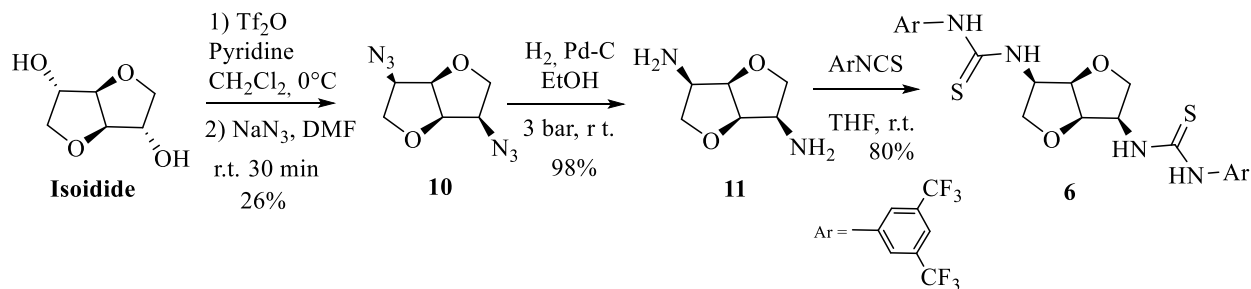
Scheme 2. Synthetic route for organocatalyst **6**.

With a series of organocatalysts in hand, we were interested to explore their potential as organocatalysts for enantioselective Friedel-Crafts alkylation of indoles with nitroalkenes Since the nitro group is a strong electron-withdrawing group, the nitroalkenes are very attractive for hydrogen-bond organocatalysis.

Our investigations started with the examination of the reaction between indole **12a** and *trans-β*-nitrostyrene **13a** in the presence of 20 mol% of the organocatalyst **2** in toluene. It was a rather slow reaction which resulted in 10% ee with moderate yield (Table 1, entry 1). Therefore, different solvents were screened in order to improve the yield and the enantioselectivity. The results are summarized in Table 1. As we have observed that the catalyst was not very soluble into toluene, we first performed the reaction in DMSO, DMF, MeCN, and EtOAc (Table 1, entries 2-5). It is worth mentioning that the reaction almost could not proceed in these solvents in which the organocatalyst **2** is perfectly soluble. It is probably due to the formation of a strong hydrogen bond interaction between the organocatalyst **2** and the solvent instead of interactions with the substrate. In chlorinated solvents, the reaction proceeded faster in CHCl₃ than in CH₂Cl₂ resulted in 75% and 20% yield respectively but, it was almost racemic (entries 6 and 7).

Although MeOH can form hydrogen bonding with both the organocatalyst and the substrate, it led to poor yielding Friedel-Crafts alkylation but without enantioselectivity (entry 8). With ethers as solvents (entries 9-12), Et₂O and *tert*-butyl methyl ether (MTBE) gave the best enantioselectivities (Table 1, entries 11 and 12). The better yield observed with MTBE is probably due to a better solubility of the organocatalyst **2** in MTBE than in Et₂O. From all the screened solvents, the best combination in term of yield and enantioselectivity was found with MTBE. Thus, this solvent was chosen in order to perform the other organocatalytic experiments. Recently, Herrera and co-workers reported that external Brønsted acids could enhance the efficiency of thiourea catalyst.[40] So we envisioned that higher enantioselectivity and reactivity might be achieved by using a suitable additive acids thus, we started to investigate the use of acid additives in this reaction.

Compared to the reaction performed without acid, the yield of the reaction is in general lower, probably due to a competition of the formation of a hydrogen bond between the catalyst and the substrate with the acid. It was observed that there is no correlation between yield, enantioselectivity and pKa value. Nevertheless, the pKa value and the nature of the acid additive, such as non-functionalized carboxylic acid or functionalized ones containing groups which are

not able to act as hydrogen bond donor find some correlation (Table 2, entries 2, 3, 7, 8). Moreover, an increase of the enantioselectivity was observed when the pKa decreased, ee reaching 37% and 39% with TCA and TFA (Table 2, entries 7 and 8). With D- and L-mandelic acid, no match or mismatch effect was observed and the chirality of the acid has no influence on the enantioselectivity; the same major isomer being formed (entries 4 and 5). Similar results have been found by Herrera et al.[40] This fact showed that chirality was preferentially controlled by the thiourea catalyst. The additive acids only activated the thiourea moiety rather than participating itself into the transition state. However, the use of sulfonic acid such as D-camphorsulfonic acid and *p*-TsOH, resulted in similar yields, but *p*-TsOH, due to strong acid character led to almost racemic product contrary to the D-camphorsulfonic acid (entries 6 and 9). Taking into account mainly the ee, we finally chose TCA as the best additive.

Table 1. Catalytic enantioselective Friedel-Crafts alkylation of indole **12a** with *trans-β*-nitrostyrene **13a** in different solvents[a]

Entry	Solvent	Yield (%)[b]	ee (%)[c]
1	toluene	30	10
2	DMSO	No reaction	-
3	DMF	No reaction	-
4	MeCN	trace	nd
5	EtOAc	trace	nd
6	CH_2Cl_2	20	<5
7	$CHCl_3$	75	<5
8	MeOH	29	<5
9	THF	trace	nd
10	Dioxane	26	14
11	Et_2O	29	30
12	MTBE	45	26

[a] Reaction conditions: **13a** (0.1 mmol), **12a** (2.0 equiv), solvent (0.4 mL), **2** (20 mol%). [b] Yield of product isolated after flash chromatography. [c] Determined by HPLC analysis using a Phenomenex® Lux 5μ cellulose-2 column.

   In order to determine the best organocatalyst, the reaction was performed at room temperature, in MTBE using 10 mol% of TCA and 20 mol% of different catalysts (Table 3). Compared to organocatalyst **2**, monothiourea **1** led to a similar yield, but without enantioselectivity (entries 1 and 2). This may be attributed to the lack of two hydrogen bonding functions. With phenyl thioureas **2**, **3** and **4** (entries 2-4), the best organocatalyst is always the compound **2**. The difference in behavior for thiourea **2** is probably due to the presence of the two CF_3 groups in 2 and 4 positions of the aromatic ring leading to an augmentation of the acidity of the hydrogen located on each thiourea function. Thus, the ability to form hydrogen bonding is enhanced and favored with organocatalyst **2**.

Table 2. Catalytic enantioselective Friedel-Crafts alkylation of indole **12a** with *trans-β*-nitrostyrene **13a** with different additives[a]
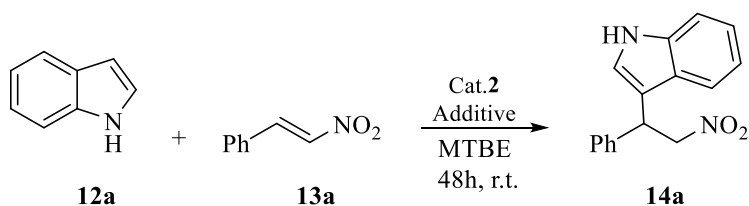
Entry	Additive (20 mol%)	pKa	Yield[b](%)	ee[c] (%)
1	-	-	45	26
2	AcOH	4.79	40	29
3	PhCOOH	4.21	29	30
4	L-Mandelic acid	3.41	29	31
5	D-Mandelic acid	3.41	30	31
6	D-camphorsulfonic acid	1.2	41	26
7	TCA	0.77	29	37
8	TFA	0.23	24	39
9	TsOH	-2.8	41	<5

[a] Reaction conditions: **13a** (0.1 mmol), **12a** (3.0 equiv), MTBE (0.4 mL), **2** (20 mol%), and TCA (20 mol%). [b] Yield of product isolated after flash chromatography. [c] Determined by HPLC analysis using a Phenomenex® Lux 5μ cellulose-2 column.

Table 3. Catalytic enantioselective Friedel-Crafts alkylation of indole **12a** with *trans-β-*nitrostyrene **13a** with different catalysts [a]
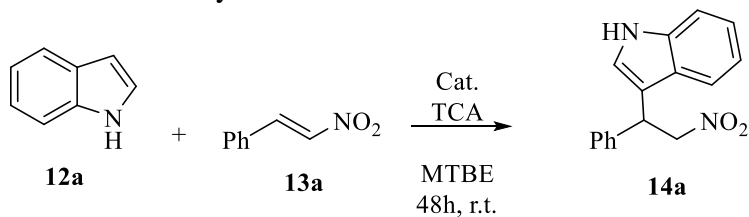
Entry	Catalyst	Yield (%)[b]	ee (%)[c]
1	**1**	29	<5
2	**2**	29	37
3	**3**	trace	nd
4	**4**	trace	nd
5	**5**	19	22
6	**6**	No reaction	-

[a] Reaction conditions: **13a** (0.1 mmol), **12a** (2.0 equiv), MTBE (0.4 mL), **1-6** (20 mol%) and TCA (20 mol%).[b] Yield of product isolated after flash chromatography. [c] Determined by HPLC analysis using a Phenomenex® Lux 5μ cellulose-2 column.

Surprisingly, with the dithiourea **6**, no reaction occurred. It was supposed that the proximity of the two thioureas groups in *endo* position prevents the intermolecular hydrogen bonding and favors the intramolecular ones (site-site interactions) (entry 6).

Besides, the effect of the loadings of the additive TCA, the concentration of the substrate and the TCA in the reaction mixture and the temperature were also examined (Table 4). A decrease in the concentration of TCA led to an increase of the yield, but the enantioselectivities were similar (entries 2-5). Nevertheless, similar results in terms of enantioselectivity and yield were found with 10 and 5 mol% TCA (Table 4, entries 4 and 5). A comparison with the experiment performed without TCA at room temperature shows that only 10 mol% TCA permits a slight increase in enantioselectivity and yield (Table 4 entries 1 and 4). Increasing the concentration of the substrate from 0.25N to 0.5N only led to an increase of the yield from 29% to 49% with a slight decrease of ee (entries 3 and 6). In opposite, a decrease of the concentration led to a significant decrease of the yield but the enantioselectivity was slightly improved (entries 7 and 8 *vs* entries 3 and 4). Using the conditions mentioned in entry 8, a longer reaction time permitted to increase the yield (entry 9). A similar enantioselectivity was observed if the reaction was performed at -10°C, but the yield decreased drastically from 43% to almost 15% (Table 4, entry 10).

Table 4. Optimization of the catalytic enantioselective Friedel-Crafts alkylation of indole **12a** with *trans-β*-nitrostyrene **13a**
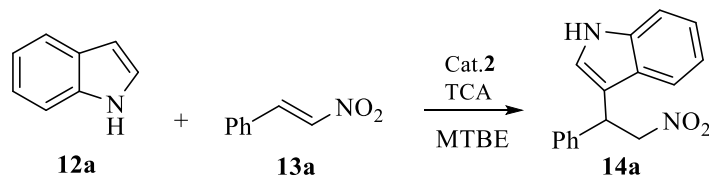
Entry	TCA (mol%)	TMBE	Time (h), T°C	Yield[a] (%)	ee[b] (%)
1	-	0.25N	48, rt	45	26
2	30	0.25N	48, rt	23	36
3	20	0.25N	48, rt	29	37
4	10	0.25N	48, rt	52	38
5	5	0.25N	48, rt	49	37
6	20	0.5N	48, rt	45	31
7	20	0.1N	48, rt	15	44
8	10	0.1N	48, rt	20	44
9	10	0.1N	168, rt	43	44
10	10	0.1N	168, -10 ºC	15	44

[a] Yield of product isolated after flash chromatography. [b] Determined by HPLC analysis using a Phenomenex® Lux 5μ cellulose-2 column.

Finally, with the optimized reaction conditions (Table 4, entry 9) we studied the influence of the electronic effects of the substituent located in the 5-position of the indole and on the *β*-nitrostyrene (Table 5). Compared to the reference reaction (entry 1), an electron-withdrawing atom such as bromine settled in the indole led to a drastic decrease in the reaction rate (5% yield entry 3) contrary to an electron-donating group such as methoxy group which has a good influence on the reaction rate but not on the enantioselectivity (entry 2).

For the reaction with different nitroalkenes bearing either electron-withdrawing groups or electron-donating groups located in the position 4 of the aromatic ring, the same range of yield and enantioselectivity were observed (Table 5, entries 4-7). On the contrary, the presence of a chlorine atom in position 2 led to lower yield and enantioselectivity (Table 5, entry 8).

Table 5. Catalytic enantioselective Friedel-Crafts alkylation of indole **12a-c** with nitroalkenes **13a-f** in the presence of thiourea catalyst **2**[a]
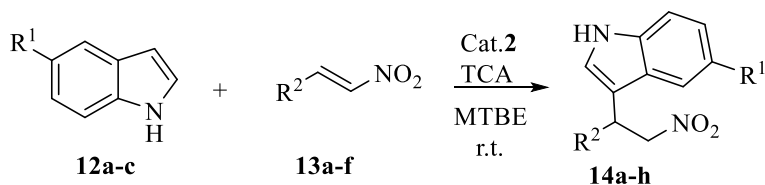
Entry	R^1	R^2	Product	Yield[b](%)	ee[c] (%)
1	H	Ph	**14a**	43	44 (*S*)[d]
2	MeO	Ph	**14b**	61	41 (*R*)[d]
3	Br	Ph	**14c**	5	48
4	H	4-Cl-Ph	**14d**	37	37 (*S*)[d]
5	H	4-F-Ph	**14e**	32	42
6	H	4-Me-Ph	**14f**	43	42 (*S*)[d]
7	H	4-MeO-Ph	**14g**	44	39 (*R*)[d]
8	H	2-Cl-Ph	**14h**	27	16

[a] Reaction conditions: **13a-f** (0.1 mmol), **12a-c** (2.0 equiv), MTBE (1.0 mL), **2** (20 mol%), and TCA (10 mol%). [b] Yield of product isolated after flash chromatography. [c] Determined by HPLC analysis using a Phenomenex® Lux 5μ cellulose-2 column. [d] Absolute configuration was determined by comparison of the optical rotation with the known compounds in the literature.[10a]

Conclusions

In conclusion, we have developed a new series of hydrogen bonding organocatalysts derived from isomannide and isoidide, used for the first time in organocatalysis. Moderate enantioselectivities and yields were achieved in Friedel-Crafts alkylations of indoles to nitroalkenes. Further investigations on its application to other enantioselective transformations are in progress.

Experimental Section

General. All experiments were carried out with anhydrous solvents in dried glassware. Commercially available materials (Aldrich or Fluka) were used without further purification. THF and CH_2Cl_2 were dried using a drying station. Flash chromatography was performed on MERCK silica gel (40-63 µm). Analytical TLCs were carried out on MERCK pre-coated silica gel 60 F254. Melting points were determined on a Reichert Thermoval apparatus and are uncorrected. Optical rotations were measured at the sodium D line with a 1-dm path length, 1-mL cell and

recorded using a Perkin-Elmer 343 polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance (200 or 400 MHz for ^{1}H, and 50 or 100 MHz for ^{13}C. NMR spectra are referenced to TMS as internal standard. FT-IR spectra were performed on a Nicolet AVATAR 370 DTGS Thermo Electron Corporation apparatus and band positions are given in cm$^-$1. High resolution mass spectra were recorded on a Waters Micromass® GCT Premier^{TM}.

Synthesis of catalysts 1-6
1,4:3,6-Dianhydro-2,5-di-*O*-(*p*-toluenesulfonyl)-D-mannitol. Under argon, to a stirred solution of isomannide (2.0 g, 13.7 mmol) in dry CH$_2$Cl$_2$ (14 mL) was added pyridine (5 mL) and DMAP (83.6 mg, 0.68 mmol). The reaction mixture was stirred at 0 ^{o}C, followed by an addition of *p*-toluenesulfonyl chloride (6.78 g, 35.4 mmol). After stirring at room temperature overnight, the reaction mixture was diluted with CH$_2$Cl$_2$ (10 mL), washed with an aqueous HCl solution (1N, 10 mL) then extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous MgSO$_4$ and concentrated under vacuum. The crude product was recrystallized with MeOH to afford **7** (5.68 g, 12.5 mmol, 91%) as a white solid. mp: 90.9-91.4 ^{o}C (lit.89-90 ^{o}C)[45], $[\alpha]_D^{20}$ + 91.0 (*c* 1.0, CHCl$_3$), ^{1}H NMR (200 MHz, CDCl$_3$) δ_H: 7.80 (4H$_{arom}$, dd, J_{HH} 8.0, 2.0 Hz, 4CH), 7.34 (4H$_{arom}$, dd, J_{HH} 8.0, 2.0 Hz, 4CH), 4.89-4.79 (2H, m, 2CH), 4.48-4.46 (2H, m, 2CH), 3.92 (2H, dd, J_{HH} 9.5, 6.8 Hz, CH$_2$), 3.72 (2H, dd, J_{HH} 9.5, 7.8 Hz, CH$_2$), 2.45 (6H, s, CH$_3$). ^{13}C NMR (50 MHz, CDCl$_3$) δ_c:145.3, 132.9, 129.9 and 127.9 (4C, phenyl), 79.9, 77.8 and 70.0 (3C, furan), 21.6 (1C, CH$_3$).
2,5-Diazido-2,5-dideoxy-1,4:3,6-dianhydro-L-iditol (80. To a stirred solution of ditosylate **7** (3.0 g, 6.6 mmol) in DMF (66 mL) was added sodium azide (1.7 g, 26.4 mmol). The reaction mixture was stirred for 3 h at 120 ^{o}C. Water (40 mL) was added and the mixture was extracted with diethyl ether (5 × 15 mL). The combined layers were dried over anhydrous MgSO$_4$ then concentrated under vacuum. The crude diazide was purified by column chromatography (cyclohexane/EtOAc, 5:1) to afford the product **8** (990 mg, 5.05 mmol, 77%) as a colorless liquid. $[\alpha]_D^{20}$ + 71.0 (*c* 2.0, CHCl$_3$), ^{1}H NMR (200 MHz, CDCl$_3$) δ_H: 4.63 (2H, s, 2CH), 4.07 (2H, dd, J_{HH} 3.8, 1.8 Hz, 2CH), 3.96 (2H, dd, J_{HH} 10.2, 1.8 Hz, CH$_2$), 3.89 (2H, dd, J_{HH} 10.2, 3.8 Hz, CH$_2$). ^{13}C NMR (50 MHz, CDCl$_3$) δ_c: 86.0, 71.8, 65.6.
2,5-Diamino-2,5-dideoxy-1,4:3,6-dianhydro-L-iditol (9). A suspension of diazide **8** (1.95 g, 9.95 mmol) and 10% Pd/C (1.06 g, 1.0 mmol) in EtOH (80 mL) was hydrogenated at 3 bar at 20 ^{o}C. After 12 h, the catalyst was filtered off and the solvent was removed under vacuum leading to the diamine **9** (1.4 g, 12.3 mmol, 98%) as a hygroscopic solid which was used whithout further purification. $[\alpha]_D^{20}$ + 18.0 (*c* 0.8, DMSO), ^{1}H NMR (200 MHz, DMSO-*d$_6$*) δ_H: 4.23 (2H, s, 2CH), 3.68 (2H, dd, J_{HH} 8.6, 4.5 Hz, 2CH), 3.41 (2H, dd, J_{HH} 8.6, 2.0 Hz, CH$_2$), 3.23 (2H, dd, J_{HH} 4.5, 2.0 Hz, CH$_2$), 1.57 (4H, brs, 2NH$_2$). ^{13}C NMR (100 MHz, DMSO-*d$_6$*) δ_c: 88.6, 74.5, 57.7.
2,5-Diazido-2,5-dideoxy-1,4:3,6-dianhydro-D-mannitol (10). Under argon, at 0 ^{o}C, to a solution of isoidide (465 mg, 3.18 mmol) and pyridine (1.6 mL, 16.0 mmol) in dry CH$_2$Cl$_2$ (10 mL) was added trifluoromethansulfonic anhydride (1.34 mL, 7.95 mmol) dropwise. After

completion of the addition, the reaction was stirred for another 15 minutes. The residue was then diluted with CH_2Cl_2, washed with an aqueous HCl solution (1N), water, saturated aqueous NH_4Cl solution and brine. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give crude ditriflate compound. This latter was directly dissolved in DMF (11 mL) and NaN_3 (434.3 mg, 6.68 mmol) was added. The reaction mixture was stirred for about 0.5 h at room temperature. Water (15 mL) was added and the mixture was extracted with diethyl ether (5 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum. The crude diazide was purified by column chromatography (cyclohexane/EtOAc, 4:1) to afford the product **10** (163.8 mg, 50%) as a colorless liquid. $[\alpha]_D^{20}$ + 298.5 (*c* 1.5, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$) δ_H: 4.71-4.66 (2H, m, 2CH), 4.08 (2H, dd, J_{HH} 7.7, 6.1 Hz, 2CH), 3.94-3.85 (2H, m, CH_2), 3.79 (2H, t, J_{HH} 7.7 Hz, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ_c: 83.3, 70.6, 62.3.

2,5-Diamino-2,5-dideoxy-1,4:3,6-dianhydro-D-mannitol (11). Following the same procedure as diamine **9**, the diazido compound **10** (286 mg, 1.46 mmol) led to the diamine **11** (200 mg, 1.39 mmol, 95%) as a hygroscopic slightly yellow solid which was used without further purification. $[\alpha]_D^{20}$ + 83.9 (*c* 0.75, CH_3OH). ^{1}H NMR (200 MHz, CD_3OD) δ_H: 4.41 (2H, dd, J_{HH} 3.2, 1.2 Hz, 2CH), 4.01 (2H, dd, J_{HH} 7.5, 7.5 Hz, 2CH), 3.38-3.54 (2H, m, CH_2), 3.30 (2H, m, CH_2). ^{13}C NMR (50 MHz, CD_3OD) δ_c: 84.7, 74.7, 57.2.

Synthesis of monothiourea 1. To a stirred solution of diamine **9** (72 mg, 0.5 mmol) in THF (8 mL) was slowly added isothiocyanate (136 mg, 0.5 mmol) in THF (2.5 mL). After stirring at room temperature for 2 h, the reaction mixture was concentrated, and the residue was purified by column chromatography (eluent: CH_2Cl_2/MeOH, 10:1 to 5:1) to afford monothiourea **1** (106 mg, 0.255 mmol, 51%) and dithiourea **2** (41 mg, 0.06 mmol, 12%). White solid, mp: 94-95 ºC; $[\alpha]_D^{20}$ + 36.5 (*c* 0.96, CH_2Cl_2); IR (ATR, cm^{-1}): 3277, 2974, 2888, 2357, 1536, 1475, 1385, 1332, 1278, 1131, 1070, 1045, 996, 960, 841, 682. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.94 (1H, brs, NH), 7.90 (2H$_{arom}$, s, 2CH), 7.62 (1H$_{arom}$, s, 1CH), 7.34 (1H, brs, NH), 4.81 (1H, d, J_{HH} 4.3 Hz, CHNHC=S), 4.73 (1H, brs, CHNH$_2$), 4.44 (1H, d, J_{HH} 4.3 Hz, 1CH), 4.05-4.01 (1H, m, 1CH), 3.92 (1H, dd, J_{HH} 9.7, 4.1 Hz, CH_2), 3.81 (1H, d, J_{HH} 9.7 Hz, CH_2), 3.74-3.68 (1H, m, CH_2), 3.58-3.56 (1H, m, CH_2), 2.68 (2H, brs, NH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ_c: 181.1 (C=S), 139.7, 132.2 (1C, q, *J* 33.5 Hz, *C*CF$_3$), 124.0, 122.9 (1C, q, *J* 272.8 Hz, CF$_3$), 119.0, 88.4, 86.5, 74.6, 71.6, 61.2, 57.7. HRMS *m/z* calcd for $C_{15}H_{16}F_6N_3O_2S$ [M+H]$^+$ = 416.0867, found 416.0850.

Synthesis of dithioureas 2, 3 and 4
General procedure. To a stirred solution of diamine **9** (1 eq.) in THF (0.35 mmol/mL) was slowly added isothiocyanate (2 eq.). After stirring at room temperature for 3 h, the reaction mixture was concentrated, and the residue was taken up in diethyl ether. The precipitate was then filtered.
Dithiourea 2. According to the general procedure, dithiourea **2** (455 mg, 80%) was obtained as a white solid. mp: 165-166 ºC; $[\alpha]_D^{20}$ - 11.1 (*c* 1.78, MeOH), IR (ATR, cm^{-1}): 3265, 1724, 1675,

1618, 1533, 1469, 1379, 1274, 1179, 1125, 985, 906, 886, 720, 681, 653. ^{1}H NMR (200 MHz, CD$_3$OD) δ_H: 8.21 (4H$_{arom}$, s, 4CH), 7.62 (2H$_{arom}$, s, 2CH), 4.87 (2H, s, 2CH), 4.75 (2H, s, 2CH), 4.07 (2H, dd, J_{HH} 9.9, 4.7 Hz, CH$_2$), 3.91 (2H, d, J_{HH} 9.9, 1.9 Hz, CH$_2$). ^{13}C NMR (50 MHz, CD$_3$OD) δ_c: 183.0 (C=S), 143.1, 132.7 (q, J 33.0 Hz, CCF$_3$), 124.7 (q, J 270.0 Hz, CF$_3$), 123.6, 117.9, 87.5, 73.1, 62.3. HRMS m/z calcd for C$_{24}$H$_{19}$F$_{12}$N$_4$O$_2$S$_2$ [M+H]$^+$ = 687.0758, found 687.0767.

Dithiourea 3. According to the general procedure, dithiourea **3** (480 mg, 83%) was obtained as a white solid. mp: 198.2-199.0 $^\circ$C, IR (ATR, cm^{-1}): 3232, 3053, 2959, 2889, 2872, 1598, 1534, 1493, 1450, 1364, 1329, 1309, 1270, 1058, 923, 909, 768, 701, 462; ^{1}H NMR (200 MHz, CD$_3$OD) δ_H: 7.42-7.29 (8H$_{arom}$, m, 8CH), 7.20-7.13 (2H$_{arom}$, m, 2CH), 4.86-4.83 (2H, m, 2CH), 4.67 (2H, s, 2CH), 4.05 (2H, dd, J_{HH} 9.7, 5.0 Hz,), 3.82 (2H, dd, J_{HH} 9.7, 2.5 Hz, CH$_2$). ^{13}C NMR (100 MHz, CD$_3$OD) δ_c: 182.9 (C=S), 140.1, 130.0, 126.5 and 125.3 (Phenyl), 87.7, 73.0, 62.4. HRMS m/z calcd for C$_{20}$H$_{23}$N$_4$O$_2$S$_2$ [M+H]$^+$ = 415.1262, found 415.1258.

Dithiourea 4. According to the general procedure, dithiourea **4** (583 mg, 90%) was obtained as a slightly yellow solid. mp: 174-176 $^\circ$C, [α]$_D^{20}$ + 49.7 (c 1.46, Acetone), IR (ATR, cm^{-1}): 3064, 2958, 2925, 2880, 1703, 1595, 1525, 1395, 1360, 1267, 1246, 1205, 1075, 906, 794, 771, 638; ^{1}H NMR (400 MHz, Acetone-d_6) δ_H: 9.06 (1H, brs, NH), 8.01-7.94 (5H$_{arom}$, m, 5CH), 7.87-7.85 (2H$_{arom}$, m, 2CH), 7.57-7.49 (9H, m, 6CH$_{arom}$ and 3NH), 7.08 (1H$_{arom}$, d, J_{HH} 6.4 Hz, 1CH), 4.88-4.85 (2H, m, 2CH), 4.45 (2H, s, 2CH), 3.95 (2H, dd, J_{HH} 9.8, 5.0 Hz, CH$_2$), 3.68 (2H, dd, J_{HH} 9.8, 2.1 Hz, CH$_2$). ^{13}C NMR (100 MHz, Acetone-d_6) δ_c: 183.5 (C=S), 135.5, 134.7, 131.1, 129.2, 128.4, 127.4, 127.3, 126.6, 126.1 and 123.6 (10C, Nap), 87.1, 72.4, 62.6. HRMS m/z calcd for C$_{28}$H$_{27}$N$_4$O$_2$S$_2$ [M+H]$^+$ = 515.1575, found 515.1527.

Synthesis of thiourea 5. To a solution of **1** (41.5 mg, 0.1 mmol) and Et$_3$N (20.2 mg, 0.2 mmol) was added L-(-)-camphorsulfonyl chloride (30 mg, 0.12 mmol). The reaction mixture was stirred at room temperature overnight. The resulting mixture was neutralized with an aqueous HCl solution (1N), extracted with CH$_2$Cl$_2$ and washed with brine. The organic layer was dried over MgSO$_4$ and concentrated under vacuum. The residue was then purified by column chromatography (cyclohexane/AcOEt, 1:2) to afford 5 (40 mg, 0.064 mmol, 64%) as a white solid. mp: 134.5-136.3°C; [α]$_D^{20}$ + 12.9 (c 1.37, CHCl$_3$), IR (ATR, cm^{-1}): 2946, 1737, 1537, 1472, 1383, 1323, 1275, 1174, 1125, 884. ^{1}H NMR (200 MHz, CDCl$_3$) δ_H: 8.61 (1H, s, NH), 8.01 (2H$_{arom}$, s, 2CH), 7.59 (1H$_{arom}$, s, 1CH), 7.16 (1H, d, J_{HH} 6.7 Hz, CH$_2$S=O), 6.16 (1H, d, J_{HH} 6.7 Hz, CH$_2$S=O), 4.86-4.73 (3H, m), 4.18-4.01 (3H, m), 3.95-3.83 (2H, m, CH$_2$), 3.51 (1H, d, J_{HH} 14.8 Hz,), 3.05 (1H, d, J_{HH} 14.8 Hz, CH$_2$C=O), 2.01-1.74 (2H, m, CCH$_2$CH), 1.49-1.39 (1H, m, CH$_2$CHCH$_2$), 1.00 (3H, s, CH$_3$), 0.88 (3H, s, CH$_3$). ^{13}C NMR (100 MHz, CDCl$_3$) δ_c: 217.3 (C=O), 181.1 (C=S), 140.2, 131.9 (q, J 33.3 Hz, CCF$_3$), 123.6, 123.0 (q, J 271.0 Hz, CF$_3$), 118.4, 87.1, 86.2, 72.8, 72.1, 60.8, 59.7, 59.1, 51.0, 48.9, 42.8, 42.7, 26.9, 26.2, 19.8, 19.3. Anal. C$_{25}$H$_{29}$F$_6$N$_3$O$_5$S$_2$ calcd. C 47.69, H 4.64, N 6.67, found C 47.86, H 5.02, N 6.61.

Synthesis of dithiourea 6. Following the general procedure as for dithiourea **2**, dithiourea **6** was obtained after column chromatography (cyclohexane/EtOAc, 2:1) as a white solid in 80 % yield. Mp: 237.8-239.0 $^\circ$C, [α]$_D^{20}$ + 32.6 (c 1.11, MeOH), IR (ATR, cm^{-1}): 3154, 3039, 2978, 2860,

1521, 1469, 1380, 1349, 1299, 1269, 1221, 1176, 1138, 1104, 1068, 1014, 969, 892, 839, 767, 724, 701, 680, 617, 585. ^{1}H NMR (200 MHz, MeOH-d_4) δ_H: 8.28 (4H$_{arom}$, s, 4CH), 7.64 (2H$_{arom}$, s, 2CH), 5.10-5.00 (2H, m, 2CH), 4.81-4.75 (2H, m, 2CH), 4.43 (2H, t, J_{HH} 8.0 Hz, CH$_2$), 3.57 (2H, t, J_{HH} 8.8 Hz, CH$_2$). ^{13}C NMR (100 MHz, MeOH-d_4) δ_c: 183.0 (C=S), 143.1, 132.7 (q, J 33.0 Hz, CCF$_3$), 124.7 (q, J 270.0 Hz, CF$_3$), 123.2, 117.9, 83.0, 72.6, 59.3. HRMS m/z calcd for C$_{24}$H$_{19}$F$_{12}$N$_4$O$_2$S$_2$ [M+H]$^{+}$ = 687.0758, found 687.0798.

General procedure for Friedel-Crafts alkylations of indoles by nitrostyrenes. To a solution of organocatalyst **2** (0.02 mmol) and TCA (0.01 mmol) in 1 mL of dry MTBE was added nitrostyrene (0.1 mmol). The solution was stirred at rt for 30 min and indole (0.2 mmol) was added in one portion. The reaction was kept stirring for 2 to 7 days. After the completion of the reaction, the mixture was purified by flash chromatography (cyclohexane/ethyl acetate, 5:1) to afford the product **14a-h**.

3-(2-Nitro-1-phenylethyl)-1H-indole (14a).[35] Oil, 41% yield, [α]$_D^{20}$ +5.6 (c 0.5, CH$_2$Cl$_2$), 44% ee [Phenomenex$^{®}$ Lux 5μ cellulose-2, isooctane/i-PrOH (90:10), Flow rate = 0.75 mL/min, UV = 254 nm, t$_R$ = 29.53 min (minor) and 34.8 min (major)], ^{1}H NMR (200 MHz, CDCl$_3$) δ_H: 8.07 (1H, brs, NH), 7.43 (1H, d, J_{HH} 7.8 Hz, 1CH, indole), 7.34-6.97 (9H$_{arom}$, m, 9CH), 5.22-5.14 (1H, m, phCHCH$_2$NO$_2$), 5.04 (1H, dd, J_{HH} 12.2, 7.4 Hz, CH$_2$NO$_2$), 4.91 (1H, dd, J_{HH} 12.2, 8.4 Hz, CH$_2$NO$_2$). ^{13}C NMR (100 MHz, CDCl$_3$) δ_c: 139.2, 136.4, 128.9, 127.7, 127.5, 126.1, 122.6, 121.6, 119.9, 118.9, 114.3 and111.4 (12C, Arom), 79.5 (1C, CH$_2$NO$_2$), 41.5 (1C, CHCH$_2$).

4.2.2 5-Methoxy-3-(2-nitro-1-phenylethyl)-1H-indole (14b).[35] White solid, Mp: 123.6-125.1 ^{o}C (lit. 123-124 ^{o}C)[35], 61% yield, [α]$_D^{20}$ + 7.4 (c 0.4, CH$_2$Cl$_2$), 41% ee [Phenomenex$^{®}$ Lux 5μ cellulose-2, isooctane/i-PrOH (80:20), Flow rate = 1.0 mL/min, UV = 254 nm, t$_R$ = 16.17 min (minor) and 35.03 min (major)], ^{1}H NMR (200 MHz, CDCl$_3$) δ_H: 7.99 (1H, brs, NH), 7.31-7.15 (6H$_{arom}$, m, 6CH), 6.92 (1H, d, J_{HH} 2.6 Hz, 1CH, indole), 6.86-6.80 (2H$_{arom}$, m, 2CH), 5.11 (1H, t, J_{HH} 8.0 Hz, CHCH$_2$NO$_2$), 5.00 (1H, dd, J_{HH} 12.1, 7.2 Hz, CH$_2$NO$_2$), 4.88 (1H, dd, J_{HH} 12.1, 8.3 Hz, CH$_2$NO$_2$), 3.74 (3H, s, OCH$_3$). ^{13}C NMR (100 MHz, CDCl$_3$) δ_c: 154.1, 139.1, 131.5, 128.8, 127.7, 127.5, 126.5, 122.3, 113.9, 112.6, 112.1 and 100.8 (12C, Arom), 79.4 (1C, CH$_2$NO$_2$), 55.8 (OCH$_3$), 41.5 (1C, CHCH$_2$).

5-Bromo-3-(2-nitro-1-phenylethyl)-1H-indole (14c). Oil, 10% yield, 48% ee [Phenomenex$^{®}$ Lux 5μ cellulose-2, isooctane/i-PrOH (95:5), Flow rate = 1.0 mL/min, UV = 254 nm, t$_R$ = 58.60 min (minor) and 67.97 min (major)], ^{1}H NMR (200 MHz, CDCl$_3$) δ_H: 8.13 (1H, brs, NH), 7.53 (1H$_{arom}$, d, J_{HH} 1.8 Hz, 1CH), 7.32-7.13 (7H$_{arom}$, m, 7CH), 7.0 (1H, d, J_{HH} 2.5 Hz, 1CH, indole), 5.10 (1H, t, J_{HH} 7.8 Hz, CHCH$_2$NO$_2$), 4.99 (1H, dd, J_{HH} 12.3, 7.5 Hz, CH$_2$NO$_2$), 4.88 (1H, dd, J_{HH} 12.3, 8.2 Hz, CH$_2$NO$_2$). ^{13}C NMR (100 MHz, CDCl$_3$) δ_c: 138.7, 135.0, 129.0, 127.8, 127.7, 127.6, 125.6, 122.7, 121.4, 113.9, 113.2 and 112.8 (12C, Arom), 79.4 (1C, CH$_2$NO$_2$), 41.2 (1C, CHCH$_2$).

4-Chloro-3-(2-nitro-1-phenylethyl)-1H-indole (14d).[35] Oil, 37% yield, [α]$_D^{20}$ – 4.5 (c 0.11, CH$_2$Cl$_2$), 37% ee [Phenomenex$^{®}$ Lux 5μ cellulose-2, isooctane/i-PrOH (90:10), Flow rate = 0.75

mL/min, UV = 254 nm, t_R = 32.65 min (minor) and 39.97 min (major)], ^{1}H NMR (400 MHz, CDCl$_3$) δ$_H$: 8.04 (1H, brs, NH), 7.37 (1H$_{arom}$, d, J_{HH} 8.1 Hz, 1CH), 7.29 (1H$_{arom}$, d, J_{HH} 8.1 Hz, 1CH), 7.25-7.16 (5H$_{arom}$, m, 5CH), 7.06 (1H$_{arom}$, td, J_{HH} 7.4, 0.9 Hz, 1CH), 6.91 (1H, d, J_{HH} 2.6 Hz, 1CH, indole), 5.11 (1H, t, J_{HH} 8.0 Hz, CHCH$_2$NO$_2$), 4.98 (1H, dd, J_{HH} 12.5, 7.3 Hz, CH$_2$NO$_2$), 4.84 (1H, dd, J_{HH} 12.5, 8.6 Hz, CH$_2$NO$_2$). ^{13}C NMR (100 MHz, CDCl$_3$) δ$_c$: 137.7, 136.4, 133.3, 129.1, 129.0, 125.8, 122.8, 121.5, 120.0, 118.7, 113.8 and 111.5 (12C, Arom), 79.2 (1C, CH$_2$NO$_2$), 40.9 (1C, CHCH$_2$).

5-Fluoro-3-(2-nitro-1-phenylethyl)-1*H*-indole (14e). Oil, 32% yield, [α]$_D^{20}$ − 7.9 (c 0.145, CH$_2$Cl$_2$), 42% ee [Phenomenex® Lux 5μ cellulose-2, isooctane/i-PrOH (90:10), Flow rate = 0.75 mL/min, UV = 254 nm, t_R = 32.55 min (minor) and 40.33 min (major)], 1H NMR (200 MHz, CDCl3) δ$_H$: 8.04 (1H, brs, NH), 7.40-6.91 (8H$_{arom}$, 1H, m, 9CH), 5.13 (1H, t, J_{HH} 8.0 Hz, CHCH$_2$NO$_2$), 5.00 (1H, dd, J_{HH} 12.3, 7.3 Hz, CH$_2$NO$_2$), 4.84 (1H, dd, J_{HH} 12.3, 8.4 Hz, CH$_2$NO$_2$).^{13}C NMR (100 MHz, CDCl3) δ$_c$: 162.0 (d, J 245.7 Hz), 136.4, 134.9, 129.3 (d, J 8.4 Hz, 2C), 125.9, 122.7, 121.4, 119.9, 118.7, 115.7 (d, J 21.8 Hz, 2C), 114.0, 111.4, 79.4 (1C, CH$_2$NO$_2$), 40.8 (1C, CHCH$_2$).

3-(2-Nitro-1-*p*-tolylethyl)-1*H*-indole (14f).[35] Oil, 43% yield, [α]$_D^{20}$ + 4.7 (c 0.16, CH$_2$Cl$_2$), 42% ee [Phenomenex® Lux 5μ cellulose-2, isooctane/i-PrOH (90:10), Flow rate = 0.75 mL/min, UV = 254 nm, t_R = 30.25 min (minor) and 34.33 min (major)], ^{1}H NMR (400 MHz, CDCl$_3$) δ$_H$: 8.02 (1H, brs, NH), 7.43 (1H$_{arom}$, d, J_{HH} 7.9 Hz, 1CH), 7.31 (1H$_{arom}$, dd, J_{HH} 7.9 Hz, 1.1 Hz, 1CH), 7.22-7.01 (6H$_{arom}$, m, 6CH), 6.95 (1H, d, J_{HH} 2.6 Hz, 1CH, indole), 5.13 (1H, t, J_{HH} 7.9 Hz, CHCH$_2$NO$_2$), 5.01 (1H, dd, J_{HH} 12.0, 7.3 Hz, CH$_2$NO$_2$), 4.88 (1H, dd, J_{HH} 12.0, 8.4 Hz, CH$_2$NO$_2$), 2.29 (3H, s, CH$_3$). ^{13}C NMR (100 MHz, CDCl$_3$) δ$_c$: 137.1, 136.4, 136.1, 129.5, 127.6, 126.1, 122.6, 121.5, 119.9, 118.9, 114.5 and 111.3 (12C, Arom), 79.6 (1C, CH$_2$NO$_2$), 41.2 (1C, CHCH$_2$), 21.0 (1C, CH$_3$).

3-(1-(4-Methoxyphenyl)-2-nitroethyl)-1*H*-indole (14g).[35] White solid, Mp: 147.6-149.6 °C (lit. 149-150 °C)[35], 44% yield, [α]$_D^{20}$ − 11.8 (c 0.11, CH$_2$Cl$_2$), 44% ee [Phenomenex® Lux 5μ cellulose-2, isooctane/i-PrOH (90:10), Flow rate = 0.75 mL/min, UV = 254 nm, t_R = 45.03 min (minor) and 51.90 min (major)], ^{1}H NMR (400 MHz, CDCl$_3$) δ$_H$: 8.09 (1H, brs, NH), 7.43 (1H$_{arom}$, d, J = 8.0 Hz, 1CH), 7.34 (1H$_{arom}$, d, J = 8.0 Hz, 1CH), 7.26-7.22 (2H$_{arom}$, m, 2CH), 7.21-7.17 (1H$_{arom}$, m, 1CH), 7.09-7.05 (1H$_{arom}$, m, 1CH), 7.00 (1H, d, J_{HH} 2.7 Hz, 1CH, indole), 6.85-6.83 (2H$_{arom}$, m, 2CH), 5.13 (1H, t, J_{HH} 8.1 Hz, CHCH$_2$NO$_2$), 5.03 (1H, dd, J_{HH} 12.2, 7.4 Hz, CH$_2$NO$_2$), 4.88 (1H, dd, J_{HH} 12.2, 8.4 Hz, CH$_2$NO$_2$), 3.76 (3H, s, OCH$_3$). ^{13}C NMR (100 MHz, CDCl$_3$) δ$_c$: 158.9, 136.5, 131.2, 128.8, 126.1, 122.6, 119.9, 114.8, 114.3, 111.3, 79.7 (1C, CH$_2$NO$_2$), 55.2 (1C, OCH$_3$), 40.8 (1C, CHCH$_2$).

3-(1-(2-Chlorophenyl)-2-nitroethyl)-1*H*-indole (14h). White solid, Mp: 136.6-138.6 °C (lit. oil)[35], 27% yield, 16% ee [Phenomenex® Lux 5μ cellulose-2, isooctane/i-PrOH (85:15), Flow rate = 0.75 mL/min, UV = 254 nm, t_R = 16.42 min (major) and 20.72 min], ^{1}H NMR (200 MHz, CDCl$_3$) 8.05 (1H, brs, NH), 7.44-7.28 (3H$_{arom}$, m,), 7.22-7.01 (5H$_{arom}$, 1H, m, 6CH), 5.73 (1H, t, J_{HH} 7.6 Hz, CHCH$_2$NO$_2$), 4.98 (1H, dd, J_{HH} 12.9, 8.2 Hz, CH$_2$NO$_2$), 4.91 (1H, dd, J_{HH} 12.9, 7.6 Hz, CH$_2$NO$_2$). ^{13}C NMR (100 MHz, CDCl$_3$) 136.4, 133.8, 130.1, 128.9, 128.8, 127.4, 127.2,

126.1, 122.7, 121.9, 120.0, 118.9, 113.2 and 111.4 (14C, Arom), 77.7 (1C, CH_2NO_2), 37.9 (1C, $CHCH_2$).

Acknowledgements

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