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1,2-Asymmetric Induction in Radical Reactions. Deuteration and Allylation Reactions of β-Oxy-*o*-Iodoanilides.

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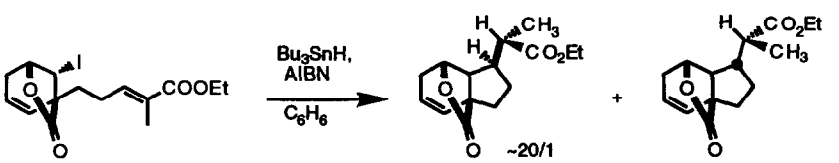
Summary: Chiral radicals were generated by radical translocation reactions of β-oxy-o-iodoanilides and their asymmetric deuteration and allylation reactions were studied.

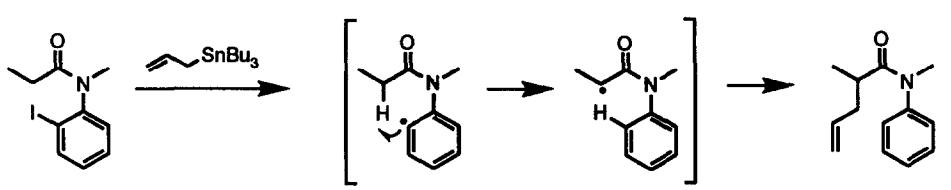
Introduction: The maturation of radicals as synthetic intermediates is being driven by their use in increasingly complex, yet selective, transformations.[2] Two rapidly moving areas that are contributing to this maturation are the control of acyclic stereochemistry[3] and the indirect use of carbon-hydrogen bonds as radical precursors (a common type of radical translocation).[4] Several years ago, Hart and Huang reported an example of a stereoselective intermolecular hydrogen transfer to an α-ester substituted radical (eq 1).[5a] In a subsequent key full paper,[5b] Hart and coworkers proposed and supported a simple, yet powerful stereochemical model for 1,2-asymmetric induction based on A-strain. At about the same time as this full paper, we observed that certain benzyl-substituted radicals also gave good 1,2-asymmetric induction in typical atom transfer reactions.[6] The promise of developing synthetically useful methods to control acyclic stereochemistry held out by these results encouraged us to undertake more detailed studies on 1,2-asymmetric induction.

eq 1



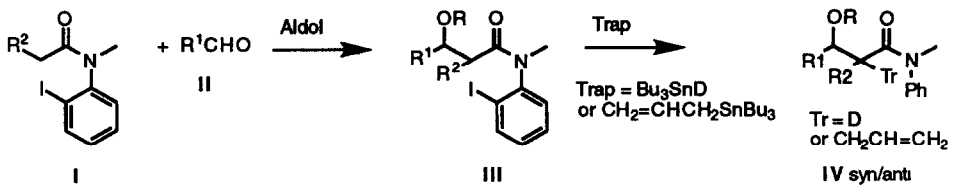
We have recently introduced *o*-iodoanilides as substrates for the generation of radicals α to carbonyl groups, and a typical example is shown in eq 2.[7] A rapid 1,5-hydrogen transfer reaction translocates the radical from the aryl ring to the carbon α to the amide. Because the lifetimes of aryl radicals are probably short compared to amide bond rotation,[8] we are fortunate that *o*-iodoanilides exist primarily (≥95%) in the CO/Ar anti rotamer. In effect, this translocation method permits the indirect use of a C–H bond adjacent to a carbonyl as a radical precursor for typical C–C bond forming reactions.

eq 2



In this paper, we describe in detail the results that we have obtained by using radical translocation reactions of *o*-iodoanilides to generate chiral radicals. The basic approach is outlined in eq 3. Aldol reaction of *o*-iodoanilide **I** and aldehyde **II** provides β-hydroxy anilide adduct **III**. Subsequent radical reduction or allylation (with or without prior functionalization of the hydroxy group) provides **IV**. In combining translocation and 1,2-induction, our goals were threefold: 1) to develop a better understanding of the factors that control rate and selectivity of hydrogen transfer from C–H bonds to carbon-centered radicals, 2) to develop a better understanding of the factors that control 1,2-asymmetric induction reactions of chiral radicals adjacent to carbonyls, and 3) to develop synthetically useful methods to prepare aldol adducts where the syn/anti stereochemistry is controlled not in the aldol reaction but in a subsequent radical reaction.

eq 3

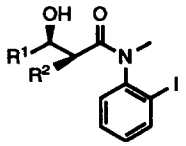


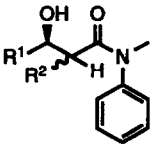
The possibilities for 1,2-asymmetric induction with β-oxy carbonyl (and related) radicals did not escape other groups, and a flurry of important contributions have come from Guindon,[9] Giese,[10] Hart,[11] and others.[12,13] In the following paper, we present additional studies with simple β-oxy ester radicals that grew out of our work with β-oxy anilides.[14] Taken together, these studies now provide a large body of experimental evidence on 1,2-asymmetric induction of carbonyl-substituted radicals, and there is no shortage of models to explain the results. However, a number of trends emerging from both our work and Hart's[5] are not readily explained by existing models. We will briefly discuss the impact of our results on transition state models in both this and the subsequent paper. The most important conclusion from this work is that both the substituents on the radical and the nature of the trapping reagent can have dramatic effects on the rates of trapping reactions. This means that existing models based heavily on ground state conformations of radicals could be inadequate.

Results: We prepared hydroxy precursors (**1a, 5a, 9a, 11a**) and products (**2aH, 6aH, 7a, 10aH, 12aH**) by standard aldol reactions of the lithium amide enolate of a substituted *o*-iodoanilide with an aldehyde (eq 3). Figure 1 summarizes the yields and anti/syn selectivities (where appropriate). Interestingly, the aldol reactions of *o*-iodoanilides gave only *syn* β-hydroxy anilides, whereas the unsubstituted anilides gave anti/syn mixtures (~1/3). All of the *o*-iodoanilides exist as pairs of diastereomers on the NMR time scale due to the axial chirality imposed by the *o*-iodoaryl group. Such axial chirality induced by twisting about the N–Ar bond is well known.[15] Rotation of the N–Ar bond is fast at ambient temperature, so we always observe equilibrium mixtures in ratios not far from 50/50. Other radical precursors and authentic samples of products (see Table 1) were prepared by standard silylation or acylation reactions of the aldol adducts.

We assigned the anti and syn protons in 2°-systems (R^2 = H) by the vicinal coupling constants ($J_{2,3}$ anti > $J_{2,3}$ syn).[16] This provides configurational assignments for the deuterated products. We were more concerned about unambiguous assignments of the 3°-precursors and (especially) products ($R^2 \neq$ H).

Figure 1. Precursors (left) and Authentic Products (right)





Precursor	R^1	R^2	Yield[a] (rotamer ratio)	Product	R^1	R^2	Yield (anti/syn)
1a	CH_3	H	98% (50/50)	**2aH**	CH_3	H	32%
5a	*t*-Bu	H	96% (60/40)	**6aH**	*t*-Bu	H	89%
				7a	*t*-Bu	C_3H_5	48%(25/75)
9a	CH_3	CH_3	69% (55/45)	**10aH**	CH_3	CH_3	57% (39/61)
11a	*t*-Bu	CH_3	94% (64/36)	**12aH**	*t*-Bu	CH_3	87% (17/83)

a) only syn diastereomers detected

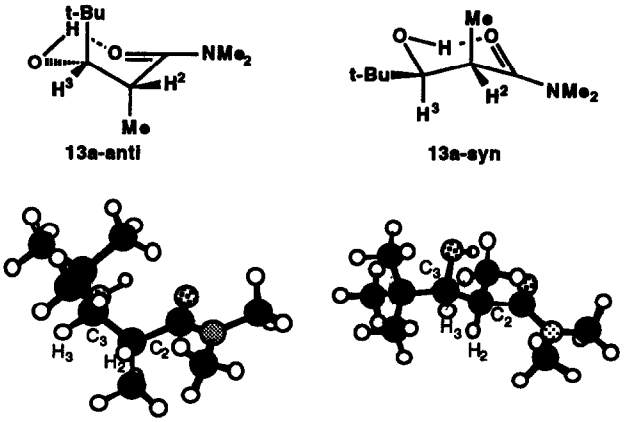
Vicinal coupling constants are no longer useful in such systems when R^1 = *t*-Bu ($J_{2,3}$ < 2 Hz for both isomers). Amide enolates are expected to have a Z geometry, and Z-enolates are expected to produce predominantly syn aldols.[16] This provides circumstantial evidence for the indicated anti/syn assignments. Further support for the assignment comes from trends[16] in the ^{13}C NMR spectra.

In the case of products **7a-anti/7a-syn**, a detailed conformational analysis secured the structure assignments. The key to this analysis was the observation that the *hydroxy* proton of **7a-anti** was a sharp downfield doublet (δ = 5.53) with an unusually large vicinal coupling constant for a proton bonded to oxygen (J = 9.0 Hz). In contrast, the hydroxy proton of **7a-syn** usually appeared as a broad, more upfield singlet (δ = 3.6–4.2), typical of rapid exchange. These data suggest that **7a-anti** has a much stronger intramolecular hydrogen bond than **7a-syn**, and that the HC–OH dihedral angle in this hydrogen bonded conformation is close to 180°.

These observations were nicely rationalized by MM2 calculations executed on a CAChe™ workstation.[17] Model compounds **13a-anti/syn** were selected to simplify the calculations by replacing the allyl and phenyl groups with methyl groups (Figure 2). This permitted a complete search of the conformational space of both molecules. The calculated global minima of **13a-anti/syn** shown in Figure 2 are in good accord with the spectra of **7a-anti/syn**. Consistent with the small coupling constants $J_{2,3}$, each isomer has an HC(2)—C(3)H dihedral angle of about 68°. The anti isomer exists in a distorted chair with "axial-like" *t*-butyl and methyl groups; however, there are no 1,3-diaxial interactions. Consistent with the large J_{CHOH}, the HC—OH angle is almost 180°. Consistent with a strong hydrogen bond, the hydroxy proton points directly towards the carbonyl group. The syn isomer also exists in a distorted chair with an axial-like methyl group and a equatorial-like *t*-butyl group. The HC–OH angle is calculated to be 38°. The weaker intramolecular hydrogen bond is caused by the gauche interaction between the methyl and the *t*-butyl group. Rotation of the C2–C3 bond to relieve this interaction pulls the hydroxy group up and away from the carbonyl group.

We selected the simple isopentyl-*o*-iodoanilide **14** shown in eq 4 as an achiral model to evaluate the planned 1,5-hydrogen transfer reactions. Reduction of **14** with tributyltin deuteride worked well, though we consistently had to add excess tin deuteride to obtain rapid, complete conversions. At concentrations

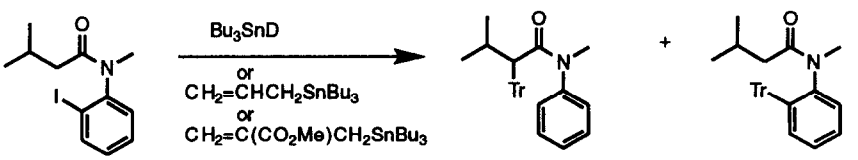
Figure 2. MM2 Minimized Conformations of **13a-anti** and **13a-syn**



Dihedral angle	Calculated angle for **13a-anti**	Observed *J* for **7a-anti**	Calculated angle for **13a-syn**	Observed *J* for **7a-syn**
HC(2)–C(3)H	67°	1.6 Hz	68°	1.6 Hz
HC(3)–OH	177°	9.0 Hz	38°	broad singlet

ranging from 0.01M to 0.1M, we detected only **15a** with the deuterium label adjacent to the carbonyl. At 1.0 M we were able to detect a small amount of label on the aromatic ring (**15a/15b** = 82/18). From these results, we can estimate that the rate constant for 1,5-hydrogen transfer is $> 5 \times 10^8\ s^{-1}$. We were initially surprised to discover that allylation of **14** was inefficient. Heating of **14** and allylstannane under Keck's standard thermal conditions[18] resulted in very slow conversion. Even after 24 h, most of **14** remained unreacted, and only traces of **16** had formed. This failure was a harbinger of problems in allylations. We later obtained evidence that the failed allylations were caused by dramatically reduced rates of the radical addition step (see below). Keck's standard photochemical conditions[18] were more efficient; after 2 d of photolysis, **14** was consumed and we isolated **16** in 57% yield. In the hopes that these amide-substituted radicals were ambiphilic,[19] we began to use 2-carbomethoxyallyl stannane[20] in place of allyl stannane. Reaction of **14** with this activated stannane was completed in 20 h, and we isolated **17** in 63% yield.

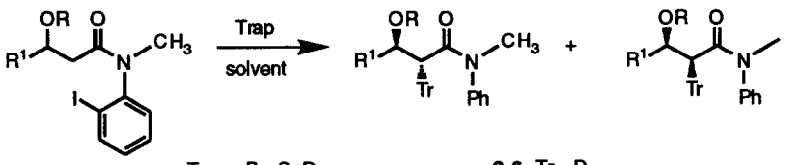
eq 4



Tables 1 (2°-systems) and 2 (3°-systems) summarize representative results of a large number of asymmetric radical reactions that we conducted. The *o*-iodoanilides were reacted with tributyltin deuteride, allyl stannane, or 2-carbomethoxyallyl stannane. Allylation reactions were conducted either without

solvent, or at 1M substrate concentration in benzene (Table 1, entries 5, 7, and 8). Reductions were conducted in benzene with 2 equiv Bu_3SnD. Initial substrate concentrations ranged from 0.5 M to neat. To probe for possible intramolecular hydrogen bonding, several reactions were conducted in DMSO and THF (entries 5, 7, 8); product ratios in these solvents did not vary significantly from benzene. Initiation was accomplished at 80°C with AIBN and at 25°C by photolysis with a Hanovia lamp. Deuterated product ratios were determined by integration of the ^1H-decoupled ^2H NMR spectra at 76 MHz and the ^1H NMR spectra at 300 MHz. For the ^2H NMR experiments, the spectrometer was unlocked and peaks are broad, so we estimate that there could be ±5% error in the deuterium ratios listed in the Tables. Allylation ratios were determined by GC or ^1H NMR integration, and isolated yields were obtained after flash chromatography.

Table 1. Reductions and Allylations of 2°-Radicals Derived From *o*-Iodo Anilides



Trap = Bu_3SnD
or $CH_2{=}CHCH_2SnBu_3$
or $CH_2{=}C(CO_2Me)CH_2SnBu_3$

2,6 Tr = D
3,7 Tr = $CH_2CH{=}CH_2$
4,8 Tr = $CH_2C(CO_2Me){=}CH_2$

Entry	Precursor (solvent)	R^1	R	Temp	anti/syn (deuteration, yield)	anti/syn (allylation, yield)
1	**1a** (C_6H_6)	CH_3	H	80°C	45/55 (**2a**, 100%)	anti-favored (**4a**)
2	**1c** (C_6H_6)	CH_3	Si(*t*-Bu)Me_2	80°C	77/23 (**2c**, 73%)	(**3c**, NR)
3	**1d** (C_6H_6)	CH_3	Si(*t*-Bu)Ph_2	80°C	80/20 (**2d**)	(**3d**, NR)
4	**1e** (C_6H_6)	CH_3	Ac	80°C	29/71 (**2e**, 89%)	25/75 (**4e**, 26%[a])
5	**5a** (C_6H_6)	*t*-Bu	H	80°C	85/15 (**6a**, 85%)	>90/<10 (**8a**, 61%)
				25°C	88/12 (**6a**, 72%)	93/7 (**7a**, 64%)
	5a (DMSO)			25°C	78/22 (**6a**)	—
	5a (THF)			25°C	82/17 (**6a**)	—
6	**5b** (C_6H_6)	*t*-Bu	$SiMe_3$	80°C	80/20 (**6b**, 44%)	—
7	**5c** (C_6H_6)	*t*-Bu	Si(*t*-Bu)Me_2	80°C	76/24 (**6c**, 40%)	(**7c**, NR)
				25°C	90/10 (**6c**)	—
	5c (DMSO)			25°C	89/11 (**6c**)	—
	5c (THF)			25°C	74/26 (**6c**)	—
8	**5e** (C_6H_6)	*t*-Bu	Ac	80°C	28/72 (**6e**)	13/87 (**7e**)
				80°C	—	20/80 (**8e**, 46%)
				25°C	17/83 (**6e**, 62%)	—
	5e (DMSO)			25°C	21/79 (**6e**)	—
	5e (THF)			25°C	24/76 (**6e**)	—
9	**5f** (C_6H_6)	*t*-Bu	$COCF_3$	80°C	50/50 (**6f**)	(**7b**, NR)

NR = no reaction. Footnotes to the Table: a) mixture of products, see eq 5.

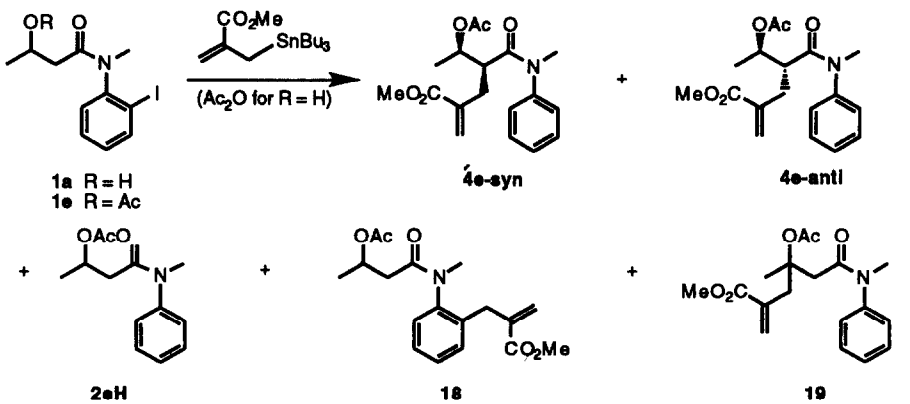
Depending on substituents, product ratios ranged from highly anti-selective through unselective to highly syn-selective. Selectivities at 25 °C were uniformly better than those at 80 °C. For the 2°-substrates (Table 1) bearing $R^1 = CH_3$, tin deuteride reductions were unselective for the free alcohol **1a** (entry

1),moderately syn-selective for the acetate **1e** (entry 4), and moderately anti-selective for the silyl ethers **1c** and **1d** (entries 2 and 3). For the silyl ethers, selectivity increased with the size of the substituents on silicon. Allylations with allyltributyl stannane were very sluggish with all these substrates, and stereoisomer ratios were not determined. Allylations with 2-carbomethoxyallyl stannane were not especially efficient or clean either (see below), but they went well enough so that some approximate anti/syn ratios could be determined. Like the tin deuteride experiments, allylation of the acetate **1e** was syn selective (entry 4). In contrast to the tin deuteride experiments, allylation of the alcohol **1a** was now anti-selective (entry 1) and the silyl ether **1d** did not react (entry 3).

For 2°-substrates bearing R^1 = *t*-Bu, tin deuteride reductions were now syn-selective for the acetate **5e** (entry 8), unselective for the trifluoroacetate **5f** (entry 9), and anti-selective for the alcohol **5a** (entry 5) and silyl ethers **5b** and **5c** (entries 6 and 7). Successful allylations were slow but reasonably clean, and they were syn-selective for the acetate **5e** (entry 8) and anti-selective for the alcohol **5a** (entry 5); the silyl ethers **5b** and **5c** could not be coaxed to undergo allylations with either reagent under any conditions.

We conducted preparative allylations of **1e** with 2-carbomethoxyallyl stannane (no solvent) to confirm our stereochemical assignments and to identify side products. Eq 5 shows the products that we isolated in a combined yield of only 26%. In addition to an inseparable mixture of **4e** (20/80, anti/syn, 54% of the products), we also isolated the reduced product **2eH** (35%, devoid of deuterium), the aromatic allylation product **18** (11%), and a trace of what we believe is the product of 1,6-hydrogen transfer **19**. We are not certain of the origin of the reduced product **2eH**. The presence of a significant amount of the aromatic allylation product **18** is undoubtedly due to the higher reactivity of 2-carbomethoxyallyl stannane relative to allyl stannane.[21] Though formed only in small amounts (<2% of the mixture), the isomer **19** provides the first example where 1,6-hydrogen transfer is competitive with 1,5-hydrogen transfer in these *o*-iodoanilides.

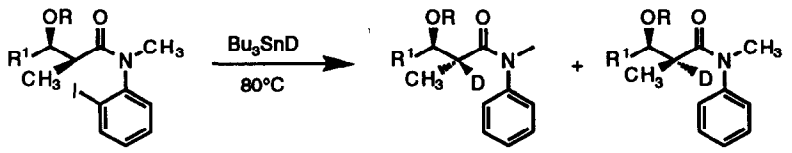
eq 5



With the pure products of eq 5 in hand, we conducted the reaction of **1a** with carbomethoxyallyl stannane, and then directly acetylated the crude product mixture. Analysis of the ^{1}H NMR spectrum of this mixture showed that the three major products were **4e-anti/2eH/18** in a ratio of 54/35/11. We could detect only traces of **4e-syn** and **19**. This experiment suggests that the allylation of the radical derived from **1a** is anti-selective; however, this allylation was again inefficient, and the isolated yields were not determined.

Table 2 lists the results of the reductions of 3°-radical precursors with tributyltin deuteride. These reductions were conducted at 80°C and 0.5 M for $R^1 = CH_3$ and without solvent for $R^1 = t$-Bu. Despite the high concentrations and temperatures, the reactions still required 2-4 d for completion. No reaction occurred at lower concentrations or temperatures, and none of these substrates reacted with allyl tributylstannane. Starting from syn precursors with $R^1 = CH_3$, the alcohol **9a** regenerates the syn product with modest selectivity (entry 1) while the methyl ether **9g** returns an anti/syn mixture (entry 2). Starting from syn precursors with $R^1 = t$-Bu, the alcohol **11a** and silyl ether **11c** regenerate predominately syn products (entries 3 and 4) whereas the acetate **11e** returns mostly the anti product (entry 5). Though substituent priorities reverse the "anti/syn" designations, the directions of the selectivities in Table 2 are the same as in Table 1. If anything, the 3°-radicals in Table 2 are marginally more selective than their 2°-analogs in Table 1.[5]

Table 2. Reductions of 3°-Radicals Derived from α-Iodoanilides



9,11 **10,12-anti** **10,12-syn**

Entry	Precursor (concentration)	R^1	R	Product	anti/syn[a]	Yield
1	**9a** (0.5M)	CH_3	H	**10a**	30/70	42%
2	**9g** (0.5 M)	CH_3	Me	**10g**	52/48	81%[b]
3	**11a** (Neat)	*t*-Bu	H	**12a**	15/85	70%
4	**11c** (Neat)	*t*-Bu	Si(*t*-Bu)Me_2	**12c**	<10/>90	ND
5	**11e** (Neat)	*t*-Bu	Ac	**12e**	80/20	47%

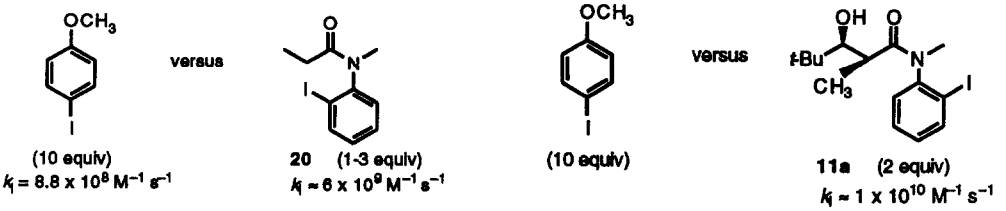
ND = not determined. [a]Ratio determined by ^1H NMR integration. ^2H NMR spectra showed <10% deuterium label on the aromatic ring. [b]Yield of an authentic sample prepared with Bu_3SnH.

The lack of reactivity of these substrates towards both tin deuteride and the allyl stannanes astounded us at first. There is a rough correlation between size and reactivity: as the radical becomes more crowded, it becomes more difficult (Bu_3SnD) or impossible (allyl stannane) to maintain chains. Within the 2°-series, the *t*-butyl substrates are less reactive than the methyl, and the substrates with large silyl groups are less reactive than the alcohols or acetates. The 3°-substrates are even less reactive than the 2°-ones. It is remarkable that the aryl iodides **11** in Table 2 require *several days* to be reduced in neat tributyltin deuteride at 80°C. These reactivity problems must be due to a slow rate in one of the chain propagation steps. But which one? Such tin-based chains consist of three propagation steps: 1) abstraction of iodine by tributyltin radical, 2) 1,5-hydrogen transfer, and 3) trapping by tin deuteride or allyl stannane. (The allyl stannane trapping is followed by an exceedingly rapid β-fragmentation.) 1,5-Hydrogen transfer is clearly not the culprit because it succeeds with reasonable efficiency even in neat tin deuteride. We estimate that $k_{1,5}$ is $\geq 10^8$ s^{-1}. This leaves iodine abstraction or trapping as the slow step.

We ruled out slow iodine abstraction by a series of competition experiments. We have recently estimated that tributyltin radical abstracts iodine from *p*-iodoanisole with $k_I = 8.8 \times 10^8$ M^{-1} s^{-1} at 80°C.[22] The reactions summarized in eq 6 were conducted by competing excess *p*-iodoanisole (10 equiv) and

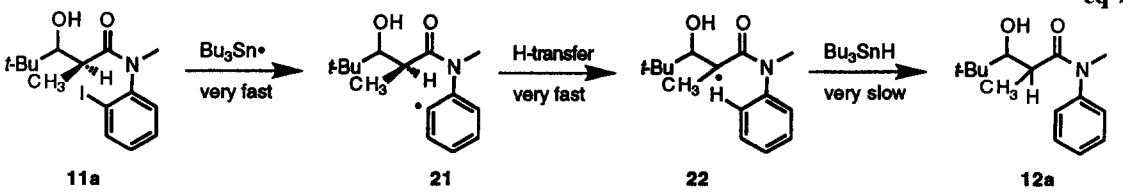
substrate **11a** or **20** (1-3 equiv) for limited Bu_3SnH (1 equiv). These experiments showed that both simple propionoyl *o*-iodoanilide **20** ($k_I \approx 6 \times 10^9$ $M^{-1}s^{-1}$) and one of the most recalcitrant substrates **11a** ($k_I \approx 1 \times 10^{10}$ $M^{-1}s^{-1}$) are significantly better iodine donors than *p*-iodoanisole.

eq 6



Eq 7 shows the steps for the tin hydride reduction of **11a**. The observations show that iodine abstraction (**11a** → **21**) and 1,5-hydrogen transfer (**21** → **22**) are very fast. By default, the bimolecular hydrogen transfer reaction between α-amide radical **22** and tin hydride must be slow. Slow trapping explains why allylations are more susceptible to failure than reductions: rate constants for radical allylations with allyl stannanes[22] are considerably lower than those for hydrogen (or deuterium) transfer reactions from tin hydride (or deuteride).

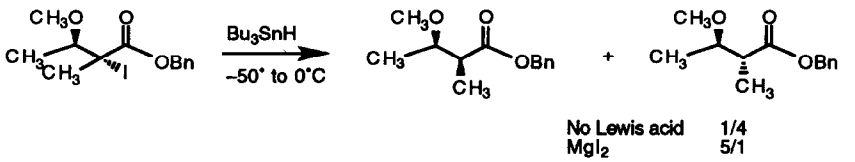
eq 7



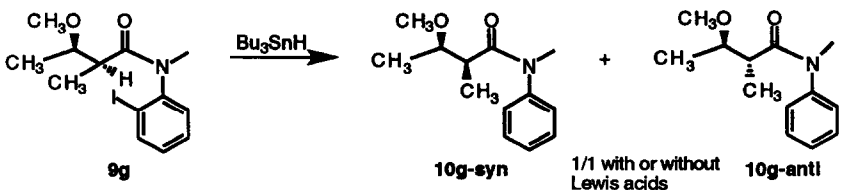
It is generally believed that typical tin hydride chains will begin to break when $k_H[SnH] \approx 10^2 - 10^3$ s^{-1}.[23] For substrate **11a**, short chains begin to propagate in the range of 1M to 5M (neat) tin hydride concentration. From these observations, we estimate that k_H for radical **22** must be $\leq 5 \times 10^3$ M^{-1} s^{-1}. This is an exceedingly low rate constant for hydrogen transfer from tin hydride. Indeed many workers tacitly assume that virtually all radicals react with tin hydride with rate constants of about 2×10^6 M^{-1} s^{-1}.[24] We discuss below the significance of this observation.

In an attempt to alter and improve the selectivities of these reactions, we conducted about a dozen experiments with **9g** in the presence of Lewis acids. Some of these experiments were modeled after the exciting report of Guindon and coworkers shown in eq 8a.[9c] Our reactions in eq 8b succeeded at 25°C or 80°C in the presence of a variety of Lewis acids like $ZnCl_2$, ZnI_2, and $MgCl_2$. The reduction of **9g** at 1.0 M in the absence of Lewis acid takes about 5 h and exhibits very little selectivity (Table 2, entry 2). In no case did the addition of a Lewis acid significantly accelerate the reaction or improve the selectivity.

eq 8a



eq 8b



Discussion: The preparative prospects of this method for 1,2-induction fall below our initial expectations. The most useful synthetic transformations are undoubtedly the allylations, but difficulties in chain propagation significantly restrict the generality of these reactions. In the 2°-series, deuterations of acetates can be used to provide syn (with large R^1 groups only) α-deuterio amides, where deuterations of silyl ethers provide anti (with large or small R^1 groups) α-deuterio amides. In the 3°-series, the reduction of the acetate suggests a method to invert the syn products of an aldol reaction into anti ones. The more general "syn selective" effect of the large silyl groups is not very useful in the 3°-series because the aldol reactions are already highly syn selective.

Despite the preparative shortcomings, our results add new colors to the growing mural of asymmetric induction in reactions of carbonyl-substituted radicals. With only a small basis set of examples, early models[3] painted a rather simple picture of 1,2-induction based on A-strain and the size of allylic substituents. These models were based heavily on considerations of favored ground state geometries of the radical. Recent results from Hart's group[5] and our own have smudged this simple picture. We will discuss more details of how our results impact on current models in the following paper.[14] Here we wish to emphasize the most important conclusion that we derive from these results: *models that are based largely on ground state minima of radicals and that ignore the interaction of the radical with the trap do not provide adequate rationalizations of the existing body of results in this field.* Realistic models must integrate the size and direction of approach of the trap and its effect on the rehybridization of the radical.

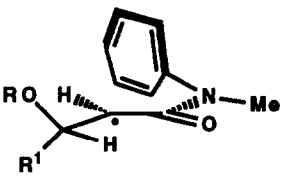
Our results in these amide systems indicate for the first time that 1,2-asymmetric induction in the reactions of such chiral radicals with achiral traps is caused by rate retardation. When stereoselection is observed, it is because the substituents adjacent to the radical retard trapping on one face of the radical more than the other.[25] Absence of selectivity may not be due to an absence of rate retardation, but instead may arise because reactions of both faces are retarded by about the same degree.

That selectivity arises from rate reductions is not surprising. An analogy can be drawn to kinetic studies of Porter[26] and Giese[10e] which show that stereoselection in the reactions of achiral radicals with chiral alkenes also arises from rate retardation. Our results suggest that this rate retardation can be very large: as much as 10^3 for reactions of these amide-substituted radicals with tributyltin hydride. Though effects in esters may not be as large as in these amides, the similarities in trends between amide and ester radicals[14] reinforce the notion that amide radicals are not unique.

Ground state minima of amide-substituted radicals can be predicted based on the theory of A-strain (see Figure 3).[3,5] If their faces are shielded by substituents, these minima could be so unreactive as to contribute little or nothing to the final product distribution. Other conformers (even those several kcal/mol higher in energy) with less unfavorable interactions between the incoming trap and the radical would then

become more reactive by default, and contribute significantly to the final product distribution. As the R^1 and OR groups become very large, both faces of conformers near the ground state minimum become highly shielded, and other rotamers with more open faces become more energetically disfavored by A-strain. Eventually, trapping slows to the point where the chains break.

Figure 3. Likely Ground State Minimum for 2°-Radicals



That the size and direction of approach of a trap must be considered is also suggested by the observations that stereoselectivities can be greatly altered by the nature of the trap. We and Hart[5] have both observed examples where low deuteration ratios translated into high allylation ratios, and we present in the subsequent paper[14] several examples where high (sometimes exceedingly high) deuteration ratios translate into low allylation ratios. The sequel to this paper presents asymmetric deuteration and allylation reactions of related ester-substituted radicals and discusses how the results impinge on current models.[14]

Experimental

General Procedure for the Coupling of Acid Chlorides and Substituted Anilines. *N*-(2-Iodophenyl)-*N*-methylethanamide. 1-(*N*-Methylamino)-2-iodobenzene (1.34 g, 5.73 mmol) in THF (1 mL) was added to 8.5 M NaOH (2 mL, 17.2 mmol) at 0°C. Acetyl chloride (815 μl, 11.45 mmol) in THF (1 mL) was added to the reaction mixture via syringe pump over 30 min. After stirring at 0°C for 30 min and at 25°C for 3 h, the reaction mixture was poured into Et_2O (or ethyl acetate) and washed with water (2 x 10 mL) and brine (1 x 10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The yield of the crude product was quantitative. In some experiments, the acid chloride was diluted with THF and added dropwise to a solution of the amine: ^{1}H NMR δ 1.80 (s, 3 H, $COCH_3$), 2.89 (s, 3 H, NCH_3), 7.08 (t, 1 H, J = 8.0 Hz), 7.29 (d, 1 H, J = 8.0 Hz), 7.43 (t, 1 H, J = 8.0 Hz), 7.94 (d, 1 H, J = 8.0 Hz); ^{13}C NMR δ 22.3, 35.6, 99.2, 128.6, 129.7, 129.9, 139.9, 146.3, 169.9; IR 3080, 2910, 1665, 770 cm^{-1}; HRMS calculated for C_7H_7NI ($M^+ - C_2H_3O$), 231.9623; measured 231.9623; LRMS *m/e* 148 (100).

***N*-(2-Iodophenyl)-*N*-methylpropanamide.** Prepared by the general procedure above from 1-(*N*-methylamino)-2-iodobenzene (1.3 mmol) and propionyl chloride (2.6 mmol). A second portion of propionyl chloride (2.6 mmol) was added after 1 h and the reaction was stirred for 24 h at 25°C. The crude product was purified by flash chromatography (50% ethyl acetate/hexanes; R_f = 0.35) to afford 345 mg (92%) of the product as a white solid: ^{1}H NMR δ 1.07 (t, 3 H, CH_2CH_3), 1.95 (q, 2 H, CH_2CH_3), 3.18 (s, 3 H, NCH_3), 7.07 (m, 1 H), 7.26 (m, 1 H), 7.42 (m, 1 H), 7.93 (m, 1 H); ^{13}C NMR δ 9.37, 27.7, 35.8, 99.7, 128.9, 129.7, 129.9, 140.1, 146.1, 173.4; IR 2978, 2938, 1667, 1470, 1380, 768 cm^{-1}; HRMS calculated for C_7H_8NI ($M^+ - C_3H_5O$), 232.9702; measured, 232.9698; LRMS *m/e* 162 (100), 233 (40).

***N*-(2-Iodophenyl)-*N*,3-dimethylbutanamide (14).** Prepared by the general procedure above from 1-(*N*-methylamino)-2-iodobenzene (2.17 mmol) and isovaleryl chloride (4.29 mmol). The product was washed with 5 M NaOH (2 x 5 mL) during workup to remove acid and acid chloride impurities. Purification by flash chromatography (20% ethyl acetate/hexanes) afforded 641 mg (93%) of **14** as a yellow oil: ^{1}H NMR δ 0.83 (d, 3 H, J = 6.7 Hz, CH_3), 0.88 (d, 3 H, J = 6.6 Hz, CH_3), 1.82 (d, 2 H, J = 7.0 Hz, CH_2), 2.18 (octet, 1 H, $CH(CH_3)_2$), 3.17 (s, 3 H, NCH_3), 7.08 (m, 1 H), 7.23 (m, 1 H), 7.42 (m, 1 H), 7.93 (m, 1 H); ^{13}C NMR δ 22.4, 22.6, 25.0, 35.6, 42.8, 99.6, 129.0, 129.5, 129.7, 139.9, 145.9, 171.7; IR 2957, 1663, 1470, 1377, 768, 727 cm^{-1}; HRMS calculated for $C_{12}H_{16}NO$

($M^+ - I$), 190.1232; measured, 190.1248; LRMS *m/e* 260 ($M^+ - C_4H_9$, 3), 233 (60), 190 (100).

***N*, 3-Dimethyl-*N*-phenylpropanamide (15aH).** Prepared by the general procedure above from *N*-methylaniline (14.0 mmol) and isovaleryl chloride (28.0 mmol). The product was washed with 5 M NaOH (2 x 5 mL) during workup to remove acid and acid chloride impurities. The crude product was purified by flash chromatography (30% ethyl acetate/hexanes; $R_f = 0.30$) to afford 2.10 g (78%) of the **15aH** as a yellow oil: ^1H NMR δ 0.83 (d, 6 H, J = 6.5 Hz, $C(CH_3)_2$), 1.95 (d, 2 H, J = 6.9 Hz, CH_2), 2.13 (m, 1 H, $HC(CH_2)_2$), 3.27 (s, 3 H, NCH_3), 7.15 (d, 2 H, J = 7.3 Hz), 7.37 (m, 3 H); ^{13}C NMR δ 22.1, 25.4, 36.8, 42.3, 127.1, 127.3, 129.3, 143.9, 171.9; IR 2957, 1663, 1377, 1420, 770, 700 cm^{-1}; HRMS calculated for $C_{12}H_{17}NO$, 191.1310; measured 191.1313; LRMS *m/e* 191 (M^+, 12), 107 (100).

General Procedure for the Synthesis of 3-Hydroxyamides by an Aldol Reaction. 3-Hydroxy-*N*-(2-iodophenyl)-*N*,4,4-trimethylpentanamide (5a). *N*-(2-Iodophenyl)-*N*-methylethanamide (790 mg, 2.87 mmol) was added to a solution of LDA (2.24 mL) in THF (120 mL) at –78°C. After 30 min at –78°C, pivaldehyde (374 μL, 3.44 mmol) was added, and after 5 more min the reaction was quenched with acetic acid (821 μL, 14.4 mmol) and saturated NH_4Cl (5 mL). The mixture was warmed to 25°C, poured into a separatory funnel containing ether (100 mL), and extracted with H_2O (2 x 50 mL). The combined aqueous layers were extracted with ether (50 mL). The organic extracts were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was purified by flash chromatography (50% ethyl acetate/hexanes) to afford 990 mg (96%) of **5a** as a white solid (mp = 78.5-81.5°C). The isolated product was a mixture of *N*-aryl bond rotamers in a 60/40 ratio as determined by ^1H NMR integration: ^1H NMR signals attributed to the major rotamer: δ 0.77 (s, 9 H, $C(CH_3)_3$), 3.19 (s, 3 H, NCH_3), 3.73 (dt, 1 H, J = 10.4, 2.2 Hz, $CHOH$), 4.18 (d, 1 H, J = 2.2 Hz, $CHOH$). Signals attributed to the minor rotamer: δ 0.75 (s, 9 H, $C(CH_3)_3$), 3.20 (s, 3 H, NCH_3), 3.56 (dt, 1 H, J = 10.5, 1.9 Hz, $CHOH$), 4.10 (d, 1 H, J = 1.9 Hz, $CHOH$). Signals overlapping: δ 1.85-2.20 (m, 4 H, $C(O)CH_2$), 7.10 (m, 2 H), 7.26 (m, 2 H), 7.44 (m, 2 H), 7.94 (m, 2 H); ^{13}C NMR δ 25.5, 25.6, 34.1, 34.2, 35.4, 35.5, 35.9, 75.7, 75.9, 99.3, 128.8, 129.2, 130.1, 130.2, 140.2, 140.4, 145.6, 173.1, 173.6 (24 resonances expected, 19 observed); IR 3460 (OH), 2955, 2870, 1644, 1472 cm^{-1}; HRMS calculated for $C_{14}H_{20}INO_2$, 361.0539; measured, 361.0539; LRMS *m/e* 304 ($M^+ - C_4H_9$, 70), 234 ($M^+ - I$, 100), 148 (50), 87 (30).

3-Hydroxy-*N*-(2-iodophenyl)-*N*-methylbutanamide 1a. Prepared by the general procedure above from *N*-(2-Iodophenyl)-*N*-methylethanamide (15.6 mmol) and acetaldehyde (16.4 mmol). The reaction was quenched after 10 min and allowed to warm to 25°C. The ^1H NMR of the crude material (4.98 g, 98%) showed that the product was clean. The product could be purified by flash chromatography (50% ethyl acetate/40% hexanes/10% MeOH). The product was observed as a 50/50 rotamer mixture about the *N*-aryl bond as determined by ^1H NMR integration: ^1H NMR δ 1.08 (m, 3 H, CH_3), 2.03 (m, 2 H, CH_2), 2.80 (br s, 1 H, OH), 3.18 (s, 3 H, NCH_3), 4.15 (m, 1 H, $C(CH_3)H$), 7.11 (m, 1 H), 7.26 (m, 1 H), 7.44 (m, 1 H), 7.94 (m, 1 H); ^{13}C NMR δ 22.2, 35.6, 41.7, 42.0, 64.2, 64.3, 99.2, 128.7, 128.9, 130.0, 140.1, 140.2, 145.1, 172.4 (22 resonances expected, 15 observed); IR 3443, 2969, 2926, 1651, 1473, 1130 cm^{-1}; HRMS calculated for ($M^+ - I$) $C_{11}H_{14}NO_2$, 192.1025; measured 192.1029; LRMS *m/e* 319 (M^+, 1.5), 304 (4), 233 (80) 192 (100).

3-Hydroxy-*N*-methyl-*N*-phenylbutanamide 2aH. This compound was inadvertently synthesized in a preparation of compound **1a** when a large excess of n-BuLi was accidentally used in the aldol reaction. The excess n-BuLi presumably transmetallated the iodine atom on the phenyl ring, and the resulting aryllithium was subsequently protonated upon aqueous workup: ^1H NMR δ 1.07 (d, 3 H, J = 6.3 Hz, CH_3), 2.09 (dd, 1 H, J = 16.2, 9.0 Hz, *H* syn to OH), 2.21 (dd, 1 H, J = 16.2, 2.4 Hz, *H* anti to OH), 3.28 (s, 3 H, NCH_3), 4.12 (m, 1 H, $CHOH$), 7.17 (m, 2 H), 7.42 (m, 3 H), *OH* proton was not observed; ^{13}C NMR δ 22.2, 41.2, 64.4, 127.1, 128.0, 129.9, 130.1, 143.2, 172.8; IR 3441 (OH), 2969, 2928, 1642, 1125 cm^{-1}; HRMS calculated for $C_{11}H_{15}NO_2$, 193.1102; measured 193.1140; LRMS *m/e* 193 (M^+, 12), 107 (100).

3-Hydroxy-*N*,4,4-trimethyl-*N*-phenylpentanamide (6aH). Method I. Prepared by the general procedure described above from *N*-methylaniline (3.35 mmol) and pivaldehyde (4.02 mmol). The crude material was purified by flash chromatography ($R_f = 0.24$ in 50% ethyl acetate/ hexanes) to afford 703 mg (89%) of the product as a colorless solid. Method II. A mixture of **5a** (150 mg, 0.42 mmol, 0.01 M), Bu_3SnH (223 μL, 0.83 mmol), and AIBN (6.8 mg, 0.042 M) in benzene (41 mL) was heated at 80°C for 45 min. The reaction mixture was concentrated under reduced pressure and partitioned between CH_3CN/hexanes (20 mL each). Concentration of the acetonitrile layer followed by flash chromatography (50% ethyl acetate/hexanes) afforded 81 mg (83%) of **6aH**: ^1H NMR δ 0.77 (s, 9

H, C(CH_3)$_3$), 2.02 (dd, 1 H, J = 10.6, 15.6 Hz, COCH_2, H syn to OH), 2.29 (dd, 1 H, J = 15.6, 1.5 Hz, COCH_2, H anti to OH), 3.29 (s, 4 H, NCH_3 and O*H*), 3.61 (d, 1 H, J = 10.4 Hz, C*H*OH), 7.20 (m, 2 H), 7.40 (m, 3 H); ^{13}C NMR δ 25.6, 34.3, 35.3, 37.3, 76.0, 127.3, 128.2, 129.9, 143.6, 173.9; IR 3447, 2955, 2870, 1638, 1595, 1497, 1389 cm^{-1}; HRMS calculated for $C_{14}H_{21}NO_2$, 235.1572; measured, 235.1572; LRMS *m/e* 235 (10), 178 (50), 134 (20), 107 (100).

3-Hydroxy-*N*-(2-iodophenyl)-*N*,2-dimethylbutanamide (9a). Prepared by the general procedure above from *N*-(2-Iodophenyl)-*N*-methylpropanamide (5.81 mmol) and acetaldehyde (8.95 mmol). The crude material was purified by flash chromatography (30% ethyl acetate/hexanes) to afford 1.35 g (69%) of the product as a white solid (86% yield based on recovered starting material). The isolated product was the syn isomer and had a 55/45 rotamer ratio as determined by ^{1}H NMR integration: ^{1}H NMR signals attributed to the major rotamer: δ 1.90 (dq, 1 H, J = 6, 1.2 Hz, C(CH_3)*H*), 3.15 (s, 3 H, NCH_3), 4.26 (dq, 1 H, J = 6.4, 1.4 Hz, C*H*OH), 7.29 (m, 1 H). Signals attributed to the minor rotamer: δ 1.13 (d, 3 H, J = 6.9 Hz, C(CH_3)H), 2.13 (q, 1 H, J = 6.9 Hz, C(CH_3)*H*), 3.19 (s, 3 H, NCH_3), 3.94 (br q, 1 H, J = 6.3 Hz, C*H*OH), 7.21 (m, 1 H). Signals overlapping: δ 1.0 (3 overlapping d, 9 H, major C(CH_3)H, minor C(OH)CH_3, major C(OH)CH_3), 3.83 (br s, 2 H, CO*H*), 7.10 (m, 2 H), 7.43 (m, 2 H), 7.93 (m, 2 H); ^{13}C NMR signals attributed to the major rotamer: δ 9.80, 19.6, 35.9, 67.6, 99.8, 128.8, 140.3, 145.5, 178.1. Signals overlapping: δ 10.5, 19.9, 36.1, 67.6, 99.0, 129.2, 140.6, 145.8, 177.1. Signals attributed to both rotamers: δ 41.5, 130.0, 130.1 (24 resonances expected, 21 observed); IR 3432, 2973, 2934, 1642, 1150, 768, 725 cm^{-1}; HRMS calculated for $C_{12}H_{16}NO_2$ (M^+ – I), 206.1181; measured, 206.1179; LRMS *m/e* 318 (M^+ – CH_3, 2), 289 (7), 233 (90), 206 (100), 162 (30).

3-Hydroxy-*N*,2-dimethyl-*N*-phenylbutanamide (10aH). Prepared by the general procedure above from *N*-methyl-*N*-phenylpropanamide (13.3 mmol) and acetaldehyde (20.0 mmol). The resulting material was purified by flash chromatography (30% ethyl acetate/hexanes) to afford 910 mg (33%) as a yellow oil (57% yield based on recovered starting material). The isolated product was a mixture of syn and anti isomers in a 64/36 ratio as determined by ^{1}H NMR integration: ^{1}H NMR signals attributed to the major erythro isomer: δ 1.01 (d, 3 H, J = 6.4 Hz, C(CH_3)OH), 1.04 (d, 3 H, J = 7.0 Hz, C(CH_3)H), 2.29 (dq, 1 H, J = 7.0, 2.7 Hz, C(CH_3)*H*), 3.26 (s, 3 H, NCH_3), 4.01 (dq, 1 H, J = 6.4, 2.7 Hz, C(OH)*H*). Signals attributed to the minor threo isomer: δ 1.12 (m, 6 H, C(OH)CH_3 and C(CH_3)H), 2.36 (m, 1 H, C(CH_3)*H*), 3.27 (s, 3 H, NCH_3), 3.68 (m, 1 H, C(OH)*H*). Signals overlapping: δ 7.19 (m, 4 H), 7.40 (m, 6 H). The O*H* signal was not observed for either isomer; ^{13}C NMR signals attributed to the major erythro product: δ 11.1, 19.9, 41.5, 67.6, 176.8. Signals attributed to the minor threo product: δ 15.3, 21.4, 42.3, 69.8, 176.2. Signals overlapping: δ 36.9, 126.9, 127.0, 127.7, 129.6, 143.3 (20 resonances expected, 16 observed); IR 3434 (OH), 2973, 1638, 774, 700 cm^{-1}; HRMS calculated for $C_{12}H_{17}NO_2$, 207.1259; measured, 207.1280; LRMS *m/e* 207 (M^+, 12), 107 (100).

3-Hydroxy-*N*-(2-iodophenyl)-*N*,2,4,4-tetramethylpentanamide (11a). Prepared by the general procedure described above from *N*-(2-Iodophenyl)-*N*-methylpropanamide (2.08 mmol) and pivaldehyde (2.49 mmol). The amide enolate was allowed to stir for 30 min at –78°C before the addition of pivaldehyde. The reaction was quenched with saturated $NaHCO_3$ (6 mL) and the crude material was purified by flash chromatography (30% ethyl acetate/hexanes) to afford 731 mg (94%) of the product as a white solid. The isolated product was the syn adduct in a 64/36 rotamer ratio about the *N*-aryl bond as determined by ^{1}H NMR integration. Less than 5% of the threo aldol was present as indicated by a small doublet (O*H* proton) observed at δ 5.1 in the ^{1}H NMR spectrum. ^{1}H NMR signals attributed to the major rotamer: δ 0.82 (s, 3 H, C(CH_3)$_3$), 1.07 (d, 3 H, J = 6.8 Hz, CH_3), 2.35 (q, 1 H, J = 13.7 Hz, C(CH_3)*H*), 3.17 (s, 3 H, NCH_3), 3.70 (br s, 1 H, C*H*OH), 4.16 (s, 1 H, CHO*H*). Signals attributed to the minor rotamer: δ 0.74 (s, 3 H, C(CH_3)), 1.18 (d, 3 H, J = 6.9 Hz, CH_3), 2.51 (q, 1 H, J = 13.7 Hz, C(CH_3)*H*), 3.19 (s, 3 H, NCH_3), 3.37 (br, s, 1 H, C*H*OH), 3.56 (br, s, 1 H, CHO*H*). Signals overlapping: δ 7.10 (m, 2 H), 7.26 (m, 2H), 7.44 (m, 2 H), 7.96 (m, 2 H). In DMSO–d_6, coalescence of the methyl doublets occured at 110°C (300 MHz). ^{13}C NMR δ 11.4, 11.6, 15.2, 26.3, 26.8, 27.2, 35.1, 35.3, 35.7, 35.9, 36.9, 37.0, 65.7, 99.0, 99.3, 128.7, 129.1, 129.8, 130.0, 130.1, 140.1, 140.4, 145.5, 145.7, 177.9, 178.5; IR 3400, 2953, 2869, 1638, 1472, 1387 cm^{-1}; HRMS calculated for $C_{14}H_{19}INO_2$ (M^+ – CH_3), 360.0461; measured, 360.0456; LRMS *m/e* 360 (30), 318 (100), 248 (100), 233 (100).

3-Hydroxy-*N*,2, 4,4-tetramethyl-*N*-phenylpentanamide 12aH. Prepared by the general procedure described above from *N*-methyl-*N*-phenylpropanamide (1.84 mmol) and pivaldehyde (2.57 mmol). The amide enolate stirred for 30 min at –78°C before the addition of pivaldehyde. The reaction was quenched with saturated $NaHCO_3$ and

the crude material was purified by flash chromatography (30% ethyl acetate/hexanes; R_f = 0.43 in 50% ethyl acetate/hexanes) to afford 400 mg (87%) of **12aH** as a white solid. The syn/anti ratio was 83/17 as determined by ^1H NMR integration. ^1H NMR signals attributed to the major syn product: δ 1.08 (d, 3 H, J = 6.7 Hz, CH_3), 2.69 (dq, 1 H, J = 6.7, 1.0 Hz, $C(CH_2)H$), 3.25 (s, 3 H, NCH_3), 3.45 (m, 1 H, CHOH), 3.67 (d, 1 H, J = 1.4 Hz, CHO*H*). Signals attributed to the minor anti product: δ 1.33 (d, 3 H, J = 7.0 Hz, CH_3), 2.49 (dq, 1 H, $C(CH_3)H$), 3.05 (m, 1 H, CHOH), 3.23 (s, 3 H, NCH_3), 5.50 (d, 1 H, J = 10.3 Hz, CHO*H*). Signals overlapping: δ 0.77 (s, 18 H, $C(CH_3)_3$), 7.18 (m, 4 H), 7.40 (m, 6 H); ^{13}C NMR of major syn product δ 12.2, 26.7, 35.3, 36.4, 37.1, 78.1, 127.1, 128.1, 129.8, 143.5, 178.2; IR 3463, 2957, 2361, 1638, 1497, 1069, 774, 702 cm^{-1}; HRMS calculated for $C_{14}H_{20}NO_2$ ($M^+ - CH_3$), 234.1494; measured 234.1494; LRMS *m/e* 234 (15), 192 (40), 163 (19), 134 (28), 107 (100).

General Procedure for the Silylation of 3-Hydroxyamides. 3-*tert*-(Butyldimethylsilyl)oxy-*N*-(2-iodophenyl)-*N*-methylbutanamide (1c). Prepared by the general silylation procedure above from **1a** (3.13 mmol) and TBSOTf (9.39 mmol). The reaction was complete in 2 h and the crude material was purified by flash chromatography (50% ethyl acetate/40% hexanes/10% methanol) to afford 632 mg (92%) of **1c** as a white solid. The isolated product had a rotamer ratio of 60/40 as determined by ^1H NMR integration of the signal for the *tert*-(butyldimethylsilyl)oxy protons. Other signals in the ^1H NMR spectrum are poorly resolved: ^1H NMR signal attributed to the major rotamer: δ 0.85 (s, 9 H, $SiC(CH_3)_2$). Signal attributed to the minor rotamer: δ 0.83 (s, 9 H, $SiC(CH_3)_3$). Signals overlapping: δ 0.03 (m, 12 H, $Si(CH_3)_3$), 1.12 (m, 6 H, CH_3), 1.98-2.28 (m, 4 H, CH_2), 3.15 (s, 6 H, NCH_3), 4.35 (m, 2 H, $C(CH_3)H$), 7.07 (m, 2 H) 7.26 (m, 2 H), 7.41 (m, 2 H), 7.92 (m, 2 H); ^{13}C NMR signals attributed to the major rotamer: δ 24.1, 43.8, 66.3, 139.9, 146.0, 170.6. Signals attributed to the minor rotamer: δ 23.8, 44.3, 140.2, 145.9, 170.3. Signals overlapping: δ –4.8, 17.9, 25.8, 35.8, 99.6, 129.1, 129.7 (28 resonances expected, 18 observed); IR 2928, 2855, 1669, 1653, 1472 cm^{-1}; HRMS calculated for $C_{16}H_{25}INO_2Si$ ($M^+ - CH_3$), 418.0699; measured, 418.0676; LRMS *m/e* 418 ($M^+ - CH_3$, 5), 376 ($M^+ - C_4H_8$, 100).

3-*tert*-(Butyldiphenylsilyl)oxy-*N*-(2-iodophenyl)-*N*-methylbutanamide (1d). Alcohol **1a** (0.33 mmol) was added to CH_2Cl_2 (2 mL) containing imidazole (0.94 mmol) and *tert*-butyldiphenylsilyl chloride (0.59 mmol) at 25°C. After 2 h, the reaction was poured into CH_2Cl_2 (15 mL) and washed with water (2 x 5 mL) and brine (2 x 1.5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was purified by flash chromatography (50% ethyl acetate/40% hexanes/10% methanol) to afford 193 mg of **1d** as a white solid. Further purification (10% ethyl acetate/hexanes) was necessary to separate **1d** from silyl-containing impurities. The isolated product had a 62/38 rotamer ratio as determined by ^1H NMR integration: ^1H NMR signals attributed to the major rotamer: δ 3.12 (s, 3 H, NCH_3), 4.46 (m, 1 H, $C(OSiR_3)H$). Signals attributed to the minor rotamer: δ 3.11 (s, 3 H, NCH_3), 4.34 (m, 1 H, $C(OSiR_3)H$). Signals overlapping: δ 1.00 (m, 18 H, $SiC(CH_3)_3$), 1.07 (m, 6 H, $C(CH_3)H$), 2.04 and 2.32 (m, 4 H, CH_2), 7.07 (m, 2 H), 7.15 (m, 2 H), 7.37 (m, 14 H), 7.62 (m, 8 H), 7.91 (m, 2 H); ^{13}C NMR signals attributed to the major rotamer: δ 23.9, 43.8, 67.4, 140.0, 146.0, 170.3. Signals attributed to the minor rotamer: δ 23.7, 44.1, 66.9, 140.2, 145.8, 170.0. Signals overlapping: δ 19.2, 26.9, 35.7, 99.6, 127.4, 129.1, 129.4, 129.7, 129.8, 133.9, 134.0, 134.4, 134.5, 135.7 (34 resonances expected, 26 observed); IR 2930, 2857, 2359, 1669, 1653 cm^{-1}; HRMS calculated for $C_{23}H_{23}INO_2Si$ ($M^+ - C_4H_9$), 500.0542; measured 500.0570; LRMS *m/e* 500 ($M^+ - C_4H_9$, 60), 199 (100).

***N*-(2-Iodophenyl)-*N*,4,4-trimethyl-3-(trimethylsilyl)oxypentanamide (5b).** Method 1. Prepared by the general silylation procedure above from *bis*-(trimethylsilyl)trifluoroacetamide (0.83 mmol) and **5a** (0.28 mmol) at 25°C for 18 h. Addional *bis*-(trimethylsilyl)trifluoroacetamide (100 μl, 0.38 mmol) was added dropwise and the reaction was stirred for 6 h. Flash chromatography (30% ethyl acetate/hexanes) of the crude material afforded 84 mg (70%) of the desired product as a white solid (mp = 88°C). The isolated product had two rotamers in a 65:35 ratio as determined by ^1H NMR integration: ^1H NMR signals attributed to the major rotamer: δ 0.71 (s, 9 H, $C(CH_3)_3$), 3.18 (s, 3 H, NCH_3), 7.27 (dd, 1 H, J_1 = 7.9 Hz, J_2 =1.4 Hz). Signals attributed to the minor rotamer: δ 0.70 (s, 9 H, $C(CH_3)_3$), 3.16 (s, 3 H, NCH_3), 7.21 (dd, 1 H, J = 7.9 Hz, 1.5 Hz). Signals overlapping: δ 0.13 (s, 18 H, $Si(CH_3)_3$), 1.88-2.24 (m, 4 H, $C(O)CH_2$), 3.99 (m, 2 H, CH), 7.05 (m, 2 H), 7.42 (m, 2 H), 7.92 (m, 2 H); ^{13}C NMR signals attributed to the major rotamer: δ 25.9, 35.0, 37.0, 99.5, 140.0, 146.3, 171.4. Signals attributed to the minor rotamer: δ 25.8, 35.2, 38.4, 99.8, 129.0, 129.7, 140.4, 146.3, 171.1. Signals overlapping: δ 0.63, 129.6, 129.8, 129.9, 130.0; IR 2955, 1669, 1471, 1383, 1098, 947, 841 cm^{-1}; HRMS calculated for ($M^+ - CH_3$) $C_{16}H_{25}INO_2Si$, 418.0699; measured, 418.0699; LRMS *m/e* 418 ($M^+ - CH_3$, 35), 376 (100), 260 (40), 73 (95).

Method 2. The product was also prepared from TMSOTf (3.32 mmol) and the alcohol **5a** (1.11 mmol) in a similar fashion to afford 2.84 mg (59%) of the product after purification.

3-(*tert*-Butyldimethylsilyl)oxy-*N*-(2-iodophenyl)-*N*,4,4-trimethylpentanamide (5c). *tert*-Butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 191 μL, 0.83 mmol) was added dropwise to a solution of **5a** (100 mg, 0.28 mmol) in DMF (3 mL) at 25°C. After 19 h, more TBSOTf (80 μL, 0.35 mmol) was added. The reaction was stirred for 4.5 h, poured into cold saturated $NaHCO_3$ (5 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was taken up in ether (20 mL) and washed with H_2O (2 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (30% ethyl acetate in hexanes) afforded 137 mg (quantitative yield) of **5c** as a white solid. The isolated product had two rotamers in a 63:37 ratio as determined by ^1H NMR integration: ^1H NMR signals attributed to the major rotamer: δ 0.06 (s, 3 H, $SiCH_3$), 0.75 (s, 9 H, $SiC(CH_3)_3$), 0.88 (s, 9 H, $C(CH_3)_3$), 3.16 (s, 3 H, NCH_3). Signals attributed to the minor rotamer: δ 0.11 (s, 3 H, $SiCH_3$), 0.71 (s, 9 H, $SiC(CH_3)_3$), 0.85 (s, 9 H, $C(CH_3)_3$), 3.15 (s, 3 H, NCH_3). Signals overlapping: δ 0.09 (s, 6 H, $SiCH_3$ major and $SiCH_3$ minor), 1.90-2.31 (m, 4 H, $C(O)CH_2$), 4.04-4.10 (m, 2 H, $CHCH_2$), 7.06 (m, 2 H), 7.24 (m, 2 H), 7.40 (m, 2 H), 7.91 (m, 2 H); ^{13}C NMR signals attributed to the major rotamer: δ 8.5, 35.5, 38.1, 99.5, 129.5, 129.7, 140.2, 146.2, 171.3. Signals attributed to the minor rotamer: δ 18.2, 35.8, 39.2, 99.7, 128.8, 129.9, 130.0, 140.5, 146.0, 170.9. Signals overlapping: δ 25.8, 25.9, 26.0, 26.1, 26.2, 26.3, 26.4, 26.5, 129.8 (30 resonances expected, 28 observed); IR 2955, 2857, 1668, 1471, 1078, 835, 775 cm^{-1}; HRMS calculated for $C_{19}H_{31}INO_2Si$ ($M^+ - CH_3$), 460.1169; measured, 460.1169; LRMS *m/e* 460 ($M^+ - CH_3$, 15), 418 (50), 332 (15), 73 (40).

***N*,4,4-Trimethyl-3-(trimethylsilyl)oxy-*N*-phenylpentanamide (6bH).** Method 1. Prepared by the general silylation procedure above from *bis*-(trimethylsilyl)trifluoroacetamide (1.28 mmol) and **5a** (0.43 mmol). The reaction mixture was stirred at 25°C for 24 h before aqueous workup. The crude product was purified by flash chromatography (50% ethyl acetate/hexanes) to afford 77 mg (59%; 74% yield based on recovered starting material) of **6bH** as a clear liquid. Method 2. A solution of **5b** (30 mg, 0.07 mmol, 0.01 M), Bu_3SnH (37 μL, 0.14 mmol), and AIBN (1.15 mg, 0.007 M) in benzene (7 mL) was heated at 80°C for 3 h. The reaction mixture was cooled to 25°C and concentrated under reduced pressure. Flash chromatography afforded 16 mg (76%) of **6bH** as a colorless liquid. ^1H NMR δ 0.14 (s, 9 H, $Si(CH_3)_3$), 0.73 (s, 9 H, $C(CH_3)_3$), 2.11 (dd, 1 H, J = 15.6, 2.5 Hz, Hα to amide and *syn* to $OSiMe_3$), 2.29 (dd, 1 H, J = 15.6, 9.4 Hz, $COCH_2$, Hα to amide and *anti* to $OSiMe_3$), 3.28 (s, 3 H, NCH_3), 3.99 (dd, 1 H, J = 9.4, 2.5 Hz, CHOH), 7.22 (m, 2 H), 7.37 (m, 3 H); ^{13}C NMR δ 0.06, 26.0, 35.2, 37.1, 37.4, 77.8, 127.5, 129.6, 149.4, 171.9 (11 resonances expected, 10 observed); IR 2957, 2363, 1653, 841 cm^{-1}; HRMS calculated for $C_{16}H_{26}NO_2Si$ ($M^+ - CH_3$), 292.1733; measured, 292.1733; LRMS *m/e* 292 ($M^+ - CH_3$, 35), 250 (100), 137 (70).

3-(*tert*-Butyldimethylsilyl)oxy-*N*,4,4-trimethyl-*N*-phenylpentanamide (6cH). Method 1. Prepared by the general silylation procedure from **6a** (0.43 mmol) and TBSOTf (1.28 mmol). The reaction mixture was stirred at 25°C for 24 h. The crude material was purified by flash chromatography (30% ethyl acetate/hexanes) to afford 173 mg (quantitative) of **6cH** as a colorless liquid. Method 2. A solution of **5c** (30 mg, 0.06 mmol, 0.01M), Bu_3SnH (35 μL, 0.13 mmol), and AIBN in benzene (6.4 mL) was heated at 80°C for 4.25 h. The reaction mixture was cooled to 25°C and concentrated under reduced pressure. Flash chromatography afforded 17 mg (77%) of **6cH** as a colorless oil. ^1H NMR δ 0.06 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$), 0.75 (s, 9 H, $SiC(CH_3)_3$), 0.88 (s, 9 H, $C(CH_3)_3$), 2.20 (d, 2 H, J = 5.4 Hz, CH_2), 3.26 (s, 3 H, NCH_3), 4.03 (t, 1 H, J = 5.4 Hz, $CHCH_2$), 7.20 (m, 2 H), 7.34 (m, 3 H); ^{13}C NMR δ −5.0, −3.7, 18.4, 26.0, 26.3, 35.6, 37.4, 37.9, 127.2, 127.4, 127.6, 129.6, 144.2, 171.8 (15 resonances expected, 14 observed); IR 2957, 2860, 1653, 1076, 835, 776 cm^{-1}; HRMS calculated for $C_{19}H_{32}NO_2Si$ ($M^+ - CH_3$), 334.2202; measured, 334.2202; LRMS *m/e* 334 ($M^+ - CH_3$, 10), 292 (100), 134 (17), 73 (29).

3-*tert*-(Butyldimethylsilyl)oxy-*N*-(2-iodophenyl)-*N*-2,4,4-tetramethylpentanamide (11c). Prepared by the general silylation procedure above from **11a** (0.80 mmol) and TBSOTf (2.4 mmol). TBSOTf (1.2 mmol) was added and the reaction mixture was stirred for 16 h. The crude material was purified by flash chromatography (20% ethyl acetate/hexanes) to afford **11c** in quantitative yield. In this case, an accurate ratio was difficult to determine. From ^{13}C NMR data, we estimated that the ratio is 55/45. ^1H NMR δ 0.16 (m, 6 H, $Si(CH_3)_2$), 0.66 (d, 9 H, J = 4.0 Hz, $SiC(CH_3)_3$), 0.92 (d, 9 H, J = 2.4 Hz, $C(CH_3)_3$), 1.04 (d, 3 H, J = 7.0 Hz, $CH(CH_3)$), 2.53 (m, 1 H, $CH(CH_3)$), 3.16 (s, 3 H, NCH_3), 3.76 (m, 1 H, $CH(OSiMe_3)$), 7.05 (m, 1 H), 7.30 (m, 1 H), 7.41 (m, 1 H), 7.93 (m, 1 H); ^{13}C NMR δ −4.3, −4.0, −3.3, −3.0, 13.2, 13.4, 18.7, 26.4, 26.5, 26.8, 27.0, 36.7, 36.9,

38.1, 39.1, 78.5, 78.7, 99.6, 100.1, 129.5, 129.8, 140.4, 140.5, 175.8, 176.8 (34 resonances expected, 25 observed); IR 2995, 1665, 1465, 1073, 833, 775, 727 cm^{-1}; HRMS calculated for $C_{17}H_{27}INO_2Si$ ($M^+ - C_4H_9$), 432.0856; measured 432.0841; LRMS *m/e* 474 ($M^+ - CH_3$, 5), 432 (100).

General Procedure for the Acetylation of 3-Hydroxyamides.

3-Acetoxy-*N*-(2-iodophenyl)-*N*-methylbutanamide (1e). Prepared by the general procedure above from DMAP (0.002 mmol), **1a** (1.69 mmol), acetic anhydride (2.54 mmol), and triethylamine (2.54 mmol). The crude material was purified by flash chromatography (50% ethyl acetate/hexanes) to afford 401 mg (66%) of **1e** as a solid (mp = 89.5-92.5°C). The isolated product had two rotamers in a 53/47 ratio as determined by ^1H NMR integration: ^1H NMR signals attributed to the major rotamer: δ 1.14 (d, 3 H, J = 6.2 Hz, CH_3), 1.86 (s, 3 H, C(O)CH_3). Signals attributed to the minor rotamer: δ 1.09 (d, 3 H, J = 6.4 Hz, CH_3), 1.88 (s, 3 H, C(O)CH_3). Signals overlapping: δ 1.99 (m, 2 H, CH_2), 2.22 (m, 2 H, CH_2), 3.06 (s, 6 H, NCH_3), 5.21 (m, 2 H, C(CH_3)*H*), 7.02 (m, 2 H), 7.19 (m, 2 H), 7.37 (m, 2 H), 7.85 (m, 2 H); ^{13}C NMR δ 20.1, 20.2, 21.4, 35.9, 40.4, 67.8, 68.3, 99.7, 129.3, 130.0, 140.3, 140.4, 145.7, 169.3, 170.2 (26 resonances expected, 15 observed); IR 2995, 2950, 1734, 1700, 1244, 727, 770 cm^{-1}; HRMS calculated for C_7H_8NI ($M^+ - C_6H_8O_3$), 232.9701; measured, 232.9718; LRMS *m/e* 318 ($M^+ - C_2H_2O$, 2), 260 (4), 233 (70), 174 (80).

3-Acetoxy-*N*-methyl-*N*-phenylbutanamide (2eH). Prepared by the general acetylation procedure above from **2aH** (0.41 mmol), triethylamine (1.24 mmol), acetic anhydride (1.24 mmol), and catalytic DMAP. The crude material was purified by flash chromatography (50% ethyl acetate/40% hexanes/10% MeOH) to afford 37 mg (38%) of **2e** as a liquid: ^1H NMR δ 1.19 (d, 3 H, J = 6.2 Hz, CH_3), 1.99 (s, 3 H, C(O)CH_3), 2.21 (dd, 1 H, J = 15.5, 6.0 Hz, Hα to amide), 2.47 (dd, 1 H, J = 15.5, 7.1 Hz, Hα to amide), 3.26 (s, 3 H, NCH_3), 5.27 (m, 1 H, Hβ to amide), 7.20 (m, 2 H), 7.37 (m, 1 H), 7.43 (m, 2 H); ^{13}C NMR δ 19.9, 21.2, 37.2, 40.0, 68.2, 127.3, 127.9, 129.8, 143.6, 169.5, 170.1; IR 2984, 2936, 1738, 1659, 1595, 1244, 775, 704 cm^{-1}; HRMS calculated for $C_{13}H_{17}NO_3$, 235.283; measured 235.1186; LRMS *m/e* 235.1209 (M^+, 9), 192 (M^+ 2), 107 (100).

3-Acetoxy-*N*-(2-iodophenyl)-*N*,4,4-trimethylpentanamide (5e). 4-Dimethylaminopyridine (DMAP, 0.014 mmol) was added to a neat solution of **5a** (1.38mmol), acetic anhydride (2.08 mmol), and triethylamine (2.08 mmol) at 25°C. After 2.5 h, the reaction mixture was poured into diethyl ether (10 mL) and washed with 1 N HCl (2 x 3 mL), 2 N NaOH (2 x 3 mL), and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash chromatography (30% ethyl acetate/hexanes) to afford the desired **5e** (quantitative yield) in a rotamer ratio of 63/37 as determined by integration of the ^1H NMR: ^1H NMR signals attributed to the major rotamer: δ 1.00 (s, 9 H, C(CH_3)$_3$), 2.09 (s, 3 H, C(O)CH_3), 3.13 (s, 3 H, NCH_3), 4.96 (dd, 1 H, J =10.2, 3.0 Hz, C*H*). Signals attributed to minor rotamer: δ 1.19 (s, 9 H, C(CH_3)$_3$), 2.05 (s, 3 H, C(O)CH_3), 3.17 (s, 3 H, NCH_3), 5.26 (dd, 1 H, J = 10.2, 3.0 Hz, C*H*). Signals overlapping: δ 2.17 (m, 4 H, CH_2), 7.08 (m, 2 H), 7.26 (m, 1 H), 7.46 (m, 2 H), 7.55 (m, 1 H), 7.94 (m, 2 H); ^{13}C NMR signals attributed to the major rotamer: δ 21.3, 34.2, 35.7, 36.2, 100.1, 140.1, 145.9, 169.9, 170.9. Signals attributed to the minor rotamer: δ 21.2, 34.5, 34.8, 36.1, 99.6, 129.2, 146.1, 170.0, 170.2. Signals overlapping: δ 25.5, 25.7, 129.3, 129.8, 129.9 (28 resonances expected, 23 observed); IR 2965, 2874, 1740, 1669, 1471, 1372, 1242, 770, 727 cm^{-1}; HRMS calculated for $C_{16}H_{22}NO_3$ ($M^+ - I$), 276.1605; measured, 276.1600; LRMS *m/e* 276 ($M^+ - I$, 20), 233 (30), 216 (100), 111 (90).

3-Acetoxy-*N*,4,4-trimethyl-*N*-phenylpentanamide (6eH). Prepared by the general acetylation procedure above from **6a** (0.61 mmol), acetic anhydride (1.82 mmol), triethylamine (1.82 mmol), and a catalytic amount of DMAP. The crude material was purified by flash chromatography (20% ethyl acetate/hexanes) to afford 133 mg (79%) of **6e** as a liquid: ^1H NMR δ 0.65 (s, 9 H, C(CH_3)$_3$), 2.08 (s, 3 H, C(O)CH_3), 2.23 (dd, 1 H, J = 10.2, 14.2 Hz, *H syn* to OAc), 2.45 (m, 1 H, H *anti* to OAc), 3.23 (s, 3 H, NCH_3), 5.01 (dd, 1 H, J = 10.0, 1.8 Hz, C*H*C(CH_3)$_3$), 7.28 (m, 2 H), 7.36 (m, 1 H), 7.45 (m, 2 H); ^{13}C NMR δ 20.9, 25.3, 34.1, 34.8, 37.4, 127.5, 127.8, 129.7, 143.9, 170.3, 170.4 (12 resonances expected, 11 observed); IR 3004, 1788, 1700, 1293, 792,723 cm^{-1}; HRMS calculated for $C_{16}H_{23}NO_3O$, 277.1678; measured 277.1701; LRMS *m/e* 277 (M^+, 7), 107 (100).

3-Acetoxy-*N*-(2-iodophenyl)-*N*,2,4,4-tetramethylpentanamide (11e). Prepared by the general procedure above from DMAP (0.008 mmol), **11a** (0.80 mmol), acetic anhydride (1.20 mmol), and triethylamine (1.20 mmol). The crude material was purified by flash chromatography (50% ethyl acetate/hexanes) to afford 312 mg (94%) of **11e** as a white solid in an 80/20 rotamer ratio: ^1H NMR signals attributed to the major rotamer: δ 0.64 (s, 9 H, C(CH_3)$_3$), 1.17 (d, 3 H, J = 6.7 Hz, CH_3), 2.10 (s, 3 H, C(O)CH_3), 2.54 (m, 1 H, C*H*), 3.12 (s, 3 H, NCH_3), 4.88 (d, 1 H, J = 2.6 Hz, C(CH_3)*H*). Signals attributed to the minor rotamer: δ 0.82 (s, 9 H, C(CH_3)$_3$), 1.15 (d, 3 H, J =

6.8 Hz, CH_3), 2.11 (s, 3 H, C(O)CH_3), 2.35 (m, 1 H, C*H*), 3.15 (s, 3 H, NCH_3), 5.35 (d, 1 H, J = 2.6 Hz, C$(CH_3)_3H$). Signals overlapping: δ 7.07 (m, 2 H), 7.26 (m, 1 H), 7.44 (m, 2 H), 7.58 (m, 1 H), 7.94 (m, 2 H); ^{13}C NMR δ 12.4, 21.0, 26.8, 35.3, 36.7, 37.6, 96.2, 100.6, 129.9, 130.0, 140.2, 146.1, 171.0, 173.8 (15 resonances expected, 14 observed; minor rotamer not observed); IR 2959, 1736, 1655, 1238 cm^{-1}; HRMS calculated for $C_{14}H_{19}INO_2$ ($M^+ - C_2H_2O$, $- CH_3$), 360.0460; measured, 360.0438; LRMS *m/e* 360 ($M^+ - C_2H_2O$, $- CH_3$, 4), 318 (25), 290 (40), 233 (25), 125 (100).

3-Trifluoroacetoxy-*N*-(2-iodophenyl)-*N*,4,4 trimethylpentanamide (5f). Trifluoroacetic anhydride (0.83 mmol) was added to a neat solution of **5a** (0.55 mmol) and triethylamine (0.83 mmol). After 3 h, the reaction mixture was poured into ether (50 mL) and washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried with $MgSO_4$ and concentrated to afford 200 mg (79%) of **5f** as a liquid. The product was clean as determined from ^1H NMR analysis, and had a rotamer ratio of 53/47. The product is easily hydrolyzed and must be kept under an inert atmosphere at all times. (The product may be further purified by flash chromatography (20% ethyl acetate/hexanes) but elimination of trifluoroacetic acid to form an α,β-unsaturated pentenamide is suspected to occur for some of the sample.) ^1H NMR signals attributed to the major rotamer: δ 0.81 (s, 9 H, C$(CH_3)_3$), 3.15 (s, 3 H, NCH_3), 5.46 (dd, 1 H, J = 11.1, 3.2 Hz, C$(CH_3)_3H$), 7.25 (m, 1 H). Signals attributed to the minor rotamer: δ 0.76 (s, 9 H, C$(CH_3)_3$), 3.14 (s, 3 H, NCH_3), 5.31 (dd, 1 H, J = 9.4, 2.9 Hz, C$(CH_3)_3H$), 7.34 (m, 1 H). Signals overlapping: δ 2.24 (m, 4 H, CH_2), 7.11 (m, 2 H), 7.46 (m, 2 H), 7.95 (m, 2 H); ^{13}C NMR δ 25.4, 34.0, 34.4, 34.6, 34.8, 35.9, 36.1, 45.9, 81.3, 82.1, 99.3, 99.6, 113.0, 116.0, 129.1, 130.2, 130.3, 140.3, 140.5, 145.4, 145.6, 168.8, 169.0 (28 resonances expected, 23 observed).

General Procedure for the Etherification of 3-Hydroxyamides.[27]

***N*-(2-Iodophenyl)-3-methoxy-*N*,2-dimethylbutamide (9g).** A mixture of powdered KOH (3.6 mmol) in DMSO (3 mL) was stirred at 25°C for 5 min. Alcohol **9a** (0.9 mmol) was added and the solution turned a dark brown. Iodomethane (1.8 mmol) was added quickly and the solution turned light yellow. After 30 minutes, a second portion of iodomethane (1.8 mmol) was added and the reaction was stirred for 2 h. The reaction was quenched with water (2mL) and worked up in ether (15 mL). The organic extracts were washed with brine (15 mL), dried with $MgSO_4$, and concentrated. The crude material was purified by flash chromatography (50% ethyl acetate/hexanes) to afford 272 mg (87%) of **9g** as a clear liquid. The product was a mixture of syn (87) and anti isomers (13); the syn isomer was also a 50/50 mixture of rotamers: ^1H NMR signals attributed to the syn rotamers: δ 1.13 (dd, 6 H, J = 6.0, 6.2 Hz, CH_3), 1.23 (dd, 6 H, J = 6.2, 5.6, CH_3), 3.15 (s, 3 H, NCH_3), 3.18 (s, 3 H, NCH_3), 3.22 (s, 3 H, OCH_3), 3.28 (s, 3 H, OCH_3). Signals attributed to the minor anti isomer: δ 0.97 (d, 3 H, J = 6.1 Hz, CH_3), 1.04 (d, 3 H, J = 7.0 Hz, CH_3), 3.21 (s, 3 H, OCH_3). Signals overlapping: δ 2.04 (m, 1 H, C*H*), 2.26 (m, 2 H, C*H*), 3.39 (m, 3 H), 7.04 (m, 3 H), 7.24 (m, 3 H), 7.36 (m, 3 H), 7.91 (m, 3 H). A 300 MHz ^1H NMR study of the mixture (DMSO-d_6) at various probe temperatures (293 K→373K) gave coelescence at a probe temp of 353 K; ^{13}C NMR δ 15.6, 15.7, 15.8, 17.0, 18.8, 36.1, 36.3, 43.1, 44.5, 56.8, 56.9, 79.0, 79.9, 99.2, 99.4, 128.9, 129.2, 129.6, 129.7, 129.9, 130.0, 140.3, 140.6, 145.7, 146.1, 174.6, 175.2 (39 resonances expected, 27 observed); IR 2975, 2934, 1680, 1102, 790, 750 cm^{-1}; HRMS calculated for $C_{12}H_{15}INO_2$ ($M^+ - CH_3$) 332.0147; measured, 332.0097; LRMS *m/e* 332 ($M^+ - CH_3$, 3), 233 (25), 220 ($M^+ - I$, 50).

***Syn* and *anti*-3-Methoxy-*N*,2-dimethyl-*N*-phenylbutanamide (10g).** Prepared by the general etherification procedure above from **10a** (60/40 syn/anti mixture, 4.35 mmol), KOH (17.4 mmol), iodomethane (8.69 mmol), and DMSO (10 mL). After 2 h, additonal iodomethane (8.69 mmol) was added and the reaction mixture stirred for 16 h. The syn and anti products were readily separated by flash chromatography (20% ethyl acetate/hexanes; R_f = 0.30 (syn) and 0.21 (anti), 50% ethyl acetate/hexanes). The yield of the syn product was 403 mg; the anti, 186 mg (61% combined). **10g-syn**: ^1H NMR δ 1.08 (d, 3 H, J = 6.2 Hz, C$(OCH_3)CH_3$), 1.12 (d, 3 H, J = 6.7 Hz, CH_3), 2.43 (m, 1 H, C*H*), 3.25 (s, 6 H, OCH_3 and NCH_3), 3.34 (m, 1 H, C$(OCH_3)H$), 7.15 (m, 2 H), 7.35 (m, 3 H); ^{13}C NMR δ 15.1, 16.9, 37.0, 43.0, 56.6, 79.2, 127.2, 127.6, 129.6, 143.7, 174.7; IR 2973, 2934, 1653, 1102 cm^{-1}; HRMS calculated for $C_{13}H_{19}NO_2$, 221.1415; measured, 221.1417; LRMS *m/e* 221 (11), 206 (10), 107 (100). **10g-anti**: ^1H NMR δ 0.93 (d, 3 H, J = 6.9 Hz, C$(OCH_3)CH_3$), 1.00 (d, 3 H, J = 6.2 Hz, CH_3), 2.46 (m, 1 H, C$(CH_3)H$), 3.25 and 3.27 (s, 6 H, OCH_3 and NCH_3), 3.51 (m, 1 H, C$(OCH_3)H$), 7.23 (m, 2 H), 7.32 (m, 1 H), 7.39 (m, 2 H); ^{13}C NMR δ 14.1, 15.7, 37.3, 42.6, 56.8, 79.1, 127.4, 127.6, 129.5, 144.0, 175.2; IR 2975, 2934, 1655, 1103 cm^{-1}; HRMS calculated for $C_{13}H_{19}NO_2$, 221.1416; measured, 221.1424; LRMS *m/e* 221 (11), 206 (8), 107 (90).

General Procedures for Allylation Reactions.

***Syn* and *anti* 2-(1-Hydroxy-2,2-dimethylpropyl)-*N*-methyl-*N*-phenyl-4-pentenamide (7a).** Method 1. A solution of allyl tributyltin (1.1 mmol) and **5a** (0.55 mmol) in dry benzene (1.10 mL, [RI] = 0.5 M) was degassed with argon and photolyzed with a Hanovia UV lamp for 48 h. The reaction was concentrated and GC analysis of the crude reaction mixture indicated an syn:anti ratio of 7:93. The mixture was purified by HPLC (20% ethyl acetate/hexanes) to afford 151 mg (64%) of **7a** in a 3:97 syn:anti ratio. A third product, tentatively assigned as 3-hydroxy-*N*,4,4-trimethyl-*N*-(2-(2-propenyl))phenylpentanamide was also isolated (yield not determined).

Method 2. A solution of **5a** (72 mg, 0.2 mmol), allyltributyltin (132 mg, 0.4 mmol), and AIBN (4 mg, 0.92 mmol) in d_6-benzene was heated at 80°C for 10 h. The solvent was removed under reduced pressure and the crude product was purified by MPLC (12.5% ethyl acetate/hexanes) to afford **7a syn/anti** in a 13/87 mixture (39.5 mg, 72%).

Method 3:[28] To a solution of LDA (2.2 mmol) in THF (10 mL) at –78°C was added a solution of *N*-methyl-*N*-phenyl-4-pentenamide (0.378 g, 2.0 mmol) in THF (2 mL). The solution was stirred for 30 min, and pivaldehyde (0.224 g, 2.6 mmol) was added quickly. The reaction mixture was kept at –78°C for an additional 30 min, and acetic acid (0.3 mL) was added. The reaction mixture was diluted with water (10 mL), and extracted with ether (3 x 10 mL). The combined organic layers were washed with water (2x) and brine (1x), and dried over $MgSO_4$. Purification by MPLC (22% ethyl acetate/hexanes) gave **7a syn/anti** (60/40) mixture (266 mg, 48%): ^{1}H NMR (C_6D_6) signals attributed to the syn product: δ 0.93 (s, 9 H, C(CH_3)$_3$), 3.08 (s, 3 H, NCH_3), 3.61 (br s, 1 H, β*H*), 4.18 (br s, 1 H, O*H*), 5.80 (m, 1 H). Signals attributed to the anti product: δ 0.98 (s, 9 H, C(CH_3)$_3$), 3.00 (s, 3 H, NCH_3), 3.46 (dd, 1 H, J_1 = 9.0 Hz, J_2 = 1.2 Hz, βH), 5.60 (m, 1 H), 6.08 (d, 1 H, J = 8.8 Hz, O*H*). Signals overlapping: δ 2.45 (m, 2 H, αH), 2.89 (m, 4 H, H_2C=C(H)CH_2), 5.06 (m, 4 H, H_2C=C), 6.82 (m, 4 H), 6.97 (m, 6 H); ^{13}C NMR δ 26.2, 35.9, 37.4, 39.0, 79.7, 117.7, 127.2, 128.4, 129.8, 135.2, 143.1, 177.0; HRMS calculated for $C_{17}H_{26}NO_2$ (M^+ + H), 276.1964; measured 276.1964; LRMS *m/e* 276, 260, 234, 218, 189, 176, 134, 123, 107, 87, 77.

Detailed Analysis of Allylation of ***1e.*** Method 1. Hexamethylditin (0.014 mmol) was added to a neat mixture of methyl 2-(*n*-tributylstannyl methyl) acrylate (0.28 mmol) and **1e** (0.14 mmol) in a small vial. The sample was heated at 80°C for 2 h and irradiated with a sunlamp. ^{1}H NMR of the crude reaction mixture showed a mixture of products in the following ratios as determined by integration of the NCH_3 protons of the products **4e-syn/4e-anti/2eH/18/19**: 47.5/12.7/16.0/23.8/not observed. The crude reaction mixture was purified by analytical HPLC (30% ethyl acetate/hexanes) to afford **4e-syn** (7 mg, 15%), **2eH** (2 mg, 4%), **4e-anti** (3 mg, 6%), **18** and an impurity (3 mg) in this order. Product **2eH** was not isolated. Experiments in which benzene was used as a solvent (0.01–0.3M) gave products **2eH**, **18**, and **19** in 2-6% of the theoretical yield. Also, as expected, the amount of **18** in the crude reaction mixture increased with an increase of reaction concentration.

2-(*N*-Methyl-*N*-phenylcarbamoyl)-4-methoxycarbonyl-1-methyl-4-pentenyl ethanoate (4e-syn): ^{1}H NMR δ 1.21 (d, 3 H, J = 6.4 Hz, (CH_3)H), 1.99 (s, 3 H, C(O)CH_3), 2.55 (d, 2 H, J = 7.0 Hz, H_2C=CCH_2), 2.85 (q, 1 H, Hα to amide), 3.21 (s, 3 H, NCH_3), 3.60 (s, 3 H, CO_2CH_3), 5.03 (m, 1 H, C(CH_3)*H*), 5.64 (d, 1 H, J = 0.8 Hz), 6.21 (d, 1 H, J = 1.5 Hz), 7.08 (m, 2 H), 7.35 (m, 3 H); ^{13}C NMR δ 18.0, 21.2, 33.2, 37.6, 51.8, 72.0, 127.9, 128.1, 128.2, 129.7, 137.5, 143.5, 167.1, 170.3, 171.9 (16 resonances expected, 15 observed); IR 2986, 2952, 1727, 1723, 1651, 1240, 776, 704 cm^{-1}; HRMS calculated for $C_{18}H_{23}NO_5$, 333.1576; measured 333.1556; LRMS *m/e* 333 (M^+, 10), 290 ($M^+ - C_2H_3O$, 4), 274 ($M^+ - C_4H_9$, 4), 227 (10), 185 (60), 167 (90), 107 (100).

2-(*N*-Methyl-*N*-phenylcarbamoyl)-4-methoxycarbonyl-1-methyl-4-pentenyl Ethanoate (4e-anti). ^{1}H NMR δ 1.22 (d, 3 H, J = 6.2 Hz, C(CH_3)H), 2.05 (s, 3 H, C(O)CH_3), 2.48 (m, 2 H, CH_2=CCH_2), 2.89 (m, 1 H, Hα to amide), 3.21 (s, 3 H, NCH_3), 3.54 (s, 3 H, CO_2CH_3), 5.01 (m, 1 H, C(CH_3)*H*), 5.67 (s, 1 H), 6.21 (d, 1 H, J = 1.5 Hz), 7.09 (m, 2 H), 7.37 (m, 3 H); ^{13}C NMR δ 17.4, 21.4, 31.9, 37.4, 46.5, 51.7, 71.9, 127.7, 127.9, 128.3, 129.5, 137.1, 143.5, 166.7, 169.7, 172.0; IR 2951, 1727, 1723, 1655, 1240 cm^{-1}; HRMS calculated for $C_{18}H_{23}NO_5$, 333.389; measured 333.1576; LRMS *m/e* 333 (M^+, 5), 290 ($M^+ - C_2H_3O$, 5), 185 (60), 167 (65), 107 (100).

***syn* and *anti* 2-(*N*-Methyl-*N*-phenylcarbamoyl)-1-*tert*-butyl-4-pentenyl Ethanoate (7e-syn + 7e-anti).** Method 1. Prepared by the Hanovia lamp allylation procedure above from **5e** (0.50 mmol) and allyl tributyltin (1.0 mmol). The reaction mixture was photolyzed for 24 h. The crude reaction mixture gave a syn/anti ratio (81:19) of products as determined by integration of the ^{1}H NMR spectra. The mixture was purified by the HPLC conditions previously mentioned to afford 65 mg (41%) of the pure syn isomer. Method 2. The syn/anti mixture

(60/40) of **7a** (0.18 mmol) was subjected to the standard acetylation procedure to afford the desired products in quantitative yield. The syn and anti acetylated products (**7e**) were separated by flash chromatography (20% ethyl acetate/hexanes; R_f (major) = 0.46, R_f (minor) = 0.36). Method 3. AIBN was added to alcohol **5a** (0.55 mmol) and allyl tributyltin (1.11 mmol) in dry benzene in a 5 mm ^{1}H NMR tube (0.5M), and the mixture was heated at 80°C for 26 h. Proton NMR of the crude reaction mixture showed mostly the anti product. The sample was first purified by flash chromatography (10% ethyl acetate/hexanes, then 50% ethyl acetate/hexanes), acetylated in the usual manner, and purified by flash chromatography (20% ethyl acetate/hexanes) to afford 66 mg (38%) of **7e-anti** as a liquid: **7e-syn**: ^{1}H NMR δ 0.65 (s, 9 H, C(CH_3)$_3$), 2.02 (s, 3 H, C(O)CH_3), 2.22 (m, 1 H), 2.50 (m, 1 H), 2.77 (m, 1 H), 3.19 (s, 3 H, NCH_3), 4.98 (m, 2 H + 1 H, C=CH_2 + C(CH_3)$_3$*H*), 5.70 (m, 1 H, C=C*H*), 7.22 (m, 2 H), 7.30 (m, 1 H), 7.40 (m, 2 H); ^{13}C NMR δ 21.0, 26.5, 32.8, 35.5, 41.9, 78.9, 116.2, 127.9, 128.0, 129.7, 136.6, 143.7, 170.5, 172.7 (15 resonances expected, 14 observed); IR 3069, 2963, 1740, 1659, 1240, 774, 669 cm^{-1}; HRMS calculated for $C_{19}H_{27}O_3N$, 317.1991; measured 317.1991; LRMS *m/e* 317 (M^+, 7), 302 ($M^+ - CH_3$, 3), 274 ($M^+ - C(O)CH_3$, 20), 188 ($M^+ - C_7H_{13}O_2$, 8), 151 (50). **7e-anti** ^{1}H NMR δ 0.71 (s, 9H, C(CH_3)$_3$), 4.82 (d, 1 H, J = 7.7 Hz, C(CH_3)$_3$*H*), 5.04 (m, 2 H), 5.70 (m, 1 H), 7.22 (m, 2 H), 7.40 (m, 3 H); ^{13}C NMR δ 21.2, 26.5, 35.4, 36.7, 37.5, 43.3, 80.2, 117.1, 127.2, 128.2, 129.5, 135.3, 169.8, 172.2 (15 resonances expected, 14 observed); IR 3004, 1792, 1692, 1260, 793, 718 cm^{-1}; HRMS calculated for $C_{19}H_{27}NO_3$, 317.1991, measured 317.1998.

***syn* and *anti* 2-(*N*-Methyl-*N*-phenylcarbamoyl)-1-*tert*-butyl-5-methoxycarbonyl-5-hexenyl Ethan-oate (8e).** Method 1. AIBN (0.03 mmol) was added to a solution of **5e** (0.35 mmol) and methyl 2-(tributylstannyl methyl) acrylate (0.70 mmol) in dry benzene (0.5 M) in a 5 mm NMR tube. After heating at 80°C for 14.5 h, the mixture was concentrated and the ^{1}H NMR of the crude reaction mixture showed the syn and anti products in a 75/25 ratio. The mixture was purified by flash chromatography (50% ethyl acetate/hexanes; R_f of A = 0.72) to afford 2 major fractions. Fraction 1 contained pure syn product (80 mg) and fraction 2 contained an syn/anti mixture of 39/61 (28 mg). The combined yield was 108 mg (87% yield). Method 2. An 11/89 syn/anti mixture of **7a** (0.030 mmol) was acetylated by using the general procedure above. Flash chromatography afforded 4 mg (35%) of pure **8e-anti** as a clear liquid. **8e-syn**: ^{1}H NMR δ 0.67 (s, 9 H, C(CH_3)$_3$), 2.07 (s, 3 H, C(O)CH_3), 2.68 (m, 2 H, CH_2), 3.0 (m, 1 H, Hα to amide), 3.11 (s, 3 H, NCH_3), 3.63 (s, 3 H, CO_2CH_3), 4.84 (s, 1 H, Hβ to amide), 5.66 (s, 1 H), 6.18 (s, 1 H), 7.05 (m, 2 H), 7.30 (m, 3 H); ^{13}C NMR δ 21.0, 26.6, 30.1, 35.8, 41.1, 51.7, 78.0, 127.8, 128.1, 128.6, 129.6, 137.7, 143.5, 167.4, 170.6, 172.5; IR 2959, 1750, 1723, 1659, 1235, 774, 704 cm^{-1}; HRMS calculated for $C_{21}H_{29}NO_5$, 375.2046; measured 375.2048; LRMS m/e 375 (M^+, 12), 246 (18), 227 (12), 209 (100). **8e-anti**: ^{1}H NMR δ 0.78 (s, 9 H, C(CH_3)$_3$), 2.08 (s, 3 H, C(O)CH_3), 2.68 (m, 2 H, CH_2), 3.15 (m, 1 H, Hα to amide), 3.17 (s, 3 H, NCH_3), 3.61 (s, 3 H, CO_2CH_3), 4.85 (d, 1 H, J = 8.6 Hz, O*H*), 5.72 (s, 1 H), 6.23 (s, 1 H), 7.05 (m, 2 H), 7.30 (m, 3 H); ^{13}C NMR δ 21.3, 26.6, 35.3, 35.7, 37.3, 43.6, 51.7, 80.3, 127.8, 128.4, 128.9, 129.5, 137.2, 143.6, 167.1, 169.7, 172.1.

2-Isopropyl-*N*-methyl-*N*-phenyl-4-pentenamide (16). Hexamethylditin (0.03 mmol) was added to a solution of tributylallyltin (0.67 mmol) and **14** (0.33 mmol) in dry benzene (0.3 M) in a 5 mm NMR tube. After 24 h of photolysis, with a Hanovia lamp, one additional equivalent (0.33 mmol) of tributylallyltin was added. After an additional 24 h of photolysis the reaction mixture was concentrated under reduced pressured and treated with I_2/DBU in the usual manner. The product was further purified by flash chromatography (50% ethyl acetate/hexanes) to afford 2 fractions. The first fraction contained the desired product and some tin impurities; the second contained what is suspected to be the reduced starting material, some desired product, and tin impurities. These two fractions were again treated with I_2/DBU to afford 44 mg (57%) of the desired product from fraction one as a yellow oil: ^{1}H NMR δ 0.82 (d, 3 H, J = 6.7 Hz, CH_3), 0.86 (d, 3 H, J = 6.7 Hz, CH_3), 1.85 (m, 1 H, Hβ to amide), 2.17 (m, 2 H, CH_2), 2.33 (m, 1 H, Hα to amide), 3.26 (s, 3 H, NCH_3), 5.02 (m, 2 H), 5.72 (m, 1 H), 7.15 (m, 2 H), 7.36 (m, 3 H); ^{13}C NMR δ 19.8, 21.3, 31.0, 35.0, 37.4, 48.3, 116.3, 127.6, 128.2, 129.4, 136.6, 144.1, 174.9; IR 2959, 1653, 774, 702 cm^{-1}; Exact mass calculated for $C_{15}H_{21}NO$, 231.1623; measured 231.1611; LRMS *m/e* 231 (M^+, 6), 216 ($M^+ - CH_3$, 2), 189 ($M^+ - C_3H_6$, 25), 107 (100).

Methyl 2-(2-(*N*-methyl-*N*-phenylcarbamoyl)-3-methylbutyl)propenoate (17). AIBN (0.02 mmol) was added to a solution of **14** (0.16 mmol) and methyl 2-(tributylstannyl methyl) acrylate (0.32 mmol) in dry benzene (0.3 M) in a 5 mm NMR tube. The tube was immersed in a 80°C bath and irradiated with a sunlamp for 22 h. The reaction mixture was concentrated, diluted with ether, and treated with I_2 and DBU.[29] The product was further purified by flash chromatography (50% ethyl acetate/hexanes) followed by a second treatment of I_2/DBU (in ether) to

afford 29 mg (63%) of the product **17** as a yellow oil: ^{1}H NMR δ 0.88 (m, 6 H, C(CH_3)$_2$), 1.82 (m, 1 H, C(CH_3)$_2H$), 2.43 (m, 3 H, CH_2 and C(O)C*H*), 3.18 (s, 3 H, NCH_3), 3.57 (s, 3 H, C(O)OCH_2), 5.65 (s, 1 H), 6.19 (s, 1 H), 7.01 (m, 2 H), 7.31 (m, 3 H); ^{13}C NMR δ 19.7, 21.4, 31.3, 33.1, 37.4, 47.9, 51.7, 127.6, 127.7, 128.2, 129.4, 138.5, 143.9, 167.2, 174.7; IR 2874, 1723, 1651, 774, 702 cm^{-1}; LRMS *m/e* 289 (M$^+$, 10), 147 (10), 183 (50), 107 (100).

1-(*N*-(2-(2-Methoxycarbonyl-2-propenyl)phenyl-2-methoxycarbamoyl)methyl)ethyl ethanoate (18). ^{1}H NMR (1:1 rotamer ratio about N–Ar bond): δ 1.21 (m, 3 H, C(CH_3)H), 1.99 (s, 3 H, C(O)CH_3), 2.10 (m, 2 H, CH_2), 2.3 (m, 2 H, CH_2 α to phenyl), 3.18 (s, 3 H, NCH_3), 3.72 (s, 3 H, CO_2CH_3), 5.30 (t, 1 H, J = 6.4 Hz, C(CH_3)*H*), 5.50 (d, 1 H), 6.34 (s, 1 H), 7.16 (m, 1 H), 7.30 (m, 3 H); ^{13}C NMR δ 20.0, 21.4, 33.2, 33.3, 36.5, 36.6, 40.0, 40.1, 52.1, 68.1, 127.6, 128.3, 128.6, 128.8, 130.6, 130.8, 136.2, 136.4, 138.4, 138.6, 142.3, 166.8, 166.9, 169.8, 170.0, 170.2 (32 resonances expected, 26 observed); IR 2919, 2851, 1727, 1723, 1657, 1599, 1244 cm^{-1}; HRMS calculated for $C_{18}H_{23}NO_5$, 333.1576; measured 333.1570; LRMS *m/e* 333 (M$^+$, 3), 290 (M$^+$ – C_2H_3O, 2), 234 (25), 69(100).

1-(*N*-Methyl-*N*-phenylcarbamoyl)methyl)-3-methoxycarbonyl-1-methyl-3-butenyl ethanoate (19). ^{1}H NMR δ 1.24 (m, 3 H, 3H_3), 2.00 (s, 3 H, C(O)CH_3), 2.27 (t, 2 H, CH_2), 2.58 (t, 2 H, CH_2), 3.27 (s, 3 H, NCH_3), 3.66 (s, 3 H, CO_2CH_3), 5.52 (s, 1 H), 6.12 (s, 1 H), 7.23 (m, 2 H), 7.36 (m, 1 H), 7.44 (m, 2 H).

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