An enantioselective Brønsted acid catalyzed enamine Mannich reaction†

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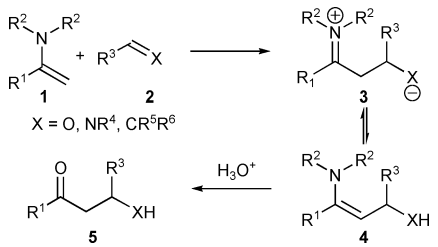
An enantioselective Brønsted acid catalyzed Mannich reaction between acetophenone derived enamines and *N*-Boc imines has been developed. Simple diol (*S*)-H_8-BINOL 11a has been identified as the optimal catalyst, to afford versatile β-amino aryl ketones in good yield and enantiomeric excess.

Interest in the use of enantiomerically pure, organic Brønsted acids as catalysts in asymmetric synthesis has soared in recent years.[1] We believed that this method of substrate activation could be employed to catalyze the enantioselective addition of pre-formed, achiral enamines to a range of electrophiles (Scheme 1). The formation of a charged intermediate **3** from neutral starting materials should give rise to preferential stabilization of the transition state over the ground state by a Brønsted acid, leading to acceleration of the reaction within the chiral space of the catalyst. In this context, we have recently reported the enantioselective addition of a hydrazone aza-enamine to imines,[2a] and the conjugate addition of enamines to nitro olefins.[3]



Scheme 1 Mechanism for the addition of enamines to electrophiles.

The Mannich reaction is an efficient method for the enantioselective synthesis of β-amino carbonyls.[4] Enantioselective, amine catalysis is effective for carbonyl substrates that can readily condense with the amine catalyst under mild, reversible conditions.[5,6] However examples involving aryl ketones tend to result in poor rates and yields due to the low propensity of these substrates to form the required enamine intermediates.[6l,6m,7] By pre-forming reactive nucleophiles of these substrates, such as enamines[8a] and silyl enol ethers[8b] this problem can be avoided. Herein we report the Brønsted acid catalyzed Mannich reaction of aryl methyl ketone enamines with *N*-Boc aldimines.

Initial studies were performed on the addition of enamine **6a**[9a] to *N*-Boc aldimine **7a**.[10] Previous work had shown that both of these substrates were amenable to Brønsted acid catalysis.[2,3] An initial catalyst screen using 20 mol% (*R*,*R*)-TADDOL **9**, (*R*)-BINOL **10**, or (*S*)-H_8-BINOL **11a** (Fig. 1), at −20 °C in toluene, was performed (Table 1, entries 2 to 4) to identify an appropriate catalytic system. Under these conditions the background reaction was slow; only 10% of the product was formed in the absence of additive after 3 days. In the presence of **9** there was a threefold increase in product formation but low levels of enantioselection were observed. With **10**, a more significant acceleration of the reaction was observed (possibly due to the greater acidity of the hydroxyl protons) but the resulting product was found to be racemic. However, with **11a** the reaction went to completion after 1 day and the desired product was obtained with a pleasing 64% ee.

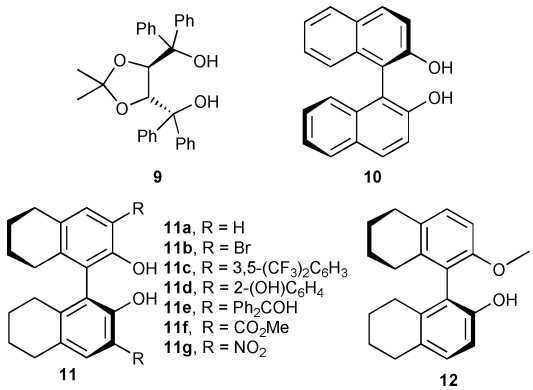
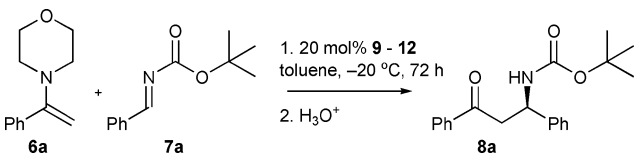


Fig. 1 Brønsted acid catalysts.

Table 1 Catalyst optimization



Entry	Catalyst	Conv.[a] (%)	Yield[b] (%)	Ee[c] (%)
1	—	10	—	0
2	(*R*,*R*)-TADDOL **9**	34	29	17
3	(*R*)-BINOL **10**	73	65	0
4	(*S*)-H_8-BINOL **11a**	100	89	63
5	**11b**	59	50	20
6	**11c**	38	33	65
7	**11d**	60[d]	48	24
8	**11e**	22	20	−21
9	**11f**	27	22	3
10	**11g**	15	10	4
11	**12**	55	36	36

[a] Conversion was measured by ^{1}H NMR against tetramethylgallic acid as an internal standard. [b] Isolated yield after column chromatography. [c] Ee was determined by HPLC analysis. [d] Conversion and yield determined after 6 days at −20 °C.

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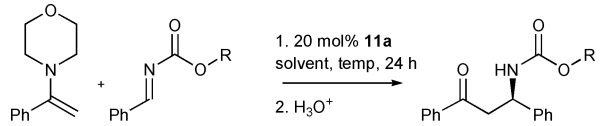
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data is available for **8**, **11e** and **11g**, **14**–**17**. See DOI: 10.1039/b616143j

Having established **11a** as a good catalyst scaffold, a range of derivatives based around this framework were synthesized and tested. Increasing the steric bulk in both of the 3 and 3′ positions (Table 1, **11b** and **11c**, entries 5 and 6) led to a significant drop in product formation and in the case of **11b** a reduced level of enantiocontrol. Addition of extra hydrogen bond donating groups in the 3 and 3′ positions (Table 1, **11d** and **11e**, entries 7 and 8), also led to a loss of catalytic activity and inversion of the facial selectivity in the case of **11e**. Placing electron-withdrawing groups in the 3 and 3′ positions increases the acidity of the 2 and 2′ hydroxyls and it was hoped that this may improve the catalytic action of **11f** and **11g**. However both **11f** and **11g** (Table 1, entries 9 and 10) showed very low catalytic activity, probably due to the formation of strong intramolecular hydrogen bonds between the electron withdrawing groups and the phenolic protons,[1a] which would prevent the catalyst from binding efficiently to the polar transition structure. The lower conversion and ee observed with monomethylated catalyst **12** (Table 1, entry 11) indicated that both the hydroxyls in the 2 and 2′ position are important for the efficacy of **11a**.

Table 2 Reaction condition optimization



Entry	Imine	R	Temp/°C	Solvent	Yield[a] (%)	Ee[b] (%)
1	**13a**	$CH_2C_6H_5$	−20	Toluene	55	52
2	**13b**	Et	−20	Toluene	62	48
3	**7a**	*t*-Bu	−20	Hexane	66	68
4	**7a**	*t*-Bu	−20	DCM	60	17
5	**7a**	*t*-Bu	−20	Et_2O	23	61
6	**7a**	*t*-Bu	−30	Toluene	80[c]	67
7	**7a**	*t*-Bu	−40	Toluene	54[d]	70
8	**7a**	*t*-Bu	−78	Toluene	25[e]	72

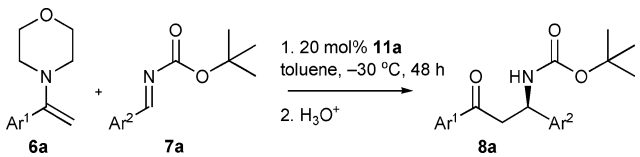
[a] Isolated yield after column chromatography. [b] Ee was determined by HPLC analysis. [c] After two days. [d] After three days. [e] After four days.

The readily available diol **11a** appeared to be the best catalyst for these reactions. In an effort to optimize the reaction, imines with different *N*-protecting groups were prepared and tested. With both the *N*-Cbz and *N*-ethoxycarbonyl aldimines (Table 2, **13a** and **13b**, entries 1 and 2) a reduction in yield and enantioselectivity was observed, confirming that *N*-Boc aldimines **7** are the electrophiles of choice. Morpholino enamines **6** were the preferred nucleophile, as the greater nucleophilicity of the corresponding pyrrolidine and piperidine enamines[9b] led to an increase in the uncatalyzed, background reaction and a reduction in enantioselectivity. As anticipated, non-protic apolar solvents such as toluene and hexane were optimal for this catalyst system (Table 2, entries 3 and 6). Toluene proved to be better at solubilizing both the catalyst and the substrates, leading to better yields of the desired product. Although lowering the temperature led to an increase in the observed ee, there was also a concurrent drop in reaction rate. As a compromise between enantioselectivity and reaction time it was decided that the reactions should be run at −30 °C in toluene using 3 equivalents of enamine. Under these conditions **8a** was isolated in 88% yield, with an ee of 67%.

The scope of this reaction was subsequently investigated. Consistently good yields (88–67%) and ees (84–60%) were observed for a range of *N*-Boc-protected *ortho*-, *meta*- and *para*-substituted aromatic and heteroaromatic aldimines **7** (Table 3, entries 1–7). Variation of the aryl group on the enamine was also tolerated (Table 3, entries 8–12).[11–13] Synthesis of **8ag** allowed the absolute stereochemistry of the products to be assigned as *R* by comparison of the specific rotation with literature values.[14]

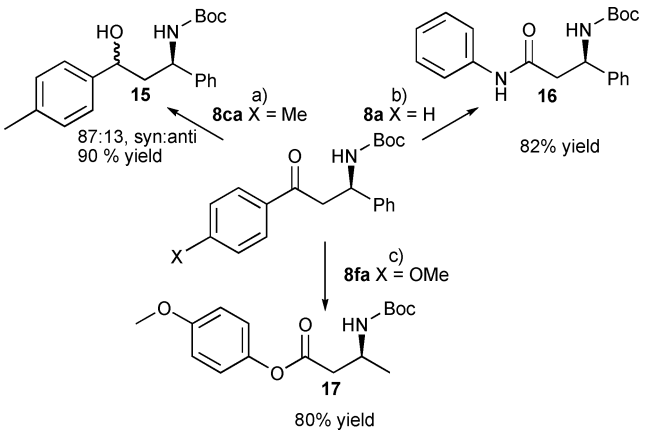
Protected β-amino adducts **8** were readily transformed into a variety of synthetically useful compounds (Scheme 2). Reduction of **8ca** with L-selectride[15] afforded 1,3-amino alcohol **15** in a pleasing yield with a 87 : 13 *syn* : *anti* ratio of diastereomers, that were easily separable by chromatography.[16] The Beckmann rearrangement of **8a** gave amide **16** in 82% yield over two steps[17] and Baeyer–Villiger oxidation of **8fa** selectively produced ester **17** in 80% yield.[18] Under all these conditions, no racemization of the final product was observed.

Table 3 Investigations into the reaction scope



Entry	Ar^1	Enamine	Ar^2	Imine	Prod.	Yield[a] (%)	ee[b] (%)
1	Ph	**6a**	Ph	**7a**	**8a**	88	67
2	Ph	**6a**	2-Furyl	**7b**	**8ab**	72 (53)[c]	73 (82)[c]
3	Ph	**6a**	2-Thienyl	**7c**	**8ac**	64	74
4	Ph	**6a**	2-Naphthyl	**7d**	**8ad**	64	84
5	Ph	**6a**	*o*-Br-C_6H_4	**7e**	**8ae**	86	68
6	Ph	**6a**	*m*-MeO-C_6H_4	**7f**	**8af**	72	71
7	Ph	**6a**	*p*-Cl-C_6H_4	**7g**	**8ag**	73	73
8	2-Naphthyl	**6b**	Ph	**7a**	**8ba**	88	69
9	*p*-Me-C_6H_4	**6c**	Ph	**7a**	**8ca**	98	68
10	*p*-F-C_6H_4	**6d**	Ph	**7a**	**8da**	92	80
11	*p*-MeO-C_6H_4	**6e**	Ph	**7a**	**8ea**	45	72
12	*m*-MeO-C_6H_4	**6f**	Ph	**7a**	**8fa**	54	60

[a] Isolated yield after column chromatography. [b] Ee was determined by HPLC analysis. [c] Figures in parentheses correspond to the yield and ee when the reaction was carried out at −40 °C for 3 days.



Scheme 2 Derivatization of β-amino aryl ketone products. *Reagents and conditions*: a) L-selectride, THF, −78 °C. b) i) $NH_2OH{\cdot}HCl$, pyridine, EtOH, rt. ii) TsCl, pyridine, benzene, rt. c) *m*CPBA, DCE, 60 °C.

In summary, the commercially available diol (*S*)-H_8-BINOL is an effective Brønsted acid catalyst for addition of morpholino enamines **6** to *N*-acyl imines **7**. Good yields and enantioselectivities are obtained with a wide range of substrates. The products of these reactions can be readily converted into a number of diverse structural motifs. Studies to determine the origin of the stereocontrol in this system are currently underway, with a view to producing an improved second generation catalyst.

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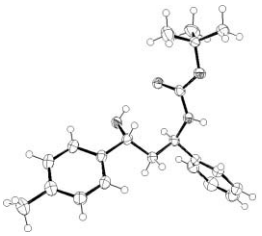

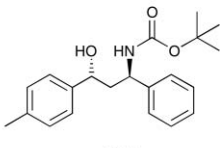

anti-15

anti-15: $C_{21}H_{17}NO_3$, $M = 341.44$, orthorhombic, $a = 19.5903(5)$, $b = 16.0570(2)$, $c = 6.0750(2)$ Å, $U = 1910.96(8)$ Å^3, measured at 180(2) K using an Oxford Cryosystems Cryostream cooling apparatus, space group $Pna2_1$, $Z = 4$, μ(Mo-Kα) = 0.079 mm^{-1}, 9683 reflections, 2364 unique ($R_{int} = 0.036$); $R_1 = 0.042$, w$R(F^2) = 0.110$ [$I > 2\sigma(I)$]. The structure was solved with SHELXS-97, and refined with SHELXL-97. CCDC reference number 626419. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b616143j.
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