Simple highly modular acyclic amine-catalyzed direct enantioselective addition of ketones to nitro-olefins†

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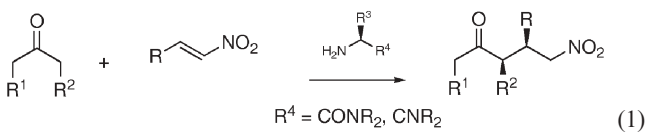
Simple, highly modular primary amino acid derivatives catalyze the direct enantioselective addition of ketones to nitro-olefins with high stereocontrol and furnish the corresponding aldol products in high yield with up to >38 : 1 dr and up to 99% ee.

The Michael reaction is an important carbon–carbon bond-forming reaction in organic synthesis.[1] As a consequence several catalytic asymmetric protocols have been developed for this fundamental reaction.[2] In recent years, an intense research effort has been made to find non-toxic chiral organic molecules as catalysts for enantioselective reactions.[3] In this context, proline[4] and *N*-terminal prolyl peptides[5] have been described as catalyst for the asymmetric Michael reaction. However, only moderate enantioselectivity is typically obtained with these natural catalysts. Proline derivatives on the other hand have been proven to be highly successful for the asymmetric nitro-Michael reaction.[6–9] However, they are generally more complex and prepared in more steps than simple amino acid or peptide catalysts. Herein, we present that simple and highly modular amino acid derivatives with a catalytic primary amine residue catalyze the direct asymmetric Michael addition of ketones to nitro-olefins with high stereoselectivity and furnish the corresponding γ-nitroketones with up to >38 : 1 dr and 99% ee.

Based on our research interest in asymmetric catalysis,[10] we recently found that acyclic aliphatic amino acids and small peptides mediate asymmetric intermolecular C–C bond forming reactions with high stereoselectivity.[11] These results made us interested in whether chiral primary amines derived from acyclic amino acids would be able to catalyze the asymmetric addition of unmodified ketones to nitro-olefins (eqn (1)). Moreover, the high modularity of the primary amines should increase the plausibility of finding novel catalysts for this important C–C bond-forming reaction.

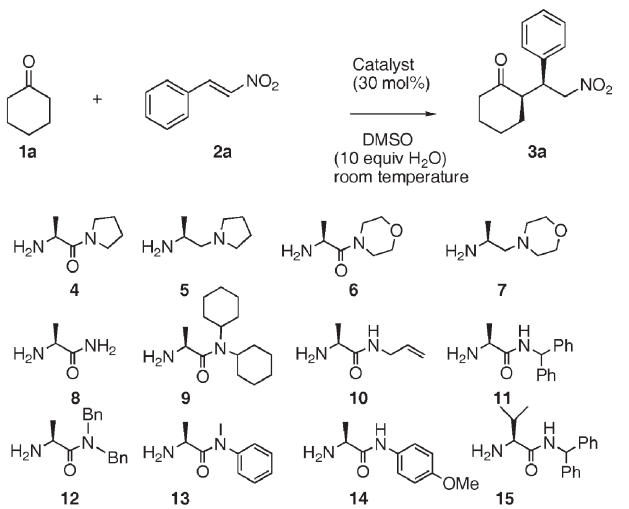


(1)

We initially screened a library of simple amino acid derived catalysts with a catalytic primary amine residue (30 mol%) for the reaction between cyclohexanone **1a** (0.75 mmol) and nitro-olefin **2a** (0.25 mmol) in wet DMSO (1 mL + 45 μL H_2O) (Table 1). A small amount of water (0.025 mmol) was added since we have found that it significantly accelerates as well as improves the stereoselectivity of primary amine-catalyzed asymmetric C–C bond-forming reactions.[11]

Notably, almost all the simple chiral amines **4–15** mediated the formation of the Michael product **3a** under the set reaction conditions and several of the amino acids exhibited high stereoselectivity for the transformation. For example, alanine derived catalysts **11** and **14** catalyzed the asymmetric formation of **3a** with 14 : 1 dr and 35: 1 dr, respectively, and 91% ee. In comparison, (*S*)-alanine furnished Michael product **3a** in trace amounts after 24 h with 6 : 1 dr and 81% ee. Furthermore, we

Table 1 Examples of screened catalysts for the direct asymmetric addition of ketone **1a** to nitro-olefin **2a**



Entry	Catalyst	Time/h	Yield (%)[a]	Dr[b]	Ee (%)[c]
1	**4**	16	60	20 : 1	59
2	**5**	16	33	17 : 1	57
3	**6**	16	62	14 : 1	46
4	**7**	16	25	14 : 1	51
5	**8**	30	21	10 : 1	63
6	**9**	42	11	5 : 1	85
7	**10**	24	11	n.d.	87
8	**11**	24	15	14 : 1	91
9	**12**	22	31	10 : 1	86
10	**13**	168	trace	n.d.	n.d.
11	**14**	23	13	35 : 1	91
12	**15**	48	21[d]	4 : 1	89

[a] Isolated yield after silica-gel column chromatography. [b] *Syn* : *anti* ratio as determined by NMR analyses. [c] Determined by chiral-phase HPLC analyses. [d] 15 mol% *p*-TsOH·H_2O was added.

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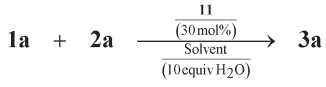
Table 2 The primary amine **11**-catalyzed direct enantioselective additions of cyclohexanone **1a** to nitro-olefin **2a**



Entry	Solvent	Additive (15 mol%)	Temp/°C	Time/h	Yield (%)[a]	Dr[b]	Ee (%)[c]
1	DMSO	—	rt	24	15	14 : 1	91
2	DMSO	TsOH[d]	rt	48	37	9 : 1	98
3	DMSO	AcOH	rt	41	29	11 : 1	86
4	DMSO	NBA[e]	rt	46	36	14 : 1	77
5	DMSO	DNBSA[f]	rt	47	37	12 : 1	98
6	CHCl3	TsOH	rt	240	18	5 : 1	44
7	NMP	—	rt	44	64	25 : 1	90
9	NMP	TsOH	rt	72	92	27 : 1	93
10	NMP	TsOH[g]	rt	45	87	19 : 1	92
11	NMP[h]	TsOH[h]		46[h]	90[h]	14 : 1[h]	93[h]
12	NMP : DMSO (9 : 1)	—	4	96	66	34 : 1	96
13	NMP : DMSO (1 : 1)	TsOH	rt	72	65	12 : 1	96
14	NMP : DMSO (1 : 1)	TsOH[i]	rt	48	trace	—	—
15	[bmin]PF_6[j]	TsOH[g]	rt	42	62	5 : 1	77

[a] Isolated yield after silica-gel column chromatography. [b] *Syn* : *anti* ratio as determined by NMR analyses. [c] Determined by chiral-phase HPLC analyses. [d] TsOH = *p*-TsOH·H_2O. [e] NBA = *p*-nitrobenzoic acid. [f] DNBSA = 2,4-dinitrobenzosulfonic acid. [g] 6 mol% TSOH. [h] 0.5 M **2a**. [i] 30 mol% TSOH. [j] [bmin]PF_6 = 1-*n*-butyl-3-methylimidazoliumhexafluorophosphate.

found that the amino acid derived amides were more efficient than the corresponding diamines under the set reaction conditions. Encouraged by these initial results, we selected catalyst **11** for further studies of the direct asymmetric addition of ketone **1a** to nitro-olefin **2a** (Table 2).

We found that the addition of a small amount of a Brønsted acid (6–15 mol%) together with the H_2O (5–10 equiv.) accelerated the chiral amine **11**-catalyzed asymmetric conjugate reactions. In this context, catalyst **11** mediated the asymmetric assembly of **3a** in up to 98% ee in the presence of a small amount of *p*-toluene sulfonic acid (*p*-TsOH, 15 mol%) or dinitrobenzosulfonic acid (DNBSA, 15 mol%). To our delight, performing the asymmetric conjugate additions in NMP (*N*-methylpyrrolidinone) significantly increased the yield and diastereoselectivity of the reactions without affecting the enantioselectivity.[12] For example, alanine amide **11** catalyzed the asymmetric formation of **3a** in 92% yield with 27 : 1 dr and 93% ee in NMP (Entry 9). Moreover, utilizing a 9 to 1 solvent mixture of NMP and DMSO further improved the diastereo- and enantioselectivity. For instance, primary amine **11** mediated the formation of **3a** in 66% yield with 34 : 1 dr and 96% ee under these reaction conditions (Entry 12). Decreasing the catalyst to acid additive ratio from 5 : 1 to a 1 : 1 ratio completely inhibited the Michael additions. Thus, catalyst **11** was deactivated by protonation of the nucleophilic primary amine component. The primary amines also catalyze the Michael reactions in ionic liquid media, which allows for the recycling of the catalysts. We next probed the alanine amide **11**-catalyzed asymmetric reactions with a set of ketones and nitro-olefins (Table 3).

The (*S*)-alanine amide **11**-catalyzed the asymmetric additions of ketones **1a–1e** to nitro-olefins **2** with high diastereo- and enantioselectivity to furnish the corresponding nitro-ketone products **3a–3h** in high yield with up to >38 : 1 dr and 99% ee. In particular, the reactions with cyclic ketones as nucleophiles gave excellent diastereo- and enantioselectivity. For instance, γ-nitro-ketone **3b** was furnished in 75% yield with 23 : 1 dr and 98% ee. The primary amine-catalyzed asymmetric additions with non-symmetric acyclic ketones proceed with excellent regioselectivity and low to good enantioselectivity. For example, nitro-ketone **3i** was isolated as a single regioisomer in 83% yield with 27% ee.

The observed *syn*-diatereoselectivity and the absolute configuration of the nitro-ketone products was explained by the plausible transition state **I** where the *Si*-face of the nitro-olefin was approached by the *Re*-face of the catalytically generated chiral enamine. (Fig. 1).[13]

The increased enantioselectivity by the addition of a small amount of water and Brønsted acid may be explained by a synergistic stabilization of transition state **I** by formation of a charge-relay system. In addition, the water and acid plausibly accelerate the reaction by facilitating the inter-conversion of the different intermediates of the catalytic enamine cycle.[14]

In summary, we have demonstrated for the first time that simple primary amino acid derivatives can catalyze the direct asymmetric addition of ketones to nitro-olefins with high regio- diastereo- and enantioselectivities. The high modularity of the catalysts together with their simple preparation enables great possibilities in finding novel selective organocatalysts for stereoselective Michael reactions by combinatorial methods. Further expansion of the use of non-toxic and inexpensive linear amino acid amides and their derivatives in environmentally benign organocatalytic asymmetric C–C bond-forming reactions, mechanistic studies and density functional theory calculations are ongoing.

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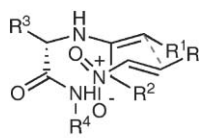
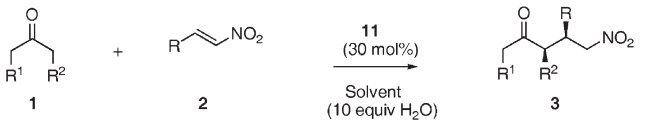
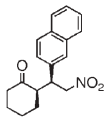
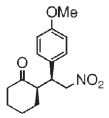
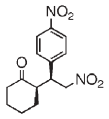
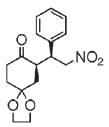
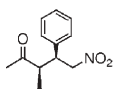
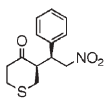
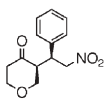
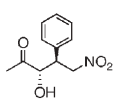


I

Fig. 1 Plausible transition state **I** for the primary amino acid amide-catalyzed asymmetric additions of ketones to nitro-olefins.

Table 3 Examples of different **11**-catalyzed direct asymmetric additions of ketones to nitro-olefins[a]



Entry	Ketone	R	Product	Condition	Yield (%)[b]	Dr[c]	Ee (%)[d]
1	**1a**	Ph	**3a**	B	92	27 : 1	93
2	**1a**	Naphtyl	 **3b**	A	75	23 : 1	98
3	**1a**	4-$MeOC_6H_4$	 **3c**	B	82	19 : 1	90
4	**1a**	4-$NO_2C_6H_4$	 **3d**	B[e]	82	34 : 1	96
5	 **1b**	Ph	 **3e**	A	68	>28 : 1	95
6	 **1c**	Ph	 **3f**	B	45	5 : 1	67
7	 **1d**	Ph	 **3g**	A	45	38 : 1	99
8	**1d**	Ph	**3g**	B	63	>38 : 1	98
9	 **1e**	Ph	 **3h**	A	72	31 : 1	90
10	 **1f**	Ph	 **3i**	B[e]	83	1 : 2	27

[a] A = To a suspension of **11** (30 mol%) in NMP : DMSO, 9 : 1 (1 mL) and H_2O (45μL, 10 equiv.) was added ketone **1** (0.75 mmol) and nitro-olefin **2** (0.25 mmol). B = The same as A but *p*-TsOH (15 mol%) was also added and the solvent was NMP. [b] Isolated yield after silica-gel column chromatography. [c] *Syn* : *anti* ratio as determined by NMR analyses. [d] Determined by chiral-phase HPLC analyses. [e] Reaction performed at 4 °C.

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