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The enantioselective addition of 1-fluoro-1-nitro(phenylsulfonyl)methane to isatin-derived ketimines†

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An asymmetric organocatalytic addition of fluorinated phenylsulfonylnitromethane to isatin-derived ketimines was developed. The reaction was efficiently catalyzed by a chiral tertiary amine, cinchonine. This methodology provides a new type of optically active compound with two adjacent quaternary carbon stereocenters in good yield (up to 96%), with moderate diastereoselectivity (up to 5.7 : 1 dr) and excellent enantioselectivity (up to 98/96% ee).

Introduction

Preparation of enantiomerically pure organic compounds bearing a quaternary stereogenic center is one of the most challenging research areas in asymmetric catalysis.[1] In addition, a quaternary 3-amino-2-oxindole moiety is a ubiquitous motif in natural products and pharmaceutical agents.[2] Among the methods developed for the preparation of such compounds, enantioselective addition of nucleophiles to isatin-derived ketimines is straightforward and probably the most efficient approach. Easy access to *N*-Boc isatin imines[3] together with its modulate reactivity towards nucleophiles and the ability to easily remove Boc protecting group from the adducts have made those imines as attractive substrates for a number of catalytic addition reactions.[4] Not only metal-based complexes (Pd, Rh, Ni,)[5] but also small organic molecules (H-bonding donors) can effectively catalyze these processes. To date a variety of organocatalytic addition reactions have been developed, including the Strecker reaction, the Mannich reaction and its vinylogous variant, the aza-Morita–Baylis–Hillman reaction, cycloadditions and others.[6] Because of their impact in medicinal research and chemical biology, the development of efficient methods for the selective introduction of fluoro-containing groups into bioactive molecules is an area of high interest.[7] However, the enantioselective addition reactions of fluoro-containing nucleophiles to isatin-derived ketimines have rarely been described.[8] Besides α-fluoro-bis(phenylsulfonyl)methane (FBSM),[9] α-fluoro-nitro(phenylsulfonyl)methane (FNSM) has also been recognized as a versatile nucleophile in various organocatalytic reactions, as demonstrated by Prakash and Olah[10] and others.[11] In this context, we herein report the highly enantioselective addition of α-fluoronitro(phenylsulfonyl)-methane to isatin-derived ketimines under mild organocatalytic conditions affording the fluoro-containing compounds bearing adjacent quaternary stereogenic centers.

Results and discussion

At the outset we decided to study the nucleophilic addition of α-fluoro-nitro(phenylsulfonyl)methane (FNSM, **2a**) to *tert*-butyl (1-benzyl-2-oxoindolin-3-ylidene)carbamate (**1a**) in the presence of cinchona alkaloids (Fig. 1). Initially, the reaction was performed with **1a** and **2a** in a 1 : 1.1 ratio at room temperature in toluene (Table 1, entry 1). It provided the desired adduct **3a**/**3a′** within a few hours in high yields (varying from 93 to 98%) and with moderate diastereoselectivity (up to 3.5 : 1). Unfortunately, the obtained enantiomeric purity of **3a** was unsatisfactory, and further screening of the reaction conditions was required. Initially, we tested the influence of temperature on the course of the reaction (Table SI 1, ESI†). Cinchonine (CN, Fig. 1) has shown the most promising results in terms of effectiveness and enantiocontrol in the model reaction performed at a lower temperature (−50 °C, entry 5). Full conversion of isatin-derived ketimine **1a** was reached within 18 hours and adduct **3a** was isolated in high yield (85%), with moderate diastereoselectivity (3.5 : 1) and excellent enantioselectivity of both diastereoisomers (96/95% ee). It is noteworthy that a further decrease in the reaction temperature led to a significant drop in the yield of **3a** (Table 1, entry 6).

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† Electronic supplementary information (ESI) available: Experimental procedure and spectral data for all prepared compounds with copies of the ^{1}H NMR, ^{13}C NMR and ^{19}F NMR and HPLC chromatographs. CCDC 1575684. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ob02408h

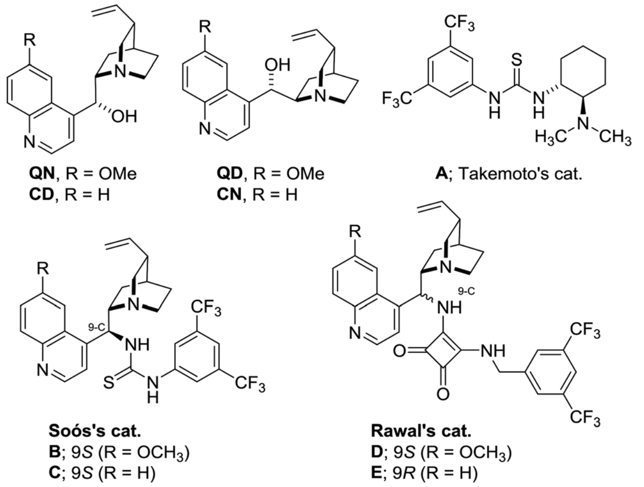
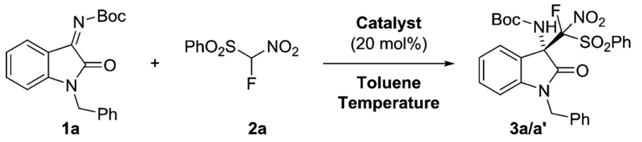


Fig. 1 Bifunctional organocatalysts screened in the reaction of ketimine **1a** with FNSM **2a**.

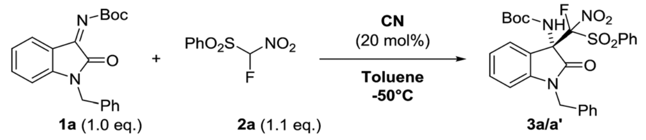
Table 1 Optimization studies on the reaction of ketimine **1a** and FNSM **2a**



Entry	Catalyst	Temp. [°C]	Time [h]	Yield^a [%]	dr ^{b}	ee ^{c} [%]
1	QN	25	18	98	1.5 : 1	−3/−3
2	QD	25	4	94	1.2:1	19/62
3	CN	25	4	97	2 : 1	77/82
4	CD	25	4	93	1.6 : 1	−60/−70
5	CN	0	8	95	2.8 : 1	85/85
6	CN	−50	18	82	3.5 : 1	96/96
7	CN	−78	168	68	4 : 1	97/96

^{a} Isolated yield after column chromatography. ^{b} Determined by ^{19}F NMR of the reaction mixture. ^{c} Determined by HPLC analysis of the purified product for two diastereoisomers.

Table 2 Solvent optimization studies on the reaction of ketimine **1a** with FNSM **2a**



Entry	Solvent	Time [h]	Yield^a [%]	dr ^{b}	ee ^{c} [%]
1	Toluene	18	85	3.5 : 1	96/95
2	DCM	19	57	2 : 1	79/86
3	$CHCl_3$	19	84	3 : 1	88/89
4	THF	96	65	1.9 : 1	22/35
5	MTBE	96	75	3 : 1	65/63
6	EtOAc	96	18	2.8 : 1	61/63
7	MeOH	96	—	—	—
8^d	DMSO	96	—	—	—

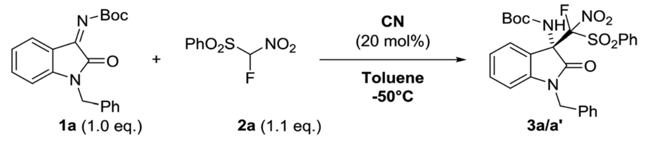
^{a} Isolated yield after column chromatography. ^{b} Determined by ^{19}F NMR of the reaction mixture. ^{c} Determined by HPLC analysis of the purified product for two diastereoisomers. ^{d} Reaction at 25 °C.

Next, we assessed the influence of the solvent in the reaction of **1a** and **2a** (Table SI 1, ESI†). As shown in Table 1, apart from toluene, the addition reaction proceeded well in several nonpolar chlorinated and etheric solvents, but with lower diastereo- and enantioselectivity and also yield (Table 2, entries 1–6). On the other hand no reaction was observed in polar protic and aprotic solvents, such as methanol and DMSO. Screening of the solvents and temperature is summarized in the ESI† (Tables SI 1) in detail.

Next, we focused on the role of the catalyst in the enantiomeric addition of **2a** to isatin-derived ketimine **1a** with respect to efficiency and stereoselectivity (Table 2). Besides cinchona alkaloids, screened initially, chiral thioureas such as Takemoto's bifunctional catalyst **A** and Soós's catalysts **B**, **C** Sharpless bases and squaramides **D**, **E** were examined in the reaction between **1a** and **2b** (Fig. 1). Surprisingly, none of the above-mentioned organocatalysts catalysed the model reaction as effectively as cinchonine (Table 3, entries 1–6, more details in the ESI†). We also screened the dependence of the reaction efficiency and selectivity on the loading of catalysts. Interestingly, no significant change in selectivity and yield was observed when 5 mol% of the catalyst was used. On the other hand a lower catalyst loading dramatically influenced the reaction time (Table 3, entry 9). A reduced yield was observed, when 2.5 mol% of the catalyst was used, nevertheless, the selectivity of the reaction was retained (Table 3, entry 10).

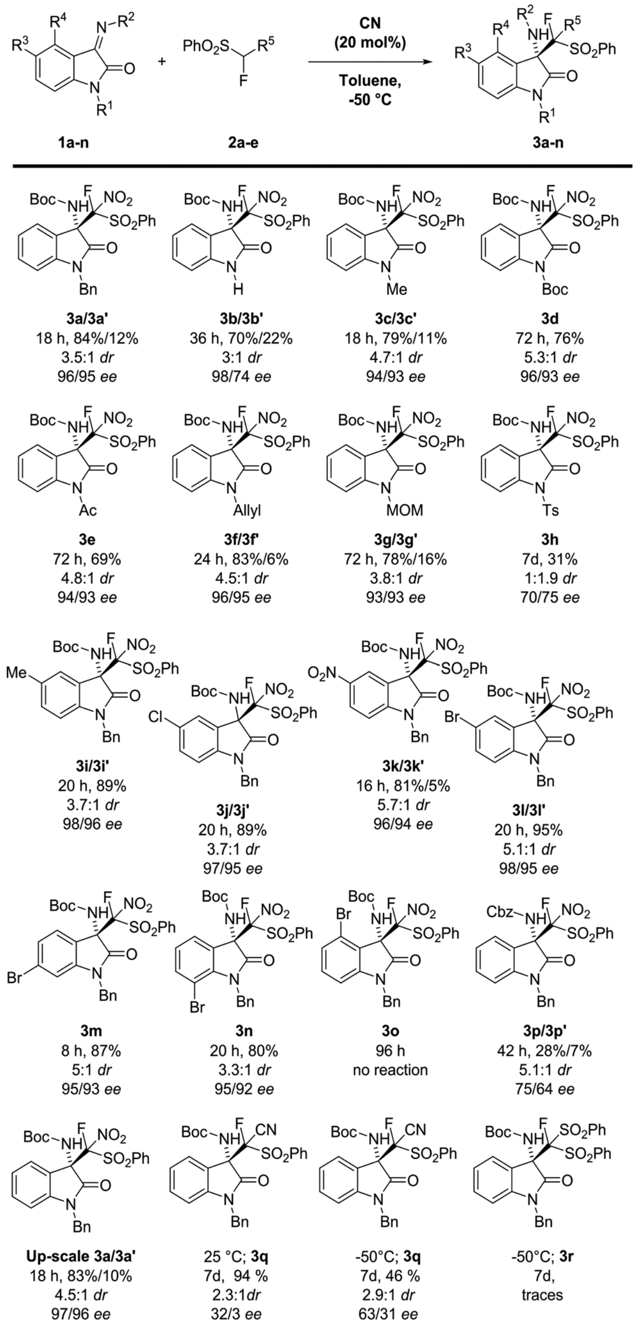
Once we uncovered the optimized reaction conditions for the enantioselective nucleophilic addition of FNSM to isatin-derived ketimine **1a**, we proceeded with the scope of the process (Scheme 1). First we studied the reactivity of FNSM towards ketimines **1a–1h** having different protecting groups on

Table 3 Catalyst optimization studies on the reaction of ketimine **1a** and FNSM **2a**



Entry	Catalyst	Time [h]	Yield^a [%]	dr ^{b}	ee ^{c} [%]
1	Takemoto's A	18	96	3.3 : 1	−27/−25
2	Soós's with QN B	18	96	3.7 : 1	64/56
3	Soós's with CD D	20	96	5.9 : 1	70/62
4	(DHQ)2AQN	24	90	4 : 1	35/28
5	Rawal's with QN E	24	89	4.3 : 1	18/47
6	Rawal's with CN F	168	76	4.5 : 1	−75/−16
7	CN (10 mol%)	24	80	3.5 : 1	96/95
8	CN (5 mol%)	36	85	3.7 : 1	96/96
9	CN (2.5 mol%)	48	68	3.6 : 1	96/95
10	—	168	—	—	—

^{a} Isolated yield after column chromatography. ^{b} Determined by ^{19}F NMR of the reaction mixture. ^{c} Determined by HPLC analysis of the purified product for two diastereoisomers.



Scheme 1 Substrate scope of ketimines **1a–p** and fluorinated sulfones **2a–3** in the organocatalytic alkylation reaction. Isolated yield after column chromatography. Determined by ^{19}F NMR of the reaction mixture. Determined by HPLC analysis of the purified product for two diastereoisomers.

the nitrogen of the 3-amino-2-oxindole moiety. The desired products **3a/3a′–3g/3g′** were prepared in good yields with high to excellent enantioselectivity (93–99% ee for the major diastereoisomer and 93–95% ee for the minor diastereoisomer). A moderate degree of diastereoselectivity (3 : 1 to 5 : 1) was obtained in the reaction of **2a** with most ketimines **1a–1h.** The highest diastereocontrol was observed in the reaction with Boc protected ketamine **1d** (dr 5 : 1). On the other hand, the reaction between **2a** and ketimine **1h** with a tosyl protecting group proceeded with low diastereo- (dr 1 : 1.9) and enantioselectivity (70/75% ee); the corresponding adduct **3h** was isolated in low yield (31%) as a mixture of diastereoisomers.

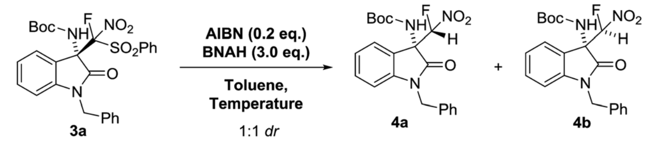
Subsequently, we focused on ketimine derivatives with different substitutions on the aromatic ring (**1i–1o**). Substitution at the 5-position on the aromatic ring of ketimines led to the formation of the corresponding products **3i–3l** in high yield (81–95%) and excellent enantiomeric excess for both enantiomers (major diastereoisomer 96–98% ee, minor diastereoisomer 94–96% ee). On the other hand, diastereoselectivity reached moderate values (dr 3.7 : 1–5.7 : 1). A significant change in reactivity was observed, when ketimine **1o** substituted at the 4-position with bromine was used. The formation of the corresponding adduct **3o** was not observed even after a prolonged reaction time (96 h). This can be probably caused due to the higher steric hindrance of the imine group with the bulky bromine substituent at the 4-position, because all other adducts **3l**, **3m** and **3n** having bromine atoms at positions 5-,6- and 7 were obtained in high yields with good levels of enantioselectivity. Replacement of the Boc group for the Cbz group on the nitrogen of the imine moiety led to a considerable drop in enantioselectivity (75/64% ee). The corresponding product **3p** was obtained in 88% yield and with good diastereoselectivity (dr 5.1 : 1).

Next, we turned our attention to other types of fluorinated sulfones **2b–e**. The nitro group was replaced by various functional groups such as nitrile, ester, acetyl, phenylcarbonyl groups, *etc*. In all cases significantly lower reactivity towards **1a** under the optimized reaction conditions (QN, toluene, −50 °C) was observed. Due to this reason we approached to set up the reactions with appropriate sulfones **2b–e** at 25 °C. It showed up that apart from the model reaction between **1a** and **2a**, reactions proceeded smoothly only with 2-fluoro-2-(phenylsulfonyl)acetonitrile (**2b**), affording product **3q** in high yield (94%) with low diastereoselectivity (dr 2.3 : 1) and unsatisfactory enantioselectivity (3/32% ee). Both the subsequential turn of temperature down to −50 °C and also the change of the solvent from toluene to DCM did not lead to improved selectivity of the reaction (dr 2.9 : 1, 30/59% ee, Scheme 1).

Next, the potential versatility of a phenylsulfanyl group as a traceless activating group was verified. The standard procedure for the removal of phenylsulfonyl group with magnesium failed.[12] Nevertheless, desulfonation of enantioenriched adducts **3a** was accomplished using AIBN as a radical agent in the presence of BNAH as a hydrogen transfer agent (Table 4).[13] α-Fluoronitro alkane **4** was isolated in 96% yield as a mixture of diastereoisomers (dr = 1 : 1) with the enantioselectivity retained (95/96% ee). Furthermore, Boc deprotection of **4a** and **4b** was successfully performed using TFA (Table 4).[14] The corresponding amines **5a** and **5b** were obtained in good yields 48% and 47%, respectively, with excellent enantiomeric excess (97/96%).

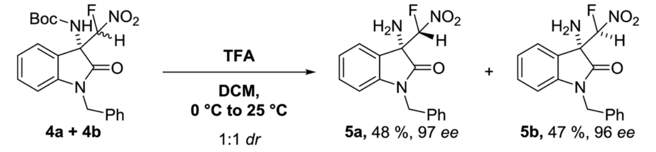
To determine the absolute configuration of alkylated products **3a**, we performed single-crystal X-ray diffraction analysis of **3a**, obtained from the reaction of ketimine **1a** with fluoro-

Table 4 Further transformation of alkylation product **3a**



Entry	Temp. [°C]	Time [h]	Yield^b [%]	ee^c [%]
1^a	60	1	84	95/94
2	Reflux	1	62	95/96
3	40	3	96	95/96

^{a} Reaction under microwave radiation. ^{b} Isolated yield after column chromatography. ^{c} Determined by HPLC analysis of the purified product for two diastereoisomers.



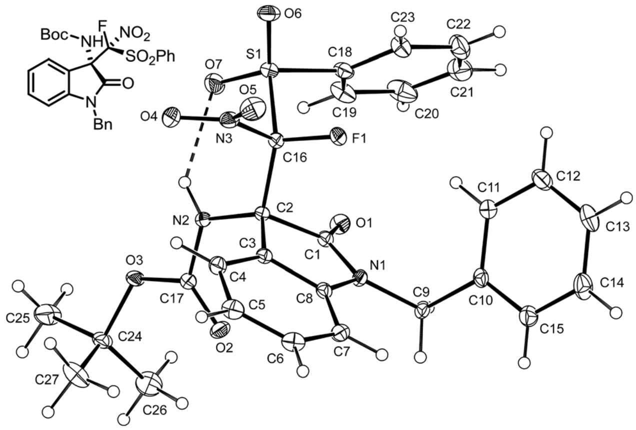


Fig. 2 View of the molecular structure of **3a**, the displacement ellipsoids at the 30% probability level. The dashed line indicates the intramolecular hydrogen bond N2–H2⋯O7, N2⋯O7 2.894(2) Å; angle on H2 138.7°.[15]

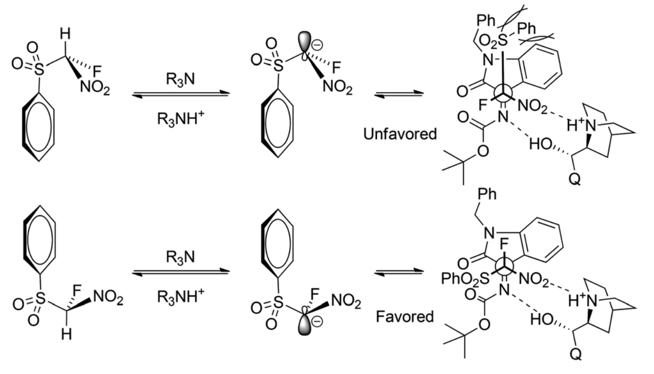


Fig. 3 Proposed transition state.

nitro(phenylsulfonyl)methane **2a** (Fig. 2). As shown in Fig. 3, the C3 and C1′ stereogenic centres have the (*S*) and (*R*) absolute configuration, respectively.

On the basis of the crystallographic analysis of **3a** an envisaged transition-state structure was proposed. As shown in Fig. 3, cinchonine can act as a dual catalyst and activate both reaction substrates *via* hydrogen bonding. The tertiary amine of the chinuclidine moiety deprotonates FNSM forming the corresponding anionic nucleophile that preferentially approaches the ketimine from the *Re*-face due to the H-bonding of the ketimine and hydroxyl groups of cinchonine.

Conclusion

In summary, we have explored the stereoselective fluoroalkylation of isatin-derived ketimines with α-fluoronitro(phenylsulfonyl) methane. The reaction was effectively catalyzed with cinchonine furnishing the corresponding adducts in good yields, with good diastereo- (dr up to 6 : 1) and high enantioselectivity (up to 98% ee). The reactivity of isatin-derived ketimines toward other fluorinated compounds was also studied. The outcome of the reported procedure was demonstrated by the preparation of rarely available β-fluoro-β-nitro amines using a desulfonylation/Boc-removal reaction sequence. Further studies and synthetic applications based on the reported methodology are currently ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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15 X-ray crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC) under deposition numbers CCDC 1575684† for **3a**.