Advanced Synthesis & Catalysis

Accepted Article

Title: Enantioselective Mannich-type Reactions to Construct CF3S-containing Stereocenters Catalyzed by Chiral Quaternary Phosphonium Salts

Authors: Gang Zhao, Lijun Xu, Longhui YU, Jun Liu, Hongyu Wang, and Changwu Zheng

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201901621

Link to VoR: http://dx.doi.org/10.1002/adsc.201901621

10.1002/adsc.201901621

COMMUNICATION

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Enantioselective Vinylogous Mannich-type Reactions to Construct CF_3S-Containing Stereocenters Catalysed by Chiral Quaternary Phosphonium Salts

Lijun Xu,[a,b] Longhui Yu,[b] Jun Liu,[b] Hongyu Wang,[b] Changwu Zheng,[c] Gang Zhao[b]*

[a] Research Center of Resource Recycling Science and Engineering, College of Arts and Sciences Shanghai Polytechnic University, 2360 Jinhai Road, Shanghai 201209, China
[b] Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China, E-mail: zhaog@sioc.ac.cn
[c] College of Pharmacy Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract: A series of benzyl trifluoromethyl sulphides bearing a nitro group were utilized as CF_3S-containing building blocks to construct chiral CF_3S-containing molecules via enantioselective vinylogous Mannich-type reactions. In such reactions, high yields and enantioselectivities were obtained using chiral quaternary phosphonium salts derived from amino acids. Moreover, a chiral cyclic urea bearing the CF_3S moiety was obtained from further transformation of the product.

Keywords: trifluoromethylthio-containing building blocks; a nitro group; enantioselectivities; vinylogous Mannich-type reactions; chiral quaternary phosphonium salts

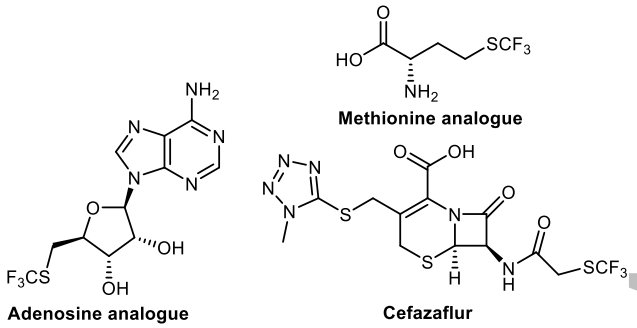
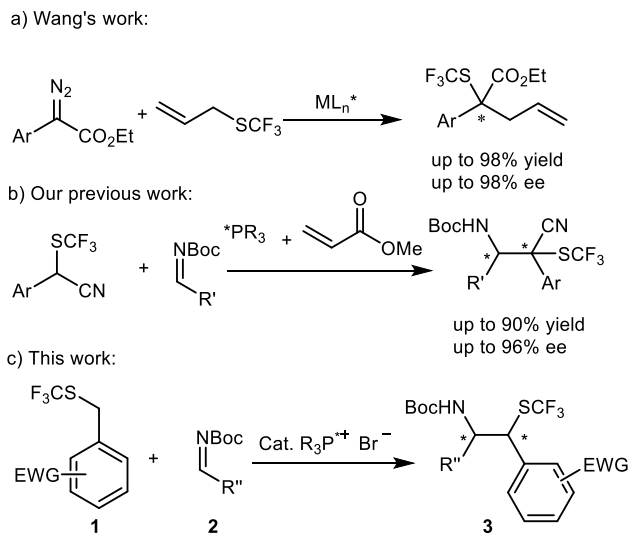


Figure 1. Examples of CF_3S-containing bioactive compounds.

The introduction of fluorine-containing moieties into drugs and biological molecules can greatly improve metabolic stability and other pharmacokinetic properties.[1] In particular, a trifluoromethylthio group (CF_3S) can significantly improve the transmembrane permeability and enhance the metabolic stability of drug candidates due to its high lipophilicity ($\pi = 1.44$) and electron-withdrawing characteristics.[2] Over the past decades, a great number of biologically active molecules containing CF_3S have been developed as important pharmacophores and agrochemicals, including methionine analogues, adenosine analogues, and cefazaflur (Figure 1).[3] Recently, extensive efforts have been focused on the direct introduction of the CF_3S group into functionalized molecules,[4] but few advances have been made in the construction of CF_3S-containing chiral centres. Generally, there are two different strategies for accomplishing the above goal: 1) direct trifluoromethylthiolation with electrophilic trifluoromethylthiolating reagents via asymmetric catalysis;[5] 2) the development of readily accessible CF_3S-containing building blocks for constructing chiral compounds. Until now, these strategies have emerged as the ideal approaches for the incorporation of CF_3S into small molecules. However, in comparison to the first direct method, the latter with higher atom economy has not been as extensively researched in the past few years. In 2017, Wang et al. developed an efficient approach for the enantioselective construction of the chiral $C(sp^3)$–SCF_3 bond via Rh(II)- and Cu(I)-catalysed [2,3]-sigmatropic rearrangements of sulfonium ylide (Scheme 1, a).[6] Our group has also reported the enantioselective Mannich-type reactions using cyano-substituted benzyl trifluoromethyl sulphides to construct tetrasubstituted carbon stereocenters via asymmetric dual-reagent catalysis (Scheme 1, b).[7] The cyano group was crucial for enhancing the reactivity of substrate, but its presence resulted in difficulties with further transformation of the product, which thereby limited the possible applications of such method.

10.1002/adsc.201901621

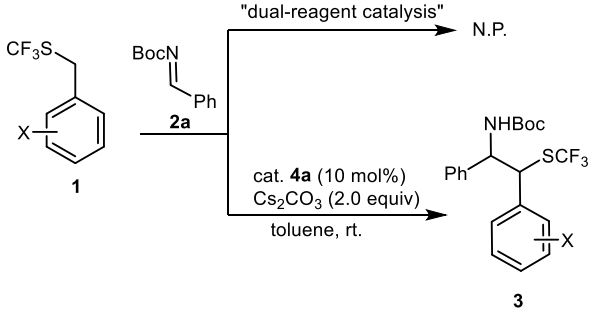


Scheme 1. Enantioselective reactions involved CF_3S-containing nucleophiles.

Hence, the development of other CF_3S-containing building blocks for constructing chiral compounds is still needed. Moreover, our attention has been drawn to the asymmetric vinylogous addition reaction for the formation of stereocenters. Fan et al.,[8] Wang et al.,[9] and Jørgensen et al.[10] have independently reported an effective vinylogous Michael reaction of aryl methyl nucleophiles bearing strongly electron-withdrawing groups with α, β-unsaturated aldehydes. Herein, benzyl trifluoromethyl sulphide with an electron-withdrawing group (**1**)[11] was evaluated as a simple and readily available CF_3S-containing building blocks for the asymmetric vinylogous Mannich-type addition (Scheme 1, c).

Initially, the vinylogous Mannich-type reaction using 2-nitrobenzyl trifluoromethyl sulphide (**1a)** with the *N*-Boc imine (**2a)** was examined via asymmetric dual-reagent catalysis (Table 1, entry 1). However, no product was observed under the previous conditions. In view of the excellent properties of quaternary phosphonium salts derived from amino acids in the asymmetric synthesis,[12] utilizing such salts might improve the above enantioselective reactions. The corresponding product **3** could be obtained with 90% yield as a mixture of diastereoisomers and 83% *ee* of major diastereoisomers when the reaction was carried out using catalyst **4a** and Cs_2CO_3 (Table 1, entry 2). After the synthesis of the diastereoisomers, control experiments were also performed to elucidate the vital role of the nitro group. For example, the reaction with $BnSCF_3$ without the nitro group (**1b**) could not proceed under the catalytic system. Additionally, other electron-withdrawing groups such as the ester (**1c**) and cyano groups (**1d**) were also tested, but no reactions were catalysed by **4a** (Table 1, entry 3–5). Moreover, the CF_3S-containing building blocks that were meta-

Table 1 Preliminary research on the activated aryl sulfanes.[a]



Entry	X, 1	3	Yield (%)[b]	*dr*[c]	*ee*(%)[c]
1[d]	*o*-NO_2, **1a**	–	N.P.	–	–
2	*o*-NO_2, **1a**	**3aa**	90	83:17	83
3	H, **1b**	–	N.P.	–	–
4	*o*-CO_2Me, **1c**	–	N.P.	–	–
5	*o*-CN,**1d**	–	N.P.	–	–
6	*m*-NO_2, **1e**	–	N.P.	–	–
7	*p*-NO_2, **1f**	**3fa**	87	57:43	12

[a] The reactions were performed with **1** (0.1 mmol), **2a** (0.2 mmol), **4a** (10 mol%) in the presence of Cs_2CO_3 (0.2 mmol) in toluene (1.0 mL) and stirred at room temperature and the product **3** was obtained as mixtures of diastereoisomers.
[b] Isolated yields of **3**.
[c] The *dr* and *ee* values were determined by chiral HPLC analysis; *ee* values of the major diastereoisomers.
[d] The condition of the asymmetric dual-reagent catalysis was shown in the supporting information.

and para-substituted with nitro groups (**1e**, **1f**) were then investigated under the same conditions (Table 1, entry 6–7). Only the *para*-substituted substrate was suitable for the reaction but with low enantioselectivity. No reaction proceeded when the *meta*-substituted benzyl trifluoromethyl sulphide was used in the reaction. Therefore, the electronic properties of the nitro group and its ortho-position on the ring could enhance the acidity of the benzyl protons[13] and thereby trigger the desired transformation via vinylogous Mannich-type addition. Furthermore, various protecting groups of the imine were also tested, including *p*-toluenesulfonyl (Ts) and benzyloxycarbonyl (Cbz), but the corresponding yields and enantioselectivities did not improve with such protecting groups.

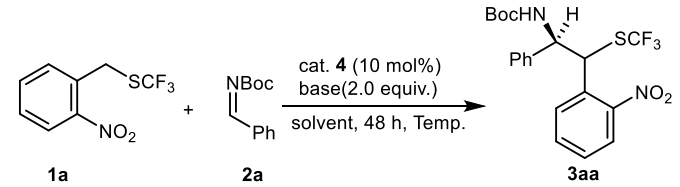
To further improve the enantioselectivity of the reaction, various catalysts, inorganic bases, and solvents were investigated. As shown in Table 2, no

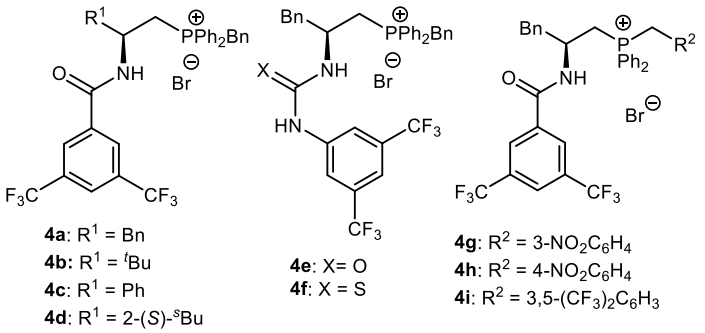
10.1002/adsc.201901621

desired products were observed when NaOAc, Na_2CO_3, or K_2CO_3 were used as the base (Table 2, entries 1–4). The reaction with the strong base KOH produced the desired product with good yield but decreased stereoselectivity (Table 2, entry 5). We found that both diastereoselectivity and enantioselectivity of the corresponding products could be greatly increased by decreasing the reaction temperature to 0 °C, albeit with extended reaction time (Table 2, entry 6). Next, a series of chiral bifunctional quaternary phosphonium salts were synthesized and evaluated as catalysts. Among the different catalysts screened, the chiral skeleton derived from L-phenylalanine performed best in terms of enantioselectivity and diastereoselectivity (Table 2, entry 6 versus entries 7–9). Moreover, the amide group of bifunctional chiral phosphine catalysts seemed to be crucial for enantiocontrol in the reaction. Replacement of this amide moiety with thiourea (**4e**) or urea (**4f**) led to inferior results (Table 2, entries 10 and 11). Further investigations determined that the different benzyl groups of the phosphonium centre were also crucial to the enantioselectivity (Table 2, entries 12–14). Catalyst **4g**, which contained the nitro group on the meta-position, performed the best under the same reaction conditions with 88% total isolated yield and 92% *ee* of the major diastereoisomers (Table 2, entry 12). We also investigated the effect of various solvents on the Mannich-type reactions, but no improvement in enantioselectivity was observed (entries 15–19).

With these optimized reaction conditions, we then turned our attention towards exploring the generality of the method with various *N*-Boc imines (**2**). As summarized in Table 3, different substituted chiral

Table 2. Optimization of chiral catalysts as well as other conditions.[a]





Entry	Cat.	Sol.	Base	T (°C)	Yield (%)[b]	*dr*[c]	*ee* (%)[c]
1	**4a**	toluene	NaOAc	rt.	N.P.	–	–
2	**4a**	toluene	Na_2CO_3	rt.	N.P.	–	–
3	**4a**	toluene	K_2CO_3	rt.	N.P.	–	–
4	**4a**	toluene	Cs_2CO_3	rt.	90	83:17	83
5	**4a**	toluene	KOH	rt	91	61:39	29
6	**4a**	toluene	Cs_2CO_3	0	89	86:14	90
7	**4b**	toluene	Cs_2CO_3	0	89	28:72	4
8	**4c**	toluene	Cs_2CO_3	0	88	75:25	67
9	**4d**	toluene	Cs_2CO_3	0	90	33:67	17
10	**4e**	toluene	Cs_2CO_3	0	81	71:39	-16
11	**4f**	toluene	Cs_2CO_3	0	77	64:36	6
12	**4g**	toluene	Cs_2CO_3	0	88	90:10	92
13	**4h**	toluene	Cs_2CO_3	0	91	72:28	11
14	**4i**	toluene	Cs_2CO_3	0	90	79:21	8
15	**4g**	DCM	Cs_2CO_3	0	89	71:29	30
16	**4g**	Et_2O	Cs_2CO_3	0	68	88:12	78
17	**4g**	THF	Cs_2CO_3	0	61	66:34	7
18	**4g**	MeCN	Cs_2CO_3	0	86	53:47	*Rac*.
19	**4g**	Mesitylene	Cs_2CO_3	0	91	90:10	91

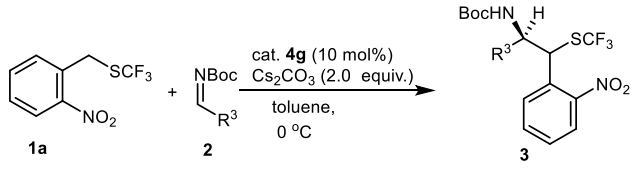
[a] Unless otherwise noted, the reactions were performed with **1a** (0.1 mmol), **2a** (0.2 mmol), the chiral chiral quaternary phosphonium salts **4** (10 mol%) in the presence of base (0.2 mmol) in solvent (1.0 mL) and stirred for 48 h and the product **3aa** was obtained as mixtures of diastereoisomers.

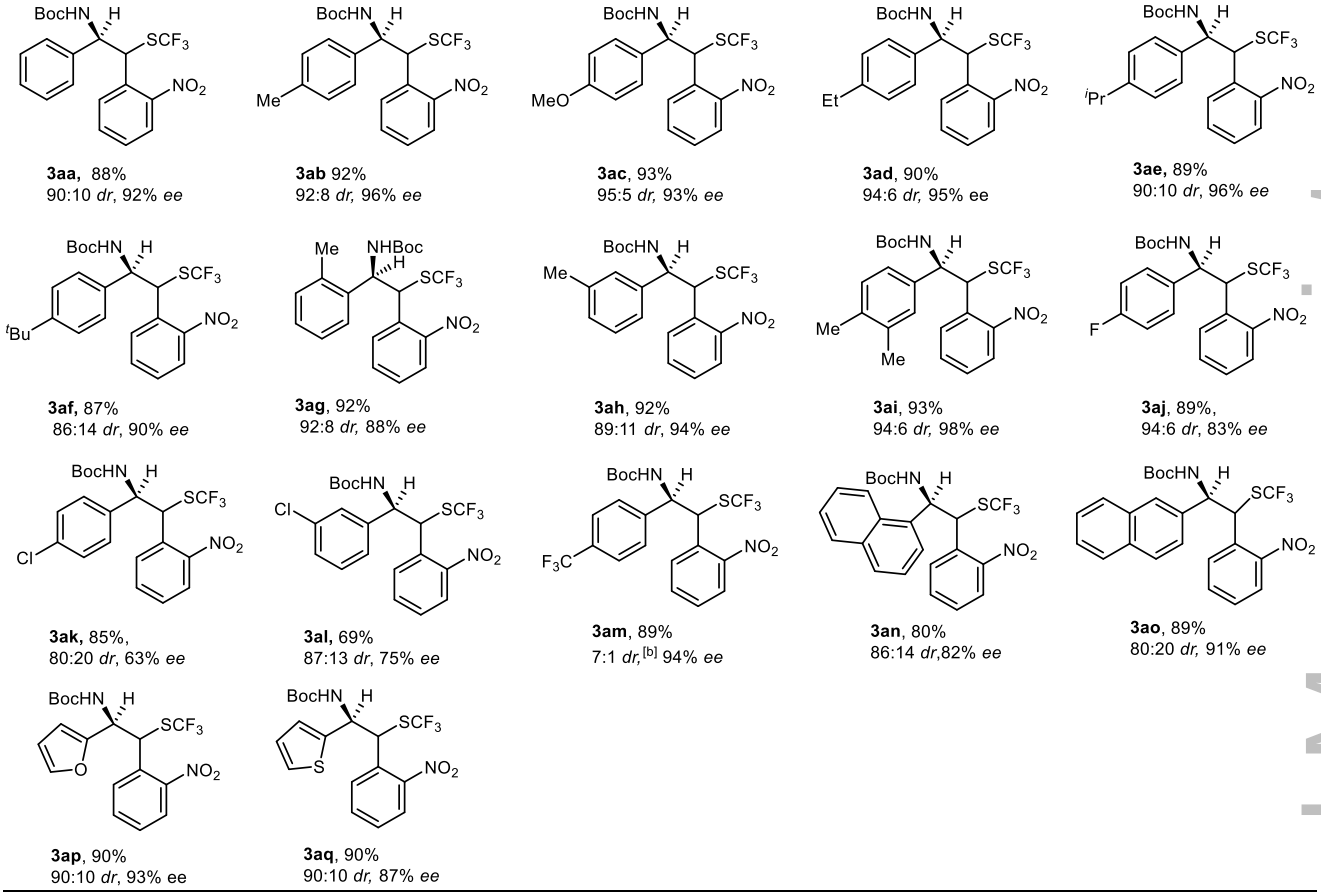
[b] Isolated yields of **3aa**; N.P. : no products.

[c] The *dr* and *ee* values were determined by chiral HPLC analysis; *ee* values of the major diastereoisomers.

CF_3S-containing amines were obtained in moderate to excellent yields of two diastereoisomers (69–93%), mostly over 90% *ee* of the major diastereoisomers and

Table 3. Scope of the Mannich-type reaction catalyzed by quaternary phosphonium catalysis.[a]





[a] Unless otherwise noted, the reactions were performed with **1a** (0.1 mmol), **2** (0.2 mmol), chiral catalyst **4g** (10 mol%) in the presence of Cs_2CO_3(0.2 mmol) in toluene (1.0 mL) at 0 °C for 48 h; The product **3** was obtained as mixtures of diastereoisomers; Isolated yields of **3**; The *dr* and *ee* values were determined by chiral HPLC analysis; *ee* values of the major diastereoisomers.

[b] The *dr* value was determined by ^{1}H NMR of the product; No ee value of the minor diastereoisomers.

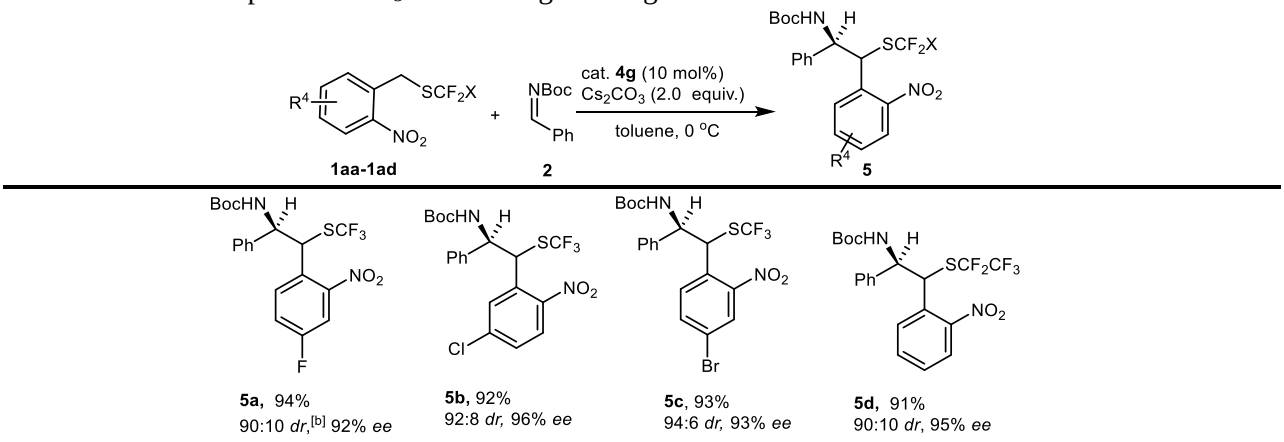
moderate levels of diastereoselectivity, including alkyl (**3ab**, **3ad**–**3ai**), alkoxyl (**3ac**) and halide (**3aj**–**3al**) groups, at different positions on the phenyl group of imines. Generally, substrates with an electron-donating group produced higher yields and *ee* values of major diastereoisomers compared with those of other substrates bearing halide groups (**3ab** versus **3aj**, **3ak**). Particularly, the aryl imine bearing dimethyl groups on the phenyl reacted efficiently to produce **3ai** in 93% yield and 98% *ee* of major diastereoisomers. While the other aryl imine possessing a CF_3 group produced the chiral amine **3am** in 89% yield and 94% *ee* of major diastereoisomers, which was probably due to steric effects. Additionally, polycyclic and heteroaryl aromatic imines were viable under the reaction conditions, with corresponding products (**3an**–**3aq**) in good yields (80–90%) and high enantioselectivities of major diastereoisomers (82–93% *ee*).

Next, the influence of different substituents on the CF_3S-containing nucleophiles (**1)** on the vinylogous Mannich-type reaction was further evaluated. As presented in Table 4, halide pronucleophiles produced the desired products in 92–94% yields **(5a**–**5c)** and 92–96% *ee* of major diastereoisomers. Additionally, the reaction proceeded smoothly with the C_2F_5 substituted sulphide to produce the product **5d** in 91% yield and 95% *ee* of major diastereoisomers. The CF_3CF_2S group has been proven to be an important moiety in several agrochemical and pharmaceutical compounds, [14] and a few methods for the preparation of analogous

CF_3CF_2S-containing compounds have been described in literature. [15]

To demonstrate the modifiability of the products, compound **3ab** (96% *ee* of major diastereoisomers) was subjected to the removal of the Boc group,

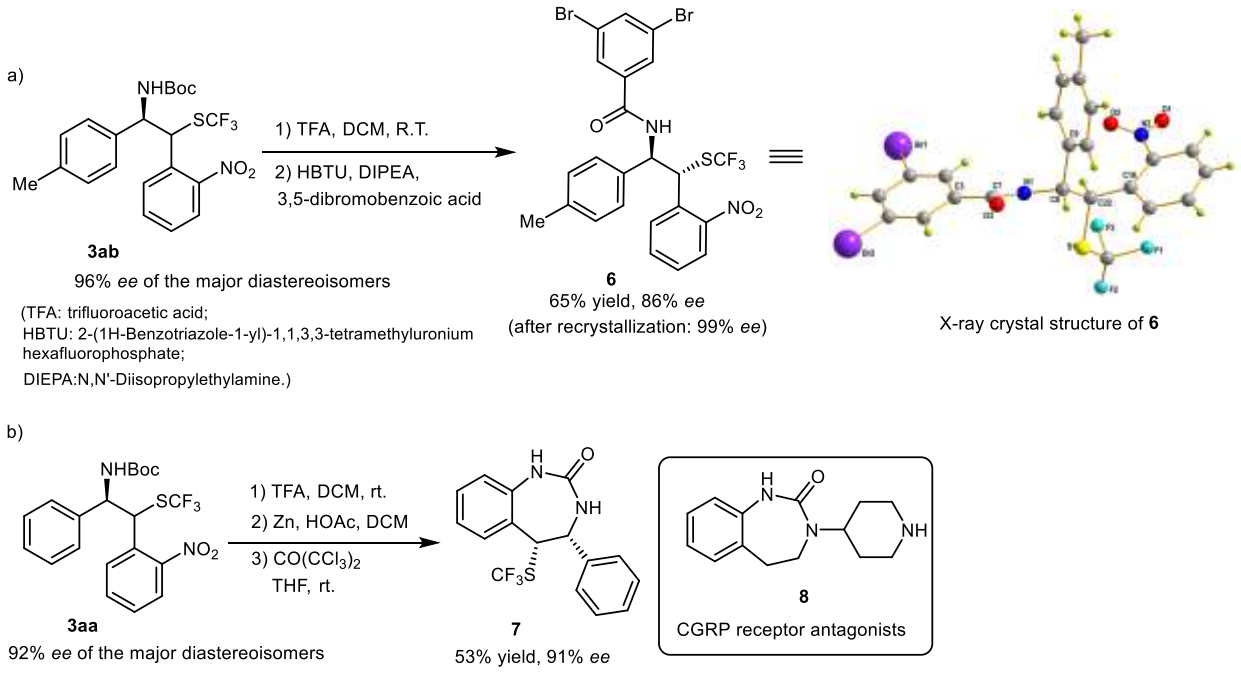
Table 4. Substrate scope of the CF_3S-containing building blocks.[a]



[a] Unless otherwise noted, the reactions were performed with **1** (0.1 mmol), **2a** (0.2 mmol), chiral catelyst **4g** (10 mol%) in the presence of Cs_2CO_3 (0.20 mmol) in toluene (1.0 mL) at 0 °C for 48 h; The product **5** was obtained as mixtures of diastereoisomers; Isolated yields of **5**; The *dr* and *ee* values were determined by chiral HPLC analysis; *ee* values of the major diastereoisomers.

[b] The *dr* value was determined by ^{1}H NMR of the product.

followed by treatment with 3,5-dibromobenzoic acid to produce the chiral amide **6** in 65% yield and 86% *ee* over two steps (Scheme 2, a). The absolute configuration of the chiral amide **6** was confirmed by X-ray crystallographic analysis, from which the absolute structure of the major diastereoisomers was deduced to be (1*R*, 2*R*). Additionally, compound **3aa** was converted to the chiral cyclic urea **7** in 53% yield while preserving the high enantioselectivity (Scheme 2, b). Notably, the seven-membered heterocyclic 1,3-benzodiazepin-2-one skeletons have constituted a core structural unit of many bioactive compounds,[16] such as compound **8**, which have been used as calcitonin gene-related peptide (CGRP) receptor antagonists for the treatment of migraines.[17]



Scheme 2. Representative transformation

Based on our previous works,[12a–12d] the mechanism of this catalyst system was considered to form a possible transition state as illustrated below. We proposed that the amide moiety of catalyst **4g** might activate the *N*-Boc imine via H-bonding interactions, while the phosphonium centre might direct the nucleophile through static electronic interactions. The nitronate anion derived from **1a** was from the *Si* face of the

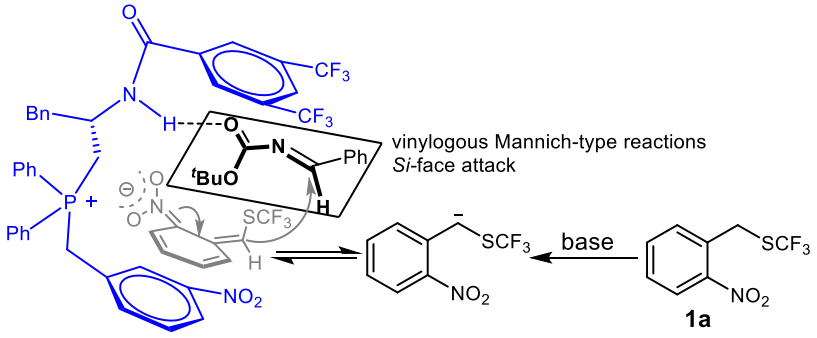


Figure 2. Possible transition state**.**

imine to avoid steric repulsion between the phenyl groups of the imine and the catalyst (Figure 2).

In summary, we have developed asymmetric vinylogous Mannich-type reactions to develop CF_3S-containing stereocenters via quaternary phosphonium catalysts. The nitro group in the substrate could be essential for the progress of the reaction due to its electronic properties and ortho-position on the ring. Additionally, the product can be further functionalized to give a chiral tetrahydrobenzodiazepin-2-one, which is a potentially useful drug development candidate, in high efficiency while maintaining high enantioselectivity. Moreover, further investigation of the mechanism and synthetic applications of this transformation are underway in our lab.

Experimental Section

A mixture of the CF_3S-containing building blocks **1** (0.1 mmol), imine **2** (0.2 mmol) and catalyst **4g** (10 mol%) in toluene (1.0 mL) were cooled to 0 ˚C before Cs_2CO_3 (0.2 mmol) was introduced. The reaction was stirred for 48 h and completed according to TLC analysis. The crude mixture were warmed to the room temperature and quenched by water (3.0 mL). The aqueous phase was extracted with EtOAc (3 × 5.0 mL), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel: petroleum ether/AcOEt = 10 : 1) to afford the products **3** or **5**.

X-Ray Crystallographic Data of 6

CCDC-1526782 (**6**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

This work was sponsored by the National Natural Science Foundation of China (Nos. 21272247, 21572247, 21871282), the Chinese Academy of Sciences (XDB 20020100) and Shanghai Sailing Program (C81YF19S001). We are grateful for the financial support from the Gaoyuan Discipline of Shanghai–Environmental Science and Engineering (Resource Recycling Science and Engineering).

References

[1] a) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886; b) D. O'Hagan, *J. Fluorine Chem.* **2010**, *131*, 1071–1081; *Chem. Soc. Rev.* **2008**, *37*, 308; c) P. Jeschke, *ChemBioChem* **2004**, *5*, 570–589; d) Y. Zhou J. Wang, Z.-N. Gu, S.-N. Wang, W. Zhu, J. L. Aceñ, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116* 422–518; e) N. Tsomaia, *Eur. J. Med. Chem.* **2015**, *94*, 459-470; f） C. Isanbor, D. O'Hagan, *J. Fluorine Chem.* **2006**, *127*, 303–319; g) S. Preshlock, M. Tredwell, V. Gouverneur, *Chem. Rev.* **2016**, *116*, 719–766.

[2] a) A. Leo, C. Hansch, D. Elkins, *Chem. Rev.* **1971**, *71*, 525–616; b) C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165–195; c) J. Chen, B. R. Dixon, J. Dumas, D. Brittelli, *Tetrahedron Lett.* **1999**, *40*, 9195–9199.

[3] X.-H. Xu, K. Matsuzaki, N. Shibata, *Chem. Rev.* **2015**, *115*, 731–764.

[4] a) G. Teverovskiy, D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011,** *50*, 7312–7314; *Angew. Chem.* **2011**, *123*, 7450–7452; b) W.-T. Xu, J.-Y. Ma, X. - A. Yuan, J. Dai, J. Xie, C.-J. Zhu, *Chem. Commun.*, **2019**, *55*, 9479–9482; c) M. Hu, C. Ni, J. Hu, *J. Am. Chem. Soc.* **2012**, *134*, 15257–15260; d); S. Dix, M. Jakob, M. N. Hopkinson, *Chem. Eur. J.* **2019**, *25*, 7635–7639; e) P. Saravanan, P. Anbarasan, *Chem. Commun.* **2019**, *55*, 4639–4642; f) C. Zhang, D. A. Vicic, *J. Am. Chem. Soc.* **2012**, *134*, 183–185; g) L.-Q. Jiang, Q. Yan, R.-K. Wang, T.-Q. Ding, W.-B. Yi, W. Zhang, *Chem. Eur. J.* **2018**, *24*, 18749–18756; h) W.-T. Xu, J.-Y. Ma, X. - A. Yuan, J. Dai, J. Xie, C.-J. Zhu, *Angew. Chem. Int. Ed.* **2018**, *57*, 10357–10361; *Angew. Chem.* **2018**, *130*, 10514–10518; i) L. Liu, X. Xu, Z. Chen, F.-L. Qing, *Angew. Chem. Int. Ed.* **2015**, *54*, 897–900; *Angew. Chem.* **2015**, *127*, 911–914; j) J. Maury, G. Force, B. Darses, D. Lebœuf, *Adv. Synth. Catal.* **2018**, *360*, 2752–2756; k) N. Fuentes, W. Kong, L. Fernández-

Sánchez, E. Merino, C. Nevado *J. Am. Chem. Soc.* **2015**, *137*, 964–973; l) H. Chachignon, E. V. Kondrashov, D. Cahard, *Adv. Synth. Catal.* **2018**, *360*, 965–971; m) X.-L. He, S. Majumder, J. Wu, C.-D. Jin, S.-R. Guo, Z.-P. Guo, M.-H. Yang, *Org. Chem. Front.*, **2019**, *6*, 2435–2440; n) S. Pan, Y. G. Huang, X.-H. Xu, F.-L. Qing, *Org. Lett.* **2017**, 19, 4624–4627; o) S. Pan, H. Li, Y. G. Huang, X.-H. Xu, F.-L. Qing, *Org. Lett.* **2017**, *19*, 3247–3250; p) S.-B. Zhang, X.-H. Xu, F.-L. Qing, *J. Fluorine Chem.* **2019**, *227*, 109367; q) X.-W. Xia, B.-C. Chen, X.-J. Zeng, B. Xu, *Adv. Synth. Catal.* **2018**, *360*, 4429–4434; r) C. Chen, Y. Xie, L. Chu, R.-W. Wang, X. Zhang, F. L. Qing, *Angew. Chem. Int. Ed.* **2012**, *51*, 2492–2495; *Angew. Chem.* **2012**, *124*, 2542–2545; s) G. Danoun, B. Bayarmagna, M. F. Grünberg, L. J. Goossen, *Chem. Sci.* **2014**, *5*, 1312–1316; t) B. Bayarmagna,; C. Matheis, E. Risto, L. J. Goossen, *Adv. Synth. Catal.* **2014**, *356*, 2343–2348; u) F. A. Baert, J. Colomb, T. Billard, *Angew. Chem. Int. Ed.* **2012**, *51*, 10382–10385; *Angew. Chem.* **2012**, *124*, 10528–10531; v) S. Alazet, L. Zimmer, T. Billard, *Angew. Chem. Int. Ed.* **2013**, *52*, 10814–10817; *Angew. Chem.* **2013**, *125*, 11014–11017; w) I. Saidalimu, T. Yoshioka, Y.-M. Liang, E. Tokunaga, N. Shibata, *Chem. Commun.*, **2018**, *54*, 8761–8764; x) C. Xu, B. Ma, Q.-L. Shen, *Angew. Chem. Int. Ed.* **2014**, *53*, 9316–9320; *Angew. Chem.* **2014**, *126*, 9470–9474; y) X. Shao, X. Wang, T. Yang, L. Lu, Q. Shen, *Angew. Chem. Int. Ed.* **2013**, *52*, 3457–3460; *Angew. Chem.* **2013**, *125*, 3541–3544; z) Y. Yang, N. Shibata, *J. Am. Chem. Soc.* **2013**, *135*, 8782–8785.

[5] a) S.-S. Li, J.-B. Wang, *Acta Chim. Sinica* **2018**, *76*, 913–924; b) T. Bootwicha, X. Liu, R. Pluta, I. Atodiresei, M. Rueping, *Angew. Chem. Int. Ed.* **2013**, *52*, 12856–12859; *Angew. Chem.* **2013**, *125*, 13093–13097; c) X.Q. Wang, T. Yang, X. Cheng, Q. Shen, *Angew. Chem. Int. Ed.* **2013**, *52*, 12860–12864; *Angew. Chem.* **2013**, *125*, 13098–13102; d) X.-L. Zhu, J.-H. Xu, D.-J. Cheng, L.-J. Zhao, X.-Y. Liu, B. Tan, *Org. Lett.* **2014**, *16*, 2192–2195; e) X. Liu, R. An, X. Zhang, J. Luo, X.-D. Zhao, *Angew. Chem. Int. Ed.* **2016**, *55*, 5846–5850; *Angew. Chem.* **2016**, *128*, 5940–5944; f) X. Liu, Y.-Y. Liang, J.-Y. Ji, J. Luo, X.-D. Zhao, *J. Am. Chem. Soc.* **2018**, *140*, 4782–4786; g) J. Luo, Q.-X. Cao, X.-H. Cao, X.-D. Zhao, *Nat. Commun.* **2018**, *9*, 527; h) T. Qin,Q.-B. Jiang, J.-Y. Ji, J. Luo, X.-D. Zhao, *Org. Biomol. Chem.*, **2019**, *17*, 1763–1766; i) J. Luo, Y.-N Liu, X.-D. Zhao, *Org. Lett.* **2017**, *19*, 3434–3437; j) M.-Y. Jin, J.-C. Li, R.-K. Huang, Y.-X. Zhou, L.-W. Chung, J. Wang, *Chem. Commun.*, **2018**, *54*, 4581–4584; k) H. Zhang, X.-B. Leng, X.-L, Wan, Q.-L. Shen, *Org. Chem. Front.* **2017**, *4*, 1051–1057.

[6] Z.-K. Zhang, Z. Sheng, W.-Z. Yu, G.-J. Wu, R. Zhang, W.-D. Chu, Y. Zhang, J.-B. Wang, *Nature Chem.* **2017**, *9*, 970–976.

[7] a) L.-J. Xu, H.-Y. Wang, C.-W. Zheng, G. Zhao, *Adv. Synth. Catal.* **2017**, *359*, 2942–2948; b) H.-Y. Wang, K. Zhang, C.-W. Zheng, Z. Chai, G. Zhao, *Angew. Chem. Int. Ed.* **2015**, *54*, 1775–1779; c) Y.-P. Lou, C.-W. Zheng, G. Zhao, Z. Li, *Org. Lett.* **2015**, *17*, 688–691; d) d) R.-M. Pan, J.-X. Zhang, C.-W. Zheng, H.-Y. Wang, D.-D. Cao, W.-G. Cao, G. Zhao, *Tetrahedron* **2017**, *73*, 2349–2358.

[8] Y. Zhang, B.-W. Wei, H. Lin, W.-R. Cui, X.-Q. Zeng, X.-L. Fan, *Adv. Synth. Catal.* **2015**, *357*, 1299–1304.

[9] T.-F. Li, J. Zhu, D.-Y. Wu, X.-M. Li, S.-N. Wang, H. Li, J. Li, W. Wang, *Chem. Eur. J.* **2013**, *19*, 9147–9150.

[10] L. Dell'Amico, X. Companyó, T. Naicker, T. M. Bräuer, K. A. Jørgensen, *Eur. J. Org. Chem.* **2013**, 5262–5265.

[11] a) M. Jiang, F.-X. Zhu, H.-Y. Xiang, X. Xu, L.-F. Deng, C.-H. Yang, *Org. Biomo. Chem.* **2015**, *13*, 6935–6939; b) T. Billard, B. R. Langlois, *Tetrahedron Lett.* **1996**, *37*, 6865–6868; c) B. R. Langlois,T. Billard, J. C. Mulatier, C. Yezeguelian, *J. Fluorine Chem.* **2007**, *128*, 851–856; d) C. Chen, X.-H. Xu, B. Yang, F.-L. Qing, *Org. Lett.* **2014**, *16*, 3372–3375; e) D.-D. Kong, Z. Jiang, S.-G. Xin, Z.-S. Bai, Y.-F. Yuan, Z.-Q. Weng, *Tetrahedron* **2013**, 69, 6046–6050.

[12] a) D.-D. Cao, J.-X. Zhang, H.-Y. Wang, G. Zhao, *Chem. Eur. J.* **2015**, *21*, 9998–10002; b) D.-D. Cao, G.-S.Fang, J.-X. Zhang, H.-Y. Wang, C.-W. Zheng, G. Zhao, *J. Org. Chem*. **2016**, *81*, 9973–9982; c) J.-X. Zhang, D.-D. Cao, H.-Y. Wang, C.-W. Zheng, G. Zhao, Y.-J. Shang, *J. Org. Chem*. **2016**, *81*, 10558–10568; d) R.-M. Pan, J.-X. Zhang, C.-W. Zheng, H.-Y. Wang, D.-D. Cao, W.-G. Cao, G. Zhao, *Tetrahedron* **2017**, *73*, 2349–2358; e) D.-D. Cao, Z. Chai, J.-X. Zhang, Z.-Q. Ye, H. Xiao, H.-Y. Wang, J.-H. Chen, X.-Y. Wu, G. Zhao, *Chem. Commun.* **2013**, 49, 5972–-5974; f) J.-K. Pan, J.-H. Wu, H.-K. Zhang, X.-Y. Ren, J.-P. Tan, L.-X. Zhu, H.-S. Zhang, C.-H. Jiang, T.-L. Wang, *Angew. Chem. Int. Ed.* **2019**, *58*, 7425–7430; g) Li.-X. Zhu, X.-Y. Ren, Z.-X. Liao, J.-K. Pan, C.-H. Jiang, T.-L. Wang, *Org. Lett.* **2019**, *21*, 8667–8672; h) J.-P. Tan, P.-Y. Yu, J.-H. Wu, Y. Chen, J.-K. Pan, C.-H. Jiang, X.-Y. Ren, H.-S. Zhang, T.-L. Wang, *Org. Lett.* **2019**, *21*, 7298–7302; i) E. Yamamoto, K. Wakafuji, Y. Mori, G. Teshima, Y. Hidani, M. Tokunaga, **2019**, *21*, 4030–4034.

[13] a) M. B. Cid, S. Duce, S. Morales, E. Rodrigo, J. L. Ruano, *Org. Lett.* **2010**, *12*, 3586–3589; b) J.-H. Do, S. Kim, *Tetrahedron Let.* **2011**, *52*, 2353–2355; c) S. Seo, S. Kim *Tetrahedron Let.* **2012**, *53*, 2809–2812; d) J.-J. Yao, X.-H. Liu, P. He, Y. Zhu, X.-J. Lian, L. Lin, X.-M. Feng, *Chem. Eur. J.* **2013**, *19*, 16424–16430.

[14] D. C. Gary, C. S. Thomas, L. M. Casandra, A. D. David, B. Kristy, V. B. Annette, H. D. William, P. C. Denise, S. N. Jaime, H. Ricky, G. S. Jack, WO2009102736, **2009**.

[15] a) J.-X. Xiang, X.-H. Xu, F.-L. Qing, *J. Fluorine Chem.* **2017**, *203*, 110–114; b) B. Exner, B. Bayarmagnai, C. Matheis, Lukas J. Goossen, *J. Fluorine Chem.* **2017**, *198*, 89–93; c) J.-J. Ma, Q.-R. Liu, G.-P. Lu, W.-B. Yi, *J. Fluorine Chem.* **2017**, *193*, 113–117; d) C. Pooput, W. R. Dolbier, M. Médebielle, *J. Org. Chem.* **2006**, *71*, 3564–3568.

[16] a) J. D. Rodgers, A. J. Cocuzza, D. M. Bilder, WO0000479A1, **2000**; US6204262B1, **2001**; b) T. Miki, M. Kori, A. Fujishima, H. Mabuchi, R. Tozawa, M. Nakamura, Y. Sugiyama, H. Yukimasa, *Bioorg. Med. Chem.* **2002**, *10*, 385; c) M. Bayssat, G. Ferrand, J. C. Depin, US4554273A, **1985**.

10.1002/adsc.201901621

[17] a) J. Schnaubelt, E. Stehle, Krueger, T. WO 2007074130A2, **2007**; b) P. L. Nichols, J. Skidmore, R. W. Ward, D. M. Wilson, WO2009000819A1, **2008**; c) C. Dengiz, S. Özcan, E. Şahin, M. Balci, *Synthesis* **2010**, *8*, 1365–1370.

10.1002/adsc.201901621

COMMUNICATION

Enantioselective Vinylogous Mannich-type Reactions to Construct CF_3S-Containing Stereocenters Catalysed by Chiral Quaternary Phosphonium Salts

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Lijun Xu,[a,b] Longhui Yu,[b] Jun Liu,[b] Hongyu Wang,[b] Changwu Zheng,[c] Gang Zhao[b]*