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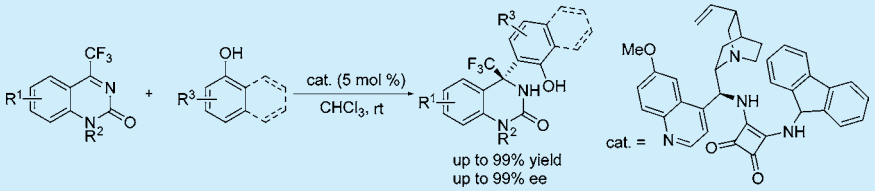
A Quinine-Squaramide Catalyzed Enantioselective Aza-Friedel–Crafts Reaction of Cyclic Trifluoromethyl Ketimines with Naphthols and Electron-Rich Phenols

Ding Zhou,[†,‡] Zheng Huang,[†,‡] Xueting Yu,[†,‡] Youxin Wang,[‡] Jian Li,[‡] Wei Wang,*[,†,‡,§] and Hexin Xie*[,†,‡]

[†]State Key Laboratory of Bioreactor Engineering, [‡]Shanghai Key Laboratory of New Drug Design, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China

[§]Department of Chemistry and Chemical Biology, University of New Mexico, Albuquerque, New Mexico 87131-0001, United States

Supporting Information



ABSTRACT: A highly enantioselective aza-Friedel–Crafts (aza-F-C) reaction of cyclic trifluoromethyl ketimines and naphthols/phenols was developed with fluorenyl-substituted quinine-squaramide as the catalyst. This protocol enables direct access to biologically important chiral trifluoromethyl dihydroquinazolinones with up to 99% yields and up to 99% ee's.

The aza-Friedel–Crafts (aza-F-C) reaction is a viable approach in the construction of new carbon–carbon bonds for nitrogen-containing compounds.[1] Fueled by the renaissance of organocatalysis,[2] the catalytic enantioselective aza-F-C processes have received considerable attention in the past decade and tremendous progress has been made.[3] In these processes, the electrophiles were largely limited to aldehyde-derived imines;[4] the employment of ketone-derived imines, which lead to synthetically important amines with chiral quaternary carbon center, is much less explored, presumably due to the low reactivity of ketimines and more difficult control of facial selectivity.[5] Furthermore, in contrast to widely used indoles and pyrroles as nucleophiles, which have been subjected to extensive studies, the asymmetric organocatalytic aza-F-C reaction of ketimine with naphthol as a donor remained elusive until very recently when Pedro documented an elegant highly enantioselective addition of naphthols to isatin-derived ketimines.[6]

Dihydroquinazolinones are a class of intriguing molecules, displaying various bioactivities, including antiobesity[7] and antiviral,[8] and serving as potent inhibitors of Na^+/Ca^{2+} exchange.[9] Notably, chiral dihydroquinazolinones DPC 961 and DPC 083 (Figure 1), featuring a trifluoromethyl group on the chiral quaternary carbon center, are potent HIV non-nucleoside reverse transcriptase inhibitors (NNRTIs).[10] It is noted that their bioactivities are highly dependent on their absolute configurations and the functionalities of the chiral quaternary carbons.[10b] As a result, recently, increasing efforts have been devoted to the asymmetric catalytic transformation of cyclic trifluoromethyl ketimines, including Mannich reaction,[11] aza-Henry reaction,[12] Strecker reaction,[13] aza-F-C reaction,[5h] hydrophosphonylation,[14] hydrogenation,[15] etc. Herein, in our continuing efforts on this topic,[12,13b,14] we wish to describe results of an organocatalytic aza-F-C reaction of trifluoromethyl ketimines and naphthols/phenols with high efficiency of enantiocontrol and yields.

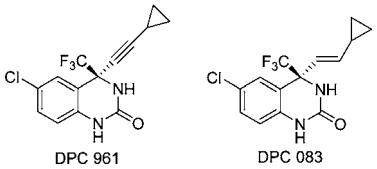


Figure 1. Structures of DPC 961 and DPC 083.

We initiated our studies with cyclic trifluoromethyl ketimine **1a** and 1-naphthol **2a** as model substrates. This aza-F-C reaction proceeded smoothly in the presence of quinine (**I**) with 41% ee while benzylated quinine (**II**)[16] appeared to be less efficient: a longer reaction time was required and a lower ee was observed (Table 1, entries 1 and 2). This suggested that a hydrogen bond might play an important role in this catalytic process. Therefore, we turned our attention to quinine-derived catalysts with stronger hydrogen-bonding donors.[17] Urea/thiourea or amide-based catalysts (**V**,[18] **VI**,[19] and **VII**[20]) turned out to be inferior for enantiocontrol (entries 5, 6, 7). It is worth noting that catalyst **VIII**,[21] which shares an identical stereoconfiguration with quinine-thiourea (**V**), afforded opposite enantioselectivity (entry 8). Cinchonine-derived squaramides,

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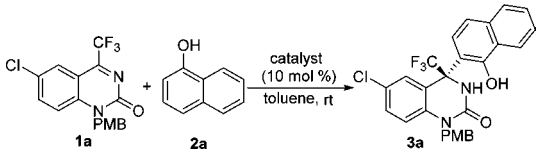
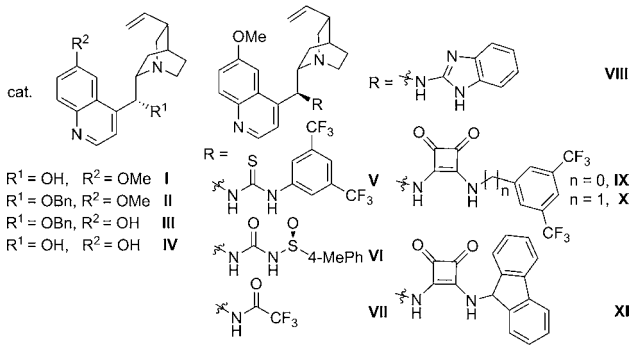
Table 1. Optimization of Reaction Conditions[a]

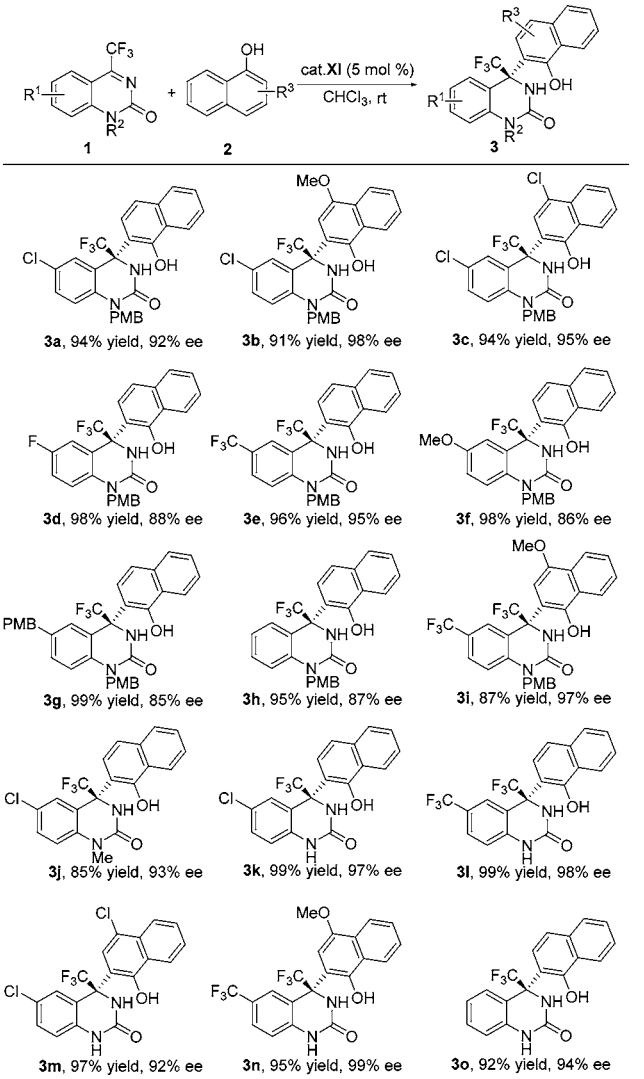


entry	catalyst	time (h)	yield (%)[b]	ee (%)[c]
1	I	4	83	41 (+)[d]
2	II	22	75	12 (−)
3	III	8	79	4 (−)
4	IV	24	22	29 (+)
5	V	3	87	29 (−)
6	VI	2	99	4 (−)
7	VII	12	nd[e]	20 (−)
8	VIII	1.5	nd[e]	51 (+)
9	IX	3	78	64 (−)
10	X	3	87	47 (−)
11	XI	1	95	85 (−)
12[f]	XI	0.5	99	93 (−)
13[f,g]	XI	1	94	92 (−)
14[f,h]	XI	1.5	97	91 (−)

[a]Unless otherwise noted, **1a** (0.054 mmol) and **2a** (0.081 mmol) with catalyst (0.0054 mmol) in toluene (0.5 mL) were stirred at rt. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral column. [d]Optical rotation. [e]Not determined. [f]With $CHCl_3$ as solvent. [g]With 5 mol % of catalyst. [h]With 1 mol % of catalyst. PMB: *p*-Methoxybenzyl.



Scheme 1. Asymmetric aza-F-C Reaction of Cyclic Ketimines 1 with Naphthols 2



first reported by Rawal's laboratory in 2008,[22] exhibit a longer distance between the two donor hydrogen atoms than that of thioureas and have been successfully employed in a wide range of asymmetric reactions as hydrogen-bond donor catalysts.[22,23] Indeed, quinine-squaramide **IX** afforded the aza-F-C adduct with slightly higher optical purity (64% ee, entry 9). Nonetheless, unfortunately, further reaction condition optimizations, including solvent, reaction temperature, and catalyst loading optimizations, failed to improve the enantioselectivity to a synthetically useful level. We conceived that a more bulky substituent on the squaramide motif of catalyst may more effectively block nucleophilic attack to ketimine **1a** from one face and thus enhance enantioselection. A fluorenyl was then introduced to the quinine-squaramide, and the resulting catalyst (**XI**), to our delight, promoted the aza-F-C process even more efficiently, delivering adduct **3a** at higher yield with, more importantly, improved enantiocontrol (entry 11). Further reaction condition optimizations increased enantioselectivity to 93% ee (entry 12). Reducing the catalyst loading to 1 mol % can still afford comparable yield and enantiopurity.

With the established optimal conditions in hand, we next explored the scope of this aza-F-C process. As shown in Scheme 1, in addition to 1-naphthol **2a**, 4-methoxy-1-naphtol and 4-chloro-1-naphthol were also compatible with this protocol, leading to the aza-F-C adducts in high yields and good to excellent enatioselectivities. But 2-naphthol was not a suitable substrate, giving no desired product. The scope of cyclic ketimine was also investigated: substrates with electron-withdrawing, electron-neutral, and electron-donating substituents (R^1) on aromatic rings can all be well tolerated in this reaction, albeit electron-rich electrophiles give slightly lower enantioselection. Remarkably, besides *N*-methyl or PMB-protected ketimines, N-substituted-free ketimines, a type of substrate typically leading to unsatisfied yields and enantioselectivities in other asymmetric transformations,[11−15,5h] can also undergo the aza-F-C process smoothly with excellent yields, with even better asymmetric induction than their N-protected counterparts in most cases (e.g., **3o**: 94% ee *vs* **3h**: 87% ee; **3k**: 97% ee *vs* **3a**: 92% ee; **3n**: 99% ee *vs* **3i**: 97% ee). The compatibility of the first example using protection-free ketimines in the asymmetric aza-F-C process underscores an important merit of this approach.

The absolute configuration of **3a** was determined to be *R* by single crystal X-ray analysis (Figure 2); other adducts were assigned analogously.

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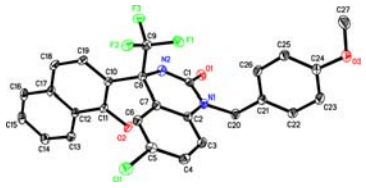
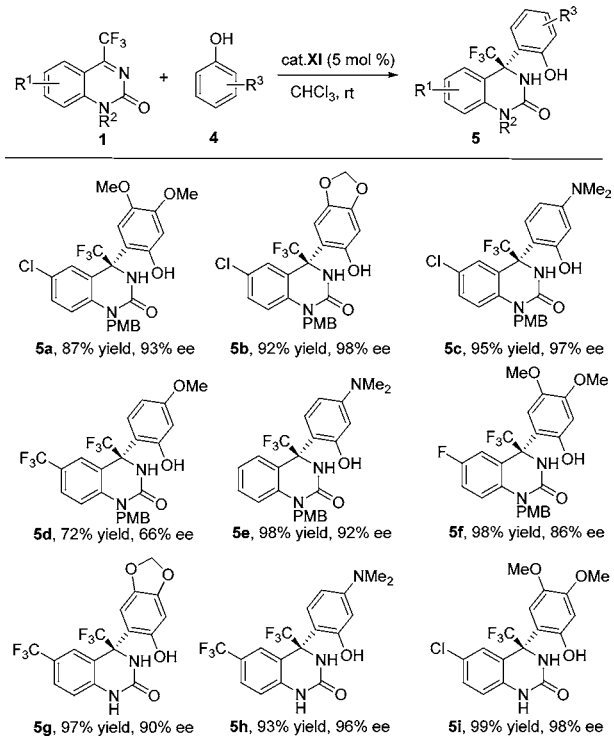


Figure 2. X-ray crystallographic structure of **3a**.

To further evaluate the substrate scope, we then probed more challenging electron-rich phenols as the aza-F-C donor, and the results are outlined in Scheme 2. Most electron-rich

Scheme 2. Asymmetric aza-F-C Reaction of Cyclic Ketimines 1 with Electron-Rich Phenols 4



phenols can afford the aza–F-C adducts in good to excellent levels of yields and ee's. Notably, 3-(dimethylamino)phenol gave rise to adduct **5c** in 95% yield and 97% ee, in contrast to the moderate enantioselectivity (63% ee) by the chiral phosphoric acid-mediated approach.[5h] And even less reactive 3-methoxyphenol can participate in this process, though in moderate yield and enantioselection. Additionally, N-unsubstituted ketimines were also well adapted in the reactions of activated phenols with up to 99% yield and 98% ee. Unsubstituted phenol, as well as 2-methoxyphenol and 3-chlorophenol, was inert for this reaction with no product forming.

The obtained aza-F-C adducts are versatile intermediates and are readily converted to other chiral building blocks. For example, in the presence of methyl iodide and potassium carbonate, methylation of **3b** was realized in 85% yield without loss of optical purity. Moreover, a vinyl can be introduced by a Stille coupling reaction[24] of triflated **3a**, leading to **7a** with full retention of enantioselectivity (Scheme 3).

To rationalize the stereochemical outcome of this asymmetric aza-F-C reaction, a transition state model is proposed in

Scheme 3. Transformations of Adducts 3b and 3a

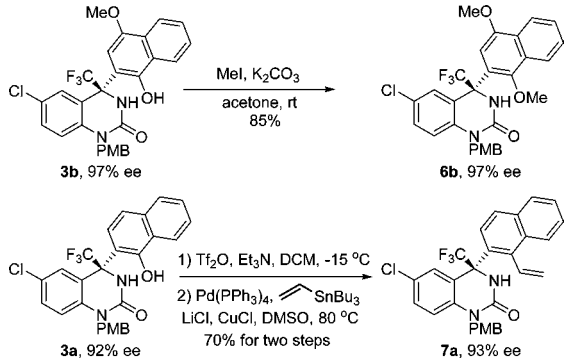


Figure 3. The quinine-squaramide catalyst **XI** promotes the reaction in a dual activation manner:[17,23] activating ketimine **1**

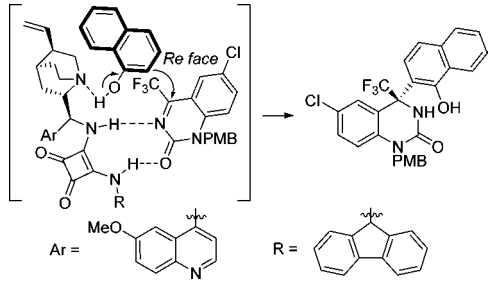


Figure 3. Proposed model of enantioselection.

through forming two H-bonds with the squaramide motif; enhancing the nucleophilicity of naphthol **2** by the tertiary amine moiety of catalyst, which directs an *Re*-face attack to ketimine and results in the *R* configuration of adduct **3**.

In summary, we have uncovered an unprecedented highly enantioselective aza-Friedel–Crafts reaction of cyclic trifluoromethyl ketimines and naphthols/phenols with fluorenyl-substituted quinine-squaramide as the catalyst, allowing direct access to trifluoromethyl dihydroquinazolinones bearing a quaternary stereocarbon center with up to 99% yields and 99% ee's. And the compatibility of protection-free ketimines in this process highlights an important merit of protocol. The biological properties of these adducts are currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge via the Internet at The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02668.

Experimental procedures, characterizations, ^{1}H NMR and ^{13}C NMR spectra, HPLC traces (PDF)

X-ray crystallographic data of **3a** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: wwang@unm.edu

*E-mail: xiehexin@ecust.edu.cn

Notes

The authors declare no competing financial interest.

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