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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 chiral tertiary amine, cinchonine. This methodology provides a new type of optically active compounds with two adjacent quaternary carbon stereocenters in good yields (up to 96%), moderated diastereoselectivity (up to 5.7:1 dr) and excellent enantioselectivities (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, quaternary 3-amino-2-oxindole moiety is an ubiquitous motif in natural products and pharmaceutical agent.[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 facile removal of Boc protection 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 those processes. To date a variety of organocatalytic addition reactions were developed, including Strecker reaction, Mannich reaction and its vinylogous variant, aza-Morita-Baylis-Hillman reaction, cycloadditions and others.[6] With the impact in medicinal research and chemical biology, development of efficient methods for selective introduction of fluoro-containing groups into bioactive molecules is an area of high interest.[7] However, the enantioselective addition reactions of fluor-containing nucleophiles to isatin-derived ketimines have been rarely describe.[8] Beside α-Fluoro-bis(phenylsulfonyl)methane (FBSM)[9] also α-fluoro-nitro(phenylsulfonyl)methane (FNSM) has been recognized as 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 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 (Figure 1). Initially, the reaction was performed with **1a** and **2a** in 1:1.1 ratio at room temperature in toluene (Table 1, Entry 1). It provided the desired adduct **3a/3a'** within few hours in high yields (varying from 93 to 98 %) and moderate diastereoselectivity (up to 3.5:1). Unfortunately, the obtained enantiomeric purity of **3a** was unsatisfactory, 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, Figure 1) has shown the most promising results in terms of effectivity and enantiocontrol on the model reaction performed at lowered temperature (-50 °C, Entry 5). Full conversion of isatin-derived ketimine **1a** was reached within 18 hours and the adduct **3a** was isolated in high yield (85 %), with moderate diastereoselectivity (3.5:1) and excellent enantioselectivity of both diastereoisomers (96/95 % *ee*). Noteworthy, further decrease of the reaction temperature led to significant drop of the yield of **3a** (Table 1, Entry 6).

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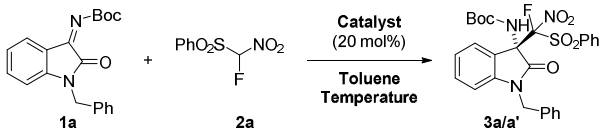
Table 1. Optimization Studies in the Reaction of Ketimine **1a** and FNSM **2a**.

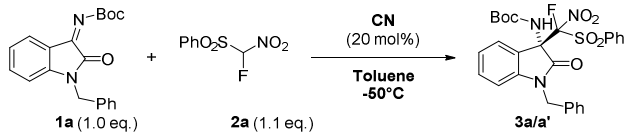


Entry	Catalyst	Temp. [°C]	Time [h]	Yield [%][a]	*d.r.*[b]	*e.e.* [%][c]
1	QN	25	18	98	1.5:1	-3/-3
2	QD	25	4	94	1.2:1	19/62
3	CN	25	4	97	2:1	77/82
4	CD	25	4	93	1.6:1	-60/-70
5	CN	0	8	95	2.8:1	85/85
6	CN	-50	18	82	3.5:1	96/96
7	CN	-78	168	68	4:1	97/96

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

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 performed 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 ESI (Tables SI 1) in details.

Table 2. Solvent Optimization Studies in the Reaction of Ketimine **1a** with FNSM **2a**.



Entry	Solvent	Time [h]	Yield [%][a]	*d.r.*[b]	*e.e.* [%][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 reaction mixture. [c] Determined by HPLC analysis of the purified product for two diastereoisomers. [d] Reaction at 25 °C.

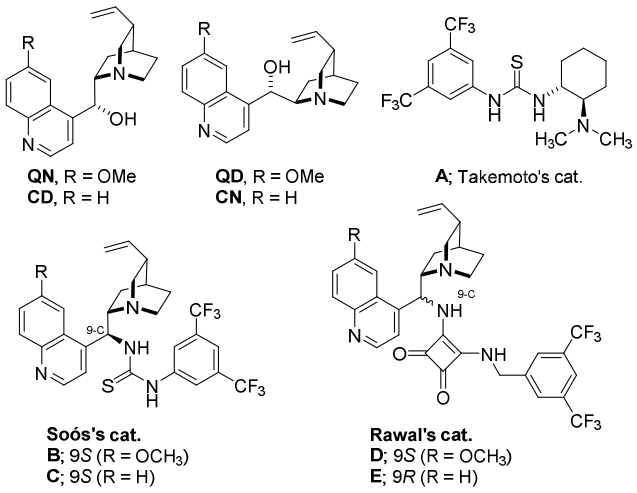


Figure 1. Bifunctional Organocatalysts Screened in the Reaction of Ketimine **1a** with FNSM **2a**.

Next, we focused on the role of the catalyst on enantiomeric addition of **2a** to isatin-derived ketimine **1a** with respect to efficiency and stereoselectivity (Table 2). Beside 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 reaction between **1a** and **2b** (Figure 1). Surprisingly, none of the above mentioned organocatalysts catalysed the model reaction as effectively as cinchonine (Table 3, Entry 1-6, more details in SI). We also screened the dependence of reaction efficiency and selectivity on 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 lowered catalyst loading dramatically influenced reaction time (Table 3, Entry 9) Reduced yield was observed, when 2.5 mol% of the catalyst was used, nevertheless, the selectivity of the reaction retained (Table 3, Entry 10).

Once we uncovered 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 nitrogen of 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 major and 93-95 % *ee* for minor diastereoisomer). Moderate degree of diastereoselectivity (3:1 to 5:1) was obtained in reaction of **2a** with most ketimines **1a-1h**. The highest diastereocontrol was observed in reaction with Boc protected ketamine **1d** (*dr* 5:1). On the other hand, the reaction between **2a** and ketimine 1h with 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.

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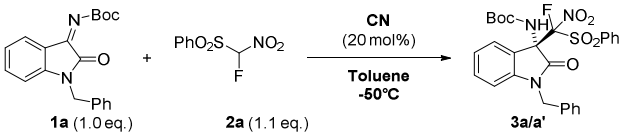
Table 3. Catalyst Optimization Studies in the Reaction of Ketimine **1a** and FNSM **2a**.



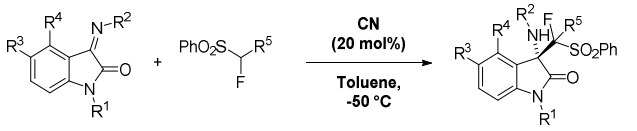
Entry	Catalyst	Time [h]	Yield [%][a]	*d.r.*[b]	*e.e.* [%][c]
1	Takemoto's **A**	18	96	3.3:1	-27/-25
2	Soós's with QN **B**	18	96	3.7:1	64/56
3	Soós's with CD **D**	20	96	5.9:1	70/62
4	$(DHQ)_2AQN$	24	90	4:1	35/28
5	Rawal's with QN **E**	24	89	4.3:1	18/47
6	Rawal's with CN **F**	168	76	4.5:1	-75/-16
7	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	-	-	-

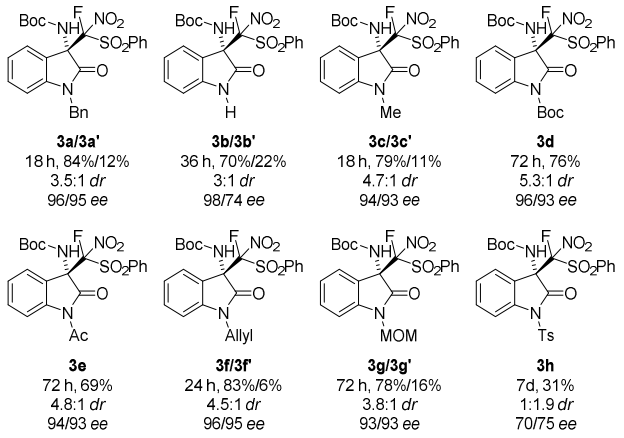
[a] Isolated yield after column chromatography. [b] Determined by ^{19}F NMR of reaction mixture. [c] Determined by HPLC analysis of the purified product for two diastereoisomers.

Subsequently, we focused on ketimine derivatives with different substitution on the aromatic ring (**1i-1o**). Substitution at 5-position on aromatic ring of ketimines led to formation of 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). Significant change in reactivity was observed, when ketimine **1o** substituted at 4-position with bromine was used. The formation of the corresponding adduct **3o** was not observed even after prolonged reaction time (96 hrs). This can be probably caused due to the higher steric hindrance of imine group with bulky bromine substituent at 4-position, because all other adducts **3l**, **3m** and **3n** having bromine atom at positions 5-,6- and 7 were obtained in high yields with good levels of enantioselectivity. Replacement of Boc group for Cbz group on nitrogen of imine moiety led to considerable drop of enantioselectivity (75/64 % *ee*). 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**. Nitro group was replaced by various functional groups such as nitrile, ester, acetyl, phenylcarbonyl group, etc. In all cases significantly lowered reactivity towards **1a** under optimized reaction conditions (QN, toluene, -50 °C) was observed. From that reason we approached to set up the reactions with appropriate sulfones **2b-e** at 25 °C. It showed up that apart from 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 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).

Scheme 1. Substrate scope of ketimines **1a-p** and fluorinated sulfones **2a-3** in organocatalytic alkylation reaction.





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

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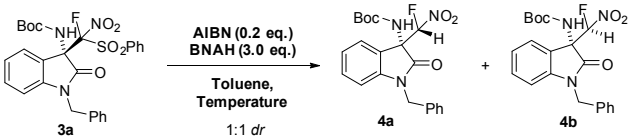
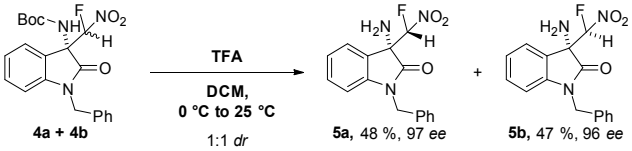
Next, the potential versatility of phenylsulfanyl group as traceless activating group was verified. Standard procedure for removal of using either Mg failed[12] Nevertheless, desulfonation of enantioenriched adducts **3a** was accomplished using AIBN as a radical agent in the presence of BNAH as hydrogen transfer (Scheme 4).[13] α-Fluoronitro alkane **4** was isolated in 96% yield as a mixture of diastereoisomers (*dr* = 1:1) with retained enantioselectivity (95/96 % *ee*). Further, Boc deprotection of **4a**, **4b** was successfully performed using TFA (Scheme 2).[14] The corresponding amines **5a** and **5b** were obtained in good yields 48 % and 47 %, respectively, with excellent enantiomeric excess (97/96%).

Scheme 2. Further transformation of alkylation product **3a**.



Entry	Temp. [°C]	Time [h]	Yield [%][b]	*e.e.* [%][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.



To determine 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-nitro(phenylsulpfonyl)methane **2a**. As shown in Figure 3, the C3 and C1' stereogenic centres have (*S*) and (*R*) absolute configuration, respectively.

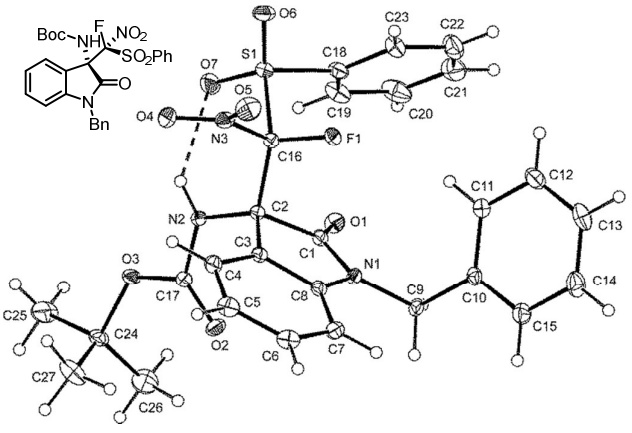


Figure 2. View on the molecular structure of **3a**, the displacement ellipsoids at 30% probability level. The dashed line indicates the intramolecular hydrogen bond N2-H2…O7, N2…O7 2.894(2) Å; angle on H2 138.7°.[15]

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

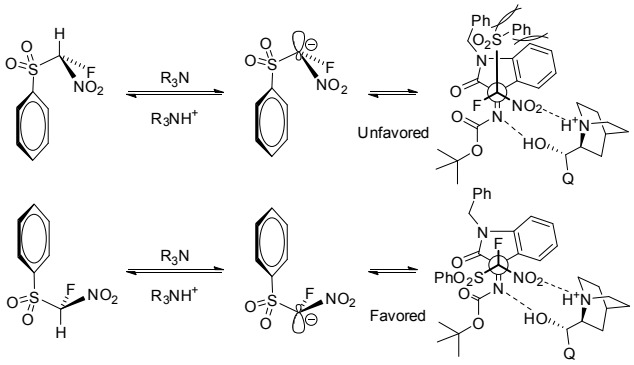


Figure 3. Proposed transition state.

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, 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. Outcome of the reported procedure was demonstrated by the preparation of rarely available β-fluoro-β-nitro amines using desulfonylation/Boc-removal reaction sequence. Further studies and synthetic applications based on the reported methodology are currently ongoing in our group.

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Conflicts of interest

There are no conflicts to declare".

Notes and references

‡Experimental procedure and spectral data for all prepared compounds with copies of the ^{1}H NMR, ^{13}C NMR and ^{19}F NMR

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and HPLC chromatographs. This material is available on Internet at http://xxxxxxxxxxx

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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** and can be obtained free of charge from the Centre via its website (www.ccdc.cam.ac.uk/getstructures).