Organocatalyzed Michael Addition Reaction by Novel (2*R*,3a*S*,7a*S*)-octahydroindole-2-carboxylic Acid, a New Fused Proline.

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Dedicated to Prof. Alberto Brandi on the occasion of his 60th birthday

Abstract: We present here the results obtained in our study on organocatalytic enantioselective Michael addition reaction of acetone to different nitroolefines using (2*R*,3a*S*,7a*S*)-octahydroindole-2-carboxylic acid ((*R*,*S*,*S*)-Oic, **5**) as a new and suitable catalyst for this process. Computational calculations support the results obtained with (*R*,*S*,*S*)-Oic versus its diastereomeric form (*S*,*S*,*S*)-Oic. The final products are obtained in good yields and moderate enantioselectivities (up to 58% ee).

Key words: Michael addition, nitroolefines, ketones, Oic, organocatalysis, enantioselectivity

In the last ten years asymmetric organocatalysis has become one of the most active and growing field of research in asymmetric catalysis and it has represented a powerful tool for performing stereoselective transformations which were classically achieved using transition-metal or enzymatic catalysis.[1] The Michael addition reaction is widely recognized as one of the most important carbon-carbon bond-forming reactions in organic synthesis.[2] Several reagent systems for this type of transformation that rely on asymmetric catalysts have been developed to date.[2,3,4] In particular, the interest for environment-friendly and non-metal catalyzed asymmetric syntheses,[1] has focused considerable attention on the development of efficient organocatalyzed Michael reactions.[3,4] In the particular case of nitroalkenes,[2a] the Michael adducts with ketones are versatile synthetic intermediates, since the nitro moiety is a strong electron-withdrawing group that can be readily derived into a range of different functionalities.[5]

Among the several studies concerning Michael addition of ketones to nitroalkenes[5,6] most of them are focused on cyclic ketones, particularly six-membered ones, which have been reported to afford best results. On the contrary, less attention has been paid to acyclic ketones which usually lead to lower ee values. In this respect the development of this process using the simplest acetone is still remained[6,7] and new effective catalysts are still desired for the development of that reaction. [4]

Recently, some of us reported the synthesis of enantiomerically pure proline analogues (2*S*,3a*S*,7a*S*)- and (2*R*,3a*S*,7a*S*)-octahydroindole-2-carboxylic acid ((*S*,*S*,*S*)-Oic, **4**)[8] and ((*R*,*S*,*S*)-Oic, **5**),[9] respectively (Figure 1), using semipreparative chiral HPLC resolution.

These structures posses particular conformational properties and they are the core structure of compounds with applications in medicinal chemistry.[10] For example, they exhibit interesting biological activities as antithrombotic, suitable molecules for the prevention of cardiovascular disorders, antiamnesic, anti-inflammatory, antiallergic and analgesic drugs.[11] However, despite of their similarity with L-proline, their ability as organocatalysts is still unexplored.

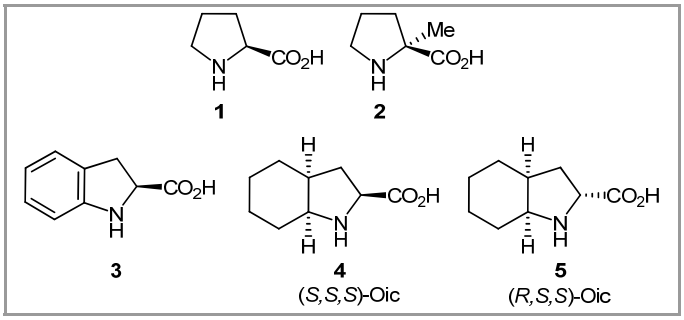
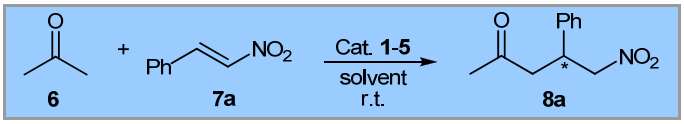


Figure 1

It is well known that a chiral secondary amine catalyzes the asymmetric conjugate addition of ketones to nitroalkenes by transforming the carbonyl group to an enamine intermediate.[12] The substituents and geometries of the enamine and nitroolefine control the stereochemical outcome of the reaction. Compared with proline catalyst, perhydroindole derivatives **4**[13,14] and **5** possess two more stereogenic centers in the backbone, and may exert stronger influences on the orientation of enamine and the nitroolefin. Hence we have undertaken a project to study the relation between absolute stereochemistry of the modified proline and enantioselectivity trying to understand the influence of the different aspects of the reaction.

We started our investigation of this asymmetric Michael addition between acetone **6** and (*E*)-β-nitrostyrene **7** catalyzed by organocatalysts **1**-**5** (Figure 1) leading to the corresponding γ-nitro ketone **8a**, as a test reaction. The results for the initial screening are reported in Table 1.

Table 1 Screening to optimize the reaction conditions[15]



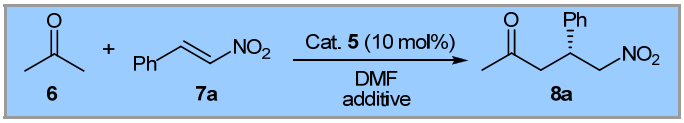
Entry	Catalyst	Solvent	Time (days)	Yield(%)[a]	ee (%)[b]
1[c]	**1**	DMSO	4.5 h	89	4 (*S*)
2	**2**	DMSO	10	n.r.[d]	n.r.[d]
3	**3**	DMSO	10	n.r.[d]	n.r.[d]
4	**4**	DMSO	2	85	22 (*S*)
5	**5**	DMSO	4	74	38 (*R*)
6	**5**	CH_2Cl_2	5	n.r.[d]	n.r.[d]
7	**5**	NMP	8	48	36(*R*)
8	**5**	MeOH	5	n.r.[d]	n.r.[d]
9	**5**	DMF	4	71	46(*R*)
10[e]	**5**	DMF	4	80	32 (*R*)
11[f]	**5**	DMF	8	77	37 (*R*)
11[g]	**5**	DMF	7	77	38 (*R*)
12[h]	**5**	DMF	7	70	39 (*R*)

[a] Isolated yields after column chromatography
[b] Determined by chiral HPLC analysis (Chiralpak IA)
[c] Ref. 6a
[d] No reaction observed
[e] 20 mol% of catalyst
[f] 5 mol% of catalyst
[g] 2 mL of solvent
[h] 0.5 mL of acetone

We performed this study by comparing our results with that previously reported using L-proline for the same reaction, as a model catalyst (Table 1, entry 1),[6] and following the course of the reaction until consumption of the nitroalkene. The low catalytic ability observed with catalyst **2**[16] (Table 1, entry 2), was probably due to the influence previously observed by conformational preferences of α-substituted proline analogues.[17] We thought that the lack of reactivity shown by catalyst **3**[18] can be explained due to its less remarkable nucleophilic character of the electron pair placed on the nitrogen atom over the aromatic ring. (Table 1, entry 3). To our surprise the best catalyst was (*R*,*S*,*S*)-Oic **5** (Table 1, entry 5) affording the final product with a slight improvement in the enantioselectivity compared with the diastereomeric form (*S*,*S*,*S*)-Oic **4**, which, interestingly, afforded the opposite enantiomer (Table 1, entry 4). Since (*R*,*S*,*S*)-Oic **5** provided the best results we decided to use this unexplored catalyst for further examinations. We continued the screening of our reaction model testing different solvents. Dichloromethane (Table 1, entry 6) and methanol (Table 1, entry 8) showed a complete lack of reactivity probably due to the poor solubility of the catalyst for the former and the well-known H-bond inhibition capability for the latter. For the rest, the solvent of choice was DMF (Table 1, entry 9). Further exploration regarding concentration (Table 1, entry 11), catalyst loading (Table 1, entries 10 and 11) and reagents ratio (Table 1, entry 12) did not improve the enantioselectivity of the process. We did not consider the possibility of performing the reaction at lower temperatures due to the long reaction times.

Notably, the preliminary result using isopropanol as an additive resulted in a considerable acceleration of the reaction furnishing a promising yield. To explore this effect, we tried different amounts of *i*PrOH as well as other alcohols as additives (Table 2).

Table 2 Screening to optimize the reaction conditions[15]



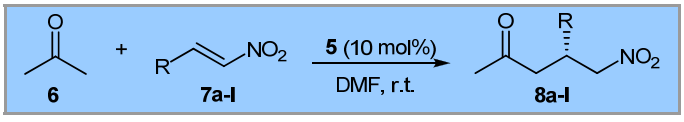
Entry	additive	Equiv.	Time (days)	Yield(%)[a]	ee (%)[b]
1	*i*PrOH	0.5	3	67	40
2	*i*PrOH	1	3	70	36
3	*i*PrOH	2	4	89	34
4	*i*PrOH	4	5	83	35
5	*i*PrOH	8	5	77	33
6	MeOH	2	4	83	36
7	EtOH	2	4	70	36
8	*t*BuOH	2	4	89	35
9[c]	*i*PrOH	1	4	14	42
10[c]	*i*PrOH	2	4	15	43

[a] Isolated yields after column chromatography
[b] Determined by chiral HPLC analysis (Chiralpak IA)
[c] Reaction performed at 0 ºC.

We were pleased to observe a strong rate-acceleration of the reaction using a small amount of *i*PrOH as an additive, although accompanied of a slight decreasing in the enantioselectivity (Table 2, entry 1). Variations in the stoichiometry (Table 2, entries 1-5) and nature (Table 2, entries 6-8) of the alcohols, or even performing the reaction at lower temperature (entries 9-10) did not improve the result obtained in absence of additive, even when similar enantioselectivities were observed but with very poor yields (entries 9-10). Therefore, we considered that the improvement in the reaction rate did not justify the use of isopropanol as an additive of the reaction.

Under the best optimized reaction conditions a variety of nitroalkenes, bearing electron-donating and electron-withdrawing groups, were explored and investigated in order to establish the scope of our Michael addition reaction, and the results are summarized in Table 3.

Table 3 Michael addition of acetone **6** to nitroolefines **7a-l**.[15]



Entry	R	time (d)	yield (%)[a]	ee (%)[b]
1	Ph (**8a**)	4	71	46
2	4-MeC_6H_4 (**8b**)	6	75	42
3	4-MeOC_6H_4 (**8c**)	10	64	35
4	2-MeOC_6H_4 (**8d**)	3	87	53
5	2-$CF_3C_6H_4$ (**8e**)	4	52	41
6	4-ClC_6H_4 (**8f**)	3	71	40
7	4-FC_6H_4 (**8g**)	4	60	40
8	2-furyl (**8h**)	4	73	58
9	4-BrC_6H_4 (**8i**)	4	62	45
10	4-OHC_6H_4 (**8j**)	10	68	33
11	4-BnOC_6H_4 (**8k**)	10	74	36
12	3,4-$Cl_2C_6H_3$ (**8l**)	2	67	44

[a] Isolated yields after column chromatography
[b] Determined by chiral HPLC analysis.

All reactions were performed at room temperature in the presence of 10 mol % of **5**, and for the reaction time indicated in Table 3. As shown above, all aromatic β-nitroalkenes react smoothly with acetone to give the desired Michael adducts **8a-m** in moderate to good yields and moderate enantioselectivities (up to 58% ee). Unfortunately, attempts using aliphatic nitroalkenes gave lower yields and ee's (for R = $PhCH_2CH_2$, ee 34% and 30% yield). No significant dependence of the enantioselectivity was observed on electronic or steric features of the substrates. On the other hand, the reaction rate seems to have a slight dependence on the electronic properties of the nitroalkene showing a lower acceleration with electron donating groups (Table 3, entries 2, 3, 10 and 11). This observation is in agreement with the fact that the rate limiting step in this reaction is the C-C bond formation, responsible of the origin of the enantioselectivity that accounts during the addition of the enamine to the nitroalkene. Indeed, both experimental[19] and theoretical[20] studies demonstrate that the C-C- bond forming step is the rate-determining one. Nevertheless, a recent study revealed that in addition to the reaction of the enamine with the nitroalkene, the hydrolysis of the enamine is also rate limiting in some extent.[21] The absolute configuration (*R*) was determined by comparison of the optical rotation values for adducts **8d**[22] and **8i**[23] with that previously reported in the literature for the same product. We assume the same TS and therefore the same configurational assignment for the rest of products **8a-m**. The stereochemistry on chiral center in position C2 on the catalyst seems to drive the absolute configuration in the final products.

To gain insight on the origin of the enantioselectivity of the studied reaction, computational studies[24] were carried out by employing DFT methods at B3LYP/6-31+G(d,p) and M062X/6-311+G(d,p)//B3LYP/6-31+G(d,p) levels considering in all instances a PCM solvent model for DMSO. [25] In spite of the levels used no determinant data could be obtained due to the close values calculated even at the highest level. The energy values obtained for the transition structures leading to (*S*)- and (*R*)-enantiomers are given in Table 4, while the optimized geometries (PCM_{DMSO}/ B3LYP/6-31+G(d,p)) are illustrated in Figure 2. Although the calculations correctly predicted an opposite enantioselectivity for **4** and **5**, differences less than 0.7 kcal/mol (M062X) were obtained between the corresponding transition structures leading to both enantiomers for each catalyst. Admittedly, these differences are only indicative that low enantioselectivities will be obtained. Accordingly, the values shown in Table 4 cannot be used as predictive values since they are within a mean error of about 2 kcal/mol following previous observations reported by Houk for M062X functional.[26]

Table 4 Total (hartrees) and relative (kcal/mol) electronic energy values for transition structures **TS1-TS4**

	Total energy (hartrees)		Relative energy (kcal/mol)	
	G (B3LYP)[a]	*G* (M062X)[b]	*G* (B3LYP)[a]	*G* (M062X)[b]
TS1[c]	-1187.782666	-1187.528351	0.62	0.00
TS2[d]	-1187.783649	-1187.527877	0.00	0.30
TS3[e]	-1187.784652	-1187.528192	0.00	0.00
TS4[f]	-1187.781419	-1187.572184	2.03	0.63

[a] Optimized structures at (PCM=DMSO)/B3LYP/6-31+G(d,p) level.
[b] Single point calculations at (PCM=DMSO)/M062X/6-311+G(d,p)//B3LYP/6-31+G(d,p) level.
[c] *Re* attack (from **4**) leading to (*R*)-isomer
[d] *Si* attack (from **4**) leading to (*S*)-isomer
[e] *Si* attack (from **5**) leading to (*S*)-isomer
[f] *Re* attack (from **5**) leading to (*R*)-isomer

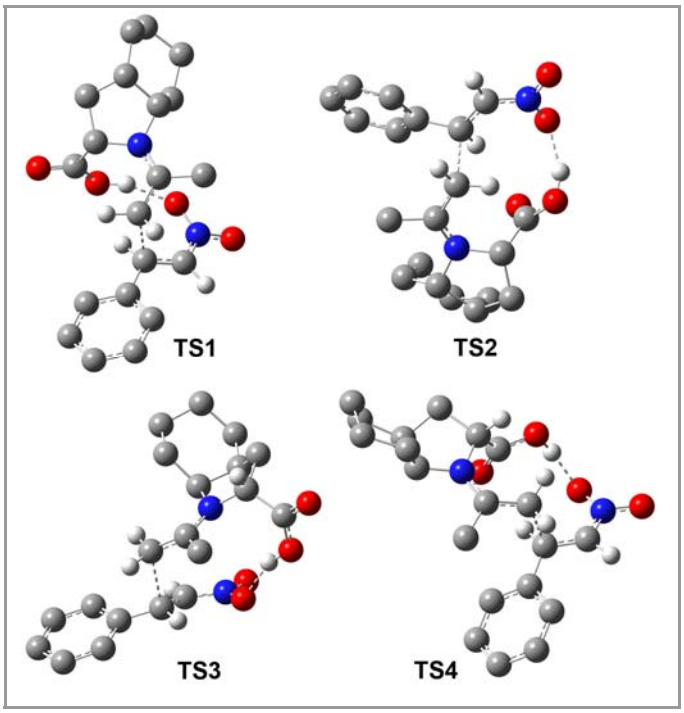


Figure 2 Optimized geometries (PCM_{DMSO}/B3LYP/6-31+G(d,p)) for transition structures **TS1-TS4**. Some hydrogen atoms have been omitted for clarity.

Calculations also predict low values of enantioselectivities with a difference of 0.3 kcal/mol between **A** and the nearest transition structure leading to the (*R*)-isomer with catalyst **4**. Similarly, a difference of 0.6 kcal/mol between **B** and the nearest transition structure leading to the (*S*)-isomer is obtained for catalyst **5**. In this respect, it is worth of note that calculations quantitatively predict the higher enantioselectivity observed for **5** withg respect to **4**.

In summary, we have reported by the first time the use of (2*R*,3a*S*,7a*S*)-octahydroindole-2-carboxylic acid **5** as a suitable organocatalyst for the less studied addition of acetone to diverse nitroolefins. The obtained results, although better than proline, are still only modest (up to 58% ee); however, this example represents an unexplored case on the variation on the pyrrolidine ring structure at positions 4 and 5. The substituents in the proline ring seem to play a very important role both in the yield and in the enantioselectivity. Further modifications in the

skeleton are being performed to pursue higher enantioselectivities and they will be published in due course.

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(15) **Typical experimental procedure**.
To a suspension of catalyst (10 mol%) and nitroalkene (0.5 mmol) in DMF (4 mL), acetone (13.5 mmol, 1 mL) was added and the resulting mixture was stirred at 25 °C for the time indicated in table 3. After that time the reaction was quenched with sat. NH_4Cl (2 x 20 mL), the layers were separated and the aqueous layer extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (2 x 20 mL), dried ($MgSO_4$), filtered and rotatory evaporated to give a residue which was purified by flash chromatography using hexane:EtOAc 7:3 as an eluent. **Selected spectral data**. **8j**: Following the general procedure, compound **8j** was obtained after 10 days at r.t. as a white solid in 66% yield. M.p. 135-136 ºC. ^{1}H NMR (CD_3OD, 400 MHz) δ = 2.05 (s, 3H), 2.88 (dd, *J* = 2.6, 7.2 Hz, 2H), 3.82-3.89 (m, 1H), 4.57 (dd, *J* = 9.2, 12.4 Hz, 1H), 4.70 (dd, *J* = 6.3, 12.4 Hz, 1H), 6.70-6.74 (m, 2H), 7.06-7.10 (m, 2H). ^{13}C NMR (CD_3OD, 100 MHz): δ = 30.4, 40.0, 47.2, 80.9, 116.5, 129.8, 131.5, 157.9, 208.8. The ee of the product was determined by HPLC using a Daicel Chiralpak IA column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min, λ= 230 nm): τ_{major} = 29.1 min; τ_{minor} = 26.9 min; HRMS calcd for $C_{11}H_{13}NNaO_4$ 246.0737; found 246.0728 [M^+ + Na]. $\alpha]_D^{22}$ = 7.3 (*c* 1.0, MeOH, 33% ee). **8k**: Following the general procedure, compound **8k** was obtained after 10 days at r.t. as a white solid in 74% yield. M.p. 131-133 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.11 (s, 3H), 2.88 (d, *J* = 7.1 Hz, 2H), 3.96 (q, *J* = 7.1 Hz, 1H), 4.55 (dd, *J* = 7.8, 12.2 Hz, 1H), 4.65 (dd, *J* = 6.8, 12.2 Hz, 1H), 5.02 (s, 1H), 6.91-6.95 (m, 2H), 7.12-7.15 (m, 2H), 7.31-7.44 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 30.3, 38.3, 46.2, 70.0, 79.6, 115.2, 127.4, 128.0, 128.4, 128.5, 130.9, 136.7, 158.3, 205.5. The ee of the product was determined by HPLC using a Daicel Chiralpak IA column (*n*-hexane/*i*-PrOH = 97:3, flow rate 1 mL/min, λ= 230 nm): τ_{major} = 44.5 min; τ_{minor} = 41.1 min; HRMS calcd for $C_{18}H_{19}NNaO_4$ 336.1206; found 336.1215 [M^+ + Na]. **8l**: Following the general procedure, compound **8l** was obtained after 2 days at r.t. as a white solid in 67% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.13 (s, 3H), 2.88 (d, *J* = 6.9 Hz, 2H), 3.97 (q, *J* = 6.9 Hz, 1H), 4.56 (dd, *J* = 8.1, 12.6 Hz, 1H), 4.67 (dd, *J* = 6.3, 12.6 Hz, 1H), 7.07 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.32 (d, *J* = 2.1 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 30.2, 38.0, 45.7, 78.8, 126.9, 129.4, 130.9, 132.0, 133.0, 139.1, 204.6. The ee of the product was determined by HPLC using a Daicel Chiralpak IA column (*n*-hexane/*i*-PrOH = 97:3, flow rate 1 mL/min, λ= 230 nm): τ_{major} = 29.1 min; τ_{minor} = 26.1 min; HRMS calcd for $C_{11}H_{11}Cl_2NNaO_3$ 298.0008; found 298.0007 [M^+ + Na]. $[\alpha]_D^{22}$ = -1.53 (*c* 1.0, $CHCl_3$, 44% ee).

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