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Chiral quinuclidine-based amine catalysts for the asymmetric one-pot, three-component aza-Baylis–Hillman reaction

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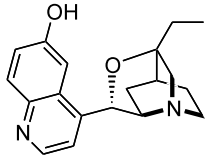
Abstract—Chiral quinuclidine derivatives were employed as catalysts in the one-pot, three-component aza-Baylis–Hillman reaction between arylaldehydes, tosylamide and alkyl acrylates or acrylonitrile. A sterically non-hindered tricyclic derivative of quinidine was found to be the most efficient catalyst in transferring its chiral information. High conversions were ensured by using a catalytic amount of titanium isopropoxide and by the addition of molecular sieves (4 Å). The adducts formed, α-methylene-β-amino acid derivatives, were obtained in good yields (up to 95%) and in enantioselectivities up to 74%.

The Baylis–Hillman reaction is a powerful route for the formation of compounds containing high functional density.[1] In the classical setup of this reaction, as reported by Baylis and Hillman in 1972, acetaldehyde and ethyl acrylate or acrylonitrile were reacted in the presence of a catalytic amount of a strong Lewis base, typically diazabicyclo[2.2.2]octane (DABCO).[2] Although, the product generated contains a new center of chirality, it was not until recently that an efficient and highly enantioselective version of the reaction was reported.[3,4] In this protocol, Hatakeyama and co-workers employed a modified cinchona alkaloid **1** as the base-catalyst for the reaction of various aldehydes with the highly reactive Michael acceptor, 1,1,1,3,3,3-hexafluoroisopropyl acrylate. Performing the reaction in DMF at low temperature (−55°C) allowed for the formation of the adducts with enantioselectivities in the range of 91–99%. The chiral catalyst used in these transformations was obtained in a one-step procedure from quinidine.[3,5]



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When Shi and Jiang employed the same catalyst for the asymmetric Baylis–Hillman reaction of aldehydes with methyl vinyl ketone or α-naphthyl acrylate at room temperature, only moderate ee values were obtained.[6]

We have recently developed a highly efficient one-pot procedure for the aza-Baylis–Hillman reaction.[7] In this three-component reaction we successfully and selectively formed α-methylene-β-amino acid derivatives starting from arylaldehydes, sulfonamides and various Michael acceptors. The key intermediate step for obtaining good chemoselectivity in this tandem transformation is a rapid in situ formation of a *N*-sulfonylimine, and we found that the latter was effectively catalyzed by a Lewis acid. Thus, the combination of Lewis basic nucleophilic catalysts like 3-hydroxy-quinuclidine (3-HQD) or DABCO together with a Lewis acid resulted in a reliable protocol for the formation of aza-Baylis–Hillman adducts. We have now studied the one-pot, three-component reaction in the presence of chiral nucleophilic amine catalysts and herein we present our results on the asymmetric aza-Baylis–Hillman reaction.

The Baylis–Hillman reaction between methyl acrylate and preformed imines was originally reported by Perlmutter and Teo in 1984.[8] After their initial study, a number of reports on the aza-Baylis–Hillman reaction were disclosed,[9] but attempts to control the enantioselectivity of the system were not made until Kündig and co-workers reported the use of imine–chromium tricarbonyl complexes possessing planar chirality as electrophiles for the in situ formed zwitterionic enolate.[10]

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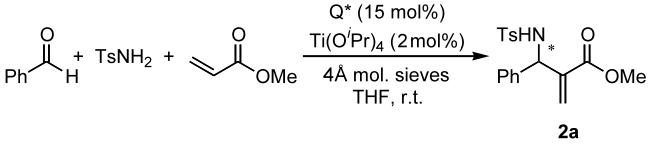
Aggarwal and co-workers employed chiral, enantiomerically pure, *N*-sulfinylimines in the aza-Baylis–Hillman reaction and the adducts were obtained with moderate to good diastereomeric ratios.[11] Recently, the use of chiral base catalysts for the aza-version of the reaction was reported by Shi and Xu.[12] They employed the quinidine derivative **1** as the nucleophilic catalyst for the reaction between preformed *N*-tosyl arylimines and methyl vinyl ketone or methyl acrylate. This particular catalyst turned out to be highly efficient in transferring its chiral information, and the adducts were obtained in up to 99% ee (methyl vinyl ketone) and 83% ee (methyl acrylate), respectively. Simultaneously with the work of Shi and Xu we examined the activity of various chiral quinuclidine-based catalysts for the one-pot, three-component reaction (Scheme 1).

One of the major drawbacks regarding the Baylis–Hillman reaction is the normally slow rate with which the reaction progresses. Several attempts have been made in order to speed up the reaction, where the most favorable ones include the use of powerful nucleophilic catalysts (sterically unhindered tertiary amines and phosphines) which are able to add reversibly to the Michael acceptor. Thus, the presence of a quinuclidine core in the Lewis base is very beneficial for the rate of the Baylis–Hillman reaction, since such tertiary amines are substantially more nucleophilic than the corresponding open structures. This effect is due to the decreased steric hindrance ensured by the locked structure around the nitrogen atom. With this in mind, we concentrated our attention towards chiral tertiary amines bearing a quinuclidine core. The model reaction



Scheme 1.

Table 1. The influence of chiral quinuclidine containing catalysts on the one-pot, three-component aza-Baylis–Hillman reaction as depicted in Scheme 1[a]

Entry	Amine (Q*)	Time (h)	Yield (%)[b]	Ee (%)[c,d]
1	**3**	24	50	5 (*S*)
2	**4**	24	80	5 (*R*)
3	**5**	144	35	40 (*R*)
4	**6**	144	60	43 (*S*)
5	**7**	96	–	–
6	**1**	48	78	68 (*R*)

[a] Reaction conditions: benzaldehyde, *p*-toluenesulfonamide and methyl acrylate (1:1:1.1), base (Q*, 15 mol%), Ti(O^{i}Pr)$_4$ (2 mol%) and molecular sieves (4 Å, 200 mg/mmol substrate) in THF (substrate concentration: 2 M) at ambient temperature.

[b] Yields determined by ^{1}H NMR using benzyl alcohol as internal standard.

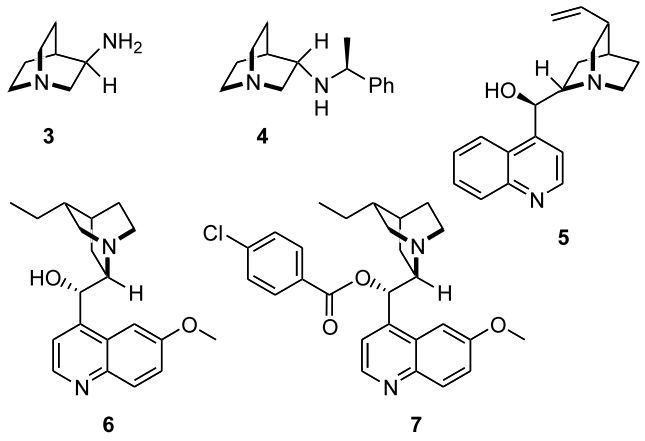
[c] Enantiomeric excess determined by ^{1}H NMR using Eu(hfc)$_3$ as chiral shift reagent.

[d] Absolute configuration determined by optical rotation.

chosen for this study was the three-component system outlined in Scheme 1, and consisted of benzaldehyde, tosylamide (1 equiv. of each component) and methyl acrylate (1.1 equiv.) and catalytic amounts of a chiral nucleophilic catalyst (Q*, 15 mol%) and titanium isopropoxide (2 mol%). The reactions were performed at ambient temperature in tetrahydrofuran in the presence of molecular sieves (4 Å), the latter had proven to be highly beneficial for in situ imine formation.[7] In our first attempts, we focused on small, chiral tertiary amines bearing a bridged nitrogen atom. (*S*)-(+)-3-Aminoquinuclidine **3**—isoelectronic with 3-HQD used in the optimized conditions of our previously developed protocol—gave a reasonably good yield after 24 h reaction time, but unfortunately very poor asymmetric induction (5% ee, entry 1, Table 1). The *N*-substituted (*R*)-isomer of 3-aminoquinuclidine **4**, containing an additional stereocenter in the secondary amine substituent, did not facilitate any improvement on the asymmetric induction. The opposite stereoisomer of the product **2a** was formed in equally poor enantiomeric excess (5%, entry 2, Table 1).

The cinchona alkaloids belong to a class of naturally occurring chiral amines where a quinuclidine core is structurally incorporated. While screening a few of the alkaloids and derivatives thereof as catalysts in the three-component protocol, we observed that the reaction rate was substantially decreased in all cases, leading to prolonged reaction times in order to achieve even moderate yields (entries 3 and 4, Table 1). Furthermore, the ester derivative **7** was completely ineffective as a catalyst for the reaction (entry 5, Table 1). The poor reactivity displayed by catalysts **5**–**7** can be attributed to (1) low basicity of the amines,[13] and (2) increased steric hindrance in close proximity to the nucleophilic quinuclidine. Additionally, the absence of a proton donor in catalyst **7** could effectively further reduce its catalytic activity. The stereochemical inductions obtained using the alkaloid ligands were considerably better than when the simple quinuclidines (**3** and **4**) were employed. Depending on the absolute configuration of the catalyst (cinchonidine **5** or hydroquinidine **6**), either of the two product isomers could be obtained in moderate enantioselectivity (entries 3 and 4, Table 1). The previously reported quinidine derivative **1**, turned out to be the most active catalyst for the three-component system. Performing the model reaction with 15 mol% of **1** as the nucleophilic catalyst resulted in the formation of the adduct **2a** in good yield and with significantly better enantioselectivity as compared to the parent alkaloids (entry 6, Table 1).[14] In addition to the amines depicted in Scheme 2 and Table 1, we also investigated the catalytic activity of some other naturally occurring chiral amines, like L-proline or (–)-sparteine. Employing these compounds as catalysts in the three-component reaction did not result in any formation of the adduct, indicating poor nucleophilicity of these amines under the present reaction conditions.

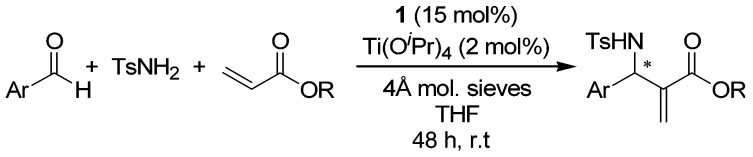
After establishing that the quinidine derivative **1** was the best catalyst for the asymmetric protocol in the one-pot, three-component aza-Baylis–Hillman reaction,

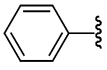
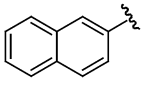
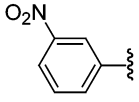
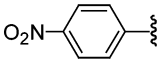
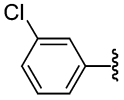
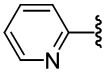
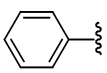


Scheme 2.

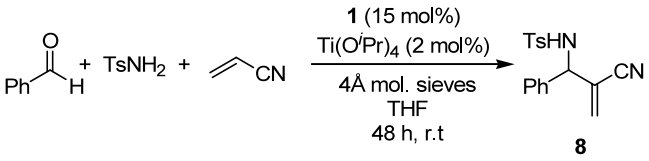
we decided to investigate the scope of the system. Performing the reaction with variously substituted arylaldehydes resulted, with one exception, in the formation of the adducts in good to excellent yields and with stereoselectivity ranging from 49 to 74% ee (Table 2).[15] Using methyl acrylate as the Michael acceptor, combined with unfunctionalized arylaldehydes resulted in good yields of the aza-products (entries 1 and 2, Table 2). The enantioselectivity obtained with 2-naphthylaldehyde was surprisingly somewhat lower than for benzaldehyde. As observed previously, electron-poor aldehydes are good substrates in the three-component reaction.[7] Excellent yields of the products **2c–e** were obtained using 3-nitro-, 4-nitro- and 3-chloro-benzaldehyde respectively (entries 3–5, Table 2). The enantioselectivity proved to be at the same level as for the model reaction. The heterocyclic compounds 2-pyridyl- and 2-furanylaldehyde reacted readily under the optimized conditions, with the latter compound giving the highest enantioselectivity in the series (entries 6 and 7, Table 2). Increasing the steric hindrance in the Michael acceptor normally results in reduced activity in the Baylis–Hillman reaction. This was clearly demonstrated using *t*-butyl acrylate in combination with benzaldehyde and tosylamide, which resulted in a poor yield and moderate enantioselectivity of adduct **2h** (entry 8, Table 2). It

Table 2. The scope of the one-pot, three-component aza-Baylis–Hillman reaction catalyzed by the quinidine derivative **1**[a]



Entry	Ar	R	Product	Yield[b] (%)	Ee[c] (%)
1		-CH_3	**2a**	78 (75)[d]	68
2		″	**2b**	79	49
3		″	**2c**	94	63
4		″	**2d**	95	61
5		″	**2e**	95	67
6		″	**2f**	95	50
7		″	**2g**	95	74
8		-Bu^t	**2h**	12	52

[a] Reaction conditions: aldehyde, *p*-toluenesulfonamide and alkyl acrylate (1:1:1.1), **1** (15 mol%), $Ti(O^iPr)_4$ (2 mol%) and molecular sieves (4 Å, 200 mg/mmol substrate) in THF (substrate concentration: 2 M) at ambient temperature. b) Yields determined by ^1H NMR using benzyl alcohol as internal standard. c) Enantiomeric excess determined by ^1H NMR using $Eu(hfc)_3$ as chiral shift reagent. d) Isolated yield.



Scheme 3.

should be noted that the three-component aza-Baylis–Hillman reactions presented in Table 2 were highly chemoselective. Hence, with the exception of entries 3 and 4 where trace amounts of the alcohol-adducts could be detected, the only products formed in the protocol were the amino-adducts. In addition to acrylates, we performed the aza-Baylis–Hillman reaction using acrylonitrile as Michael acceptor (Scheme 3). This reaction resulted in moderate yield (45%) and enantioselectivity (53% ee) of product **8**.

In conclusion, we have demonstrated the use of chiral quinuclidine-derivatives as catalysts in the one-pot, three-component aza-Baylis–Hillman reaction. Poor reactivity and selectivity was obtained using simple quinuclidines and the alkaloids, cinchonidine and hydroquinidine, whereas the quinidine derivative **1** proved to act as an efficient catalyst for the transformation. High chemical yields were obtained using variously substituted arylaldehydes and the products were obtained in stereoselectivity ranging from 49 to 74% ee.

Acknowledgements

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14. Performing the reaction at 0°C did not improve the enantioselectivity.
15. General experimental procedure exemplified for the formation of **2a**. In a dried flask, *p*-toluenesulfonamide (171 mg, 1 mmol) and the quinidine derivative **1** (50 mg, 0.15 mmol) were measured together with molecular sieves (4 Å, 200 mg). THF (0.5 mL), benzaldehyde (101 μL, 1 mmol), methyl acrylate (99 μL, 1.1 mmol) and $Ti(O^iPr)_4$ (6 μL, 0.02 mmol) were added and the reaction mixture was stirred for 48 h at ambient temperature. The mixture was filtered through a thin layer of Celite, which was rinsed three times with THF (5 mL). The solvent was evaporated and to the crude were added methanol (15 mL) and aqueous sulfuric acid (10 mL, 1 M). The solution was stirred for 1 h, then methanol was evaporated. The remaining acidic solution was diluted with water and extracted with dichloromethane (3×15 mL). The organic phase was then successively washed with $NaHCO_3$ (sat.), NaOH (1 M), water and brine, and dried over Na_2SO_4. Evaporation of the solvent gave 260 mg (75%) of the pure product as a white crystals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.61 (s, 3H), 5.31 (d, J=8.9 Hz, 1H), 5.61 (d, J=8.9 Hz, 1H), 5.83 (s, 1H), 6.22 (d, J=0.7 Hz, 1H), 7.13–7.25 (m, 7H), 7.68 (d, J=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.72, 52.20, 59.31, 126.64, 127.45, 127.98, 128.10, 128.80, 129.70, 137.84, 138.74, 138.81, 143.61, 165.98; MS (MALDI-TOF) (m/z) 384.071 (MK+) 368.094 (MNa+) 346.103 (MH+). $[\alpha]_D$=+16.8 (c 1.01, $CHCl_3$).