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Efficient monoacylation of symmetrical secondary alkanediamines and synthesis of unsymmetrical diacylated alkanediamines. A new L-proline-based organocatalyst

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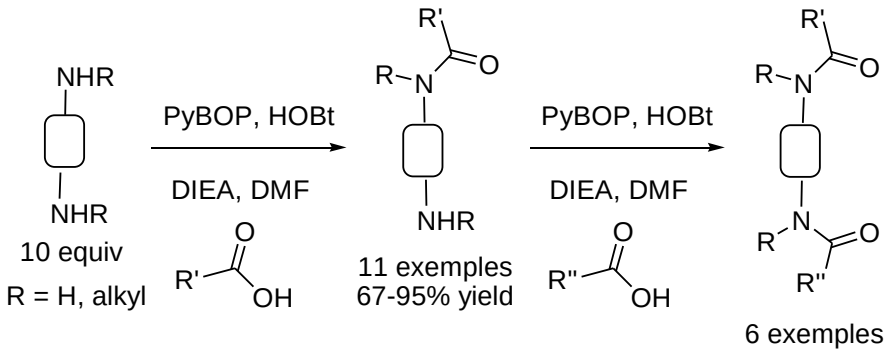
Abstract

A simple procedure was developed for the monoacylation of several unprotected alkanediamines with carboxylic acids by using PyBOP-HOBt as coupling agent in the presence of DIEA at room temperature. Yields were moderate with primary alkanediamines and good to excellent with linear or cyclic secondary ones. To illustrate the utility of these monoacylated products, six unsymmetrical diacylated alkanediamines were synthesized. In addition, one of these compounds was evaluated as organocatalyst in an asymmetric aldol reaction.



Keywords: Monoacylated alkanediamines, unsymmetrical diacylated alkanediamines, pseudopeptidic derivatives, organocatalyst

Introduction

Unsymmetrical diacylated alkanediamines (**A**, Fig. 1) are a widely occurring structural component incorporated into numerous interesting molecules usually evaluated for biological purposes. Examples can be found in the field of fluorescent molecular probes[1-9] and bioactive compounds.[10-17] As shown in Figure 1, the synthetic strategy leading to unsymmetrical diacylated alkanediamines involves a mono acylated alkanediamine (**B**) as precursor. For the synthesis of **B**, in order to avoid the formation of the parasite diacylated product, the common strategy normally used by investigators is the sequence consisting in the acylation of a pre-monoprotected alkanediamine (**C**) followed by the protecting group cleavage. A myriad of examples using this tedious and time-consuming strategy exists in the literature.[1-18]

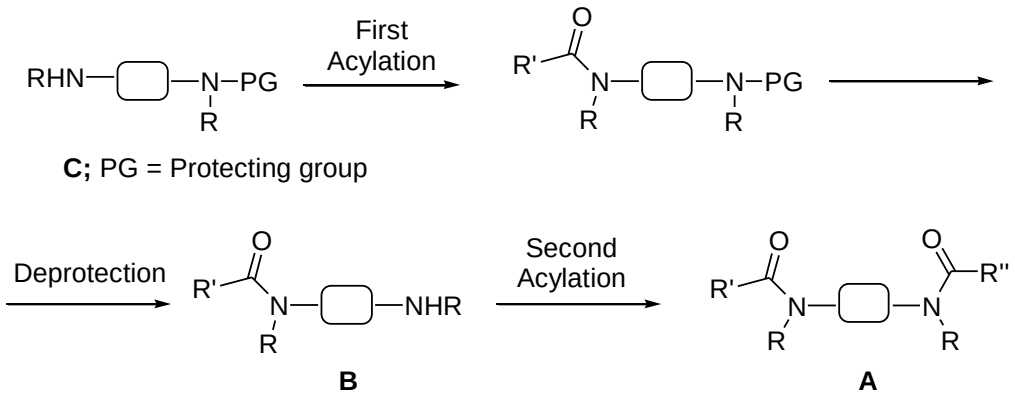


Figure 1. Strategy for the classical synthesis of unsymetrical diacylated alkanediamines **A**.

In this paper we describe a shorter strategy leading to monoacylated (**B**) and diacylated alkanediamines (**A**), which doesn't require the use of a pre-monoprotected alkanediamine (**C**). This strategy is particularly efficient for secondary alkanediamines.

Monoacylated symmetrical alkanediamines (**B**) are valuable scaffolds that appear in the chemical structure of several biologically active compounds in medicinal chemistry. Figure 2 provides representative examples including the cardiotonic agent vesnarinone[19] (**1**) and the antihypertensive agents doxazosin (**2**), prazosin (**3**) and terazosin (**4**).[20]

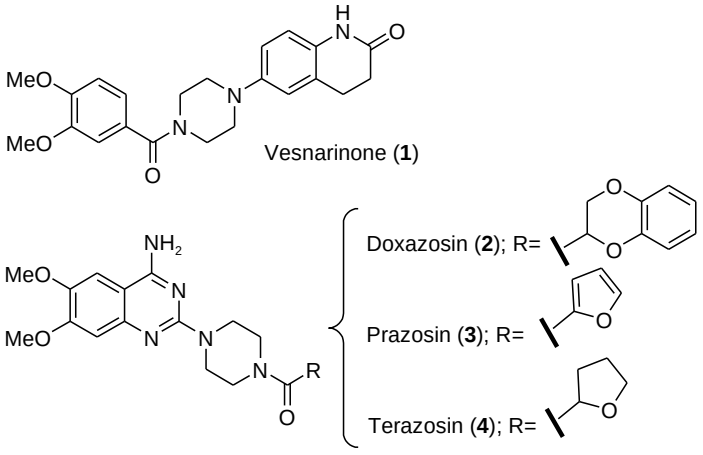


Figure 2. Bioactive compounds bearing a monoacylated moiety.

However, monoacylation of symmetrical diamines remains difficult.[21] Thus, treating a symmetrical alkanediamine with one equivalent of an acylating agent is expected to yield a statistical distribution of products comprising unreacted starting alkanediamine and the mono- and diacylated products (Fig. 3). Consequently, the maximum theoretical yield of the monoacylated product reach 50% with the yield of the diacylated material not exceeding 25%. Unfortunately, the diacylated products are often formed predominantly or exclusively, even though the alkanediamine is present in large excess over the acylating agent. Such finding was attributed by Sayre and co-workers[22] to a mixing problem due to the rapidity of the acylation reaction. Thus, the initial monoacylated product formed at the interface between the drop of the acylated agent and the alkanediamine solutions is acylated a second time at this interface before being dispersed in the reaction medium.

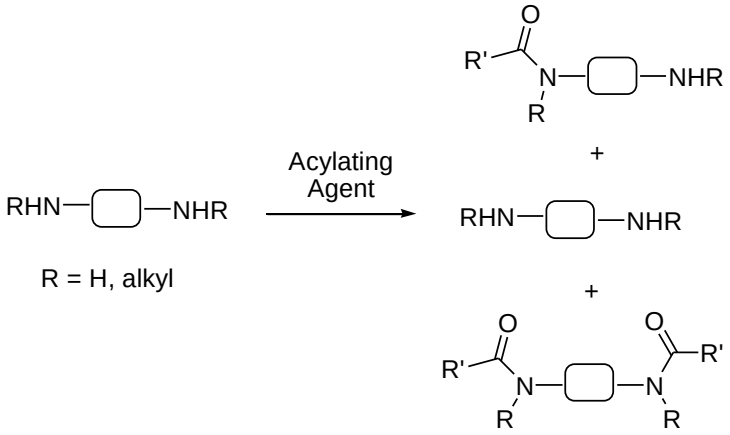


Figure 3. Acylation of unprotected alkanediamines.

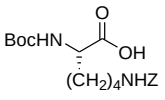
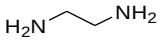
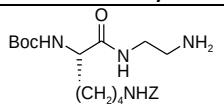
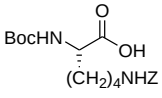
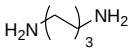
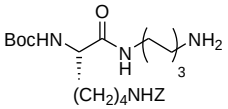
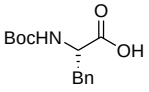
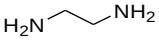
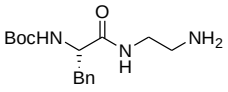
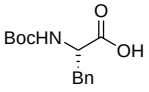
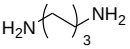
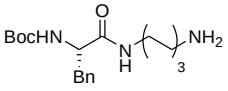
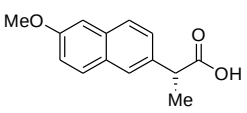
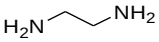
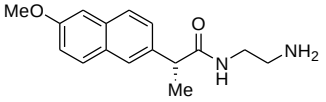
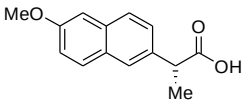
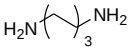
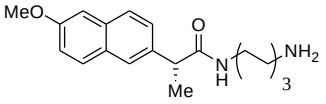
In light of this, monoacylation of symmetrical diamines has attracted considerable interest from the synthetic community and several methodologies have already been published. Thus, in the case of alkanediamines with short hydrocarbon chains one can minimize diacylation at a controlled pH.[23-24] By increasing reactant dilution and decreasing reactivity of the acylating agent, Sayre reached a statistical yield for the mono-acylation of 1,2-ethanediamine and 1,4-butanediamine.[22] Furthermore, Chou's group obtained monoacylated products in excellent yields by one-pot neat reaction of aliphatic or aromatic carboxylic esters and alkanediamines.[25] Wang's strategy focused on the reaction of one equivalent of an acylating agent with the previously prepared alkanediamine Li di-anion.[26] The same group also reached monoacylation by using 9-BBN to protect one of the two amino groups.[27] By using ionic immobilization of piperazine and homopiperazine to sulfonic acid-functionalized silica gel, monoacylation was also realized.[28] Lai reported a convenient method for preparing aryl monoacylated piperazine derivatives by using trimethylacetic arylcarboxylic anhydrides.[29] Fang developed a protocol leading to monoacylated alkanediamines by reacting phenyl esters with a phenyl carbonate as acylation agents in the presence of water.[30] Finally, most recently, Bandgar obtained a series of monoacylated piperazine derivatives by the reaction of carboxylic acids with 2-chloro-4,6-dimethoxy-1,3,5-triazine.[31] Most of the synthetic methods described above suffer from drawbacks, notably the use of drastic reaction conditions or aggressive reagents or are limited to aryl acylations. Therefore, there still exists a need to develop simply and general procedures more efficient than those currently in existence.

Results and Discussion

In this context, our interest in acylated alkanediamines arose from a desire to access a convenient monoacylation procedure for the preparation of secondary and tertiary amides by reaction of carboxylic acids with linear or cyclic alkylenediamines. Thus, we accomplished the synthesis of monoacylated derivatives starting from commercially available carboxylic acids, which were coupled to the corresponding inexpensive alkanediamine in excess utilizing PyBOP-HOBt[32-34] as coupling agent in the presence of DIEA and DMF as a solvent. The desired monoacylated alkanediamines could be obtained after purification by column chromatography on silica gel in moderated yields for primary amines to excellent yields for secondary ones.

As shown in Table 1, we first examined the monoacylation of two primary alkanediamines (1,2-ethanediamine and 1,6-hexanediamine) using *N*-Boc-protected lysine (**5**, entries 1 and 2), *N*-Boc-protected phenylalanine (**6**, entries 3 and 4) and (*S*)-naproxen (**7**, entries 5 and 6) as acylating agents. As expected, the corresponding monoacylated alkanediamines were obtained in low to moderate yields due to the concomitant presence of the corresponding diacylated analogues in a range of 20-30%. Thus, while 1,2-ethanediamine led to **8**, **10** and **12** in disappointing yields (30-31%), 1,6-hexanediamine furnished the corresponding monoacylated products **9**, **11** and **13** in yields ranging from 51 to 56%.

Table 1. Monoacylated primary alkanediamines prepared by PyBOP/HOBt coupling

Entry	Carboxylic acid	Alkanediamine	Monoacylated amine	Yield (%)
1	 **5**		 **8**	30
2	 **5**		 **9**	56
3	 **6**		 **10**	31
4	 **6**		 **11**	51
5	 **7**		 **12**	31
6	 **7**		 **13**	55

Interestingly, as we carried out the monoacylation of cyclic alkanediamines (piperazine and homopiperazine, Table 2) using the same conditions described before (*vide supra*), the reaction crudes were proved by LC-MS to contain only traces of the contaminant diacylated alkane diamines. The use of an excess of alkane diamine was necessary to avoid the formation of significant amounts of the corresponding diacylated alkanediamines. Consequently, the corresponding monoacylated piperazine and homopiperazine derivatives were obtained, after purification by column chromatography on silica gel, in good to high yields (67-96%). As shown in Table 2, monoacylated homopiperazine compounds were obtained in somewhat lower yields than

piperazine analogues (compare entries 1,3 and 5 with entries 2,4 and 6. (*S*)-Naproxen was reacted with a linear secondary amine (entry 7) yielding the corresponding tertiary amide **25** in 96% yield and confirming that the nucleophilic power of cyclic diamines and not their constrained form was responsible for their better reactivity compared to primary amines. In order to demonstrate the general scope of this procedure, we also prepared in good yields *N*-acylpiperazines **26**-**28** (entries 8-10) as precursors of vesnarinone (**1**) and the antihypertensive agents doxazosin (**2**) and a prazosin 2-thienyl analogue respectively in addition to compound **29** bearing a linear chain.[35]

Table 2. Monoacylated secondary alkanediamines prepared by PyBOP/HOBt coupling

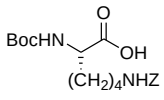
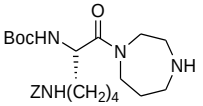
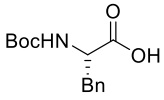
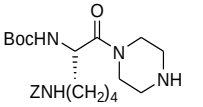
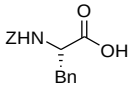
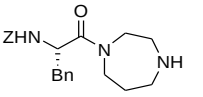
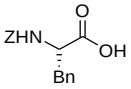
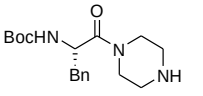
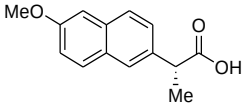
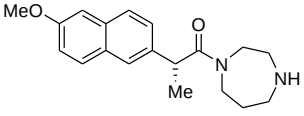
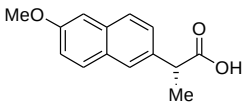
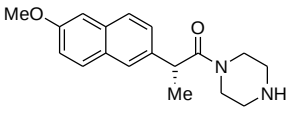
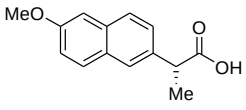
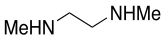
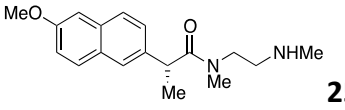
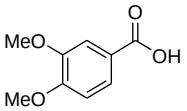
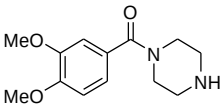
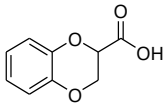
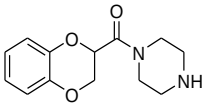
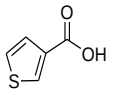
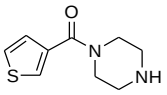
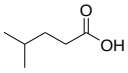
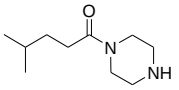
Entry	Carboxylic acid	Alkanediamine	Monoacetylated amine	Yield (%)
1	 **5**		 **19**	70
2	 **5**		 **20**	94
3	 **14**		 **21**	87
4	 **6**		 **22**	95
5	 **7**		 **23**	79
6	 **7**		 **24**	93
7	 **7**		 **25**	96
8	 **15**		 **26**	88
9	 **16**		 **27**	84

Table 2. Continued

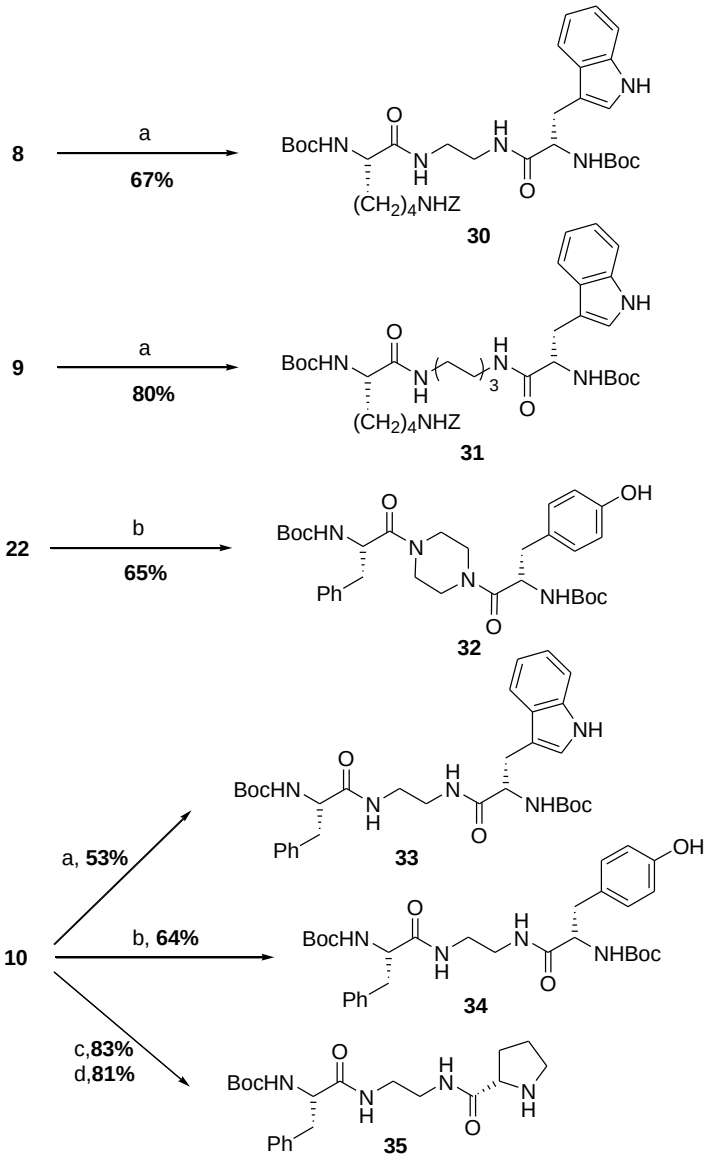
Entry	Carboxylic acid	Alkanediamine	Monoacetylated amine	Yield (%)
10	 **17**		 **28**	67
11	 **18**		 **29**	98

The synthetic potential of this methodology was further exemplified by using the monoacylated alkanediamines in hand as intermediates for the construction of unsymmetrical diacylated alkanediamines. Thus, in a first time, we synthesized a series of six pseudopeptidic derivatives which were studied as supramolecular receptors for non-steroidal antiinflammatory drugs.[36-37] For this meaning, as detailed in Scheme 1, in compounds **8**, **9** and **10**, the remaining free amine was coupled to commercially available Boc-tryp-OH by using the PyBOP/HOBt methodology[32-34] in the presence DIEA obtaining the pseudopeptidic models **30**, **31** and **33** in good yields. Analogously, we carried out the coupling of compounds **10** and **22** with Boc-tyr-OH providing models **32** and **34**. Finally, the *N*-monoacylated compound **10** was reacted with Z-Pro-OH giving, after cleavage of the proline amine protecting group, the unsymmetrical diacylated piperazine **35**.

During the last years, L-proline-based compounds have been successfully employed in asymmetric organocatalysis enlarging the scope of the natural amino acid.[38-41] In this context, we decided to evaluate the catalytic properties of the proline-based compound **35**.

As a benchmark reaction, we examined the aldol reaction between *p*-nitrobenzaldehyde and acetone. The results of this study are reported in Table 3.

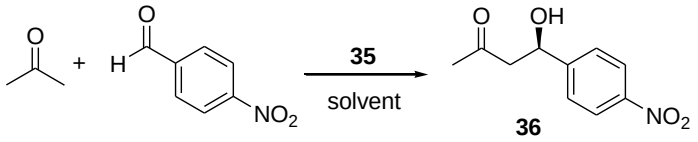
In our initial experiments, we screened various solvent systems by using 30 mol % catalyst **35** to promote the reaction (entries 1-4). Thus, in a 1:4 acetone/DMSO mixture,[42] after stirring the homogenous reaction mixture for 8 days at room temperature, chiral-phase HPLC analysis revealed that the expected aldol product **36** was formed in 19% ee. When using DMF instead of DMSO as a co-solvent, the reaction took place in 5 days improving slightly the enantioselectivity. With the system acetone/AcCN (1:4), after 3 days, the ee was enhanced to 36% with a 92% of conversion rate. The use of chloroform as a co-solvent induced lower enantioselectivity and gave a shorter reaction time. We decided then to conduct the reaction with acetone serving as an only solvent. Thus, aldol **36** was formed in 46% ee (entry 5). By decreasing the catalyst loading to 10%, the reaction rate increased and the ee dropped dramatically (entry 6). By further reduction of the amount of the catalyst (5%) only 54% of conversion was achieved after 3 days with a comparable enantiomeric excess (entry 7). The increase of the quantity of catalyst (50%) considerably accelerated the reaction (4h) but resulted in a lower enantioselectivity (entry 8). Finally, we studied the influence of the reaction temperature in the enantioselectivity (entries 9-11). Thus, when the reaction was carried out at 0°C, the ee increased to 52%. The best result was obtained when the reaction proceeded at -20°C giving the hydroxyketone **36** in 69% yield and 72% ee. Further decrease of the reaction temperature to -30°C reduced somewhat the ee value (66%).



Scheme 1. Synthesis of unsymmetrical diacylated alkanediamines. Reagents and conditions: **a:** Boc-Trp-OH, PyBOP (1 equiv), HOBt (2 equiv), DIEA (2 equiv) in anhydrous DMF, 24 h; **b:** Boc-Tyr-OH, PyBOP (1 equiv), HOBt (2 equiv), DIEA (2 equiv) in anhydrous DMF, 24 h; **c:** Z-Pro-OH, PyBOP (1 equiv), HOBt (2 equiv), DIEA (2 equiv) in anhydrous DMF, 24 h; **d:** H_2, $Pd(OH)_2/C$, EtOH.

Interestingly, when the reaction was conducted by using L-proline as a catalyst with acetone serving as a solvent, no reaction occurred after 3 days stirring of the heterogeneous mixture (entry 12). We attributed this lack of reactivity to the low solubility of proline in acetone. In order to get the completion of the reaction promoted by proline, a 1:4 acetone/DMSO solvent system is necessary (entries 13 and 14).[42,43] Compared to the described conditions using proline as catalyst at room temperature or at -20°C (entries 13 and 14), we observed similar yield and enantioselectivity by using our proline-based organocatalyst **35** at -20°C. However, it is worth mentioning that in our case the use of DMSO, which is not easy to remove, as a co-solvent was not necessary.

Table 3. Aldol Reaction between *p*-Nitrobenzaldehyde and Acetone Catalyzed by proline derivative **35**



Entry	Catalyst	% mol	Solvent	T(C°)	Time (h)	Conversion (%)[a,b]	ee (%)[a,c]
1	**35**	30	Acetone/DMSO (1:4)	rt	192	97	19
2	**35**	30	Acetone/DMF (1:4)	rt	120	100	26
3	**35**	30	Acetone/AcCN (1:4)	rt	72	92	36
4	**35**	30	Acetone/$CHCl_3$ (1:4)	rt	24	96	27
5	**35**	30	Acetone	rt	24	94	46
6	**35**	10	Acetone	rt	72	94	29
7	**35**	5	Acetone	rt	72	54	28
8	**35**	50	Acetone	rt	4	100	40
9	**35**	30	Acetone	0	24	100	52
10	**35**	30	Acetone	-20	24	100	72[d]
11	**35**	30	Acetone	-30	24	95	66
12	L-Pro	30	Acetone	0	72	0	-
13	L-Pro[20]	30	Acetone/DMSO (1:4)	rt	24	100	76
14	L-Pro[21]	30	Acetone/DMSO (1:4)	-20	24	100	71

[a]Conversion and enantioselectivity of the aldol product were determined by analytical chiral HPLC analysis on a chiralpak AS-H column, detection at 270 nm. [b]No secondary products were observed by analytical chiral HPLC analysis. [c]The absolute configuration of the major enantiomer was assigned by comparison with literature data. [d]Compound **36** was isolated with 69 % yield.

Conclusions

In conclusion, a convenient protocol to obtain monoacylated acyclic and cyclic alkanediamines has been developed. We have demonstrated that this is a general procedure leading to secondary, and more efficiently to tertiary amides, and illustrated its utility by preparing in good yields three monoacylated piperazine derivatives as key intermediates in the synthesis of bioactive compounds. This simple procedure provides a practical and timely method for the synthesis of unsymmetrical diacylated alkanediamines, avoiding the employment of any pre-protected alkanediamine as we have demonstrated by the synthesis of six pseudopeptidic derivatives. This protocol is particularly useful for the acylation of inexpensive alkanediamines with precious carboxylic acids. We strongly believe that this methodology will find broad application in synthetic organic chemistry. In addition, one of these compounds was tested as organocatalyst in an asymmetric aldol reaction showing similar results to that described in the literature employing proline. Further studies focusing on new applications of this promising proline-based catalyst and analogues are now under investigation.

Experimental Section

General. All reagents and solvents were purchased from commercial sources. Reactions were conducted in flame-dried glassware under an argon atmosphere. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 or 400 MHz and at 75 or 101 MHz in CD_3OD or DMSO-d_6. Chemical shifts are given in ppm and reported to the residual solvent peak (CD_3OD 3.31 ppm and 49.00 ppm; DMSO-d_6 2.50 ppm and 39.52 ppm). Data are reported as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants, and integration. Analytical TLC were performed on silica gel 60 F_{254} plates. Column chromatographies were carried out on silica gel 60 (63-200 µm). High- resolution mass spectra (HRMS) were measured using electrospray ionization (ESI) and Q-Tof detection. Melting points were measured with a Büchi apparatus and are reported uncorrected.

General procedure for the synthesis of monoacylated diamines. In a typical procedure, alkanediamine (0.014 mol) was suspended in 20 ml DMF. Diisopropylethylamine (DIEA, 0.48 ml, 2.78 mmol) was added, followed by the appropriate carboxylic acid (1.39 mmol), 1-Hydroxybenzotriazole (HOBt, 380 mg, 2.78 mmol) and PyBOP (720 mg, 1.39 mmol). The reaction was allowed to proceed at room temperature 24-30 hours. DMF was then removed by evaporation under reduced pressure and the resultant residue was suspended in ethyl acetate and treated with an aqueous saturated solution of $NaHCO_3$. Phases were separated and the aqueous one extracted with ethyl acetate. The organic layers were dried over magnesium sulfate and rotary evaporated to produce a crude yellow oil, which was purified by column chromatography (silica, CH_2Cl_2/MeOH 4:1).

For the description of compounds **8**, **10**, **30**, **31**, **32**, **33**, see reference 18.

***tert*-Butyl (*S*)-1-(6-aminohexylcarbamoyl)-5-(benzylami-nopentylcarbamoyl)carbamate (9)** was prepared following the general procedure from **5** (528 mg, 1.39 mmol) yielding compound of **9** as a white solid (372 mg, 56%). mp < 30°C. ^{1}H NMR (300 MHz, CD_3OD): δ 7.90 (sl, 1H), 7.35-7.26 (m, 5H), 5.07 (s, 2H), 3.94-3.91 (m, 1H), 3.27-3.09 (m, 2H), 2.93-289 (m, 2H), 1.71-1.29 (m, 14H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, CD_3OD): δ 175.3, 159.0, 157.8, 138.4, 129.5, 129.0, 128.7, 80.6, 67.3, 56.3, 41.4, 40.7, 39.9, 33.0, 30.5, 30.1, 28.7, 28.4, 27.1, 26.9, 24.1. HRMS (ESI): *m/z* calcd for $C_{25}H_{43}N_4O_5$: 479.3233 $[M+H]^+$; found 479.3228.

***tert*-Butyl-(*S*)-1-(6-aminohexylcarbamoyl)-2-phenylethyl-carbamate (11)** was prepared following the general procedure from **6** (369 mg, 1.39 mmol) yielding compound **11** as a white solid (258 mg, 51%). mp 60-62°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.98 (s, 0.25H), 7.83-7.80 (m, 1H), 7.61 (s large, 2H), 7.28-7.16 (m, 5H), 6.83 (d, 0.75H, *J* = 8.5 Hz), 4.13-4.07 (m, 1H), 3.11-2.88 (m, 4H), 2.76 (t, 2H, *J* = 7.6 Hz), 1.54-1.46 (m, 2H), 1.40-1.20 (m, 8H), 1.30 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 171.4, 160.9, 155.2, 138.1, 129.2, 128.0, 126.2, 78.0, 55.8, 38.8, 38.3, 37.8, 28.9, 28.8, 28.2, 27.0, 26.0, 25.8, 25.5. HRMS (ESI): *m/z* calcd for $C_{20}H_{34}N_3O_3$: 364.2595 $[M+H]^+$; found 364.2603.

(*R*)-*N*-(2-Aminoethyl)-2-(2-methoxynaphthalen-6-yl)pro-panamide (12) was prepared following the general procedure from **7** (320 mg, 1.39 mmol) yielding compound **12** as a white solid (117 mg, 31%). mp 121-123°C. ^{1}H NMR (300 MHz, CD_3OD): δ 7.74-7.70 (m, 2H), 7.42 (dd, 1H, *J* 8.5, 1.8 Hz), 7.20 (d, 1H, *J* 2.4 Hz), 7.11 (dd, 1H, *J* 9.0, 2.5 Hz), 3.89 (s, 3H), 7.78 (q, 1H, *J* 7.1 Hz), 3.53-3.46 (m, 1H), 3.36-3.33 (m, 1H), 3.07-2.96 (m, 2H), 1.53 (d, 3H, *J* 7.1 Hz). ^{13}C NMR (75 MHz, CD_3OD): δ 178.6, 159.2, 137.7, 135.3, 130.4, 130.2, 128.3, 127.0, 126.9, 120.0, 55.7, 47.4, 40.8, 38.5, 18.8. HRMS (ESI): *m/z* calcd for $C_{16}H_{21}N_2O_2$: 273.1598 $[M+H]^+$; found 273.1627.

(*R*)-*N*-(6-Aminohexyl)-2-(2methoxynaphthalen-6-yl)pro-panamide (13) was prepared following the general procedure from **7** (320 mg, 1.39 mmol) yielding compound **13** as a white oil (258 mg, 55%). ^{1}H NMR (300 MHz,

CD_3OD): δ 7.82 (sl, 1H), 7.72-7.68 (m, 3H), 7.42 (d, 1H, *J* 8.6 Hz), 7.19 (sl, 1H), 7.11-7.08 (m, 1H), 3.86 (s, 3H), 3.74 (q, 1H, *J* 7.1 Hz), 3.21-3.08 (m, 2H), 1.51-1.44 (m, 4H), 1.50 (d, 3H, *J* 7.1 Hz), 1.35-1.17 (m, 4H). ^{13}C NMR (75 MHz, CD_3OD): δ 177.2, 159.01, 138.1, 135.0, 130.3, 130.2, 128.1, 127.1, 126.7, 119.8, 106.6, 55.7, 47.4, 40.6, 40.1, 30.0, 28.3, 27.0, 26.7, 18.7. HRMS (ESI): *m/z* calcd for $C_{20}H_{29}N_2O_2$: 329.2229 $[M+H]^+$; found 329.2217.

***tert*-Butyl (*S*)-6-aminobenzylcarbamoyl-1-(1,4-diazepan-1-yl)-1-oxohexan-2-ylcarbamate (19)** was prepared following the general procedure from **5** (528 mg, 1.39 mmol) yielding compound **19** as a white solid (449 mg, 70%). mp 88-90°C. ^{1}H NMR (300 MHz, CD_3OD): δ 7.35-7.27 (m, 5H), 5.07 (s, 2H), 4.41-4.33 (m, 1H), 4.17-3.92 (m, 2H), 3.73-3.33 (m, 4H), 3.29-3.07 (m, 4H), 2.29-1.96 (m, 2H), 1.74-1.28 (m, 6H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, CD_3OD): δ 175.2, 159.0, 158.4, 158.3, 138.5, 129.5, 128.9, 128.7, 80.8, 67.3, 52.4, 52.3, 47.8, 47.2, 46.7, 45.9, 45.8, 43.7, 41.2, 32.1, 30.5, 28.7, 27.1, 26.0, 24.1, 23.8. HRMS (ESI): *m/z* calcd for $C_{24}H_{39}N_4O_5$: 463.2915 $[M+H]^+$; found 436.2922.

***tert*-Butyl (*S*)-6-aminobenzylcarbamoyl-1-(piperazin-1-yl)-1-oxohexan-2-ylcarbamate (20)** was prepared following the general procedure from **5** (528 mg, 1.39 mmol) yielding compound **20** as a white solid (585 mg, 94%). mp < 25°C. ^{1}H NMR (400 MHz, CD_3OD): δ 7.34-7.25 (m, 5H), 5.06 (s, 2H), 4.47-4.44 (m, 1H), 3.70-3.44 (m, 4H), 3.16-3.05 (m, 2H), 2.95-2.83 (m, 4H), 1.70-1.28 (m, 6H), 1.42 (s, 9H). ^{13}C NMR (75 MHz, CD_3OD): δ 173.1, 159.0, 157.9, 138.5, 129.5, 129.0, 128.7, 80.6, 67.3, 51.6, 47.0, 46.4, 46.0, 43.4, 41.3, 32.7, 30.5, 28.7, 23.8. HRMS (ESI): *m/z* calcd for $C_{23}H_{37}N_4O_5$: 449.2764 $[M+H]^+$; found 449.2768.

Benzyl (*S*)-1-(1,4-diazepan-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamate (21) was prepared following the general procedure from **14** (416 mg, 1.39 mmol) yielding compound **21** as a white solid (461 mg, 87%). mp 88-90°C °C. ^{1}H NMR (300 MHz, CD_3OD): δ 7.35-7.24 (m, 10H), 5.09-5.01 (m, 2H), 4.78-4.66 (m, 1H), 3.98-3.86 (m, 1H), 3.72-3.60 (m, 1H), 3.48-3.39 (m, 1H), 2.98 (d, 2H, *J* 7.5 Hz), 2.92-2.83 (m, 5H), 2.12-1.82 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD): δ 174.3, 138.1, 137.8, 137.7, 130.6, 129.6, 129.5, 129.0, 128.7, 128.7, 128.3, 128.2, 67.7, 54.0, 53.8, 47.0, 45.8, 45.1, 43.4, 39.2, 39.1, 26.5, 25.7. HRMS (ESI): *m/z* calcd for $C_{22}H_{28}N_3O_3$: 382.2131 $[M+H]^+$; found 382.2130.

***tert*-Butyl (*S*)-1-oxo-3-phenyl-1-(piperazin-1-yl)propan-2-ylcarbamate (22)** was prepared following the general procedure from **6** (369 mg, 1.39 mmol) yielding compound **22** as a white solid (440 mg, 95%). mp 124-126 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.29-7.13 (m, 5H), 4.61-4.47 (m, 1H), 3.81 (s large, 1H), 3.54-3.36 (m, 4H), 2.89-2.56 (m, 6H), 1.31 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.9, 155.1, 137.7, 129.5, 128.1, 126.4, 78.1, 51.2, 44.3, 44.2, 40.8, 37.4, 28.2, 27.9. HRMS (ESI): *m/z* calcd for $C_{18}H_{28}N_3O_3$: 334.2131 $[M+H]^+$; found 334.2137.

(*R*)-1-(1,4-Diazepan-1-yl)-2-(2-methoxynaph-thalen-6-yl)propan-1-one (23) was prepared following the general procedure from **7** (320 mg, 1.39 mmol) yielding compound **23** as a white solid (343 mg, 79%). mp > 230 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.82 (d, 1H, *J* 8.7 Hz), 7.81 (d, 1H, *J* 8.8 Hz), 7.74 (s, 1H), 7.44 (dd, 1H, *J* 8.4, 1.4 Hz), 7.32 (d, 1H, *J* 2.0 Hz), 7.19 (dd, 1H, *J* 8.9, 2.4 Hz), 4.25-4.18 (m, 1H), 3.90 (s, 3H), 3.81-3.34 (m, 5H), 3.22-2.91 (m, 3H), 2.83-2.68 (m, 1H), 1.96-1.66 (m, 2H), 1.41(d, 1H, *J* 6.7 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.9, 172.8, 157.2, 137.2, 137.1, 133.2, 133.1, 129.1, 128.5, 127.3, 127.2, 126.2, 126.1, 125.5, 125.4, 118.8, 105.8, 55.2, 47.1, 47.0, 45.6, 45.5, 45.4, 45.2, 44.4, 43.8, 42.1, 41.7, 41.6, 25.8, 25.7, 24.9, 20.9, 20.7. HRMS (ESI): *m/z* calcd for $C_{19}H_{25}N_2O_2$: 313.1916 $[M+H]^+$; found 313.1926.

(*R*)-2-(2-Methoxynaphthalen-6-yl)-1-(piperazin-1-yl)pro-pan-1-one (24) was prepared following the general procedure from **7** (320 mg, 1.39 mmol) yielding compound **24** as a white solid (386 mg, 93%). mp > 220 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.78 (d, 2H, *J* 8.7 Hz), 7.67 (s, 1H), 7.36 (dd, 1H, *J* 8.4, 1.6 Hz), 7.28 (d, 1H, *J* 2.4 Hz), 7.14 (dd, 1H, *J* 8.9, 2.5 Hz, *J* Hz), 4.22 (q, 1H, J 6.8 Hz), 3.62-3.56 (m, 3H), 3.35-3.31 (m, 1H), 2.89-2.73 (m, 3H), 2.35-2.30 (m, 1H), 1.35 (d, *J* 6.8 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 171.5, 157.1, 137.1,

133.0, 129.1, 128.5, 127.3, 126.1, 125.3, 118.8, 105.8, 55.2, 43.9, 41.1, 40.2, 20.5. HRMS (ESI): *m/z* calcd for $C_{18}H_{23}N_2O_2$: 299.1760 $[M+H]^+$; found 299.1758.

(*R*)-2-(2-Methoxynaphthalen-6-yl)-*N*-methyl-*N*-(2-(me-thylamino)ethyl)propanamide (25) was prepared following the general procedure from **7** (320 mg, 1.39 mmol), yielding compound **25** as a white oil (401 mg, 96%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.65 (d, 1H, *J* 8.5 Hz), 7.61 (d 1H, *J* 9.0 Hz), 7.54 (sl, 1H), 7.25 (dd, 1H, *J* 8.5, 1.7 Hz), 7.11 (d, 1H, *J* 2.3 Hz), 7.02 (dd, 1H, *J* 9.0, 2.5 Hz), 4.08 (q, 1H, *J* 6.8 Hz), 3.92-3.85 (m, 1H), 3.80 (s, 3H), 3.14-3.01 (m, 4H), 2.89 (s, 3H), 2.64 (s, 3H), 1.37 (d, 3H, *J* 6.8 Hz). ^{13}C NMR (75 MHz, CD_3OD): δ 178.2, 159.2, 137.5, 135.2, 130.5, 130.1, 128.8, 126.9, 126.8, 120.1, 106.6, 55.7, 51.7, 46.3, 44.3, 36.5, 34.1, 20.8. HRMS (ESI): *m/z* calcd for $C_{18}H_{25}N_2O_2$: 301.1911 $[M+H]^+$; found 301.1914.

(3,4-Dimethoxyphenyl)(piperazin-1-yl)metha-none (26) was prepared following the general procedure from **15** (253 mg, 1.39 mmol yielding compound **26** as a white solid (306 mg, 88%). mp > 200 °C (decomp.). ^{1}H NMR (300 MHz, CD_3OD): δ 7.07-7.04 (m, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.79-3.66 (m, 4H), 3.12-3.01 (m, 4H). ^{13}C NMR (75 MHz, CD_3OD): δ 172.6, 152.1, 150.3, 128.3, 121.6,112.4, 112.1, 56.5, 56.4 45.4. HRMS (ESI): *m/z* calcd for $C_{13}H_{19}N_2O_3$: 251.1396 $[M+H]^+$; found 251.1398.

(2,3-Dihydrobenzo[b][1,4]dioxin-2-yl)(pipera-zin-1-yl)-methanone (27) was prepared following the general procedure from **16** (250 mg, 1.39 mmol) yielding compound **27** as a white solid (291 mg, 84%). mp 57-59 °C. ^{1}H NMR (300 MHz, CD_3OD): δ 6.93-6.81 (m, 4H), 5.07 (dd, 1H, J 7.1, 2.6 Hz) 4.41 (dd, 1H, J 11.8, 2.6 Hz), 4.22 (dd, 1H, J 11.8, 7.1 Hz), 3.80-3.48 (m, 4H), 2.95-2.79 (m, 4H). ^{13}C NMR (75 MHz, CD_3OD): δ 167.3, 144.5, 144.0, 123.0, 122.6, 118.2, 118.1, 71.4, 66.1, 47.2, 46.6, 46.0, 43.4. HRMS (ESI): *m/z* calcd for $C_{13}H_{17}N_2O_3$: 249.1239 $[M+H]^+$; found 249.1240.

(Piperazin-1-yl)(thiophen-2-yl)methanone (28) was prepared following the general procedure from **17** (178 mg, 1.39 mmol yielding compound **28** as a white solid (182 mg, 67%). mp > 230 °C (decomp.). ^{1}H NMR (300 MHz, CD_3OD): δ 7.68 (dd, 1H, *J* 5.0, 1.1 Hz), 7.48 (dd, 1H, *J* 3.7, 1.1 Hz), 7.15 (dd, 1H, *J* 5.0, 3.7 Hz), 3.99-3.96 (m, 4H). ^{13}C NMR (75 MHz, CD_3OD): δ 165.9, 136.5, 131.2, 131.1, 128.3, 44.4. HRMS (ESI): *m/z* calcd for $C_9H_{13}N_2OS$: 197.0749 $[M+H]^+$; found 197.0745.

4-Methyl-1-(piperazin-1-yl)pentan-1-one (29) was prepared following the general procedure from **18** (161 mg, 1.39 mmol) yielding compound **29** as a white solid (161 mg, 98%). mp °C. ^{1}H NMR (300 MHz, CD_3OD): δ 3.69-3.65 (m, 4H), 3.11-3.01 (m, 4H), 2.40-2.35 (m, 2H), 1.61-1.38 (m, 3H), 0.87 (d, 6H, *J* 6.5 Hz). ^{13}C NMR (75 MHz, CD_3OD): δ 174.7, 49.8, 45.0, 44.8, 44.6, 40.5, 35.0, 31.7, 28.7, 22.5.

***tert*-Butyl (*S*)-1-(2-aminoethyl-(2-pyrrolidine carbamoyl)-carbamoyl)-2-phenylethylcarbamate (34)**. The mono-acylated diamine **10** (472 mg, 1.5 mmol) was dissolved in 22 ml DMF. To the resultant solution were added DIEA (0.57 ml, 3.4 mmol) followed by *Z*-protected proline (421 mg, 1.7 mmol), 1-hydroxybenzotriazole (HOBt, 456 mg, 3.4 mmol) and PyBOP (879 mg, 1.7 mmol). The reaction was allowed to proceed at room temperature until judged complete by HPLC, typically 24–30 h. DMF was then removed by evaporation under reduced pressure and the resulting residue was suspended in ethyl acetate and treated with an aqueous saturated solution of $NaHCO_3$. Phases were separated and the aqueous one extracted with ethyl acetate. The organic layers were dried over magnesium sulfate and rotary evaporated to produce a crude yellow oil, which was purified by column chromatography (silica, CH_2Cl_2/MeOH 10:1) leading to compound **34** as a white solid (687 mg, 83%). mp 157-158°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.19 (m, 10H), 6.64 (s large, 1.5H), 5.38 (s large, 0.5H), 5.21 (d, 1H, *J* 12.4 Hz), 5.08 (d, 1H, *J* 11.8 Hz), 4.36-4.13 (m, 2H), 3.57-2.95 (m, 8H), 2.17-1.82 (m, 4H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 172.6, 156.0, 137.4, 136.7, 129.7, 128.9, 128.8, 128.5, 128.2, 127.1, 80.3, 67.7, 61.2, 56.4, 47.4, 39.5, 39.0, 38.9, 29.7, 28.6, 24.9. HRMS (ESI): *m/z* calcd for $C_{29}H_{39}N_4O_6$: 539.2870 $[M+H]^+$; found 539.2863.

***tert*-Butyl (*S*)-1-(2-aminoethyl-[1-benyl-(2-pyrrolidine carbamoyl)carbamoyl)-2-phenylethylcarbamate (35)**. A solution of 0.216 g of the *Z*-protected amine derivative **34** was prepared in 15 mL of ethanol degassed with argon and two drops of AcOH. Under a positive argon flow, 33 mg of $Pd(OH)_2$ catalyst was slowly added to the vigorously stirring degassed solution. After 4 h, the suspensionwas filtered through Celite. The Celite pad was washed with more ethanol and the filtrate was concentrated under vacuum. The resultant white solid was recristallized in DCM/ether. Compound **35** (0.131 g, 81%) was obtained as a white solid. mp 57-58°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.30-7.19 (m, 5H), 4.25-4.21 (m, 1H), 3.71-3.7 (m, 1H), 3.27-3.21 (m, 4H), 3.10-2.94 (m, 3H), 2.84-2.79 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 176.4, 174.7, 138.7, 130.5, 129.4, 127.7, 80.7, 61.6, 57.7, 47.9, 40.0, 39.9, 39.4, 31.8, 28.7, 26.7. HRMS (ESI): *m/z* calcd for $C_{21}H_{33}N_4O_4$: 405.2502 $[M+H]^+$; found 405.2509.

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Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra of the new compounds **9**, **11**-**13**, **19**-**29**, and **34**-**35** can be found in the supplementary material file.

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