JOC*Note*

Generation and Intermolecular Reactions of 3-Indolylacyl Radicals

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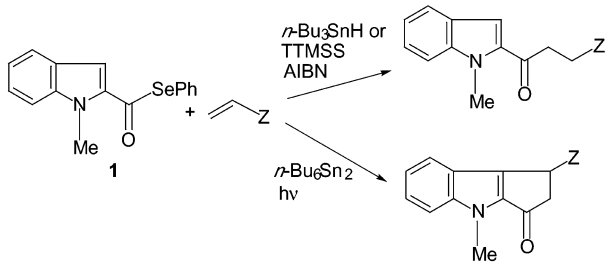
Abstract: The generation of 3-indolylacyl radicals from the corresponding phenyl selenoesters and the scope of their participation in intermolecular addition reactions to carbon−carbon double bonds under both reductive and nonreductive conditions have been studied.

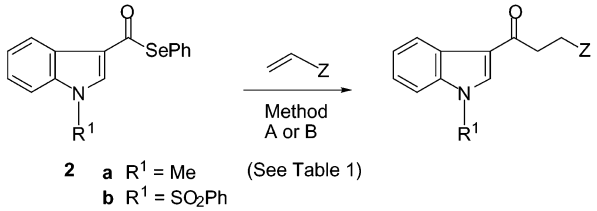
Radical reactions have become an important tool in synthetic organic chemistry.[1] In particular, inter- and intramolecular addition of nucleophilic acyl radicals[2] to multiple (mainly C−C) bonds constitutes a useful method for the preparation of unsymmetrical ketones. The reaction of selenoesters with stannyl and tris(trimethylsilyl)-silyl radicals is one of the most practical ways to generate these radical intermediates.[2] Boger has reported the acyl transfer reaction of a series of alkyl and aryl phenyl selenoesters to alkenes using *n*-Bu_3SnH as the radical mediator.[3,4] More recently, we have described how 2-indolylacyl radicals derived from phenyl selenoesters (e.g., **1**, Scheme 1) efficiently participate in intermolecular addition reactions with electron-deficient alkenes under reductive conditions to give 1,4-dicarbonyl compounds bearing the 2-acylindole moiety.[5] Furthermore, under nonreductive conditions (*n*-Bu_6Sn_2, *hν*) 2-indolylacyl radicals undergo a novel cascade reaction involving an addition−oxidative cyclization sequence to give cyclopenta[*b*]indol-3-ones.[6]

On the basis of these precedents, we reasoned that the regioisomeric *3-indolyl*acyl radicals should also participate in similar reactions, thus providing access to a variety of 3-acylindole compounds, which are versatile

SCHEME 1



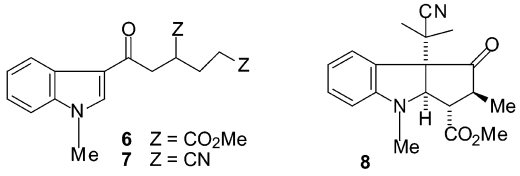
SCHEME 2



starting materials for the synthesis of indole derivatives. This Note deals with our results in the unprecedented generation of 3-indolylacyl radicals from phenyl selenoester precursors[7] and their role in intermolecular reactions with alkenes.

The use of reductive conditions from selenoesters **2a**,**b** (Scheme 2) and the alkene acceptors depicted in Table 1 was first investigated. Satisfactorily, the 3-indolylacyl radical derived from **2a** reacted productively with alkenes bearing electron-withdrawing groups in yields generally higher than those previously obtained in the 2-acylindole series.[5]

Using simple, unsubstituted electron-deficient alkenes and 2-cyclohexenone (entries 1−3) afforded the corresponding addition products **3**−**5** in good yields (76−82%) following Method A (*n*-Bu_3SnH, AIBN), with little or no competitive acyl radical reduction (0−5%) and no evidence of competitive decarbonylation. More importantly, these reactions could be conducted using only a 1.5-fold excess of the alkene acceptor, which is unusual in intermolecular radical additions. In fact, when reactions reported in entries 1 and 2 were carried out with the more common 4- or 5-fold excess of the alkene, the desired adducts **3** and **4** were isolated in lower yields (40−50%) together with significant amounts (15−30%) of the respective bis-addition products **6** and **7**.



However, premature reduction of the intermediate radical to the indolecarbaldehyde partially competed with

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(1) (a) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon: Oxford, 1991; Vol. 4, pp 715−777, 779−831. (b) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301−856. (c) Renaud, P.; Sibi, M. P., Eds. *Radicals in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2001.

(2) For recent reviews on acyl radicals, see: (a) Ryu, I.; Sonoda, N.; Curran D. P. *Chem. Rev.* **1996**, *96*, 177−194. (b) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991−2069.

(3) (a) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1989**, *54*, 1777−1779. (b) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1992**, *57*, 1429−1443.

(4) For more recent examples of intramolecular addition reactions from alkyl phenyl selenoesters, see: (a) Double, P.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2005−2007. (b) Evans, P. A.; Raina, S.; Ahsan, K. *Chem. Commun.* **2001**, 2504−2505, and references therein.

(5) Bennasar, M.-L.; Roca, T.; Griera, R.; Bosch, J. *Org. Lett.* **2001**, *3*, 1697−1700.

(6) Bennasar, M.-L.; Roca, T.; Griera, R.; Bosch, J. *J. Org. Chem.* **2001**, *66*, 7547−7551.

(7) For an isolated example of the generation of a 3-indolylacyl radical from an indole-3-glyoxylic acid under oxidative (Minisci) conditions, see: Doll, M. K.-H. *J. Org. Chem.* **1999**, *64*, 1372−1374.

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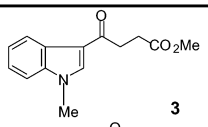
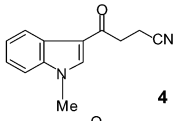
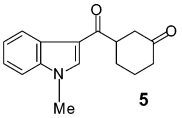
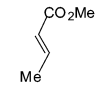
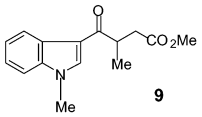
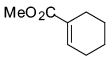
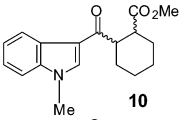
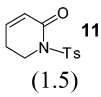
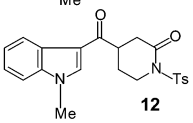
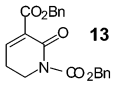
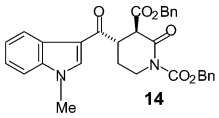
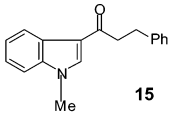
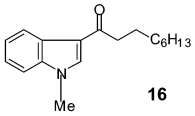
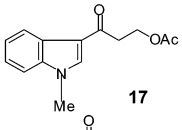
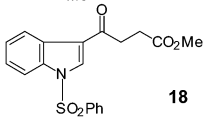
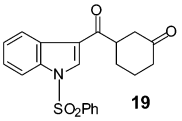
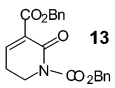
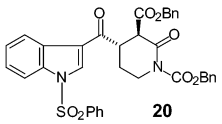
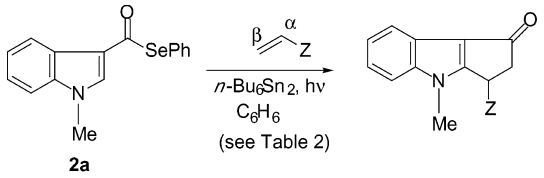
TABLE 1. Intermolecular Addition Reactions of 3-Indolylacyl Radicals Derived from Phenyl Selenoesters 2a,b

entry	indole derivative	alkene acceptor (equiv.)	product	method[a]	yield (%)[b]
1	**2 a**	 (1.5)	 **3**	A	82
2	**2 a**	 (1.5)	 **4**	A	80
3	**2 a**	 (1.5)	 **5**	A	76
4	**2 a**	 (5)	 **9**	A B	45[c,d] 47
5	**2 a**	 (5)	 **10**	A	51[c,e]
6	**2 a**	 **11** (1.5)	 **12**	A B	43[c] 64
7	**2 a**	 **13** (1.5)	 **14**	B	72
8	**2 a**	 (5)	 **15**	A	50
9	**2 a**	 (5)	 **16**	B	45
10	**2 a**	 (5)	 **17**	B	25[c]
11	**2 b**	 (5)	 **18**	A	55
12	**2 b**	 (5)	 **19**	B	35[c]
13	**2 b**	 **13** (5)	 **20**	B	30[c]

[a] Method A: *n*-Bu_3SnH, AIBN, C_6H_6. Method B: TTMSS, AIBN, C_6H_6. [b] Isolated yields. [c] Recovering of the corresponding 3-indolecarbaldehyde in 15−25% (50% for entry 10). [d] See text. [e] A 3:1 mixture of cis/trans stereoisomers.

SCHEME 3



the addition process when, for electronic or steric reasons, less reactive acceptors were used (entries 4−6). Using the poorer hydrogen-atom donor tris(trimethylsilyl)-silane[8] (TTMSS, AIBN, Method B) as the radical mediator in the reactions with methyl crotonate or methyl 1-cyclohexenecarboxylate (entries 4 and 5) did not significantly improve the yield of the addition products. In the former case, minor amounts (17%) of tricyclic indoline **8** were also isolated (see below). In contrast, starting from **2a** and a small excess of lactams **11** and **13** (entries 6 and 7) under the conditions of Method B provided good yields of 3-indolyl 4-piperidyl ketones **12** and **14** (64 and 72%, respectively).

As expected,[3,5] styrene worked reasonably well as an acceptor (50%, entry 8) under Method A conditions. The unexpectedly high yield (45%) obtained with an unactivated alkene (1-octene, entry 9) under Method B conditions was particularly noteworthy and illustrates the high reactivity of the 3-indolylacyl radical derived from **2a**. More in accordance with previous reports,[2b,3,9] the analogous reaction with an electron-rich alkene (entry 10) provided a modest yield (25%) of the adduct **17**, the indolecarbaldehyde being the major product (50%).

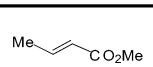
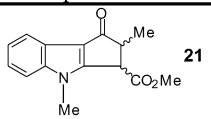
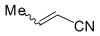
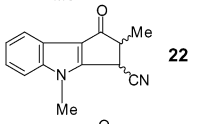
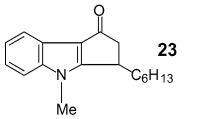
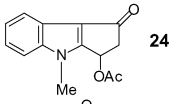
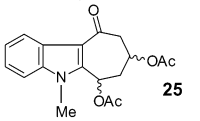
When some of the above reactions were extended to selenoester **2b**, which bears a strong electron-withdrawing group at the nitrogen, significant differences in the reactivity of the corresponding intermediate acyl radicals were observed, presumably reflecting the influence of the electronic properties of the indole ring on their nucleophilic character.[10] In all cases (entries 11−13), the yields of the addition products **18**−**20** were lower and, with the exception of the reaction with methyl acrylate (entry 11), reduction was a competitive process even under Method B conditions.

We next studied the reactions of selenoester **2a** with alkene acceptors under nonreductive conditions (*n*-Bu_6Sn_2, *hν*, Scheme 3). We expected a radical cascade reaction similar to that observed from selenoester **1** (Scheme 1),[6] which would now involve an intermolecular 3-indolylacyl radical addition followed by an oxidative cyclization[11] at the indole 2-position.[12]

As can be observed in Table 2, the desired annulation process took place with methyl crotonate or crotonitrile (entries 1 and 2) to give the corresponding cyclopenta-

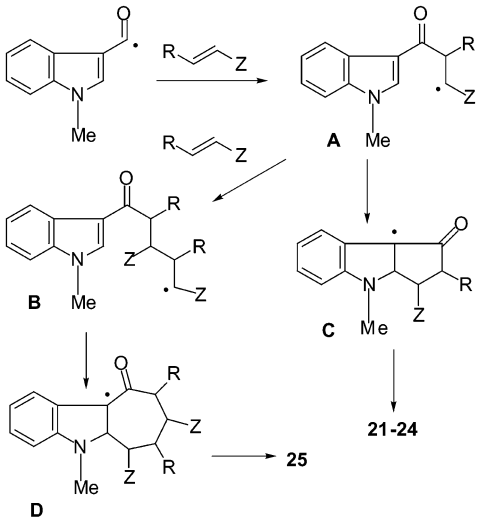
(8) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188−194.
(9) Dang, H.-S.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 67−75.
(10) Small differences in the redox properties of arylacyl radicals depending on the substitution of the ring have been reported. However, the relationship between these parameters and the nucleophilic character of the radical is not well understood. For a discussion, see: Daasbjerg, K.; Pedersen, S. U.; Lund, H. In *General Aspects of the Chemistry of Radicals*; Alfassi, Z. B., Ed.; Wiley: Chichester, UK, 1999; pp 385−427.
(11) The oxidative cyclization mechanism mediated by Me_6Sn_2 has been discussed: (a) Josien, H.; Ko, S. B.; Bom, D.; Curran, D. P. *Chem. Eur. J.* **1998**, *4*, 67−83. (b) Bowman, W. R.; Bridge, C. F.; Cloonan, M. O.; Leach, D. C. *Synlett* **2001**, 765−768.

TABLE 2. *n*-Bu_6Sn_2-Mediated Reactions of Phenyl Selenoester 2a with Alkene Acceptors

entry	alkene acceptor	addition-cyclization product	yield[a] (%)
1		 **21**	32[b]
2		 **22**	20[c]
3		 **23**	15
4		 **24**	15
		 **25**	15[b]

[a] Isolated yields. [b] A 6:1 mixture of trans/cis stereoisomers. [c] A 1:1 mixture of cis/trans stereoisomers.

SCHEME 4



[*b*]indol-1-ones **21** and **22** in moderate yields (32 and 20%, respectively). However, only complex mixtures were obtained with acrylonitrile or methyl acrylate, which had proved to be the best acceptors under reductive conditions. A similar result was obtained with other electron-deficient alkenes such as dimethyl fumarate or methyl 1-cyclohexenecarboxylate.

These results can be rationalized by considering the radical cascade reactions depicted in Scheme 4. Whereas the intermolecular addition to the acceptor was expected to be a fast reaction, the subsequent cyclization of the resultant electrophilic (Z = CO_2Me or CN) radical **A** (or **B**, if a double addition occurs) at the also electrophilic 2-position of the 3-acylindole[13] giving the benzylic radical **C** (or **D**) must be electronically unfavored.[14] In fact, the 5-endo cyclization[15] leading to the strained cyclopenta-[*b*]indole nucleus was only observed when *β*-methyl-substituted alkenes were used as acceptors, probably due to the presence of a methyl group in the radical adduct **A**, which would help to mitigate the above-mentioned unfavorable factors (Thorpe−Ingold effect).[16,17] The isolation of indoline **8**, which formally derives from the reaction of radical **C** (Z = CO_2Me, R = Me) with AIBN,[6,18] made evident that the radical cascade addition−cyclization sequence had already occurred from methyl crotonate under reductive conditions (TTMSS−AIBN)

Taking into account the above mechanistic considerations, we expected that using unactivated or electron-rich alkenes in this radical cascade reaction would result in a slower addition step, but in an electronically more favorable cyclization of the nucleophilic radical **A** at the indole 2-position. Accordingly, whereas 1-octene reacted sluggishly with selenoester **2a** (entry 3, 15%), vinyl acetate was more efficient leading to a 1:1 mixture of tricyclic compounds **24** and **25** in higher yield (30%, entry 4), the latter coming from the bis-addition radical **B** through the benzylic radical **D**.

In conclusion, a variety of 3-indolyl ketones, mainly 1,4-dicarbonyl compounds (keto esters, keto nitriles, keto lactams, diketones), can be prepared through the reaction of 3-indolylacyl radicals with appropriate acceptors under reductive conditions. Since the 3-position of indole is the preferred site for electrophilic substitution, there are several methods for the direct acylation at this position.[19] However, as these methods are not usually very compatible with acid- or base-sensitive indole compounds, our radical route can provide an alternative approach to 3-indolyl ketones under mild conditions.[20] On the other hand, under nonreductive conditions, 3-indolylacyl radicals are less efficient than 2-indolylacyl radicals in promoting the radical cascade addition−cyclization sequence leading to the cyclopenta[*b*]indole nucleus when electron-deficient alkenes are used as acceptors, although this annulation process is observed with electron-rich alkenes.

(12) For similar radical cascade reactions involving final cyclizations onto indoles and related heterocycles, see: (a) Chuang, C.-P.; Wang, S.-F. *Synth. Commun.* **1994**, *24*, 1493−1505. (b) Ozaki, S.; Mitoh, S.; Ohmori, H. *Chem. Pharm. Bull.* **1996**, *44*, 2020−2024. (c) Miranda, L. D.; Cruz-Almanza, R.; Pavón, M.; Romero, Y.; Muchowski, J. M. *Tetrahedron Lett.* **2000**, *41*, 10181−10184.

(13) Aldabbagh, F.; Bowman, W. R.; Mann, E.; Slawin, A. M. Z. *Tetrahedron* **1999**, *55*, 8111−8128.

(14) As expected from these mechanistic considerations, no productive reaction was observed from *N*-benzenesulfonyl selenoester **2b**.

(15) For a related example, see: (a) Gribble, G. W.; Fraser, H. L.; Badenock J. C. *Chem. Commun.* **2001**, 805−806. For more common 5-exo cyclizations onto the indole ring, see inter alia: (b) Ziegler, F. E.; Jeroncic, L. O. *J. Org. Chem.* **1991**, *56*, 3479−3486. (c) Moody, C. J.; Norton, C. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2639−2643. (d) Hilton, S. T.; Ho, T. C. T.; Pljevaljcic, G.; Schulte, M.; Jones, K. *Chem. Commun.* **2001**, 209−210 and references therein.

(16) (a) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 682−684. (b) For a recent example, see: Fujita, M.; Matsushima, H.; Sugimura, T.; Tai, A.; Okuyama, T. *J. Am. Chem. Soc.* **2001**, *123*, 2946−2957.

(17) However, no reaction was observed with methyl methacrylate.

(18) For a discussion on the role of azo radical initiators in the oxidative cyclization step onto aromatic systems, see: Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett.* **2001**, *42*, 7887−7890.

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Experimental Section

General Procedures. Reaction courses and product mixtures were routinely monitored by TLC on silica gel (precoated F_{254} plates). Drying of organic extracts during the workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of the solvents was accomplished under reduced pressure with a rotatory evaporator. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.04−0.06 mm). Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ solution, using TMS as internal reference. Microanalyses and HRMS were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona. Lactams **11** and **13** were prepared according to literature procedures.[21]

General Procedure for Intermolecular Addition Reactions of 3-Indolylacyl Radicals to Alkene Acceptors using *n*-Bu$_3$SnH−AIBN. *n*-Bu_3SnH (0.8 mmol) in C_6H_6 (3 mL) was added over a period of 1 h (syringe pump) to a heated (reflux) solution of selenoester **2a**,**b** (0.64 mmol), the alkene acceptor (0.9 or 3.2 mmol), and AIBN (0.06 mmol) in C_6H_6 (6 mL). After an additional 2−3 h at reflux, the solution was concentrated under reduced pressure. The residue was partitioned between hexanes (5 mL) and acetonitrile (5 mL), and the polar layer was washed with hexanes (3 × 5 mL) to remove tin compounds. The solvent was removed, and the crude product was chromatographed (flash, hexanes−AcOEt). The results are given in Table 1. Eluents, melting points, NMR data, and HRMS or elemental analyses of selected compounds are given below.

Methyl 4-(1-Methyl-3-indolyl)-4-oxobutanoate (3): 75:25 hexanes−AcOEt; mp 110−112 °C; ^{1}H NMR (200 MHz) δ 2.79 (t, J = 7 Hz, 2H), 3.19 (t, J = 7 Hz, 2H), 3.70 (s, 3H), 3.79 (s, 3H), 7.30 (m, 3H), 7.74 (s, 1H), 8.35 (m, 1H); ^{13}C NMR δ (50.3 MHz) δ 28.3 (CH_2), 33.6 (CH_3), 34.2 (CH_2), 51.8 (CH_3), 109.6 (CH), 115.9 (C), 122.4 (CH), 122.5 (CH), 123.3 (CH), 126.1 (C), 135.3 (CH), 137.3 (C), 173.7 (C), 192.8 (C). Anal. Calcd for $C_{14}H_{15}NO_3 \cdot 1/4H_2O$: C, 67.32; H, 6.25; N, 5.61. Found: C, 67.17; H, 6.40; N, 5.53.

3-(1-Methyl-3-indolylcarbonyl)cyclohexanone (5): 1:1 hexanes−AcOEt; mp 111−112 °C; ^{1}H NMR (200 MHz) δ 1.70−2.20 (m, 4H), 2.40 (m, 2H), 2.48 (dd, J = 4.2, 13.8 Hz, 1H), 2.82 (dd, J = 11, 14.6 Hz, 1H), 3.52 (m, 1H), 3.86 (s, 3H), 7.30 (m, 3H), 7.75 (s, 1H), 8.39 (m, 1H); ^{13}C NMR (50.3 MHz) δ 25.3 (CH_2), 29.0 (CH_2), 33.7 (CH_3), 41.2 (CH_2), 43.9 (CH_2), 47.3 (CH), 109.7 (CH), 114.7 (C), 122.5 (CH), 122.9 (CH), 123.6 (CH), 126.4 (C), 135.3 (CH), 137.6 (C), 195.1 (C), 211.2 (C); HRMS calcd for $C_{16}H_{17}NO_2$ 255.1259, found 255.1262.

General Procedure for the Intermolecular Addition Reactions of 3-Indolylacyl Radicals to Alkene Acceptors using TTMSS−AIBN. TTMSS (1.28 mmol) and AIBN (1.28 mmol) in C_6H_6 (4 mL) were added over a period of 2 h (syringe pump) to a heated (reflux) solution of selenoester **2a**,**b** (0.64 mmol) and the alkene acceptor (0.9 or 3.2 mmol) in C_6H_6 (12 mL). After an additional 2−3 h at reflux, the solution was concentrated under reduced pressure. Workup as above gave the crude product, which was chromatographed (flash, hexanes−AcOEt). The results are given in Table 1. Eluents, melting points, NMR data, and HRMS or elemental analyses of selected compounds are given below.

Indoline 8: 9:1 hexanes−AcOEt; ^{1}H NMR (300 MHz) δ 1.10 (d, J = 6.8 Hz, 3H), 1.29 and 1.45 (2 s, 6H), 2.46 (dd, J = 7.6, 13 Hz, 1H), 2.69 (dddd, J = 6.8, 12.8 Hz, 1H), 2.87 (s, 3H), 3.83 (s, 3H), 4.46 (d, J = 7.6 Hz, 1H), 6.45 (d, J = 8 Hz, 1H), 6.73 (td, J = 1.2, 7.6 Hz, 1H), 7.23 (td, J = 1.2, 7.6 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 12.2 (CH_3), 22.0 (CH_3), 22.4 (CH_3), 31.5 (CH_3), 38.0 (C), 49.0 (CH), 50.2 (CH), 52.6 (CH_3), 64.2 (C), 70.7 (CH), 107.1 (CH), 118.1 (CH), 120.8 (C), 123.0 (C), 126.6 (CH), 130.5 (CH), 150.3 (C), 174.3 (C), 210.4 (C).

***trans*-1,3-Bis(benzyloxycarbonyl)-4-(1-methyl-3-indolylcarbonyl)-2-piperidone (14):** AcOEt; mp 58−60 °C; ^{1}H NMR (200 MHz) δ 2.05 and 2.20 (2 m, 2H), 3.73 (m, 1H), 3.73 (s, 3H), 4.0 (m, 2H), 4.26 (d, J = 10 Hz, 1H), 5.10 and 5.15 (2 d, J = 16 Hz, 2H), 5.29 (s, 2H), 7.15−7.40 (m, 13H), 7.71 (s, 1H), 8.35 (m, 1H); ^{13}C NMR (50.3 MHz) δ 26.8 (CH_2), 33.7 (CH_3), 43.3 (CH), 44.2 (CH_2), 52.8 (CH), 67.3 (CH_2), 68.9 (CH_2), 109.8 (CH), 114.3 (C), 122.5 (CH), 123.0 (CH), 123.8 (CH), 126.4 (C), 127.8−128.5 (6 CH), 135.1 (2 C), 136.3 (CH), 137.6 (C), 153.2 (C), 167.7 (C), 168.7 (C), 192.9 (C). Anal. Calcd for $C_{31}H_{28}N_2O_6$: C, 70.98; H, 5.38; N, 5.34. Found: C, 70.75; H, 5.56; N, 5.54.

General Procedure for the *n*-Bu$_6$Sn$_2$-Mediated Reactions of Phenyl Selenoester 2a with Alkenes. Selenoester **2a** (0.65 mmol), the alkene acceptor (2.60 mmol), and *n*-Bu_6Sn_2 (0.80 mmol) in C_6H_6 (30 mL) were refluxed under sun-lamp irradiation (300 W) for 24 h. The solution was concentrated under reduced pressure. Workup as above gave the crude product, which was chromatographed (flash, hexanes−AcOEt). The results are given in Table 2.

Methyl 2,4-Dimethyl-1-oxocyclopenta[*b*]indole-3-carboxylate (21): 6:1 mixture of stereoisomers; 1:1 hexanes−AcOEt. Major trans isomer: ^{1}H NMR (200 MHz) δ 1.48 (d, J = 7.6 Hz, 3H), 3.25 (qd, J = 3, 7.2 Hz, 1H), 3.76 (s, 3H), 3.80 (s, 3H), 3.85 (d, J = 3 Hz, 1H), 7.25−7.35 (m, 3H), 7.96 (m, 1H); ^{13}C NMR (50.3 MHz) δ 17.0 (CH_3), 31.3 (CH_3), 47.9 (CH), 52.6 (CH), 52.9 (CH_3), 110.2 (CH), 118.8 (C), 121.1 (C), 121.4 (CH), 122.6 (CH), 124.0 (CH), 143.4 (C), 160.9 (C), 170.7 (C), 195.2 (C); HRMS calcd for $C_{15}H_{15}NO_3$ 257.1052, found 257.1046.

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Supporting Information Available: Experimental procedure for the preparation of **2a**,**b**, characterization data for compounds **2a**,**b**, **4**, **6**, **7**, **9**, **10**, **12**, **15**−**20**, and **22**−**25**, and ^{1}H and ^{13}C NMR for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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