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Direct, Two-Step Synthetic Pathway to Novel Dibenzo[*a,c*]phenanthridines

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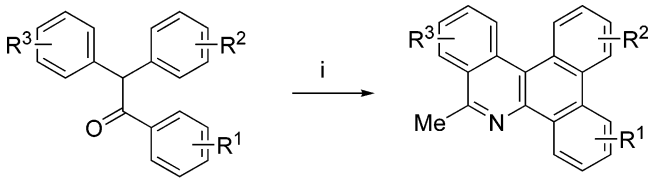

i: 1. P_2O_5, CH_3CN. 2. PIFA, $BF_3{\cdot}OEt_2$, CH_2Cl_2

Novel dibenzo[*a,c*]phenanthridines are prepared regioselectively by the application of a straightforward synthetic pathway, starting from new 3,4-diaryl- and 3,4-dihydro-3,4-diarylisoquinolines prepared via Ritter-type heterocyclization and the more classical two-step reductive amination/Bischler−Napieralski cyclization of triarylethanones, respectively. A comparative study of nonphenolic oxidative coupling methodologies provides a highly efficient procedure, based on the hypervalent iodine reagent phenyliodine(III) bis(trifluoroacetate) (PIFA), to accomplish the final coupling step.

Introduction

Phenanthro[9,10]fused heterocycles are of interest in many aspects. They constitute not only the core of several naturally ocurring products (tylophorine, antofine, or cryptopleurine, inter alia)[1] but also a group of biological agents that present very interesting pharmacological properties related to the planarity of the system and consequently to its DNA-chain intercalating ability,[2] which make them suitable for antineoplastic or mutagenic applications.[3,4]

In addition, the high charge mobility of this heterocyclic system provides pronounced photoconducting, optoelectrical switching, and photovoltaic properties,[5] which are key features in the field of dye lasers and electroluminescence.[6] Therefore, during the last few years, phenanthro[9,10]heterocycles have gained much attention because of their promising applications in the development of optical materials, information recordings such as holography, lithographic plates for printing, and electronic equipment.[7]

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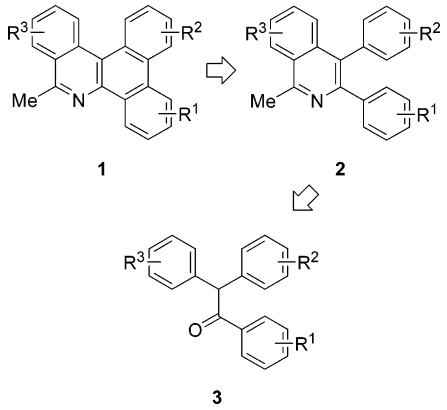
Following our investigations of the synthesis of new phenanthrofused heterocycles,[8] we planned the construction of an appealing pentacyclic system, dibenzo[*a,c*]-phenanthridines (**1**), with an inherent interest because of their close relationship to biologically active benzo[*c*]-phenanthridine alkaloids.[9] Certainly, these isoquinoline derivatives are well known for their powerful antitumor and antileukemic properties,[10,11] but the high toxicity associated with some of the active members of this family of alkaloids[12] has led to the search for new potentially active analogues[13] such as the dibenzo[*a,c*]phenanthridines (**1**).

Hence, in connection with our recent works on the arylation of acetophenones and deoxybenzoins,[14] 1,2,2-triarylethanones (**3**) were selected as suitable precursors in developing a synthetic approach to the target pentacyclic system (**1**) based on a ketone heterocyclization and biaryl coupling of the generated diarylisoquinoline intermediates (**2**). Despite the variety of methodologies that are known for biaryl bond formation, the need for substrates suitably halogenated or sulfonated for cross coupling procedures, such as Ullmann, Suzuki, or Stille reactions,[15] or limitations concerning substitution patterns in photochemical approaches[16] encouraged us to attempt a more simple way, oxidative coupling, which was already explored by our group in the synthesis of other phenanthroheterocycles.[8,17] Moreover, the synthesis of a number of natural products such as tylophorine,[18] rufescine,[19] kreysigine,[20] and gomisine[21] have been efficiently accomplished in the past few years by means of synthetic pathways based on phenol ether coupling procedures. Therefore, we planned to extend the scope of the oxidative coupling procedure toward the preparation of new dibenzo[*a,c*]phenanthridines (**1**). The most outsanding results are described in this paper.



Results and Discussion

Synthesis of 3,4-Diarylisoquinolines. Although it is scarcely exploited, the Ritter-type heterocyclization of benzyl ketones with nitriles in the presence of a dehydrating agent constitutes a simple and efficient approach to the synthesis of isoquinolines.[22] According to the retrosynthetic scheme shown above, we envisaged that this method could be applied to complex substrates such as 1,2,2-triarylethanones (**3**), which are readily prepared from the corresponding aryl- and/or diaryl ketones,[14] to provide direct access to the desired 3,4-diarylisoquinolines (**2**).

Initially, we selected a range of suitably alkoxylated triarylethanones (**3a**−**f**) as starting materials to fit the electronic requirements of the final oxidative biaryl coupling step. Thus, the treatment of such electron-rich ketone derivatives (**3a**−**f**) with acetonitrile in the presence of phosphorus pentoxide at room temperature afforded the 3,4-diarylisoquinolines (**2a**−**f**) in moderate to high yields (Table 1).

Taking into account the possibility of both aryl groups attached to the C-2 position in triarylethanones (**3**) undergoing an intramolecular cyclization,[23] we must point out the regioselectivity of the performed reaction because in all cases the only isomer observed is the one corresponding to the heterocyclization with the more alkoxylated arene ring. In addition, the good yields obtained for isoquinolines **2e** and **2f** cannot be dis-

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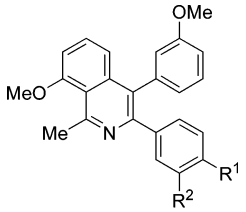
(23) The mechanistic pathway to explain the formation of isoquinolines in these kinds of reactions has been reported previously, proving that the last stage of the reaction includes an intramolecular electrophilic substitution leading to the isoquinoline core. See ref 22a.

regarded, especially if the lack of activating substituents at the diarylmethyl moiety of ketones **3e**−**f** is considered. Although to a lesser extent, the concomitant formation of 8-methoxylated isomer **2l** along with the main product **2d** features a weak point in the regioselectivity of the presented protocol.

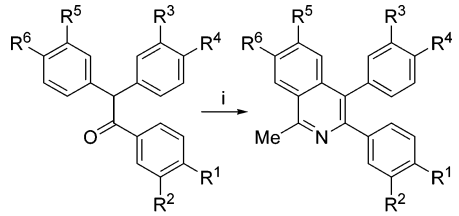
Encouraged by these results and in order to evaluate the scope and limitations of the procedure, a new series of less active ketone derivatives (**3g**−**k**) were submitted to the above optimized conditions. Nevertheless, initial attempts to synthesize isoquinolines from such triarylethanones, including several Lewis-acid-promoted assays,[24] afforded the unreacted starting material. Finally, the desired 3,4-diarylisoquinolines (**2**) were obtained successfully by heating the solvent at reflux (Table 1). In this context, it is interesting that there is a total absence of other heterocyclic systems that are commonly found as side products (e.g., pyrimidines) in these types of reactions, even when proceeding at high temperatures.[25] Such different behavior in our case suggests that the double substitution of the carbon at the α position in the triarylethanones prevented such annoying reactions from leading selectively to the target isoquinolines (**2**). Nevertheless, by increasing the temperature, we observed more 8-methoxylated regioisomers (**2m** and **2n**).



$R^1 = R^2 =$ OMe **2l**
$R^1 = R^2 =$ H **2m**
$R^1 =$ Me, $R^2 =$ H **2n**

Additional information about the structure of one of the heterocycles, 3,4-diphenylisoquinoline (**2g**), was obtained from its X-ray diffraction analysis. The crystallographic study revealed that both 3-aryl and 4-aryl substituents were in a puckered conformation relative to the isoquinoline ring system, as shown in Figure 1 . (The puckering angles for C(5)−C(4)−C(13)−C(14) and C(13)−C(14)−C(17)−C(18) were 72.2 and 54.9°, respectively.) This significant deviation from the coplanarity, caused by a decrease in the steric hindrance and previously observed in other heterocyclic systems with adjacent diaryl substitution,[26] has been associated with a lower conjugation degree along the ring systems. Evidence that reinforces the latter explanation is the longer the length of the bond distances between the isoquinoline and 4-aryl and 3-aryl rings (C(14)−C(17), 1.489(3) Å and C(4)−C(13), 1.492(3) Å, respectively) the more twisted

TABLE 1. 3,4-Diarylisoquinolines (2)



3 **2**

i: P_2O_5, MeCN, rt or ↑↓, 16h

3	R^1	R^2	R^3	R^4	R^5	R^6	**2** (%)[a]
3a	OMe	OMe	H	H	OMe	OMe	**2a** (94)[b]
3b	OMe	OMe	OMe	H	OMe	OMe	**2b** (74)[b]
3c	OMe	OMe	H	NO_2	OMe	OMe	**2c** (51)[b]
3d	OMe	OMe	OMe	H	OMe	H	**2d** (60)[b,c]
3e	OMe	OMe	H	F	H	F	**2e** (75)[b]
3f	OMe	OMe	H	H	H	H	**2f** (78)[b]
3g	H	H	H	H	H	H	**2g** (77)[d]
3h	Me	H	H	H	H	H	**2h** (75)[d]
3i	H	H	H	H	OCH_2O		**2i** (76)[d]
3j	H	H	OMe	H	OMe	H	**2j** (43)[d,e]
3k	Me	H	OMe	H	OMe	H	**2k** (45)[d,f]

[a] Isolated yield. [b] Reaction was performed at room temperature. [c] 15% of **2l** was also isolated. [d] Reaction was performed at reflux. [e] 33% of **2m** calculated from the relative integration of the ^{1}H NMR signals in the crude mixture was also found. [f] 37% of **2n** calculated from the relative integration of the ^{1}H NMR signals in the crude mixture was also found.

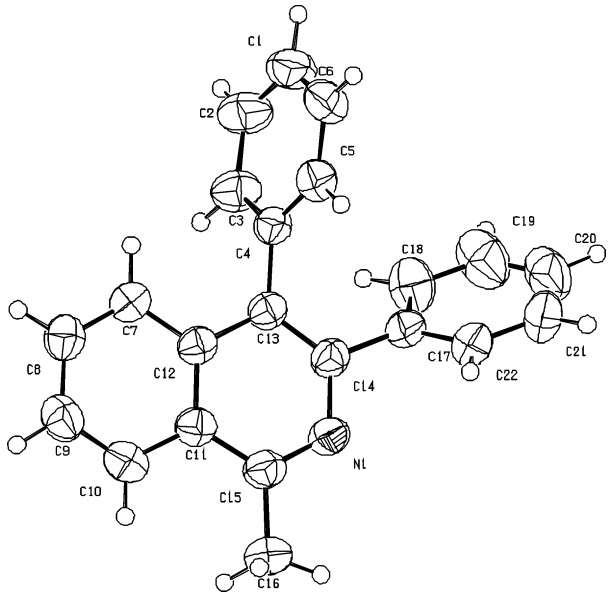


FIGURE 1. ORTEP view of 3,4-diphenyl-1-methylisoquinoline (**2g**) showing the atomic numbering scheme.

the aryl ring is. The remaining determined values for angles and bonds are in agreement with those already reported for other compounds with structural resemblance to 3,4-diarylisoquinolines, such as 3-aryl-[27] and 3,4-diaryl-5,6,7,8-tetrahydroisoquinoline.[28]

(24) It has been shown that the addition of Lewis acids could significantly increase the yield of these reactions. The effect of such additives has been studied in: Fodor, G.; Nagubandi, S. *Tetrahedron* **1980**, *36*, 1279−1300.

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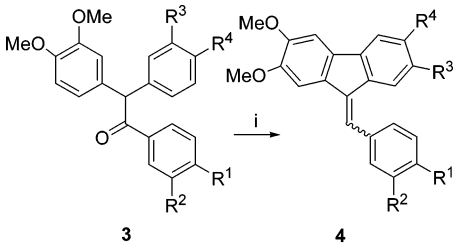
TABLE 2. 9-Benzylidene-9*H*-fluorenes (4)



3 4

i: P_2O_5, MeCN, rt, 16h

3	R^1	R^2	R^3	R^4	4 (%)[a]
3l	OMe	OMe	OMe	OMe	**4a** (77)
3m	Me	H	OMe	OMe	**4b** (75)
3n	H	H	OMe	OMe	**4c** (71)
3o	OMe	OMe	OCH_2O		**4d** (50, 86/14[b])
3p	OMe	OMe	H	OMe	**4e** (76, 74/26[b])

[a] Isolated yield. [b] Cis/trans ratio, calculated from the relative integration of the ^{1}H NMR signals.

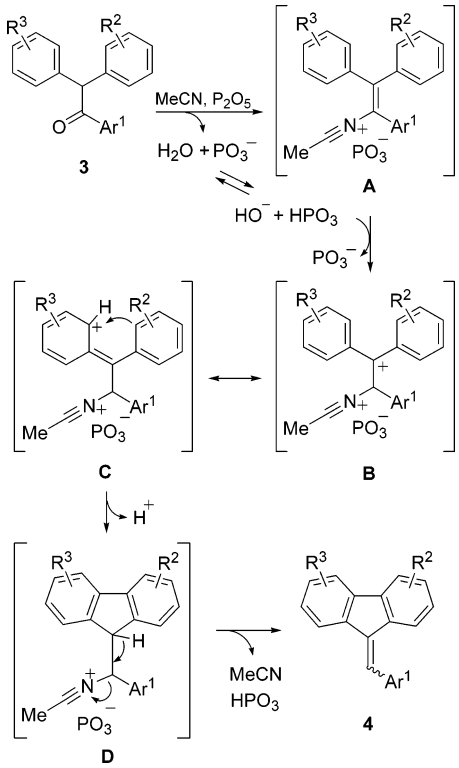
Finally, regarding the activity shown by triarylethanones (**3**) as substrates for the synthesis of 3,4-diarylisoquinolines (**2**), it can be observed that the reactivity of the process is governed unexpectedly by the nature of the benzoyl group. Thus, when the aromatic ring next to the carbonyl group is activated electronically, the reaction proceeds at room temperature, whereas in the absence of strongly electron-donating substituents, the reaction takes place only under solvent reflux regardless of the substituents at the diarylmethyl moiety.

Taking into account the a priori requirement of polymethoxylaled derivatives for the final oxidative coupling step, we submitted an additional series of ketones (**3l**−**p**) to the optimized heterocyclization conditions. Surprinsingly, 9-benzylidene-9*H*-fluorenes (**4**) were obtained as the main products (Table 2), and all attemps to promote cyclization to the derivatives (**2**) were unsuccessful, providing target **2** in very low yields (<7%).[29]

To explain such unexpected results in the presence of alkoxy groups in the para position of both aromatic rings attached to the tertiary carbon in all of the substrates, we must consider **3l**−**p**. Therefore, even lacking further evidences, we suggest tentatively that the formation of fluorenes (**4**), which could be related to isoquinolines by common intermediate **A**, followed a mechanistic pathway starting with an initial protonation of vinylogous nitrilium salt **A**. The corresponding carbocation intermediate (**B** ↔ **C**), strongly stabilized when *p*-alkoxy substituents are present in the diarylmethyl cationic framework, may then undergo an intramolecular electrophilic substitution followed by the loss of acetonitrile and phosphoric acid, thus generating fully conjugated fluorene **4** (Scheme 1).

Although useless for our synthetic aims, it cannot be forgotten that, despite the limitation imposed by the requirement of *p*-electrondonating substituents, the reported results constitute an appealing alternative procedure for the synthesis of pharmacologically interesting benzylidenefluorenes.[30,31]

SCHEME 1



A more established approach to the isoquinoline framework consists of the reductive amination/heterocyclization of benzyl ketones.[32] In view of the failure of the Ritter-type protocol when applied to polymethoxylated ethanones **3l**−**p**, reductive amination/heterocyclization of the latter substrates was envisaged as a suitable complementary route toward the same end (Scheme 2).

Despite the previous reports,[33] attempts to carry out the transformation of triarylethanone **3l** into the required amine derivative employing Leuckart reductive amination procedures (HCO_2NH_4, $HCONH_2$, and HCO_2H) failed, affording an unresolved multicomponent mixture at high temperature (180−200°C),[34] whereas the unreacted starting material was recovered under milder

(29) A range of reaction conditions, varying the amounts of reagents, reaction time, temperature, and even adding Lewis acids as activating agents were assayed, but in all cases polymethoxylated triarylethanone **3l** failed to give the corresponding isoquinoline, thus recovering unreacted starting material or leading to benzylidenefluorene **4a**.

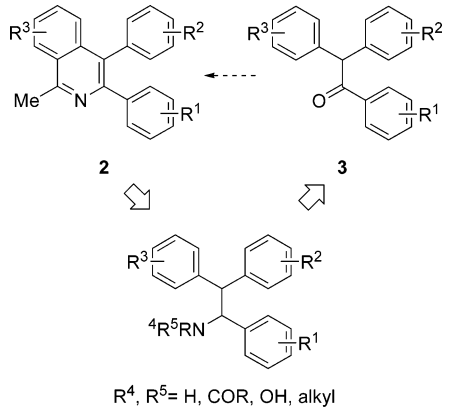
(30) Several benzylidenefluorene derivatives exhibit very interesting pharmacological applications, for example, as hypolipidemic, antidiabetic, and antiinflamatory agents or in the treatment of malaria. See: (a) Wiesner, J.; Henschker, D.; Hutchinson, D. B.; Beck, E.; Jomaa, H. *Antimicrob. Agents Chemother.* **2002**, *46*, 2889−2894. (b) Bindschedler, M.; Lefevre, G.; Degen, P.; Sioufi, A. *Am. J. Trop. Med. Hyg.* **2002**, *66*, 293−298. (c) Watanabe, M.; Ando, T.; Asa, T.; Uegaki, Y.; Oide, H.; Yoneda, F. (Fujimoto Brothers K. K.; Japan) JP20000125, 2000; *Chem. Abstr. 132*, 107947. (d) Yoneda, F.; Muraoka, S.; Oide, H.; Watabe, M.; Urabe, K.; Takeuchi, I. (Fujimoto Brothers K. K.; Japan) JP20010724, 2001; *Chem. Abstr. 135*, 117231. (e) Uhrich, K. E.; Macedo, B. (USA) US20020808, 2002; *Chem. Abstr. 137*, 150228.

(31) Benzylidenefluorenes have been commonly prepared by the suitable functionalization of fluorene derivatives. See: (a) Yan, C.-G.; Sun, J. *Synth. Commun.* **2000**, *30*, 3809−3814. (b) Mladenova, G.; Chen, L.; Rodríguez, C. F.; Siu, K. W. M.; Johnston, L. J.; Hopkinson, A. C.; Lee-Ruff, E. *J. Org. Chem.* **2001**, *66*, 1109−1114.

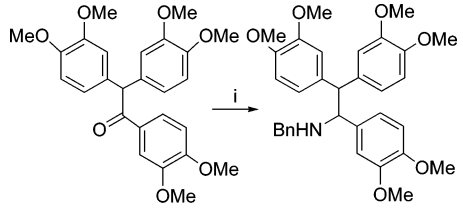
(32) (a) Badía, D.; Domínguez, E.; Lete, E.; Villa, M.-J. *Trends Heterocycl. Chem.* **1991**, 2−11. (b) Sotomayor, N.; Vicente, T.; Domínguez, E.; Lete, E.; Villa, M.-J. *Tetrahedron* **1994**, *50*, 2207−2218. (c) Carrillo, L.; Badía, D.; Domínguez, E.; Anakabe, E.; Osante, I.; Tellitu, I.; Vicario, J. L. *J. Org. Chem.* **1999**, *64*, 1115−1120.

(33) Loupy, A.; Monteux, D.; Petit, A.; Aizpurua, J. M.; Domínguez, E.; Palomo, C. *Tetrahedron Lett.* **1996**, *37*, 8177−8180.

SCHEME 2



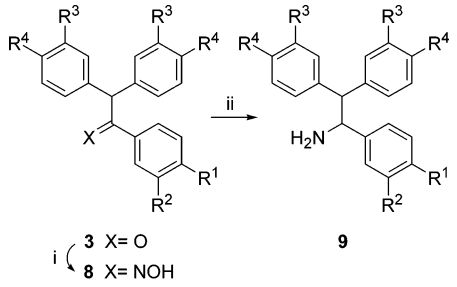
SCHEME 3



conditions. Similar results were obtained with the application of several procedures for the reductive amination via imine intermediates.[35] In fact, reductive amination of deoxybenzoins via imines has been reported to proceed in high yields using either $TiCl_4$ or Ti(*i*PrO)$_4$ as the carbonyl activator/water scavenger and $NaBH_4$ or $NaBH_3CN$ as C=N the reducing agent,[36] but in our hands, when triarylethanone **3l** was submitted to the latter conditions only 24% yield of benzylamine **7** was achieved (Scheme 3).

Fortunately, the synthesis of the desired amines (**9**) was successfully accomplished via oximes (Table 3). Thus, the treatment of the selected triarylethanones (**3j**−**m**) with hydroxylamine hydrochloride[37] afforded the intermediate oximes (**8**) as a mixture of anti and syn isomers,[38] which were, without further purification, submitted to the Zn/HCOOH (aq) reductive conditions,[39] leading to the corresponding amines (**9**) with moderate to high overall yields.

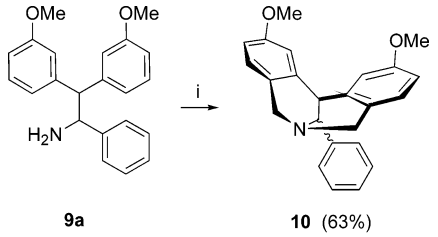
TABLE 3. Synthesis of Triarylethylamines (9)



R^1	R^2	R^3	R^4	**9** (%)[a]
H	H	OMe	H	**9a** (90)
Me	H	OMe	H	**9b** (61)
OMe	OMe	OMe	OMe	**9c** (50)
Me	H	OMe	OMe	**9d** (52)

[a] Isolated overall yield calculated from the corresponding ketones (**3**).

SCHEME 4



We proceeded to the cyclization of the obtained amine intermediates next. Pictet−Spengler reaction[40] conditions were initially applied to amine **9a**, surprisingly providing dibenzoazocine derivative **10** as the main product,[41] formed in a double heterocyclization process probably favored by the activation of both *β*-aryl groups in the amine substrate (Scheme 4). Nevertheless, acetylation

(34) A careful examination of the crude mixture (^{1}H RMN, ^{13}C RMN, and EIMS) revealed the presence of diaryl ketone derivatives, probably generated by the oxidative cleavage of the alpha bond of the carbonyl group in the triarylethanone substrate.

(35) (a) Senboku, H.; Kajizuka, Y.; Hasegawa, H.; Fujita, H.; Sugimone, H.; Orito, K.; Tokuda, M. *Tetrahedron* **1999**, *55*, 6465−6474. (b) Berdini, V.; Cesta, M. C.; Curti, R.; D'Anniballe, G.; Di Bello, N.; Nano, G.; Nicolini, L.; Topai, A.; Allegretti, M. *Tetrahedron* **2002**, *58*, 5669−5674. (c) Firouzabadi, H.; Iranpoor, N.; Alinezhad, H. *Bull. Chem. Soc. Jpn*. **2003**, *76*, 143−151.

(36) (a) Battacharyya, S.; Neidigh, K. A.; Avery, M. A.; Williamson, J. S. *Synlett* **1999**, 1781−1783. (b) Vicario, J. L.; Badía, D.; Domínguez, E.; Carrillo, L. *J. Org. Chem.* **1999**, *64*, 4610−4616. (c) Horiguchi, Y.; Kodama, H.; Nakamura, M.; Yoshimura, T.; Hanezi, K.; Hamada, H.; Sahito, T.; Sano, T.; *Chem. Pharm. Bull.* **2002**, *50*, 253−257.

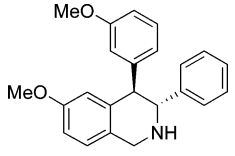
(37) (a) Sotomayor, N.; Domínguez, E.; Lete, E. *J. Org. Chem.* **1996**, *61*, 4062−4072. (b) Kai, H.; Nakai, T. *Tetrahedron Lett.* **2001**, *42*, 6895−6897.

(38) The differences among the chemical shift values of the α-methynic proton in the ^{1}H NMR spectra of both isomers were used to assign the stereochemistry. See: Karabatsos, G. J.; Hsi, N. *Tetrahedron* **1967**, *23*, 1079−1095. See also ref 37a.

(39) (a) Shi, G.-Q.; Cai, W.-L. *J. Org. Chem.* **1995**, *60*, 6289−6295. Other procedures for the reduction of oximes are described in: (b) Lagu, B.; Wetzel, J. M.; Forray, C.; Patane, M. A.; Bock, M. G. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2705−2707. (c) Zimmer, R.; Orschel, B.; Scherer, S.; Reissig, H.-U. *Synthesis* **2002**, 1553−1563. (d) Yamazaki, K.; Atobe, M.; Kibayashi, C. *Tetrahedron Lett.* **2002**, *43*, 7979−7982. Attempts to perform the reduction of oxime **8a** employing the LAH reagent according to the method reported in ref 39b provided the corresponding amine derivative (**9a**) with a lower yield (52%).

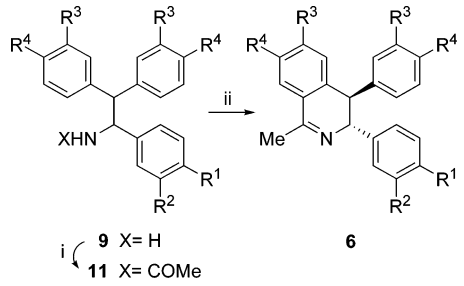
(40) (a) Waley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 151−190. (b) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797−1842.

(41) Only a low yield of desired tetrahydroisoquinoline **5** (31%) was obtained after a careful choice of the temperature, reaction times, and relative amount of paraformaldehyde, but the unavoidable formation of dibenzazocine derivative **10** led us to search for a more reliable synthetic approach.



5

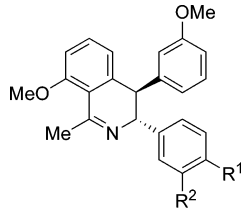
TABLE 4. Synthesis of Acetamides (11) and 3,4-dihydroisoquinolines (6)



R^1	R^2	R^3	R^4	**11** (%)[a]	**6** (%)[a]
H	H	OMe	H	**11a** (65)	**6a** (57)[b]
Me	H	OMe	H	**11b** (72)	**6b** (67)[c]
OMe	OMe	OMe	OMe	**11c** (60)	**6c** (81)[d]
Me	H	OMe	OMe	**11d** (67)	**6d** (76)[d]

[a] Isolated yield. [b] 20% of **6e** calculated from the relative integration of the ^{1}H NMR signals in the crude mixture was also detected. [c] 13% of **6f** calculated from the relative integration of the ^{1}H NMR signals in the crude mixture was also detected. [d] 10 equiv of P_2O_5 was added.

of amines (**9**, Ac_2O, ↑↓)[42] followed by Bischler−Napieralski cyclization[43] provided the target 3,4-dihydroisoquinolines (**6**, Table 4)[44] successfully. In a fashion similar to the Ritter-type heterocyclization approach, 8-methoxylated isomers **6e**−**f** were also formed.



R^1= R^2= H **6e**
R^1= Me, R^2= H **6f**

In light of these results, the direct heterocyclization reaction of benzyl ketones with nitriles promoted by a dehydrating agent constitutes a simple and efficient approach to 3,4-diarylisoquinolines starting from 1,2,2-triarylethanone derivatives. Nevertheless, despite of an increase in the number of reaction steps, a reductive amination/Bischler−Napieralski cyclization sequence could be considered as an advantageous complementary procedure for access to partially hydrogenated polymethoxylated isoquinolines, especially when considering the limitations shown by the Ritter-type one-pot process to synthesize such kinds of polysubstituted compounds.

Synthesis of Dibenzo[*a,c*]phenanthridines. Oxidative coupling reactions, formerly developed for phenols[45] and later extended to phenol ethers and other oxygenated electron-rich arenes,[46] are affected by anodic oxidation[47] or, using several oxidants, mostly heavy metal reagents.[48] In recent years, the use of hypervalent iodine(III) reagents, in particular, phenyliodine(III) diacetate (PIDA) and phenyliodine(III) bis(trifluoroacetate) (PIFA), which are less toxic and easier to handle, have received much attention.[49]

Accordingly, a whole array of oxidizing agents was assayed on diarylisoquinoline **2a** to promote the target oxidative coupling reaction.

As shown in Table 5, although the access to the target pentacyclic system was achieved by using several reagents, only TTFA and PIFA provided good yields (Table 5, entries 5 and 13). Nevertheless, the employment of thallium(III) oxidant TTFA was discarded because of its high toxicity and environmental harmfulness,[51] and PIFA was chosen as the most convenient oxidizing agent to affect, together with $BF_3{\cdot}OEt_2$ as the activating agent in CH_2Cl_2 at low temperature, biaryl linkage in the desired dibenzophenanthridines (**1**). From the series of fully aromatized derivatives prepared by the above-explained Ritter-type heterocyclization, we chose isoquinolines **2a**−**g** and **2k** to apply such optimized oxidative coupling conditions (Table 6).

According to the moderate to good yields and the high regioselectivity obtained in most cases, it can be concluded that the PIFA-mediated biaryl oxidative coupling procedure constitutes a simple and efficient final step in our approach to target pentacyclic system **1**. Moreover, it should be pointed out that the desired coupling products were obtained, in comparison to the more electronically favored substrates, with similar yields from less-activated **2a** and **2f** precursors or even deactivated fluoro derivative **2e**. Nevertheless, the scope of this procedure is determined by the requirement of electron-donating substituents in at least one arene to promote an oxidative coupling reaction, as can be deduced from the lack of reactivity exhibited by nonsubstituted isoquinoline **2g** or **2k**, which bear only one activating group. Previous reports on the mechanism involved in oxidative coupling reactions have proposed that electron-rich aryl

(42) Tyvorskii, V. I.; Bobrov, D. N.; Kulinkovich, O. G.; Aelterman, W.; DeKimpe, N *Tetrahedron* **2000**, *56*, 7313−7318.

(43) Waley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 74−150.

(44) The J_{H3-H4} vicinal coupling constant values in ^{1}H RMN spectra (9.9−12.3 Hz) were used to assign the stereochemistry of dihydro- and tetrahydroisoquinolines **6** and **5**, respectively. It has been observed that these large values are supported by the trans diaxial relationship between C3 and C4 hydrogens. Accordingly, derivatives **5** and **6** have been depicted showing such relative stereochemistry. See: Nicoletti, M.; O'Hagan, D.; Slawin, A. M. Z. *J. Chem. Soc., Perkin Trans. 1* **2002**, 116−121.

(45) *Oxidative Coupling of Phenols*; Taylor, W. I., Battersby, A. R., Eds.; Dekker: New York, 1967.

(46) (a) Whiting, D. A. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 659−703. (b) Oxidative activation of aromatic rings: an efficient strategy for arene functionalization; Quideau, S.; Feldman, K. S., Eds.; *Tetrahedron Symposium-in-Print 85* **2001**, *Vol. 57*, 265−424.

(47) Chapuzet, J.-M.; Simonet, J. *Tetrahedron* **1991**, *47*, 791−798.

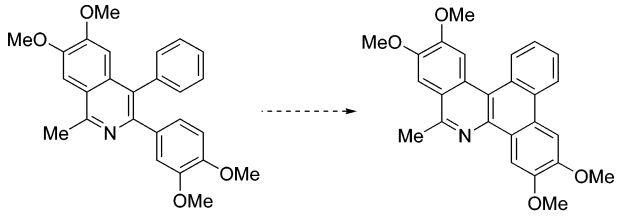
(48) (a) Keserú, G. M.; Nógrádi, M. *Stud. Nat. Prod. Chem.* **1998**, *20*, 263−322. See also ref 17b.

(49) (a) Kita, Y.; Takada, T.; Gyoten, M.; Tohma, H.; Zenk, M. H.; Eichhorn, J. *J. Org. Chem.* **1996**, *61*, 5857−5864. (b) Kita, Y.; Arisawa, M.; Gyoten, M.; Nakajima, M.; Hamada, R.; Tohma, H.; Takada, T. *J. Org. Chem.* **1998**, *63*, 6625−6633. (c) Wirth, T.; Hirt, U. H. *Synthesis* **1999**, 1271−1287. (d) Moreno, I.; Tellitu, I.; Herrero, M. T.; SanMartin, R.; Domínguez, E. *Curr. Org. Chem.* **2002**, *6*, 1433−1452.

(50) Cu(OH)Cl·TMEDA was easily prepared by the treatment of CuCl with TMEDA in 95% methanol and oxygen bubbling. See: Nakajima, M.; Miyoshi, I.; Kanayama, K.; Hashimoto, S.-I. *J. Org. Chem.* **1999**, *64*, 2264−2271.

(51) Rusyniak, D. E.; Kao, L. W.; Nanagas, K. A.; Kirk, M. A.; Furbee, R. B.; Brizendine, E. J.; Wilmot, P. E. *J. Toxicol., Clin. Toxicol.* **2003**, *41*, 137−142.

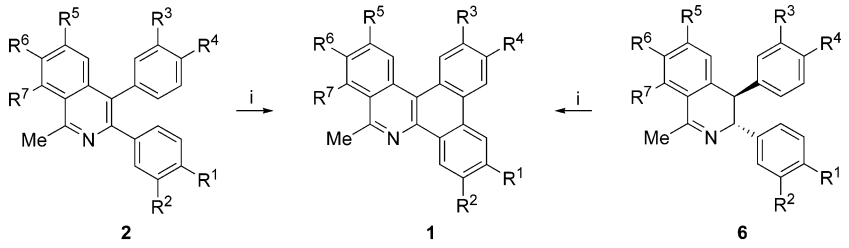
TABLE 5. Selected Oxidative Coupling Assays Performed on Isoquinoline 2a



entry	reaction conditions	product (%)[a]
1	VOF_3 (3 equiv), $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 2 h	**1a** (55)
2	VOF_3 (3 equiv), TFA[b], CH_2Cl_2, −40 °C → rt, 20 h	**1a** (4)
3	$FeCl_3$ (6 equiv), CH_2Cl_2, rt, 7 h	**1a** (53)
4	$RuO_2{\cdot}H_2O$ (4 equiv), TFA[b], $BF_3{\cdot}OEt_2$, TFAA[c], CH_2Cl_2, rt, 7 h	**1a** (41)
5	TTFA[d] (1.05 equiv), $BF_3{\cdot}OEt_2$, CCl_4, MeCN, −40 °C → rt, 65 h	**1a** (93)
6	$TiCl_4$ (2 equiv), $MeNO_2$, 0 °C → rt, 26 h	[e]
7	Ag_2O (1.4 equiv), CH_2Cl_2, rt, 17 h	[e]
8	Cu(OH)Cl·TMEDA[f,50] (0.05 equiv), O_2, CH_2Cl_2, rt, 16 h	[e]
9	$CuCl_2{\cdot}2H_2O$ (1 equiv), $BnNH_2$, MeOH, anisole, rt, 56 h	[e]
10	$Pd(OAc)_2$ (0.3 equiv), $Cu(OAc)_2$, AcOH ↑↓, 24 h	[e]
11	$Pd(OAc)_2$ (1 equiv), AcOH ↑↓, 18 h	[e]
12	PIFA[g] (1.1 equiv), CF_3CH_2OH, −40 °C, 3 h	[e]
13	PIFA[g] (1.1 equiv), $BF_3{\cdot}OEt_2$, CH_2Cl_2, −40 °C, 2 h	**1a** (75)

[a] Isolated yield. [b] TFA: CF_3COOH. [c] TFAA: $(CF_3CO)_2O$. [d] TTFA: $Tl(OCOCF_3)_3$. [e] Recovery of the starting material (>90%). [f] Cu(OH)Cl·TMEDA: hydroxo copper(II) chloride-(*N,N,N′,N′*-tetramethylethylenediamine) complex. [g] PIFA: $PhI(OCOCF_3)_2$.

TABLE 6. Synthesis of Dibenzo[*a,c*]phenanthridines (1)



i: PIFA, $BF_3{\cdot}OEt_2$, CH_2Cl_2, -40°C, 2h

substrate	R^1	R^2	R^3	R^4	R^5	R^6	R^7	**1** (%)[a]
2a	OMe	OMe	H	H	OMe	OMe	H	**1a** (75)
2b	OMe	OMe	OMe	H	OMe	OMe	H	**1b** (86)
2c	OMe	OMe	H	NO_2	OMe	OMe	H	**1c** (42)[b]
2d	OMe	OMe	OMe	H	OMe	H	H	**1d** (61)
2l	OMe	OMe	OMe	H	OMe	H	OMe	**1e** (80)
2e	OMe	OMe	H	F	H	F	H	**1f** (75)
2f	OMe	OMe	H	H	H	H	H	**1g** (72)
2g	H	H	H	H	H	H	H	[c]
2k	Me	H	OMe	H	OMe	H	H	[c]
6a	H	H	OMe	H	OMe	H	H	[c]
6b	Me	H	OMe	H	OMe	H	H	[c]
6c	OMe	OMe	OMe	OMe	OMe	OMe	H	**1h** (72)
6d	Me	H	OMe	OMe	OMe	OMe	H	**1i** (75)

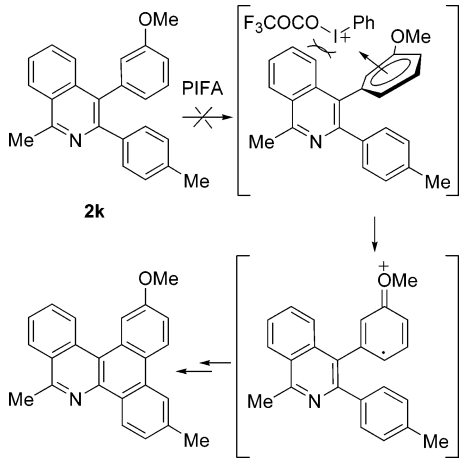
[a] Isolated yield. [b] The reaction was performed with TTFA as the oxidant (procedure described in Table 5, entry 5) afforded 73% yield of **1c**. [c] Recovery of the starting material (>90%).

groups can efficiently stabilize the aromatic radical cation intermediate generated from a charge-transfer complex by a single electron transfer (SET) process[52] so it can undergo nucleophilic attack from another aromatic ring. In our case, we suggest that the failure in the coupling of weakly activated substrates would probably rely on the difficulty of formation of the charge-transfer complex either because of the lack of electron-donating groups or steric reasons, as exemplified in Scheme 5.

Finally, the optimized coupling conditions were also applied to 3,4-dihydro-3,4-diarylisoquinolines (**6**) to promote one-pot oxidative coupling/aromatization.[53] An additional reason for such assays was to clarify the behavior shown by isoquinoline **2k** because the relatively small

(52) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684−3691.

SCHEME 5



steric hindrance of dihydro derivatives (**6**) in comparison to fully aromatized systems (**2**)[54] could favor the generation of the above-mentioned charge-transfer complex, thus affording the corresponding coupled product.

Again, from the four dihydroisoquinolines (**6**) assayed, only the electronically activated derivatives (**6c**−**d**) underwent oxidative coupling. Therefore, we suggest, discarding other hypotheses based on steric hindrance[55] and further activation/deactivation promoted by the isoquinoline nucleus or even weak nucleophilicity of the 3-(4-methylphenyl)ring, that the 4-(3-methoxyphenyl)ring is not active enough to undergo the required SET process and is responsible for the lack of reactivity of substrates **2k** and **6a** and **b**.

Conclusions

In summary, we have developed a straightforward and general method for the synthesis of unreported dibenzo[*a,c*]phenanthridines, featuring ketone-heterocyclization and biaryl coupling of the so-obtained 3,4-diarylisoquinoline intermediates as the key steps. The Ritter-type heterocyclization of 1,2,2-triarylethanones with nitriles promoted by a dehydrating agent provides a direct and simple approach to 3,4-diarylisoquinolines. Altogether, the more classical two-step reductive amination/Bischler−Napieralski cyclization sequence constitutes a complementary route, especially amenable to polymethoxylated substrates, that allowed us to construct the isoquinoline core in a lower oxidation state. Furthermore, the target pentacyclic system was achieved successfully from both fully aromatized and dihydrogenated isoquinoline intermediates by an efficient nonphenolic oxidative coupling procedure mediated by the hypervalent iodine reagent phenyliodine(III) bis(trifluoroacetate) (PIFA).

Experimental Section

General Procedure for the Ritter-Type Heterocyclization of Triarylethanones (3). To a solution of triarylethanone **3** (1 mmol) in dry acetonitrile (40 mL), we added P_2O_5 (33 mmol) portionwise at room temperature under argon. The reaction mixture was stirred at room temperature for 16 h, the solvent was removed in vacuo, and water (50 mL) and CH_2Cl_2 (20 mL) were added. The resulting solution was basified with NaOH (20 mL of 10% solution in water) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated in vacuo to give a residue that was purified by flash chromatography on silicagel using 0−30% EtOAc/CH_2Cl_2 as the eluent.

6,7-Dimethoxy-3-(3,4-dimethoxyphenyl)-1-methyl-4-phenylisoquinoline (2a). Yield 94%. White powder: mp 199−200 °C (MeOH); R_f: 0.54 (20% EtOAc/CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.99 (3H, s), 3,55 (3H, s), 3.76 (3H, s), 3.82 (3H, s), 4.06 (3H, s), 6.74 (1H, d, *J* 8.3 Hz), 6.76 (1H, d, *J* 1.9 Hz), 6.90 (1H, s), 7.07 (1H, dd, *J* 8.3, 1.9 Hz), 7.23−7.26 (2H, m), 7.31−7.41 (4H, m); ^{13}C NMR (63 MHz, $CDCl_3$): δ 22.7, 55.3, 55.6, 55.9, 103.6, 104.4, 110.3, 113.5, 121.8, 122.8, 127.0, 127.8, 128.4, 131.0, 132.6, 133.5, 138.3, 147.5, 147.7, 149.2, 152.2, 154.8; FTIR (neat film, cm^{-1}): 1618, 1255, 1028; EIMS (*m/z*, %): 415 (M^+, 100), 398 (19); HRMS calcd for $C_{26}H_{25}NO_4$, 415.1784; found, 415.1774. Anal. Calcd for $C_{26}H_{25}NO_4$: C, 75.16; H, 6.06; N, 3.37. Found: C, 75.12; H, 6.04; N, 3.45.

General Procedure for the Reductive Amination of Triarylethanones (3) via Oximes. Synthesis of Triarylethylamines (9). A solution of triarylethanone **3** (0.90 mmol) and hydroxylamine hydrochloride (5.4 mmol) in dry pyridine (18 mL) was refluxed for 2−2.5 h. The reaction mixture was allowed to cool to room temperature and evaporated to dryness in vacuo, and the residue was partitioned between water (10 mL) and CH_2Cl_2 (10 mL). The organic extract was washed with water (2 × 10 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated in vacuo. Without performing further purification, the resulting mixture was dissolved in the smallest amount of THF, 70% aqueous formic acid (17 mL) was added, and zinc powder (26.7 mmol) was added portionwise over 30 min after cooling the solution with an ice bath. The reaction mixture was stirred for 17−19 h at room temperature, filtered on sand, and washed with EtOAc. The filtrate was neutralized with a concentrated ammonia solution to pH 8 and then extracted with EtOAc (3 × 30 mL). The organic phase was washed with water (50 mL), dried over anhydrous sodium sulfate, and evaporated in vacuo to give a residue that was purified by flash chromatography on silicagel using 10−40% EtOAc/CH_2Cl_2 or 2−5% MeOH/CH_2Cl_2 as the eluent.

2,2-Bis(3-methoxyphenyl)-1-phenylethylamine (9a). Yield 90%. Colorless oil; R_f: 0.48 (2% MeOH/CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.81 (2H, bs), 3.63 (3H, s), 3.80 (3H, s), 4.07 (1H, d, *J* 10.3 Hz), 4.68 (1H, d, *J* 10.3 Hz), 6.56 (1H, dd, *J* 8.3, 2.0 Hz), 6.62 (1H, dd, *J* 2.4, 2.0 Hz), 6.70 (1H, d, *J* 7.9 Hz), 6.78 (1H, dd, *J* 7.9, 2.4 Hz), 6.97−7.03 (2H, m), 7.08 (1H, d, *J* 8.3 Hz), 7.14−7.31 (6H, m); ^{13}C NMR (63 MHz, $CDCl_3$): δ 54.9, 55.1, 59.7, 60.7, 111.1, 111.7, 114.4, 114.5, 120.6, 120.7, 127.0, 127.5, 128.0, 128.9, 129.7, 143.5, 143.6, 143.8, 159.0, 159.8; FTIR (neat film, cm^{-1}): 3382−3290, 1600, 1262, 1048; EIMS (*m/z*, %): 331 (M-2, 3), 106 (100); HRMS calcd for $C_{22}H_{23}NO_2$, 333.1729; found, 333.1723. Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.32; H, 6.91; N, 4.22.

(53) Because only one equivalent of the oxidant PIFA was employed for such a tandem reaction, the aromatization step might be atributed to the action of either PIFA itself or other reducible species such as iodobenzene. On the basis of previous results from our group, we have assumed that the coupling process constitutes the initial step. In our hands, isolation of coupled but not aromatized products has not been possible so far. See: (a) Moreno, I.; Tellitu, I.; Domínguez, E.; SanMartin, R. *Eur. J. Org. Chem.* **2002**, 2126−2135. See also: (b) Ihara, M.; Takino, Y.; Fukumoto, K.; Kametani, T. *Tetrahedron Lett.* **1988**, *29*, 4135−4138.

(54) It can be suggested that the sp3 hybridization of C3 and C4 could reduce the steric hindrance of 3-aryl and 4-aryl substituents in dihydroisoquinolines (**6**).

(55) According to the good yield obtained from dihydroisoquinoline **6d** in which, as in **6b** and **2k**, the activated arene is in C4, it can be deduced that there is a possible formation of a charge-transfer complex at that position.

(3*R,4*R**)-6-Methoxy-4-(3-methoxyphenyl)-3-phenyl-1,2,3,4-tetrahydroisoquinoline (5).**[44] Formaldehyde (0.1 mmol, 0.02 mL of a 38% solution in water) was added to a stirred solution of amine **9a** (0.29 mmol) in the smallest amount of THF and HCl (5.6 mL of 1 M solution in water) under argon at room temperature. The resultant stirred mixture was heated to 60 °C for 4 days. After cooling, the suspension was basified with a concentrated ammonia solution to pH 8 and then extracted with CH_2Cl_2 (3 × 5 mL). The organic phase was dried over anhydrous sodium sulfate and evaporated in vacuo to give a residue that was purified by flash chromatography on silicagel using 35% EtOAc/Et_2O as the eluent, affording tetrahydroisoquinoline **5** (31%) as white powder: mp 138−139 °C (Et_2O); R_f: 0.40 (35% EtOAc/Et_2O); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.79 (1H, bs), 3.63 (3H, s), 3.65 (3H, s), 3.98 (1H, d, *J* 9.2 Hz), 4.12 (1H, d, *J* 14.6 Hz), 4.15 (1H, d, *J* 9.2, Hz), 4.32 (1H, d, *J* 14.6 Hz), 6.36−6.47 (2H, m), 6.49 (1H, d, *J* 7.9 Hz), 6.67 (1H, dd, *J* 8.3, 2.7 Hz), 6.73 (1H, dd, *J* 8.7, 2.7 Hz), 7.02−7.20 (7H, m); ^{13}C NMR (63 MHz, $CDCl_3$): δ 48.7, 53. 4, 55.1, 55.3, 67.1, 111.6, 112.2, 114.8, 115.5, 122.1, 126.8, 127.2, 127.4, 127.7, 128.1, 128.8, 139.5, 142.1, 144.7, 157.9; FTIR (neat film, cm^{-1}): 3312, 1607, 1260, 1034; EIMS (*m*/*z*, %): 345 (M^+, 20), 340 (36), 238 (68), 224 (22), 209 (100), 195 (24), 165 (38), 152 (25), 132 (22), 127 (10), 115 (10), 106 (12), 91 (16); HRMS calcd for $C_{23}H_{23}NO_2$, 345.1729; found, 345.1718. Anal. Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.05. Found: C, 79.92; H, 6.77; N, 4.11.

13-Phenyl-7,12-dihydro-2,10-dimethoxy-5*H*-6,12-methano-dibenzo[*c*,*f*]azocine (10). Formaldehyde (4.4 mmol, 0.88 mL of a 38% solution in water) was added to a stirred solution of amine **9a** (0.30 mmol) in the smallest amount of THF and HCl (5.6 mL of 1 M solution in water) under argon at room temperature. The resultant stirred mixture was heated to 60 °C for 3 days. After cooling, the suspension was basified with concentrated ammonia solution to pH 8 and then extracted with CH_2Cl_2 (3 × 5 mL). The organic phase was dried over anhydrous sodium sulfate and evaporated in vacuo to give a residue that was purified by flash chromatography on silicagel using 10% EtOAc/CH_2Cl_2 as the eluent, affording dibenzoazocine **10** (63%) as white powder: mp 146−147 °C (Et_2O); R_f: 0.48 (35% EtOAc/Et_2O); ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.69 (1H, d, *J* 17.8 Hz), 3.77 (3H, s), 3.79 (3H, s), 4.11 (1H, d, *J* 17.4 Hz), 4.12 (1H, d, *J* 17.4 Hz), 4.20 (1H, s), 4.49 (1H, s), 4.77 (1H, d, *J* 17.8 Hz), 6.54 (1H, dd, *J* 8.3, 2.4 Hz), 6.68 (1H, dd, *J* 8.3, 2.7 Hz), 6.70 (1H, d, *J* 8.3 Hz), 6.86 (1H, d, *J* 2.7 Hz), 6.89 (1H, d, *J* 2.4 Hz), 6.98 (1H, d, *J* 8.3 Hz), 7.16−7.27 (3H, m), 7.44 (2H, d, *J* 7.1 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ 39.2, 52.1, 55.1, 55.3, 58.9, 59.4, 111.4, 112.0, 112.8, 112.9, 126.3, 126.6, 126.7, 126.9, 127.5, 128.1, 139.7, 139.9, 142.3, 157.7; FTIR (neat film, cm^{-1}): 1611, 1258, 1034; EIMS (*m*/*z*, %): 357 (M^+, 70), 358 (14), 356 (100), 265 (12), 253 (12); HRMS calcd for $C_{24}H_{23}NO_2$, 357.1729; found, 357.1722. Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.69; H, 6.53; N, 3.87.

General Procedure for the Synthesis of *N*-Triarylethylacetamides (11). Triarylethylamine **9** (1.38 mmol) was treated with acetic anhydride (9.68 mmol) at reflux for 1 h. After cooling, the excess anhydride was evaporated in vacuo, and the residue was purified by flash chromatography on silicagel using 0−40% hexane/EtOAc as the eluent.

***N*-[2,2-Bis(3-methoxyphenyl)-1-phenylethyl]acetamide (11a).** 65%. Beige oil; R_f: 0.36 (30% hexane/EtOAc); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.78 (3H, s), 3.64 (3H, s), 3.75 (3H, s), 4.23 (1H, d, *J* 9.9 Hz), 5.79 (1H, dd, *J* 9.9, 8.7 Hz), 6.02 (1H, d, *J* 8.7 Hz), 6.61 (1H, d, *J* 8.7 Hz), 6.62 (1H, s), 6.71 (1H, dd, *J* 8.7, 7.5 Hz), 6.79 (1H, d, *J* 7.5 Hz), 6.81 (1H, s), 7.05 (1H, dd, *J* 7.5, 7.5 Hz), 7.16−7.27 (6H, m); ^{13}C NMR (63 MHz, $CDCl_3$): δ 23.1, 54.9, 55.1, 55.6, 57.4, 111.7, 112.2, 114.2, 120.6, 127.1, 127.2, 128.1, 129.1, 129.5, 141.2, 142.5, 142.8, 159.2, 159.6, 169.1; FTIR (neat film, cm^{-1}): 3380, 1648, 1600, 1261, 1042; EIMS (*m*/*z*, %): 148 (70), 106 (100), 79 (12); HRMS calcd for $C_{24}H_{25}NO_3$, 375.1834; found, 375.1827. Anal. Calcd for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.70; H, 6.77; N, 3.64.

General Procedure for the Bischler−Napieralski Heterocyclization of Triarylethylacetamides (11). Synthesis of 3,4-Diaryl-3,4-dihydroisoquinolines (6).[44] $POCl_3$ (5.1 mmol) was added dropwise at room temperature, under strictly anhydrous conditions, to a stirred solution of acetamide **11** (0.63 mmol) in dry acetonitrile (30 mL). The resulting solution was refluxed for 2−3 h and after cooling, the solvent was removed in vacuo and the residue was treated with NaOH (15 mL of 10% solution in water). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic extracts were dried over anhydrous sodium sulfate and evaporated in vacuo to give a residue that was purified by flash chromatography on silicagel using 10% EtOAc/CH_2Cl_2 and 5% MeOH/CH_2Cl_2 as the eluent. By the use of this procedure, we prepared compounds **6a** and **6b**. However, the preparation of 3,4-dihydroisoquinolines **6c** and **6d** required the addition of 6.3 mmol of P_2O_5.

(3*R,4*R**)-6-Methoxy-4-(3-methoxyphenyl)-1-methyl-3-phenyl-3,4-dihydroisoquinoline (6a).** 57%. Yellow oil; R_f: 0.57 (10% EtOAc/CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.51 (3H, s), 3.69 (3H, s), 3.71 (3H, s), 4.06 (1H, d, *J* 10.3 Hz), 4.87 (1H, dd, *J* 9.9, 1.6 Hz), 6.42 (1H, d, *J* 2.4 Hz), 6.55 (1H, s), 6.65 (1H, d, *J* 7.5 Hz), 6.71 (1H, dd, *J* 8.1, 2.4 Hz), 6.82 (1H, dd, *J* 8.3, 2.4 Hz), 7.11−7.20 (6H, m), 7.57 (1H, d, *J* 8.3 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ 23.3, 50.5, 54.9, 55.1, 67.4, 111.8, 113.8, 114.9, 121.4, 122.4, 126.5, 127.1, 127.5, 127.9, 129.2, 141.0, 142.8, 143.1, 159.2, 161.5, 163.4; FTIR (neat film, cm^{-1}): 1604, 1252, 1031; EIMS (*m*/*z*, %): 357 (M^+, 100), 266 (12); HRMS calcd for $C_{24}H_{23}NO_2$, 357.1729; found, 357.1727. Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.58; H, 6.41; N, 3.96.

General Procedure for the PIFA-Mediated Oxidative Coupling Reaction of Isoquinolines 2 and 6. Synthesis of Dibenzo[*a*,*c*]phenanthridines (1). A solution of PIFA (0.11 mmol) in dry dichloromethane (1 mL) was added to a stirred solution of isoquinoline **2** or **6** (0.1 mmol) in dry dichloromethane (1.5 mL) at −40 °C under argon. After adding $BF_3{\cdot}Et_2O$ (0.12 mmol), the resulting blue solution was stirred for 2 h at −40 °C and quenched with Na_2CO_3 (3 mL of 10% solution in water). The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL), and the combined organic extracts were dried over anhydrous sodium sulfate and evaporated in vacuo to give a residue that was purified by flash chromatography on silicagel using 10% EtOAc/CH_2Cl_2 as the eluent.

10-Methyl-6,7,12,13-tetramethoxydibenzo[*a*,*c*]phenanthridine (1a). Yield 75%. Beige powder: mp 215−216 °C (MeOH); R_f: 0.70 (10% EtOAc/CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.03 (3H, s), 4.05 (6H, s), 4.12 (3H, s), 4.18 (3H, s), 7.38 (1H, s), 7.56 (1H, ddd, *J* 8.3, 7.9, 1.2 Hz), 7.62 (1H, ddd, *J* 8.3, 7.9, 1.2 Hz), 7.91 (1H, s), 8.24 (1H, s), 8.54 (1H, d, *J* 7.9 Hz), 8.76 (1H, s), 8.80 (1H, d, *J* 7.9 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ 23.3, 55.9, 56.0, 103.2, 104.9, 105.5, 106.8, 117.0, 122.5, 123.1, 124.6, 125.1, 126.0, 126.1, 127.7, 128.3, 128.9, 130.1, 139.5, 148.5, 149.5, 149.8, 151.8, 155.0; FTIR (neat film, cm^{-1}): 1617, 1260, 1027; EIMS (*m*/*z*, %): 413 (M^+, 100), 398 (13), 367 (12); HRMS calcd for $C_{26}H_{23}NO_4$, 413.1627; found, 413.1619. Anal. Calcd for $C_{26}H_{23}NO_4$: C, 75.53; H, 5.61; N, 3.39. Found: C, 75.58; H, 5.57; N, 3.37.

General Procedure for the TTFA-Mediated Oxidative Coupling Reaction of Isoquinolines (2). Synthesis of Dibenzo[*a*,*c*]phenanthridines (1). $BF_3{\cdot}OEt_2$ (3.3 mmol) was added dropwise to a stirred mixture of diarylisoquinoline **2c** (0.1 mmol) and TTFA (0.105 mmol) in dry CCl_4 (6 mL) and dry acetonitrile (6 mL) at −40 °C under Ar. After 5 min of stirring at −40 °C, the resulting suspension was allowed to warm to room temperature and stirred for 65 h. This solution was treated with NaOH (50 mL of 10% solution in water), and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated in vacuo to give a residue that

was purified by flash chromatography on silicagel using 10% EtOAc/CH_2Cl_2 as the eluent.

10-Methyl-3-nitro-6,7,12,13-tetramethoxydibenzo[*a*,*c*]-phenanthridine (1c). 73%. Orange powder: mp 231−232 °C (MeOH); R_f: 0.47 (10% EtOAc/CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.09 (3H, s), 4.06 (3H, s), 4.11 (3H, s), 4.14 (3H, s), 4.18 (3H, s), 7.49 (1H, s), 7.83 (1H, s), 8.07 (1H, s), 8.22 (1H, d, *J* 9.1 Hz), 8.75 (1H, s), 8.80 (1H, d, *J* 9.1 Hz), 9.28 (1H, s); ^{13}C NMR (63 MHz, $CDCl_3$): δ 23.4, 56.1, 56.2, 103.0, 105.2, 105.6, 106.3, 115.9, 118.5, 118.9, 122.6, 124.1, 126.5, 128.3, 128.7, 129.8, 132.6, 141.1, 144.9, 148.9, 150.5, 152.5, 157.2; FTIR (neat film, cm^{-1}): 1617, 1508, 1347, 1265, 1045; EIMS (*m*/*z*, %): 458 (M^+, 100), 443 (10), 428 (14), 412 (12); HRMS calcd for $C_{26}H_{22}N_2O_6$, 458.1478; found, 458.1466. Anal. Calcd for $C_{26}H_{22}N_2O_6$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.19; H, 4.81; N, 6.16.

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Supporting Information Available: Experimental details, spectroscopy data and ^{1}H NMR/^{13}C NMR spectra for compounds **1**−**2** and **4**−**11**, and X-ray crystallographic data for compound **2g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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