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Core-structure-inspired asymmetric addition reactions: enantioselective synthesis of dihydrobenzoxazinone- and dihydroquinazolinone-based anti-HIV agents

Shen Li and Jun-An Ma*

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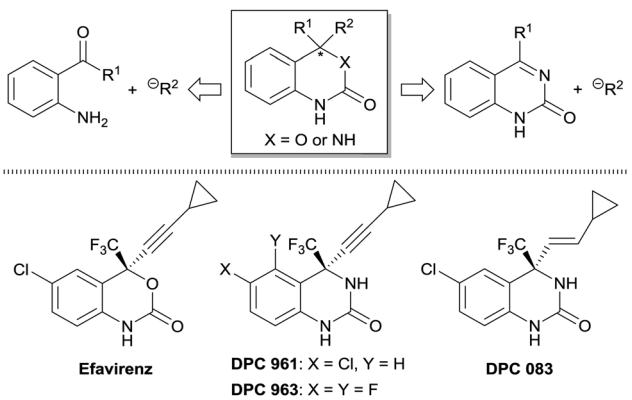
Dihydrobenzoxazinones and dihydroquinazolinones are the core units present in many anti-HIV agents, such as Efavirenz, DPC 961, DPC 963, and DPC 083. All these molecules contain a trifluoromethyl moiety at the quaternary stereogenic carbon center with *S* configuration. The enantioselective addition of carbon nucleophiles to ketones or cyclic ketimines could serve as a key step to access these molecules. This tutorial review provides an overview of significant advances in the synthesis of dihydrobenzoxazinone- and dihydroquinazolinone-based anti-HIV agents and relative analogues, with an emphasis on asymmetric addition reactions for the establishment of the CF_3-containing quaternary carbon centers.

Key learning points

(1) Dihydrobenzoxazinones and dihydroquinazolinones are the core units present in anti-HIV agents Efavirenz, DPC 961, DPC 963, and DPC 083.
(2) Advances in the asymmetric synthesis of Efavirenz are reviewed.
(3) Advances in the asymmetric synthesis of DPC 961 and DPC 963 are reviewed.
(4) Advances in the asymmetric synthesis of DPC 083 are reviewed.
(5) Asymmetric syntheses of the analogues of Efavirenz, DPC 961 and DPC 083 are described.

1. Introduction

Dihydrobenzoxazinones and dihydroquinazolinones are the core units present in lots of bioactive molecules with high therapeutic potential for the treatment of many diseases.[1–4] The importance of these structures is fully demonstrated by a series of potent non-nucleoside reverse transcriptase inhibitors (NNRTIs) for the treatment of human immunodeficiency virus (HIV) infection, such as Efavirenz, DPC 961, DPC 963, and DPC 083 (Scheme 1).[5–8] Dihydrobenzoxazinone-based Efavirenz is now one of the widely prescribed drugs used in combination therapy for first-line treatment of HIV.[9] Dihydroquinazolinones-based DPC 961, DPC 963, and DPC 083 are second-generation NNRTI candidates with enhanced potency compared to Efavirenz.[10] All these compounds contain the trifluoromethyl moiety at the quaternary stereogenic carbon center with *S* configuration. Biological evaluation revealed that the *R* enantiomer was inactive in the *in vitro* reverse transcriptase inhibition assay. Therefore, the establishment of the CF_3-containing quaternary carbon center in the dihydrobenzoxazinone and dihydroquinazolinone scaffolds in an enantioselective manner presents the main challenge for the preparation of these anti-HIV agents.



Scheme 1 Retrosynthetic analysis of dihydrobenzoxazinone- and dihydroquinazolinone-based anti-HIV agents.

Retrosynthetic analysis reveals that the enantioselective addition of carbon nucleophiles to ketones or cyclic ketimines

Department of Chemistry, Tianjin University, and Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300072, P. R. China. E-mail: majun_an68@tju.edu.cn

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could serve as a key step to access these molecules. This concept was first proved to be feasible by Merck's elegant work on the asymmetric preparation of NNRTI candidates in 1995.[11] Since then, over the past 20 years, great efforts have been made in the asymmetric synthesis of these anti-HIV agents through the asymmetric addition reactions by using stoichiometric quantities of chiral auxiliaries and reagents, or catalytic amounts of chiral catalysts. Moreover, the established methods benefit for the exploration of new NNRTIs based on dihydrobenzoxazinone and dihydroquinazolinone units. This tutorial review aims at providing an overview of significant advances in the synthesis of dihydrobenzoxazinone- and dihydroquinazolinone-based anti-HIV agents and relative analogues, with an emphasis on asymmetric addition reactions for the establishment of the CF_3-containing quaternary carbon centers. It is our hope that the achievements summarized in this review would encourage chemists both in academia and in the pharmaceutical industry to direct their efforts towards not only in the improvement of the efficiency of established processes, but also in development of new anti-HIV agents.

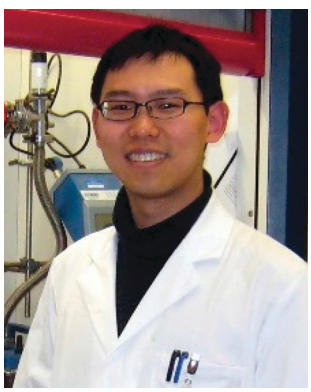
2. Enantioselective synthesis of Efavirenz

2.1. Stoichiometric asymmetric transformations

In 1995, the Merck research laboratories reported a practical procedure for the asymmetric synthesis of Efavirenz.[12] The key step in this process is an enantioselective 1,2-addition of lithium cyclopropylacetylide to trifluoroethanone **1** in the presence of ephedrine-based chiral auxiliary **3** (Scheme 2a). Upon strict control of reagent stoichiometry and reaction conditions, the addition reaction could be complete within minutes to provide chiral tertiary alcohol **4** with 98% ee. After a simple recrystallization, optically pure adduct **4** (>99.5% ee) was obtained in 93% yield. Further transformation of **4** through a sequential cyclization/deprotection (or deprotection/cyclization) process (*via* the intermediate **5** or **6**) gave rise to the formation of Efavirenz (Scheme 2b).[13]

The major drawback of the above process is its requirement of at least 2 equivalents of cyclopropylacetylene **2**, 2 equivalents of chiral controller **3**, and 4 equivalents of *n*-butyllithium to generate 1 equivalent of adduct **4**. By using a stoichiometric amount of acetylene **2** and a stoichiometric amount of ephedrine derivative **3**, only 50% conversion of trifluoroethanone **1** was observed. ^{6}Li-NMR and ^{13}C-NMR analyses revealed that stable aggregate **7** was formed as a C_2-symmetrical cubic tetramer at ambient temperature (Scheme 2c). Subsequent asymmetric addition of **7** to trifluoroethanone **1** at low temperature resulted in the formation of another tetramer **8**. The *in situ* IR-monitoring of this reaction progress demonstrated that aggregate **8** was much less reactive compared with **7**, and inhibited the subsequent 1,2-addition.[14–16] To eliminate this limitation, one more portion of lithium acetylide is prerequisite for the regeneration of reactive aggregate **7**.[17] However, some drop of the enantioselectivity indicated that there is a practical limit on the number of recycles possible.

Obviously, there is still room to improve the asymmetric synthesis of Efavirenz in view of two points: (1) the established enantioselective 1,2-addition of lithium cyclopropylacetylide to trifluoroethanone **1** required the use of excess amounts of nucleophile as well as chiral controller, and (2) a protection/deprotection sequence could not be excluded. It would be more straightforward and efficient for the synthesis of Efavirenz if the asymmetric addition could be done in the presence of a protecting group-free substrate by using stoichiometric amounts of acetylene and chiral reagent. In 1999, Tan and co-workers at Merck successfully developed a zinc-mediated enantioselective alkynylation of unprotected trifluoroethanone **9** (Scheme 3).[18] The complexation of diethylzinc with chiral ephedrine derivative **3** and achiral 2,2,2-trifluoroethanol led to the formation of zinc alkoxide, which was treated with chloromagnesium cyclopropylacetylide **10**, followed by the addition of trifluoroethanone **9** to



Shen Li

Shen Li was born in Tianjin, China. He received his BS degree from Nankai University in 2004 and his PhD under the supervision of Professor Qi-Lin Zhou at Nankai University in 2009. Then, he joined the research group of Professor Benjamin List at Max-Planck-Institut für Kohlenforschung as a postdoctoral fellow. Since December of 2011 he joined the Department of Chemistry at Tianjin University, where he was appointed to an associate professor. His research interests focus on the development of new synthetic methods, asymmetric catalysis, and synthesis of natural products.

Jun-An Ma

Jun-An Ma completed his PhD under the supervision of Professor Run-Qiu Huang at Nankai University in 1999. Then, he stayed there to work with Professor Qi-Lin Zhou before taking up postdoctoral fellowships with Dr Dominique Cahard (CNRS, France) and Professor Manfred T. Reetz (Germany) from 2003 to 2005. He also spent several months as a JSPS fellow with Professor Mikiko Sodeoka (RIKEN, Japan). Since July of 2005 he joined the Department of Chemistry at Tianjin University, where he was appointed to a full professor. His research interests focus on new synthetic methods, asymmetric catalysis, and organofluorine chemistry.

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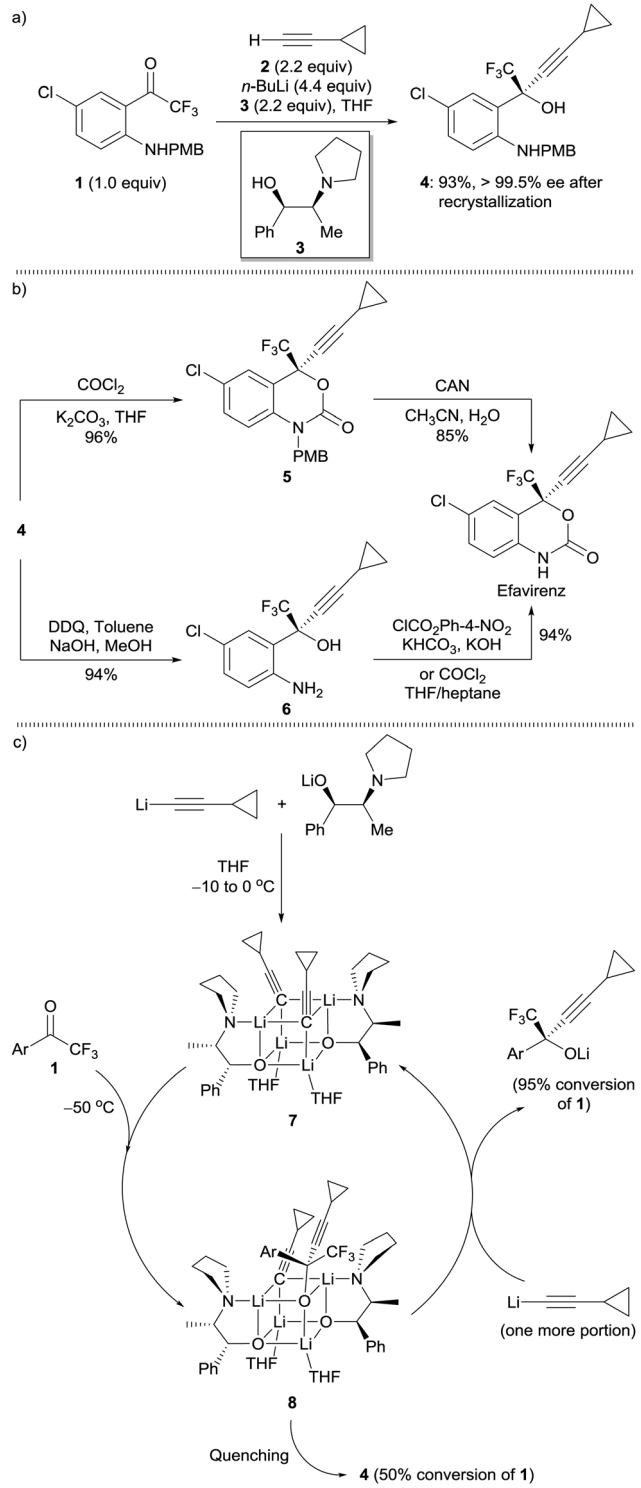
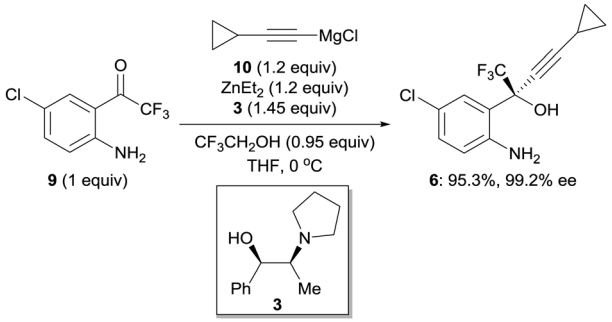


Scheme 2 Procedure for the asymmetric synthesis of Efavirenz developed by Merck research laboratories. (a) Enantioselective 1,2-addition of lithium cyclopropylacetylide to trifluoroethanone **1** in the presence of chiral ephedrine derivative **3**. (b) Conversion of adduct **4** into Efavirenz. (c) Proposed addition mechanism and multiple cycles.

afford chiral tertiary alcohol **6** in 95.3% isolated yield with up to 99.2% ee. Notably, this addition reaction could be conducted under mild conditions without the need of the cumbersome



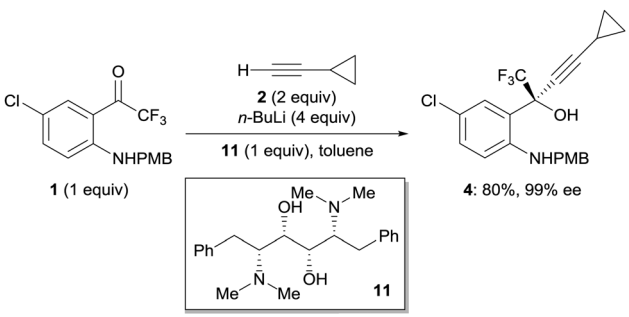
Scheme 3 Chiral zinc-mediated enantioselective alkynylation of unprotected trifluoroethanone **9**.

protection/deprotection sequence, and the amounts of acetylene and chiral controller could be reduced from 2.2 equivalents to 1.2 and 1.45 equivalents, respectively. Thus, this efficient process was considered as an important cornerstone in the synthesis of Efavirenz.

Multifunctional amino alcohols were shown to be an interesting class of ligands in the enantioselective alkynylation reactions of aldehydes and ketones.[19] Based on the previous reports, Jiang and co-worker evaluated their own developed C_2-symmetrical amino alcohol **11** as a chiral promoter in the asymmetric 1,2-addition of lithium cyclopropylacetylide to trifluoroethanone **1** (Scheme 4).[20] Interestingly, one equivalent of **11** was sufficient to promote the desired 1,2-addition, giving key intermediate **4** towards Efavirenz in 80% yield with excellent enantioselectivity (99% ee).

2.2. Catalytic asymmetric addition reactions

Compared to stoichiometric asymmetric transformations, catalytic asymmetric routes are competitive and even superior synthetic methods. Over the past few years, some efforts have been made toward the realization of catalytic enantioselective alkynylation of aryl trifluoroethanones,[21–25] and several protocols for the catalytic enantioselective synthesis of Efavirenz have emerged in the literature. For example, enantiomerically enriched intermediate **6** has been employed as a chiral amino alcohol ligand for the catalytic asymmetric alkynylation of starting substrate **9**. This elegant process, defined as the asymmetric autocatalysis,[26] was first used by Carreira and co-workers in 2011 for the synthesis of Efavirenz (Scheme 5).[27] By using a substoichiometric amount of



Scheme 4 Asymmetric alkynylation of trifluoroethanone **1** with chiral C_2-symmetrical amino alcohol **11**.

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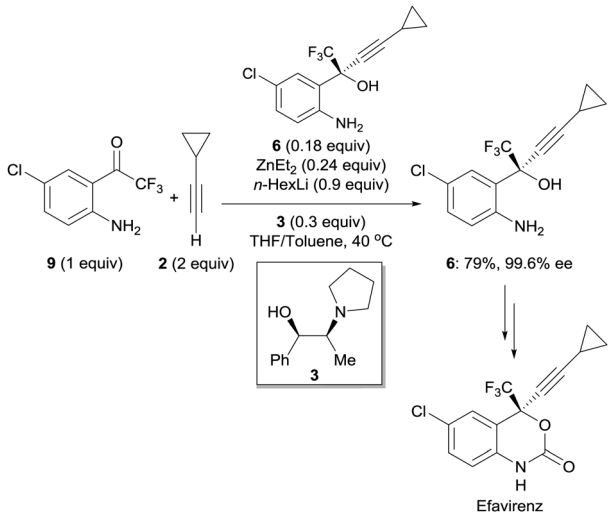
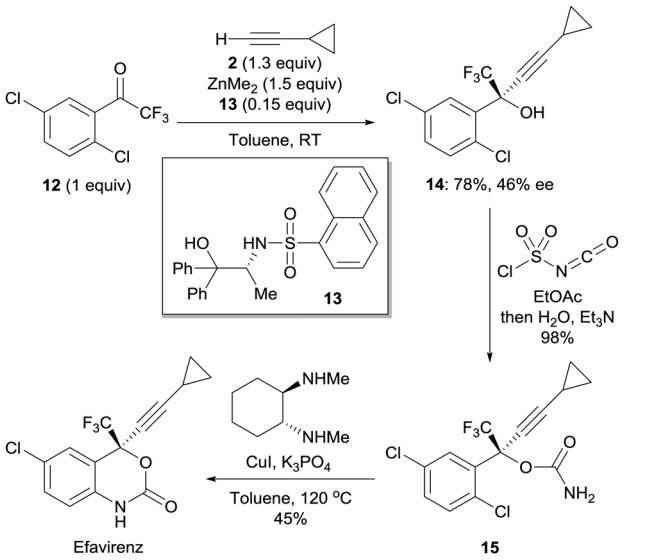
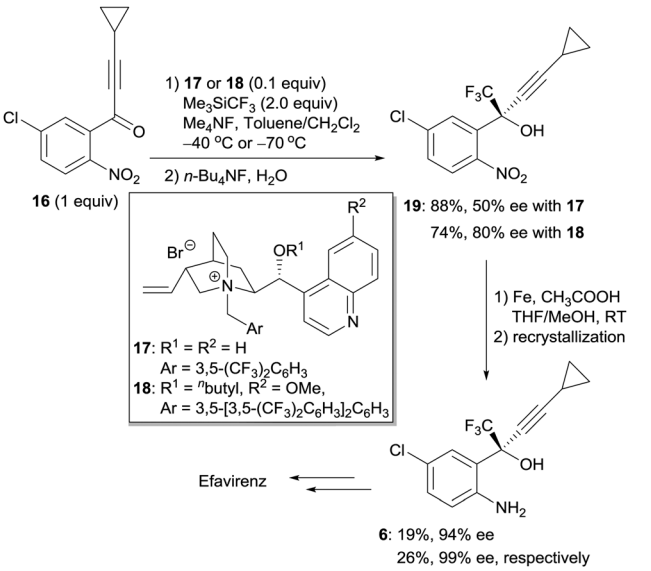


Scheme 5 Autocatalytic asymmetric alkynylation of trifluoroethanone **9**.



Scheme 6 Lonza's procedure for the asymmetric synthesis of Efavirenz.



Scheme 7 Organocatalytic asymmetric trifluoromethylation of alkynylketone **16** for the synthesis of Efavirenz.

adduct **6** (18 mol%) as a chiral autocatalyst, the authors documented that the asymmetric addition of zinc acetylide to trifluoroethanone **9** could be performed with substoichiometric quantities of diethylzinc and ligand (1*R*,2*S*)-*N*-pyrrolidinylnorephedrine **3** to afford expected adduct **6** in 79% yield and 99.6% ee. It is worthy of note that in the absence of an ephedrine additive the product was formed as a racemate. Thus, the autocatalytic effect in this procedure is rather special, requiring a second chiral ligand as an external chiral component. Following this attractive process, the manufacturing cost of Efavirenz might be substantially reduced in comparison to that of the existing stoichiometric process.

Recently, Dai and co-workers at Lonza provided an alternative approach for the catalytic asymmetric synthesis of Efavirenz.[28] In the presence of chiral amino alcohol **13**, the addition reaction of lithium cyclopropylacetylide to trifluoro-ethanone **12** proceeded smoothly to give desired tertiary alkynol **14** in 78% yield with 46% ee (Scheme 6). Alcohol **14** was then reacted with chlorosulfonyl isocyanate to afford carbamate **15**, which underwent a copper-catalyzed Ullman-type cyclization to establish the dihydrobenzoxazinone core structure of Efavirenz. Inspired by this process, Seeberger and co-workers described a three-step flow synthesis of *rac*-Efavirenz, which is represented to be the shortest route until now.[29]

From the viewpoint of synthetic organofluorine chemistry, the chiral tertiary alcohol motif in Efavirenz could also be constructed by an enantioselective trifluoromethylation of alkynylketone. Such a strategy was put into practice by Shibata and co-workers in 2011.[30] In the presence of a catalytic amount of cinchonidine derivative **17** and Me_4NF, the organocatalytic asymmetric trifluoromethylation of alkynylketone **16** with Me_3SiCF_3 proceeded smoothly to afford chiral tertiary alcohol **19** in 88% yield, albeit with a moderate enantioselectivity of 50% ee (Scheme 7). Further optimization of the catalyst structure led to superior cinchonidine-based catalyst **18** bearing two alkyoxyl groups and a bulkier benzyl group, which remarkably improved the enantiocontrol in the asymmetric trifluoromethylation step to 80% ee with a yield of 74%.[31] With chiral tertiary alcohol **19** in hand, the asymmetric synthesis of Efavirenz was completed in a two-step process: the chemoselective reduction of the nitro group in **19** furnished corresponding aniline **6**, which underwent ring-closure using Merck's procedure[13] to afford Efavirenz. This metal-free synthetic route towards Efavirenz would be an important complement to the previous manufacturing processes based on the organometallic asymmetric addition reactions.

3. Asymmetric synthesis of DPC 961 and DPC 963

3.1 Diastereoselective 1,4-addition reactions

In 2000, Magnus and co-workers at DuPont described a chiral auxiliary-directed diastereoselective 1,4-addition reaction for the synthesis of CF_3-substituted chiral dihydroquinazolinone units,

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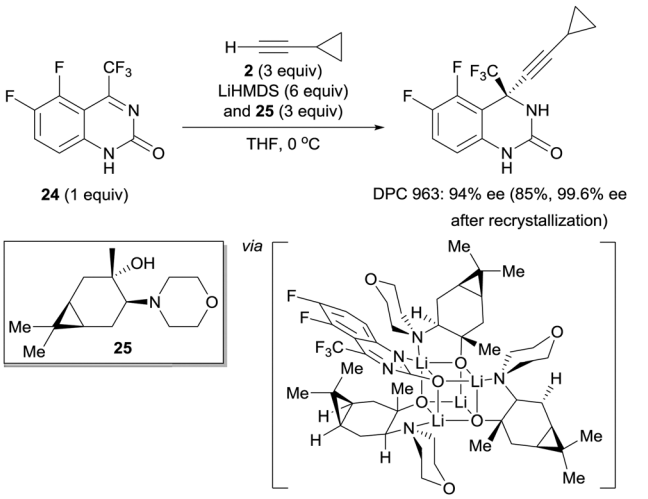
which enabled the preparation of DPC 961 in a highly stereoselective manner.[32] This procedure was started from the reaction of hydrate hydrochloride keto-aniline **20** with (*R*)-(+)-α-methylbenzyl isocyanate to afford hemiaminal **21** bearing a chiral auxiliary (Scheme 8). Subsequent treatment of **21** with thionyl chloride *in situ* generated CF_3-substituted 2(3*H*)-quinazolinone **22**, which was directly trapped by an excess of chloromagnesium cyclopropylacetylide **10** to give dihydroquinazolinone **23** in 95% conversion with the diastereomeric excess (de) around 92%. Recrystallization from methanol gave the single diastereomer of **23** in 85% isolated yield. By the exposure of **23** to wet 2,2,2-trifluoroacetic acid or warm formic acid, DPC 961 was obtained in good yield. Although 2(3*H*)-quinazolinone **22** was too reactive to isolate, the existence of such an intermediate was fully characterized by ^{19}F-NMR, ^{13}C-NMR, and *in situ* IR analyses.[33]

3.2 Enantioselective 1,2-addition reactions

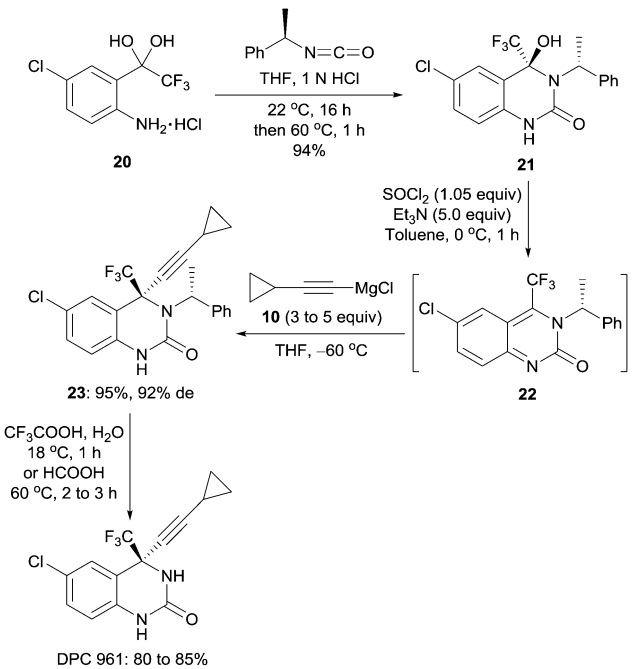
It is surprising that the extension of the above-mentioned 1,4-addition as a synthetic route to DPC 963 led to an unexpected 1,2-addition reaction, therefore, an alternative approach to access DPC 963 was required. Inspired by the fundamental work on the preparation of the first NNRTI candidate at Merck research laboratories,[11] an enantioselective addition of lithium cyclopropylacetylide to cyclic ketimine **24** was developed and applied to the synthesis of DPC 963 by Nugent and co-workers at DuPont (Scheme 9).[34] The asymmetric addition was carried out by using lithium bis(trimethylsilyl)amide (LiHMDS) as a strong base and readily available chiral amino alcohol **25** as a chiral ligand. The optimal outcome in terms of yield and enantioselectivity was associated with a 3 : 1 ratio of chiral amino



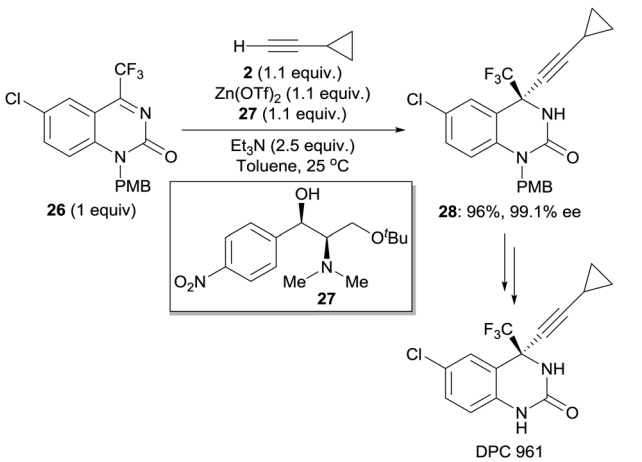
Scheme 9 Synthesis of DPC 963 *via* asymmetric addition of lithium cyclopropylacetylide to ketimine **24**.

alcohol **25** to ketimine **24**. Under these conditions, the desired product DPC 963 was obtained with 94% ee. Further improvement in the enantioselectivity was achieved through a single recrystallization. NMR spectroscopic investigation and DFT (density functional theory) calculations by Collum and co-workers revealed that the reaction could proceed *via* the external attack of lithium cyclopropylacetylide on a mixed tetramer containing chiral ligand **25** and ketimine **24** (3 : 1).[16,35]

In pursuit of a more practical process for the asymmetric synthesis of dihydroquinazolinone-based anti-HIV agents, Jiang and co-worker examined the asymmetric alkynylation of cyclic ketimine **26** with acetylene **2** in the presence of a chiral zinc complex.[36] The use of amino alcohol **27** as a chiral ligand, in combination with $Zn(OTf)_2$ and trimethylamine, could promote the addition to furnish precursor **28** of DPC 961 in high yield with excellent enantioselectivity (Scheme 10). A comparable result of 96% yield with over 99% ee was obtained when the reaction was carried out on a 100 gram scale. Other advantages



Scheme 8 Synthesis of DPC 961 *via* asymmetric addition of magnesium cyclopropylacetylide **10** to 2(3*H*)-quinazolinone **22**.



Scheme 10 Synthesis of DPC 961 *via* asymmetric alkynylation of ketimine **26** mediated by a chiral zinc complex.

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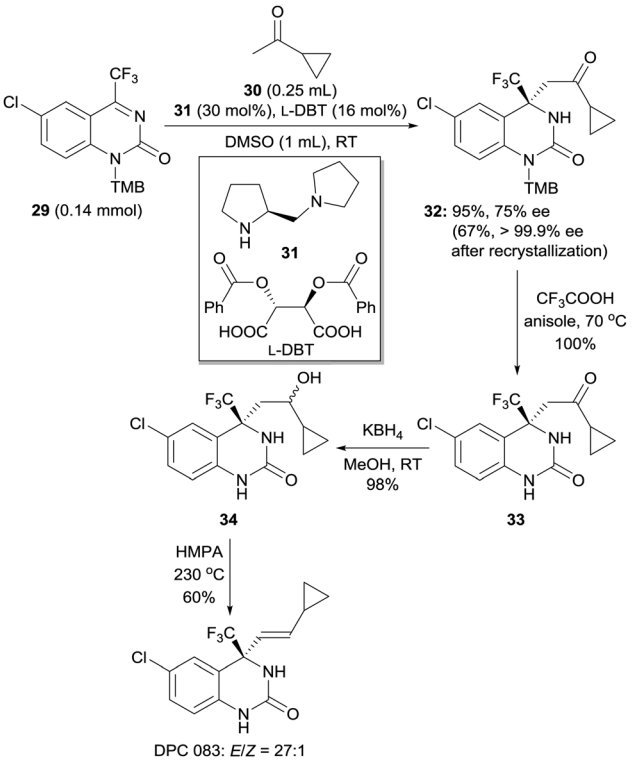
of this reaction included the requirement of only 1.1 equivalents of the nucleophile and the chiral ligand, the mild reaction conditions, and the ready availability of chiral amino alcohol **27**. Moreover, the chiral ligand could be recovered and recycled at least three times without loss of yield and enantioselectivity.

4. Enantioselective synthesis of DPC 083

4.1 Catalytic asymmetric Mannich reactions

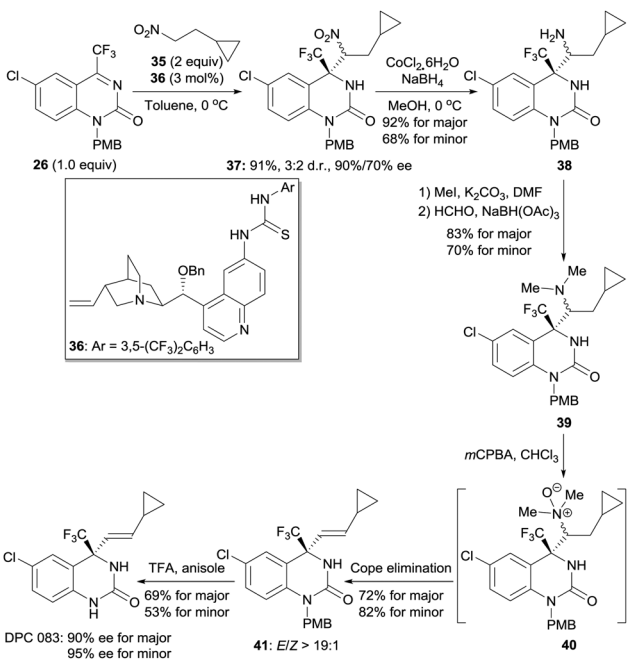
DPC 083 was first obtained by the reduction of DPC 961 with lithium aluminum hydride and provided superior coverage of wild type and mutant HIV variants relative to Efavirenz,[7,8] therefore, a catalytic enantioselective process for the direct synthesis of DPC 083 was highly desired.

The enantioselective Mannich reaction of ketimines is considered as one of the most powerful transformations to access chiral tertiary amines and related units.[37] In 2008, Jiang and co-workers developed a new process for the asymmetric synthesis of DPC 083.[38] The key step for the construction of the dihydroquinazolinone structure bearing a chiral quaternary carbon center was an organocatalytic asymmetric Mannich reaction (Scheme 11). Under the catalysis of a chiral diamine-Brønsted acid salt, cyclic ketimine **29** reacted with cyclopropyl methyl ketone **30** to afford valuable intermediate **32** towards DPC 083 in 95% yield with 75% ee. Attempts to improve the enantioselectivity by recrystallization led to an interesting self-discrimination. Two enantiomers with opposite configuration formed a heterochiral dimer through multiple hydrogen bonds and precipitated from ethanol, whereas enantiomerically pure adduct **32** (>99.9% ee) could be obtained from mother liquor in a yield of 67%. With compound **32** in hand, the synthesis of DPC 083 was completed in three steps. Removal of the protecting group and reduction afforded intermediates **33** and **34** in nearly quantitative yields. The essential *trans* C=C double bond in DPC 083 was generated by a sequential dehydration.



Scheme 11 Synthesis of DPC 083 *via* an organocatalytic asymmetric Mannich reaction.

The nitro-Mannich reaction, also known as the aza-Henry reaction,[39] provides another opportunity to access the dihydroquinazolinone core units. In 2011, Wang and co- workers nicely demonstrated that the nitro-Mannich reaction between cyclic ketimine **26** and (2-nitroethyl)cyclopropane **35** could serve as a key step for the asymmetric preparation of DPC 083 (Scheme 12).[40] Under the catalysis of chiral quinine thiourea **36**, the nitro-Mannich reaction enabled the construction of chiral dihydroquinazolinone **37** in 91% yield with a 3 : 2 diastereomeric ratio. The major isomer (90% ee) had a higher ee value than that of the minor one (70% ee). Separation of the two diastereoisomers by column chromatography was feasible, and both of them could be converted into DPC 083 by the identical process. Reduction of the nitro group in **37** gave corresponding amine **38**, which underwent a sequential methylation/reductive amination to afford *N*,*N*-dimethylation product **39**. Treatment of **39** with 3-chloroperoxybenzoic acid (*m*-CPBA) (*via* the intermediate **40**) followed by an *in situ* Cope elimination gave rise to the formation of **41** with the *trans* C=C double bond exclusively. The final target DPC 083 was obtained after removal of the PMB group from **41**. No racemisation was observed during the transformation of the major isomer. However, an unexpected enhancement of enantioselectivity was



Scheme 12 Synthesis of DPC 083 *via* an organocatalytic asymmetric nitro-Mannich reaction.

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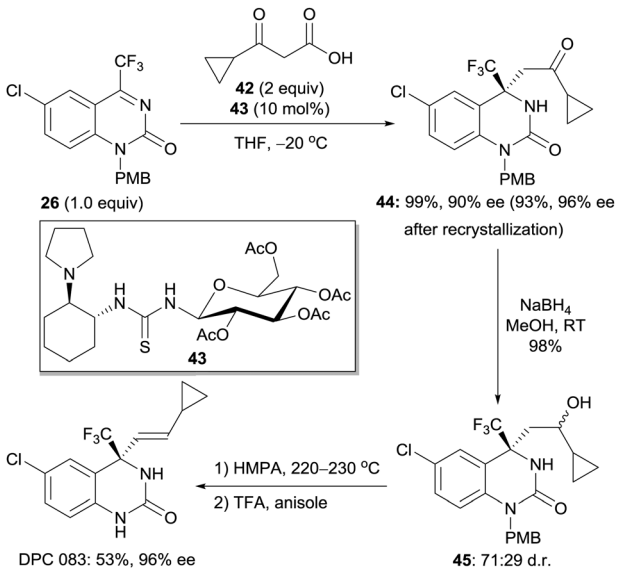
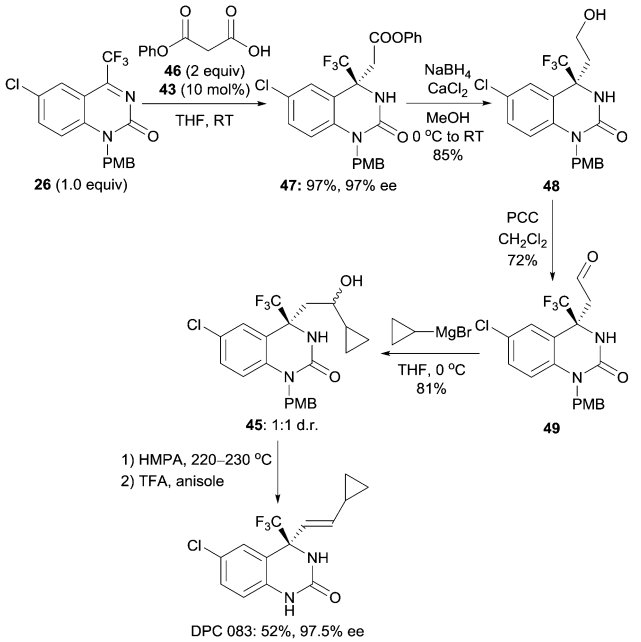
observed for the minor isomer as the end product DPC 083 was obtained with 95% ee.

Another efficient and practical process for the asymmetric synthesis of DPC 083 was developed by Ma and co-workers by means of an organocatalytic enantioselective decarboxylative Mannich reaction of β-ketoacids.[41] In the presence of a saccharide-derived amino thiourea catalyst **43**,[42] the decarboxylative Mannich reaction between cyclic ketimine **26** and cyclopropyl-3-oxopropanoic **42** proceeded smoothly to give dihydroquinazolinone-based adduct **44** in nearly quantitative yield with 90% ee (Scheme 13). Further improvement of the ee value to 96% ee was achieved after a single recrystallization. It is worthy of note that the presence of an *N*-PMB group at ketimine **26** proved to be essential for achieving a high level of asymmetric induction, which means that the protection/deprotection steps have to be involved in the preparation of DPC 083. Starting from **44**, reduction of the carbonyl group gave alcohol **45** as a 71 : 29 mixture of diastereomers in 98% yield. Direct dehydration of the diastereomeric mixture and subsequent removal of the PMB group afforded the desired product DPC 083 in 53% yield with 96% ee.

Shortly after, Ma and co-workers expanded the decarboxylic Mannich protocol to the reaction of less reactive malonic acid half oxyesters with cyclic ketimines.[43] The same bifunctional organocatalyst **43** once again proved to be efficient to promote the decarboxylic Mannich reaction between ketimine **26** and 3-oxo-3-phenoxypropanoic acid **46**, delivering chiral dihydroquinazolinone **47** in 97% yield with 97% ee (Scheme 14). The asymmetric synthesis of DPC 083 was completed within 5 steps by using **47** as a starting material. Reduction of the phenol ester group in **47** yielded primary alcohol **48** in 85% yield. Subsequently, oxidation of the alcohol motif to the corresponding aldehyde, followed by 1,2-addition with cyclopropylmagnesium bromide gave intermediate **45** with a diastereomeric ratio of 1 : 1. With **45** in hand, DPC 083 was obtained based on the previous procedure.[41]



Scheme 13 Synthesis of DPC 083 *via* an organocatalytic asymmetric decarboxylative Mannich reaction of β-ketoacids.



Scheme 14 Synthesis of DPC 083 *via* an organocatalytic asymmetric decarboxylative Mannich reaction of malonic acid half oxyesters.

4.2 Catalytic asymmetric Strecker reactions

The asymmetric Strecker reaction between ketimines and cyanide is one of the most important reactions to enable the construction of a chiral quaternary carbon center, and its corresponding adducts can be readily converted into chiral nitrogen-containing compounds.[44] In 2012, Ma and co-workers introduced an organocatalytic enantioselective Strecker reaction of cyclic ketimine **26** as a key step for the asymmetric synthesis of DPC 083.[45] With only 1 mol% of cinchona alkaloid-based thiourea **50**, Strecker adduct **51** from ketimine **26** and trimethylsilylformonitrile (TMSCN) was obtained in 99% yield with 96% ee (Scheme 15). Reduction of the cyano group in **51** gave aldehyde intermediate **52**. A Wittig reaction was carried out to establish the C=C double bond formation, however, giving the *cis*-isomer of **41** as the major product. Subsequent attempt on the isomerization of **41** was successful to deliver (*Z*)-**41** in 70% yield. Finally, removal of the PMB protecting group to afford the desired DPC 083 was achieved. During these transformations, no racemization of the quaternary stereogenic center occurred.

5. Enantioselective synthesis of relative analogues

5.1 Enantioselective diynylation reactions

It was reported that the drug resistance to Efavirenz occurred in a small fraction of the patient population. Toward this end, pursuit of new NNRTIs with a better resistance profile is still particularly demanding.[46]

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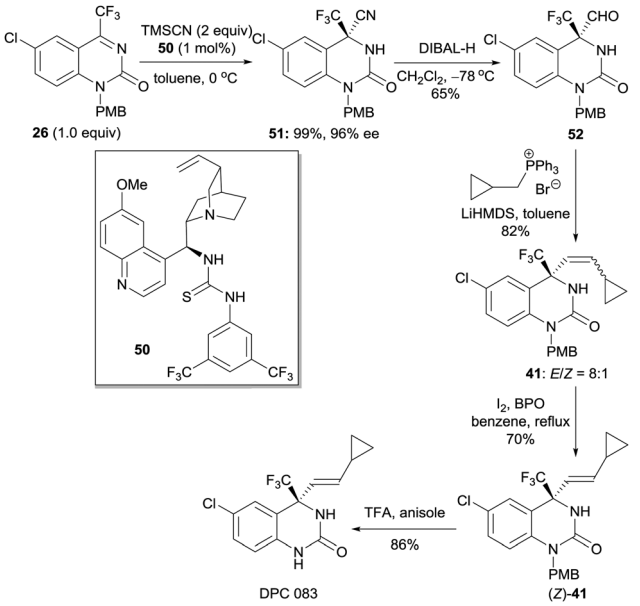
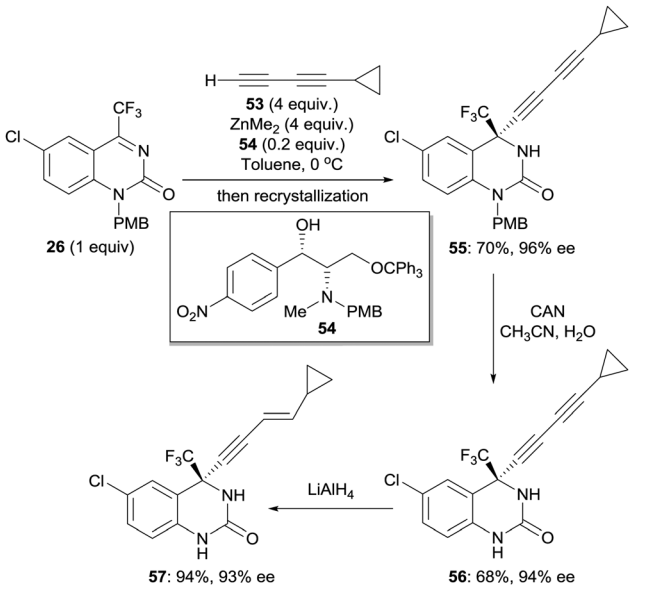


Scheme 15 Synthesis of DPC 083 *via* an organocatalytic asymmetric Strecker reaction.

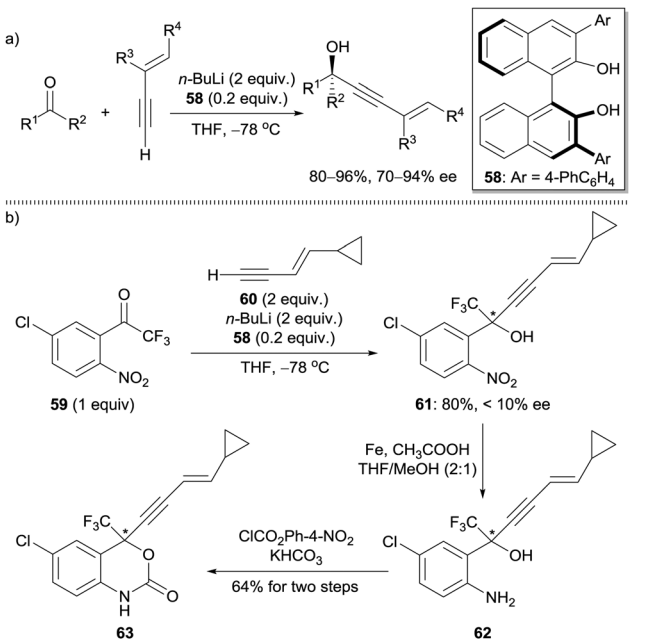


Scheme 16 Asymmetric diynylation of ketimine **26** and the synthesis of the DPC 961 and DPC 083 analogues.

Conjugated diynes are potentially intriguing building blocks as they exist in an array of compounds with diverse biological activities.[47] Installation of conjugated diynes within dihydroquinazolinone units may provide a library of NNRTI candidates with improved drug potency. In 2012, Ma and co-workers developed a zinc-mediated enantioselective addition of terminal 1,3-diyne **53** to cyclic ketimine **26** (Scheme 16).[48,49] In the presence of a catalytic amount of chiral additive **54**, a series of dihydroquinazolinone-based chiral compounds bearing a quaternary carbon center and a conjugated diyne motif were obtained in 86–98% yields and 70–96% ee. For most of the products, further improvement in the enantiopurity could be achieved by simple recrystallization. As a DPC 961 analogue, compound **56** was obtained by deprotection of addition product **55** in 68% yield with 94% ee. Reduction of **56** with lithium aluminium hydride gave eneyne **57** with *E* conformation exclusively, which featured a very similar structure to DPC 083.

5.2 Enantioselective enynylation reactions

Recently, Ma and co-workers conduced a short synthesis of the Efavirenz enyne analogue.[50] The key step in this process was a lithium-mediated enantioselective 1,2-addition of enynes (*e.g.* **60**) to ketones in the presence of a catalytic amount of chiral binaphthol **58** (Scheme 17a). This reaction was suitable for various nonfluorinated ketones, giving a broad variety of chiral tertiary propargylic alcohols in 80–96% yields with 70–94% ee. However, the extension of this protocol to trifluoroethanone **59** led to a dramatic drop in the stereocontrol, giving desired chiral tertiary alcohol **61** in 80% yield, albeit with 10% ee (Scheme 17b). Reduction of the nitro group in **61** gave corresponding aniline **62**, which then reacted with 4-nitrophenyl chloroformate to afford dihydrobenzoxazinone **63**, an analogue of the anti-HIV drug Efavirenz.



Scheme 17 (a) Asymmetric enynylation of ketones and (b) preparation of the Efavirenz analogue.

6. Concluding remarks

With the established asymmetric processes of chiral auxiliaries, thousands of kilograms of efavirenz, DPC 961, and DPC 083 have been prepared in the clinical, launch and sale quantities. What is more, recent advances in catalytic enantioselective synthesis of these anti-HIV drugs will provide new and attractive tools to reach even higher stereoselectivities. This should stimulate further developments in the large-scale industrial production. On the other hand, considering the drug-resistant virus strains,

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continuous efforts should be made toward the exploration of new dihydrobenzoxazinone- and dihydroquinazolinone-based NNRTI candidates with diverse functional groups.

Abbreviations

BPO	Benzoyl peroxide
CAN	Ceric ammonium nitrate
m-CPBA	3-Chloroperoxybenzoic acid
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DFT	Density functional theory
DIBAL-H	Diisobutylaluminium hydride
HIV	Human immunodeficiency virus
HMPA	Hexamethylphosphoramide
LiHMDS	Lithium bis(trimethylsilyl)amide
NNRTI	Non-nucleoside reverse transcriptase inhibitor
OTf	Trifluoromethanesulfonate
PCC	Pyridinium chlorochromate
PMB	4-Methoxybenzyl
TFA	2,2,2-Trifluoroacetic acid
TMB	2,4,6-Trimethylbenzyl
TMSCN	Trimethylsilylformonitrile

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