Hydrogen-Bonding as a Stereocontrolling Element in Free-Radical *C*-Allylation Reactions: Vicinal, Proximal, and Remote Asymmetric Induction in the Amino Acid Series

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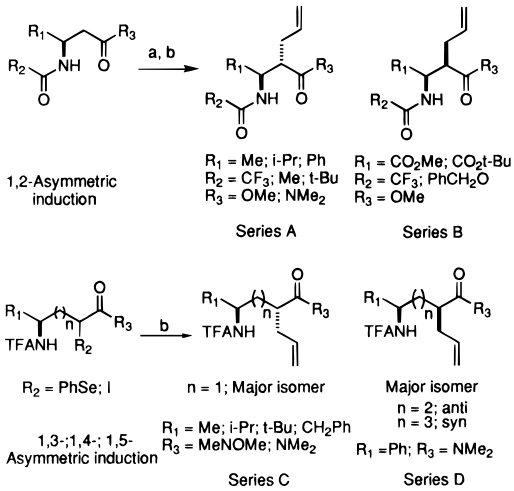
Stereocontrolled bond-forming reactions by free-radical processes in *acyclic* molecules are currently among the more challenging areas in asymmetric synthesis.[1] Recent advances in this area have generally focused on the utilization of derivatives of carboxylic acids with appropriate chiral auxiliaries[2] and on exploiting the presence of β-alkoxy substituents and other resident groups.[3] A model for the transition state in such reactions involving 1,2-asymmetric induction has been proposed by Hart and Krishnamurthy[4] and further elaborated upon by Curran and co-workers.[5] The general consensus is that, with few exceptions, the high diastereoselectivity is the result of a combination of minimized allylic 1,3-strain and torsional strain[6] and of stereoelectronic effects.[7,8] The notion that intramolecular H-bonding might play a role in the *C*-deuteration[9] and *C*-allylation[2d] of β-hydroxycarbalkoxy and amide α-radicals has been alluded to and experimentally tested with unrewarding[4] or inconclusive results.[5]

Continuing our studies[10] on the reactivity and stereochemical issues related to α-carbalkoxy radicals,[11] we report herein examples of remarkably high stereoselectivity in 1,2-induction[2,3] and unprecedented 1,3-, 1,4-,[12] and 1,5-asymmetric inductions in the free-radical *C*-allylation of α-acyl radicals derived from a series of *N*-substituted acyclic amino acid derivatives (Scheme 1),[13] *by exploiting intramolecular H-bonding as a stereocontrolling element.*

Scheme 1[a]



[a] Reaction conditions: (a) LDA, PhSeBr, THF, −78 °C; (b) allyltributylstannane, AIBN, *hν*, toluene or dichloromethane, −40 °C or −20 °C.

Treatment of the readily available α-selenophenyl or α-iodo esters or amides of β-N-substituted amino acid derivatives with allytributylstannane[14] led to a quasi exclusive formation of the *anti-C*-allyl derivatives, regardless of the nature of the β-alkyl (aryl) substituent tested so far (Scheme 1, series A; Table 1, entries 1−3).[15] Changing the β-substituent to a carbomethoxy group resulted in a complete reversal of selectivity, giving the *syn-C*-allylated product, while maintaining high stereoselectivity (Scheme 1, series B; Table 1, entries 4 and 5).[15]

Using DMSO instead of toluene as solvent resulted in an erosion or reversal of selectivity,[15] thus demonstrating the role of the polarity of the solvent[4] on the prevailing conformers in the transition state of these reactions and the dominant role that intramolecular H-bonding may play in controlling conformational mobility.

In an effort to study the influence of intramolecular H-bonding on the stereoselectivity of *C*-allylation, we extended the reaction to a series of γ-, δ-, and ω-amino acid derivatives (Scheme 1, series C, D). Unprecedented levels of proximal 1,3-induction were obtained with the *N*-trifluoroacetyl and *N*,*N*-dimethyl or *N*-methoxy-*N*-methyl amide derivatives (Table 1, entries 6−10). The selectivity was somewhat lower in the case where R_1 = Me and Ph (Table 1, entries 9 and 10). However, extending the distance between the electronically most favored hydrogen-bonding partners (*N*-TFA and $CONMe_2$) led to surprisingly good 1,4-*anti*- and 1,5-*syn* selectivity (Table 1, entries 11 and 12; Scheme 1, series D, n = 2, 3, respectively).

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(15) For details, see supporting information. *Anti*/*syn* designations refer to the relative orientations of substituents in an extended zig-zag chain.

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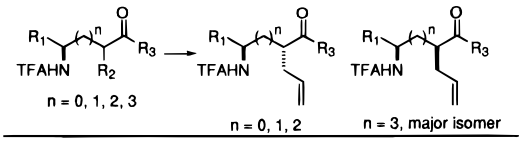
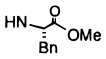
Table 1



entry	n	R_1	R_2	R_3	anti/syn[a]	yield(%)[b]
1	0	Me	SePh	OMe; NMe_2	>98:2[c]	90
2	0	i-Pr	SePh	OMe	>98:2[c]	79
3	0	Ph	SePh	OMe; NMe_2	>98:2[d,e,f]	76
4	0	CO_2Me	SePh	OMe	4:96[g]	74
5	0	CO_2Bu-t	SePh	OMe	5:95[h]	71
6	1	i-Pr	I	MeNOMe	88:12[i]	83
7	1	t-Bu	I	MeNOMe	89:11[i]	72
8	1	CH_2Ph	I	MeNOMe	87:13[j,k]	82
9	1	Ph	SePh	NMe_2	62:38[i]	97
10	1	Me	I	MeNOMe	75:25[i]	72
11	2	Ph	I	NMe_2	86:14[e,g]	79
12	3	Ph	I	NMe_2	26:74[e,g,k]	72
13	0	Me	SePh		>98:2[l]	96

[a] Ratio determined by ^{1}H NMR of the crude sample. Entries 3, 9, 11, and 12 correspond to racemic products. [b] Isolated yield. [c] Stereochemistry determined by analogy to entry 3, and by NOE studies of the corresponding *N*-Boc-pyrrolidine derivative after cyclization with $Hg(OAc)_2$; see ref 15. [d] Stereochemistry determined by converting into *N*-Piv product, which was proved by X-ray single crystal analysis. [e] Ratio determined by HPLC analysis. [f] Ratio for NMe_2 amide remained unchanged at 30 °C. [g] Stereochemistry correlated by chemical means; see ref 15. [h] The nitrogen atom was protected with Cbz instead of TFA. [i] Stereochemistry by analogy to the product in entry 8. [j] *Anti/syn* 86:14, 64% for *N*,*N*-dimethyl derivative. [k] X-ray single crystal analysis. [l] Reaction done at 0 °C.

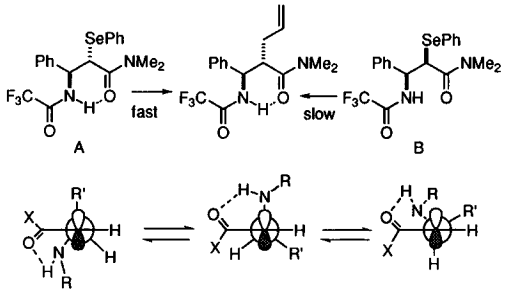
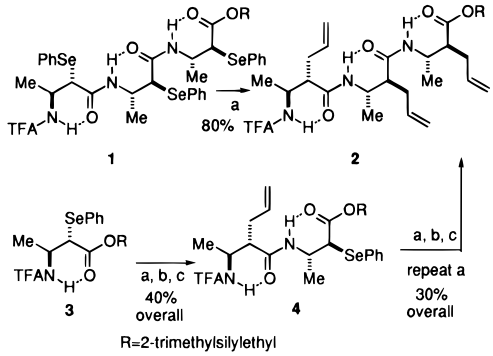


Figure 1. Proposed H-bonded radical intermediates favoring *anti* attack in 1,2-asymmetric induction (series A). Shaded lobe indicates preferred side of attack by allylstannane.

The quasi exclusive formation of *anti*-products in series A (1,2-induction) can be interpreted on the basis of the prevalence of ground state and transition state conformations, in which H-bonding plays a dominant role in favoring a pseudo six-membered ring. Interestingly, the (*2S*)-*anti* isomer **A** (Figure 1), with a distinctive FT-IR H-bonding band at 3293 cm^{-1},[16] reacted faster than the (*2R*)-*syn* isomer **B** (FT-IR 3410 cm^{-1}).

Finally, we demonstrate the versatility of the methodology

Scheme 2[a]



[a] Reaction conditions: (a) allyltributylstannane, AIBN, *hν*, toluene, −40 °C; (b) TBAF, THF; (c) peptide formation, PyBOP, *i*-Pr_2NEt, CH_3CN, with the corresponding amine salt (ref 15).

in iterative, and one-step, multiple *C*-allylation protocols leading to the tripeptide congener **2** (Scheme 2). Thus, *C*-allylation of the (*2S*)-tri-α-phenylseleno peptide derivative **1** gave a major product **2**, whose structure and stereochemistry was confirmed by an independent stepwise synthesis via amide coupling of enantiopure *C*-allyl precursors. Alternatively, *C*-allylation of **3**, amide formation, and iteration of the process on the α-phenylseleno dipeptide ester **4** also gave **2** (Scheme 2).[15,17,18]

We have shown that H-bonding can be a strong stereocontrolling element in the free-radical *C*-allylation of a variety of acyclic amino acid derivatives. The diastereomerically pure or enriched products are versatile chirons for further manipulations[19] and for the design of unnatural oligomeric amino acid motifs with potentially interesting three-dimensional arrays.[20] Results pertaining to these and related studies will be communicated in due course.

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Supporting Information Available: Physical constants, chemical correlations, experimental procedures, NMR and FT-IR spectra, and HPLC and X-ray analyses for the compounds described herein (36 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and internet access instructions.

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