The asymmetric vinylogous Mannich reaction of dicyanoalkylidenes with α-amido sulfones under phase-transfer conditions†

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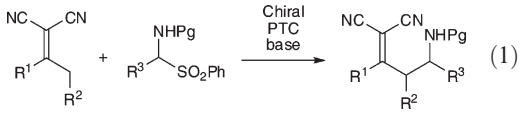
The stereoselective vinylogous Mannich reaction of dicyanoalkylidenes under phase-transfer catalytic conditions utilizing stable α-amido sulfones as imine precursors is presented; a rigid pyrrolidinium salt acts as the phase-transfer catalyst, giving access to the amino alkylated products in generally good yield and up to 95% ee.

Stereoselective C–C bond formation is a main goal in organic chemistry and within the past years organocatalysis has had a great share in offering versatile solutions to this challenge.[1] A number of different reactions have been developed for various compounds and, among these compounds, activated alkylidenes have shown interesting reactivity, leading to a number of accounts on stereoselective γ- and α-functionalizations.[2] To further explore the potential of activated alkylidenes as nucleophiles, we became interested in the vinylogous Mannich reaction of these alkylidenes under phase-transfer catalytic conditions (eqn (1)).



(1)

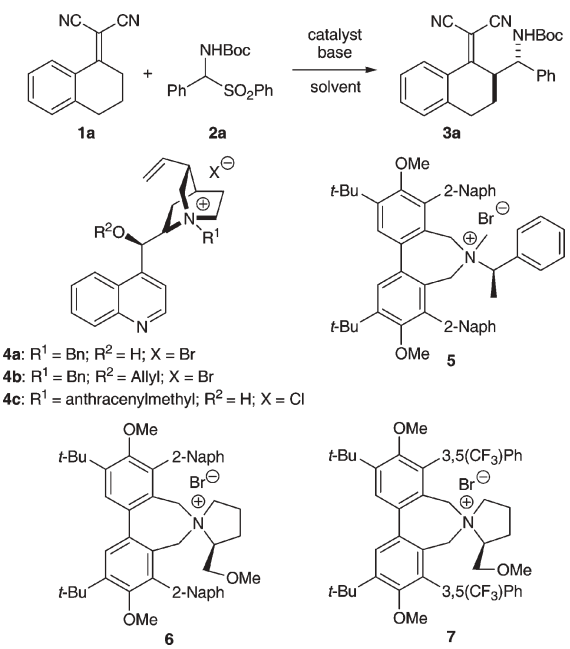
The Mannich reaction is, in analogy to the aldol reaction, a versatile method to build up 1,3-functional groups. A plethora of stereoselective synthetic protocols have been published and, among them, a broad range rely on the activation of the nucleophile or electrophile by an organocatalyst.[3] In contrast, the vinylogous Mannich reaction is far less established, still requiring the development of new entries into this field.[4]

Very often *N*-acylimines are used as electrophiles in the Mannich reaction due to their higher reactivity compared to alkylimines, generally allowing also for an easier removal of the protecting group. Unfortunately, these compounds suffer from an inherent instability making certain precautions in handling and storage necessary.[5] A couple of recent publications report on a very elegant approach where *N*-acylimines are prepared *in situ* from α-amido sulfones under asymmetric phase-transfer conditions, reacting them with different electrophiles to afford optically active products.[6]

Considering the high practicability of a phase-transfer catalytic reaction,[7] especially in view of the most convenient *in situ* preparation of the *N*-acylimine from the corresponding α-amido sulfone, we thought it to be of interest if an activation of the allylic position in the activated alkylidenes might be possible under phase-transfer conditions without causing deleterious side reactions. A recent communication on the stereoselective vinylogous Mannich reaction mediated by a bifunctional thiourea catalyst prompted us to present our own results on the Mannich reaction of dicyanoalkylidenes with α-amido sulfones under phase-transfer catalytic conditions.[4c]

We started our investigation using dicyanoalkylidene **1a** derived from tetralone, reacting it with Boc-protected α-amido sulfone **2a** in presence of solid K_2CO_3 and applying various chiral quaternary ammonium salts (Scheme 1, Table 1).

Initially, we focussed on salts derived from *Cinchona* alkaloids **4** and we were pleased to find that the reaction proceeded smoothly at room temperature, affording the vinylogous Mannich product **3a** as a single regioisomer. Complete conversion of **1a** was achieved in all cases. Starting with commercially available *N*-benzylcinchonidinium bromide **4a**, the amino alkylated product was obtained stereoselectively, albeit only with moderate enantioselectivity (44% ee, Table 1, entry 1). Derivatisation of the catalyst motif revealed that the 9-OH functionality had to be unprotected to maintain enantioinduction (entry 2). Additionally, increasing the size of the substituent R^1 at the nitrogen atom led to a gain in enantioselectivity (entry 3). An extensive screening of the reaction



Scheme 1 Vinylogous Mannich reaction between **1a** and **2a** applying different phase-transfer catalysts.

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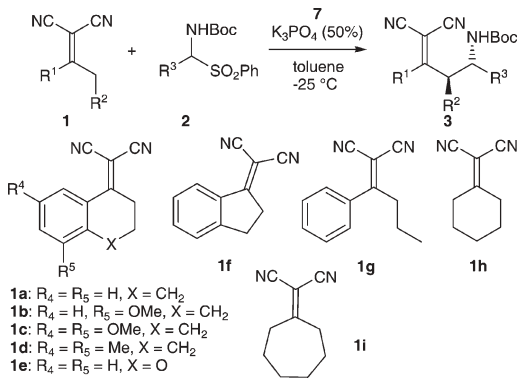
Table 1 Screening of the reaction conditions for the vinylic Mannich reaction between **1a** and **2a**[a]

Entry	Catalyst	Solvent (concentration/mol L^{-1})	Base	Temperature/°C (time/h)[b]	ee (%)[c]
1	**4a**	Tol (0.12)	K_2CO_3, s	2 (24)	(−)-44
2	**4b**	Tol (0.12)	K_2CO_3, s	2 (24)	(−)-3
3	**4c**	Tol (0.12)	K_2CO_3, s	2 (24)	(−)-53
4	**4d**[d]	Tol (0.12)	K_2CO_3, s	2 (24)	(−)-4
5	**4c**	Tol (0.04)	K_2CO_3, s	2 (24)	(−)-62
6	**4c**	Tol (0.04)	K_2CO_3, s	−15 (72)	(−)-64
7	**4c**	CH_2Cl_2 (0.04)	K_2CO_3, s	2 (3.5)	(−)-8
8	**4c**	Et_2O (0.04)	K_2CO_3, s	2 (22)	(−)-28
9	**4c**	Tol–Et_2O 4 : 1 (0.04)	K_2CO_3, s	2 (23)	(−)-59
10	**4c**	Tol (0.04)	K_2CO_3 (50%)	2 (92)	(−)-65
11	**4c**	Tol (0.04)	Cs_2CO_3 (66%)	2 (18)	(−)-67
12	**4c**	Tol (0.04)	KOH (30%)	−25 (14)	(−)-75
13	**5**[e]	Tol (0.04)	KOH (30%)	−25 (18)	(+)-72
14	**6**[e]	Tol (0.04)	KOH (30%)	−25 (18)	(+)-29
15	**7**[e]	Tol (0.04)	KOH (30%)	−25 (18)	(+)-80
16	**7**[e]	**Tol (0.04)**	**K_3PO_4 (50%)**	**−25 (24)**	**(+)-88**

[a] Reactions performed at a 0.05 mmol scale (**1a**) with 1.2 eq. of **2a**, 0.1 eq. catalyst and 2.0 eq. or 0.2 mL, respectively, of base. [b] All reactions showed complete conversion on TLC after the time indicated in brackets. [c] Of the *anti*-isomer, determined *via* CSP-HPLC analysis (see supporting information for details). [d] *N*-Anthracenylmethylcinchoninium chloride. [e] Catalyst loading of 3 mol% was employed.

parameters using **4c** as catalyst showed that the reaction was best carried out in toluene; any polar solvent induced a decrease in enantioselectivity (entries 7, 8). Furthermore, diluting the reaction mixture helped to improve the enantioselectivity to 62% ee (compare entries 3 and 5). Applying an aq. KOH solution (30%) at −25 °C finally made the product **3a** accessible with an ee of 75% (entry 12). Surprisingly, performing the reaction in the presence of the pseudoenantiomeric catalyst **4d** derived from cinchonine, normally yielding the opposite enantiomer of the product, simply led to a significant lower enantioselectivity; however, to our surprise, the same enantiomer was formed (entry 4). This shortcoming, in addition to the moderate enantioselectivity, drove our attention to a different class of catalysts developed by Lygo *et al.*[8] Characteristic for these catalysts is a rigid binaphthyl backbone accommodating a chiral secondary amine. So far, they have only been applied to the alkylation of glycine imines. Compared to the *Cinchona* alkaloids they offer a different spatial arrangement around the cationic center which might allow the formation of a tighter ion-pair, resulting in better face selection of the nucleophile.[9] Testing a few of these catalysts under the elaborated reaction conditions, it turned out that the catalyst **7** performed best (entries 13–16). To our delight, the reaction could be accomplished at a catalyst loading of only 3 mol% without affecting the enantioselectivity or the yield. Using K_3PO_4 (50%) instead of KOH (30%) additionally increased the enantioselectivity from 80% ee to 88% ee (entry 16).



Scheme 2 Substrate scope for the vinylogous Mannich reaction.

Under the optimized conditions, we investigated the scope of the vinylogous Mannich reaction, subjecting a variety of dicyanoalkylidenes and α-amido sulfones to these conditions (Scheme 2, Table 2). The alkylidene **1a** could be reacted smoothly with a range of α-amido sulfones derived from aromatic and heteroaromatic aldehydes in very good yields and with good to very good enantioselectivities (Table 2, entries 1–8).

Generally, phenyl substituents bearing electron-withdrawing groups gave higher enantioselectivities compared to one with an electron-donating group (entries 2–4, 6). Substrates with substituents in *ortho*-, *meta*- and *para*-positions reacted comparably to the benchmark reaction in terms of enantio- and diastereoselectivity. Applying substrate **2f** bearing a 4-methoxyphenyl

Table 2 Allylic Mannich reaction of various dicyanoalkylidenes **1** and α-amido sulfones **2**[a]

Entry	Substrate	R^3	Isolated yield (%)	dr[b]	ee (%)[c]
1	**1a**	Ph **2a**	95 **3a**	99 : 1	88 (88)[d]
2	**1a**	4-Br–Ph **2b**	87 **3b**	99 : 1	93 (93)[d]
3	**1a**	3,4-Cl–Ph **2c**	95 **3c**	99 : 1	83 (81)[d]
4	**1a**	4-F–Ph **2d**	96 **3d**	99 : 1	88
5	**1a**	2-Me–Ph **2e**	95 **3e**	99 : 1	85
6	**1a**	4-OMe–Ph **2f**	92 **3f**	>90 : 1	75
7	**1a**	2-Furanyl **2g**	95 **3g**	>90 : 1	92
8	**1a**	2-Thiophenyl **2h**	87 **3h**	>90 : 1	77
9	**1b**	Ph **2a**	93 **3i**	99 : 1	87
10	**1c**	Ph **2a**	95 **3j**	99 : 1	83
11	**1d**	Ph **2a**	90 **3k**	99 : 1	88
12	**1e**	Ph **2a**	96 **3l**	99 : 1	93
13	**1f**	Ph **2a**	58 **3m**	99 : 1	83
14	**1g**	Ph **2a**	77 **3n**	10 : 1	89
15	**1h**[e]	Ph **2a**	74 **3o**	99 : 1	74
16	**1i**[e]	Ph **2a**	81 **3p**	10 : 1	89
17	**1b**	4-Br–Ph **2b**	nd **3q**[f]	99 : 1	95

[a] Reactions performed at a 0.20 mmol scale (**1**) with 1.05 eq. **2**, 0.03 eq. **7** and 0.3 mL K_3PO_4 (50%) in 4.8 mL toluene at −25 °C. [b] From NMR spectroscopy. [c] Of the *anti*-isomer, determined *via* CSP-HPLC analysis (see supporting information for details). [d] Values in brackets refer to the opposite enantiomer. [e] 0.06 eq. catalyst employed. [f] nd = not determined.

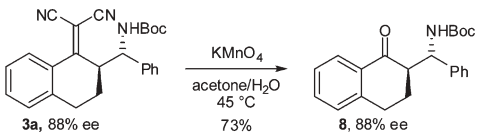
group, as well as the amido sulfones **2g** and **2h** containing a furanyl and thiophenyl substituent, respectively, resulted in slightly diminished diastereoselectivities.

The generality for the γ-functionalization prompted us to also examine the reaction for a series of dicyanoalkylidenes **1b–1i** (entries 9–16). Good to very good results were obtained with dicyanoalkylidenes derived from cyclic aryl ketones bearing substituents on the aromatic moiety and for the chromanone derivative **1e**, respectively. Decreasing the ring size of the saturated moiety to a five-membered ring still gave good enantioselectivity, although a drop in yield was observed (entry 13). Besides the quite rigid substrates **1a–f**, more flexible dicyanomethylene derivatives synthesized from cyclohexanone and cycloheptanone could be successfully transformed into the corresponding mono-amino alkylated products with good stereoselectivities and satisfactory yields (entries 15, 16). Even the non-cyclic derivative **1g** furnished the vinylogous Mannich product under the reaction conditions, albeit with relatively low diastereoselectivity (entry 14). Furthermore, substrate **1f** turned out to be less reactive compared to the so-far tested substrates, making a higher reaction temperature necessary (2 °C).[10]

The absolute configuration of the two new-formed stereocenters was assigned, *via* X-ray analysis of compound **3q**, to be (1*S*,2*S*).[11] To our delight, the opposite enantiomers of compounds **3** could be obtained in comparable enantioselectivity by applying the catalyst ***ent*-7**, synthesized from (*R*)-2-(methoxymethyl)pyrrolidine.

The obtained Mannich products are valuable synthetic intermediates and can be utilized for a variety of transformations. Considering the dicyanomethylene group as a masked ketone, the double bond cleavage is highly desirable to deliver the corresponding amino ketone, an important synthetic intermediate for various natural products and bioactive compounds. Especially in the case of the tetralone derivatives, there are only rare reports on the direct stereoselective α-functionalization, in particular the Mannich reaction, of this type of ketone.[12]

We could accomplish the double bond cleavage using $KMnO_4$ at slightly elevated temperatures, giving access to amino ketone **8** without decrease in the enantioselectivity (eqn (2)).



3a, 88% ee — 73% — **8**, 88% ee (2)

In summary, we report the first allylic functionalization of dicyanoalkylidenes under phase-transfer catalytic conditions, namely the Mannich reaction utilizing α-amido sulfones as imine precursors in the presence of a pyrrolidinium phase-transfer catalyst. This highly practicable approach gives access to a variety of aminoalkylated alkylidene compounds starting from benzocyclic, simple cyclic and open-chain dicyanomethylene derivatives in generally good to high yields and enantioselectivities in the range of 74 to 95% ee.

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10 Applying α-alkyl amido sulfones led to full conversion of the dicyanoalkylidene, but the product was obtained as a mixture of α- and γ-adducts.

11 X-Ray crystal structure analysis of **3q**: $C_{26}H_{26}BrN_3O_3$, M = 508.41, colorless crystal, triclinic, space group $P\bar{1}$, a = 5.4654(2), b = 10.5477(3), c = 11.0731(3) Å, α = 73.134(1), β = 89.326(1), γ = 78.226(2)°, U = 597.26(3) Å^3, T = 100(2) K, Z = 1, μ = 1.753 mm^{-1}, R_{int} = 0.0265, $R1$ = 0.0299, w$R2$ = 0.0662 ($I > 2\sigma(I)$). CCDC 636578. For crystallographic data in CIF or other electronic format, see DOI: 10.1039/b702172k.

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