

Organocatalytic Asymmetric Strecker Reaction of Di- and Trifluoromethyl Ketoimines. Remarkable Fluorine Effect

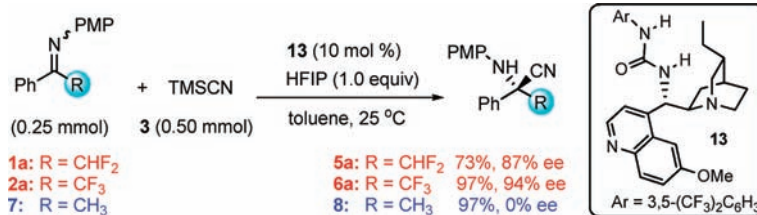
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ABSTRACT



A highly enantioselective Strecker reaction of difluoromethyl and trifluoromethyl ketoimines was developed. Remarkable fluorine effect on the reactivity and selectivity is observed and discussed.

The selective introduction of difluoromethyl (CF₂H) or trifluoromethyl (CF₃) groups has become a powerful strategy to modulate the properties of organic molecules.¹ For example, the CF₂H group can serve as a more lipophilic hydrogen bond donor than OH and NH groups,^{2a} which is very useful in drug design. α -Difluoromethylornithine^{2b} is a rationally designed drug for sleeping sickness. As a result, the synthesis of

optically active compounds with a CF₂H or CF₃ group at the chiral center has received great attention. While much progress has been made in the enantioselective trifluoromethylation,³ catalytic asymmetric difluoromethylations⁴ are less developed. Because of the challenges in the creation of tetrasubstituted carbon stereogenic centers,⁵ the catalytic asymmetric synthesis of α -CF₂H bearing tetrasubstituted carbon is rare,⁶ and no catalytic asymmetric addition of nucleophiles to α -CF₂H ketoimines was reported. Furthermore, there are very limited reports based on α -CF₃ ketoimines,⁷ despite achievements in the catalytic asymmetric reactions based on α -CF₃ ketones.³

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(1) (a) Hunter, L. *Beilstein J. Org. Chem.* 2010, DOI: 10.3762/bjoc.6.38. (b) Lectard, S.; Hamashima, Y.; Sodeoka, M. *Adv. Synth. Catal.* 2010, 352, 2708. (c) O'Hagan, D. *Chem. Soc. Rev.* 2008, 37, 308. (d) Smart, B. E. *J. Fluorine Chem.* 2001, 109, 3. (e) Schlosser, M. *Angew. Chem., Int. Ed.* 1998, 37, 1496.

(2) (a) Erickson, J. A.; McLoughlin, J. I. *J. Org. Chem.* 1995, 60, 1626. (b) Bey, P.; Gerhart, F.; Dorsselaer, V. V.; Danzin, C. *J. Med. Chem.* 1983, 26, 1551.

(3) For reviews, see: (a) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* 2011, 111, 455. (b) Valero, G.; Company, X.; Rios, R. *Chem.—Eur. J.* 2011, 17, 2018. (c) Tur, F.; Mansilla, J.; Lillo, V. J.; Saá, J. M. *Synthesis* 2010, 1909. (d) Uneyama, K.; Katagiri, T.; Amii, H. *Acc. Chem. Res.* 2008, 41, 817. (e) Shibata, N.; Mizuta, S.; Kawai, H. *Tetrahedron: Asymmetry* 2008, 19, 2633.

(4) For reviews, see: (a) Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* 2009, 7465. For selected examples, see: (b) Liu, J.; Hu, J. *Chem.—Eur. J.* 2010, 16, 11443. (c) Ni, C.; Liu, J.; Zhang, L.; Hu, J. *Angew. Chem., Int. Ed.* 2007, 46, 786. (d) Prakash, G. K. S.; Hu, J.; Mathew, T.; Olah, G. A. *Angew. Chem., Int. Ed.* 2003, 42, 5216.

(5) For reviews, see: (a) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* 2007, 5969. (b) Shibasaki, M.; Kanai, M. *Chem. Rev.* 2008, 108, 2853. (c) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* 2007, 5, 873. (d) Bella, M.; Gasperi, T. *Synthesis* 2009, 1583.

(6) As far as we know, only two example were reported: (a) Nie, J.; Zhang, G.-W.; Wang, L.; Fu, A.; Zheng, Y.; Ma, J.-A. *Chem. Commun.* 2009, 2356. (b) Bandini, M.; Sinisi, R.; Umami-Ronchi, A. *Chem. Commun.* 2008, 4360.

(7) (a) Lauzon, C.; Charette, A. B. *Org. Lett.* 2006, 8, 2743. (b) Sukach, V. A.; Golovach, N. M.; Pirozhenko, V. V.; Rusanov, E. B.; Vovk, M. V. *Tetrahedron: Asymmetry* 2008, 19, 761. (c) Fu, P.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* 2008, 130, 5530. (d) Enders, D.; Gottfried, K.; Raabe, G. *Adv. Synth. Catal.* 2010, 352, 3147. (e) Huang, G.; Yang, J.; Zhang, X. *Chem. Commun.* 2011, 47, 5587.

Enantioenriched α -tetrasubstituted α -aminonitriles with an α -CF₂H or CF₃ group are versatile for the synthesis of the fluorinated C ^{α} -tetrasubstituted α -amino acids and diamines,⁸ interesting subjects of medical investigation.⁹ However, no catalytic asymmetric synthesis of α -CF₂H α -tetrasubstituted α -aminonitriles was reported, and chiral auxiliary controlled methods were unsuccessful.^{9d,e} As for the α -CF₃-substituted α -tetrasubstituted α -aminonitriles, Enders et al. reported the first catalytic method during this work, which could give a variety of products in excellent ee, but the reaction time was generally long.^{7d} In our efforts in the synthesis of tetrasubstituted carbon stereogenic centers,¹⁰ we tried to develop a catalytic asymmetric Strecker reaction¹¹ of α -CF₂H- or CF₃-substituted ketimines¹² using (thio)urea catalysts.¹³ Here, we report our results.

During the preparation of racemic samples, we found that thiourea **4**^{13a} failed to catalyze the reaction of both **1a** and **2a** with TMSCN. In contrast, nonfluorinated ketimine **7** could afford the desired product **8** in 48% yield (Figure 1, eq 1). This result was counterintuitive since both CF₂H and CF₃ groups might enhance the electrophilicity of **1a** and **2a** toward cyanide addition. We speculated that the presence of α fluorine atom interfered with the H-bonding interaction of imine with both urea hydrogens, as Jacobsen proposed.^{13d,14}

To test this hypothesis, we conducted a theoretical calculation based on a simplified *N,N'*-dimethylthiourea–imine system (see the Supporting Information). The favorable binding model of imine **1a** or **2a** with thiourea was **A** or **B**

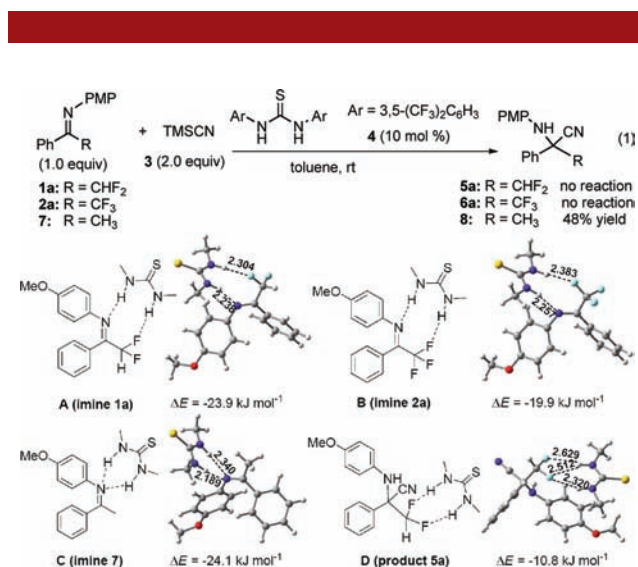


Figure 1. Optimized structures of hydrogen-bonded complexes. The interaction energy on hydrogen bond (ΔE) was calculated at the B3LYP/6-311G(d,p) level. The basis set superposition error (BSSE) and zero-point energy corrections were included in it.

(Figure 1), where imine nitrogen interacted with one thiourea hydrogen and one of the α -fluorine atoms with the other thiourea hydrogen. In contrast, ketimine **7** preferred a bridged structure **C**, with imine **7** hydrogen-bonded to both thiourea hydrogens. The two kinds of double-hydrogen-bonding interactions can stabilize complexes **A**, **B** and **C** with 23.9, 19.9, and 24.1 kJ mol⁻¹, respectively. This establishes a plausible explanation for the much higher reactivity of imine **7**: the bridging interaction shown in complex **C** could accelerate the reaction via the stabilization of the negatively charged nitrogen intermediate, as the activation of carbonyl groups by the oxyanion hole of the enzyme.^{13a,15} Analogous calculations also revealed single hydrogen-bonded structures for the product aminonitrile–catalyst complexes and **D**, for example (see the Supporting Information).

The above results suggested that thiourea catalyst alone was inefficient to develop a highly enantioselective Strecker reaction of imine **1a** or **2a** with TMSCN, which prompted us to use a Lewis base to activate the nucleophile TMSCN.¹⁶ The reaction of easily available imine **2a** and TMSCN was chosen for optimization, which was run in toluene at room temperature. Some typical results were shown in Table 1. As expected, no reaction took place if chiral urea catalysts **9** or **10** were used (entries 1 and 3). Interestingly, the combination of a chiral thiourea catalyst **9** with an achiral Lewis base catalyst DMAP afforded the desired product **6a** in 66% yield and 25% ee (entry 2), which demonstrated that dual activation concept indeed worked in this reaction. If using the combined catalyst **10** and DMAP, the

(8) For reviews, see: (a) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359. (b) Smits, R.; Cadicamo, C. D.; Burger, K.; Koksh, B. *Chem. Soc. Rev.* **2008**, *37*, 1727. (c) Mloston, G.; Objalska, E.; Heimgartner, H. *J. Fluorine Chem.* **2010**, *131*, 829.

(9) For reviews, see: (a) Qiu, X.-L.; Qing, F.-L. *Eur. J. Org. Chem.* **2011**, 3261. (b) Czekelius, C.; Tzschuche, C. C. *Synthesis* **2010**, 543. (c) Yoder, N. C.; Kumar, K. *Chem. Soc. Rev.* **2002**, *31*, 335. For auxiliary-controlled asymmetric synthesis, see: (d) Bravo, P.; Capelli, S.; Meille, S. V.; Seresini, P.; Volonterio, A.; Zanda, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2321. (e) Huguenot, F.; Billac, A.; Brigaud, T.; Portella, C. *J. Org. Chem.* **2008**, *73*, 2564. (f) Ogu, K.; Matsumoto, S.; Akazome, M.; Ogura, K. *Org. Lett.* **2005**, *7*, 589. (g) Wang, H.; Zhao, X.; Li, Y.; Lu, L. *Org. Lett.* **2006**, *8*, 1379.

(10) (a) Liu, Y.-L.; Wang, B.-L.; Cao, J.-J.; Chen, L.; Zhang, Y.-X.; Wang, C.; Zhou, J. *J. Am. Chem. Soc.* **2010**, *132*, 15176. (b) Cao, J.-J.; Zhou, F.; Zhou, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4976.

(11) (a) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. *Chem. Rev.* **2011**, *111*, 2626. (b) Yet, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 875. (c) Gröger, H. *Chem. Rev.* **2003**, *103*, 2795. (d) Merino, P.; Marqués-López, E.; Tejero, T.; Herrera, R. P. *Tetrahedron* **2009**, *65*, 1219.

(12) For reviews on catalytic asymmetric Strecker reaction of ketimines, see: (a) Connon, S. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1176. (b) Spino, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 1764. For selected examples, see: (c) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634. (d) Wang, J.; Hu, X.; Jiang, J.; Gou, S.; Huang, X.; Liu, X.; Feng, X. *Angew. Chem., Int. Ed.* **2007**, *46*, 8468. (e) Abell, J. P.; Yamamoto, H. *J. Am. Chem. Soc.* **2009**, *131*, 15118.

(13) For reviews on urea catalysis, see: (a) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187. (b) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. For urea-catalyzed Strecker reaction, see: (c) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867. (d) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012. (e) Pan, S. C.; Zhou, J.; List, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 612. (f) Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. *Nature* **2009**, *461*, 968.

(14) For an example of F...H–N hydrogen bonding, see: (a) Zhao, X.; Wang, X.-Z.; Jiang, X.-K.; Chen, Y.-Q.; Li, Z.-T.; Chen, G.-J. *J. Am. Chem. Soc.* **2003**, *125*, 15128. For reviews, see: (b) Shimoni, L.; Glusker, J. P. *Struct. Chem.* **1994**, *5*, 383. (c) Dunitz, J. D.; Taylor, R. *Chem.–Eur. J.* **1997**, *3*, 89. For the elucidation of reaction paths by computational methods on hydrogen bonding, see: (d) Etzenbach-Effers, K.; Berkessel, A. *Top. Curr. Chem.* **2010**, *291*, 1.

(15) Branney, C.; Carlqvist, P.; Magnusson, A.; Hult, K.; Brinck, T.; Berglund, P. *J. Am. Chem. Soc.* **2003**, *125*, 874 and references therein.

(16) For reviews on Lewis base catalysis, see: (a) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560. For selected examples of cinchona alkaloid catalyzed addition of TMSCN to electrophiles, see: (b) Huang, J.; Corey, E. J. *Org. Lett.* **2004**, *6*, 5027. (c) Tian, S.-K.; Hong, R.; Deng, L. *J. Am. Chem. Soc.* **2003**, *125*, 9900.

product **6a** was obtained in lower yield and ee (entry 4), suggesting that the enantioselectivity and reactivity was greatly influenced by the structure of urea catalysts and Lewis base catalysts. Based on the above results, we focused on the use of bifunctional Brønsted acid–Lewis base catalysts. Quinidine-derived bifunctional thiourea catalyst **11** could afford the product **6a** in 21% yield with 84% ee (entry 5). To our delight, dihydroquinine derived thiourea catalyst **12**¹⁷ improved the ee to 92% (entry 6). The corresponding urea catalyst catalyst **13** further improved the ee to 94% (entry 7). The position of the thiourea moiety of the catalyst obviously influenced the stereocontrol, and Deng's catalyst **14** afforded **6a** in only 7% ee (entry 8). To confirm the importance of bifurcated hydrogen bonding interactions of urea moiety with imine **2a**, other bifunctional catalysts **15–17** were also tried, and none of them could afford product **6a** in good ee (entries 9–11). Catalyst **18**, without Brønsted acid moiety, failed to catalyze the reaction (entry 12).

Although excellent ee for product **6a** was obtained, the reactivity is not satisfactory (entry 7). We further tried the use of alcoholic additives to improve the reactivity of the Strecker reaction.¹⁸ We screened a series of alcohols and phenols and found that the addition of alcohols or phenols indeed accelerated the reaction, but most of them resulted in the diminished ee of product **6a**. It turned out that (CF₃)₂CHOH (HFIP)¹⁸ was promising, and the use of HFIP (1.0 equiv) as additive could promote the reaction to finish within 2 days without loss of ee, which gave product **6a** in 97% yield with 94% ee (entry 13). Increasing the amount of HFIP to 2 equiv lowered the ee for product **6a**, possibly because of the background reaction (entry 14). We further examined other solvents using catalyst **13**, but toluene still turned out to be the best. In light of this, the optimum conditions was determined to run the reaction in toluene at 25 °C in the presence of 10 mol % of catalyst **13** and 1.0 equiv of HFIP. It also turned out that nonfluorinated imine **7** was more reactive than imine **1a** and **2a**, and α -CF₂H ketoimine **1a** was the least reactive when using catalyst **13**, whether in the presence of HFIP or not (for details, see the Supporting Information).

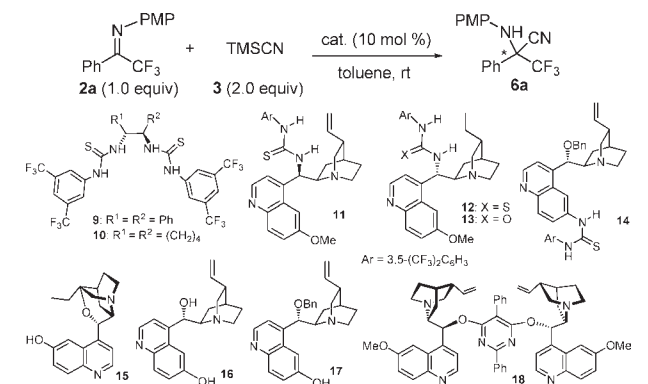
Interestingly, fluorinated imine **1a** and **2a** afforded the desired product **5a** and **6a** in 87% and 94% ee under optimized conditions, respectively. In contrast, the non-fluorinated imine **7** provided only racemic product **8**. The remarkable fluorine effect on enantiofacial control supported the proposed models **A** and **B** in Figure 1.¹⁹

(17) (a) Peschiulli, A.; Quigley, C.; Tallon, S.; Gun'ko, Y. K.; Connon, S. J. *J. Org. Chem.* **2008**, *73*, 6409. (b) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett* **2005**, 603. (c) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967. For reviews, see: (d) Connon, S. J. *Chem. Commun.* **2008**, 2499. (e) Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, 1229.

(18) For the reaction of TMSCN and alcohol, see: (a) Mai, K.; Patil, G. *J. Org. Chem.* **1986**, *51*, 3545. For the use of (CF₃)₂CHOH (HFIP) as additives, see: (b) Evans, D. A.; Rovis, T.; Kozłowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134.

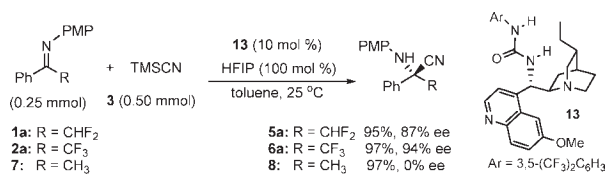
(19) We tried in vain to synthesize the α -CH₂F ketoimines, which are not reported in the literature by a SciFinder search.

Table 1. Condition Optimization



entry ^a	cat.	additives	time (d)	yield ^b (%)	ee ^c (%)
1	9		5		
2	9	DMAP (10 mmol %)	5	66	25
3	10		5		
4	10	DMAP (10 mmol %)	5	19	11
5	11		5	21	84
6	12		5	37	92
7	13		5	40	94
8	14		5	36	7
9	15		5	16	20
10	16		5	4	13
11	17		5	17	10
12	18		5		
13	13	HFIP (100 mmol %)	2	97	94
14	13	HFIP (200 mmol %)	2	95	90

^a On a 0.10 mmol scale. ^b Isolated yield. ^c By HPLC analysis.



The remarkable fluorine effects on both the reactivity and enantioselectivity is very impressive. While a few reports shown that the coordination of fluorine atom to metals might alter the stereoselectivity of reactions with fluorine-containing compounds,²⁰ it is not reported that the binding model of the (thio)urea catalyst and imines can be changed if substituting a CH₃ group of the substrate for a CF₂H or CF₃ group, which dramatically influences both the reactivity and enantioselectivity. This finding might be useful for the design of new asymmetric catalytic addition of nucleophiles to α -CF₂H or CF₃ ketoimines.

At the optimized reaction conditions, we then examined the substrate scope. First, different substituted α -CF₂H ketoimines **1a–p** were examined (Table 2). Four different *para*-substituted aniline-derived imines **1a–d** were first tried (entries 1–4), and the *p*-chloroaniline-derived imine **1d**

(20) For a review, see: (a) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1. Also see: (b) Hanamoto, T.; Fuchikami, T. *J. Org. Chem.* **1990**, *55*, 4969. (c) Sparr, C.; Gilmour, R. *Angew. Chem., Int. Ed.* **2010**, *49*, 6520.

Table 2. Strecker Reaction of α -CF₂H Ketoimines **1**

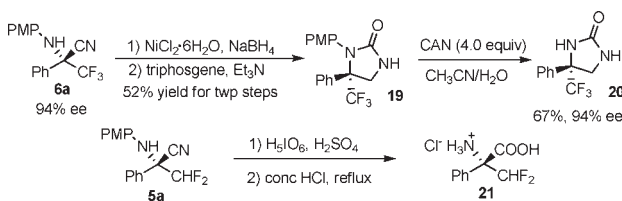
entry ^a	1	R	R ¹	5	yield ^b (%)	ee ^c (%)
1 ^d	1a	Ph	PMP	5a	73	87
2 ^d	1b	Ph	<i>p</i> -EtOC ₆ H ₄	5b	89	86
3 ^d	1c	Ph	<i>p</i> -BrC ₆ H ₄	5c	89	86
4 ^d	1d	Ph	<i>p</i> -ClC ₆ H ₄	5d	85	89
5 ^d	1e	<i>p</i> -MeC ₆ H ₄	PMP	5e	92	85
6 ^d	1f	<i>m</i> -MeC ₆ H ₄	PMP	5f	89	86
7 ^d	1g	<i>p</i> -MeOC ₆ H ₄	PMP	5g	70	80
8 ^d	1h	<i>p</i> -TMSOC ₆ H ₄	PMP	5h	62	86
9 ^d	1i	<i>p</i> -ClC ₆ H ₄	PMP	5i	94	92
10 ^d	1j	2-naphthyl	PMP	5j	81	87
11 ^e	1k	<i>m</i> -MeC ₆ H ₄	<i>p</i> -ClC ₆ H ₄	5k	75	92
12 ^e	1l	<i>m</i> -MeOC ₆ H ₄	<i>p</i> -ClC ₆ H ₄	5l	72	87
13 ^e	1m	<i>m</i> -ClC ₆ H ₄	<i>p</i> -ClC ₆ H ₄	5m	90	87
14 ^e	1n	<i>p</i> -FC ₆ H ₄	<i>p</i> -ClC ₆ H ₄	5n	84	88
15 ^e	1o	2-thienyl	<i>p</i> -ClC ₆ H ₄	5o	61	86
16 ^f	1p	<i>c</i> -hexyl	<i>p</i> -ClC ₆ H ₄	5p	42	77

^aOn a 0.25 mmol scale. ^bIsolated yield. ^cDetermined by chiral HPLC analysis. ^dAt 25 °C, 2–4 d. ^eAt –20 °C, 5 d. ^fAt 25 °C, 6 d.

reacted with TMSCN obviously faster than imine **1a** and **1b** and afforded the corresponding product **5d** in 89% ee (entry 4). Different α -aryl-substituted α -CF₂H ketoimines **1e–o** all afforded the desired products **5e–o** in high to excellent ee (entries 5–15). α -Cyclohexyl-substituted imine **1p** afforded the corresponding product **5p** in 77% ee. It should be noted that imines **1a–p** were all used in a mixture of *Z* and *E* isomers because the isolation of pure *Z* or *E* isomer failed,²¹ but imines **2^{7d}** and **7** were obtained and used as a pure isomer.

Trifluoromethyl ketoimine **2** worked efficiently under this condition (Table 3) and could be scaled up to 5.0 mmol using 5 mol % of catalyst **9** without loss of ee (entry 2). All of the α -aryl α -CF₃ ketoimines **2a–k** afforded the desired products **6a–k** in excellent yield and ee (entries 1–12). α -Alkyl- α -CF₃ ketoimines **2l–n** also worked well to give the desired products **6l–n** in high ee (entry 13–15). Differently substituted aniline-derived imines **2o–r** also worked well (entries 16–19).

The utility of the α -amino nitriles was demonstrated by the following transformations. Product **6a** could be converted to trifluoromethylated imidazolidinone **20** in three steps without loss of ee. Compound **5a** could be transformed to α -CF₂H C ^{α} -tetrasubstituted α -amino acid **21** in 66% yield in two steps.



In conclusion, we have developed a general method for the catalytic asymmetric Strecker reaction of both α -CF₂H and α -CF₃ ketoimines and TMSCN, which was carried out

Table 3. Strecker Reaction of α -CF₃ Ketoimine **2**

entry ^a	2	R ²	R ³	6	yield (%) ^b	ee (%) ^c
1	2a	Ph	PMP	6a	97	94
2 ^d	2a	Ph	PMP	6a	95	94
3	2b	<i>p</i> -MeC ₆ H ₄	PMP	6b	93	94
4	2c	<i>m</i> -MeC ₆ H ₄	PMP	6c	97	95
5	2d	<i>p</i> -MeOC ₆ H ₄	PMP	6d	90	94
6	2e	<i>m</i> -MeOC ₆ H ₄	PMP	6e	95	93
7	2f	<i>p</i> -BrC ₆ H ₄	PMP	6f	95	93
8	2g	<i>p</i> -ClC ₆ H ₄	PMP	6g	95	93
9	2h	<i>p</i> -FC ₆ H ₄	PMP	6h	89	93
10	2i	<i>p</i> -CF ₃ C ₆ H ₄	PMP	6i	96	96
11	2j	2-naphthyl	PMP	6j	97	96
12	2k	2-thienyl	PMP	6k	93	93
13	2l	Me	PMP	6l	83	89
14	2m		PMP	6m	72	87
15 ^e	2n	<i>c</i> -Hexyl	PMP	6n	60	86
16	2o	Ph	<i>p</i> -EtOC ₆ H ₄	6o	95	93
17	2p	Ph	<i>p</i> -FC ₆ H ₄	6p	91	91
18 ^f	2q	Ph	<i>p</i> -BrC ₆ H ₄	6q	98	86
19	2r	Ph	<i>p</i> -ClC ₆ H ₄	6r	98	88

^aOn a 0.25 mmol scale. ^bIsolated yield. ^cDetermined by chiral HPLC analysis. ^dOn a 5.0 mmol scale, 5 mol % of catalyst, 3 d. ^eReaction time: 6 d. ^fThe absolute configuration of product **6q** was assigned to be *R* by X-ray analysis (see the Supporting Information).

in air using easily available bifunctional catalyst. A strong fluorine effect on the reactivity and enantiofacial control was observed. Based on the theoretical calculations and experimental data, we proposed a new recognition model of (thio)urea catalyst and α -CF₂H- or CF₃-substituted ketoimines. Experiments are now underway in our laboratory to develop new asymmetric reactions for the synthesis of chiral compounds with di- or trifluoromethyl at the carbon center on the basis of this new binding model.

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Supporting Information Available. Experimental procedures and characterizations, copies of ¹H NMR and ¹³C NMR of new compounds, and HPLC profiles. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(21) For the preparation of imine **1**, see: Kirij, N. V.; Babadzhanova, L. A.; Movchun, V. N.; Yagupolskii, Y. L.; Tyrre, W.; Naumann, D.; Fischer, H. T. M.; Scherer, H. *J. Fluorine Chem.* **2008**, *129*, 14.