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Catalytic Asymmetric Construction of Tertiary Carbon Centers Featuring an α-Difluoromethyl Group with CF_2H-CH_2-NH_2 as the "Building Block"

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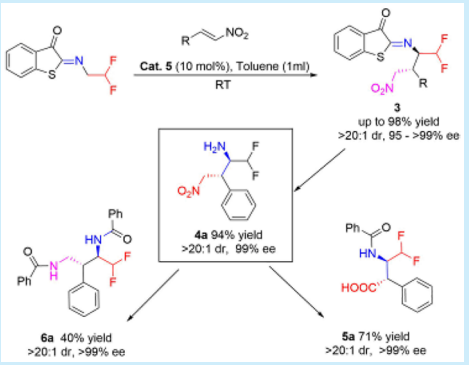
ABSTRACT: We report here for the first time a novel difluoromethylated ketimine building block condensed by thioisatin and difluoroethylamine, offering efficient access to a broad range of enantioenriched products bearing difluoroethylamine units (27 examples, ≤98% yield, >99% ee) in the presence of quinine-derived squaramide. Further transformation of the intermediate would generate a variety of versatile functional blocks like α-difluoromethyl amines, β-amino acid, and β-diamine with retention of the enantiomeric excess at the difluoromethyl-bound carbon.



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It is well-known that hydrogen bonding plays a critical role in the specific interactions of bioactive compounds with chiral receptors like enzymes and proteins, and therefore, it has a wide range of applications in drug design. However, a series of potentially undesirable effects may follow because of the high sensitivity and reactivity of traditional hydrogen bond donors like thiols.[1] It is gratifying that the difluoromethyl group (CF_2H) has exhibited useful properties as a chemically inert surrogate of alcohols, thiols, and other polar functional groups.[2] The incorporation of a difluoromethyl group into various molecules could not only avoid adverse reactions[3] caused by original polar groups and retain a key recognition element for biologic targets but also provide additional benefits due to the effect of fluoroalkyl groups on the physical and biological properties of molecules.[4−7] For instances, upon replacement of 1α-OH groups with 1-CF_2H of calcitriol derivatives, the toxic calcemic activity of target compounds could be greatly decreased (≤20-fold).[3] In addition, the improvement of the inhibition of hepatitis C virus NS3 protease has been successfully achieved through the exchange of a sulfhydryl group and a difluoromethyl group.[8]

A growing amount of attention being paid to difluoromethyl groups in the field of pharmaceutical chemistry has inspired substantial research efforts that aimed to develop general methods for the controlled introduction of difluoromethyl groups into a wide scope of substrates, yet only a handful of effective strategies for the construction of enantioenriched tertiary and quaternary centers bearing CF_2H groups have emerged. To date, the direct fluorination method has not yet been extensively studied.[9] Although excellent enantioselectivity has been achieved in the development of difluoromethylation methods targeting C_{sp^3}–C_{CF_2H} bond construction, the substrate scope of those reports was limited to chiral auxiliary-based imines, mostly based on a precisely designed catalytic model.[10−15] Preparing synthetic building blocks bearing preinstalled CF_2H groups on the prechiral center has been the most widely studied strategy, taking advantage of the easy preparation of fluorinated substrates and the diversity of addition reactions. Seminal works by Funabiki have enabled asymmetric addition of C^{α}-difluoromethyl-substituted aldimines with acetone.[16] Subsequently, the use of diverse imines as precursors for stereoselectively introducing difluoromethyl groups has been reported successively by Zhou and Wang,[17] Qing,[18] and Pozo and Fustero.[19] In those reports, aromatic groups attached to the N-end of the imine were not easily removed, hindering the further application of such blocks. When aldehydes,[20−22] ketones,[23−31] and alkenes,[32−36] carrying a difluoromethyl group, acted as CF_2H-containing building blocks, metal catalytic conditions were normally used.

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Given the limited types of synthetic blocks, we considered that invention of a stable building block could provide an attractive method, easy to implement, for accessing enantioenriched difluoromethyl group-bearing compounds, particularly if it would facilitate the preparation of a wide array of molecular architectures containing the CF_2H groups. Herein, we first reported a building block based on O'Donnell Schiff bases, condensed by thioisatin and difluoroethylamine, which is an active methylene compound prone to alkylation with electrophiles. The block would provide a new, potentially powerful avenue for the enantioselective synthesis of desired compounds bearing γ-nitro-β,β-difluoroethylamine units that could be extended to a series of derivatives possessing useful functional handles such as α-difluoromethyl amines, β-amino acids, and β-diamines when nitroalkene derivatives were chosen as another candidate substrate.

In the past several decades, bifunctional organocatalysts derived from cinchona alkaloids have shown versatile ability in asymmetric alkylation of O'Donnell Schiff base derivatives.[37−40] Hence, initial evaluation of the proposed alkylation was carried out using quinine-derived thiourea **C1** (Figure 1)

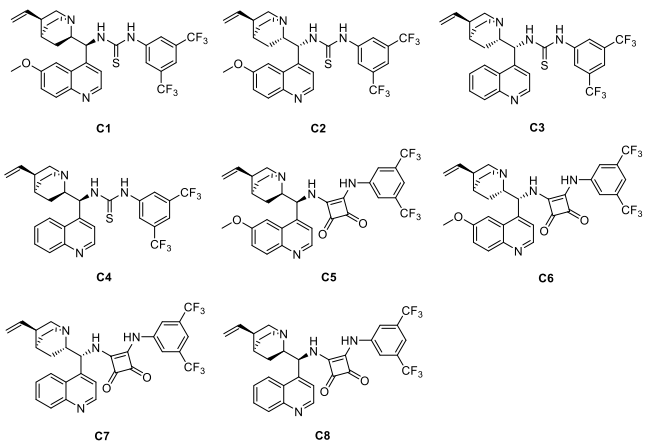
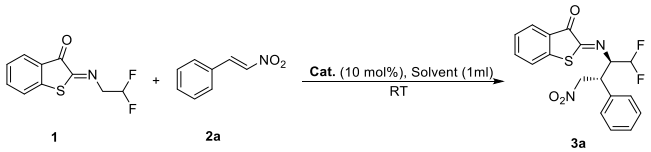


Figure 1. Structures of the catalysts.

as the precatalyst and (*E*)-(2-nitrovinyl)benzene **2a** as the acceptor in toluene at room temperature. Gratifyingly, the desired product **3a** was obtained in 85% yield and 92% ee (Table 1, entry 1). Further extensive evaluation of different cinchona-based thiourea and squaramide [**C2**−**C8** (Figure 1)] provided pretty good yields and enantioselectivity (Table 1, entries 2−8), and quinine-derived squaramide **C5** proved to be the best (Table 1, entry 5).

The influence of solvents and temperature then was studied, showing that the enantioselectivity and yields of reactions were extremely dependent on the solvents used while the ee value of the products was almost unaffected by temperature. The best results were obtained in toluene, furnishing stereoisomer **3a** in 88% yield and 98% ee (Table 1, entry 5). Solvents such as tetrahydrofuran and ethyl acetate led to good performance in terms of yields and ee values (Table 1, entries 9 and 10, respectively). Remarkably, no product was observed in the polar solvent dichloromethane and the protic solvent methanol (Table 1, entries 11 and 12, respectively). In the dipolar solvents acetone and acetonitrile, moderate yields and ee values were obtained (Table 1, entries 13 and 14, respectively). In contrast, the reaction enantioselectivity and diastereoselectivity remained excellent at different temperatures albeit

Table 1. Screening of Reaction Conditions[a]



1 2a 3a

entry	catalyst	solvent	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**C1**	toluene	6	85	>20:1	92
2	**C2**	toluene	6	88	>20:1	−84
3	**C3**	toluene	6	66	>20:1	−88
4	**C4**	toluene	6	80	>20:1	93
5	**C5**	toluene	4	88	>20:1	98
6	**C6**	toluene	4	68	>20:1	−97
7	**C7**	toluene	4	77	>20:1	−96
8	**C8**	toluene	4	61	>20:1	94
9	**C5**	THF	5	96	>20:1	94
10	**C5**	EA	6.5	93	>20:1	87
11	**C5**	DCM	24	nr	–	–
12	**C5**	MeOH	24	nr	–	–
13	**C5**	acetone	24	85	>20:1	88
14	**C5**	acetonitrile	48	68	>20:1	89
15[e]	**C5**	toluene	6	82	>20:1	97
16[f]	**C5**	toluene	8	69	>20:1	97
17[g]	**C5**	toluene	4	89	>20:1	97
18[h]	**C5**	toluene	6	69	>20:1	97
19[i]	**C5**	toluene	9	trace	–	–

[a]Reaction conditions: *N*-2,2-difluoroethylthioisatin ketimines **1** (0.10 mmol), β-nitrostyrenes **2a** (0.15 mmol), catalyst (10 mol %), solvent (1 mL), room temperature. [b]Isolated yield. [c]Determined by chiral HPLC analysis or ^{1}H NMR. [d]Determined by chiral phase HPLC analysis. [e]At 0 °C. [f]At −10 °C. [g]At 35 °C. [h]With 5 mol % catalyst. [i]With 1 mol % catalyst.

with a slight increase or decrease in yield (Table 1, entries 15−17). In addition, an impressive decrease in yields is seen in Table 1 when a range of lower catalyst loadings were used (Table 1, entries 18 and 19). Under 1% catalyst loading, only traces of products were observed (Table 1, entry 19).

The scope of the reaction was investigated (Scheme 1) under the optimal conditions (Table 1, entry 5) using a wide range of β-nitrostyrenes possessing halo substituents such as F (**3d**, **3f**, and **3j**), Cl (**3c** and **3k**), and Br (**3d**, **3g**, and **3l**) or alkyl substituents such as OMe (**3e**, **3h**, and **3m**) and Me (**3n**) on phenyl moieties. Notably, the enantioselectivity of the asymmetric alkylation process was not influenced by the electronic effect of the substituents, whereas the reactivities of 2-substituted nitrostyrenes were significantly reduced compared with those of 3- or 4-substituted substituents. This fact shows that greater steric hindrance might exist when the *ortho*-substituted nitroalkenes combined with *N*-2,2-difluoroethylthioisatin ketimines, and the increase in the reaction energy barrier resulted in a lower reaction conversion rate. To determine the absolute configuration of our products, we grew crystals of compound **3l** and subjected them to X-ray crystallographic analysis (Scheme 1). Regardless, substrates with strong coordination abilities, such as those with a trifluoromethyl (**3i** and **3o**) and double halogen atoms (**3p** and **3q**) on phenyl moieties, still underwent the asymmetric addition to afford the desired products in good yields and enantioselectivities. Only when the hydroxyl group was introduced at the *ortho* position of the benzene ring did the yield decrease sharply to 46%.

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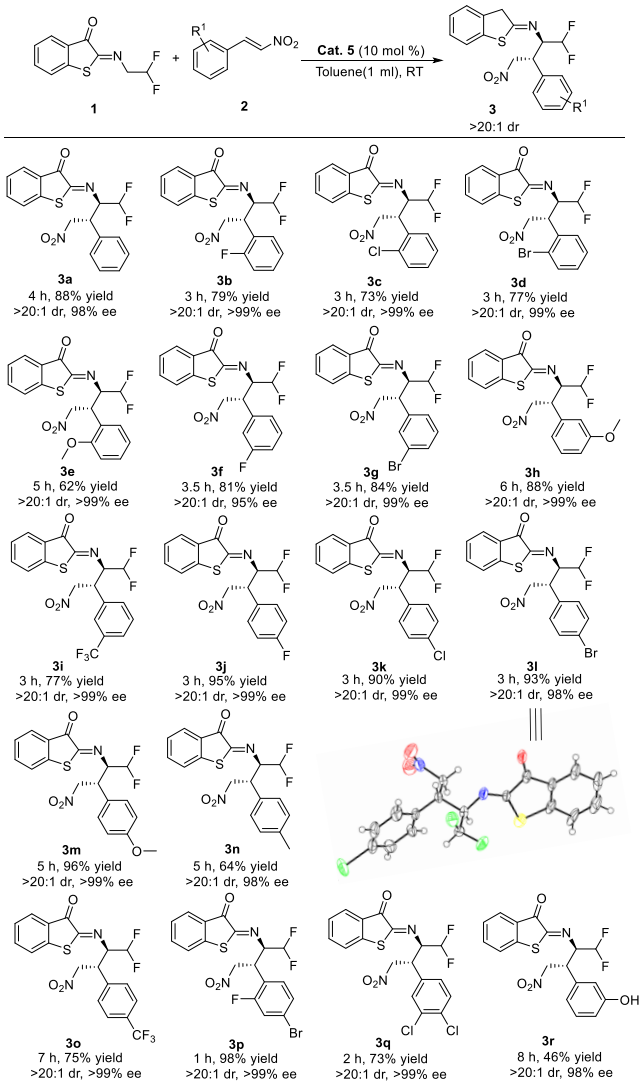
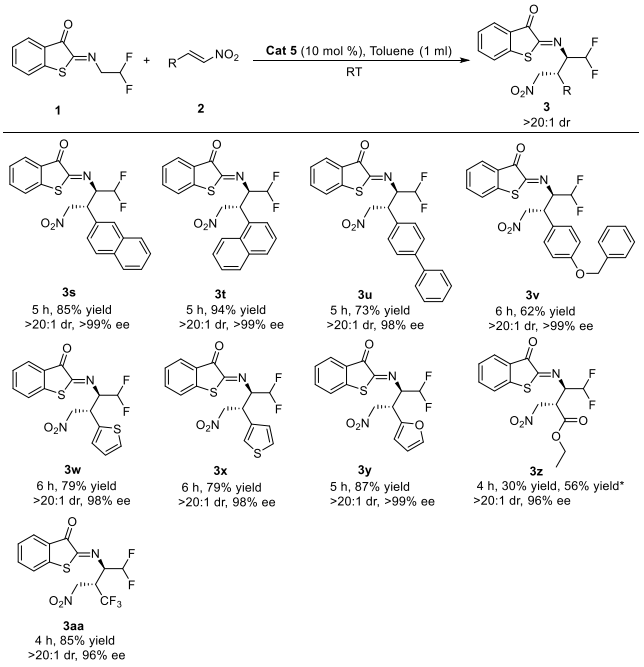
Scheme 1. Scope of β-Nitrostyrenes[a]



[a]The reaction time required for each substrate is given. The yields of the isolated products are reported. The ee values and dr values were determined by HPLC analysis or ^{1}H NMR.

Non-benzene ring-substituted nitroethylenes were also studied. The naphthyl groups of substrates **2** did not hinder the reaction process, and the reactions afforded corresponding product **3s** and **3t** (Scheme 2) in good yield and ee. Biphenyl-containing substrate **2u** was tolerated and gave product **3u** in 73% yield and 98% ee. (*E*)-1-(Benzyloxy)-4-(2-nitrovinyl)-benzene **2v** could be transformed successfully under the reaction conditions, as well. Asymmetric alkylation of *N*-2,2-difluoro-ethylthioisatin ketimines with either a thiophene (**3w** and **3x**) or a furan (**3y**) moiety at the α-position of nitroethylene proceeded smoothly. Even ethyl acetate-containing compound **1z** and CF_3-containing compound **1aa** were also accommodated with minimal impact on enantioselectivity (**3z** and **3aa**, respectively). Although **3z** was obtained in 30% yield, the yield could be increased to 56% when the reaction temperature was increased to 40 °C. To further study the effect of the increase in temperature on the reaction yield, the reaction of substrates **1** and **2a** was carried out at 50 °C, with a decrease in the catalyst loading to 5%. The desired product **3a** was obtained in 70% yield and 97% ee, which shows that the

Scheme 2. Scope of Non-Benzene Ring-Substituted Nitroethylene[a]



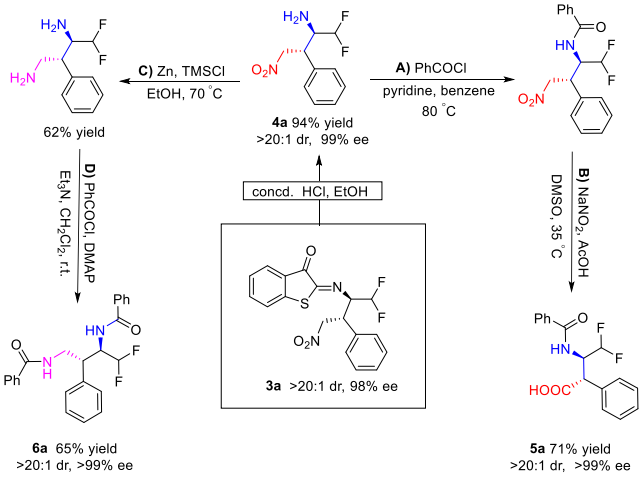
[a]The reaction time required for each substrate is given. The yields of the isolated products are reported. The ee values and dr values were determined by HPLC analysis or ^{1}H NMR. *At 40 °C.

loading of catalyst has a greater impact on the yield of the reaction than the reaction temperature. Under lower catalyst loadings, the desired yield cannot be achieved just by increasing the reaction temperature.

To showcase the practical utility of our new building blocks, we conducted a 2.0 mmol reaction and obtained **3a** in 85% yield and 98% ee.

As noted at the outset, enantioenriched difluoromethylated products are extremely versatile intermediates for the synthesis of important families of compounds bearing CF_2H groups bound to defined stereogenic centers. Several illustrative examples are provided. First, hydrolysis product **4a** (Scheme 3), with a chiral α-difluoromethyl amine unit showing performance better than those of tri- or monofluoromethyl

Scheme 3. Application of Our Developed Building Blocks



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substitutents in regulating the basicity and bioavailability of biologically active molecules,[4] could be offered by removal of thioisatin units under mild acidic conditions. Further reduction of **4a** enables the facile preparation of the chiral α-difluoromethylated vicinal diamine whose synthetic methods were rarely reported,[11] albeit with their ubiquity in natural products.[41] Conversion to **6a** was performed to accurately determine the ee value. The nitryl group in product **4a** could be oxidized to yield the CF_2H-substituted β-amino acid (**5a**) in 92% yield without loss of ee. Such amino acids, different from their α counterparts, are being used to solve the problem of antibiotic resistance. It is very important that none of the conversion processes described above resulted in erosion of the stereochemical purity.

On the basis of the X-ray crystallographic structure of product **3l**, a potential transition mechanism was proposed. As shown in Figure 2, first, the tertiary amine of the squaramide

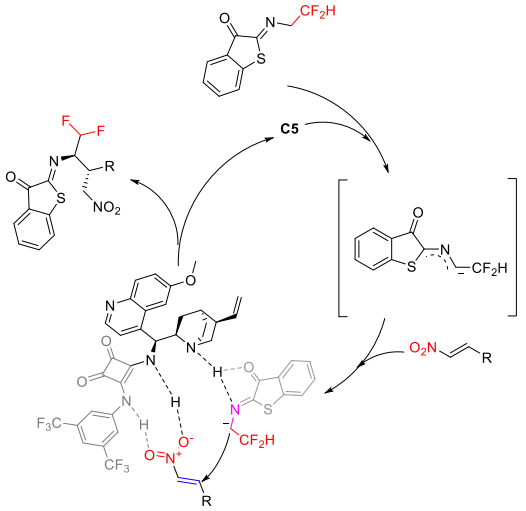

Figure 2. Potential transition mechanism.

catalyst deprotonates ketimine to furnish the methylene ylide intermediate while the squaramide moiety binds and activates the nitroalkene through hydrogen bonds. Subsequently, the bifunctional catalyst drew the two substrates closer in a special way, and the C anion attacked the nitroalkene to give the desirable product.

In summary, we have developed a novel building block from simple starting materials and revealed a promising approach for stereoselective construction of functionalized difluoromethyl-containing adducts with excellent efficiency, remarkable enantioselectivity, and excellent functional group tolerance. Noteworthy is the fact that the newly developed asymmetric alkylation of *N*-2,2-difluoroethylthioisatin ketimines with nitroalkene derivatives has obvious advantages in terms of high reactivity, easy accessibility of raw material, mild reaction conditions, and simple workup, which could effectively simplify the synthesis of α-difluoromethyl-substituted targets. Furthermore, the approach offers a broadly applicable platform enabling efficient access to other useful chiral difluoromethyl-containing building blocks bearing versatile functional groups via further transformation and thus expands the application of this block for research in chemistry, biology, and medicine.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00497.

Representative experimental procedures, details of experiments, necessary characterization data for all new compounds, and NMR spectra for all compounds (PDF)

Accession Codes

CCDC 2059639 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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