The ultra high pressure conjugate addition of indoles to electron-deficient olefins

Paul Harrington and Michael A. Kerr

Abstract: The addition of indole and methyl indole at both high and ambient pressures to a series of Michael acceptors under the influence of ytterbium triflate was investigated. Under ambient pressure the more reactive and less sterically hindered electrophiles gave the expected 3-alkylated indoles in good to excellent yields. The more problematic Michael acceptors were subjected to pressures of 13 kbar. In all cases a dramatic reduction in reaction time and a significant improvement in yields was observed. In the cases involving 3-methylcyclohex-2-en-1-one, a by-product was formed and was characterized by single crystal X-ray diffraction. α,β-Unsaturated ketones gave the best yields. Enals tended to polymerize while enoates proved to be much too unreactive. A particularly reactive malonate derived ester and β-nitrostyrene gave good yields at ambient pressures.

Key words: hapalindole, indole, Michael addition, high pressure, ytterbium triflate, Lewis acid.

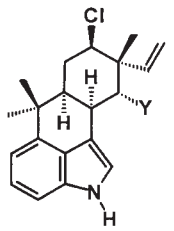
Résumé : On a étudié la réaction d'addition de l'indole et du méthylindole sur une série d'accepteurs de Michael sous l'influence de triflate d'ytterbium et à des pressions tant ambiante qu'élevée. À la pression ambiante, les électrophiles les plus réactifs présentant le moins d'encombrement stérique conduisent, avec des rendements allant de bons à excellents, aux indoles alkylés en position 3 attendus. Les accepteurs de Michael plus problématiques ont été soumis à des pressions de 13 kbar. Dans tous les cas, on a observé une réduction dramatique du temps de réaction et une amélioration significative des rendements. Dans les cas impliquant la 3-méthylcyclohex-2-én-1-one, il se forme un sous-produit qui a été caractérisé par diffraction des rayons X par un cristal unique. Les cétones α,β-insaturées donnent les meilleurs rendements. Les énals tendent à se polymériser alors que les énolates se sont avérés beaucoup moins réactifs. Un malonate particulièrement réactif, obtenu à partir de l'ester et du β-nitrostyrène, donne de bons rendements à des pressions ambiantes.

Mots clés : hapaindole, indole, addition de Michael, pression élevée, triflate d'ytterbium, acide de Lewis.

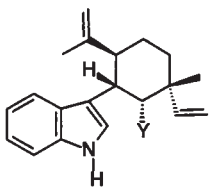
[Traduit par la Rédaction]

Introduction

We have recently been involved in studies directed towards the total synthesis of a class of bioactive indole alkaloids known as the hapalindoles. These cytotoxic compounds are a class of at least 20 members, isolated from the blue-green algae *Hapalosiphon fontinalis* by Moore et (1). The algae were isolated from soil samples collected from the Marshall Islands in 1981 and showed antibacterial, antimycotic, and antialgal activities. Initial reports disclosed the presence of two related compounds, hapalindole A and B (1*a*). Hapalindole A is responsible for the bulk of the biological activity. Three years later, the same group reported the structures of an additional 18 related compounds isolated from the same organism (1*b*). The structures possess either the tetracyclic framework present in hapalindole A and B or a tricyclic skeleton (possibly a biogenetic precursor) represented by hapalindoles C and D. There is large variation in the stereochemistry of the compounds; many have a diastereomeric relationship. This class of compounds provides an excellent opportunity for both stereochemical confirmation of the reported structures by synthesis and for the preparation of certain members for biochemical studies.



1 hapalindole A: Y = NC
2 hapalindole B: Y = NCS



3 hapalindole C: Y = NC
4 hapalindole D: Y = NCS

The study of the chemistry of these compounds (2) as well as activity towards the synthesis of interesting natural products has been steady. There have been several syntheses of a few members of this class of compounds to date (3). Our retrosynthesis of hapalindole C (Scheme 1) centers around the nucleophilic addition of an indole moiety **6** to a suitable terpenoid fragment **7** to produce the key intermediate **5**. Subsequent conversion to the target molecule **3** would involve only the addition of the geminally disposed vinyl

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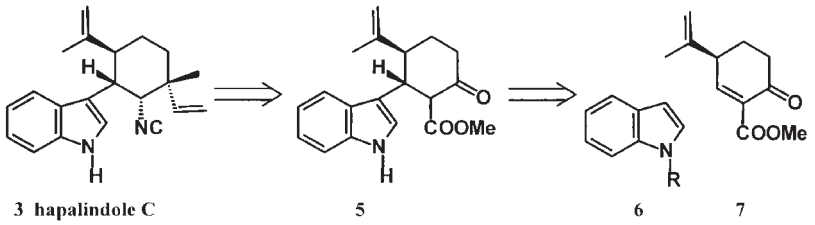
P. Harrington and M.A. Kerr.[2] Department of Chemistry, Acadia University, Wolfville, NS B0P 1X0, Canada.

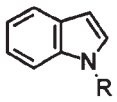
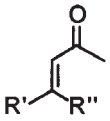
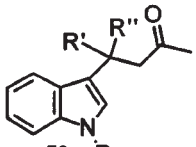
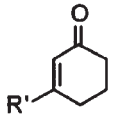
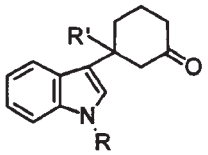
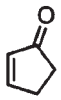
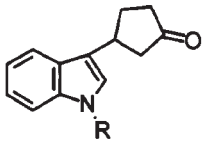
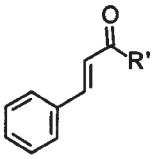
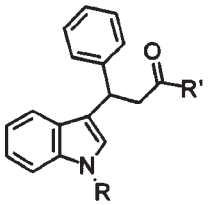
[1]Revision received July 8, 1998.
[2]Author to whom correspondence may be addressed. Telephone: (902) 585-1109. Fax: (902) 542-1454. E-mail: michael.kerr@acadiau.ca

Scheme 1. Proposed retrosynthesis of hapalindole C.



3 hapalindole C 5 6 7

Table 1. Ambient pressure alkylations of indoles with α,β-unsaturated ketones catalyzed by $Yb(OTf)_3$.

Entry	Indole	Enone	Time	Product(Yield)	Recovered Indole
					
1	R = H	R' = R'' = H	22h	72	0
2	R = Me	R' = R'' = H	7h	73	10
3	R = H	R' = Me, R'' = H	14h	85	0
4	R = Me	R' = Me, R'' = H	10h	95	0
5	R = H	R' = Me, R'' = Me	7d	19	63
6	R = Me	R' = Me, R'' = Me	7d	38	8
7	R = Me	R' = i-Pr, R'' = H	4d	77	0
					
8	R = H	R' = H	7d	44	3
9	R = Me	R' = H	7d	37	4
10	R = Me	R' = Me	7d	3	54
					
11	R = Me		4d	95	2
					
12	R = H	R' = Me	7d	16	44
13	R = Me	R' = Me	7d	10	40
14	R = H	R' = Ph	7d	52	32
15	R = Me	R' = Ph	7d	93	4

[1] 

and methyl substituents and conversion of the ester to an isonitrile. The use of the menthane class of terpenes as starting materials would imply that this approach has the potential to provide homochiral material.

While one could envision the addition of the indole fragment via an organometallic species such as a Grignard reagent or a copper derivative (via the readily available 3-haloindole), we were intrigued by the natural enamine character, which is present in indoles and imparts a relatively high degree of nucleophilicity to the 3-position (4). Because of our interest in the use of hyperbaric conditions to promote useful chemical reactions, we were curious as to whether or not the nucleophilicity of the indole would be sufficient to add to Michael acceptors and whether the nucleophilicity would be enhanced at ultra high pressures.

The addition of indole to electron-deficient olefins is not a new reaction; however, the utility of this process is restricted in that only highly reactive Michael acceptors can be used with acceptable results (5). Recently Kotsuki et al. disclosed their results of a study that investigated the addition of indoles to epoxides at ultra high pressures using catalysts such as ytterbium triflate and silica gel (6). At almost the same time, we reported our preliminary results (7), which showed that indoles add in a 1,4-fashion to α,β-unsaturated ketones under the influence of ytterbium triflate (eq. [1]). In this paper we wish to provide details of the preliminary study as well as report the results of our work involving the ultra high pressure variant of this reaction.

Ytterbium triflate has become, in recent years, a widely used Lewis acid in organic synthesis (8). While researching Lewis acids for use at elevated pressures, a report by Jenner indicated that ytterbium triflate might be a suitable candidate (9). The reaction in eq. [1] may also be considered to be a type of Friedel–Crafts alkylation, a class of reactions that has seen the use of lanthanide triflates (10).

Results and discussion

When investigating the effects of pressure on a reaction it is prudent to run the reaction at ambient pressure in order to isolate and quantify the effects of pressure on the reaction course. During such a reaction it was noticed that indoles added to many of the Michael acceptors under the influence of ytterbium triflate *at ambient pressures*. Table 1 summarizes the results of the addition of indole and 1-methylindole to a series of α,β-unsaturated ketones under ambient pressure. A methyl group was chosen as a simple model for alkyl-derived protecting groups for the nitrogen (i.e., benzyl, methoxymethyl, etc.). The use of an electron-withdrawing substitiuent (i.e., a *p*-toluenesulphonyl group) on the indole nitrogen greatly attenuated the nucleophilic character of the indole and the reactions with the Michael acceptors were suppressed. The 1-triisopropylsilyl derivative underwent the conjugate addition but at a slower rate and with the concomitant loss of the silyl protecting group. The absence of catalyst resulted in low yields of addition with only the most reactive Michael acceptors (methyl vinyl ketone, β-nitrostyrene).

Several trends from Table 1 are worthy of note. As expected, steric hindrance plays an important role in the success or failure of the reaction; an increase in steric bulk on the Michael acceptor generally impedes the reaction. A single β-substituent on the enone does little to slow the reaction (entries 3 and 4) while a second β-substituent greatly reduces the reactivity of the olefin towards the indole (entries 5 and 6 and entry 10). The fact that reactions involving *trans*-3-pentene-2-one (entries 3 and 4) provide improved yields over methyl vinyl ketone (entries 1 and 2) may be due to the fact that the former enone is much less prone to polymerization as a side reaction. Overall, the reactions were quite clean with the only major contaminant being the unreacted starting materials. If this methodology is to be truly useful for the synthesis of the hapalindoles, substrates such as cyclohexenone must work well. Under ambient pressures, the cyclohexenones gave surprisingly low yields with relatively little starting material recovered. An interesting by-product was formed in 6% yield in the reaction of 1-methylindole with 3-methyl-2-cyclohexenone. The ^{1}H and ^{13}C NMR spectra of this by-product were complicated and the structure remained a mystery for some time. The identity of the compound was ultimately found to be the triindolyl cyclohexane **8** using single crystal X-ray diffraction. A complete set of crystallographic data for compound **8** is available as supplementary material.[3] The ORTEP representation is shown in Fig. 1.[4,5] In hindsight, the formation of this material is not surprising. The addition of a single molecule of the indole in a 1,4-fashion would afford a ketone that may undergo what may be considered a vinylogous ketalization reaction.

The fact that a simple ketone can undergo such a reaction under these conditions was confirmed by the fact that when two equivalents of indole were combined with one equivalent of cyclohexanone, **9** was formed as the sole product (eq. [2]). This type of reaction catalyzed by protic acid has

[3] Supplementary material may be purchased from: The Depository of Unpublished Data, Document Delivery, CISTI, National Research Council of Canada, Ottawa, Canada, K1A 0S2. Tables of atomic coordinates and bond lengths and angles have also been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from: The Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, 12 Union Road, Cambridge, CB2 1EZ, U.K. Tables of structure factors are no longer being deposited, and may be obtained on request from the author.

[4] The figure shows one molecule of acetonitrile, which was co-crystallized.

[5] Empirical formula: $C_{36}H_{38}N_4$ (acetonitrile included): fw = 526.70, space group $P2_1/n$, a = 13.893(3) Å, b = 8.213(2) Å, c = 26.097(5) Å, V = 2969.3(11) Å^3, ρ_c = 1.178 mg/m^3, T = 293 K, λ = 1.54178 Å.

[2]

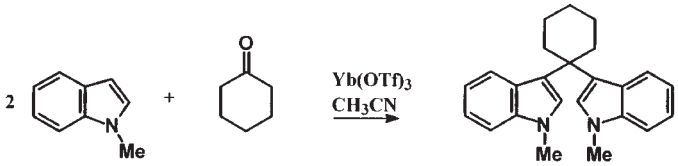


Fig. 1. ORTEP representation of by-product **8**.

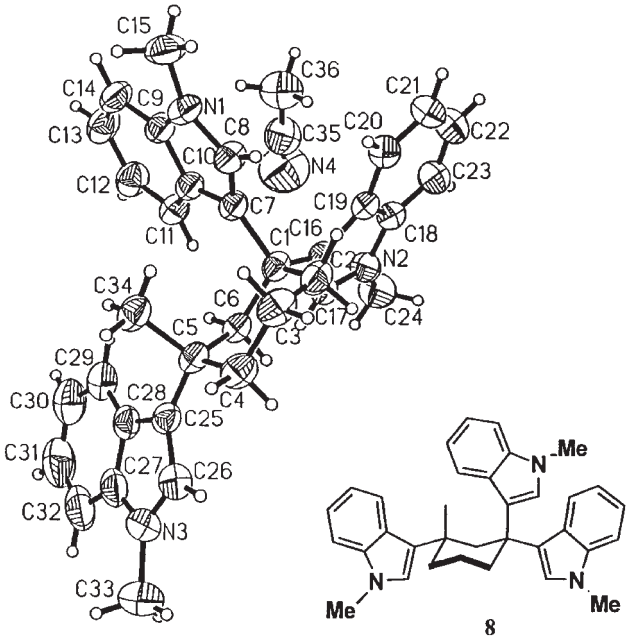
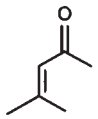
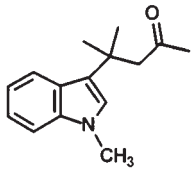
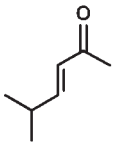
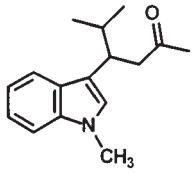
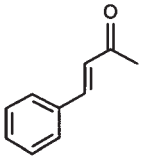
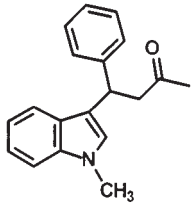
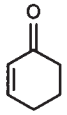
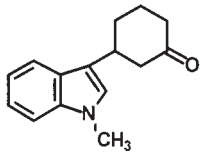
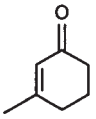
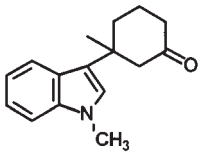
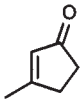
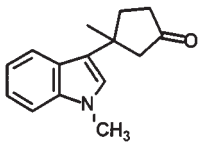


Table 2. $Yb(OTf)_3$ catalyzed alkylations of 1-methylindole with α,β-unsaturated ketones at 13 kbar.

Entry	Enone	Time	Product	Yield
1		2d		72
2		18h		84
3		26h		67
4		2d		56
5		7d		11
6		5d		3

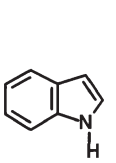
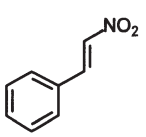
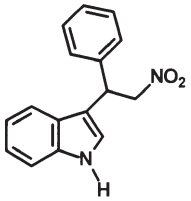
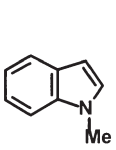
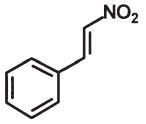
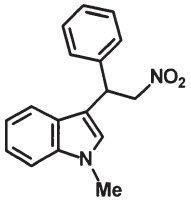
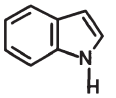
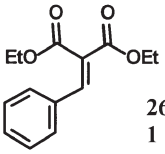
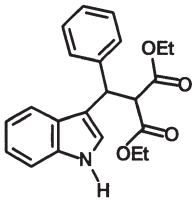
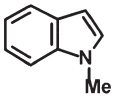
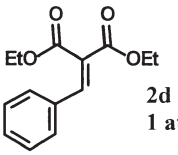
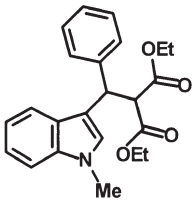
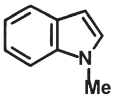
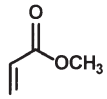
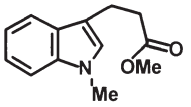
been reported (11). In addition, Wang and co-workers disclosed formally this same observation using a host of lanthanide triflates (12).

Cyclopent-2-en-1-one underwent addition in 95% yield; significantly higher than cyclohex-2-ene-1-one (entry 9). Finally, note that even when the β-substituent on the enone is a rather bulky isopropyl group (entry 7), the yield is still quite high.

The most notable limitation apparent from the results in Table 1 is that in cases where steric hindrance is significant, this methodology fails to produce useful amounts of adducts. In an effort to overcome this difficulty, reactions using these substrates were subjected to hyperbaric conditions (Table 2). In general, the reactions were performed at 13 kbar (1 bar = 100 kPa) using acetonitrile as the solvent.[6] In all cases, there was a notable reduction in reaction time and an increase in the yield of adduct. The most dramatic increase in isolated yield was observed with 4-phenyl-3-buten-2-one as the Michael acceptor (67% compared to 10% under ambient conditions, entry 3). Also of note is the fact that under these conditions, *N*-methyl indole added to cyclohex-2-en-1-one in 56% yield, an improvement from the 37% yield observed under ambient conditions. The same enones bearing an additional β-substituent proved extremely unreactive even under high-pressure conditions; however, small amounts of the expected adducts were isolated and characterized. The fact that high pressure facilitates the addition of indoles to enones is not surprising since formation of the transition state should result in a significant reduction in molar volume. (13). The use of high pressures to promote conjugate additions is not new and has been reported (14).

[6] Although a thorough screening of solvents was not performed, a brief experimental survey revealed that acetonitrile is the solvent of choice for these reactions.

Table 3. $Yb(OTf)_3$ catalyzed alkylations of indoles with other Michael acceptors.

Entry	Indole	Electrophile	Conditions	Product	Yield
1			2d 1 atm		89
2			18h 1 atm		39
3			26h 1 atm		77
4			2d 1 atm		68
5			7d 13 kbar		8

For the sake of exploring the general scope of this reaction, other electrophiles were also subjected to the above conditions and with some success. While many common electron-deficient olefins (phenyl vinyl sulphone, acrylonitrile, ethyl cinnamate, methyl propiolate, crotonaldehyde, and cinnnamaldehyde) failed to give satisfactory results, several reactive Michael acceptors proceeded to give the expected products (Table 3). As expected, β-nitrostyrene (entries 1 and 2) was quite reactive at ambient pressure. The fact that 1-methylindole gave an abnormally low yield is curious and may be due to the formation of a series of by-products that were not characterized. Note that even the reaction with a highly reactive diester such as diethyl benzalmalonate (entries 3 and 4) was sluggish and took several days to go to completion, albeit in good yield. Methyl acrylate was unreactive at ambient pressure but gave an isolable amount of material under hyperbaric conditions.

Finally, it should be noted that when 2-carbomethoxy-2-cyclohexenone was treated with indole in the presence of $Yb(OTf)_3$, a small amount of the desired Michael adduct was formed. The low yield may be attributed to the tendency of these types of compounds to exist, to a large degree, in the enol form.

In summary, we have shown that the use of ytterbium triflate to catalyze the addition of indoles to α,β-unsaturated ketones provides a useful complement to the existing methods available for the 3-alkylation of indole. Of interst to us for the synthesis of hapalindole alkaloids is the fact that cyclohexenones can be made to undergo reaction in acceptable yields under hyperbaric conditions, in contrast to more disappointing results using ambient conditions. Using this methodology, we intend to pursue as targets the interesting class of hapalindole alkaloids. Progress towards this end will be reported in due course.

Experimental section

General

Melting points were determined using a MEL-TEMP II melting point apparatus and are uncorrected. NMR spectra were obtained using a Bruker AM250 spectrometer in $CDCl_3$ as the solvent and are recorded in parts per million downfield from tetramethylsilane. ^1H NMR spectra were recorded at 250 MHz and ^{13}C NMR spectra were recorded at 63 MHz. Infrared spectra were measured on a Perkin–Elmer model 683 infrared spectrophotometer using a thin film of the compound on a sodium chloride plate. Mass spectra were recorded using a CEC model 21-11-B double-focusing mass spectrometer using a heated quartz direct-introduction probe with an 8000 V accelerating voltage. Crystallographic analysis was performed using a Rigaku AAFC5R diffractometer with a 12 MW rotating anode X-ray generator. Thin-layer chromatography was performed on E. Merck precoated TLC plates (Silica gel 60 F-254). Flash column chromatography was performed with EM Science Silica gel 60 (230–400 mesh). High-pressure reactions were performed in a LECO Tem-Pres HPC-200 chemical reactor in heat shrinkable Teflon® tubes. Samples for melting point determination were recrystallized from methylene chloride and hexanes. Commercial reagents and solvents were used as supplied without further purification.

Typical procedure for the ambient pressure reaction of indoles with α,β-unsaturated ketones

To a solution of the indole in acetonitrile was added the enone as a solid or a neat liquid. Ytterbium trifluoromethanesulphonate trihydrate was added and the mixture was stirred in a capped flask for the required amount of time. After thin-layer chromatography indicated the disappearance of starting material or after 1 week, which ever came first, the solvent was removed in vacuo and the residue was taken up in diethyl ether. Filtration of the ether suspension through a pad of Celite® followed by removal of the solvent in vacuo yielded the crude reaction product, which was purified by flash chromatography on a column of silica gel (elution with an appropriate mixture of ethyl acetate and hexanes).

4-(3-Indolyl)-2-butanone (Table 1, entry 1)

Standard procedure: indole (263 mg, 2.24 mmol), methyl vinyl ketone (500 μL, 6.11 mmol), $Yb(OTf)_3 \cdot 3H_2O$ (28 mg, 42 μmol), acetonitrile (2 mL). The mixture was stirred for

4 h after which time an additional 300 μL of methyl vinyl ketone (3.66 mmol) was added. After a total time of 22 h, the mixture was worked up in the usual way. Flash chromatography using gradient elution (20–50% EtOAc – hexanes) afforded 304 mg pure material (72%) as a white solid, mp 95–96°C. R_f = 0.31 (30% EtOAc – hexanes). IR (thin film), ν: 3315, 1700 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 2.14 (s, 3H), 2.84 (t, *J* = 7.3 Hz, 2H), 3.05 (tm, *J* = 7.3 Hz, 2H), 6.98 (dm, *J* = 2.4 Hz, 1H), 7.12 (td, *J* = 7.0, 1.2 Hz, 1H), 7.19 (td, *J* = 7.0, 1.2 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.59 (d, *J* = 7.0 Hz, 1H), 7.98 (bs, 1H). ^{13}C NMR (63 MHz, $CDCl_3$), δ: 19.4, 30.1, 44.1, 111.3, 115.1, 118.7, 119.3, 121.6, 122.1, 127.2, 136.4, 209.0. MS (70 eV), *m*/*e*: 188 (M+1), 187 (M$^+$), 131, 130(100), 117, 115, 42. HRMS (for $C_{12}H_{13}NO$): 187.0997 (calcd.); 187.1008 (found).

4-(3-(1-Methylindolyl))-2-butanone (Table 1, entry 2)

Standard procedure: 1-methylindole (273 mg, 2.08 mmol), methyl vinyl ketone (500 μL, 6.11 mmol), $Yb(OTf)_3 \cdot 3H_2O$ (31 mg, 46 μmol), acetonitrile (2 mL). The mixture was stirred for 7 h and worked up in the usual way. Flash chromatography using gradient elution (10–30% EtOAc – hexanes) afforded 307 mg pure material (73%) as a white solid. R_f = 0.33 (30% EtOAc – hexanes). IR (neat), ν: 3040, 2905, 1700, 1475, 1460, 735 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 2.13 (s, 3H), 2.82 (t, *J* = 7.6 Hz, 2H), 3.03 (tm, *J* = 7.6 Hz, 2H), 3.72 (s, 3H), 6.83 (s, 1H), 7.10 (ddd, *J* = 8.2, 6.7, 1.5 Hz, 1H), 7.22 (td, *J* = 7.9, 6.7, 1.5 Hz, 1H), 7.28 (dm, *J* = 7.9 Hz, 1H), 7.57 (dm, *J* = 7.6 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$), δ: 19.1, 30.0, 32.5, 44.2, 109.1, 113.5, 118.7 (two carbons), 121.5, 126.3, 127.5, 136.9, 208.9. MS (70 eV), *m/e*: 202(M+1), 201(M$^+$), 158, 145, 144(100), 143, 115. HRMS (for $C_{13}H_{15}NO$): 201.1154 (calcd.); 201.1123 (found).

4-(3-Indolyl)-2-pentanone (Table 1, entry 3)

Standard procedure: indole (258 mg, 2.20 mmol), 3-penten-2-one (500 μL, 5.12 mmol), $Yb(OTf)_3 \cdot 3H_2O$ (33 mg, 49 μmol), acetonitrile (2 mL). The mixture was stirred for 14 h and worked up in the usual way. Flash chromatography using gradient elution (20–50% EtOAc – hexanes) afforded 375 mg pure material (85%) as a white solid. R_f = 0.33 (30% EtOAc – hexanes). IR (neat), ν: 3400, 3045, 2950, 2915, 1705, 1610, 735 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 1.38 (d, *J* = 7.0 Hz, 3H), 2.08 (s, 3H), 2.70 (dd, *J* = 16.2, 8.2 Hz, 1H), 2.93 (dd, *J* = 16.2, 6.1 Hz, 1H), 3.63 (m, 1H), 6.93 (d, *J* = 2.1 Hz, 1H), 7.11 (ddd, *J* = 8.2, 7.3, 1.5 Hz, 1H), 7.18 (ddd, *J* = 8.2, 7.0, 1.5 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 8.02 (bs, 1H). ^{13}C NMR (63 MHz, $CDCl_3$), δ: 21.3, 27.1, 30.4, 51.5, 111.4, 119.1, 119.3, 120.2, 121.0, 122.1, 126.3, 136.6, 208.9. MS (70 eV), *m/e*: 201 (M$^+$), 158, 145, 144(100), 143, 42. HRMS (for $C_{13}H_{15}NO$): 201.1154 (calcd.); 201.1190 (found).

4-(3-(1-Methylindolyl))-2-pentanone (Table 1, entry 4)

Standard procedure: 1-methylindole (295 mg, 2.25 mmol), 3-penten-2-one (500 μL, 5.12 mmol), $Yb(OTf)_3 \cdot 3H_2O$ (33 mg, 49 μmol), acetonitrile (2 mL). The mixture was stirred for 10 h and worked up in the usual way. Flash chromatography using gradient elution (5–20% EtOAc – hexanes) afforded 461 mg pure material (95%) as a yellow oil. R_f = 0.41 (30% EtOAc – hexanes). IR (neat), ν: 3040, 2950, 2870, 1700, 1605, 1540, 1475, 1415, 1345, 1320, 1260, 1220, 1145, 1125, 1095, 1005, 755, 735 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 1.36 (d, *J* = 7.0 Hz, 3H), 2.08 (s, 3H), 2.68 (dd, *J* = 16.2, 8.2 Hz, 1H), 2.91 (dd, *J* = 15.9, 6.1 Hz, 1H), 3.61 (m, 1H), 3.70 (s, 3H), 6.81 (s, 1H), 7.09 (tm, *J* = 7.3 Hz, 1H), 7.21 (tm, *J* = 7.5 Hz, 1H), 7.27 (dm, *J* = 7.6 Hz, 1H), 7.62 (dm, *J* = 7.6 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$), δ: 21.5, 27.0, 30.4, 32.6, 51.6, 109.3, 118.7, 119.2, 119.5, 121.6, 125.0, 126.6, 137.2, 208.6. MS (70 eV), *m/e:* 215(M$^+$), 172, 159, 158(100), 115. HRMS (for $C_{14}H_{17}NO$): 215.1310 (calcd.); 215.1309 (found).

4-(3-Indolyl)-4-methyl-2-pentanone (Table 1, entry 5)

Standard procedure: indole (263 mg, 2.24 mmol), mesityl oxide (500 μL, 4.36 mmol), $Yb(OTf)_3 \cdot 3H_2O$ (32 mg, 47 μmol), acetonitrile (2 mL). The mixture was stirred for 7 d and worked up in the usual way. Flash chromatography using gradient elution (10–20% EtOAc – hexanes) afforded 91 mg pure material (19%) as a yellow oil. R_f = 0.37 (30% EtOAc – hexanes). IR (neat), ν: 3400, 2950, 2915, 1685, 1450, 1410, 1345, 1325, 1235, 1200, 1115, 1100, 1005, 760, 735 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 1.53 (s, 6H), 1.72 (s, 3H), 2.95 (s, 2H), 6.89 (d, *J* = 2.4 Hz, 1H), 7.08–7.21 (m, 2H), 7.34 (dm, *J* = 7.3 Hz, 1H), 7.80 (dm, *J* = 7.9 Hz, 1H), 8.01 (bs, 1H). ^{13}C NMR (63 MHz, $CDCl_3$), δ: 28.9, 29.7, 31.8, 34.5, 55.1, 111.7, 119.1, 120.6, 120.7, 121.7, 123.5, 125.5, 137.2, 209.5. MS (70 eV), *m/e*: 216 (M+1), 215(M$^+$), 200, 159, 158(100), 157, 143, 142, 115, 42. HRMS (for $C_{14}H_{17}NO$): 215.1310 (calcd.); 215.1324 (found).

4-(3-(1-Methylindolyl))-4-methyl-2-pentanone (Table 1, entry 6)

Standard procedure: 1-methylindole (290 mg, 2.21 mmol), mesityl oxide (500 μL, 4.36 mmol), $Yb(OTf)_3 \cdot 3H_2O$ (31 mg, 46 μmol), acetonitrile (2 mL). The mixture was stirred for 7 d and worked up in the usual way. Flash chromatography using gradient elution (10–20% ethyl acetate – hexanes) afforded 195 mg pure material (38%) as a yellow oil. R_f = 0.49 (30% EtOAc – hexanes). IR (neat), ν: 3020, 2940, 1700, 1605, 1535, 1475, 1415, 1350, 1230, 1145, 1100, 1010, 980, 760, 730 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 1.53 (s, 6H), 1.73 (s, 3H), 2.94 (s, 2H), 3.73 (s, 3H), 6.79 (s, 1H), 7.11 (ddd, *J* = 8.2, 7.0, 1.2, 1H), 7.22 (ddd, *J* = 7.9, 7.0, 1.2 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.79 (dd, *J* = 7.9, 1.2 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$), δ: 29.0, 31.9, 32.7, 34.5, 55.2, 109.7, 118.7, 120.9, 121.3, 122.2, 125.4, 126.0, 137.8, 209.2. MS (70 eV), *m/e*: 230 (M+1), 229 (M$^+$), 173, 172 (100), 130, 115. HRMS (for $C_{15}H_{19}NO$): 229.1467 (calcd.); 229.1473 (found).

4-(3-(1-Methylindolyl))-5-methyl-2-hexanone (Table 1, entry 7)

Standard procedure: 1-methylindole (307 mg, 2.34 mmol), 5-methyl-3-hexen-2-one (500 μL, 3.79 mmol), $Yb(OTf)_3 \cdot 3H_2O$ (30 mg, 44 μmol), acetonitrile (2 mL). The mixture was stirred for 4 d and worked up in the usual way. Flash chromatography using gradient elution (5–20% EtOAc – hexanes) afforded 438 mg pure material (77%) as a low-melting solid. R_f = 0.50 (30% EtOAc – hexanes). IR (neat), ν: 2940, 2915, 2860, 1700, 1475, 1460, 1415, 1360, 1345, 1320, 1250, 1225, 1150, 1125, 1005, 730 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 0.86 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* =

6.7 Hz, 3H), 1.96 (s, 3H), 2.05 (m, 1H), 2.78–2.86 (m, 2H), 3.30 (td, *J* = 6.7, 6.4 Hz, 1H), 3.71 (s, 3H), 6.79 (s, 1H), 7.08 (ddd, *J* = 7.5, 6.7, 1.3, 1H), 7.19 (td, *J* = 7.4, 1.0 Hz, 1H), 7.26 (dm, *J* = 7.9 Hz, 1H), 7.63 (dm, *J* = 7.9 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$), δ: 20.4, 20.6, 30.1, 32.7, 32.8, 39.2, 47.2, 109.2, 115.9, 118.6, 119.5, 121.3, 126.7, 127.7, 136.9, 209.3. MS (70 eV), *m*/*e*: 244 (M+1), 243 (M^+), 201, 200 (100), 186, 158, 157, 143, 69. HRMS (for $C_{16}H_{21}NO$): 243.1623 (calcd.); 243.1626 (found).

3-(3-Indolyl)cyclohexanone (Table 1, entry 8)

Standard procedure: indole (241 mg, 2.06 mmol), 2-cyclohexen-1-one (500 μL, 5.16 mmol), $Yb(OTf)_3 \cdot 3H_2O$ (30 mg, 44 μmol), acetonitrile (2 mL). The mixture was stirred for 2 d and an additional 9 mg (15 μmol) of catalyst was added. The mixture was stirred for an additional 5 d and worked up in the usual way. Flash chromatography using gradient elution (10–30% EtOAc – hexanes) afforded 192 mg pure material (44%) as a pale yellow solid, mp 106–107°C. R_f = 0.26 (30% EtOAc – hexanes). IR (neat), ν: 3270, 2940, 2860, 1695, 1610, 1485, 1440, 1420, 1330, 1255, 1210, 1175, 1100, 1050, 1020, 1000, 870, 800, 755, 730 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 1.78–2.08 (m, 3H), 2.25 (m, 1H), 2.38–2.46 (m, 2H), 2.62 (ddd, *J* = 14.0, 10.5, 1.1 Hz, 1H), 2.79 (ddt, *J* = 14.0, 4.6, 1.5 Hz, 1H), 3.42 (m, 1H), 6.95 (dd, *J* = 2.4, 0.6 Hz, 1H), 7.11 (ddd, *J* = 7.8, 7.0, 1.2 Hz, 1H), 7.19 (ddd, *J* = 7.8, 6.9, 1.5 Hz, 1H), 7.35 (dm, *J* = 7.9 Hz, 1H), 7.61 (dm, *J* = 7.9 Hz, 1H), 8.12 (bs, 1H). ^{13}C NMR (63 MHz, $CDCl_3$), δ: 24.9, 31.8, 36.0, 41.6, 48.1, 111.4, 119.0, 119.4, 119.6, 120.5, 122.2, 126.2, 136.5, 212.1. MS (70 eV), *m*/*e*: 214 (M+1), 213 (M^+), 170, 157, 156(100), 144, 143, 130, 128, 117. HRMS (for $C_{14}H_{15}NO$): 213.1154 (calcd.); 213.1166 (found).

3-(3-(1-Methylindolyl))cyclohexanone (Table 1, entry 9)

Standard procedure: 1-methylindole (268 mg, 2.04 mmol), 2-cyclohexen-1-one (500 μL, 5.16 mmol), $Yb(OTf)_3 \cdot 3H_2O$ (34 mg, 50 μmol), acetonitrile (2 mL). The mixture was stirred for 7 d and worked up in the usual way. Flash chromatography using gradient elution (10–30% EtOAc – hexanes) afforded 171 mg pure material (37%) as a yellow oil. R_f = 0.37 (30% EtOAc – hexanes). IR (neat), ν: 3040, 2920, 2855, 1700, 1605, 1540, 1460, 1415, 1365, 1305, 1250, 1210, 1145, 1120, 1045, 1005, 795, 730 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 1.78–2.08 (m, 3H), 2.23 (m, 1H), 2.38–2.46 (m, 2H), 2.60 (ddd, *J* = 14.0, 10.4, 1.2 Hz, 1H), 2.78 (ddt, *J* = 14.0, 4.6, 1.5 Hz, 1H), 3.43 (m, 1H), 3.73 (s, 3H), 6.82 (d, *J* = 0.6 Hz, 1H), 7.10 (ddd, *J* = 7.9, 7.3, 1.2 Hz, 1H), 7.22 (ddd, *J* = 8.2, 7.5, 1.2 Hz, 1H), 7.29 (td, *J* = 8.2, 1.1 Hz, 1H), 7.60 (td, *J* = 7.9, 0.9 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$), δ: 24.9, 32.0, 32.7, 35.9, 41.6, 48.3, 109.4, 118.2, 118.9, 119.1, 121.8, 125.3, 126.6, 137.2, 211.9. MS (70 eV), *m*/*e*: 228 (M+1), 227 (M^+,100), 184, 170, 157, 144, 115. HRMS (for $C_{15}H_{17}NO$): 227.1311 (calcd.); 227.1302 (found).

3-Methyl-3-(3-(1-methylindolyl))cyclohexanone (Table 1, entry 10)

Standard procedure: 1-methylindole (292 mg, 2.23 mmol), 3-methyl-2-cyclohexen-1-one (400 μL, 3.53 mmol), $Yb(OTf)_3 \cdot 3H_2O$ (37 mg, 55 μmol), acetonitrile (2 mL). The mixture was stirred for 7 d and worked up in the usual way. Flash chromatography using gradient elution (10– 30% EtOAc – hexanes) afforded 16 mg pure material (3%) as a yellow oil. R_f = 0.36 (30% EtOAc – hexanes). IR (neat), ν: 3030, 2920, 1690, 1535, 1475, 1410, 1365, 1320, 1300, 1275, 1235, 1215, 1140, 1130, 1100, 1010, 730 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 1.41–1.59 (m, 1H), 1.53 (s, 3H), 1.76–1.94 (m, 2H), 2.24–2.32 (m, 2H), 2.46 (d, *J* = 14.4 Hz, 1H), 2.58 (m, 1H), 2.89 (dd, *J* = 14.4, 1.5 Hz, 1H), 3.70 (s, 3H), 6.80 (s, 1H), 7.08 (ddd, *J* = 8.3, 7.3, 1.2 Hz, 1H), 7.21 (tm, *J* = 7.3 Hz, 1H), 7.29 (d, *J* = 8.2, Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$), δ: 22.4, 29.6, 32.7, 36.8, 40.0, 41.0, 54.4, 109.6, 118.5, 120.3, 120.9, 121.5, 125.4, 126.9, 137.8, 212.5. MS (70 eV), *m*/*e*: 242 (M+1), 241 (M^+,100), 226, 198, 184, 171, 131(100), 130, 42. HRMS (for $C_{16}H_{19}NO$): 241.1467 (calcd.); 241.1488 (found).

3-(3-(1-Methylindolyl))cyclopentanone (Table 1, entry 11)

Standard procedure: 1-methylindole (322 mg, 2.45 mmol), 2-cyclopenten-1-one (500 μL, 6.18 mmol), $Yb(OTf)_3 \cdot 3H_2O$ (32 mg, 47 μmol), acetonitrile (2 mL). The mixture was stirred for 4 d and worked up in the usual way. Flash chromatography using gradient elution (20–30% EtOAc – hexanes) afforded 496 mg pure material (95%) as a yellow oil. R_f = 0.38 (30% EtOAc – hexanes). IR (neat), ν: 3040, 2945, 2920, 2870, 1730, 1605, 1475, 1415, 1395, 1365, 1320, 1310, 1235, 1145, 1125, 1005, 730 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 2.03–2.52 (m, 5H), 2.71 (dd, *J* = 18.3, 7.6 Hz, 1H), 3.67 (m, 1H), 3.70 (s, 3H), 6.80 (d, *J* = 0.6 Hz, 1H), 7.11 (ddd, *J* = 7.9, 6.7, 1.5 Hz, 1H), 7.23 (td, *J* = 7.3, 1.2 Hz, 1H), 7.29 (dm, *J* = 8.1 Hz, 1H), 7.59 (td, *J* = 7.9, 0.9 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$), δ: 30.0, 32.6, 33.6, 38.1, 45.4, 109.4, 116.9, 118.8, 119.1, 121.8, 124.7, 126.9, 137.3, 219.3. MS (70 eV), *m*/*e:* 214 (M+1), 213 (M^+,100), 184, 170, 158 157, 156 144. HRMS (for $C_{15}H_{17}NO$): 213.1154 (calcd.); 213.1167 (found).

4-(3-Indolyl)-4-phenyl-2-butanone (Table 1, entry 12)

Standard procedure: indole (250 mg, 2.13 mmol), benzalacetone (370 mg, 2.53 mmol), $Yb(OTf)_3 \cdot 3H_2O$ (31 mg, 46 μmol), acetonitrile (2 mL). The mixture was stirred for 7 d and worked up in the usual way. Flash chromatography using gradient elution (10–50% EtOAc – hexanes) afforded 89 mg pure material (16%) as a white solid, mp 98–99°C. R_f = 0.27 (30% EtOAc – hexanes). IR (neat), ν: 3400, 3050, 3020, 2910, 1695, 1590, 1485, 1445, 1405, 1345, 1330, 1230, 1215, 1150, 1090, 1000, 735, 695 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 2.09 (s, 3H), 3.17 (dd, *J* = 16.2, 7.9 Hz, 1H), 3.27 (dd, *J* = 16.2, 7.3 Hz, 1H), 4.85 (bt, *J* = 7.6 Hz, 1H), 6.98 (dd, *J* = 2.4, 0.6 Hz, 1H), 7.03 (ddd, *J* = 7.9, 7.0, 1.2 Hz, 1H), 7.13–7.35 (m, 7H), 7.44 (dd, *J* = 7.0, 1.2 Hz, 1H), 8.04 (bs, 1H). ^{13}C NMR (63 MHz, $CDCl_3$), δ: 30.4, 38.4, 50.4, 111.2, 118.8, 119.4, 121.4, 122.2, 126.4, 126.5, 127.7, 128.5, 136.6, 144.0, 207.8. MS (70 eV), *m*/*e*: 264 (M+1), 263 (M^+,100), 221, 220, 207, 206, 42. HRMS (for $C_{18}H_{17}NO$): 263.1310 (calcd.); 263.1312 (found).

4-(3-(1-Methylindolyl))-4-phenyl-2-butanone (Table 1, entry 13)

Standard procedure: 1-methylindole (290 mg, 2.21 mmol), benzalacetone (386 mg, 2.64 mmol), $Yb(OTf)_3 \cdot 3H_2O$

(34 mg, 50 μmol), acetonitrile (2 mL). The mixture was stirred for 7 d and was worked up in the usual way. Flash chromatography using gradient elution (10–30% EtOAc – hexanes) afforded 63 mg pure material (10%) as a yellow oil. R_f = 0.31 (30% EtOAc – hexanes). IR (neat), ν: 3045, 3015, 2920, 1700, 1590, 1540, 1475, 1410, 1360, 1345, 1320, 1235, 1145, 1070, 1005, 730, 695 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$), δ: 2.07 (s, 3H), 3.14 (dd, *J* = 16.2, 7.9 Hz, 1H), 3.25 (dd, *J* = 16.2, 7.3 Hz, 1H), 3.73 (s, 3H), 4.85 (bt, *J* = 7.6 Hz, 1H), 6.80 (s, 1H), 7.00 (tm, *J* = 7.5 Hz, 1H), 7.11–7.32 (m, 7H), 7.42 (dm, *J* = 7.9 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$), δ: 30.3, 32.7, 38.3, 50.4, 109.2, 117.3, 118.9, 119.5, 121.7. 126.3, 126.9, 127.7, 128.5, 137.3, 144.1, 207.5. MS (70 eV), *m*/*e*: 278 (M+1), 277 (M^+,100), 221, 220, 218, 204. HRMS (for $C_{19}H_{19}NO$): 277.1467 (calcd.); 277.1464 (found).

3-(3-Indolyl)-3-phenylpropiophenone (Table 1, entry 14)

Standard procedure: indole (253 mg, 2.16 mmol), chalcone (528, 2.54 mmol), $Yb(OTf)_3 \cdot H_2O$ (34 mg, 50 μmol), acetonitrile (2 mL). The mixture was stirred for 7 d and was worked up in the usual way. Flash chromatography using gradient elution (10–30% EtOAc – hexanes) afforded 366 mg pure material (52%) as a white solid, mp 131–132°C. R_f = 0.36 (30% EtOAc – hexanes). IR (neat), ν: 3410, 3045, 3020, 1670, 1590, 1570, 1485, 1440, 1405, 1325, 1255, 1195, 1090, 1010, 995, 970, 735, 690 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$), δ: 3.71 (dd, *J* = 16.8, 7.6 Hz, 1H), 3.81 (dd, *J* = 16.8, 6.7 Hz, 1H), 5.06 (bt, *J* = 7.3 Hz, 1H), 6.95 (d, *J* = 2.4 Hz, 1H), 7.00 (td, *J* = 7.5. 0.9 Hz, 1H), 7.10–7.55 (m, 12H), 7.92 (dm, *J* = 7.0 Hz, 1H), 7.97 (bs, 1H). ^{13}C NMR (63 MHz, $CDCl_3$), δ: 38.2, 45.2, 111.2, 119.3, 119.4, 119.6, 121.5, 122.1, 126.3, 126.6, 127.7, 128.1, 128.5, 128.6, 133.1, 136.6, 137.1, 144.3, 198.6. MS (70 eV), *m*/*e*: 326 (M+1), 325 (M^+), 220, 207, 206 (100), 178, 105, 77. HRMS (for $C_{23}H_{19}NO$): 325.1467 (calcd.); 325.1472 (found).

3-(3-(1-Methylindolyl))-3-phenylpropiophenone (Table 1, entry 15)

Standard procedure: 1-methylindole (287 mg, 2.19 mmol), chalcone (535, 2.57 mmol), $Yb(OTf)_3 \cdot 3H_2O$ (32 mg, 47 μmol), acetonitrile (2 mL). The mixture was stirred for 7 d and was worked up in the usual way. Flash chromatography using gradient elution (5–70% EtOAc – hexanes) afforded 687 mg pure material (93%) as a pale yellow solid, mp 181–182°C. R_f = 0.41 (30% EtOAc – hexanes). IR (neat), ν: 3050, 2910, 1665, 1590, 1560, 1535, 1475, 1440, 1405, 1360, 1325, 1305, 1290, 1235, 1145, 730, 690 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$), δ: 3.69 (s, 3H), 3.74–3.79 (m, 2H), 5.06 (bt, *J* = 7.3 Hz, 1H), 6.83 (s, 1H), 7.00 (td, *J* = 6.7, 1.2 Hz, 1H), 7.14–7.52 (m, 12H), 7.93 (dm, *J* = 7.0 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$), δ: 37.2, 38.2, 45.4, 109.2, 117.8, 118.9, 119.6, 121.7, 126.3, 127.0, 127.9, 128.1, 128.5, 128.6, 133.0, 137.2, 137.4, 144.4, 198.5. MS (70 eV), *m*/*e:* 340 (M+1), 339 (M^+), 234, 221, 220 (100). HRMS (for $C_{24}H_{21}NO$): 339.1623 (calcd.); 339.1628 (found).

2-(3-Indolyl)-2-phenylnitroethane (Table 3, entry 1)

Standard procedure: Indole (295 mg, 2.52 mmol), β-nitrostyrene (468 mg, 3.14 mmol), $Yb(OTf)_3 \cdot 3H_2O$ (31 mg, 46 μmol), acetonitrile (2 mL). The mixture was stirred for 30 h and was worked up in the usual way. Flash chromatography using gradient elution (10–30% EtOAc – hexanes) afforded 596 mg pure material (89%) as a pale yellow solid, mp 102–103°C. R_f = 0.34 (30% EtOAc – hexanes). IR (neat), ν: 3420, 3050, 3020, 1595, 1545, 1485, 1445, 1415, 1370, 1330, 1255, 1215, 1090, 1000, 965, 740, 695 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$), δ: 4.92 (dd, *J* = 12.4, 8.4 Hz, 1H), 5.04 (dd, *J* = 12.4, 7.5 Hz, 1H), 5.17 (bt, *J* = 7.9 Hz, 1H), 6.98 (d, *J* = 2.8 Hz, 1H), 7.06 (td, *J* = 7.5, 0.9 Hz, 1H), 7.15–7.35 (m, 7H), 7.43 (dm, *J* = 7.9 Hz, 1H), 8.03 (bs, 1H). ^{13}C NMR (63 MHz, $CDCl_3$), δ: 41.6, 79.6, 111.4, 119.0, 120.0, 121.7, 122.7, 126.1, 127.6, 127.8, 129.0, 136.5, 139.2. MS (70 eV), *m*/*e*: 267 (M+1), 266 (M^+, 100), 220, 219, 218, 217, 206, 204, 42. HRMS (for $C_{16}H_{14}N_2O_2$): 266.1055 (calcd.); 266.1055 (found).

2-(3-(1-Methyl-indolyl))-2-phenylnitroethane (Table 3, entry 2)

Standard procedure: 1-methylindole (287 mg, 2.19 mmol), β-nitrostyrene (387 mg, 2.59 mmol), $Yb(OTf)_3 \cdot 3H_2O$ (37 mg, 55 μmol), acetonitrile (2 mL). The mixture was stirred for 19 h and was worked up in the usual way. Flash chromatography using gradient elution (10–50% EtOAc – hexanes) afforded 241 mg pure material (39%) as a white solid, mp 94–95°C. R_f = 0.38 (30% EtOAc – hexanes). IR (neat), ν: 3050, 3020, 2910, 1595, 1540, 1465, 1445, 1415, 1370, 1325, 1240, 1150, 1120, 1075, 1005, 735, 695 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$), δ: 3.71 (s, 3H), 4.91 (dd, *J* = 12.5, 8.6 Hz, 1H), 5.03 (dd, *J* = 12.4, 7.5 Hz, 1H), 5.17 (bt, *J* = 7.9 Hz, 1H), 6.84 (d, *J* = 0.6 Hz, 1H), 7.06 (ddd, *J* = 7.9, 6.6, 1.5 Hz, 1H), 7.18–7.33 (m, 7H), 7.44 (td, *J* = 7.9, 0.9 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$), δ: 32.9, 41.6, 79.6, 109.6, 112.8, 119.0, 119.5, 122.3, 126.4, 126.6, 127.5, 127.8, 128.9, 137.3, 139.4. MS (70 eV), *m*/*e*: 281 (M+1), 280 (M^+, 100), 235, 234, 233, 221, 220, 218, 217, 157, 146, 115, 77, 50. HRMS (for $C_{17}H_{16}N_2O_2$): 280.1212 (calcd.); 280.1204 (found).

Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-phenyl propanoate (Table 3, entry 3)

Standard procedure: indole (255 mg, 2.18 mmol), diethyl benzalmalonate (600 mg, 2.68 mmol), $Yb(OTf)_3 \cdot 3H_2O$ (32 mg, 47 μmol), acetonitrile (2 mL). The mixture was stirred for 4 d and was worked up in the usual way. Flash chromatography using gradient elution (20–50% EtOAc – hexanes) afforded 610 mg pure material (77%) as a white solid, mp 164–165°C. R_f = 0.30 (30% EtOAc – hexanes). IR (neat), ν: 3440, 1735, 1705, 1445, 1360, 1310, 1260, 1240, 1180, 1165, 1145, 1085, 740, 695 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$), δ: 0.97 (t, *J* = 7.0 Hz, 3H), 1.00 (t, *J* = 7.0 Hz, 3H), 3.97 (q, *J* = 7.1 Hz, 2H), 4.00 (q, *J* = 7.1 Hz, 2H), 4.29 (d, *J* = 11.9 Hz, 1H), 5.08 (d, *J* = 11.6 Hz, 1H), 7.02 (ddd, *J* = 7.8, 7.0, 0.9 Hz, 1H), 7.09–7.30 (m, 6H), 7.34–7.38 (m, 2H), 7.54 (dd, *J* = 7.9, 0.6 Hz, 1H), 8.05 (bs, 1H). ^{13}C NMR (63 MHz, $CDCl_3$), δ: 13.8 (two carbons), 42.9, 58.4, 61.5 (two carbons), 111.0, 116.9, 119.4, 119.5, 129.9, 122.2, 126.8, 128.2, 128.4, 136.2, 141.4, 167.9, 168.1. MS (70 eV), *m*/*e:* 366 (M+1), 365 (M^+), 246, 207, 206 (100). HRMS (for $C_{22}H_{23}NO_4$): 365.1627 (calcd.); 365.1660 (found).

Ethyl 2-ethoxycarbonyl-3-(3-(1-methylindolyl))-3-phenyl propanoate (Table 3, entry 4)

Standard procedure: 1-methylindole (270 mg, 2.06 mmol), diethyl benzalmalonate (600 mg, 2.68 mmol), $Yb(OTf)_3 \cdot 3H_2O$ (35 mg, 52 μmol), acetonitrile (2 mL). The mixture was stirred for 2 d and was worked up in the usual way. Flash chromatography using gradient elution (10–30% EtOAc – hexanes) afforded 530 mg pure material (68%) as a white solid, mp 87–88°C. R_f = 0.37 (30% EtOAc – hexanes). IR (neat), ν: 2925, 2870, 1735, 1695, 1605, 1535, 1460, 1415, 1360, 1020, 860, 735, 695 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$), δ: 0.98 (t, *J* = 7.2 Hz, 3H), 0.99 (t, *J* = 7.0 Hz, 3H), 3.71 (s, 3H), 3.97 (q, *J* = 7.2 Hz, 2H), 3.99 (q, *J* = 7.0 Hz, 2H), 4.27 (d, *J* = 11.6 Hz, 1H), 5.06 (d, *J* = 11.9 Hz, 1H), 7.01 (s, 1H), 7.02 (td, *J* = 7.3, 1.4 Hz, 1H), 7.09–7.25 (m, 6H), 7.36 (dm, *J* = 7.0 Hz, 1H), 7.55 (dt, *J* = 7.9, 0.6 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$), δ: 13.7 (two carbons), 32.7, 42.8, 58.4, 61.3, 61.4, 109.0, 115.3, 118.9, 119.4, 121.7, 125.6, 126.6, 127.1, 128.1, 129.4, 136.9, 141.6, 167.8, 168.0. MS (70 eV), *m*/*e*: 380 (M+1), 379 (M^+), 233, 221, 200 (100), 218, 217, 206. HRMS (for $C_{23}H_{25}NO_4$): 379.1783 (calcd.); 379.1811 (found).

Typical procedure for the high-pressure reaction of indoles with α,β-unsaturated ketones

The indole and the enone were dissolved in acetonitrile in a length of 1 cm diameter heat- shrinkable Teflon® tubing (about 10 cm in length) that had been clamped at one end using a brass clamp. The catalyst was added and the contents of the tube were mixed. Excess air was squeezed from the reaction vessel and the tube was then sealed with another brass clamp. The vessel was placed in the high-pressure reactor and was subjected to 1.2 GPa (13 kbar) for an appropriate period of time. The solvent was removed in vacuo and the crude residue was purified by flash chromatography on a column of silica gel (elution with an appropriate mixture of ethyl acetate and hexanes).

4-(3-(1-Methylindolyl))-4-methyl-2-pentanone (Table 2, entry 1)

Standard procedure: 1-methylindole (288 mg, 2.20 mmol), mesityl oxide (500 μL, 4.36 mmol), $Yb(OTf)_3 \cdot 3H_2O$ (33 mg, 49 μmol), acetonitrile (2 mL). The mixture was pressurized for 2 d and was worked up in the usual way. Flash chromatography using gradient elution (10–20% EtOAc – hexanes) afforded 360 mg pure material (72%) as a yellow oil. The material was identical in all respects to the compound prepared under ambient pressure (Table 1, entry 6).

4-(3-(1-Methylindolyl))-5-methyl-2-hexanone (Table 2, entry 2)

Standard procedure: 1-methylindole (2.92 mg, 2.23 mmol), 5-methyl-3-hexen-2-one (500 μL, 3.79 mmol), $Yb(OTf)_3 \cdot 3H_2O$ (33 mg, 49 μmol), acetonitrile (2 mL). The mixture was pressurized for 18 h and was worked up in the usual way. Flash chromatography using gradient elution (5–20% EtOAc – hexanes) afforded 455 mg pure material (84%) as a low-melting solid, identical in all respects to the compound prepared under ambient pressure (Table 1, entry 7).

4-(3-(1-Methylindolyl))-4-phenyl-2-butanone (Table 2, entry 3)

Standard procedure: 1-methylindole (295 mg, 2.25 mmol), benzalacetone (547 mg, 3.74 mmol), $Yb(OTf)_3 \cdot 3H_2O$ (33 mg, 49 μmol), acetonitrile (2 mL). The mixture was pressurized for 26 h and was worked up in the usual way. Flash chromatography using gradient elution (20– 30% EtOAc – hexanes) afforded 417 mg pure material (67%) as a yellow oil, identical in all respects to the compound prepared under ambient pressure (Table 1, entry 13).

3-(3-Indolyl)cyclohexanone (Table 2, entry 4)

Standard procedure: indole (276 mg, 2.36 mmol), 2-cyclohexen-1-one (500 μL, 5.16 mmol), $Yb(OTf)_3 \cdot 3H_2O$ (33 mg, 49 μmol), acetonitrile (2 mL). The mixture was pressurized for 2 d and was worked up in the usual way. Flash chromatography using gradient elution (20–30% EtOAc – hexanes) afforded 263 mg pure material (52%) as a pale yellow solid, identical in all respects to the compound prepared under ambient pressure (Table 1, entry 8).

3-Methyl-3-(3-(1-methylindolyl))cyclohexanone (Table 2, entry 5)

Standard procedure: 1-methylindole (292 mg, 2.23 mmol), 3-methyl-2-cyclohexen-1-one (400 μL, 3.53 mmol), $Yb(OTf)_3 \cdot 3H_2O$ (32 mg, 47 μmol), acetonitrile (2 mL). The mixture was pressurized for 7 d and was worked up in the usual way. Flash chromatography using gradient elution (10–30% EtOAc – hexanes) afforded 59 mg pure material (11%) as a yellow oil, identical in all respects to the compound prepared under ambient pressure (Table 1, entry 9).

3-Methyl-3-(3-(1-methylindolyl))cyclopentanone (Table 2, entry 6)

Standard procedure: 1-methylindole (316 mg, 2.41 mmol), 3-methyl-2-cyclopenten-1-one (500 μL, 5.05 mmol), $Yb(OTf)_3 \cdot 3H_2O$ (31 mg, 46 μmol), acetonitrile (2 mL). The mixture was pressurized for 5 d and was worked up in the usual way. Flash chromatography using gradient elution (10–30% EtOAc – hexanes) afforded 17 mg pure material (3%) as a yellow oil. IR (thin film), ν: 2940, 2910, 2860, 1730, 1600, 1475. 1455, 1410, 1390, 1365, 1320, 1230, 1145, 1120, 730 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$), δ: 1.60 (s, 3H), 2.13–2.37 (m, 3H), 2.44 (d, *J* = 17.7 Hz, 1H), 2.58 (m, 1H), 2.80 (d, *J* = 17.7 Hz, 1H), 3.73 (s, 3H), 6.78 (s, 1H), 7.11 (ddd, *J* = 8.1, 6.7, 1.4 Hz, 1H), 7.24 (tm, *J* = 7.5 Hz, 1H), 7.32 (dm, *J* = 7.9 Hz, 1H), 7.71 (dd, *J* = 7.9, 0.9 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$), δ: 28.0, 32.7, 35.8, 36.9, 39.9, 51.9, 109.7, 118.7, 119.8, 120.6, 121.7, 125.0, 126.5, 135.5, 200.9. MS (70 eV), *m*/*e*: 227 (M^+,100), 212, 198, 184, 172, 171 (100), 156, 144. HRMS (for $C_{15}H_{17}NO$): 227.1311 (calcd.); 227.1315 (found).

Methyl 3-(3-(1-methylindolyl))-propanoate (Table 3, entry 5)

Standard procedure: 1-methylindole (322 mg, 2.45 mmol), methyl acrylate (500 μL, 5.55 mmol), $Yb(OTf)_3 \cdot 3H_2O$ (36 mg, 53 μmol), acetonitrile (2 mL). The mixture was pressurized for 7 d and was worked up in the usual way. Flash chromatography using gradient elution (5–30% EtOAc – hexanes) afforded 40 mg pure material (8%) as a yellow

oil. R_f = 0.49 (30% EtOAc – hexanes). IR (neat), ν: 2935, 2910, 2840, 1730, 1545, 1460, 1425, 1370, 1315, 1180, 1155, 1125, 1110, 1060, 730 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$), δ: 2.73 (t, *J* = 7.6 Hz, 2H), 3.11 (t, *J* = 7.6 Hz, 2H), 3.69 (s, 3H), 3.74 (s, 3H), 6.88 (s, 1H), 7.13 (ddd, *J* = 7.8, 6.7, 1.2 Hz, 1H), 7.25 (td, *J* = 7.3, 1.2 Hz, 1H), 7.31 (dm, *J* = 7.2 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$), δ: 20.5, 32.6, 35.0, 51.6, 109.2, 113.4, 118.8 (two carbons), 121.6, 126.3, 127.5, 137.0, 173.9. MS (70 eV), *m*/*e*: 217 (M^+), 145, 144 (100), 143, 131, 130, 77. HRMS (for $C_{13}H_{15}NO_2$): 217.1103 (calcd.); 217.1107 (found).

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