were 9.5% and 7.8%, respectively. Omission of the water made **22** the major product, but both products were always formed under a variety of acidic reaction conditions. Modest separation was realized by TLC with 50% ethyl acetate/petroleum ether as eluent.

Aminal 21. ^{1}H NMR: 3.94 (m, 1 H), 3.71 (s, 3 H), 3.35 (s, 3 H), 2.85 (d, 1 H, J = 9.7 Hz), 2.71 (d, 1 H, J = 14.7 Hz), 2.45-2.3 (m, 3 H), 2.1-1.9 (m, ca. 4 H), 1.8-1.5 (m, ca. 4 H), 1.66 (s, 3 H), 1.62 (s, 3 H) ppm. FT-IR: 2952, 1732 (br) cm^{-1}. MS (EI): 369, 311.

Acetal 22. ^{1}H NMR: 3.93 (dd, 1 H, J = 10.9, 3.2 Hz), 3.77 (s, 3 H); 3.45 (s, 3 H), 2.90 (m, 1 H), 2.65 (m, 1 H), 2.6-2.5 (m, 1 H), 2.5-2.2 (m, 5 H), 2.1-1.9 (m, 3 H), 1.6-1.4 (m, ca. 3 H) ppm. FT-IR: 1777, 1739 (contains a right shoulder) cm^{-1}. MS (EI): 311. ^{13}C NMR: 207.5, 173.0, 172.0, 110.1, 63.8, 52.9, 52.5, 51.8, 41.7, 37.2, 33.2, 29.6, 29.0, 28.9, 16.4 ppm.

Reduction of Ketone 18 with Lithium in Liquid Ammonia. To the blue solution prepared from 3 mg of lithium wire and 1 mL of liquid ammonia (distilled from Na^0) was added ketone **18** (3.4 mg, 0.012 mmol) in 0.5 mL of THF containing 2.5 μL of MeOH. After stirring for 1 h at -78 °C, the reaction mixture was partitioned between $CHCl_3$ and pH 7 buffer. Evaporation of the organic layer furnished 4 mg of crude product, whose ^{1}H NMR spectral data and TLC behavior (15% MeOH/EtOAc) were identical with those reported above for **17**.

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1,1′-Carbonylbis(3-methylimidazolium) Triflate: An Efficient Reagent for Aminoacylations

Ashis K. Saha, Peter Schultz, and Henry Rapoport*

Contribution from the Department of Chemistry, University of California, Berkeley, California 94720. *Received August 18, 1988*

Abstract: Amino acid carboxyl activation and subsequent coupling with nucleophiles frequently suffer from uncertain risks of racemization, complex reagent preparation, or troublesome side-product removal. All of these difficulties are eliminated with a new, simple reagent, 1,1′-carbonylbis(3-methylimidazolium) triflate (CBMIT), obtainable readily by bis-alkylation of carbonyldiimidazole with methyl triflate. Via a highly reactive acyl imidazolium intermediate, CBMIT couples amino acid components or amino acids and alcohols to give peptides and esters, easily isolated in high yield. The reaction medium remains free of any base, and no loss of optical activity is observed.

The subject of carboxyl activation of N-blocked amino acids, though explored in great detail, continues to attract new interest. The conventional coupling methods, utilizing reagents such as DCC, azides, carbonyldiimidazole, active esters, or anhydrides, though widely used, are not free of limitations.[1] Often, few or no options are available for demanding applications in both O-acylation (esters) and N-acylation (peptides). The esterification reaction, in particular, suffers from poor yields, long reaction times, and unacceptable amounts of racemization.

In studies on the synthesis of the 3′-terminal aminoacyl oligonucleotides of tRNA, we required a method for esterification that would satisfy the criteria of simple reagent preparation, mild coupling conditions, and retention of optical purity. Most conventional methods as well as those developed recently[2] did not meet these requirements. The reagent that has attracted most use in the synthesis of aminoacyl tRNA[3] is carbonyldiimidazole (CDI), due to the mild conditions under which it can be used. However, CDI has obvious drawbacks in that the intermediate acyl imidazolides are sluggish toward O-acylation,[4] and substantial racemization in the acyl component has also been reported.[5]

We have shown earlier, in past work from this laboratory, that alkylation of the imidazole nitrogen of (benzyloxycarbonyl)-imidazole with Meerwein's reagent greatly enhanced its reactivity as a CBZ-transfer reagent to poorly nucleophilic DNA bases.[6] Correspondingly, therefore, we projected that alkylation of the imidazole ring in acyl imidazoles should lead to highly reactive acyl-transfer species. The risks of racemization would be minimized if the coupling reaction could be conducted in the total absence of base. A direct route to acyl imidazolium salts such as **2** would be realized, if a bis-alkylated CDI could be obtained. One key feature in designing such a highly reactive version of CDI would have to be the choice of the counteranion as it must be nonbasic and nonnucleophilic. We herein describe the easily prepared reagent 1,1′-carbonylbis(3-methylimidazolium) triflate (CBMIT)[7] and its use in the preparation of complex, optically pure esters and peptides in high yields and under remarkably mild conditions.

Results and Discussion

The readily available, excellent alkylating reagent methyl triflate was chosen for alkylation of CDI, since the trifluoromethane-

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(7) The presumed preparation of a bis-alkylated CDI was postulated in ref 2c; however, no proof of its formation was given. Furthermore, a reactive halide counteranion was involved, and no applications in the coupling of chiral components were presented.

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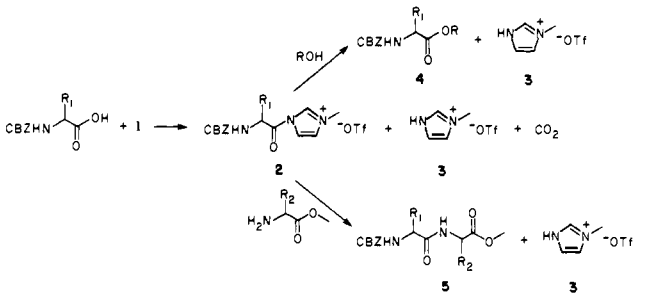
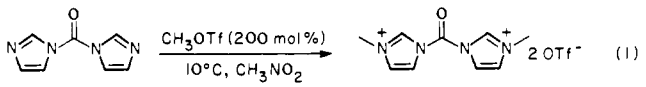
Scheme I. Activation and Coupling



sulfonate anion best satisfies our criterion of being nonreactive. Thus, when CDI was treated in solution with 200 mol % of methyl triflate, the bis-charged compound CBMIT was spontaneously formed (reaction 1). Due to its extremely polar nature, this salt



1, CBMIT

precipitates from most solvents that are compatible with methyl triflate. However, it is easily soluble in nitromethane and for all the work described here, dry nitromethane became the solvent of choice. Evaporation of the solvent in vacuo or precipitation by addition of dry ether produces a white solid, which though sensitive to moisture can be handled for brief periods in the air. Analysis by proton NMR revealed complete disappearance of resonances from CDI and the appearance of a similarly symmetric compound in which the ring C-2 methine resonance shifted downfield to δ 8.9 from 8.2 ppm. The two *N*-methyl groups appeared as one singlet at δ 4.0 ppm. Additional evidence was obtained from a solution FAB mass spectrum, where a (M^+ – triflate) ion was detected. That the bis-alkylation was >99% complete was proved by a FAB mass spectral doping assay. For synthetic purposes, CBMIT can be generated in solution, just prior to use, but if protected from moisture it can also be stored as a nitromethane solution or as a white granular solid, obtained when precipitated from nitromethane by treatment with dry ether.

The reaction of a CBZ-blocked amino acid with CBMIT leads to rapid evolution of CO_2 to give the acyl imidazolium triflate **2** (Scheme I), the identity of which again can be established by proton NMR and FAB mass spectra. When an alcohol or an amine (e.g., an amino acid methyl ester) is exposed to the acyl imidazolium salt **2**, ester or amide formation occurs with ease. While most amide couplings are complete in <15 min at room temperature, ester formations require 1–3 h. The optimized isolated yields in a variety of test cases for both ester and amide formation ranged from 85 to 98%. It should be noted that during each stage of the process, activation and coupling, 100 mol % of *N*-methylimidazolium trilfate (**3**) is formed, thus maintaining a neutral milieu during the reaction.

A series of esters and peptides (Table I) were synthesized by CBMIT coupling, with emphasis on difficult cases. Among the esters to be noted is entry 4, where the sterically hindered, secondary alcohol *l*-menthol was esterified with CBZ-phenylalanine in high yield. Amino acid esters of long-chain C-18 alcohols are of pharmacological value,[8] and the synthesis of the octadecyl ester of CBZ-phenylalanine (entry 3) demonstrates this application of CBMIT coupling. Formation of the depsipeptide bond is demonstrated in entries 5 and 6. In the first case, entry 5, the coupled product between CBZ-glycine and ethyl *dl*-lactate was obtained in 95% yield. With the optically active compounds CBZ-L-alanine and methyl L-phenyllactate, entry 6, coupling occurred in 94% yield. The potential utility of CBMIT in the synthesis of aminoacyl oligonucleotides is illustrated by the esterification of the cytidine derivative in entry 7. In all cases an excess (200 mol %) of the acyl donor was used and the reaction was monitored by TLC for the disappearance of the alcohol. When the stoichiometry of acyl donor in esterification was 100 mol %, the ester was obtained in 70% yield in 1 h, along with the recovered components, as would be expected for bimolecular kinetics.

Table I. Summary of Aminocylations

entry	acyl donor	acceptor	product[a]	% yield[b]
1	C_6H_5COOH	$C_6H_5CH_2OH$	$C_6H_5COOCH_2C_6H_5$	100
2	CBZPhe	EtOH	CBZPheOEt	95
3	CBZPhe	$H_3C(CH_2)_{17}OH$	$CBZPheO(CH_2)_{17}CH_3$	95
4	CBZPhe	*l*-menthol	CBZPheO-menthol	98
5	CBZGly	(±)-CH_3CHO-$HCO_2C_2H_5$	(CBZGlyO)(CH_3)-$CHCO_2C_2H_5$	95
6	CBZAla	L-$C_6H_5CH_2CH$-$OHCO_2CH_3$	(CBZAlaO)$(CH_2C_6H_5)$-$CHCO_2CH_3$	94
7	CBZPhe	HO-Cyt[c]	CBZPheOCyt	91
8	CBZGly	$LeuOCH_3$	$CBZGlyLeuOCH_3$	90
9	CBZPhe	$LeuOCH_3$	$CBZPheLeuOCH_3$	94
10	CBZPhe	$ValOCH_3$	$CBZPheValOCH_3$	90
11	CBZAla	$ValOCH_3$	$CBZAlaValOCH_3$	80
12	CBZAla	$SerOCH_3$	$CBZAlaSerOCH_3$	92
13	CBZSer	$LeuOCH_3$	$CBZSerLeuOCH_3$	72
14	CBZAla	$Asp(OCH_3)_2$	$CBZAlaAsp(OCH_3)_2$	96
15	CBZPhe	*N*-$MeLeuOCH_3$[d]	$CBZPheNMeLeuOCH_3$	70
16	CBZAib[e]	$AibOCH_3$	$CBZAibAibOCH_3$	81
17	BOCAla	$Asp(OCH_3)_2$	$BOCAlaAsp(OCH_3)_2$	85
18	BOC(OBn)-Ser	$ValOCH_3$	BOC(OBn)SerVal-OCH_3	92
19	CBZPhe	$PheValOCH_3$	$CBZPhePheValOCH_3$	81

[a] All products were characterized by LC, NMR, mass spectral, and elemental (C, H, N) analytical data. [b] All yields are chromatographed, isolated yields. [c] HO-Cyt = 4-*N*-CBZ-5'-(dimethoxytrityl)-2'-(*p*-methoxybenzyl)cytosine. [d] *N*-MeLeu = *N*-methylleucine. [e] Aib = α-methylalanine.

The acyl imidazolium salt **2** could just as readily be trapped by an amino acid ester for peptide synthesis (entries 8–19, Table I). The particularly difficult, sterically hindered amino acids valine and α-methylalanine (Aib) could be used as either acyl acceptors (entries 10, 11, and 16) or donors (entry 16) to give dipeptides in high yields. When the acyl acceptor is a secondary amine, e.g., *N*-methyl-L-leucine (entry 15), the peptide bond can be made with equal efficiency. Protection of the hydroxy group as in serine was not necessary as demonstrated in entries 12 and 13. Use of another functionalized acyl acceptor, dimethyl aspartate, is demonstrated in entry 14.

The CBMIT reaction medium could potentially be slightly acidic from the presence of trace amounts of triflic acid in stored batches of reagent solution. Although this poses no problem with CBZ-blocked aminoacyl donors, it might be incompatible with other N-protecting acid-labile groups such as the *tert*-butoxycarbonyl (BOC) group. When an older (1 mo) sample of the methyl triflate reagent was used in the preparation of CBMIT, some loss of the BOC group was indeed evident. This was easily controlled, however, by premixing the *N*-BOC amino acid with 5–10% of *N*-methylimidazole prior to reaction with CBMIT. The preparation of *N*-BOC-$AlaAspOCH_3$ (entry 17) and *N*-BOC-OBn-$SerValOCH_3$ (entry 18) in high yields demonstrates this application of CBMIT to BOC-protected amino acids.

The peptide chain can also be extended from the N-terminus as illustrated in the coupling of CBZ-phenylalanine with phenylalanylvaline methyl ester (entry 16). As is common with most current peptide coupling procedures, chain extension from the amino terminus is the most efficacious route, since an excess (200 mol %) of the acyl donor can be used in coupling to the growing chain and racemization is minimized. Initial results indicate that chain extension from the carboxyl terminus for purposes of segment condensation is also feasible without racemization, and this process will be pursued in a future publication.

The question of chiral integrity of the acyl component was investigated by extensive HPLC and high-resolution NMR doping experiments. For the esterification reaction, the acylation of menthol (entry 4) was considered a good test case. Similarly, the peptides CBZ–phenylalanylleucine methyl ester (entry 8) and CBZ-phenylalanylvaline methyl ester (entry 10) were examined as test systems. In all cases, the products from optically pure

(8) Penney, C. L.; Shah, R.; Landi, S. *J. Org. Chem.* **1985**, *50*, 1457.

components were examined by doping with an authentic mixture of the corresponding diastereomers as a standard. The diastereomeric excesses were determined to be greater than 99.5/0.5 (entry 4, HPLC), 99.75/0.25 (entry 8, HPLC), and 99.75/0.25 (entry 10, NMR). The esterification reaction (entry 4) was further investigated by recovering the unreacted donor, CBZ-phenylalanine, and subjecting it to coupling with valine methyl ester. Upon examination using the NMR doping technique, the peptide thus formed showed a diastereomeric excess of greater than 99.75/0.25. This establishes that the acyl donor undergoes no significant loss of chirality during the course of the activation and coupling and during its lifetime in the reaction mixture. The peptide from *N*-methylleucine (entry 15) was also examined by proton NMR doping experiments and, allowing for the small amount of racemate present in the commercial supply (proved by independent optical assay), the extent of racemization was determined to be <1%.

The retention of chiral integrity in the product esters and peptides along with the simplicity of reagent preparation and product isolation, high yields, mild conditions, and enhanced reactivity associated with CBMIT coupling should make it widely applicable for complex N- and O-acylations. Other applications of CBMIT coupling, including its use in sulfonyl and phosphoryl activation and in the synthesis of Leuch's type anhydrides, are under current investigation.

Experimental Section

Melting points were obtained on a Büchi (capillary) apparatus and are uncorrected. Proton NMR spectra were determined on a Bruker AM 400 (400 MHz) or Bruker AM 500 (500 MHz) instrument, were recorded in $CDCl_3$ unless otherwise indicated, and are expressed as δ downfield shift from Me_4Si. Coupling constants are given in hertz. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley. Fast atom bombardment mass spectra were obtained on a Kratos MS-50 instrument. High-performance liquid chromatography (HPLC) was performed on an Altex analytical system at a flow rate of 1.0 mL/min, using a Si-Microsorb column with monitoring at 260 nm. Ace Michael–Miller glass columns (25 × 130 mm or 40 × 240 mm, 230–400-mesh silica gel 60 (EM Reagents) were used for MPLC. Analytical thin-layer chromatography (TLC) was done with aluminum-backed silica plates (Merck). Tetrahydrofuran (THF) and diethyl ether were distilled from lithium aluminum hydride, dimethylformamide (DMF) was distilled from CaH_2 under reduced pressure, and nitromethane was purified by treatment with CaH_2 (overnight) followed by distillation under atmospheric pressure.[9] Methyl trifluoromethanesulfonate was prepared as described.[10] All amino acids have an L configuration unless otherwise indicated.

1,1′-Carbonylbis(3-methylimidazolium) Triflate (CBMIT, 1). Methyl triflate (2 mmol, 0.226 mL) was added dropwise via a syringe to a solution of carbonyldiimidazole (1 mmol, 162 mg) in nitromethane (2 mL) at 10 °C (ice–water bath). The reaction is very fast and the CBMIT thus generated is used directly for acyl activation. The solvent may be removed in vacuo to give a pale white residue: mp 78–80 °C; ^{1}H NMR δ 8.86 (s, 2 H), 7.44 (m, 2 H), 7.16 (m, 2 H), 4.00 (s, 6 H); FABMS (sulfolane) $[(M - CF_3SO_3) + 2\ H]^+ = 343$.

The purity of CBMIT was established by treating freshly generated CBMIT with water. Carbon dioxide was evolved and 200 mol % of *N*-methylimidazolium triflate (**3**) was formed. A FAB mass spectrum of the product showed peaks corresponding to *N*-methylimidazole ($MH^+ = 83$) and imidazole ($MH^+ = 69$) in a ratio of 97/3. When this mixture was doped with 1 and 5% imidazole, the relative peak heights changed from 97/3 to 93/7 and 81/19, respectively. These data clearly established that methylation of CDI to give CBMIT was >99% complete.

General Procedure for Esterification via CBMIT. Preparation of CBZ-phenylalanyl Octadecanoate (Entry 3). A solution of CBMIT (1 mmol, prepared as above) was cannulated into a suspension of CBZ-phenylalanine (1 mmol, 299 mg) in nitromethane (2 mL). After 5 min, when CO_2 evolution ceased, a solution of 1-octadecanol (0.4 mmol, 108 mg) in THF (4 mL) was added via a syringe. The reaction was quenched with water (1 mL) after 3 h, and the mixture was extracted into ether, washed with 5% aqueous Na_2CO_3 (5 mL) and brine (5 mL), and dried over anhydrous Na_2SO_4. The crude product was further purified by column chromatography on 20 g of silica gel 60, eluting with 10% EtOAc/hexane: yield 209 mg, 95%; R_f 0.4 (20% EtOAc/hexane); mp 71 °C; ^{1}H NMR δ 7.36–7.30 (m, 5 H), 7.28–7.20 (m, 3 H), 7.11–7.09 (m, 2 H), 5.26 (d, 1 H, J = 8 Hz, NH), 5.09 (m, 2 H), 4.65 (m, 1 H), 4.08 (AB q, 2 H, J = 6.5 Hz, $\Delta\nu$ = 11.5 Hz), 3.10 (dd, 2 H, J = 6 Hz, 6 Hz), 1.57 (m, 2 H), 1.26 (m, 30 H), 0.88 (t, 3 H, J = 7 Hz). Anal. Calcd for $C_{35}H_{53}NO_4$: C, 76.2; H, 9.6; N, 2.5. Found: C, 76.1; H, 9.7; N, 2.6.

Preparation of 4-*N*-CBZ-3′-*O*-(*N*-CBZ-phenylalanyl)-5′-*O*-(dimethoxytrityl)-2′-*O*-(4-methoxybenzyl)cytidine (Entry 7). The general procedure for esterification as delineated above was used to prepare this compound from CBZ-phenylalanine (0.15 mmol, 45.5 mg), CMIT (0.15 mmol), and N^4-CBZ-5′-*O*-DMTr-2′-OMBncytidine (0.075 mmol, 60 mg): yield after chromatography, 75 mg, 91%; R_f 0.56 (10% MeOH/$CHCl_3$); FABMS (TG/G) MH^+, 1081; ^{1}H NMR δ 8.36 (d, 1 H, Br), 7.4–7.2 (m, 27 H), 6.82 (m, 6 H), 6.12 (s, 1 H), 5.3 (d, 1 H, br), 5.20 (s, 2 H), 5.12 (m, 4 H), 4.70 (m, 3 H), 4.22 (m, 3 H), 3.76 (s, 6 H), 3.55 (s, 6 H), 3.32 (d, 1 H), 3.16–2.85 (m, 2 H). Anal. Calcd for $C_{63}H_{60}N_4O_{13}$: C, 70.0; H, 5.5; N, 5.2. Found: C, 70.0; H, 5.3; N, 5.2.

General Procedure for Peptide Synthesis via CBMIT. Preparation of CBZ-phenylalanylvaline Methyl Ester (Entry 10). A solution of CBMIT (2 mmol, in 4 mL of nitromethane) was added to a suspension of CBZ-phenylalanine (2 mmol, 600 mg) in nitromethane (4 mL). After 5 min, when CO_2 evolution ceased, valine methyl ester (liberated from the corresponding hydrochloride, 1 mmol, 168 mg) in THF/DMF (4/2 mL) and *N*-methylmorpholine (1 mmol, 112 μL) were added, and the reaction was stirred for 30 min. The reaction mixture was then treated with water (1 mL), extracted into ethyl acetate (20 mL), washed with 5% aqueous Na_2CO_3 (5 mL), 5 N HCl (5 mL), and brine (5 mL), and dried over anhydrous Na_2SO_4. The crude product was further purified by medium-pressure liquid chromatography, eluting with 20% EtOAc/hexane: yield 371 mg, 90%; R_f 0.50 (50% EtOAc/hexane); mp 81–83 °C; ^{1}H NMR δ 7.37–7.15 (m, 10 H), 6.64 (d, 1 H, J = 8.7 Hz), 5.64 (d, 1 H, J = 8.5 Hz), 5.05 (s, 2 H), 4.54 (m, 1 H), 4.46 (dd, 1 H, J = 5.2, 8.7 Hz), 3.66 (s, 3 H), 3.05 (m, 2 H), 2.06 (m, 1 H), 0.84 (d, 3 H, J = 7 Hz), 0.81 (d, 3 H, J = 7 Hz). Anal. Calcd for $C_{23}H_{28}N_2O_5$: C, 67.0; H, 6.8; N, 6.8. Found: C, 66.7; H, 6.6; N, 6.7.

General Procedure for Peptide Synthesis with *N*-BOC-Protected Amino Acids. Preparation of *t*-BOC-OBn-SerValOMe (Entry 18). A solution of *N*-*t*-BOC-*O*-benzylserine (0.25 mmol, 73.8 mg) and *N*-methylimidazole (0.025 mmol, 2 μL) in nitromethane (100 μL) was added via a syringe to a freshly generated solution of CBMIT (0.25 mmol in 0.5 mL of nitromethane). After 5 min, when CO_2 evolution ceased, valine methyl ester [liberated from the corresponding hydrochloride (0.125 mmol, 21 mg) in 1/1 THF/DMF (0.5 mL) and *N*-methylmorpholine (0.125 mmol, 14 μL)] was added and the reaction was stirred for 30 min. Water (0.5 mL) was then added, and the mixture was extracted into ethyl acetate (2 × 10 mL), washed with saturated $NaHCO_3$ (5 mL) and water (5 mL), and dried over anhydrous Na_2SO_4. The crude product was further purified by flash chromatography, eluting with 30% EtOAc/hexane: yield 47 mg, 92%; R_f 0.5 (50% EtOAc/hexane); ^{1}H NMR (two rotational isomers) δ 7.28–7.20 (m, 5 H), 7.04 (d, 0.5 H, J = 7 Hz), 6.81 (d, 0.5 H, J = 7 Hz), 5.38 (s, br, 1 H), 4.54–4.41 (m, 3 H), (m, br, 1 H), 3.91–3.83 (m, 1 H), 3.642 (s, 1.5 H), 3.639 (s, 1.5 H), 3.55–3.50 (m, 1 H), 2.07 (m, 1 H), 1.382 (s, 4.5 H), 1.379 (s, 4.5 H), 0.83 (d, 3 H, J = 7 Hz), 0.76 (d, 3 H, J = 7 Hz); FABMS (TG/G) MH^+, 409, MH − 100 (−*t*-BOC), 309 (base peak). Anal. Calcd for $C_{21}H_{32}N_2O_6$: C, 61.8; H, 7.8; N, 6.9. Found: C, 61.6; H, 7.8; N, 6.8.

Preparation of CBZ-alanylphenyllactic Acid Methyl Ester (Entry 6). *N*-CBZ-alanine (1 mmol, 223 mg) was added under a stream of N_2 to a freshly generated solution of CBMIT (1 mmol in 2 mL of nitromethane). After 5 min, as the evolution of CO_2 ceased, phenyllactic acid methyl ester (0.5 mmol, 90 mg) in dry DMF (1 mL) was added, and the reaction was stirred for 30 min. A saturated aqueous solution of $NaHCO_3$ (2 mL) was added, and the reaction mixture was extracted into ethyl acetate (2 × 10 mL). The organic layer was washed with saturated $NaHCO_3$ (2 mL) and brine (2 mL) and dried over anhydrous Na_2SO_4. The crude product was purified by a rapid flash chromatography (4 g of SiO_2, 30% EtOAc/hexane): yield 181 mg, 94%; R_f 0.25 (20% EtOAc/hexane); ^{1}H NMR δ 7.36–7.19 (m, 10 H), 5.27 (dd, 1 H, J = 4.4, 3.6 Hz), 5.24 (d, 1 H, br, NH), 5.10 (s, 2 H), 4.43 (q, 1 H, J = 7.2 Hz), 3.70 (s, 3 H), 3.17 (AB q, 2 H, J = 4.4, 8.0 Hz, $\Delta\nu$ = 31 Hz), 1.45 (d, 3 H, J = 7.2 Hz). Anal. Calcd for $C_{21}H_{23}NO_6$: C, 65.5; H, 6.0; N, 3.6. Found: C, 65.7; H, 6.0; N, 3.7.

Determination of Optical Purity. The L,L isomers were prepared from optically pure components, and the diastereomeric mixtures (L,L/D,L) were prepared from optically pure acyl donor (L) and racemic acceptor molecules. The former was doped in solution with the latter in varying amounts (0.25%, 0.5%, 1%, 2%, etc.) and the HPLC traces were recorded. In every case, the increase in the height of the minor peak (D,L) relative to the major peak (L,L) was recorded. The smallest value of the

(9) For a treatise on, and explosion hazards of, nitromethane, see: *Pure Appl. Chem.* **1986**, *58*, 1541.

(10) Stang, P. J.; Hanack, M.; Subramanium, L. R. *Synthesis* **1982**, 85.

percent dope for which a relative increase in the minor peak height could be observed established the detection limit. The same principle was applied in the case of the NMR determination of optical purity for CBZPheValOMe (entry 8). The proton NMR resonances ($CDCl_3$, 400 MHz) for the side-chain methyl groups in valine appeared as sets of clearly resolved doublets at δ 0.84 and 0.81 (L,L isomer) and δ 0.75 and 0.72 (D,L isomer). The sweep was narrowed to focus on this region and at maximized digital resolution, the relative increases in the peak heights for the later set of doublets were recorded against the percent dope amounts.

Registry No. 1, 120418-31-7; **3**, 99257-94-0; CDI, 530-62-1; $PhCOOCH_2Ph$, 120-51-4; CbzPheOEt, 28709-70-8; CbzPheO-$(CH_2)_{17}CH_3$, 120418-34-0; CbzPheO-menthol, 98210-62-9; (±)-$CbzGlyOCH(CH_3)COOEt$, 120418-35-1; CbzAlaO-(*S*)-$CH(CH_2Ph)$-COOMe, 120445-32-1; CbzPheOCyt, 120418-36-2; CbzGlyLeuOMe, 17331-93-0; CbzPheLeuOMe, 3850-45-1; CbzPheValOMe, 4818-08-0; CbzAlaValOMe, 4864-38-4; CbzAlaSerOMe, 19542-34-8; CbzSer-LeuOMe, 17331-94-1; $CbzAlaAsp(OMe)_2$, 120418-37-3; CbzPheNMe-LeuOMe, 120418-38-4; CbzAibAibOMe, 6671-25-6; $BOCAlaAsp-(OMe)_2$, 120418-39-5; BOC(OBn)SerValOMe, 120418-40-8; CbzPhe-PheValOMe, 120418-41-9; PhCOOH, 65-85-0; CbzPhe, 1161-13-3; CbzGly, 1138-80-3; CbzAla, 1142-20-7; CbzSer, 1145-80-8; CbzAib, 15030-72-5; BOCAla, 15761-38-3; BOC(OBn)Ser, 23680-31-1; $H_3C(C-H_2)_{17}OH$, 112-92-5; (±)-$CH_3CH(OH)COOEt$, 2676-33-7; L-$PhCH_2CH(OH)COOMe$, 13673-95-5; HO-Cyt, 120418-42-0; LeuOMe, 2666-93-5; ValOMe, 4070-48-8; SerOMe, 2788-84-3; $Asp(OMe)_2$, 6384-18-5; *N*-MeLeuOMe, 35026-08-5; AibOMe, 13257-67-5; PheVa-lOMe, 80870-38-8; *l*-menthol, 2216-51-5.

Supplementary Material Available: Physical and analytical data for all new compounds not included in the Experimental Section (3 pages). Ordering information is given on any current masthead page.

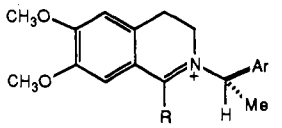
Stereoselective Nucleophilic Additions to the Carbon–Nitrogen Double Bond. 2. Chiral Iminium Ions Derived from "Second Generation" Chiral Amines†

Richard P. Polniaszek* and Craig R. Kaufman

Contribution from the Paul M. Gross Chemical Laboratories, Duke University, Durham, North Carolina 27706. *Received September 21, 1988. Revised Manuscript Received February 7, 1989*

Abstract: "Second generation" chiral amines (1*S*)-(−)-1-(2-chlorophenyl)ethylamine (**4**) and (1*S*)-(−)-1-(2,6-dichlorophenyl)ethylamine (**5**) have been prepared from commercially available (*S*)-(−)-α-phenethylamine. These chiral reagents have been incorporated into chiral iminium ions of structural type **1**. The iminium ions **1a–c** undergo highly diastereoselective hydride reduction to afford chiral, 1-substituted tetrahydroisoquinolines. The sense of asymmetric induction was unambiguously assigned in selected cases by chemical correlation with (*S*)-(−)-salsolidine and (*S*)-(−)-norlaudanosine.

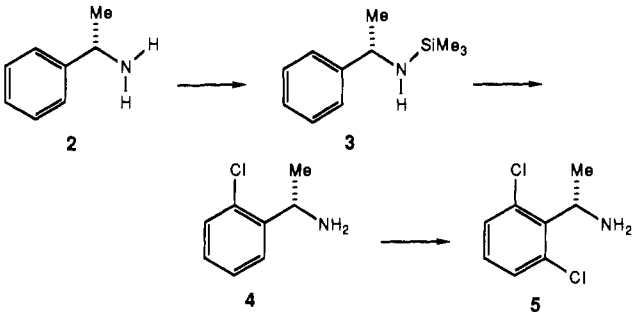
Iminium ions form an important set of electrophiles which participate in carbon–carbon bond forming reactions.[1] We have been interested in obtaining information regarding the transition-state geometry associated with the addition of nucleophiles to chiral iminium ions.[2] Herein we report highly stereoselective hydride reductions of chiral iminium ions of structural type **1**.



1a: Ar = phenyl
1b: Ar = 2-chlorophenyl
1c: Ar = 2,6-dichlorophenyl

The chirality resident in substrates **1** was derived from (*S*)-(−)-α-phenethylamine. Key to this study was the preparation of derivatives of α-phenethylamine which, relative to the parent structure, possess enhanced steric differences between the aryl and methyl groups. It was assumed that the degree of stereoselection observed in reduction of iminium ions **1** would be governed by steric factors. The single stereogenic center appended to the nitrogen atom of the iminium ion moiety in **1a–c** creates different steric environments on the two iminium ion diastereofaces in the ground state and/or transition state of the nucleophilic addition reaction. It was anticipated that increasing the relative size difference between methyl and aryl groups in iminium ions **1** would selectively increase the steric crowding of one iminium ion diastereoface and enhance hydride-reduction diastereoselection in the series **1a** → **1b** → **1c**.

Preparation of Reagents 4 and 5. The strategy employed in preparing "second generation" chiral amines **4** and **5** involved



2 **3** **4** **5**

functionalization of the 2- and 2,6-positions of the aromatic ring of α-phenethylamine via directed-metalation reactions. (*S*)-(−)-α-Phenethylamine (**2**) ($[\alpha]_D$ = −39° (neat), 96.5% ee)[3] was monosilylated[4] (2 equiv of $(TMS)_2NH$, 0.04 equiv of $(NH_4)_2SO_4$,

† Taken in part from the M.S. thesis of Kaufman, C. R., Duke University, 1988.

(1) Paukstelis, J. V., Cook, A. G. In *Enamines: Synthesis, Structure, and Reactions*, 2nd ed.; Cook, A. G., Ed.; Marcel Dekker: New York, 1988; Chapter 6. Bohme, H., Haake, M. In Bohme, H., Viehe, H. G. (Ed.) *Iminium Salts in Organic Chemistry*, Part 1; Bohme, H., Viehe, H. G., Eds.; Wiley: New York, 1976; pp 107–224.

(2) Polniaszek, R. P.; McKee, J. A. *Tetrahedron Lett.* **1987**, *28*, 4511. Kametani first reported the reduction of **1a** (R = Me) with $NaBH_4$ at 0 °C to proceed with a diastereoselectivity of 72:28. This material was subsequently converted to *S*-(−)-salsolidine by hydrogenolysis: Kametani, T.; Okawara, T. *J. Chem. Soc. Perkin Trans. 1* **1977**, 579.

(3) Highest observed $[\alpha]_D$ = −40.4° (neat): Cope, A. C.; Ganellin, C. R.; Johnson, H. W., Jr.; Van Auken, T. V.; Winkler, H. J. J. *J. Am. Chem. Soc.* **1963**, *85*, 3276. The amine was purchased from Aldrich Chemial Co. We also assayed the enantiomeric excess by preparation of the corresponding Mosher amides with (+)-MPTA-DCC. Capillary GC analysis of the amides (DB-5, 200 °C, 25 psi) afforded a diastereomeric ratio of 98:2.

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