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Organocatalytic asymmetric aza-Michael addition of aniline to chalcones under solvent-free conditions

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ABSTRACT

The first enantioselective Michael addition of aniline to chalcones was promoted by cheap and commercially available chincona alkaloids under solvent-free conditions. Variously substituted chalcones were examined as substrates giving the conjugate adducts in moderate to good enantioselectivity. The simple experimental procedure had no work-up and short reaction times, which are the notable advantages.

1. Introduction

Over the past decade, the use of chiral organic molecules as catalysts[1] has represented an important area of research, and is recognized as an efficient and reliable strategy for the asymmetric synthesis of valuable chiral compounds.[2] This type of catalysis has several benefits when compared to the use of transition metal complexes. The metal-free organic catalysts are usually more stable, commercially available, non-toxic, less expensive and allow us to perform the reactions in mild conditions.

Due to the operational and economical advantages associated with organocatalysis, many enantioselective organocatalytic reactions for C–C bond formation have been developed, while only a few examples have been reported for aza-Michael addition.[3]

The aza-Michael reaction, involving the conjugate addition of nitrogen nucleophiles to α,β-unsaturated carbonyl compounds, allows us to generate a C–N bond, so that it constitutes an important step in the synthesis of bioactive natural compounds.[4] Most of the aza-Michael organocatalytic reactions are amine catalyzed and proceed via an enamine or iminium intermediate[5] can avoid the possible competition between the nucleophile and the catalyst that can compromise the enantiomeric excess. Consequently, the appropriate choice of the nucleophile represents a critical factor for obtaining a good level of enantioselectivity.

A different approach involves the use of organic molecules driving the enantioselective addition of the nucleophile onto the acceptor by hydrogen bonding, but it should be noted that only a few examples have been reported.[6] Particularly, poorly nucleophilic amine derivatives, such as hydrazones,[6a] benzylhydroxylamines[6c] and indoles,[6d] have been used, while no examples of a direct conjugate amination involving the use of an amine as a nucleophile has been reported.

Furthermore, all of these reactions are performed in organic solvent and the necessity to use dilute conditions to improve the ee is sometimes required.[6a] With all of these precedents in mind, we decided to explore the ability of aniline to react as a nucleophile with chalcones for the asymmetric aza-Michael reaction by hydrogen bond activation. Herein, we report the first enantioselective organocatalytic solvent-free aza-Michael addition of aniline to chalcones using cinchona alkaloids as catalysts.

2. Results and discussion

Preliminarily, a control experiment performed on chalcone **1a** (Fig. 1), chosen as representative substrate, pointed out the very poor contribution given by the background non-asymmetric reaction: in fact, the corresponding adduct **3a** was obtained in only 3% yield after 24 h (Fig. 2).

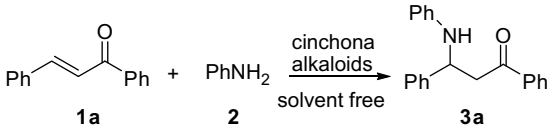

Figure 1.

As shown in Table 1, activation of the carbonyl functionality by hydrogen bonding was found to promote the formation of adduct **3a** in rather high yields with all the organocatalysts tested (0.1 equiv) (Fig. 2), used under solvent-free conditions. However, only cinchonine **c** afforded a promising level of enantioselectivity.

Notably, less satisfactory results were obtained by carrying out the reaction at −20 °C (entries 7 and 8) while a significant improvement both in terms of efficiency and enantioselectivity

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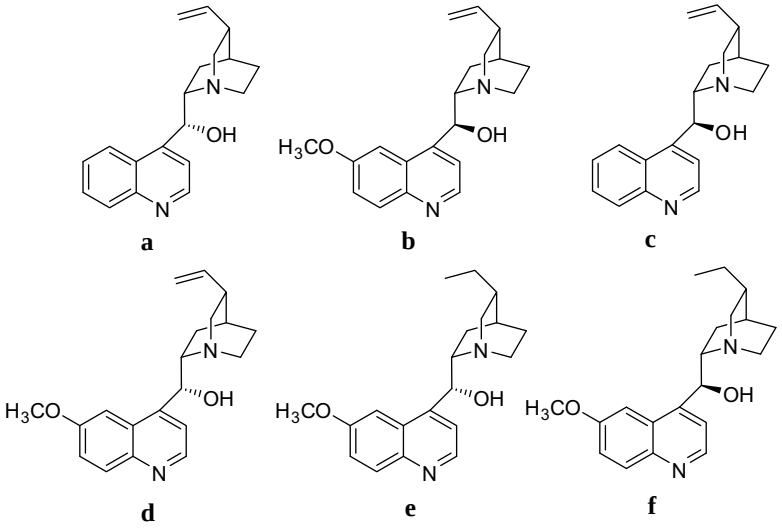

Figure 2.

Table 1
Asymmetric aza-Michael addition of aniline to **1a** promoted by cinchona alkaloids

Entry	Organocatalyst[a]	Time (h)	Yield **3a**[b] (%)	ee **3a**[c] (%)
1	Cinchonidine **a**	20	>99	−16
2	Quinidine **b**	20	>99	3
3	Cinchonine **c**	20	75	49
4	Quinine **d**	20	88	9
5	Hydroquinine **e**	20	80	0
6	Hydroquinidine **f**	20	88	1
7	Cinchonine[d] **c**	18	48	43
8	Cinchonidine[d] **a**	20	35	−8
9	Cinchonine **c**	24	>99	58

[a] The reactions were performed using 0.25 mmol of chalcone, 0.5 mmol of aniline in presence of 10 mol % catalyst without solvent at room temperature.
[b] The yields refer to the chromatographically pure compounds.
[c] The enantiomeric excess was determined by HPLC analysis using CHIRALPAK AD-H column.
[d] The reaction was performed at −20 °C.

was observed by increasing the organocatalyst **c** loading to 0.2 equiv (Table 1, entry 9). In fact, cinchonine **c** was the most effective catalyst resulting in quantitative conversion and leading to 58% of enantiomeric excess in reduced reaction times when compared to the usual 2–5 days requested for other aza-Michael organocatalyzed reactions.[6a–c]

One of the problems in the organocatalytic aza-Michael reaction is the possible competition between the nucleophile and the catalyst; in fact the amine reagent could lead to the generation of an achiral intermediate and therefore to the formation of a racemic product. To verify this possibility, we decided to carry out the reaction in the presence of a reduced amount of aniline (1.2 equiv) which caused a decrease in yield and ee (88% yield; 49% ee). This result further confirms that no formation of an iminum ion occurs, due to the low nucleophilicity of aniline, as already observed in the control experiment performed in the absence of organocatalyst.

The catalytic properties of cinchonine can be reasonably explained through the proposed transition state model of Jorgensen, in which the hydroxyl group of catalyst establishes a hydrogen bond with the carbonyl and the quinuclide group is linked to the aniline.[6a]

Having found an optimal protocol for the reaction, we proceeded to examine the scope and limitation of the method using variously substituted chalcones as substrates (Fig. 3).

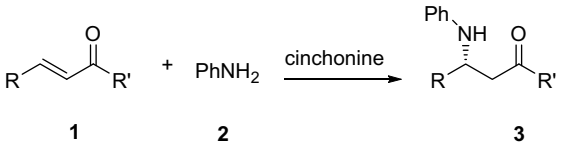

Figure 3.

Table 2
Solvent-free aza-Michael addition of $PhNH_2$ to chalcones catalyzed by 20 mol % cinchonine

Entry	R	R′	*t*/*T* (h/rt)	Prod.	Yield[a] (%)	ee[b] (%)
1	Ph	Ph	24	**3a**	>99	58
2	4-$MeOC_6H_4$	Ph	48	**3b**	44	49
3	4-MeC_6H_4	Ph	24	**3c**	76	42
4	2-Thienyl	Ph	24	**3d**	50	35
5	2-Furyl	Ph	24	**3e**	68	35
6	3-$OMeC_6H_4$	Ph	24	**3f**	81	40
7	4-ClC_6H_4	Ph	24	**3g**	72	27
8	Ph	4-$MeOC_6H_4$	48	**3h**	45	49
9	Ph	4-MeC_6H_4	24	**3i**	50	52
10	Ph	4-ClC_6H_4	24	**3m**	>99	31
11	4-$NO_2C_6H_4$	Ph	24	**3n**	48	11[c]

[a] The yields refer to chromatographically pure compounds.
[b] The enantiomeric excess was determined by HPLC analysis using CHIRALPAK AD-H column.
[c] The reaction was performed using 10 mol % cinchonine at room temperature.

The corresponding products were obtained in 24 h (except for entries 2 and 8) at room temperature in good yield and with enantioselectivities varying from 27% to 58%. As shown in Table 2, the presence of a substituent on the benzoyl ring resulted in a slightly higher enantiomeric excess when compared to the effect displayed on the other aromatic moiety (entries 8, 9, 10 vs entries 2, 3, 7).

Moreover, the introduction of electron-withdrawing substituent as a nitro group, led to a significant decrease in yield and enantioselectivity (Table 2, entry 11).

3. Conclusion

In conclusion, we have developed the first example of a solvent-free asymmetric aza-Michael addition of aniline to chalcones catalyzed by a commercially available and inexpensive cinchona

alkaloid. In all cases, the reactions can be performed without a solvent, thanks to the very good solubility in aniline of the differently substituted chalcones used. The simple experimental procedure, the solvent-free conditions and, thus the absence of work-up, short reaction times, good conversions and enantioselectivities are the notable advantages of the protocol.

4. Experimental

4.1. General

All chemicals were purchased from Sigma–Aldrich and were used without any further purification. TLC was performed on Silica Gel 60 F_{254} 0.25 mm on glass plates (Merck) and non-flash chromatography was performed on silica gel (0.063–0.200 mm) (Merck). All ^{1}H NMR and ^{13}C NMR spectra were recorded with a DRX 400 MHz Bruker instrument, by using $CDCl_3$ (δ = 7.26 ppm in ^{1}H NMR spectra and δ = 77.0 ppm in ^{13}C NMR spectra) as solvent (400.135 MHz for ^{1}H and 100.03 MHz for ^{13}C). Data for ^{1}H NMR are reported as follows: chemical shift (δ in ppm, multiplicity (s singlet, d doublet, t triplet, dd doublet of doublets, m multiplet) and coupling constant (J in hertz). Optical rotations were measured on a JASCO DIP-1000 polarimeter operating at the sodium D line at room temperature. Concentration is given in g/100 ml. IR spectra were recorded on a Bruker spectrometer. The HPLC analyses were performed with Waters Associates equipment (Waters 2487 Dual λ absorbance Detector) using CHIRALPK AD-H column with Hexane/Isopropyl alcohol mixtures and flow rate as indicated. HPLC methods were calibrated with the corresponding racemic mixtures.

Mass spectrometry analysis was carried out using an electrospray spectrometer Waters 4 micro quadruple.

The elemental analyses were calculated with FLASH EA 1112 Thermo equipment.

The known compounds (Table 2, entries 1, 2, 4, 5, 7 and 11) have been identified by comparison of spectral data with those reported.[7] The absolute configurations of the optically active compounds **3g** and **3n** were determined on the basis of the measured specific rotations compared with literature values.[8] All the other absolute configurations were assigned by analogy.

4.2. Typical experimental procedure

To a mixture of chalcone (0.25 mmol) and cinchonine (0.05 mmol), 2 equiv (0.5 mmol) of aniline was added and the resulting solution was stirred at room temperature for 24 h. TLC indicated the completion of the reaction. The crude mixture was directly purified by column chromatography (silica gel, petroleum ether/ethyl acetate mixtures) to obtain pure products.

4.2.1. 1-Phenyl-3-(phenylamino)-3-*p*-tolylpropan-1-one 3c

White solid m/z 316.5 [M+H$^+$], 338 [M+Na$^+$]; IR (KBr, neat) 3446, 1683, 1661, 1580; $[\alpha]_D$ = +3.9 (c 0.5, $CHCl_3$) 42% ee; HPLC analysis Chiralpak AD-H hexane/*i*PrOH 98:2 flow rate 0.7 ml t_R (major) = 55.29, t_R (minor 57.65 min; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92 (2H, d, J = 7.4 Hz); 7.56 (1H, t, J = 7.4 Hz); 7.45 (2H, t, J = 7.6 Hz); 7.3 (2H, d, J = 7.9 Hz); 7.15–708 (4H, m); 6.66 (1H, t, J = 7.4 Hz); 6.57 (2H, d, J = 7.9 Hz); 4.99 (1H, ft, J = 7.1); 4.52 (1H, br s), 3.52 (1H, dd, J = 16.1; 5.2 Hz); 3.41 (1H, dd; J = 16.1; 7.6 Hz); 2.32 (3H, s) ^{13}C NMR ($CDCl_3$, 400 MHz): δ 198.3; 147.5; 140.4; 137.4; 133.8; 129.9; 129.5; 129.1; 128.6; 126.7; 117.1; 114.2; 54.9; 46.8; 21.5. Anal. Calcd for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44. Found: C, 83.60; H, 4.32; N, 4.30.

4.2.2. 3-(3-Methoxyphenyl)-1-phenyl-3(phenylamino)propan-1-one 3g

White solid m/z 332 [M+H$^+$], 354 [M+Na$^+$]; IR (KBr, neat) 3365, 1675, 1576, 1487 cm^{-1}; $[\alpha]_D$ = −12.5 (c 0.5, $CHCl_3$) 40% ee; HPLC analysis Chiralpak AD-H hexane/*i*PrOH 90:10 flow rate 0.6 ml t_R (major) = 31.95, t_R (minor) = 36.87 min; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92 (2H, d, J = 7.8 Hz); 7.57 (1H, t, J = 7.2 Hz); 7.45 (2H, t, J = 7.8 Hz); 7.25 (1H, t, J = 7.7 Hz); 7.12–7.01 (4H, m); 6.79–6.77 (1H, m); 6.67 (1H, t, J = 7.3 Hz); 6.58 (2H, d, J = 7.8 Hz); 4.98 (1H, dd, J = 8.3; 5.1 Hz); 4.55 (1H, br s); 3.77 (3H, s); 3.51 (1H, dd, J = 16.1; 5.1 Hz); 3.43 (1H, dd, J = 16.1; 8.3 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 198.7; 160.5; 147.6; 145.4; 134.6; 133.4; 129.1; 128.1; 119.7; 118.22; 114.4; 133.3; 112.2; 55.7; 54.8; 46.8; Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.60; H, 6.50; N, 4.10.

4.2.3. 1-(4-Xhlorophenyl)-3-phenyl-3-(phenylamino)propan-1-one 3m

Yellow solid m/z 336 [M+H$^+$], 338 [M+Na$^+$]; IR (KBr, neat) 3448, 1679, 1504, 1285; $[\alpha]_D$ = −5.8 (c 0.55, $CHCl_3$) 31% ee; HPLC analysis Chiralpak AD-H hexane/*i*PrOH 80:20 flow rate 0.6 ml t_R (major) = 18.6, t_R (minor) = 23.6 min; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83 (2H, d, J = 8.5 Hz); 7.45–7.40 (4H, m) 7.33 (2H, t, J = 7.3 Hz); 7.27–7.23 (1H, m); 7.11 (2H, t, J = 8.2 Hz); 6.69 (1H, t, J = 8.2 Hz); 6.58 (2H, d, J = 8.2 Hz); 5.02 (1H, ft, J = 5.9 Hz); 4.54 (1H, br s); 3.47 (1H, dd, J = 16.1; 5.5 Hz); 3.41 (1H, dd, J = 16.1; 7.2 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 197.6; 147.4; 145.9; 143.3; 140.4; 130.1; 129.7; 129.4; 127.9; 126.9; 121.9; 118.4; 114.3; 55.18; 46.7; Anal. Calcd for $C_{21}H_{18}ClNO$: C, 75.11; H, 5.40; N, 4.17; O, 4.76. Found: C, 75.05; H, 5.50; N, 4.12.

4.2.4. 1-(4-Methoxyphenyl)-3-phenyl-3-(phenylamino)propan-1-one 3i

White solid m/z 332 [M+H$^+$], 354 [M+Na$^+$]; 370 [M+K$^+$]; IR (KBr, neat) 3430, 1680, 1547, 1261, 1171; $[\alpha]_D$ = −5.2 (c 0.5, $CHCl_3$) 49% ee; HPLC analysis Chiralpak AD-H hexane/*i*PrOH 90:10 flow rate 0.6 ml t_R (major) = 43.9, t_R (minor) = 51.5 min; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89 (2H, d, J = 8.8 Hz); 7.44 (2H, d, J = 7.5 Hz); 7.32 (2H, t, J = 7.5 Hz); 7.24 (1H, t, J = 7.2 Hz); 7.08 (2H, d, J = 8.8 Hz); 6.65 (1H, t, J = 7.3 Hz); 6.55 (2H, d, J = 7.7 Hz); 4.97 (1H, dd, J = 7.7; 5.0 Hz); 4.61 (1H, br s); 3.86 (3H, s); 6.45 (1H, dd, J = 15.7; 5.0 Hz); 3.34 (1H, dd, J = 15.7; 7.7 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 197.2; 164.1; 147.5; 143.6; 131.1; 129.5; 129.2; 127.7; 126.8; 118.1; 114.3; 114.2; 55.9; 55.4; 46.4; Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.57; H, 6.45; N, 4.15.

4.2.5. 3-Phenyl-3-(phenylamino)-1-*p*-tolylpropan-1-one 3l

White solid m/z 316 [M+H$^+$] 338 [M+Na$^+$]; IR (KBr, neat) 3387, 1667, 1602, 1504; $[\alpha]_D$ = −16.0 (c 0.5, $CHCl_3$) 52% ee; HPLC analysis Chiralpak AD-H hexane/*i*PrOH 98:2 flow rate 0.8 ml t_R (major) = 35.6, t_R (minor) = 39.7 min; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83 (2H, d, J = 8.2 Hz); 7.46 (2H, d, J = 7.2 Hz); 7.34 (2H, t, J = 7.2 Hz); 7.26–7.24 (3H, m); 7.11 (2H, t, J = 7.4 Hz); 6.69 (1H, t; J = 7.4 Hz); 6.57 (2H, d, J = 8.2 Hz); 5.01 (1H, dd, J = 7.6; 5.1 Hz); 4.60 (1H, br s); 3.50 (1H, dd, J = 16.0; 5.1 Hz); 3.39 (1H, dd, J = 16.0; 7.6 Hz); 2.41 (3H, s); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 198.4, 147.5; 144.8; 143.6; 135.2; 129.8; 129.5; 129.3; 128.8; 127.7; 126.8; 118.2; 114.2; 55.3; 46.7; 22.1; Anal. Calcd for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N,4.44. Found: C, 83.60; H, 6.60, N, 4.35.

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