Internally Reuse Waste: Catalytic Asymmetric One-Pot Strecker Reaction of Fluoroalkyl ketones, Anilines and TMSCN by Sequential Catalysis

Yun-Lin Liu,*[,ab] Xiao-Ping Yin,[a] and Jian Zhou*[,ac]

ABSTRACT We report a highly enantioselective one-pot facile synthesis of fluorinated C^{α}-tetrasubstituted amino nitriles from α-fluoroalkyl α-aryl ketones, anilines, and TMSCN through a sequential *p*-TsOH catalyzed ketimine formation and chiral bifunctional tertiary amine mediated asymmetric Strecker reaction. This one-pot approach has two important advantages. First, it greatly improves the overall yield of the synthesis of chiral C^{α}-tetrasubstituted fluorinated aminonitriles from ketones, because the purification of α-fluorinated ketimines by column chromatography suffers from great yield loss. Second, it represents the first example of asymmetric tandem reactions that can simultaneously reuse the by-product and catalyst from the upstream step as a promoter and an additive to improve the reactivity and enantioselectivity of the subsequent catalytic enantioselective reaction, respectively. It could utilize the by-product H_2O generated in-situ from the ketimine formation step to activate TMSCN to form HCN, and concurrently reuse the remaining *p*-TsOH acid as an additive to improve enantioselectivity.

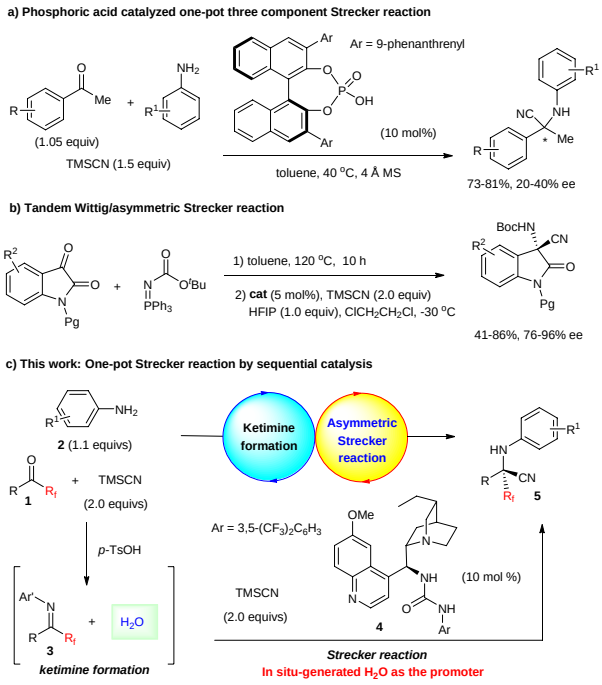
KEYWORDS one-pot, enantioselective, Strecker reaction, fluorine, α-aminonitrile

Introduction

Catalytic asymmetric Strecker reactions represent a powerful tool for the synthesis of optically active α-amino nitriles, valuable precursors to natural and unnatural α-amino acids, 1,2-diamines, and heterocycles.[1] Despite much progress, most known protocols are based on preformed imines, although the original Strecker reaction reported in 1850 was conducted in a one-pot fashion from achiral carbonyl compounds, amines, and cyanide sources.[2] The development of one-pot Strecker reaction of carbonyl compounds, amines, and cyanating reagents could save time, resources and labor on the purification of imines, and avoid yield loss as well. However, this research is still undeveloped. To date, only three successful one-pot catalytic enantioselective Strecker reaction of aldehydes, amines, and cyanating reagents have been reported by the groups of Kobayashi[3], List[4] and Feng[5], independently.

The corresponding one-pot Strecker reaction of achiral ketones is still very challenging, because the ketimine formation is more difficult than aldimine synthesis. Usually, it requires an acid catalyst and excess amines to facilitate the ketimine synthesis.[6-9] However, the remaining acid catalyst, excess amines and by-products may have negative influence on the Strecker reaction. Therefore, attempts to develop one-pot Strecker reaction from ketones met with little success, although significant achievements had been made in enantioselective cyanosilylation of ketimines, since the seminar work of Shibasaki[6], Yamamoto[7], Jacobsen[8] and Feng[9] groups. In 2008, Ma et al tactfully used a phosphoric acid to catalyze a one-pot three-component Strecker reaction of aryl methyl ketones, aromatic amines and trimethylsilyl cyanide (TMSCN), affording the desired products in 20-40% ee (Scheme 1a).[10] Later in 2013, we developed an aza-Wittig/asymmetric Strecker reaction sequence to provide the cyanation products in up to 96% ee (Scheme 1b).[11] However, such a Wittig based protocol is only limited to highly active ketones, isatins, and by-product Ph_3PO was found to have negative influence on enantiofacial control. In view of the importance of chiral C^{α}-tetrasubstituted amino nitriles, it is highly desirable to develop new strategies to develop asymmetric one-pot Strecker reaction of achiral ketones. Here, we report a highly enantioselective one-pot Strecker reaction of α-fluorinated α-aryl ketones **1**, aromatic amines **2** and TMSCN through a sequential *p*-TsOH and chiral bifunctional tertiary amine catalysis (Scheme 1c).

Scheme 1 One-pot Strecker reaction



Results and Discussion

Optically active C^{α}-tetrasubstituted α-aminonitriles featuring an α-CF_2H or CF_3 group are important synthons to the fluorinated C^{α}-tetrasubstituted α-amino acids and diamines,[12] interesting targets to medical investigation. We had previously developed a highly enantioselective Strecker reaction of *N*-aryl α-CF_3 or CF_2H ketimines **3**[13a] to prepare such fluorinated chiral building blocks, using 10 mol% of dihydroquinine-derived bifunctional urea **4**[14] as the catalyst, during our continuation in the cyanation of ketones[15] and ketimines.[11,13] However, despite the good results, 1.0 equiv of

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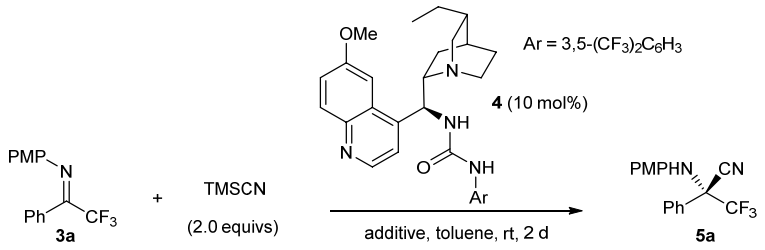
expensive 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) must be used as the additive to accelerate the reaction (Table 1, entry 1).[13a] Furthermore, the synthesis of α-CF_3 or CF_2H ketimines **3** from the corresponding fluorinated ketones **1** generally suffered from low isolated yields (20-81%, usually less than 50%),[13c] possibly due to the partial hydrolysis during the purification process by silica gel column chromatography. Due to the high cost of fluoalkylated ketones, the development of a one-pot Strecker reaction to alleviate the yield loss in ketimine synthesis would greatly improve the practicality of this method.

With our interest in multicatalyst promoted asymmetric tandem reactions,[16,17] we considered to combine the Brønsted acid catalyzed ketimine formation with bifunctional chiral tertiary amine-urea catalyzed Strecker reaction, for two reasons: 1) due to the possible influence of C-F…H-X interactions,[18] Brønsted acids were found to be unable to mediate the Strecker reaction of α-CF_3 or CF_2H ketimines **3**,[19] which obviated the worry about the possible racemic reaction caused by achiral acid; 2) the water generated in ketimine formation might be utilized to activate TMSCN, to facilitate the Strecker reaction. However, the development of the desired sequence is not as trivial as it first appeared, due to two obvious challenges. First, the acid catalyst used for ketimine formation must be compatible with chiral bifunctional tertiary amine **4**, the optimum catalyst for the following asymmetric Strecker reaction. Because we found that the ketimine formation requires the use of strong acid such as *p*-toluenesulfonic acid (*p*-TsOH), capable of protonating the tertiary amine moiety of the catalyst **4**, which led to catalyst poison. Fortunately, the use of only 1 mol% *p*-TsOH could mediate the ketimine formation well in toluene, the best solvent for the Strecker reaction. Second, excess aniline and by-product water formed in the first step must have no severe detrimental effect on the enantioselectivity of the asymmetric Strecker reaction. With this idea in mind, we first examined the influence of each reaction component of the ketimine formation on the reactivity and enantioselectivity of the Strecker reaction of preformed ketimine **3a**, as shown in Table 1.

Table 1 Control experiments



Entry[a]	Additive	Yield/%[b]	Ee/%[c]
1[d]	HFIP (100 mol%)	97	94
2	-	33	94
3	*p*-TsOH (1 mol%)	31	94
4	$PMPNH_2$ (10 mol%)	47	89
5	H_2O (100 mol%)	97	89
6	*p*-TsOH (1 mol%) + $PMPNH_2$ (10 mol%)	38	94
7	*p*-TsOH (1 mol%) + $PMPNH_2$ (10 mol%) + H_2O (100 mol%)	98	94

[a] On a 0.25 mmol scale; [b] Isolated yield; [c] Determined by chiral HPLC analysis. [d] Reference 13a, reaction finished within 1 day.

As expected, without any additive, the reaction of ketimine **3a** and TMSCN proceeded very slowly, affording the desired adduct **5a** in only 33% yield, even after two days (entry 2). Then we checked the influence of *p*-TsOH, excess $PMPNH_2$ and by-product H_2O from the ketimine formation step on the subsequent asymmetric Strecker reaction. No obvious influence on the yield and enantioselectivity was observed when using 1 mol% of *p*-TsOH as the additive (entry 3). If 10 mol% of $PMPNH_2$ was added, slightly improved yield (47%) but inferior ee (89%) were obtained, possibly because $PMPNH_2$, as a Lewis base, could mediate the racemic reaction to some extent (entry 4). Remarkably, the yield was dramatically improved to 97% in the presence of 100 mol% of H_2O (entry 5), which unambiguously indicated the acceleration effect of H_2O, albeit the ee value of product **5a** (89% ee) slightly suffered. Interestingly, when both 1 mol% *p*-TsOH and 10 mol% $PMPNH_2$ were added, product **5a** was obtained in 94% ee despite the yield (38%) was still unsatisfactory (entry 6). Gratifyingly, a combination of *p*-TsOH (1 mol%), $PMPNH_2$ (10 mol%) and H_2O (100 mol%) could substantially enhance the yield of product **5a** to 98%, and achieve 94% ee (entry 7).

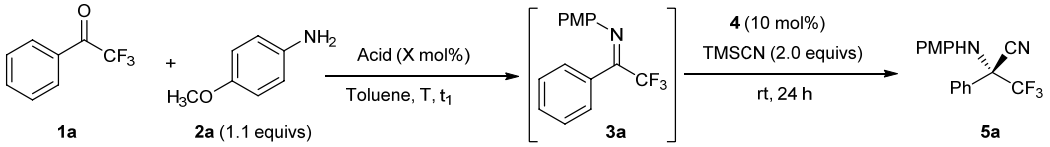
These results shown in Tables 1 are very intriguing, suggesting the dramatic acceleration effect of by-product H_2O generated *in situ* from ketimine formation on the reactivity of Strecker reaction, and the beneficial effect of remaining *p*-TsOH on the enantioselectivity of dihydroquinine-derived urea catalyst **4** mediated Strecker reaction of fluorinated ketimines. The NMR analysis revealed that no matter mixing 1.0 equiv of H_2O or HFIP with 2.0 equivs of TMSCN, characteristic peaks corresponding to HCN could be monitored after 15 minutes (See supporting information). Therefore, it was believed that the role of H_2O was possibly to activate TMSCN to form the more active HCN as the cyanating reagent, similar to that of HFIP. However, how the presence of *p*-TsOH had a beneficial influence on the enantiofacial control awaits further studies. Nevertheless, these data confirmed the feasibility of developing the designed tandem sequence shown in Scheme 1c.

In the following, we tried combining the acid catalyzed ketimine formation with the enantioselective Strecker reaction mediated by catalyst **4**. Considering the acid catalyst used for the ketimine formation had a positive influence on the enantiofacial control of the subsequent Strecker reaction, we next evaluated different acid catalysts for the ketimine formation. Because the best solvent for the Strecker reaction was toluene, we optimized different bench-stable sulfonic acids and carboxylic acids for the

ketimine formation, which was conducted in a one-pot tandem sequence fashion, as shown in Table 2. The initial acid catalyzed α-CF_3 ketone **1a** (0.25 mmol) and 1.1 equiv of $PMPNH_2$ **2a** was run in a screw-capped pressure tube at 100 °C in 1 mL toluene, in the presence of 1.0 mol% acid. After **1a** was consumed by TLC analysis (typically 24 hrs), the mixture was cooled down, followed by the addition of 2.0 equivs of TMSCN and 10 mol% thiourea **4** for the following Strecker reaction at room temperature. Some typical results were summarized in table **2**. First, *p*-TsOH was tried, and it efficiently catalyzed the synthesis of α-CF_3 ketimine **3a**, which readily underwent the subsequent asymmetric Strecker reaction to afford the desired product **5a** in 87% total yield and 94% ee (entry 1). The good yield and excellent ee value achieved by this one-pot process is very impressive, as the ee value was parallel to that obtained from preformed ketimine **5a** that we had previously reported. However, the screening of a variety of different sulfonic acids such as benzenesulfonic acid, naphthalene-2-sulfonic acid and 4-nitrobenzenesulfonic acid resulted in no improvement in the isolated yields (73-82%) and enantioselectivities (87-91%) of product **5a** (entry 2-4). Benzoic acid proved to be impotent to catalyze the ketimine formation due to its weak acidity (entry 5). These results demonstrated that the use of a Brønsted acid catalyst with appropriate pKa vaule was crucial to achieve excellent reaction outcomes.

To reduce the reaction time for ketimine formation step, we then next examined the influence of reaction temperature and catalyst loading of *p*-TsOH. It turned out that the ketimine formation could complete within 12 h if the reaction mixture was heated at 145 °C, furnishing product **5a** in 88% yield and 94% ee (entry 7). However, increasing the *p*-TsOH loading from 1 mol% to 10 mol% had adverse effect on product ee and yield (entry 7-10). The use of 10 mol% of *p*-TsOH inhibited the Strecker reaction as it might completely protonate the tertiary amine moiety of the chiral catalyst **4**, thus led to the loss of catalytic activity (entry 10). Finally, a convenient procedure for the one-pot tandem process was established as follows: after the *p*-TsOH (1 mol%) catalyzed ketimine formation finished at 145 °C (12 hrs), the resulting reaction mixture was cooled down to room temperature, followed by the successive addition of 10 mol% chiral tertiary amine catalyst **4** and TMSCN (2.0 equivs). The Strecker reaction was run at room temperature till the full disappearance of the ketimine by TLC analysis.

Table 2 Condition optimization for the one-pot tandem sequence.



1a **2a** (1.1 equivs) **3a** **5a**

Entry[a]	Acid	X/mol%	Temp/°C	t_1/h	Yield/%[b]	Ee/%[c]
1	*p*-toluenesulfonic acid	1	110	24	87	94
2	benzenesulfonic acid	1	110	24	81	90
3	naphthalene-2-sulfonic acid	1	110	24	82	91
4	4-nitrobenzenesulfonic acid	1	110	24	73	87
5	benzoic acid	1	110	24	-	-
6	*p*-toluenesulfonic acid	1	130	12	82	93
7	*p*-toluenesulfonic acid	1	145	12	88	94
8	*p*-toluenesulfonic acid	2	145	12	86	93
9	*p*-toluenesulfonic acid	5	145	12	79	91
10	*p*-toluenesulfonic acid	10	145	12	-	-

[a] 0.25 mmol scale in 0.5 mL of toluene; [b] Isolated yield; [c] Determined by chiral HPLC.

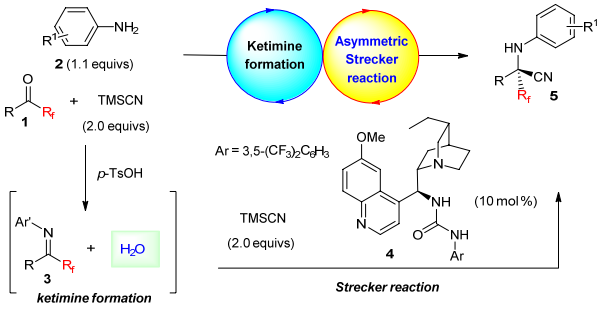
Under the aforementioned optimized procedure, we then examined the substrate scope of α-fluoroalkyl ketone **1** and anilidines **2**. As shown in table 3, this tandem sequence was amenable to a variety of α-aryl α-CF_3 ketones **1** with either electron-rich or electon-poor substituents on the aromatic ring, affording structurally diversified α-CF_3 quaternary α-amino nitriles **5a-g** in generally good to excellent yields (86-95%) and enantioselectivities (83-94% ee). The reaction of 2-naphthyl and 2-furyl substituted α-CF_3 ketones also proceeded smoothly, giving the corresponding products **5h** and **5i** in 85% and 49% yield with 91% ee and 92% ee, respectively. However, α-alkyl α-CF_3 ketones **1j** and **1k** were not suitable substrates, possibly because the corresponding ketimines were less stable under non-anhydrous conditions (the corresponding preformed ketimines are viable substrates under the Strecker reaction condition[13a]). Further studies showed that various less reactive α-aryl and α-heteroaryl α-CF_2H ketones **1l-o** also worked well with *para*-anisidine **2a** or *p*-chloroaniline **2b** and TMSCN, leading to the corresponding Strecker adducts **5l-o** in 67-87% yield with 74-87% ee, albeit with prolonged reaction time (2-4 d).

By this procedure, we further tried several special fluoralkyl ketones **1p-t**. The corresponding ketimines of such expensive fluoroalkylated ketones had not been used for enantioselective Strecker reaction, although optically active compounds featuring an α-CHFCl, α-CF_2Cl, α-CF_2Br, α-C_2F_5 or α-C_3F_7 substituent at the chiral carbon stereocenter are very interesting targets for medicinal researches. The α-CHFCl ketone **1p** provided product **5p** in 55% yield, 1.6:1 dr and 43% ee for the major diastereomer (the preformed ketimines afforded **5p** in 74% ee). The ee value was lower than that of the corresponding α-CF_2H or α-CF_3 adducts **5**, which was in accordance with our previous finding that C-F…H-X interactions played an important role in enantiofacial control.[13a] Other α-amino nitriles (**5q-t**) bearing different fluoroalkyl groups were also obtained in 14-57% total yield and 79-89% ee. The low yield of **5r** was possibly because ketone **1r** was thermodynamically less stable, and that of product **5t** was related to the difficulties in ketimine formation due to the sterically congested nature of α-$CF_2CF_2CF_3$ substituted ketone **1t**.

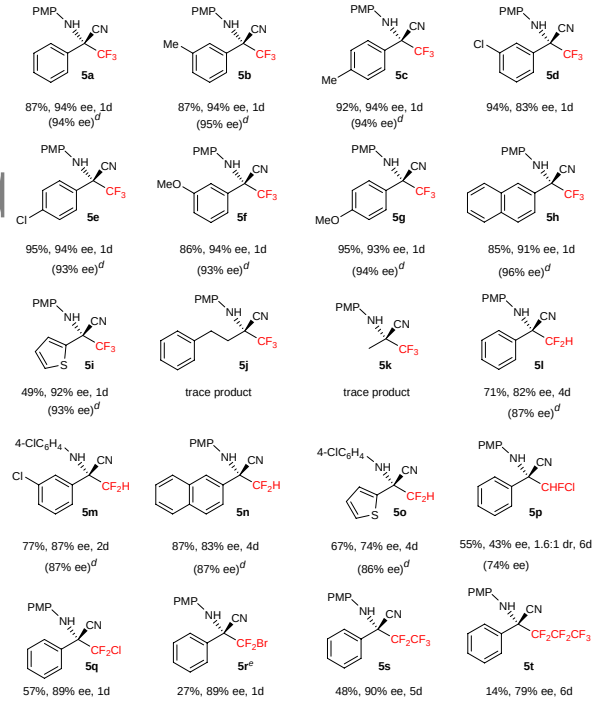
The high yield and excellent enantioselectivities obtained by this one-pot tandem procedure is very interesting, considering that they are achieved without the use of 1.0 equiv of HFIP to enhance the reactivity of the asymmetric Strecker reaction. As indicated in eleven examples, the ee value of the desired products is comparable to that obtained by using preformed ketimines

(shown in parenthesis under the specific adduct), although there was an obvious decrease in the ee value of **5o** and **5p**. In addition, this one-pot process gave the desired α-fluoroalkyl α-amino nitriles in much higher total yield, because the yield loss during the purification of the corresponding ketimines was avoided. It should be noted that this one-pot protocol represents the first asymmetric tandem reaction that can simultaneously reuse the by-product and catalyst from the upstream step as a promoter and an additive to improve the reactivity and enantioselectivity of the subsequent catalytic enantioselective reaction, respectively. Despite ever-increasing interest in developing such sustainable tandem reactions,[20,21] successful examples are still very limited, and this work unambiguously demonstrates the potential of waste self-utilizing asymmetric tandem sequences for the cost-effective synthesis of value-added chiral products, as well as in improving the synthetic efficiency.

Table 3 Substrate scope of one-pot ketimine formation/asymmetric Strecker reaction tandem sequence[a-d].



Conclusions



[a] 0.25 mmol scale in 0.5 mL of toluene; [b] Isolated yield; [c] The ee was determined by chiral HPLC; [d] The ee values shown in parenthesis correspond to literature report (ref 13a) obtained by using preformed ketimines; [e] The reaction temperature for ketimine formation was 100 °C.

In summary, we have developed a highly enantioselective one-pot approach for the efficient synthesis of optically active α-fluoroalkyl substituted C^{α}-tetrasubstituted amino nitriles via the sequential *p*-TsOH mediated ketimine formation and chiral bifunctional urea **4** catalyzed enantioselective Strecker reaction of diverse α-fluorinated α-aryl ketones, aromatic amines and TMSCN. The resulting α-fluoroalkyl α-amino nitriles are valuable building blocks to various chiral compounds featuring a fluoroalkyl group at the chiral center.[22] It is worth mentioning that although significant achievements have been made in enantioselective trifluoromethylation, methods for catalytic asymmetric creation of carbon stereocenters bearing other types of fluoroalkyl groups still very limited.[22h-l] The internal utilization of in-situ formed by-product H_2O as a reagent to convert TMSCN to more reactive HCN, and the reuse of *p*-TsOH as additives to benefit the enantioselectivity of the subsequent asymmetric Strecker reaction make our protocol operationally simple for practical synthesis of valuable α-fluoroalkylated α-amino nitriles. Further studies are focused on the detailed reaction mechanism and the extension of substrate scope to non-fluoroalkylated ketones.

Experimental

General procedure: To a 10.0 mL sealed tube were successively added *p*-TsOH (0.0025 mmol), α-fluorinated ketone **1** (0.25 mmol), aromatic amine **2** (0.275 mmol) and 0.5 mL of anhydrous toluene. The reaction mixture was stirred vigorously at 145 °C till full consumption of ketone **1** as monitored by TLC (about 12 h). The resulting reaction mixture was then cooled to room temperature, followed by the addition of chiral tertiary amine **4** (14.5 mg, 0.025 mmol) and TMSCN (67.0 μL, 0.50 mmol). Stirring was continued at room temperature for appropriate time indicated in Table 3. The reaction mixture was directly subjected to column chromatography using petroleum ether/ethylacetate (from 20:1-10:1) as the eluent to afford the pure desired α-fluorinated aminonitriles **5**.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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Page No.

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