NHC-catalyzed Enantioselective Hetero-[10+2] Annulation

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Abstract

The higher-order cycloadditions are powerful strategies for construction of polycycles in one step, however an efficient and concise version for asymmetric induce is limited. N-heterocyclic carbenes are widely used organocatalysts for asymmetric synthesis and will be an ideal choice for enantioselective higher-order cycloadditions. Here we report an enantioselective [10+2] annulation between catalytically formed aza-benzofulvene intermediates and trifluoromethyl ketone derivatives. This protocol exhibits a wide scope, high yields and good ee values, reflecting a robust and efficient higher-order cycloaddition. Density functional theory (DFT) calculations provided an accurate prediction of the reaction enantioselectivity, and in-depth insight to the origins of stereocontrol.

Introduction

In the past few decades, the use of chiral *N*-heterocyclic carbenes (NHCs) as asymmetric organocatalysts¹⁻¹⁰, with the associated advantages of their easily operation and of carrying out enantioselective transformations in benign environment and under mild reaction conditions, has led to an impressive and continuous growth. Specifically, the NHC-catalyzed asymmetric cycloaddition for the assembly of chiral mono- or polycyclic molecules has received attractive and broad attention, driven by the predominance of these chiral cyclic structures in natural products and pharmaceuticals^{11,12}. In this content, normal order cycloadditions (cycloaddition that involves $\geq 6\pi$ -electron components) have been investigated in NHC catalysis in terms of *in situ* generated active enolate^{13,14} or dienolate intermediates¹⁵ (Fig. 1a). These pioneer works include [2+2]¹⁶⁻²⁰, [2+3]²¹⁻²³, [2+4]²⁴⁻²⁹, [4+2]³⁰⁻³⁵, etc^{36,37}. In 2008, Ye¹⁸ and Smith¹⁶ simultaneously realized a NHC-catalyzed [2+2] cycloaddition of enolates with imines, yielding versatile chiral *b*-lactams. The enantioselective [2+3] cycloaddition of enolates with oxaziridines or nitrovinylindoles has been reported by Ye²¹ and Enders²² groups, using NHC organocatalysis, independently. Asymmetric carben-catalyzed [2+4] reaction of enolates with azadienes was also disclosed by Bode²⁴ *et al.* to furnish chiral dihydropyridinones. In addition to enolates, NHC-bounded dienolates have also been successfully studied in [4+2]³⁰ or [4+3]³⁸ cycloadditions to generate six- or seven-membered heterocycles, respectively.

Although the above-mentioned normal order cycloaddition reactions are widely explored, the higher-order cycloaddition ($\geq 6\pi$ -electrons) has received a high level of attention and is somehow used to concisely construct polycycles in one step fashion. Significant progress of highly stereoselective higher-order cycloadditions has been made in recent years³⁹⁻⁴¹. Elegant relevant works in this direction involve Feng's Ni-catalyzed [8+2] cycloaddition of azaheptafulvenes with alkylidene malonates^{42,43}. The Jørgensen group enriched this field by developing a series of highly enantioselective cycloaddition reactions (e.g. [8+2]^{44,45}, [6+4]⁴⁶ and [10+4]⁴⁷) promoted via enamine catalysis. However, to a certain extent⁴⁸⁻⁵¹, this class of higher-order cycloadditions suffers from some drawbacks (i.e. difficult stereocontrol and lack of periselectivity), thus resulting in a slower growth than normal order cycloaddition. Despite the difficulties ahead, some encouraging progress was still achieved in the

direction of NHC catalysis⁵²⁻⁵⁵. Glorious⁵⁶ and Rovis⁵⁷ reported a [8+2] cycloaddition of NHC-bounded o-quinodimethane intermediates (8p-electron) with ketones, respectively (Fig. 1b)^{58,59}. A recent Chi's⁶⁰ work indicated that salicylaldehydes could be oxidized to generate NHC-bounded o-quinone methide intermediates (8p-electron), which participated in a [8+2] cycloaddition with electrophile trifluoromethyl ketones. Besides above accomplishments, Cheong and Scheidt⁶¹ then successfully found that the NHC-bounded aza-o-quinone methide intermediates (8p-electron), first generated from a decarboxylation of *N*-methylisatoic anhydrides, could react with trifluoromethyl ketones to deliver enantioenriched dihydrobenzoxazin-4-ones via a [8+2] cycloaddition strategy.

In brief, NHC-catalyzed cycloadditions ranged from [2+2] to [8+2] have been extensively investigated over the past few years, but there is a remarkable lack of higher order cycloadditions (e.g. [10+2]^{62,63}, [14+2]). Although the intricately competitive pathways make the reaction-control difficult, these higher-order cycloadditions can provide a direct way to efficiently build polycyclic scaffolds. Herein, we report a hetero-[10+2] higher-order cycloaddition of indole-2-carbaldehydes with trifluoromethyl ketone derivatives, proceeding via an NHC-bounded aza-benzofulvene intermediate. This discovery represents the initial use of NHC-bounded aza-arylfulvene intermediates in catalytic and enantioselective [10+2] or [14+2] reaction. In addition, in medicinal chemistry, the incorporation of "F"-containing fragments normally provides an effective route to enhance the metabolic stability, as well as other chemical or physical properties, of target molecules⁶⁴⁻⁶⁶. Based on the importance of polycyclic structures and incorporated "F"-containing fragments, the potential of these synthesized molecules in drug discovery is worth our expectation.

Results

Reaction Optimization.

We commenced our studies by investigating the reaction of indole-2-carbaldehyde 1a and 2,2,2-trifluoroacetophenone 2a as the model substrates, K₂CO₃ as the base, DQ as the oxidant, tetrahydrofuran (THF) as the solvent, and the results are briefly summarized in Table 1. When *L*-phenylalanine-derived triazolium NHC precatalyst A was exploited, the expected cycloadduct 3a was not observed. Replacing mesitylene group with pentafluorophenyl group triazolium NHC precatalyst B gave desired product 3a in 40% yield and 0% ee, whereas the use of precatalyst C and D resulted in almost no reaction. To our delight, when indanol-derived triazolium catalyst E was tested, the [10+2] cycloadduct 3a was successfully formed in 61% yield with 35% ee and implies that this highly enantioselective [10+2] annulation can be achieved in the presence of ideal conditions. The catalytic performance could be further improved by changing the X group of precatalyst E from H to NO₂ (entry 6). After evaluating bases and solvents, we found that a combination of PhCO₂Na as the base and hexane as the solvent gave the product 3a in 80% yield and 88% ee (entry 10). Improvements in yield and enantioselectivity were found when thiourea was used as the additive to form 3a (entry 12, 85% yield, 91% ee).

Substrate Scope.

With the optimal catalytic system in hand, we moved our attention to explore the generality of this asymmetric higher order [10+2] annulation. As illustrated in Scheme 2, by reacting with indole-2-carbaldehyde 1a, an array of aryl trifluoromethyl ketones 2 were examined firstly. In the reactions to generate the [10+2] cycloadducts 3, yields and enantioselectivities were found to be independent on the electronic properties of the substituents on aryl group in 2 (3b-i). When the heteroaryl trifluoromethyl ketones were reacted with indole-2-carbaldehyde 1a under optimal conditions, an [10+2] annulation was efficiently realized in all cases (3j-n). Reactions attempted using the alkyl trifluoromethyl ketones gave their corresponding [10+2] cycloadducts in good yields with high ee values (3o and 3p). Whereas the alkenyl trifluoromethyl ketone 2q was reacted with 1a, product 3q was also obtained in a good yield (73%) but with a slightly diminished enantioselectivity (72% ee). Switching the fluorinated substituent from CF₃ to CF₂H, ClCF₂ or C₂F₅ in ketones, synthetic useful yields and high to excellent enantioselectivities were still obtained under current conditions (3r-t).

Next, we turned our focus to investigate the scope of substrate 1. Different substituents and substitution patterns on the indole skeleton were examined comprehensively. Electron- withdrawing substituents such as halo (4a and 4b) units on the phenyl ring of the aldehyde substrates were well tolerated. Electron-releasing groups such as methyl (4c, 4e, 4f and 4g) and methoxyl unit (4d) could also be installed on the indole scaffold of the aldehyde substrates. It is worth to noting that this [10+2] protocol could be extended to a higher order [14+2] cycloaddition, affording their corresponding cycloadducts (4h and 4i) in good enantioselectivities albeit with acceptable but dropped yields under the current standard conditions. The absolute configuration of 3e (CCDC 1961662) was determined by single-crystal X-ray analysis and other products were assigned by analogy.

Postulated Mechanism:

A postulated catalytic mechanism of [10+2] annulation is summarized in Fig. 4. The addition of NHC precatalyst F to aldehyde 1 in the presence of base generates Breslow intermediate I^{67,68}, which is subsequently oxidized to the key NHC-bounded aza-benzofulvene intermediate II. A mass correlating to intermediate II was observed via high-resolution mass spectrometry (See SI (supplementary information) for details). This critical intermediate II can promote a cascade Michael /acylation sequence, a C-O bond is formed via II to form intermediate III, which undergoes N-acylation to release the NHC catalyst F for next catalytic cycle. At current stage, the concerted [10+2] pathway for this reaction can't be ruled out in the absence of evidences (for more details, please see SI).

To further reveal the enantioselectivity of this [10+2] annulation, density functional theory (DFT) calculation was performed to study the key step of nucleophilic attack of intermediate II onto trifluoroacetophenone. As shown in Figure 1, two transition states named TS(II-III)*R* and TS(II-III)*S* was located, where the *re*- or *si*-face of trifluoroacetophenone was attacked respectively. The calculated

relative free energy of transition state TS(III-IV)*R* is 5.0 kcal/mol lower than that of TS(II-III)*S*, which predicts that the generation of *R*-configuration product 4a is favorable. The calculated result is consistent with experimental observations. The geometry of those two transition states are also given in Fig. 5. After the absorption of indole reactant onto NHC catalyst, a strong π - π stacking between indolyl moiety and the aryl in NHC catalyst can significantly stabilize the deprotonated indolyl moiety. The π - π attraction is clearly shown in calculated noncovalent interaction (NCI) maps (we also carried our kinetic experiment to prove it, please see SI). When the nucleophilic attack occurs, trifluoromethyl of trifluoroacetophenone appears at the more bulky inner side in transition state TS(II-III)*R*. It is more favorable than the case in transition state TS(II-III)*S* that phenyl group is set to inner side. The NCI map of transition state TS(II-III)*R* clearly reveals that the repulsion between phenyl group of trifluoroacetophenone and the NHC catalyst leads to instability of transition state TS(III-IV)*S*, while this repulsion is absent in transition state TS(II-III)*R*.

Synthetic transformations and applications:

Our protocol is amenable for large-scale preparation. For example, the use of standard conditions was sufficient to produce 4d (1.29 g) in 92% yield and with 90% ee (Fig. 6a). A facile Pd-catalyzed Suzuki coupling of 3d with 4-methoxyphenylboronic acid 5 led to product 6 in a 72% yield and with a remained enantioselectivity (Fig. 6b).

Discussion

In summary, a unique NHC-catalyzed enantioselective hetero-[10+2] annulation of indole-2-carbaldehydes with trifluoromethyl ketone derivatives has been developed. This process generates a new NHC-bounded aza-benzofulvene as a key intermediate. This new protocol allows the rapid assembly of enantioenriched polycycles from readily available starting materials under mild conditions. DFT calculations elucidated the origins of the [10+2] process. Further investigations on new NHC-bounded aza-arylfulvene as active intermediate in asymmetric synthesis are currently ongoing in our laboratory.

Methods

Synthesis of 3/4.

To a flame-dried Schlenk reaction tube equipped with a magnetic stir bar, was added the precatalyst F (15.4 mg, 0.03 mmol), DQ (90.0 mg, 0.22 mmol), additive H (5.0 mg, 0.01 mmol), PhCO₂Na (28.8 mg, 0.20 mmol), 1 (0.20 mmol) and 4Å MS (60 mg). The Schlenk tube was closed with a septum, evacuated and refilled with argon atmosphere. Hexane (2.0 mL) and 2 (0.24 mmol) was added. The mixture was then stirred at 25 °C and monitored by TLC until 1 was consumed. The mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (hexane/EtOAc = 100:1) to afford the desired product 3 or 4.

Declarations

Data availability

For ^1H , ^{13}C NMR and high-performance liquid chromatography spectra of compounds in this manuscript, see Supplementary Information. The supplementary crystallographic data for this paper could be obtained free of charge from The Cambridge Crystallographic Data Centre (3e: CCDC 1961662) via www.ccdc.cam.ac.uk/data_request/cif.

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Author contributions

Q. P. P. conducted main experiments. S. J. L. and Y. L. conducted the computational studies. B. Z. and D. H. G. prepared several starting materials, including substrates. J. W. conceptualized and directed the project, and drafted the manuscript with the assistance from co-authors. All authors contributed to discussions.

Competing interests

The authors declare no competing interests.

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Figures

Figure 1

NHC-catalyzed normal and higher order cycloaddition. a NHC-catalyzed normal order cycloaddition. b NHC-catalyzed high order cycloaddition. c NHC-catalyzed higher order cycloaddition (this work).

Figure 2

Scope of ketones. Reaction conditions: 1a (0.2 mmol), 2 (0.24 mmol), cat. F (15 mol %), additive H (5 mol %), PhCO_2Na (0.20 mmol) and DQ (0.22 mmol), hexane (2.0 mL), room temperature, 4Å MS (60 mg), Ar, 36-96 h.

Figure 3

Scope of indole-2-carbaldehydes **1**. Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol), cat. **F** (15 mol %), additive **H** (5 mol %), PhCO₂Na (0.20 mmol) and DQ (0.22 mmol), hexane (2.0 mL), room temperature, 4Å MS (60 mg), Ar, 36-96 h. bDCM-Hexane (1:5) was used.

Figure 4

Postulated mechanistic pathways.

(a) Structures of transition states, Gibbs free energy barriers and distortion energies

(b) NCI analysis

Figure 5

The DFT investigation on the enantioselectivity of the [10+2] annulation. a The two transition states of TS(II-III)R and TS(II-III)S Gibbs free energy barriers and distortion energies comparing. b NCI analysis of the TS(II-III)R and TS(II-III)S.

Figure 6

Gram scale synthesis and transformation. a Reaction conditions: 1e (4.0 mmol), 2a (4.8 mmol), F (0.60 mmol), DQ (4.4 mmol), additive H (0.20 mmol), PhCO₂Na (4.0 mmol), Hexane (33.4 mL) and DCM (6.6 mL), room temperature, 4Å M.S. (600 mg), Ar, 40 h. b Reaction conditions: 3d (0.05 mmol), 5 (0.10 mmol), K₂CO₃ (0.10 mmol) and Pd(PPh₃)₄ (0.005 mmol), toluene (0.5 mL), 80 °C, 18 h.

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