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New Types of Reactivity of α,β-Unsaturated *N*,*N*-Dimethylhydrazones: Chemodivergent Diastereoselective Synthesis of Functionalized Tetrahydroquinolines and Hexahydropyrrolo[3,2-*b*]indoles

Vellaisamy Sridharan,[a] Pascual Ribelles,[a] Verónica Estévez,[a] Mercedes Villacampa,[a] M. Teresa Ramos,[a] Paramasivan T. Perumal,[a, b] and J. Carlos Menéndez*[a]

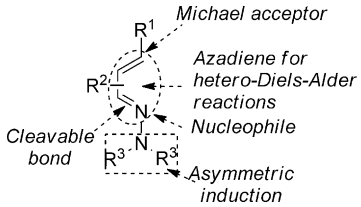
Abstract: The indium trichloride-catalyzed reaction between aromatic imines and α,β-unsaturated *N*,*N*-dimethylhydrazones in acetonitrile afforded 1,2,3,4-tetrahydroquinolines bearing a hydrazone function at C4 through a one-pot diastereoselective domino process that involves the formation of two C–C bonds and the controlled generation of two stereocenters, one of which is quaternary. This reaction constitutes the first example of an α,β-unsaturated dimethylhydrazone that behaves as a dienophile in a hetero Diels–Alder reaction. The related reaction between anilines, aromatic aldehydes, and methacrolein dimethylhydrazone in $CHCl_3$ with $BF_3{\cdot}Et_2O$ as catalyst afforded polysubstituted 1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*b*]indoles as major products through a fully diastereoselective ABB′C four-component domino process that generates two cycles, three stereocenters, two C–C bonds, and two C–N bonds in a single operation.

Keywords: domino reactions · heterocycles · Lewis acids · multicomponent reactions · stereoselectivity

Introduction

Chemodivergent reactions are one of the keys for the generation of molecular diversity and complexity from simple and inexpensive starting materials. This type of chemistry is one of the most promising paradigms in the discovery of new bioactive compounds and has also become one of the main challenges for organic synthesis.[1] Herein, we present an example of chemodivergence associated with the reaction conditions and catalyst in the diastereoselective synthesis of two classes of synthetically and biologically relevant nitrogen heterocycles.

α,β-Unsaturated *N*,*N*-dialkylhydrazones are versatile building blocks in organic synthesis that have attracted intense interest recently.[2] The 1-azadiene unit is employed in hetero Diels–Alder reactions with a normal electron demand, thanks to the electron-releasing effect of the dialkylamino substituent.[3] Furthermore, the β-carbon atom is an excellent Michael acceptor, the azomethine nitrogen atom is a good nucleophile, and the C=N double bond can be cleaved under hydrolytic, oxidative, and reductive conditions to release the free carbonyl group. Finally, the use of chiral substituents at the nitrogen atom attached to the azadiene system allows asymmetric induction in some of the previously mentioned reactions[4] (Scheme 1).



Scheme 1. Main types of reactivity of α,β-unsaturated *N*,*N*-dialkylhydrazones.

Quinoline and its derivatives are among the most important nitrogen heterocycles.[5] 1,2,3,4-Tetrahydroquinolines in particular show a wide range of interesting biological activities,[6] and therefore much effort has been devoted to their preparation.[7] One of the most versatile methods for the synthesis of 1,2,3,4-tetrahydroquinolines is the Povarov reaction, that is, the formal imino Diels–Alder reaction between *N*-arylimines and electron-rich dienophiles in the presence of Lewis acids.[8] As previously mentioned, α,β-unsaturated imines can be employed as the diene component in hetero Diels–Alder reactions with a normal electron demand, thus leading to pyridine and fused-pyridine derivatives. Because

[a] Dr. V. Sridharan, P. Ribelles, V. Estévez, Prof. M. Villacampa, Prof. M. T. Ramos, Prof. P. T. Perumal, Prof. J. C. Menéndez
Departmento de Química Orgánica y Farmacéutica
Universidad Complutense
Facultad de Farmacia, 28040 Madrid (Spain)
Fax: (+34) 91-3941822
E-mail: josecm@farm.ucm.es

[b] Prof. P. T. Perumal
Organic Chemistry Division
Central Leather Research Institute
Chennai 600 020 (India)

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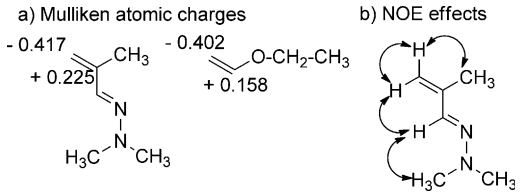
this type of reaction requires the unsaturated imines to be electron rich, the imines have to be modified by the introduction of electron-releasing groups on the nitrogen atom, normally dimethylamino,[9] and in some other cases acetylamino[10] or 1-*tert*-butyldimethylsilyloxy,[11] substituents to compensate for the electron-withdrawing effect of the nitrogen atom. We reasoned that the same electron-releasing effect should be expected to increase the electron density of the C2–C3 bond of the hydrazone sufficiently to allow its participation in Povarov-type chemistry. This expectation was supported by ab initio calculations at the B3LYP-6-31G* level, which reveal a very similar electron density for the carbon atoms in this bond and for the C=C bond in ethyl vinyl ether, a typical Povarov dienophile (see Scheme 2 and the Supporting Information). This study required the prior determination of the conformation of unsaturated dimethylhydrazones, which was established to be s-*trans* by NOE interaction studies.[12]



Scheme 2. a) Comparison of Mulliken atomic charges for **2** and ethyl vinyl ether. b) Conformational study of **2**.

Results and Discussion

We first undertook the study of the reaction between aromatic imine **1a** and methacrolein dimethylhydrazone (**2**) and hoped to use the latter compound as the dienophile rather than the diene for the first time in an imino Diels–Alder reaction, which would lead to an aza version of a type-1 vinylogous Povarov reaction,[13] a previously unknown transformation.[14] Besides the mechanistic novelty of this reaction, it would also be synthetically relevant because it could generate tetrahydroquinolines bearing a functional group and a quaternary stereocenter at C4. The corresponding, simpler reaction with alkyl vinyl ethers that leads to 4-alkoxy-2-aryl-1,2,3,4-tetrahydroquinolines has been reported.[15]

Due to our interest in cerium(IV) ammonium nitrate (CAN) as a catalyst in synthesis,[16,17] we started our investigation by studying the reaction in its presence with acetonitrile as the solvent (Table 1, entry 1). Unfortunately, the desired tetrahydroquinoline **3a** was obtained only in moderate yields accompanied by two additional products, namely, a small amount of an unexpected product, later identified as indolopyrrole **4a**, and benzaldehyde *N*,*N*-dimethylhydrazone (**5a**), a transimination compound that arises from the exchange of the hydrazone unit of **2** and the aldehyde unit of **1**, which was isolated as the major product. The results obtained in our optimization study of the reaction were aimed at maximizing the yield of tetrahydroquinoline **3** and are summarized in Table 1. We first studied the effect of other Lewis acids, such as scandium, ytterbium, and dysprosium triflates, which all afforded tetrahydroquinoline **3a** and **4a** in yields of around 50 and 10–15%, respectively, together with the transimination product **5** in amounts similar to those of **3a** (Table 1, entries 2–6). These results were not improved in the presence of less conventional catalysts, such as potassium hydrogen sulfate, triphenylphosphonium perchlorate, or boron trifluoride etherate (Table 1, entries 7–9, respectively). Indium trichloride was the only catalyst that furnished **3a** as the major product (Table 1, entry 10). This reagent is a mild and water-tolerant Lewis acid that is highly efficient in activating nitrogen-containing compounds such as imines and hydrazones[18] and was chosen for further studies aimed at the synthesis of derivatives of **3**.

Table 1. Catalyst optimization for the synthesis of **3a**.[a]

Entry	Catalyst	Catalyst loading [mol%]	*t* [h]	**3a**/**4a**/**5a**[b]
1	CAN	5	1	28:19:53
2	$Sc(OTf)_3$	5	24	33:15:52
3	$Sc(OTf)_3$	10	2	51:11:38
4	$Yb(OTf)_3$	10	2	48:trace:52
5	$Dy(OTf)_3$	10	1	46:16:38
6	$Dy(OTf)_3$	10	5	47:12:41
7	$KHSO_4$	10	5	28:14:58
8	triphenylphosphonium perchlorate	10	3	33:12:55
9	$BF_3{\cdot}Et_2O$	10	1	38:15:47
10	$InCl_3$	10	2	64:5:31

[a] Solvent was acetonitrile. [b] Calculated from the ^{1}H NMR spectra of the crude reaction products. All reactions proceeded in 100% conversion. CAN = cerium(IV) ammonium nitrate, OTf = trifluoromethanesulfonate.

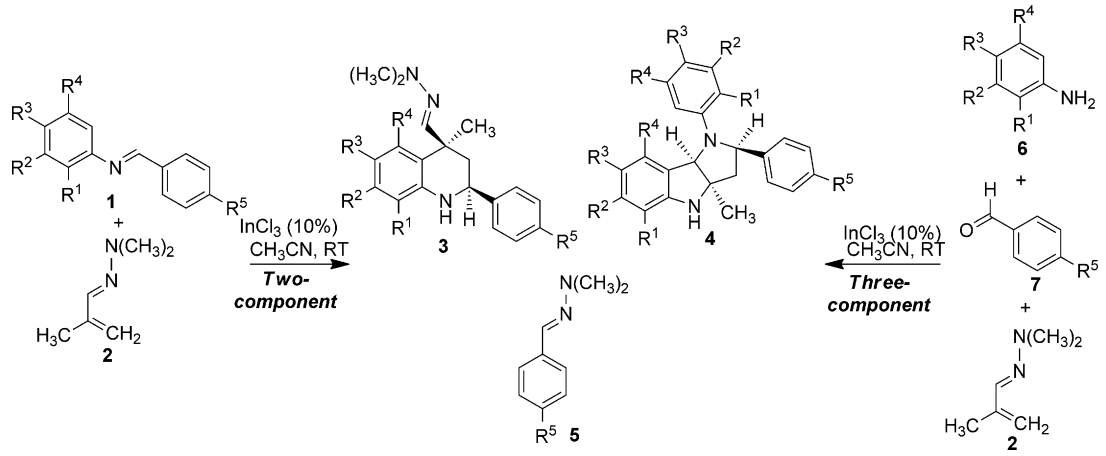
We briefly examined the model reaction in several solvents with varying polarities to optimize the reaction medium (Table 2); however, we found no improvement over the original solvent of acetonitrile, which was employed for the subsequent reactions directed at the preparation of tetrahydroquinolines.

Table 2. Solvent optimization for the synthesis of **3a**.[a]

Entry	Solvent	*t* [h]	**3a**/**4a**/**5a**[b]
1	CH_3CN	2	64:5:31
2	THF	6	0:0:22[c]
3	CH_2Cl_2	6	27:17:44[d]
4	$CHCl_3$	6	38:15:47
5	EtOH	6	51:14:35

[a] Catalyst: 10 mol% $InCl_3$. [b] Calculated from the ^{1}H NMR spectra of the crude reaction products. All the reactions proceeded with 100% conversion, except for entries 2 and 3. [c] Compound **1a** was recovered in 78% yield. [d] Compound **1a** was recovered in 12% yield.

We next examined the scope of the reaction in terms of the electron density on both aromatic rings by starting from diarylimines containing both electron-releasing and - withdrawing groups on both aryl rings (e.g., **1**) and compound **2**.



Scheme 3. Two- and three-component versions of the reaction between imines (or anilines plus aldehydes) and methacrolein dimethylhydrazone (**2**).

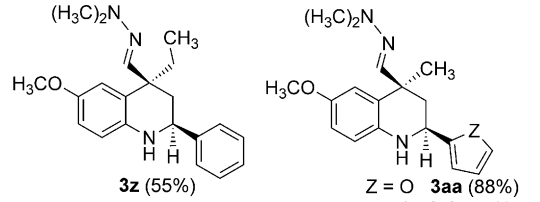
The main general conclusion that may be obtained from the data shown in Scheme 3 and Table 3 is that electron-releasing substituents on the imine ring that came from an arylamine diminished the side products, thus leading to excellent yields of the C4-functionalized tetrahydroquinolines **3**. On the other hand, electron-withdrawing substituents afforded transimination compounds **5** as the major products. The nature of the substituents on the ring that came from the aromatic aldehydes affected neither the rate of the reaction nor the product ratio. In summary, the reaction gave access to tetrahydroquinolines with combinations of substituents at all the possible carbon atoms, except C3, and always in fully diastereoselective fashion regarding the substitution at C2 and C4. We also studied a three-component version of the reaction and started from anilines **6**, aldehydes **7**, and unsaturated hydrazone **2**. This one-pot protocol increased the yield of **4**, but it also increased the amount of undesired **5** (see the second half of Table 3). The use of two equivalents of the arylamine and changes to the order of reagent addition did not alter these results significantly.

Some additional reactions were carried out to further extend the generality of the method, and the products ob-

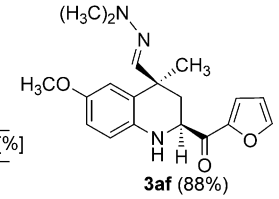
Table 3. Synthesis of tetrahydroquinolines through two- and three-component $InCl_3$-catalyzed reactions of **2**.

Entry	Compound	R^1	R^2	R^3	R^4	R^5	Two-component reaction			Three-component reaction			
							t [h]	Yield of **3** [%][a]	**3/4/5**[b]	*t* [h]	Yield of **3** [%][a]	**3/4/5**[b]	Conditions[e]
1	**a**	H	H	H	H	H	2	58	64:5:31	2	37	41:18:41	B
2	**b**	H	H	Me	H	H	2	71	73:9:18	2	30	35:23:42	B
3	**c**	H	H	OMe	H	H	2	90	93:0:7	2	19	23:23:54	A
4	**d**	H	Me	H	H	H	2	60[c]	64:11:25	–	–	–	–
5	**e**	H	Me	H	Me	H	2	56	64:11:25	2	27	34:27:39	A
6	**f**	Me	H	Me	H	H	2	80	83:0:17	–	–	–	–
7	**g**	H	H	F	H	H	2	34	38:0:62	–	–	–	–
8	**h**	H	H	Cl	H	H	2	27	33:0:67	2	11	13:0:87	A
9	**i**	H	H	H	H	Cl	2	71	77:5:18	–	–	–	–
10	**j**	H	H	H	H	Me	2	71	75:7:18	–	–	–	–
11	**k**	H	H	Me	H	Cl	2	76	81:0:19	2	40	46:16:38	C
12	**l**	H	H	OMe	H	Cl	3	87	91:0:9	3	56	64:7[d]: 29	C
13	**m**	H	H	OMe	H	Me	2	93	95:0:5	3	33	39:14[d]: 47	A
14	**n**	OMe	H	H	H	Cl	3	70	75:0:25	2	64	71:0:29	B
15	**o**	H	H	H	H	OMe	2	51	57:11:32	–	–	–	–
16	**p**	H	H	Me	H	OMe	2	72	78:0:22	2	53	60:10[d]:30	A
17	**q**	H	H	OMe	H	OMe	2	80	86:0:14	–	–	–	–
18	**r**	Me	H	Me	H	Cl	3	79	87:0:13	3	73	81:0:19	A
19	**s**	Me	H	Me	H	OMe	3	83	88:0:12	3	76	83:0:17	B
20	**t**	Me	H	Me	H	Me	5	81	87:0:13	5	60	67:0:33	B
21	**u**	Me	H	Me	H	Br	3	80	88:0:12	3	72	80:0:20	A
22	**v**	Me	H	H	H	H	–	–	–	2	61	71:0:29	B
23	**w**	Me	H	H	H	Cl	5	64	84:0:16	5	63	83:0:17	B
24	**x**	H	H	NMe_2	H	H	1.5	68	78:0:22	–	–	–	–
25	**y**	H	OMe	H	OMe	Me	2	72	75:10:15	–	–	–	–

[a] Yield of the isolated product. [b] Calculated from the ^{1}H NMR spectra of the crude reaction products. All the reactions proceeded with 100% conversion. [c] The imine used for this reaction was 90% pure. [d] In these cases, the minor compound **4** could not be isolated in pure form. [e] See the Experimental Section for details.



Cmpd	R^2	R^3	R^4	Yield [%]
3ac	H	OMe	H	88
3ad	H	Me	H	86
3ae	Me	H	Me	85

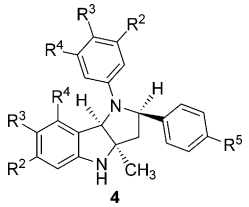


Scheme 4. Additional examples that increase the scope of the two-component tetrahydroquinoline synthesis that use Method A in all cases.

tained are summarized in Scheme 4. These examples, which were carried out through the two-component protocol, show that the tetrahydroquinoline synthesis tolerates substituents other than a methyl group at C4 (i.e., **3z**), aromatic substituents other than a phenyl ring (i.e., **3aa** and **3ab**), and also nonaromatic (i.e., **3ac**–**3ae**) and acyl substituents at C2 (i.e., **3af**). Some attempts were made to employ C3-substituted dimethylhydrazones, thus leading to C3-substituted tetrahydroquinolines, although only complex mixtures were obtained.

The reaction that leads to **4** is interesting because the 1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*b*]indole system is almost unknown[19] in spite of the considerable synthetic and pharmacological interest of the regioisomeric hexahydropyrrolo-[2,3-*b*]indole species, which is present in a large number of alkaloids.[20] This transformation is also important because it can be considered to be one of the very few examples of a reaction taking place through an ABB′C multicomponent mechanism. The final product arises from three starting materials but contains four different structural units, two of which come from one component that acts with two different chemical roles in a chemodifferentiated fashion. Processes of this type have attracted much attention recently because of their ability to generate molecular diversity and complexity from a limited number of starting materials.[21] In an effort to increase the product selectivity in favor of **4**, we employed our previous optimization studies to select $BF_3{\cdot}Et_2O/CHCl_3$ as the most promising catalyst/solvent combination and carried out the reactions using a three-component protocol. According to our expectations, the yield of **4** under these conditions rose up to 93%, although they were still accompanied by transimination products and, in most cases, by small amounts of the corresponding tetrahydroquinolines (Table 4). In an effort to further optimize the yield of **4**, we reasoned that the formation of these compounds involves an intermolecular nucleophilic attack that competes with the intramolecular attack, thus leading to **3** (see the mechanistic proposal in Scheme 5). For this reason, we hoped that by carrying out the reaction in a more concen-

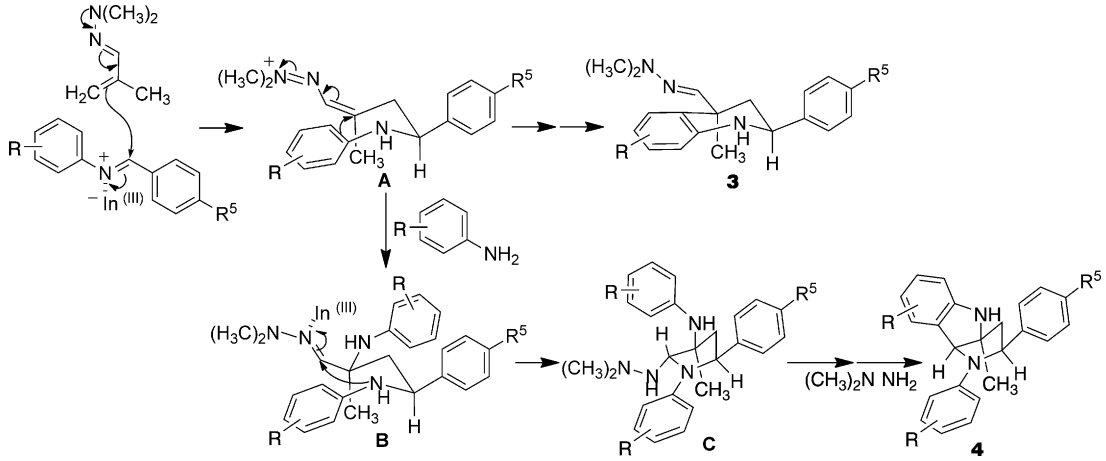
Table 4. Improved synthesis of **4**.[a]



4

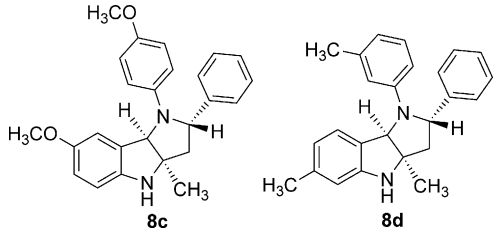
Entry	Cmpd	R^2	R^3	R^4	R^5	Yield [%][b]
1	**4a**	H	H	H	H	68
2	**4b**	H	Me	H	H	59
3	**4c**	H	OMe	H	H	58[c]
4	**4d**	Me	H	H	H	75
5	**4e**	Me	H	Me	H	93
6	**4k**	H	Me	H	Cl	38
7	**4o**	H	H	H	OMe	59

[a] Conditions: $CHCl_3$, $BF_3{\cdot}Et_2O$, RT, 2 h. [b] Yield of isolated products. [c] Obtained as an approximate 1:1 mixture of diastereomers.



Scheme 5. Mechanistic proposal for the formation of **3** and **4**.

trated solution we could achieve better product selectivity in favor of **4**. Although this assumption turned out to be correct, these conditions had the disadvantage of decreasing the diastereoselectivity of the process that led to **4** and afforded the other possible diastereomers **8**, which was shown by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures. Although this result was not synthetically useful, we isolated two of the compounds **8** to fully characterize them (Scheme 6). This result serves to introduce a note of



Scheme 6. Structure of two examples of derivatives of **8.**

caution over the use of highly concentrated conditions in Lewis acid-catalyzed cyclization reactions due to the possible loss of diastereoselectivity. It is relevant to mention at this point that the reaction that started from *para*-anisidine also lacked diastereoselectivity, even under the normal dilution conditions, and afforded an equimolecular mixture of **4c** and **8c**. The use of a larger excess of aniline was also attempted as a way to increase the yield of **4**, but it mainly favored the transimination reaction.

The structures and relative configurations of **3** and **4** were determined by spectroscopic analysis combined with single-crystal X-ray diffraction data (Figure 1). Compounds **3** have a *cis* relationship between the C2 hydrogen atom and the C4 methyl group. This relationship was initially established by NOE interactions studies that showed a correlation peak between the H2 and C4–CH_3 signals, which is only consistent with a *cis* arrangement for these substituents because both are axial. Subsequently, this conclusion was confirmed by an X-ray diffraction study of **3b** (Figure 1). Compounds **4** were also isolated in diastereomerically pure form, and their proposed stereochemistry is based on the NOESY correlations between the methyl group and the two hydrogen atoms attached to the stereogenic carbon atoms, which was confirmed by X-ray diffraction studies of **4e**. The most characteristic ^{1}H NMR signals of **4** were the singlet at approximately $\delta = 5.2$ ppm due to the 8b proton, and the ^{13}C NMR signals at approximately $\delta = 65$, 70, and 75 ppm due to the three carbon atoms adjacent to the nitrogen atoms.

The mechanism proposed for the formation of **3** and **4** is summarized in Scheme 5. The Lewis acid-activated imine is attacked by the electron-rich hydrazone to afford the Michael acceptor **A**, which may then undergo a Friedel–Crafts-type cyclization reaction to afford the Povarov product **3**, which takes place through a chairlike transition state and leads to a preference for an equatorial arrangement of the bulky dimethylhydrazono and aryl substituents, thus giving the observed stereochemistry of **3**. Alternatively, **A** can

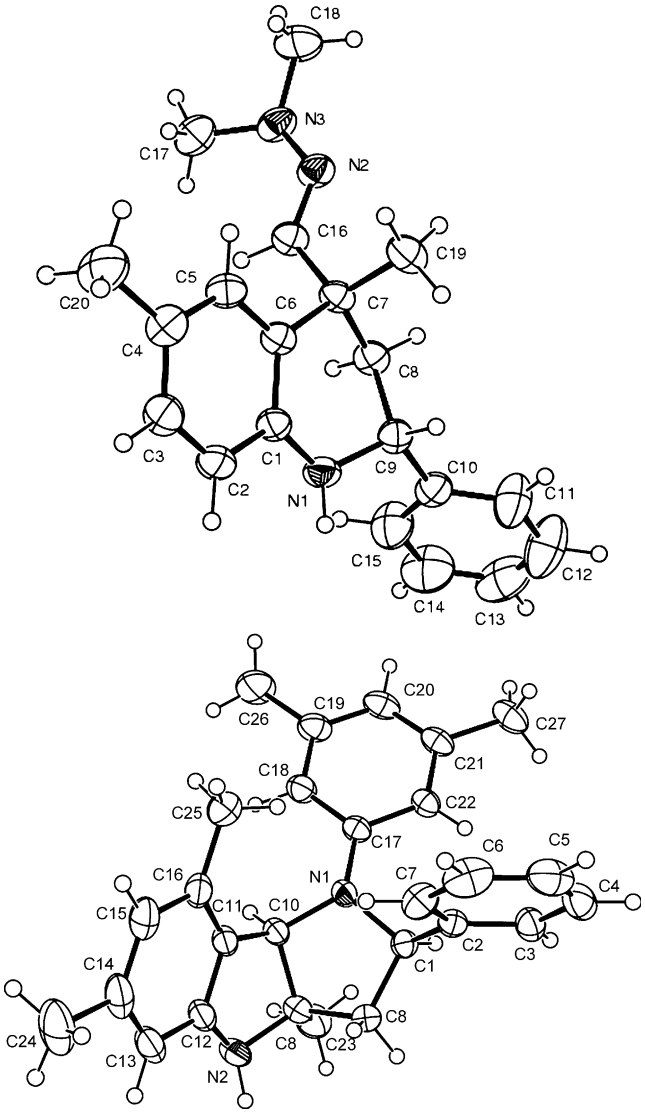
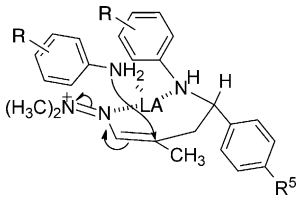


Figure 1. ORTEP plot for compounds **3b** (top) and **4e** (bottom).

accept a second arylamine molecule to generate intermediate **B**. This attack takes place from the face of the hydrazone C=N opposite to the carbon chain containing the aryl and arylamino substituents, thereby explaining the observed diastereoselectivity provided that **A** is in the conformation shown in Scheme 5, which would be stabilized by intramolecular hydrogen bonding. Indium trichloride activates the cyclization of **B** to the pyrrolidine intermediate **C**, which subsequently furnishes the observed indolopyrrole **4**, presumably by elimination of a dimethylhydrazine molecule to give an intermediate iminium cation that finally undergoes a Friedel–Crafts-type intramolecular cyclization reaction. The generation of an iminium cation from **C** should be favored by the presence of electron-releasing substituents at the aniline ring and is supported by the observation that **4** was not obtained at all when the reactions were carried out with aniline compounds bearing electron-withdrawing groups (Table 1, entry 1 versus entries 7 and 8). The pro-

posed mechanism is consistent with the fact that *ortho*-substituted arylamines failed to give indolopyrroles **4** (Table 3, entries 6, 14, and 18–23) because the Michael addition of arylamines to the corresponding intermediates **A** is sterically hindered. The lower diastereoselectivity found for the formation of **4** in more concentrated solutions can be explained by the increased probability of attack of the second aniline molecule by the "inner" side of the Michael acceptor through coordination of the nucleophile with the Lewis acid and any of the two electron-rich nitrogen atoms of intermediate **B** (Scheme 7). This proposal would also account for the lack of diastereoselectivity in the case of **4c**, in which the presence of a strong electron donor (i.e., OMe group) *para* to the aniline nitrogen atom and the NH group in intermediate **B** would favor this type of coordination.



Scheme 7. Proposed explanation of the decreased diastereoselectivity of **4** in concentrated solutions. LA = Lewis acid.

The source of the second aniline molecule must be explained to rationalize the formation of **4** in the two-component protocol. Although the Lewis acid-catalyzed hydrolysis of starting imine **1** from traces of water in the solvent might be invoked, we have never observed the other hydrolysis product, namely, aldehyde **7**. Furthermore, in an independent experiment, imine **1a** was recovered after being submitted to our usual reaction conditions for several hours in the absence of the other reaction component **2**. Related transimination reactions have been explained through a [2+2] cycloaddition/retrocycloaddition sequence,[22] which would afford the observed products **5** and *N*-arylmethacroleinimines in our case. These compounds are known to be highly unstable[23] and therefore can be expected to rapidly evolve to the corresponding aniline and a methacrolein molecule, the volatility of which would preclude its isolation.

Conclusion

The indium trichloride-catalyzed Povarov-type reaction between aromatic imines and α,β-unsaturated *N*,*N*-dimethylhydrazones in acetonitrile gives ready access to biologically and synthetically relevant 1,2,3,4-tetrahydroquinolines bearing a hydrazone function at C4 through a one-pot diastereoselective domino process that involves the formation of two C–C bonds and the controlled generation of two stereocenters, one of which is quaternary. This reaction constitutes the first example of an α,β-unsaturated dimethylhydrazone that behaves as a dienophile in a hetero Diels–Alder reaction and the first type-I vinylogous Povarov reaction. The presence of the dimethylhydrazone group is interesting in that it may allow further functionalization, either directly or with prior cleavage.[2] Modified reaction conditions (i.e., $CHCl_3$ as the solvent and $BF_3{\cdot}Et_2O$ as the catalyst) allowed the isolation of polysubstituted 1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*b*]indoles as major products through an ABB′C four-component reaction that generates two cycles, two C–C bonds, and two C–N bonds in a single operation, while creating three stereocenters, one of which is quaternary, in a fully diastereoselective fashion.

Experimental Section

General: See the Supporting Information for the general experimental details.

General protocol for the synthesis of tetrahydroquinoline derivatives 3 by reactions of imines 1 and methacrolein dimethylhydrazone (2): Imines **1** were prepared by the standard procedure of heating equimolecular amounts of the appropriate aniline and aldehydes to reflux in ethanol for 3 h. The solid that formed by precipitation was removed by filtration after cooling. $InCl_3$ (10 mol%) was added to a stirred solution of pure imine **1** (3 mmol) and **2**[24] (3.6 mmol) in acetonitrile (20 mL). The reaction mixture was stirred for the time period specified in Table 3. After completion of the reaction as indicated by TLC analysis, the reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (4× 10 mL). The extracts were dried over anhydrous Na_2SO_4 and evaporated. Purification was achieved by column chromatography on silica gel with petroleum ether/ethyl acetate (95:5, v/v) as the eluent.

General protocols for the three-component reactions between anilines 6, aldehydes 7, and α,β-unsaturated dimethylhydrazones:

Method A: Equimolar quantities of the appropriate aniline **6** and aldehyde **7** were mixed well without any solvent for 5–10 min. The reaction mixture was dissolved in acetonitrile (20 mL for a scale of 3 mmol) and stirred. $InCl_3$ (10 mol%) followed by **2** (1.2 equiv) were added to this solution, which was stirred for the time period specified in Table 3. After completion of the reaction, as indicated by TLC analysis, workup and purification were performed as mentioned in the two-component method.

Method B: An equimolar mixture of the appropriate aniline **6** and aldehyde **7** was heated to reflux in ethanol for 1 h. The ethanol was evaporated, and the reaction mixture was dissolved in acetonitrile (20 mL for a scale of 3 mmol) and stirred. Compound **2** (1.2 equiv) and $InCl_3$ (10 mol%) were added to the reaction mixture, which was stirred for the time period specified in Table 3. After completion of the reaction, as indicated by TLC analysis, workup and purification were performed as in the two-component method.

Method C: An equimolar mixture of the appropriate aniline **6** and aldehyde **7** was dissolved in a minimum amount of CH_2Cl_2 (1 mL for 3 mmol of reactant). The solution was mixed well and became solid within 1 or 2 min. The solid was dissolved in acetonitrile (20 mL for a scale of 3 mmol) and stirred. Compound **2** (1.2 equiv) and $InCl_3$ (10 mol%) were added to the reaction mixture, which was stirred for the time period specified in Table 3. After completion of the reaction, as indicated by TLC analysis, workup and purification were performed as in the two-component method.[25]

Characterization data for representative compounds are given below. For data corresponding to the full set of compounds, see the Supporting Information.

(±)-(2*S,4*S**)-4-[(2,2-Dimethylhydrazono)methyl]-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline (3a)**: M.p. 72–73 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.66 (s, 3H), 1.91 (dd, J = 13.1, 2.5 Hz, 1H), 2.15 (dd, J = 13.1, 11.8 Hz, 1H), 2.82 (s, 6H), 4.21 (brs, 1H), 4.63 (dd, J = 11.8, 2.5 Hz, 1H), 6.63–6.80 (m, 3H), 7.09–7.17 (m, 2H), 7.31–7.55 ppm (m, 5H);

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 28.4, 41.2, 43.9, 44.6, 53.5, 115.0, 118.1, 127.2, 127.9, 128.2, 129.2, 129.3, 144.5, 144.8, 145.1 ppm (two aromatic signals are merged); IR (neat) $\tilde{\nu}$ = 3376.7, 2967.6, 2850.3, 1603.8, 1483.8, 1313.8, 1157.7, 1011.1 cm^{-1}; elemental analysis (%) calcd for $C_{19}H_{23}N_3$: C 77.78, H 7.90, N 14.32; found: C 77.97, H 7.68, N 13.99.

(±)-(2*S,4*S**)-4-[(2,2-Dimethylhydrazono)methyl]-4,7-dimethyl-2-phenyl-1,2,3,4-tetrahydroquinoline (3d)**: Viscous liquid; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.60 (s, 3H), 1.86 (dd, J = 12.9, 2.7 Hz, 1H), 2.08 (dd, J = 12.9, 11.8 Hz, 1H), 2.29 (s, 3H), 2.77 (s, 6H), 4.12 (brs, 1H), 4.58 (dd, J = 11.8, 2.7 Hz, 1H), 6.45 (d, J = 1.1 Hz, 1H), 6.57 (dd, J = 7.8, 1.1 Hz, 1H), 6.82 (s, 1H), 7.00 (d, J = 7.8 Hz, 1H), 7.34–7.51 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 21.6, 28.3, 40.9, 43.9, 44.7, 53.4, 115.5, 119.1, 124.3, 127.1, 128.1, 129.1, 129.2, 137.7, 144.5, 144.6, 145.3 ppm; IR (neat) $\tilde{\nu}$ = 3366.3, 2966.4, 2852.0, 1618.0, 1577.5, 1469.8, 1317.3, 1179.7, 1010.4 cm^{-1}; elemental analysis (%) calcd for $C_{20}H_{25}N_3$: C 78.14, H 8.20, N 13.67; found: C 78.22, H 7.97, N 13.40.

(±)-(2*S,4*S**)-2-(4-Chlorophenyl)-4-[(2,2-dimethyl-hydrazono)methyl]-4-methyl-1,2,3,4-tetrahydroquinoline (3i)**: M.p. 90–91 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.59 (s, 3H), 1.83 (dd, J = 13.2, 2.0 Hz, 1H), 2.06 (dd, J = 13.2, 11.1 Hz, 1H), 2.78 (s, 6H), 4.13 (brs, 1H), 4.57 (dd, J = 11.1, 2.0 Hz, 1H), 6.62 (d, J = 8.4 Hz, 1H), 6.67 (s, 1H), 6.74 (t, J = 7.1 Hz, 1H), 7.04–7.12 (m, 2H), 7.37 (d, J = 8.6 Hz, 2H), 7.43 ppm (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 28.5, 41.1, 43.8, 44.6, 52.9, 115.1, 118.4, 127.2, 127.9, 128.6, 129.3, 133.6, 143.1, 144.5, 144.7 ppm (two aromatic signals are merged); IR (neat) $\tilde{\nu}$ = 3374.3, 2965.0, 2851.2, 1603.9, 1488.2, 1312.5, 1257.7, 1090.4, 1013.8 cm^{-1}; elemental analysis (%) calcd for $C_{19}H_{22}ClN_3$: C 69.61, H 6.76, N 12.82; found: C 69.59, H 6.62, N 12.83.

(±)-(2*S,4*S**)-4-[(2,2-Dimethylhydrazono)methyl]-2-(4-methoxyphenyl)-4,6-dimethyl-1,2,3,4-tetrahydroquinoline (3p)**: M.p. 119–120 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.59 (s, 3H), 1.80 (dd, J = 13.1, 2.6 Hz, 1H), 2.07 (dd, J = 13.1, 11.6 Hz, 1H), 2.25 (s, 3H), 2.78 (s, 6H), 3.85 (s, 3H), 4.00 (brs, 1H), 4.51 (dd, J = 11.6, 2.6 Hz, 1H), 6.53 (d, J = 8.3 Hz, 1H), 6.70 (s, 1H), 6.86–6.89 (m, 2H), 6.93 (d, J = 8.7 Hz, 2H), 7.40 ppm (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 20.9, 28.4, 41.2, 43.9, 44.8, 52.9, 55.8, 114.4, 115.0, 127.1, 127.2, 128.2, 128.5, 129.6, 136.7, 142.5, 145.5, 159.5 ppm; IR (neat) $\tilde{\nu}$ = 3366.4, 2956.1, 2852.5, 1612.1, 1506.5, 1467.1, 1247.4, 1172.8, 1034.2 cm^{-1}; elemental analysis (%) calcd for $C_{21}H_{27}N_3O$: C 74.74, H 8.06, N 12.45; found: C 74.35, H 7.93, N 12.41.

(±)-(2*RS*,4*RS*)-4-[(2,2-Dimethylhydrazono)methyl]-2-(4-methoxyphenyl)-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline (3q): M.p. 94–95 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.60 (s, 3H), 1.81 (dd, J = 13.2, 2.5 Hz, 1H), 2.08 (dd, J = 13.2, 11.6 Hz, 1H), 2.77 (s, 6H), 3.76 (s, 3H), 3.85 (s, 3H), 3.89 (bs, 1H), 4.48 (dd, J = 11.6, 2.5 Hz, 1H), 6.56 (dd, J = 7.5, 1.4 Hz, 1H), 6.67–6.70 (m, 3H), 6.93 (d, J = 8.7 Hz, 2H), 7.40 ppm (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 28.6, 41.6, 43.9, 44.7, 53.0, 55.8, 56.3, 113.9, 114.4, 114.8, 115.9, 128.2, 128.5, 136.7, 139.1, 145.1, 152.5, 159.5 ppm; IR (neat) $\tilde{\nu}$ = 3363.2, 2950.8, 2831.5, 1611.1, 1503.3, 1466.3, 1246.4, 1172.4, 1035.5 cm^{-1}; elemental analysis (%) calcd for $C_{21}H_{27}N_3O_2$: C 71.36, H 7.70, N 11.89; found: C 71.28, H 7.48, N 11.95.

(±)-(2*S,4*S**)-4-[(2,2-Dimethylhydrazono)methyl]-2-(2-furyl)-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline (3aa)**: Pale-orange viscous liquid; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.56 (s, 3H), 2.00 (dd, J = 13.1, 2.6 Hz, 1H), 2.23 (t, J = 12.9 Hz, 1H), 2.78 (s, 6H), 3.75 (s, 3H), 4.03 (brs, 1H), 4.61 (dd, J = 11.5, 2.4 Hz, 1H), 6.28 (dt, J = 3.2, 0.7 Hz, 1H), 6.38 (dd, J = 3.2, 1.8 Hz, 1H), 6.55–6.73 (m, 4H), 7.41 ppm (dd, J = 1.8, 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 27.9, 39.9, 40.4, 43.3, 46.8, 55.7, 105.1, 110.2, 113.4, 114.1, 115.9, 128.3, 137.5, 141.7, 144.3, 152.3, 156.4 ppm; IR (neat) $\tilde{\nu}$ = 3362.2, 2952.5, 2851.4, 1504.6 cm^{-1}; elemental analysis (%) calcd for $C_{18}H_{23}N_3O_2$: C 68.98, H 7.40; N 13.41; found: C 69.12, H 7.47, N 13.41.

(±)-(2*RS*,4*RS*)-Ethyl 4-[(2,2-dimethylhydrazono)methyl]-4-methyl-6-methoxy-1,2,3,4-tetrahydroquinoline-2-carboxylate (3ac): Pale yellow viscous liquid; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.34 (t, J = 7.1 Hz, 3H), 1.51 (s, 3H), 1.97 (dd, J = 12.8, 11.8 Hz, 1H), 2.11 (dd, J = 12.8, 3.3 Hz, 1H), 2.79 (s, 6H), 3.73 (s, 3H), 4.13 (dd, J = 11.8, 3.3 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 6.60–6.67 ppm (m, 4H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 14.6, 27.4, 37.8, 40.8, 43.7, 51.6, 56.2, 61.8, 113.9, 114.2, 116.4, 128.4, 136.9, 143.7, 152.6, 173.6 ppm; IR (neat) $\tilde{\nu}$ = 3387.6, 2978.0, 2853.4, 1738.2, 1504.4, 1232.0, 1042.9 cm^{-1}; elemental analysis (%) calcd for $C_{17}H_{25}N_3O_3$: C 63.93, H 7.89, N 13.16; found: C 63.94, H 7.63, N 13.03.

Synthesis of hexahydropyrrolo[3,2-*b*]indoles 4: The suitable aniline **7** (2 equiv) and aldehyde **6** (1 equiv) were mixed well without any solvent for 5–10 min. The reaction mixture was dissolved in $CHCl_3$ (15 mL for a scale of 3 mmol) and stirred. $BF_3{\cdot}Et_2O$ (10 mol%) followed by **2** (1.2 equiv) were added to the reaction mixture, which was stirred for the time period specified in Table 3. After completion of the reaction, as indicated by TLC analysis, the reaction mixture was mixed with water (10 mL) and extracted with $CHCl_3$ (3×10 mL). The extracts were dried over anhydrous Na_2SO_4 and evaporated. Purification was achieved by column chromatography on silica gel with petroleum ether/ethyl acetate (95:5, v/v) as the eluent.[25]

(±)-(2*R,3a*R**,8b*R**)-3a-Methyl-1,2-diphenyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*b*]indole (4a)**: M.p. 174–175 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.57 (s, 3H), 2.21 (dd, J = 12.3, 9.2 Hz, 1H), 2.53 (dd, J = 12.3, 7.0 Hz, 1H), 3.90 (brs, 1H), 4.88 (dd, J = 9.2, 7.0 Hz, 1H), 5.16 (s, 1H), 6.69 (d, J = 7.8 Hz, 1H), 6.77–6.84 (m, 3H), 6.91 (td, J = 7.5, 0.8 Hz, 1H), 7.18–7.29 (m, 8H), 7.64 ppm (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 25.5, 50.1, 64.6, 69.3, 74.8, 111.3, 113.5, 117.3, 120.1, 126.0, 126.2, 127.3, 129.1, 129.4, 129.5, 131.6, 144.0, 147.9, 149.4 ppm; IR (neat) $\tilde{\nu}$ = 3356.5, 2960.3, 2866.9, 1597.9, 1501.8, 1351.6, 1251.7, 1152.0 cm^{-1}; elemental analysis (%) calcd for $C_{23}H_{22}N_2$: C 84.63, H 6.79, N 8.58; found: C 84.41, H 6.80, N 8.76.

(±)-(2*R,3a*R**,8b*R**)-7-Methoxy-3a-methyl-1-(4-methoxyphenyl)-2-phenyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*b*]indole (4c)**: M.p. 147–148 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.60 (s, 3H), 2.03 (dd, J = 12.6, 9.3 Hz, 1H), 2.50 (dd, J = 12.6, 6.2 Hz, 1H), 3.53 (s, 3H), 3.71 (s, 3H), 4.64 (dd, J = 9.3, 6.2 Hz, 1H), 5.39 (s, 1H), 6.40 (d, J = 2.3 Hz, 1H), 6.57–6.77 (m, 6H), 7.17–7.33 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 27.3, 52.9, 55.8, 56.1, 62.7, 69.3, 75.4, 110.9, 113.1, 114.3, 115.3, 121.3, 127.0, 127.1, 128.8, 129.5, 140.1, 143.3, 145.2, 153.0, 153.3 ppm; IR (neat) $\tilde{\nu}$ = 3355.0, 2956.4, 2830.5, 1602.9, 1510.4, 1491.2, 1239.8, 1036.7 cm^{-1}; elemental analysis (%) calcd for $C_{25}H_{26}N_2O_2$: C 77.69, H 6.78, N 7.25; found: C 77.83, H 6.72, N 7.35.

(±)-(2*S,3a*R**,8b*R**)-7-Methoxy-3a-methyl-1-(4-methoxyphenyl)-2-phenyl-1,2, 3,3a,4,8b-hexahydropyrrolo[3,2-*b*]indole (8c)**: M.p. 108–111 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.51 (s, 3H), 2.13 (dd, J = 12.2, 9.8 Hz, 1H), 2.45 (dd, J = 12.2, 6.7 Hz, 1H), 3.75 (s, 3H), 3.81 (s, 3H), 4.74 (dd, J = 9.8, 6.7 Hz, 1H), 5.01 (s, 1H), 6.60–6.83 (m, 6H), 7.15–7.25 ppm (m, 6H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 24.7, 49.5, 55.7, 56.1, 64.4, 69.1, 75.4, 111.7, 112.5, 113.7, 114.2, 114.7, 125.6, 126.8, 128.6, 133.8, 141.8, 142.2, 143.5, 151.5, 151.6 ppm; IR (neat) $\tilde{\nu}$ = 3343.4, 2927.2, 1510.2, 1489.0, 1242.8, 1037.3, 815.0 cm^{-1}; elemental analysis (%) calcd for $C_{25}H_{26}N_2O_2$: C 77.69, H 6.78, N 7.25; found: C 77.34, H 6.54, N 6.98.

(±)-(2*R,3a*R**,8b*R**)-1-(3,5-Dimethylphenyl)-3a,6,8-trimethyl-2-phenyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*b*]indole (4e)**: M.p. 216–217 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.47 (s, 3H), 2.19 (dd, J = 11.8, 10.5 Hz, 1H), 2.26 (s, 6H), 2.30 (s, 3H), 2.42 (s, 3H), 2.43 (dd, J = 11.8, 7.3 Hz, 1H), 3.85 (brs, 1H), 4.81 (dd, J = 10.5, 7.3 Hz, 1H), 5.21 (s, 1H), 6.36 (s, 1H), 6.48 (s, 3H), 6.54 (s, 1H), 7.20–7.32 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 19.8, 21.8, 22.3, 24.4, 49.3, 66.4, 69.3, 74.6, 110.0, 112.1, 119.6, 123.5, 126.0, 126.5, 127.2, 129.1, 136.2, 138.6, 138.9, 145.2, 149.2, 149.9 ppm; IR (neat) $\tilde{\nu}$ = 3346.2, 2961.6, 2919.4, 1597.2, 1454.1, 1352.4, 1298.2, 1206.1, 1152.3, 1065.2 cm^{-1}; elemental analysis (%) calcd for $C_{27}H_{30}N_2$: C 84.77, H 7.90, N 7.32; found: C 84.59, H 7.95, N 7.39.

(±)-(2*R,3a*R**,8b*R**)-2-(4-Methoxyphenyl)-3a-methyl-1-phenyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*b*]indole (4o)**: M.p. 148–149 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.52 (s, 3H), 2.15 (dd, J = 12.2, 9.3 Hz, 1H), 2.47 (dd, J = 12.2, 7.0 Hz, 1H), 3.76 (s, 3H), 4.80 (dd, J = 9.3, 7.0 Hz, 1H), 5.10 (s, 1H), 6.65–6.90 (m, 6H), 7.11–7.28 (m, 6H), 7.59 ppm (d, J = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 25.4, 50.2, 55.6, 64.0, 69.2, 74.7, 111.3, 113.4, 114.4, 117.2, 120.0, 126.1, 127.1, 129.3, 129.5, 135.9, 147.8, 149.3, 158.9 ppm; IR (neat) $\tilde{\nu}$ = 3357.8, 2958.7, 2836.0, 1597.7, 1501.8, 1464.2, 1353.8, 1245.2, 1170.5, 1035.1 cm^{-1}; elemental analysis (%) calcd for $C_{24}H_{24}N_2O$: C 80.87, H 6.79, N 7.86; found: C 80.66, H 6.95, N 8.09.

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