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Per(poly)fluoroalkanesulfinamides assisted diastereoselective three-component inverse-electron-demand aza Diels–Alder reaction†

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A highly diastereoselective three-component inverse-electron-demand aza Diels–Alder reaction assisted by per(poly)fluoro-alkanesulfinamides is presented, providing a broad spectrum of highly functionalized piperidine derivatives with excellent *endo/exo* and *facial* diastereoselectivities. The electron-withdrawing perfluoroalkyl groups are crucial for the success of this reaction under mild conditions and facilitate monitoring the process and stereoselectivities of the reaction. The synthetic potential of these cycloadducts is also highlighted.

The asymmetric aza Diels–Alder reaction is among the most powerful and convergent strategies for the stereoselective construction of highly valuable piperidine derivatives.[1,2] As a complementary alternative to the well established formal cycloaddition of dienes and imines, Boger and co-workers introduced inverse-eletron-demand aza Diels–Alder (IEDDA) reactions of *N*-sulfonyl-1-aza-1,3-butadienes and electron-rich alkenes,[3] which is a very appealing strategy in view of the generally exhibited high regiospecificity and diastereoselectivity. In contrast to the formal cycloaddition, however, very few precedents have been disclosed on the asymmetric variants of these reactions, probably due to the low reactivity of 1-azadienes and high propensity of both azadienes and dienophiles to decompose in the presence of Lewis acids.[4-7] Recently, Boger and co-workers developed an asymmetric IEDDA reaction of *N*-sulfonyl-1-aza-1,3-butadienes and enol ethers bearing chiral auxiliaries,[5] and later asymmetric IEDDA reaction of 1-azadienes catalyzed by Lewis acids[6] and organocatalysts[7] were also reported, providing efficient protocols to access a wide variety of optically active compounds of the piperidine type. One drawback with these methods is, however, the removal of (hetero)arylsulfonyl groups, which requires harsh conditions.[8]

Up to now, the chiral auxiliary strategy is still an important technology in asymmetric synthesis from a practical point of view, because the separation of diastereomeric products prior to the cleavage of the chiral auxiliary provides enantiomerically pure products. Sulfinamides, as efficient chiral auxiliaries, have

been widely used in the asymmetric synthesis of amines.[9] One of their appealing advantages is *the convenience to remove the sulfinyl residue from the products*. However, their application in asymmetric IEDDA reaction of 1-azadienes met with significant challenges: (i) due to the lower electron-withdrawing ability of sulfinyl group compared to that of the sulfonyl moiety, the asymmetric IEDDA reaction of *N*-sulfinyl-1-aza-1,3-butadienes with electron-rich olefins was usually conducted under harsh thermal conditions (high temperature or high pressure). Accordingly, either the DA adducts could only exist as reaction intermediates and subsequent aromatization occurred automatically,[10] or the facial selectivity of the reaction of specified substrates was rather low;[11] (ii) the asymmetric three-component variant remains unknown. Therefore the development of novel chiral auxiliaries and new strategies to improve this reaction and extend the reaction scope is still of great significance.

Recently, we reported a diastereoselectivity-switchable and regio-specific hetero Diels–Alder reaction of *N*-sulfinyl per(poly)fluoroalkanesulfinamides with dienes, wherein the chiral induction potential of per(poly)fluoroalkanesulfinamides (PFSAs) was initially demonstrated.[12] On this basis, we became interested in the synthetic potential of PFSAs as novel chiral auxiliaries. Herein we describe a highly diastereoselective three-component IEDDA reaction of α,β-unsaturated ketones, PFSAs and enol ethers. The success of this reaction relies on the strong electron-withdrawing ability of the per(poly)fluoroalkyl groups.

As a starting point, different per(poly)fluoroalkanesulfinamides **2a–d** were prepared from per(poly)fluoroalkyl iodides according to the procedures previously developed by us.[12] Then the three-component reaction of trifluoromethyl α,β-unsaturated ketone **1a**, 2-chlorotetrafluoroethanesulfinamide (**2a**) and ethyl vinyl ether (**3a**) was investigated. After surveying the reaction conditions by varying the water scavenger, solvent, temperature and stoichiometry, we were pleased to find that the reaction occurred readily in CH$_2$Cl$_2$ at room temperature in the presence of 3.0 equiv. Ti(O*i*Pr)$_4$, affording the DA adduct **4a** as a single diastereomer[13] in 65% yield (Table 1, entry 1). Using the most popular *tert*-butanesulfinamide (**2e**) or sterically less demanding *n*-butanesulfinamide (**2f**) as chiral auxiliaries under otherwise identical conditions afforded no DA cycloadducts but the corresponding imine intermediates, undoubtedly owing to the low reactivity of the imine intermediates (Table 1, entries 5 and 6). Other PFSAs (**2b–2d**) were also employed in the three-component IEDDA reaction. All these reactions furnished the corresponding DA adducts with

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Table 1 Effect of sulfinyl groups on the three-component IEDDA reaction[a]
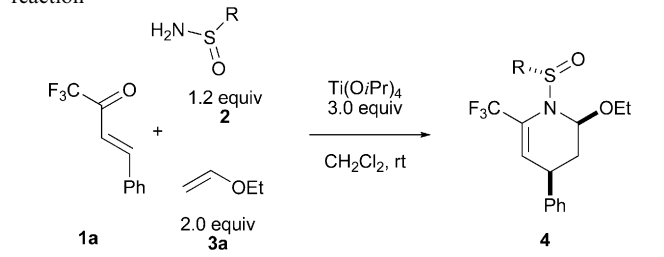
entry	R (2)	4	yield (%)[b]	endo:exo[c]	facial selectivity[c]
1	ClF$_2$CF$_2$C (2a)	4a	65	>35:1	21:1
2	CF$_3$ (2b)	4b	63	>50:1	10:1
3	PhCF$_2$ (2c)	4c	42	>50:1	18:1
4	nC$_4$F$_9$ (2d)	4d	59	>40:1	19:1
5	tBu (2e)	—	—[d]	—	—
6	nBu (2f)	—	—[d]	—	—

[a] Racemic sulfinamides were used. [b] Isolated yield of the major *endo* adduct after column chromatography. [c] Determined by ^{19}F NMR and diagnostic ^{1}H NMR. [d] Only the corresponding imine was isolated.

Table 2 Scope of the dienophiles in the three-component IEDDA reaction[a]
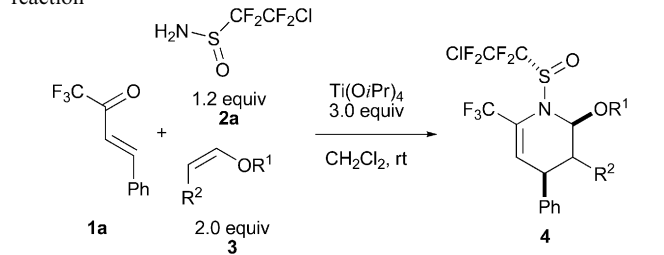
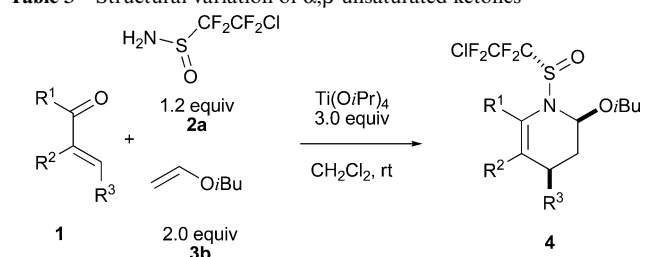| entry	R^1	R^2	4	yield (%)[b]	endo:exo[c]	facial selectivity[c]
1	iBu	H	4e	63	>50:1	26:1
2	nBu	H	4f	67	>80:1	25:1
3	Cy	H	4g	63	16:1	12:1
4	Et	=CH$_2$	4h	46	10:1	8:1
5	—C$_2$H$_4$—		—	—	—	—

[a] Racemic sulfinamide 2a was used. [b] Isolated yield of the major *endo* adduct after column chromatography. [c] Determined by ^{19}F NMR and diagnostic ^{1}H NMR.

good to excellent *endo/exo* and facial diastereoselectivities (Table 1, entries 2–4). The reactivities of the sulfinimines produced *in situ* in the cycloaddition step were proportional to the electron-withdrawing abilities of per(poly)fluoroalkyl groups, which were observed in the following sequence: nC$_4$F$_9$ > CF$_3$ ≈ ClF$_2$CF$_2$C > PhCF$_2$. Among them, sulfinamide 2a provided the best facial selectivity.

The scope of this three-component cycloaddition protocol was explored next. As shown in Table 2, a series of dienophiles were firstly evaluated in the three-component reaction with 1a and 2a under the optimized reaction conditions. In general, monosubstituted vinyl ethers with primary or secondary alkyl substituents at oxygen afforded the cycloadducts smoothly in good yields with good to excellent *endo/exo* and facial diastereoselectivities (Table 2, entries 1–3). Good diastereoselectivity was also observed when allenic ethyl ether (3e) was used as dienophile (Table 2, entry 4). However, in the case of cyclic vinyl ethers such as dihydrofuran
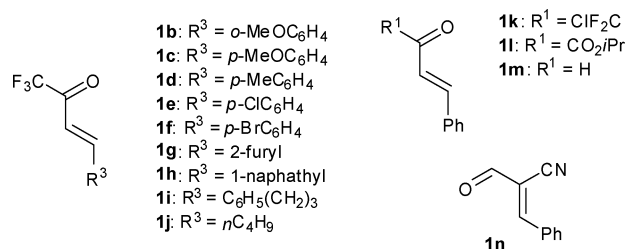
(3f), no desired cycloadducts were obtained owing to the rapid decomposition of ethers in the presence of Lewis acid additive (Table 2, entry 5).

As for the 1-azadiene counterpart, a variety of ketones 1a–1n were surveyed using isobutyl vinyl ether (3b) as the dienophiles under the above conditions (Table 3). Good yields and high levels of *endo*-selectivity and facial diastereoselectivity were achieved in most cases. Aryl substituents of varied electronic and steric nature at the β position (R^3) were well tolerated (Table 3, entries 2–7), with the exception that the bulky naphthyl substituent remarkably lowered the facial selectivity of the corresponding DA adduct 4p (Table 3, entry 8). Decrease in diastereoselectivities was also observed in the asymmetric IEDDA reaction of ketones with aliphatic substituents at the β position (R^3), and the yields were generally quite low with the emergence of byproducts formed by the direct DA reactions of α,β-unsaturated ketones and 3b (Table 3, entries 9–10). Substituents at the carbonyl carbon (R^1) exhibited a pronounced effect on the *endo*-selectivity and facial diastereoselectivity. While the CO$_2$iPr group greatly improved the *endo*-selectivity and facial diastereoselectivity of

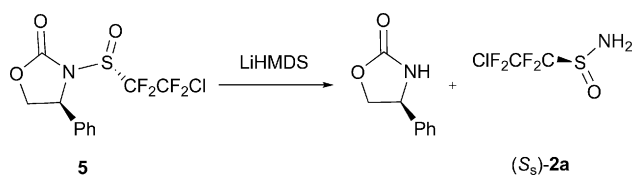# Table 3 Structural variation of α,β-unsaturated ketones[a]

entry	1	4	yield (%)[b]	endo:exo[c]	facial selectivity[c]
1	1a	4e	63	>50:1	26:1
2	1b	4j	65	>60:1	21:1
3	1c	4k	59	43:1	21:1
4	1d	4l	64	53:1	21:1
5	1e	4m	67	>40:1	50:1
6	1f	4n	59	42:1	22:1
7	1g	4o	46	38:1	21:1
8	1h	4p[d]	60	26:1	14:1
9	1i	4q	38	21:1	10:1
10	1j	4r	32	21:1	17:1
11	1k	4s	47	27:1	17:1
12	1l	4t	68	>100:1	>100:1
13	1m	—	—[e]	—	—
14	1n	4v	57 (20)[f]	>100:1	2.6:1

[a] Racemic sulfinamide 2a was used. [b] Isolated yield of the major *endo* adduct after column chromatography. [c] Determined by ^{19}F NMR and diagnostic ^{1}H NMR. [d] The diastereoselectivities were further confirmed by GC-MS analysis of the crude products. [e] Only the corresponding imine was isolated. [f] Isolated yield of the minor *endo* product in parentheses.

1b: R^3 = o-MeOC$_6$H$_4$
1c: R^3 = p-MeOC$_6$H$_4$
1d: R^3 = p-MeC$_6$H$_4$
1e: R^3 = p-ClC$_6$H$_4$
1f: R^3 = p-BrC$_6$H$_4$
1g: R^3 = 2-furyl
1h: R^3 = 1-naphathyl
1i: R^3 = C$_6$H$_5$(CH$_2$)$_3$
1j: R^3 = nC$_4$H$_9$

1k: R^1 = ClF$_2$C
1l: R^1 = CO$_2$iPr
1m: R^1 = H

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the reaction (Table 3, entry 12), the *endo*-selectivity and facial diastereoselectivity were relatively lower in the case of CF_2Cl (Table 3, entry 11). Cinnamaldehyde (**1m**) without an electron-withdrawing group gave no DA adducts due to the low reactivity of the imine intermediate formed in the reaction (Table 3, entry 13). Although the *endo/exo* diastereoselectivity of the DA adduct of acrylonitrile (**1n**) was quite good, the facial diastereoselectivity was only 2.6 : 1, similar to that of the *p*-tolyl substituent counterpart (Table 3, entry 14).[11] It is worth mentioning that the two *endo* products could be easily separated by column chromatography or recrystallization and obtained in pure form respectively.

To further demonstrate the utility of PFSAs as chiral auxiliaries in the asymmetric IEDDA reaction, sulfinamide (S_S)-**2a** was successfully prepared in enantiopure form (>99% ee) by ammonia hydrolysis of 2-chlorotetrafluoroethanesulfinyl-oxazolidione (**5**)[14] with LiHMDS (Scheme 1). The enantioselective three-component IEDDA reaction was then conducted with (S_S)-**2a** and no racemization was observed with product (S_S,2S,4R)-**6** as shown by chiral HPLC analysis (>99.9% ee). The DA adduct (S_S,2S,4R)-**6** could be smoothly converted into a number of valuable compounds (Fig. 1). Limited attempts at direct desulfination of (S_S, 2S,4R)-**6** led only to decomposition.[11] Upon heating in THF, however, disubstituted pyridine **7** was produced efficiently.[10] The transformation of (S_S,2S,4R)-**6** into its 2-hydroxy derivative **8** was readily achieved in 58% yield with complete stereoselectivity[15] by treatment with BCl_3 in CH_2Cl_2, whereas the RO group was removed chemoselectively to give compound **9** by nucleophilic replacement with Et_3SiH/BCl_3 at ambient temperature. Deprotection of compound **9** was achieved conveniently with HCl/Et_2O in MeOH. Without purification, intermediate imine **10**[16] was reduced with $NaBH_3CN$ directly to give a single diastereomer of trifluoromethylated piperidine **11**,[1a,17] a fluorinated common subunit found in compounds of varied pharmacological activities, in 71% total yield with 98% ee.

Fig. 1 Synthetic potential of the cycloadducts.

of these PFSAs in the asymmetric synthesis are in progress in our laboratory.

Scheme 1 Preparation of sulfinamide (S_S)-**2a**.

In conclusion, we have developed a highly stereoselective three-component IEDDA reaction assisted by PFSAs, providing an efficient method for the synthesis of highly functionalized piperidine derivatives (especially trifluoromethylated ones[18]) with excellent *endo/exo* selectivities and facial diastereoselectivities. Initial experiments that highlight the synthetic potential of these piperidine derivatives and the convenient removal of the per(poly)fluoroalkanesulfinyl groups were also presented. It is noteworthy that the use of these PFSA auxiliaries made it possible to monitor the process and stereoselectivities of the reaction conveniently by ^{19}F NMR spectroscopy. Moreover, the one-pot three-component reaction avoided the manipulation of the unstable imine intermediates, extending the scope of IEDDA reaction to specific substrates. Further studies on the applications
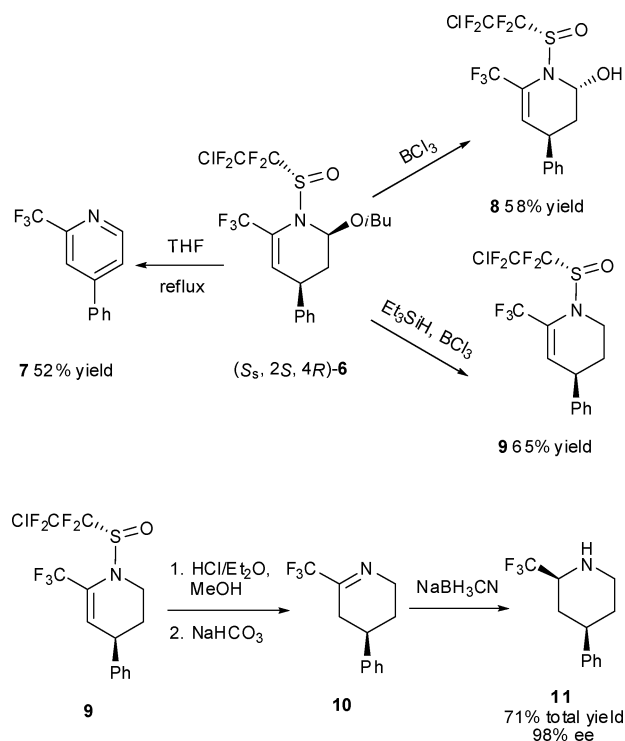
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