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Stereoselectivity of the Reactions of N-Phthaloyl Iminium Ions and Amino-Substituted Radicals Derived from Threonine

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Abstract: Reactions of phthalimido-substituted radicals of type **B** and iminium ions of type **C** have been investigated. Similar stereoselectivities were observed in both cases and explained by a model based on minimization of allylic 1,3-strain. The first intermolecular radical addition to the a β -substituted dehydroamino acid is reported. Copyright © 1996 Published by Elsevier Science Ltd

Recent studies on the stereochemical outcome of radical reactions have demonstrated that the models previously developed for ionic reactions can be applied to this class of reactions.¹ For instance, parallels between carbonyl substituted radicals and enolates² as well as oxygen-substituted radicals and ketones or aldehydes³ have been scrutinized towards to 1,2-asymmetric induction. Recently we have demonstrated that dialkylamino-substituted radicals react stereoselectively following the allylic strain model^{4,5} (Figure 1, **A**) as previously proposed for the reduction of imines and iminium salts.⁶

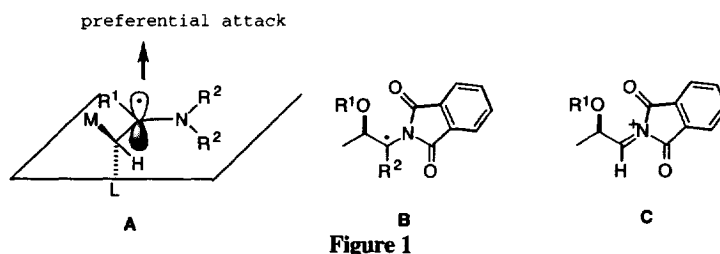
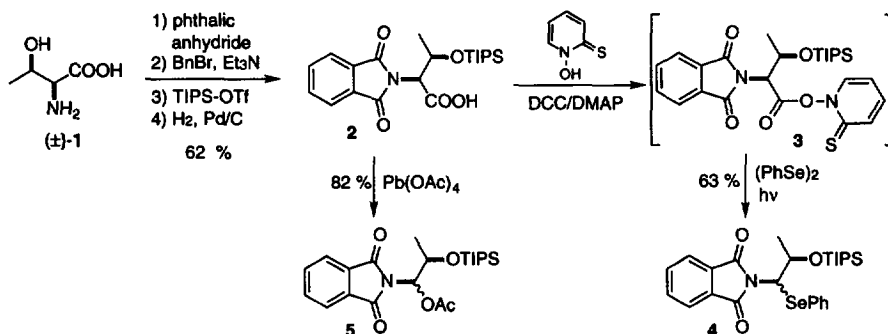


Figure 1

This report describes our efforts in the area comparing phthaloylated radicals^{7,8} of type **B** and iminium ions of type **C** derived from (\pm)-threonine.

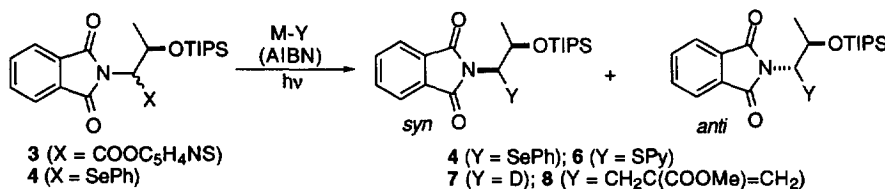
Preparation of radical and iminium ion precursors. The N-phthaloylated O-silylated carboxylic acid **2** was prepared in 4 steps (62 % overall yield) from (\pm)-threonine **1** according to Scheme 1. Treatment of **2** with 1-hydroxy-2-thiopyridone/DCC/DMAP gave the Barton ester **3**.⁹ This compound was immediately used for radical reactions without purification. Sun lamp irradiation of **3** in the presence of diphenyldiselenide gave the N,Se-acetal **4** which is a convenient and stable radical precursor. The N,O-acetal **5** was prepared by oxidative decarboxylation of **2** with lead tetraacetate and used as starting material for the generation of phthalyliminium ions.



Scheme 1

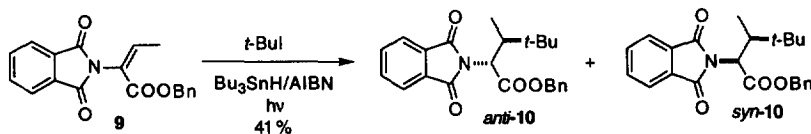
Radical reactions (Table 1). Irradiation of **3** with a 300 W sun lamp gave the pyridylthio derivative **6** as a 3.7:1 *syn/anti* mixture of isomers (entry 1). In the presence of $(\text{PhSe})_2$, the N,Se-acetal **4** was formed in a *syn/anti* 2.3:1 ratio (entry 2). Deuteration of **4** with $\text{Bu}_3\text{SnD/AIBN}$ gave **7** as a 5.6:1 mixture of isomers (entry 3).^{8,10} Surprisingly, the allylation reaction with methyl 2-[(tributylstannyl)methyl]propenoate (entry 4) gave **8** with lower selectivity (*syn/anti* 1.6:1).¹¹

Table 1. Radical reactions



Entry	Precursor	Radical trap (M-Y)	Product	Yield %	<i>syn/anti</i>
1	3	-	6	65	3.7:1
2	3	$(\text{PhSe})_2$	4	63	2.3:1
3	4	Bu_3SnD	7	73	5.6:1
4	4	$\text{CH}_2=\text{C}(\text{COOMe})\text{CH}_2\text{SnBu}_3$	8	84	1.6:1

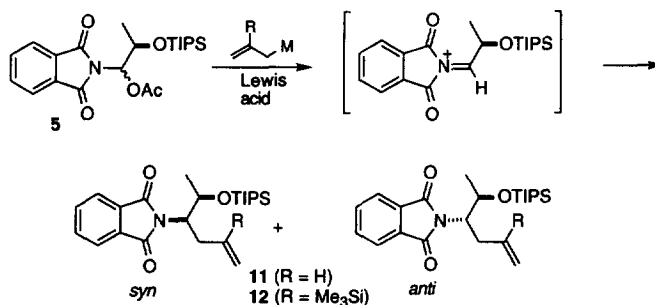
Addition of *t*-butyl radical to the dehydroamino acid derivative **9** gave **10** in 41 % yield as a *anti/syn* 2.3:1 mixture of isomers (Scheme 2).¹² This reaction represents to our knowledge the first example of intermolecular radical addition to a β -substituted dehydroamino acid.¹³ The strong electron-demanding character of the phthaloyl group counterbalances the deactivating effects of the amino moiety and of the β -methyl substituent.



Scheme 2

Reactions of phthaloyl iminium ions (Table 2). Different Lewis acids were tested for the reaction of the N,O-acetal **5** with allyltrimethylsilane (entries 1-3). A large excess of $\text{BF}_3 \cdot \text{OEt}_2$ (5 equiv.) in refluxing chloroform was necessary to run the reaction. TMS-triflate (2.1 equiv.) in refluxing dichloromethane gave also the desired compound **11** (50 %) but EtAlCl_2 (2 equiv.) was the most efficient Lewis acid for this reaction (74 %; -78°C to r.t.).¹⁴ The stereoselectivity is not influenced by the nature of the Lewis acid and the *syn* isomer is formed preferentially (*syn/anti* 8.0:1). However, the nature of the nucleophile was important. Reaction with a trimethylsilyl substituted propenylstannane (entry 4) gave **12** with lower selectivity (*syn/anti* 2.5:1).

Table 2. Iminium ion reactions



Entry	R	M	Product	Temp. [$^\circ\text{C}$]	Yield %	<i>syn/anti</i>
1	H	SiMe ₃	11	61	67	8.0:1
2	H	SiMe ₃	11	40	50	8.0:1
3	H	SiMe ₃	11	$-78 - \text{r. t.}$	74	8.0:1
4	SiMe ₃	SnBu ₃	12	$-78 - \text{r. t.}$	60	2.5:1

Discussion. The selectivities observed in radical and ionic reactions can be rationalized by considering the ground state conformation of the reactive intermediates. As expected from our work⁴ as well as Giese's work,⁷ the radical **D** lies in the conformation depicted in Figure 2, which is controlled by allylic 1,3-strain interactions. The iminium ion **E** possess a very similar minimum energy conformation which minimizes allylic 1,3-strain effects (in both cases, the N-C bond possesses a partial double bond character). Reaction from the less hindered face, *anti* to the bulky OTIPS, produces the major diastereoisomer. The stereoselectivity observed in the radical addition to the dehydroamino acid derivative **9** can be explained by the model **F**. Interestingly, this model minimizes the allylic 1,3-strain with the phthalimido function and not the allylic strain with the ester group.

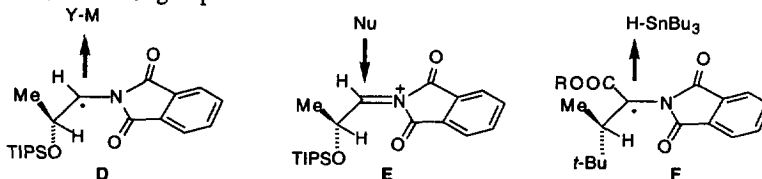


Figure 2

The difference of selectivity between the radical deuteration and allylation is not clear at the moment and may be attributed to stereoelectronic effects.

In conclusion, we have demonstrated that the phthaloyl group is a useful protective group for amino substituted radicals and iminium ions. It allows a good control of the stereoselectivity with highly predictable stereochemistry based on the allylic strain model.

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- A degassed solution of **4** (258 mg, 0.50 mmol), Bu₃SnD (292 mg, 1.00 mmol) and AIBN (16 mg) in benzene (4 ml) was irradiated for 12 h at 10 °C under N₂. After evaporation of the solvent, the residue was dissolved in CH₂Cl₂ and treated for 1 h at r.t. with sat. aq. KF. The organic phase was dried (MgSO₄), evaporated and the residue purified by flash chromatography to give **7** (132 mg, 73 %). ¹H-NMR (360 MHz, CDCl₃): 7.86-7.69 (m, 4H); 4.32 (quint, 1H, J = 6.1); 3.74 (d, 1H, J = 6.1, major isomer); 3.60 (d, 1H, J = 7.0, minor isomer); 1.20 (d, 1H, J = 6.1); 1.05 (s, 21H).
- The relative configurations of **4**, **6-8**, **11-12** have been deduced from the coupling constant in ¹H-NMR spectra and proved by chemical correlation. Further details will be published in a forthcoming full paper.
- We attributed the *anti* configuration to the major isomer of **10** by comparison of its ¹H- and ¹³C-NMR spectra with the data reported in reference 7a.
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- A solution of **5** (210 mg, 0.50 mmol) and allyltrimethylsilane (0.24 ml, 1.50 mmol) in CH₂Cl₂ (2 ml) was treated under N₂ with 1 M EtAlCl₂ in hexane (1.0 ml, 1.0 mmol) at -78 °C. The reaction mixture was allowed to warm to r.t. After 24 h, it was diluted with CH₂Cl₂, washed with 10 % Na₂CO₃ and water and dried (MgSO₄). Removal of the solvent and flash chromatography gave **11** (149 mg, 74 %). ¹H-NMR (360 MHz, CDCl₃, major isomer): 7.82-7.69 (m, 4H); 5.67 (m, 1H); 4.96 (dd, 1H, J = 17.1, 1.3); 4.87 (dm, 1H, J = 10.3); 4.58 (dq, 1H, J = 9.0, 6.1); 4.13 (td, 1H, J = 9.4, 5.9); 2.85 (m, 2H); 1.13 (d, 3H, J = 6.1), 1.08 (m, 21H).

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