Organocatalysis

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Bifunctional Cinchona Alkaloid Thiourea Catalyzed Highly Efficient, Enantioselective Aza-Henry Reaction of Cyclic Trifluoromethyl Ketimines: Synthesis of Anti-HIV Drug DPC 083**

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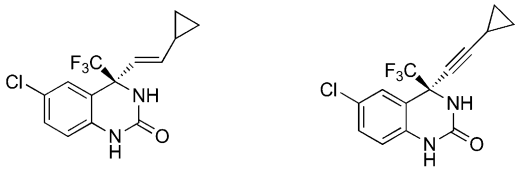
The aza-Henry reaction is a powerful method for C–C bond formation.[1] Moreover, the versatile nitro group can be conveniently transformed into a variety of new functional groups, which are highly valuable in the preparation of related analogues in drug discovery. In recent years, significant efforts have been directed toward the development of catalytic asymmetric aza-Henry reactions.[1] However, the electrophilic substrates have been largely confined to imines derived from aldehydes.[1,2] The development of an efficient protocol for an enantioselective aza-Henry reaction of ketimines to generate a chiral quaternary center remains elusive because of the lower reactivity of ketimines and difficulties in enantiofacial discrimination. To our knowledge, to date, there has been only one report, by Feng and co-workers, of a chiral *N*,*N*′-dioxide copper complex (20 mol%) catalyzed asymmetric aza-Henry reaction between acyclic ketimines and nitromethane; this reaction proceeded with good enantioselectivities (71–96% *ee*) but generally in poor yields (21–70%).[3]

Dihydroquinazolinones, as an important class of heterocyclic compounds are characterized by their broad spectrum of intriguing biological properties, such as antiviral[4] and antiobesity activities,[5] and their use in the treatment of cardiovascular diseases[6] and pain.[7] Notably, among these compounds, drug candidates DPC 083 and DPC 961, bearing a chiral trifluoromethyl moiety, are potent HIV-1 nonnucleoside reverse transcriptase inhibitors (Scheme 1).[1] It is believed that the trifluoromethyl motif plays a pivotal role in the bioactivity. Accordingly, efficient approaches to valuable chiral molecular architectures with sites for functional group diversification are of considerable synthetic and biological importance. Furthermore, catalytic enantioselective syntheses of DPC 083 and DPC 961 are needed. Given the important challenge of the construction of a functionalized quaternary stereogenic center in the dihydroquinazolinone scaffolds, significant efforts have been made but with limited success. The approaches reported to date mainly rely on chiral auxiliaries to control the stereoselectivity.[8] An atom-economical catalytic enantioselective process is more attractive but, to our knowledge, such a method giving a useful level of enantioselectivity (>90% *ee*) is an unmet synthetic issue.[9]



Scheme 1. Structures of anti-HIV drug candidates DPC 083 and 961.

Herein, we report a novel highly efficient organocatalytic enantioselective aza-Henry reaction for the preparation of the enantioenriched trifluoromethyl dihydroquinazolinones. Notably, a highly efficient hydrogen-bond-mediated enantioselective addition of nitroalkanes to ketimines has been achieved for the first time under mild reaction conditions in high yields using as low as 1 mol% catalyst loading. Furthermore, we also observed that the trifluoromethyl group is critical for not only biological activity,[10] but also for chemical reactivity. Finally, the highly enantioselective synthesis of DPC 083 has been achieved using the aza-Henry reaction as a key step.

We envisioned that a catalytic enantioselective aza-Henry reaction could be realized by the reaction of 2(1*H*)-quinazolinones **1** with versatile nitroalkanes to generate chiral dihydroquinazolinones (Table 1). Accordingly, our investigation began with the model reaction between trifluoromethylquinazolin-2(1*H*)-one (**1a**; 1.0 equiv) and nitromethane (**2a**; 2.0 equiv) in the presence of quinine (**4a**; 10 mol%) as the catalyst in CH_2Cl_2 at room temperature (Table 1, entry 1).[11] A good yield (88%) was achieved but a disappointing enantiomeric excess (24%) was observed (Table 1, entry 1). Quinine thiourea (e.g., Soós catalyst; **4b**),[12] which has two more hydrogen-bond donors than quinine, proved to be a better promoter in the aza-Henry reaction; a shorter reaction time along with a better yield was obtained, but with only marginal improvement in the enantiocontrol (31% *ee*; Table 1, entry 2). Blocking the hydrogen-bond donor of quinine by protecting the 9-OH with phenanthrenyl (PHN; catalyst **4c**)[13] resulted in no reaction (Table 1, entry 3). Catalyst **4d**[13] bearing two hydroxy moieties allowed the reaction to proceed with dramatically improved enantiose-

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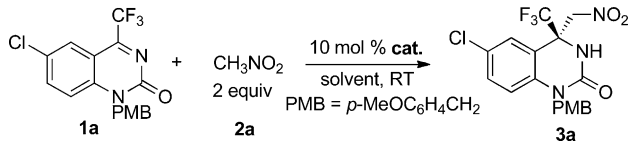
Table 1: Exploration of the catalytic enantioselective aza-Henry reaction of ketimine **1a** with nitromethane **2a**.[a]



Entry	Cat.	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**4a**	CH_2Cl_2	28	88	−24
2	**4b**	CH_2Cl_2	6	96	31
3	**4c**	CH_2Cl_2	58	<10	n.d.[e]
4	**4d**	CH_2Cl_2	58	75	69
5	**4e**	CH_2Cl_2	28	78	93
6	**4f**	CH_2Cl_2	1	96	94
7	**4f**	toluene	0.8	97	96
8	**4f**[d]	toluene	6	97	95

[a] Unless specified, see the Experimental Section for the reaction conditions. [b] Yields of the isolated products. [c] Determined by HPLC analysis on a chiral staionary phase (Chiralpak AS-H). [d] 1 mol% of **4f** was used. [e] Not determined.

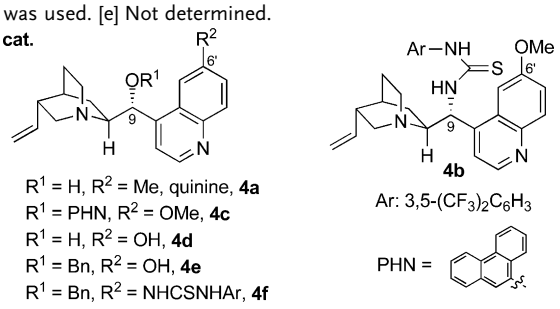
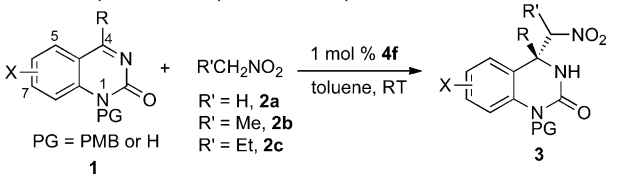


Table 2: Scope of **4f**-catalyzed aza-Henry reactions.[a]



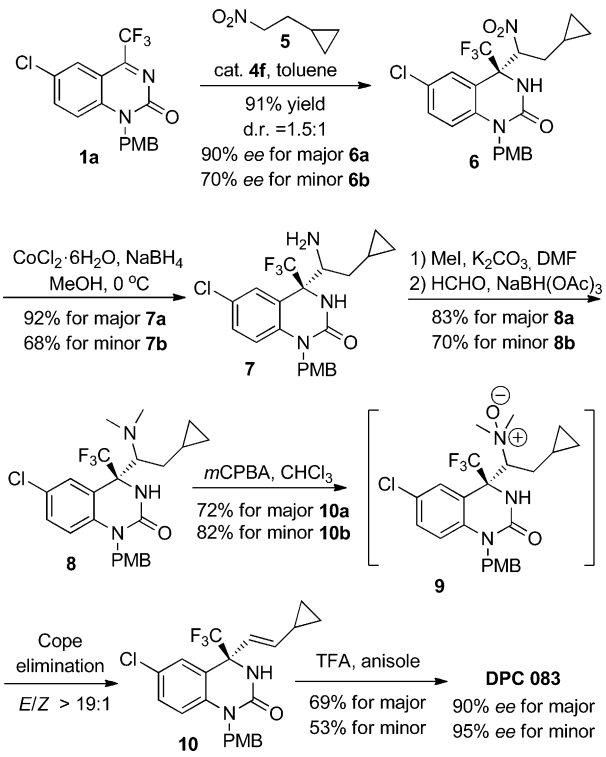
Entry	X, R, P, R′, **3**	*t* [h]	Yield [%][b]	*ee* [%][c]
1	6-Cl, CF_3, PMB, H, **3a**	6	97	95
2	6-Br, CF_3, PMB, H, **3b**	7.5	89	95
3	6-I, CF_3, PMB, H, **3c**	6.5	89	94
4	6-F, CF_3, PMB, H, **3d**	4	97	96
5	6-PMB, CF_3, PMB, H, **3e**	7	91	95
6	5-MeO, CF_3, PMB, H, **3f**	17	89	98
7	6-MeO, CF_3, PMB, H, **3g**	17	93	96
8	H, CF_3, PMB, H, **3h**	6	96	96
9	6-Cl, CF_3, PMB, Me, **3i**	22	50:27[e]	87.82[d]
10[f]	6-Cl, CF_3, PMB, Me, **3i**	16	72:23[g]	93:92[d]
11	6-Cl, CF_3, PMB, Et, **3j**	28	49:23[h]	88:82[d]
12[f]	6-Cl, CF_3, PMB, Et, **3j**	36	61:30[i]	92:93[d]
13[j]	H, Me, PMB, H, **3k**	46	–	–
14[j]	H, Ph, PMB, H, **3l**	46	–	–
15[j]	6-Cl, CF_3, H, H, **3m**	41	–	–

[a] Unless specified, see the Experimental Section for the reaction conditions. [b] Yields of the isolated product. [c] Determined by HPLC analysis on a chiral stationary phase (Chiralpak AS-H or Chiralcel OD-H or OJ-H). [d] Major/minor isomers. [e] The d.r. = 1.8:1, as determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [f] Reaction at 0°C. [g] The d.r. = 3:1, as determined by ^{1}H NMR spectroscopy. [h] The d.r. = 2:1, as determined by ^{1}H NMR spectroscopy. [i] The d.r. = 2:1, as determined by ^{1}H NMR spectroscopy. [j] No reaction.

lectivity (69% *ee*; Table 1, entry 4), thus suggesting that the 6′-OH group might play a key role in governing the enantiocontrol. Accordingly, catalyst **4e**[13] with the 9-OH group protected by a benzyl group was designed to probe the effect. To our delight, a significant improvement in the enantioselectivity (93% *ee*) was observed without any reduction in the reaction yield (78%; Table 1, entry 5). Replacement of the 6′-OH group by a thiourea moiety, a stronger hydrogen-bond donor, led to catalyst **4f**,[14] which displayed a higher catalytic activity with a significantly shortened reaction time and excellent yield and *ee* value (1 h, 96% yield, and 94% *ee*; Table 1, entry 6). A similar observation was first reported in the study by Hiemstra and co-workers of the Henry reaction of aldehydes with **4f**.[14] A screen of solvents revealed that toluene was the optimal medium for the process (Table 1, entry 7). Remarkably, the use of as low as 1 mol% of **4f** was sufficient, and comparable results were achieved (Table 1, entry 8).

Under the optimized reaction conditions, the scope of the aza-Henry reaction was explored (Table 2). It was found that the **4f**-catalyzed aza-Henry reaction was applicable to a variety of substrates to give trifluoromethylquinazolin-2(1*H*)-ones in high yields with good to excellent enantioselectivities. The reactions were unaffected by the electronic nature of the substituents on the aromatic rings. No matter whether there were electron-withdrawing (Table 2, entries 1–4), electron-donating (Table 2, entry 5–7), or electron-neutral (Table 2, entry 8) groups on the phenyl ring of the quinazolinones the reactions proceeded efficiently to afford the products with high yields and enantioselectivities. A variety of the nitroalkanes **2** were also investigated. Nitroethane and 1-nitropropane furnished nitroquinazolinones in good yields and with good enantioselectivities (Table 2, entries 9 and 11). Lowering reaction temperatures to 0°C led to an improvement in the d.r., *ee* value, and reaction yield (Table 2, entries 10 and 12). Notably, two adjacent stereogenic centers were created simultaneously, although with moderate diastereoselectivity, and the diastereomers could be separated by column chromatography on silica gel. A limitation of the process was also identified; the replacement of the trifluoromethyl group on the quinazolinones with a methyl or phenyl group led to a dramatic decrease in the reactivity of the substrates. No addition products were detected, and all starting materials remained unreacted, as determined by ^{1}H NMR analysis (Table 2, entries 13 and 14), thus indicating that the strong electron-withdrawing trifluoromethyl group is critical for the reaction to occur. Finally, it was found that the PMB protecting group was also pivotal, as no reaction occurred when it was removed (Table 2, entry 15). The configuration of the products was determined by single-crystal X-ray analysis of **3b** (see Figure S1 in the Supporting Information).[15]

Having developed the catalytic highly enantioselective aza-Henry reaction, we applied it to the synthesis of anti-HIV drug DCP 083 (Scheme 2). The **4f**-catalyzed aza-Henry reaction between **1** and nitrocyclopropylalkane **5** under the



Scheme 2. Synthesis of DPC 083.

optimized reaction conditions (see Table 2 and the Supporting Information) enabled the installation of the requisite quaternary stereogenic center in 91% yield with the two isomers formed in a 1.5:1 ratio. The major isomer **6a** (90% *ee*) had a higher enantioselectivity than that of the minor one **6b** (70% *ee*). The two isomers could be separated by column chromatography and they were both converted into target DPC 083 in parallel by the following route. Reduction of the nitro group in **6a** and **6b** using $CoCl_2{\cdot}6H_2O$ and $NaBH_4$ in MeOH at 0 °C gave the respective amines **7a** and **7b** in 92% and 68% yields, respectively. N-dimethylation of the resulting amino group presented challenging problems. The employment of the commonly used iodomethane (> 3 equiv) as the methylation reagent resulted in a mixture of mono- and bisproducts. An alternative reductive amination method using formaldehyde and $NaBH(OAc)_3$ gave rise to a complicated reaction mixture, which contained some of the desired bismethyl product. Extensive attempts to optimize the reaction conditions led us to the use of two sequential reactions. Treatment of **7a** and **7b** with MeI in the presence of K_2CO_3 gave the mono- and bismethylation products as a mixture, which after a subsequent reductive amination of the monomethyl products furnished clean bisproducts **8a** and **8b** in high yields (83% and 70%, respectively). The generation of the essential *trans* C=C bonds was realized by a Cope elimination reaction, after numerous attempts. The prerequisite *N*-oxide precursors **9a** and **9b** were obtained by treatment with *m*CPBA. The resulting *N*-oxides spontaneously underwent Cope elimination reactions in "one pot" to afford olefin **10** in 72% and 82% yields, respectively, over the two steps. Notably, in both cases, *trans* products were obtained exclusively, as determined by ^{1}H NMR analysis. Finally, the removal of the PMB group could be achieved by treatment of **10** with TFA in the presence of anisole to give the target DPC 083 in 69% and 53% yield, respectively. The spectral data of DPC 083 are in full agreement with those described in the literature ($[\alpha]_D^{28} = -17.6°$ ($c = 0.01$ g cm^{-3}, CH_3OH), 90% *ee*; $[\alpha]_D^{28} = -19.8°$ ($c = 0.004$ g cm^{-3}, CH_3OH), 95% *ee*; lit.[9] $[\alpha]_D^{20} = -22.5°$ ($c = 0.004$ g cm^{-3}, CH_3OH), > 99.9% *ee*). During these transformations, notably, no racemination of the quaternary stereogenic center was observed for **6a**, based on the chiral HPLC analysis of the product DPC 083. However, interestingly, a dramatic enhancement of enantioselectivity for **6b** (70% *ee*) was seen as the end product DPC 083 was obtained with 95% *ee*. This result is due to the substantial enrichment of the *S* enantiomer during the transformation of **6b** into **7b** (from 70% to 88% *ee*).

In conclusion, driven by the lack of highly enantioselective catalytic reactions for the synthesis of biologically significant trifluoromethyl hydroquinazolinones and the anti-HIV drug candidate DPC 083, we have developed the first highly efficient aza-Henry reaction of cyclic ketimines using simple quinine thioureas as the catalyst with as low as 1 mol% loading under mild reaction conditions. To the best of our knowledge, the study represents the first example of an organocatalytic asymmetric aza-Henry reaction using cyclic ketimines that leads to chiral quaternary carbon centers. Moreover, the aza-Henry reaction serves as a key step in the asymmetric preparation of anti-HIV drug DPC 083, thus demonstrating the synthetic utility of the aza-Henry reaction adducts. Investigations into the bioactivity of these products and their applications in diversity-oriented synthesis are currently being pursued.

Experimental Section

General Procedure (Table 2; entry 1 as an example): Nitromethane **2a** (0.12 mmol) was added to a mixture of quinazolin-2(1*H*)-one **1a** (0.06 mmol) and catalyst (**4f**, 0.0006 mmol) in toluene (0.5 mL) at RT. The resulting mixture was then stirred at RT until reaction was completed in 6 h. The pure product was obtained after purification by column chromatography on silica gel (ethyl acetate/hexanes 1:1), ready for compound characterization and chiral HPLC analysis.

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[15] The structure of a compound derived from molecule **3b** was determined by X-ray crystal analysis. CCDC 841456 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.

