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N-Heterocyclic carbenes as chiral Brønsted base catalysts: a highly diastereo- and enantioselective 1,6-addition reaction†

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Highly diastereo- and enantioselective 1,6-addition of 1,3-ketoamides to *p*-quinone methides (*p*-QMs) using chiral NHCs as Brønsted base catalysts is developed. The reaction is based on the utilization of a 1,3-ketoamide having acidic N–H that forms a chiral ion-pair consisting of the enolate and the azolium ion. Different β-ketoamides and functionalized *p*-QMs are applicable to the reaction. Synthetic application of the method is demonstrated *via* the preparation of highly enantioenriched β and γ-lactam derivatives.

Introduction

N-Heterocyclic carbenes (NHCs) are the most versatile organocatalysts. Consequently, asymmetric catalysis with chiral NHCs involves covalent interaction with the activated substrate, Lewis acid–base interaction with the reagent (Scheme 1a and 1b)[1] and hydrogen bonding interaction with the substrate using a proton shuttle (Scheme 1c).[2] Although asymmetric NHC catalysis *via* ion-pair interaction with substrates by utilizing the intrinsic Brønsted base characteristic of NHCs[3] has drawn significant interest, it remains highly challenging (Scheme 1d).[4] Herein, we present a catalytic and highly stereoselective 1,6-addition reaction of *p*-QMs using NHCs as Brønsted base catalysts (Scheme 1e).

Scheme 1 Different modes of substrate activation for asymmetric NHC-catalysis.

p-QM scaffolds are found in many natural products[5] and serve as key reactive intermediates in several chemical, medicinal and biological processes.[6] Consequently, efforts have been devoted to developing organocatalytic asymmetric nucleophilic addition to *p*-QM.[7] However, attempts at developing enantioselective 1,6-addition of enolizable nucleophiles to *p*-QMs using chiral NHCs as Brønsted bases remains largely unsuccessful.[8] To employ NHCs as Brønsted base catalysts for asymmetric 1,6-addition of *p*-QMs, we anticipated that the substrate should have a lower pK_a value than the NHC. We thus envisioned that easily enolizable 1,3-ketoamides containing an acidic N–H group would be appropriate nucleophiles. It is expected that an *in situ* generated NHC having a pK_a value in the range of 17–19 [3a] may deprotonate the ketoamide (pK_a ≈ 10–12),[9] furnishing a chiral ion-pair[10] comprising the enolate and the azolium ion. The *in situ* generated chiral enolate is expected to react with *p*-QM, thus providing enantioselectivity to the final product.

Results and discussion

Our studies were commenced using *p*-QM **1a** and the β-ketoamide **2a** as model substrates under various reaction conditions with a series of chiral NHCs (see the ESI†). Following initial optimization, a variety of amides possessing different aromatic amines were assayed using 20 mol% of **3g**, 16 mol% of LiHMDS, 20 mol% of HFIP and 4 Å MS in toluene (Table 1). The β-ketoamide derived from aniline afforded product **4a** with poor stereoselectivity (entry 1). Enantioselectivity of the reaction could not be improved using β-ketoamide **4b** or **4c** having

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Table 1 Reaction development[a]

Entry	Amide	Temp. (°C)	h	dr	ee (%)	Conv. (%)
1	**2a**	0	12	64 : 36	44, 48	95
2	**2b**	0	12	73 : 27	27, ND	50
3	**2c**	0	12	65 : 35	30, 12	70
4	**2d**	0	12	80 : 20	68, 14	70
5	**2e**	0	12	70 : 30	70, 10	50
6	**2f**	0	12	67 : 33	66, 20	60
7	**2g**	0	12	83 : 17	70, 15	70
8	**2h**	0	12	95 : 5	73[b]	50
9[c]	**2h**	0	12	97 : 3	85[b]	75
10[c]	**2h**	−20	14	98 : 2	95[b]	70
11[c]	**2h**	−40	20	98 : 2	98[b]	97[d]
12[c,e]	**2h**	−40	24	98 : 2	98[b]	93[d]

[a] Reaction conditions: **1a** (0.05 mmol), **2a–h** (0.05 mmol), LiHMDS (16 mol%), HFIP (20 mol%), 4 Å MS (35 mg) in toluene (1.0 mL); dr determined by ^{1}H NMR and HPLC analysis; ee determined by HPLC analysis on a chiral stationary phase. [b] ee of the major diastereoisomer is given. [c] Reaction performed without using HFIP. [d] Isolated yield. [e] Reaction performed on a 0.1 mmol scale using 15 mol% of **3g**. ND = not determined.

a phenyl substituent at the *para* or *meta* position of the aniline ring (entries 2 and 3). However, introducing a phenyl group at the *ortho* position of the aniline moiety of β-ketoamide was found to be beneficial, delivering product **4d** in 68% ee with the amide **2d** (entry 4). Based on this result, different β-ketoamides **2e–h** containing bulky substituents at the *ortho* position of the aniline unit were prepared and examined. No considerable improvement in the stereoselectivity of the products, **4e–g**, was realized with the ketoamides **2e–g** (entries 5–7). The sterically demanding ketoamide **2h**, however, delivered product **4h** with a slight improvement in stereoselectivity (entry 8). Interestingly, the reaction efficacy was improved further with the amide **2h**, when the reaction was performed in the absence of HFIP (entry 9). This result may indicate that HFIP interferes in the formation of a tight ion-pair comprising the enolate and the azolium ion.[11] By carrying out the reaction at reduced temperature, product **4h** was obtained in excellent yield and stereoselectivity (entries 10 and 11). Importantly, the loading of precatalyst **3g** could also be reduced to 15 mol% without diminishing the overall reaction efficiency (entry 12).

The substrate scope of the reaction was then evaluated varying both *p*-QMs and amides (Table 2). A series of *p*-QMs with different substituents at the aromatic ring and quinone moiety were first investigated with the amide **2h**. Accordingly, the reaction furnished the desired products **5–7** in excellent yields and stereoselectivity with *p*-QMs having benzene, *p*-tolyl and *p*-biphenyl substituents. While a moderate yield of product **8** was obtained with *o*-tolyl substituted *p*-QM, the stereoselectivity remained excellent. *p*-QMs bearing F, Cl and Br substituents at any position of the aromatic ring were easily transformed into the corresponding products **9–11** in excellent yields and stereoselectivity. Substrates having electron rich substituents like OMe (**12**), NMe_2 (**13**), SMe (**14**), O-allyl (**15**) and OAc (**16**) or electron deficient functional groups such as CF_3 (**17**), cyano (**18**), ester (**19**), keto (**20**) and nitro (**21**), irrespective of their position, were applicable to the reaction. Naphthyl substituted *p*-QM was converted to product **22**. Heteroaromatic rings, for instance, pyridine (**23**), furan (**24**) and thiophene (**25**), were tolerated in this catalytic reaction. A slight decrease in ee values was realized by replacing the *tert*-butyl group of the quinone ring with methyl or isopropyl substituents (products **26** and **27**). Interestingly, the catalytic asymmetric process could be extended to the challenging alkylated *p*-QM, providing the expected product **28** in good yield, albeit with moderate stereoselectivity. Substrate scope studies were then carried out using different amides with **1a**. The amide **2i** (R^3 = Me and Ar^1 = quinolin-8-yl) afforded product **29** in good yield and stereoselectivity. Likewise, different α-aroylacetamides **2j–m** were found to be suitable for the reaction, furnishing the desired products **30–33** in good yields and enantioselectivity. Absolute configurations of 2*S*, 3*R* were determined for compound **11** using single-crystal X-ray analysis.[12]

To illustrate the synthetic utility of the reaction, a preparative scale experiment using 0.97 g of *p*-QM **1a** and 0.68 g of amide **2i** was performed, which resulted in 1.25 g of product **29** in good yield and stereoselectivity (dr = 98:2, ee = 97%, Scheme 2a). Furthermore, a variety of valuable enantioenriched compounds were prepared from product **29** through simple chemical transformations (Scheme 2b, see the ESI†). Accordingly, $NaBH_4$ reduction of ketone **29** afforded the alcohol **34a** having three contiguous stereogenic centres in good yield and excellent ee along with a minor diastereoisomer **34b** (see the ESI†). Compound **34b** was separated by column chromatography. The major diastereoisomer **34a**, whose structure was confirmed by single crystal X-ray analysis, was transformed into the spirocyclic γ-lactam **35** in one step *via* PIDA oxidation. The removal of the *tert*-butyl group from the alcohol **34a** with $AlCl_3$ afforded the phenol **36** in good yield without diminishing its original stereoselectivity. The mesyl protection of the alcohol **34a** provided compound **37** in good yield. The absolute configuration of compound **37** was unambiguously determined by single-crystal X-ray analysis.[12] Compound **37** was then converted to the enantioenriched β-lactam **38** in good yield with excellent stereocontrol. Furthermore, the synthesis of biologically relevant enantioenriched triarylmethane **39** was achieved with excellent yield and ee value upon the treatment of **29** with hydrazine hydrate.

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Table 2 Substrate scope[a]

[a] Reaction conditions: **1a–y** (0.1 mmol), amides (0.1 mmol), **3g** (15 mol%), LiHMDS (12 mol%), 4 Å MS (70 mg) in toluene (2.0 mL); isolated yields. [b] Reaction performed at −78 °C. [c] Reaction performed with amide **2i**. Diastereoisomeric ratio (dr) determined by ^{1}H NMR and HPLC analysis. Enantiomeric excess (ee) determined by HPLC analysis on a chiral stationary phase.

For a better understanding of the reaction mechanism, several other experiments were carried out (see the ESI†). It was observed that the reaction afforded the desired product with a similar reactivity and ee value using NaHMDS/KHMDS *in lieu* of LiHMDS as the base. These results indicate that the metal ion of the base may not have any considerable effect on the reaction outcome. Using a preformed NHC as the catalyst, the reaction afforded the desired product with an identical stereoselectivity albeit with a very low reactivity. The importance of the acidic N–H group of β-ketoamide was established by carrying out the reaction using *N*-methylated amide, which resulted in complete inhibition of the catalytic process (see the ESI†). Additionally, the *in situ* formation of the NHC under our reaction conditions was confirmed by performing the well-established oxidative annulation reaction between cinnamaldehyde and acetylacetone using precatalyst **3g** (see the ESI†). This was further established by ^{1}H NMR spectroscopy studies. It was found that the ^{1}H NMR resonance at 10.76 ppm corresponding to the iminium C2–H of **3g** disappeared when **3g** was treated with LiHMDS. However, the ^{1}H NMR signal reappeared upon adding an equimolar amount of the β-ketoamide **2h** into the solution (see the ESI†). These observations may indicate that the initially

Scheme 2 Synthetic applications.

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Scheme 3 Proposed activation pathway.

Fig. 1 Probable transition state of the reaction.

formed NHC deprotonates the acidic N–H of **2h**, thus forming a chiral ion-pair involving the azolium ion and enolate.

For mechanistic consideration, two possible reaction pathways are proposed for the reaction (Scheme 3). The reaction may involve hydrogen bonding interaction between the NHC and the β-ketoamide (Scheme 3, **A**). Alternatively, it may proceed through a chiral ion-pair intermediate consisting of the enolate and the azolium ion (Scheme 3, **B**). By reconciling the reported pK_a values of the similar NHC and β-ketoamide with the results obtained in our preliminary mechanistic studies, we tend towards the ion-pair interaction between the NHC and the substrate. Finally, the activated nucleophile undergoes addition reaction with the *p*-QM to deliver the desired product with excellent stereocontrol. Further studies are surely required to establish the actual mode of NHC-catalysis for this reaction.

Based on the crystal structure analysis of product **11**, the observed high stereoselectivity of the addition product is explained through the proposed transition state (TS) in which the Re-face of *p*-QM **1h** approaches the chiral enolate due to hydrogen bonding activation and π–π interaction as shown in Fig. 1.

Conclusions

In conclusion, we have introduced a new mode of asymmetric NHC-catalysis through ion-pair interaction between a catalyst and a nucleophile. The novel catalytic method enables highly diastereo- and enantioselective 1,6-conjugate addition of 1,3-ketoamides to *p*-QMs using NHCs as Brønsted bases. The reaction furnishes the desired products with excellent stereoselectivity (ee and dr) and yields. Synthetic application of the method is demonstrated by the preparation of several valuable materials with excellent stereoselectivity.

Conflicts of interest

There are no conflicts of interest to declare.

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12 CCDC 1831345, 1831346 and 1831347 contain the supplementary crystallographic data for **11**, **34a** and **37**, respectively (see also the ESI†).

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