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Enantiospecific Synthesis of α-Amino Ketones and β-Amino Alcohols from the Reaction of *N*-(9-Phenylfluoren-9-yl)-Alanine Oxazolidinone with Organolithium Reagents

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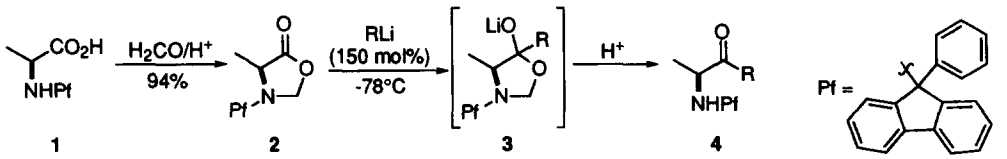
Abstract: Enantiomerically pure *N*-(9-phenylfluoren-9-yl) α-amino ketones were prepared by reaction of the *N*-Pf-alanine-derived oxazolidinone with organolithium reagents. α-Amino ketones thus obtained could be stereoselectively reduced to the corresponding *syn* or *anti* β-amino alcohols depending upon the nature of the reducing agent. Copyright © 1996 Elsevier Science Ltd

Enantiomerically pure *N*-protected α-amino ketones[1] and β-amino alcohols[2] are of great importance in natural product synthesis and pharmacological research. α-Amino acids have been employed as precursors of α-amino carbonyl compounds[3] mainly by adapting conventional methodologies for the conversion of carboxylic acid derivatives into ketones: *N*-acyl (acetyl, benzoyl, ethoxycarbonyl, and bencenesulfonyl) amino acids have been converted into the corresponding ketones in good yields by reaction with organolithium reagents;[4] alternatively, carboxyl-activated α–amino acid derivatives (acid chlorides,[4d] thiopyridyl esters,[5] and *N*-methoxy-*N*-methylamides)[6] afforded the corresponding ketones when treated with organolithium or Grignard reagents. We report herein that an *N*-(9-phenylfluoren-9-yl) (Pf) amino acid ester (actually an oxazolidinone) behaves as an excellent aminoacylating agent towards organolithium reagents, giving rise to enantiomerically pure *N*-Pf-amino ketones in excellent yields. Our approach is shown in the Scheme:



1 2 3 4

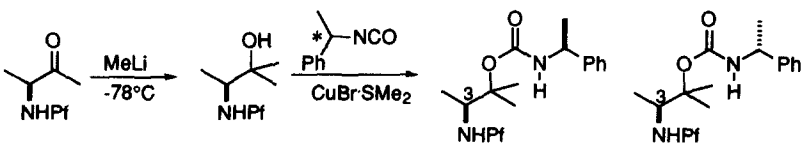
Table 1

	RLi	Product	Yield (%)
1.	MeLi	**4a**, R = Me	92
2.	MeLi (0°C)	**4a**, R = Me	72
3.	*n*-BuLi	**4b**, R = *n*-Bu	90
4.	*t*-BuLi	**4c**, R = *t*-BuLi	94
5.	PhLi	**4d**, R =Ph	94

Thus when oxazolidinone **2**, prepared by reaction of *N*-(9-phenylfluoren-9-yl)-L-alanine (**1**)[7] with excess aqueous formaldehyde and catalytic *p*-TsOH,[8,9,10] was reacted with several organolithium reagents at -78°C, *N*-Pf-amino ketones **4**[10] were obtained in excellent yields (Table 1).[11] Careful NMR analysis of the crude reaction mixtures showed them to be devoid of the corresponding tertiary alcohols, which would have resulted from overaddition of the nucleophile to the carboxy group. The key to the success of this unusual transformation rests on the extremely high stability of the reaction intermediates **3**. We believe that the Pf group plays a significant role in the stabilization of intermediate **3**, since reaction of the Cbz-protected analogue of oxazolidinone **2** with MeLi gave a complex mixture of compounds where no amino ketone could be detected. A tribute to the stability of **3** can be seen from entry 2 of Table 1: the addition of MeLi can be carried out even at 0°C with only some sacrifice in the yield (no tertiary alcohol was detected in the crude reaction mixture).

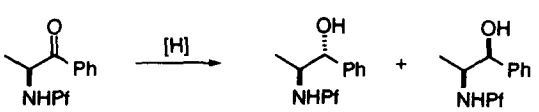
We attribute the beneficial effect of the Pf group to its ability to act as a ligand of the Li^+ in **3** through a cation-π interaction.[12] In fact, MNDO calculations on **3** (R=Me, monomeric species, Li^+ coordinated to two molecules of THF) showed that its most stable conformation places the Li^+ snugly within the fluorenyl π-cloud.[13]

A key point in the preparation of amino ketones from amino acids is the question of the enantiomeric purity of the products. We determined the enantiomeric purity of amino ketone **4a** obtained by treatment of **2** with MeLi at 0°C for 10 min. Thus, treatment of alcohol **5**, obtained in 62 % yield by reaction of **4a** with MeLi at -78°C, with (*R*) and (*S*)-phenylethyl isocyanate gave the corresponding diastereomeric carbamates **6a**[10] and **6b**.[10] ^1H NMR analysis of mixtures of **6a** and **6b** showed that their ratios of diastereomers (dr) were > 99:1; thus, the ratio of enantiomers (er) in **5** and **4a** must be > 99:1.[14]



4a **5** **6a** **6b**

We next studied the stereoselective reduction of α-amino ketones **4** to β-amino alcohols. For this purpose phenyl ketone **4d** was chosen as the substrate since it should provide the ephedrine-type systems **7a,b** (Table 2).



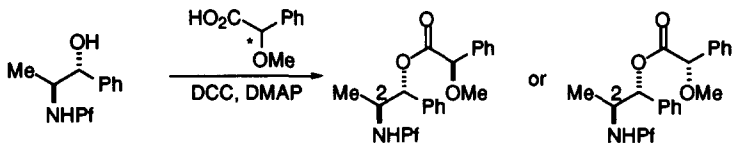
4d **7a** **7b**

Table 2

[H]	Solvent	Ratio
L-Selectride®	Toluene	1 : 18
BH_3·SMe	THF	16 : 1

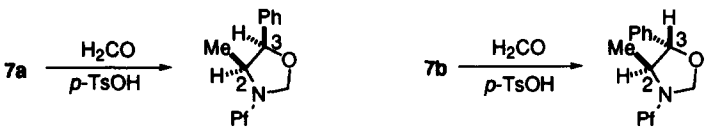
After careful optimization of the reaction conditions (reducing agent, solvent and reaction temperature) we found that **4d** could be stereoselectively reduced to give either **7a**[10] or **7b**[10] quantitatively (Table 2).

The configuration of the newly created stereocentre in alcohol **7a** was determined by reaction of **7a** with (*R*) and (*S*)-methoxyphenylacetic acids (CH_2Cl_2 DCC, DMAP).[15] Thus, esters **8a**[10] and **8b**[10] were obtained in 94% and 92% yields, respectively. Upfield displacements of the H2 and the methyl group hydrogens ^1H NMR signals were observed for carbamate **8a** with respect to those shown by **8b**, which allowed us to assign an *R* configuration based upon the model proposed by Trost for the establishment of the absolute configuration of secondary alcohols.[15]



7a **8a** **8b**

To further secure these assignments oxazolidines **9a,b** were prepared. Treatment of alcohols **7a** and **7b** with aqueous formaldehyde and catalytic *p*-TsOH in THF afforded **9a**[10] and **9b**[10] (92% and 96% yield, respectively). **9a** showed a strong nOe between H2 and H3 while **9b** did not show an nOe between H2 and H3, confirming the previous assignments.



9a **9b**

We have, thus, developed an efficient, enantiospecific preparation of protected α-amino ketones from *N*-Pf-amino acid-derived oxazolidinones, and have shown that they can be stereodivergently reduced to the corresponding β-amino alcohols. Extension of this methodology to oxazolidinones derived from more highly functionalized amino acids is currently being investigated and will be reported in due course.

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References and notes

1. (a) Fisher, L. E.; Muchowski, J. M. *Org. Prep. Proced. Int.* **1990**, *22*, 399-484. (b) Pace, R. D.; Kabalka, G. W. *J. Org. Chem.* **1995**, *60*, 4838-4844.
2. Tramontini, M. *Synthesis* **1982**, 605-644.
3. Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1531-1546.
4. (a) Klix, R. C.; Chamberlin, S. A.; Bhatia, A. V.; Davis, D. A.; Hayes, T. K.; Rojas, F. G.; Koops, R. W. *Tetrahedron Lett.* **1995**, *36*, 1791-1794. (b) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1866-1875. (c) Knudsen, C. G.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 2260-2266. (d) Buckley III, T. F.; Rapoport, H. *J. Am. Chem. Soc.* **1981**, *103*, 6157-6163.
5. Jennings-White, C.; Almquist, R. G. *Tetrahedron Lett.* **1982**, *23*, 2533-2534.

6. (a) Reetz, M. T.; Drewes, M. W.; Lennick, K.; Schmitz, A.; Holdgrün, X. *Tetrahedron: Asymmetry* **1990**, *1*, 375-378. (b) Dufour, M. N.; Jouin, P.; Poncet, J.; Pantaloni, A.; Castro, B. *J. Chem. Soc., Perkin Trans I* **1986**, 1895-1899. (c) Hamby, J. M.; Hodges, J. C. *Heterocycles* **1993**, *35*, 843-850.
7. Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236-239.
8. Paleo, M. R.; Castedo, L.; Domínguez, D. *J. Org. Chem.* **1993**, *58*, 2763-2767.
9. Preparation of **2**: to a stirred solution of **1** (1.0 g, 3.0 mmol) in THF (25 ml) was added aqueous formaldehyde (26%, 7.0 mL, 60 mmol) and *p*-TsOH (60 mg, 0.3 mmol), and stirred at rt, under Ar, for 24 h. The reaction mixture was then partitioned between Et_2O and sat $NaHCO_3$, the organic layer was washed with H_2O and brine, dried (Na_2SO_4) and concentrated. The product was not stable under chromatographic conditions, and, thus, the residue was recrystallised from CH_2Cl_2-hexanes to give **2** as white crystals (975 mg, 94% yield): mp 179-180°C (CH_2Cl_2-hexanes); ^1H NMR δ 1.25 (d, 3H, *J*= 7.3 Hz), 3.12 (q, 1H, *J*= 7.3 Hz), 5.11 (d, 1H, *J*= 7.5 Hz), 5.23 (d, 1H, *J*= 7.5 Hz), 7.23-7.46 (m, 11H), 7.69 (m, 2H); ^{13}C NMR δ 16.4, 54.7, 77.1, 82.8, 120.3, 125.5, 125.8, 127.0, 127.9, 128.2, 128.4, 128.8, 129.1, 129.4, 140.0, 141.1, 142.5, 145.9, 147.1, 177.6; IR 1780 cm^{-1}; $[\alpha]^{20}_D$= -92° (c 1.0, $CHCl_3$). Anal. Calcd. for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found: C, 80.78; H, 6.00; N, 4.23.
10. All new compounds showed the expected spectral properties and gave satisfactory elemental analyses.
11. Typical procedure for the formation of α-amino ketones. Preparation of **4a**: a solution of **2** (150 mg, 0.44 mmol) in THF (10 mL) was cooled to -78°C and treated with MeLi (1.6 M in Et_2O, 0.66 mmol, 410μL). After stirring for 2 h at -78°C, the reaction mixture was quenched by addition of HCO_2Et (55μL, 0.68 mmol), stirred for 5 min; AcOH (200 μL, 3.5 mmol) was then added. The cooling bath was removed and the reaction mixture was further stirred for 14 h, partitioned between sat $NaHCO_3$ and EtOAc (20 mL); the organic layer was washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (SiO_2, CH_2Cl_2: hexanes, 2:1) to give **4a** as a white solid (133 mg, 92% yield): mp 117-118°C (CH_2Cl_2-hexanes); ^1H NMR δ 0.98 (d, 3H, *J*= 7.1 Hz), 1.62 (s, 3H), 2.70 (q, 1H, *J*=7.1 Hz), 3.4 (bs, 1H), 7.10-7.43 (m, 11H), 7.67 (bd, 2H, *J*= 7.2 Hz); ^{13}C NMR δ 20.5, 26.7, 57.5, 73.2, 119.7, 119.9, 125.4, 126.2, 126.3, 127.2, 127.8, 128.0, 128.3, 140.2, 141.0, 144.7, 149.8, 150.1, 212.0; IR 1710 cm^{-1}; $[\alpha]^{20}_D$=-200° (c 1.0, $CHCl_3$). Anal. Calcd. for $C_{23}H_{21}NO$: C, 84.37; H, 6.46; N, 4.28. Found: C, 84.31; H, 6.86; N, 4.40.
12. (a) Kumpf, R. A.; Dougherty, D. A. *Science* **1993**, *261*, 1708-1710. (b) Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934-946.
13. The intramolecular acylation of *N*-Pf-*o*-lithiophenylalanine-derived oxazolidinones to give *N*-Pf-amino indanones has been reported.[8] In this case extremely low temperatures (-90°C) and strict stoeichiometric control had to be employed to avoid overaddition of the organolithium reagent (used to generate the *o*-lithiophenylalanine) to the carboxyl group. MNDO calculations on these system showed that the Li^+ in the corresponding intermediates cannot bind to the fluorenyl ring of the Pf group.
14. A 99:1 mixture of **6a**:**6b** showed two signals clearly distinguishable for H3. The spectra of crude **6a** or **6b** showed only one signal for H3.
15. (a) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370-2374.

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