JOC Article

Revisiting the Ullmann−Ether Reaction: A Concise and Amenable Synthesis of Novel Dibenzoxepino[4,5-*d*]pyrazoles by Intramolecular Etheration of 4,5-(*o*,*o*′-Halohydroxy)arylpyrazoles

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A concise synthesis of a series of novel dibenzoxepino[4,5-*d*]pyrazoles was accomplished by implementation of an intramolecular Ullmann-ether reaction on *o*,*o*′-halohydroxy-4,5-diarylpyrazoles mediated by CuBr·DMS. An alternative useful approach based on the palladium-catalyzed biaryl−ether linkage formation (Buchwald−Hartwig reaction) was also successfully applied, offering limitations with regard to the steric demand of the substituents. The synthesis of the key *o*,*o*′-halohydroxy-4,5-diarylpyrazole intermediates proceeds through the construction of the heterocyclic ring by a tandem amine-exchange/heterocyclization sequence of 3-*N*,*N*-(dimethylamino)-1,2-diarylpropenones with phenylhydrazine followed by basic hydrolysis for deprotection. The enamino ketone precursors were conveniently prepared from the corresponding *O*-sulfonyloxy and *O*-benzoyloxy ortho-substituted 1,2-diarylethanones, starting from inexpensive salicylaldehyde or phenylacetic derivatives. Preliminary binding affinity experiments against peripheral and central nervous system receptors have been done with negative results.

Introduction

A variety of medicinally important compounds containing a dibenzo[*b*,*f*]oxepine framework have attracted considerable attention because of their unique biological activity. Bermoprofen, an eminent example of this type of compound, has found extensive clinical use as a nonsteroid antiinflammatory agent.[1] Over the last past few years, dibenzoxepine derivatives containing a fused heteroaromatic ring at 4,5-positions have served as leads for the development of a new class of psychoactive drugs.[2] In fact, the introduction of newer tetracyclic compounds, such as savoxepine or maroxepine,[3] has provided a different outlook in the field of pharmacotherapy for the treatment of depression, compulsive behavior, anxiety disorders, and, in particular, schizophrenic psychoses.[4] Concretely, the piperidine ORG 4428 (beloxepin) and pyrrolidine ORG 5222 represent the members of a growing class of new potential antidepressant drugs, showing an improved tolerance and potent activity compared with other classical psychopharmaceuticals.[5] Most of these molecules elicit significant effects upon biological systems in such a way that the mechanism of action on the central nervous systems remains elusive. This might be related to the affinity of these compounds for the 5-HT_2 or D_2-dopamine receptors in brain, as

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(1) Nagai, Y.; Irie, A.; Nakamura, H.; Hino, K.; Uno, H.; Nishimura, H. *J. Med. Chem.* **1982**, *25*, 1065−1070.

(2) For a review, see: Missir, A.; Limban, C.; Stecoza, C.; Morusciag, L.; Chirita, I. *Farmacia* **1998**, *46*, 17−30.

(3) (a) Bischoff, S. In *Novel Antipsychotic Drugs*, Meltzer: New York, 1992, pp. 117−134. (b) Storni, A. *Actual Chim. Ther.* **1989**, *16*, 143−150.

(4) For reviews, see: (a) Zimmermann, K.; Waldmeier, P. C.; Tatton, W. G. *Pure Appl. Chem.* **1999**, *71*, 2039−2046. (b) Sperling, W.; Demling, J. *Drugs Today* **1997**, *33*, 95−102. (c) Claghorn, J.; Lesem, M. D. *Prog. Drug Res.* **1996**, *46*, 243−262.

(5) For lead references on the synthesis and biological evaluations of ORG 4428 (Beloxepin) and ORG 5222 and patent claims, see: (a) Prinsse, E. P. M.; Koek, W.; Kleven, M. S. *Eur. J. Pharmacol.* **2000**, *388*, 57−67. (b) Miguel-Hidalgo, J. J. *Drugs* **2000**, *2*, 85−92. (c) Van Bemmel, A. L.; Vermeeren, M. T. G.; Ruigt, G.; Sennef, C. *Neuropsychobiology* **1999**, *40*, 107−114. (d) Andrews, J. S. *Patent* WO 9932108 (*Chem. Abstr. 131*, 54031). (e) van Delft, A. M. L.; Ruigt, G. S. F.; van Proosdij, J. N. *Neuropsychopharmacology* **1994**, *10*, (Suppl. Part 2), 24. (f) Delbressine, L. P. C.; Wieringa, J. H. *Patent* WO 9523600. (g) Room, P.; Tielemans, A. J. P. C.; de Boer, T.; VanDelft; A. M. L.; Jeroen, J. A. D. M. *Eur. J. Pharmacol.* **1991**, *205*, 233−240. (h) Costall, B.; Domeney, A. M.; Kelly, M. E.; Naylor, R. J.; Tomkins, D. M. *Pharmacol. Biochem. Behav.* **1990**, *35*, 607−615. (i) Ruigt, G. S. F.; van Proosdij, J. N. *Eur. J. Pharmacol.* **1990**, *183*, 1467−1468.

(6) Andree, B.; Halldin, C.; Vrijmoed-De Vries, M.; Farde, L. *Psychopharmacol.* **1997**, *131*, 339−345. Several (diazabicycloalkyl)-dibenzoxepines have exhibited activity as D_2-dopamine receptor antagonists: Power, P. L.; Rakhit, S. U.S. Patent 5703072 (*Chem. Abstr. 128*, 88936).

(7) Few natural products containing an oxepine ring have been isolated to date. For example, see: (a) Pacharin, a constituent of the heartwood of *Bauhinia racemosa lamk*: Comber, M. F.; Sargent, M. V. *J. Chem. Soc., Perkin Trans 1* **1990**, *5*, 1371−1373. (b) Isolation of a bioactive dihydrobenzodioxepin from *Juncus effusus:* Della-Greca, M.; Fiorentino, A.; Molinaro, A.; Monaco, P.; Previtera, L. *Phytochemistry* **1993**, *34*, 1182−1184. Isolation and characterization of new natural dibenzo[*b*,*f*]oxepines (Artocarpols) from the root bark of *Artocarpus rigida* have recently been achieved. Several of them have exhibited potent antiinflammatory effects: (c) Artocarpol A: Chung, M.-I.; Ko, H.-H.; Yen, M.-H.; Lin, C.-N.; Yang, S.-Z. Tsao, L.-T.; Wang, J.-P. *Helv. Chim. Acta* **2000**, *83*, 1200−1204. (d) Artocarpols C and D: Ko, H.-H.; Lin, C.-N.; Yang, S.-Z. *Helv. Chim. Acta* **2000**, *83*, 3000−3005. (e) Artocarpol F: Ko, H.-H.; Yang, S.-Z.; Lin, C.-N. *Tetrahedron Lett.* **2001**, *42*, 5269−5270.

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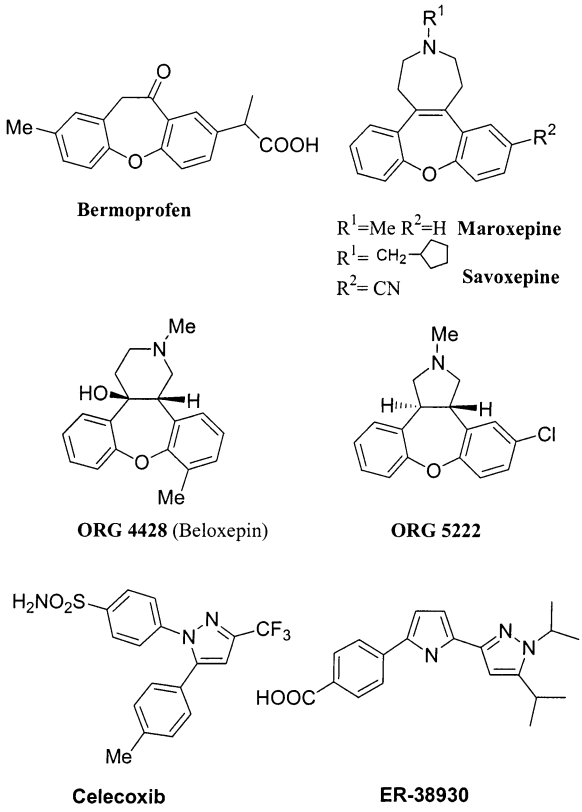
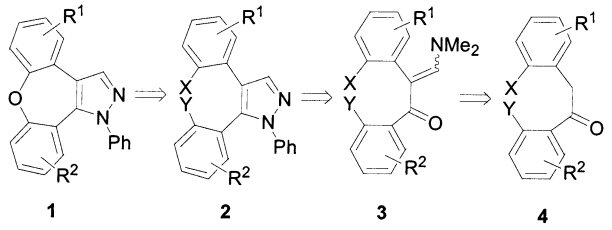
CHART 1



reported for ORG 5222,[5a,6] or to the ability for selective adrenalin reuptake, as in the case of beloxepin.[5e,i] Likewise, and despite their scarce appearance in nature,[7] there has been an increased interest of late in dibenzoxepino-fused heterocycles, because of their wide range of applications in pharmaceutical industry, as reflected by a vast number of reports and patent claims.[8,9]

Taking into account the important role played by the pyrazole nucleus as a pharmacophore element in a recent variety of synthetic bioactive compounds, such as the recently marketed nonsteroidal antiinflammatory drug celecoxib (Celebrex)[10] and other therapeutic agents,[11] we envisioned the preparation of a new type of pyrazolo-fused compounds, dibenzoxepino[4,5-*d*]pyrazoles **1**, as



potential psychoactive substances. Perusal of the literature revealed that photocyclization of halosubstituted acetophenone derivatives,[12] intramolecular Friedel–Crafts acylation,[13] and cyclodehydration of phenoxyphenylacetic acid derivatives[13] are the most commonly used methods for the preparation of dibenzo[*b*,*f*]oxepines,[13] but the methods are often limited by the need of a preformed diaryl ether framework. Moreover, many of these methods suffer from some drawbacks, including the use of toxic and/or hazardous materials, strongly acidic conditions, unsatisfactory yields, longer reaction times, and lack of selectivity (inter alia). In this context and in connection with our previous contributions for the synthesis of phenanthro-fused heterocycles,[14] herein we report a facile, practical protocol to construct these oxygen-containing benzoannealed seven-membered heterocycles **1** as illustrated in the retrosynthetic scheme below. Our proposed synthetic approach was based upon the rationale that a flexible synthetic route could be derived from the postponement of the heterocyclic ring closure, which constitutes a scarcely applied strategy for the preparation of dibenzoxepines.[15] This notion of using *o*,*o*′-halohydroxy-4,5-diarylpyrazoles **2** as the key intermediates is particularly attractive taking into account

(8) Diverse applications of dibenzoxepino-fused heterocycles have been claimed: (a) Analgesic agents: Martin, L. L.; Setescak, L. L. U.S. Patent 4576960 (*Chem. Abstr.*:*104*, 224840). (b) Antiarthritic agent: Cherkofsky, S. C.; Sharpe, T. R. U.S. Patent 4198421 (*Chem. Abstr. 93*, 71783). (c) Antihistamine agents: Kumazawa, T.; Ohsima, E.; Obase, H. *Patent* JP 61152673 (*Chem. Abstr. 106*, 4904). (d) Antiespasmodic agents: Bracaccio, G.; Lettieri, G.; Monforte, P.; Larizza, A. *Farmaco* **1982**, *37*, 711–718. (e) Anti-neurodegenerative agents: Zimmermann, K.; Roggo, S.; Betschart, C. *Patent* WO 9745422 (*Chem. Abstr. 128*, 61439). (f) Antioxidants: Jinno, S.; Okita, T. *Heterocycles* **1999**, *51*, 303–314. (g) Tracheal smooth muscle relaxants: Yamashita, S.; Takeo, J.; Jinno, S.; Kogure, Y.; Onuki, H.; Okita, T.; Hata, J.; Fukuda, Y.; Ohtsuka, N. Patent WO 9725985 (*Chem. Abstr. 127*, 149089). (h) Antipsychotic, cardiovascular and gastroprotectors: Gil-Lopetegui, P.; Fernández-Gadea, F. J.; Meert, T. F. Patent WO 97338991, and (i) Antiasthmatic and respiratory tract hypersensitiviness inhibitors: Jinno, S.; Okita, T.; Ohtsuka, N.; Yamashita, S.; Hata, J.; Takeo, J. Patent WO 0075127 (*Chem. Abstr. 134*, 29329).

(9) These type of compounds have also exhibited efficiency for the treatment of diseases such as: (a) Asthma: Lever, O. W.; King, A. N.; Harfenist, M.; Chao, E. Y. H. Patent WO 9015599 (*Chem. Abstr. 16*, 20960). (b) Arteriosclerosis: Nakazawa, H.; Ando, K.; Kuge, Y.; Sugaya, T.; Kasai, M.; Tomioka, S. Patent JP 06306070 (*Chem. Abstr. 122*, 160492). (c) Cancers related to estrogen regulation disorders: Kanamaru, T.; Hida, T.; Muroi, M. *Patent* EP 342665 (*Chem. Abstr. 113*, 5954).

(10) *Drug Data Rep.* **2000**, *22*, 376–378.

(11) (a) A number of synthetic pharmacophores, with the activities indicated as follows, are based upon a diaryl-substituted pyrazole motif: (a) Neuropsychiatric disorders. Application of corticotropin releasing factor (CRF) as receptor modulators: Gilligan, P. J.; Robertson, D. W.; Zaczek, R. *J. Med. Chem.* **2000**, *43*, 1641–1660. (b) Application of ER-38930, a retinoic acid receptor (RARa) agonist for dermatologic and immunological diseases: Hibi, S.; Tagami, K.; Kikuchi, K.; Yoshimura, H.; Tai, K.; Hida, T.; Tokuhara, N.; Yamauchi, T.; Nagai, M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 623–625. See also: Kikuchi, K.; Hibi, S.; Yoshimura, H.; Tai, K.; Hida, T.; Tokuhara, N.; Yamauchi, T.; Nagai, M. *Med. Chem. Lett.* **2000**, *10*, 619–622. Likewise, particularly appealing is the potency exhibited by this kind of heterocycle as (c) estrogen receptor a-selective agonists: Stauffer, S. R.; Coletta, C. J.; Tedesco, R.; Nishiguchi, G.; Carlson, K.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2000**, *43*, 4934–4947. (d) Interleukine-2 (IL-2) inhibitors: Djuric, S. W.; BaMaung, N. Y.; Basha, A.; Liu, H.; Luly, J. R.; Madar, D. J.; Sciotti, R. J.; Tu, N. P.; Wagenaar, F. L.; Wiedeman, P. E.; Zhou, X.; Ballaron, S.; Bauch, J.; Chen, Y.-W.; Chiou, X. G.; Fey, T.; Gauvin, D.; Gubbins, E.; Hsieh, G. C.; Marsh, K. C.; Mollison, K. W.; Pong, M.; Shaughnessy, T. K.; Sheets, M. P.; Smith, M.; Trevillyan, J. M.; Warrior, U.; Wegner, C. D.; Carter, G. W. *J. Med. Chem.* **2000**, *43*, 2975–2981.

(12) Nagaoka; H.; Kamino, S.; Onuki, H. Patent JP 10204079 (*Chem. Abstr. 129*, 189246).

(13) Rosowsky, A. In *The Chemistry of Heterocyclic Compounds: 7-membered Heterocyclic Compounds containing Oxygen and Sulfur*; Weissberger, A., Taylor, E. C., Eds., Wiley-Interscience: New York, 1972; pp 154–176 and references therein.

(14) (a) Olivera, R.; SanMartin, R.; Domínguez, E. *J. Org. Chem.* **2000**, *65*, 6398–6411. (b) Olivera, R.; SanMartin, R.; Domínguez, E. *J. Org. Chem.* **2000**, *65*, 7010–7019. (c) Olivera, R.; SanMartin, R.; Domínguez, E. *Synlett* **2000**, *7*, 1028–1030.

(15) (a) de la Fuente, M. C.; Castedo, L.; Domínguez, D. *Tetrahedron* **1996**, *52*, 4917–4924. (b) Burden, P. M.; Capper, H. R.; Allan, R. D.; Johnston, G. A. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3291–3294.

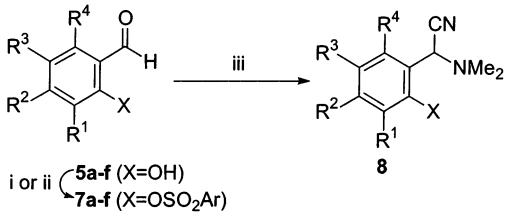
the recent advances in the chemistry of diaryl ethers.[16,17] Likewise, we intend to expand the scope of our methodology for the preparation of diarylpyrazoles,[14b] by amine-exchange reaction/heterocyclization of hydrazines with enamino ketones **3**, readily available from deoxybenzoins **4**. The latter tactic is becoming widespread as the method of choice for the synthesis of pyrazoles;[18] moreover, using suitable 1,4-dinucleophilic components enables the development of versatile routes to other classes of heterocycles.[19]

Herein we report our full results on the synthesis of dibenzoxepino[4,5-*d*]pyrazoles via final formation of the biaryl ether linkage along with preliminary pharmacological evaluation.

Results and Discussion

1. Synthesis of 2,2′-(Halohydroxy)deoxybenzoins. We have recently reported that the alkylation of 2-haloaryl α-aminocarbonitriles with 2-haloarylmethyl halides constitutes an excellent method for the preparation of 2,2′-dihalodeoxybenzoins,[14a] enabling the construction of adequately functionalized phenanthro[9,10-*d*]heterocycles.[14b,c] In this context, salicylaldehyde and ortho-halogenated aldehyde derivatives **5** seemed to be a suitable starting material to supply the aforementioned deoxybenzoins. Nevertheless, in our initial approach, attempts to synthesize α-aminonitriles derived from salicylaldehyde on standard conditions (KCN/Me_2NH·HCl) proved to be unsuccessful.[20] In view of this observation, and considering the tendency of *o*-hydroxyaryl-3-enamino ketones to give isoflavones under basic conditions,[21] it was decided to protect salicylaldehyde derivatives as the corresponding arylsulfonates **7** at this early stage under standard conditions (Scheme 1). The choice of this sparingly utilized but extremely robust hydroxyl-protecting group[22] corresponds to the necessity to endure the range of conditions required during the aminomethylenation and heterocyclization steps.

SCHEME 1[a]



[a] Reagents and conditions: (i) $ArSO_2Cl$, py, 80 °C. (ii) $ArSO_2Cl$, K_2CO_3, rt (for **7f**). (iii) KCN, Me_2NH·HCl, MeCN, H_2O, rt.

As shown in Table 1, α-aminonitriles **8**[23] were obtained in moderate to high yields except for sulfonates **7b−d** bearing electron-withdrawing substituents, leading to an unresolved multicomponent mixture. All the same, al-

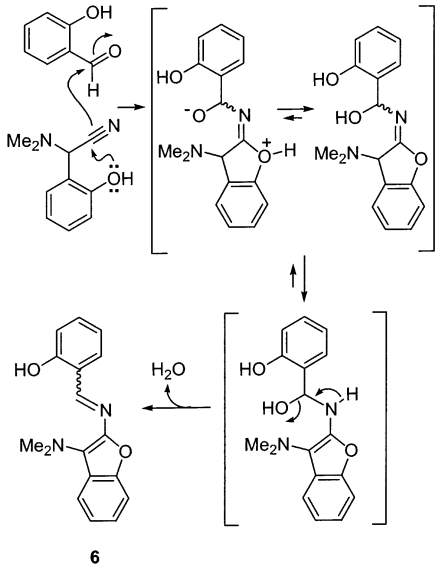
(16) For recent reviews and monographs: (a) Sawyer, J. S. *Tetrahedron* **2000**, *56*, 5045−5065. (b) Theil, F. *Angew. Chem., Int. Ed.* **1999**, *111*, 2345−2347. (c) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *111*, 2046−2067. (d) Chiu, C. K.-F. In *Comprehensive Organic Functional Groups Transformations*, Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon Press: Cambridge, 1995; Vol. 2, Chapter 2.13, pp 683−685.

(17) Other leading references on the topic: (a) Kuwabe, S.-I.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202−12206. (b) Torraca, K. E.; Huang, X.; Parrish, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 10776−10781. (c) Torraca, K. E.; Kuwabe, S.-I.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12907−12908. (d) Cundy, D. J.; Forsyth, A. S. *Tetrahedron Lett.* **1999**, *39*, 7979−7982. (e) Woiwode, T. F.; Rose, C.; Wandless, T. J. *J. Org. Chem.* **1998**, *63*, 9594−9596. (f) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933−2936. (g) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395−3396. (h) Lindley, J. *Tetrahedron* **1984**, *40*, 1433−1456.

(18) (a) Pleier, A.-K.; Glas, H.; Grosche, M.; Sirsch, P.; Thiel, W. R. *Synthesis* **2001**, 55−62. (b) Okada, E.; Tsukushi, N.; Shimomura, N. *Synthesis* **2000**, 1822−1824.

(19) (a) Braun, R. U.; Zeitler, K.; Müller, T. J. J. *Org. Lett.* **2000**, *2*, 4181−4184. (b) Müller, T. J. J.; Braun, R. U.; Ansorge, M. *Org. Lett.* **2000**, *2*, 1967−1970. (c) Tyvorskii, V. I.; Bobrov, D. N.; Kulinkovich, O. G.; Aelterman, W.; De Kimpe, N. *Tetrahedron* **2000**, *56*, 7313−7318. (d) Dawood, K. M.; Kandeel, Z. E.; Farag, A. M. *Heteroatom Chem.* **1999**, *10*, 417−422. (e) Bejan, E.; Aït-Hadou, H.; Daran, J.-C.; Balavoine, G. G. A. *Eur. J. Org. Chem.* **1998**, 2907−2912.

(20) Upon first encountering the facility with which 3-(dimethylamino)-2-hydroxybenzylidene-aminobenzofuran **6** is produced when starting from commercial salicylaldehyde, protection of hydroxyl functionality became necessary. We speculate that the formation of this benzofuran could arise from the attack of the forming α-aminonitrile to the remaining aldehyde, triggered by the intramolecular addition of the hydroxyl nucleophile at the adjacent cyano group. Equilibration of the initially formed imine, followed by dehydration, would render the detected benzofuran, as illustrated below. Isolation and complete structural elucidation of **6** was not possible due to extensive decomposition over the purification process. ^1H and ^{13}C NMR analysis of chromatographed fractions provided clear evidence for the structure of **6**. GC/MS spectrum showed a concordance of 99% when compared with the authentic one contained in a Wiley MS database.



6

(21) Pelter, A.; Ward, R. S.; Ashdown, D. H. J. *Synthesis* **1978**, 843−846 and references therein.

(22) (a) Kuntz, H.; Waldman, H. In *Comprehensive Organic Synthesis*; Trost; B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 3.1, pp 643−663. (b) Kocienski, P. J. In *Protecting Groups*, 2nd ed.; Enders, D., Noyori, R., Trost, B. M., Eds.; Thieme: Stuttgart, 1994; pp 21−85.

(23) Syntheses of α-aminonitriles and corresponding starting ortho-iodinated aldehydes were performed according to the method reported in ref 14a.

(24) Under a variety of related conditions, 4-nitro-2-phenylsulfonyloxybenzaldehyde **7d** failed to give the corresponding alcohol, leading to gummy, crude mixtures of difficult manipulation.

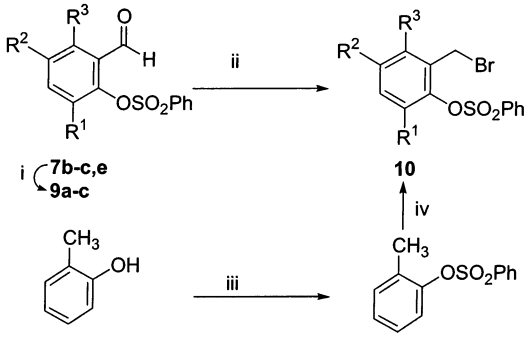
(25) Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1972**, *51*, 2289−2299. Attempts to perform bromination of the so-obtained alcohols with HBr in acetic acid yielded mainly the acetyl derivatives as a result of the high reactivity of the desired bromomethyl compounds. Concretely, when 5-chloro-2-(phenylsulfonyloxy)phenyl]methanol **9b** was submitted to such conditions, a mixture of the target bromide **10b** (23% yield) and 5-chloro-2-(phenylsulfonyloxy)phenyl]-methyl acetate **10e** (41% yield) was afforded.

TABLE 1. Synthesis of Arylsulfonates 7 and α-Aminonitriles 8

R^1	R^2	R^3	R^4	X	**7** (%)[a]	**8** (%)
H	H	H	H	OTs	**7a** (90)	**8a** (88)[a]
Cl	H	Cl	H	OSO_2Ph	**7b** (74)	-[b]
H	H	Cl	H	OSO_2Ph	**7c** (79)	-[b]
H	NO_2	H	H	OSO_2Ph	**7d** (61)	-[b]
H	H			OSO_2Ph	**7e** (87)	**8e** (56)[c]
H	NEt_2	H	H	OSO_2Ph	**7f** (52)[d]	**8f** (84)[c]
H	H	H	H	I	**7g** (91)	**8g** (85)[a]
H	OMe	OMe	H	I	**7h** (72)	**8h** (89)[a]

[a] Yield of pure crystallized compound. [b] Multicomponent mixture was obtained. [c] Isolated yield. [d] $ArSO_2Cl/K_2CO_3$ system was required instead of typical protection conditions, which gave an intractable mixture including the target sulfonate **7f** in a valueless yield (12%).

SCHEME 2[a]



[a] Reagents and conditions: (i) LAH, THF, rt; (ii) CBr_4, PPh_3, DCM, rt; (iii) $PhSO_2Cl$, py, 80 °C; (iv) NBS, AIBN, CCl_4, 95 °C.

TABLE 2. Arylmethyl Derivatives 9 and 10 Prepared

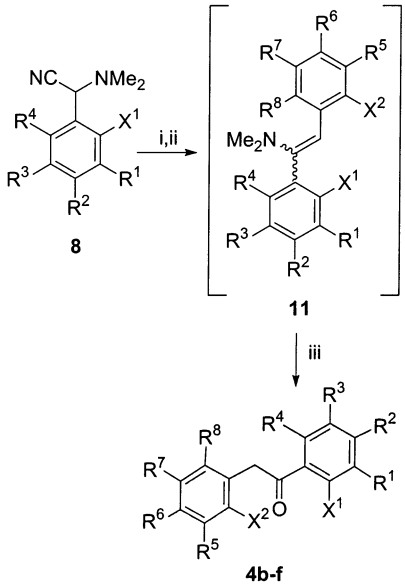
R^1	R^2	R^3	**9** (%)	**10** (%)
Cl	Cl	H	**9a** (99)[a]	**10a** (68)[c]
H	Cl	H	**9b** (97)[a]	**10b** (72)[c]
H			**9c** (85)[b]	**10c** (62)[c]
H	H	H	-	**10d** (83)[a]

[a] Yield of pure crystallized compound (Et_2O). [b] Yield of pure crystallized compound ($CHCl_3$). [c] Yield of pure chromatographed compound.

dehydes **7b**−**e** were used as counterparts for the substitution reaction of α-aminonitriles after a reduction/bromination sequence (Scheme 2). Initial reduction with LAH proceeded quantitatively to provide arylmethanols **9**, except for nitro derivative **7d**.[24] Thus, while application of the system CBr_4/PPh_3[25] afforded the arylmethyl bromides **10a**−**c**, brominated derivative **10d** was obtained by action of NBS catalyzed by AIBN on *o*-cresol previously sulfonylated (Table 2).

Adequate combination of deprotonated α-aminonitriles **8** with arylmethyl bromides **10** or commercial 2-iodobenzyl chloride,[26] followed by acidic hydrolysis, afforded the desired deoxybenzoins **4a**−**f** in moderate yields (Scheme 3, Table 3). Interestingly, this alkylation proceeds through a mixture of *Z*,*E*- ethenylamines **11**, as concluded from

SCHEME 3[a]



[a] Reagents and conditions: (i) NaH, DMF, −19 °C; (ii) **10**, −19 °C to room temperature; (iii) concd HCl, MeOH, H_2O, 90 °C.

the analysis of the NMR and MS spectra of the crude reactions.[27] This result contrasts with the diasteroselective obtention of *E*-ethenylamines when an analogous reaction was applied to the preparation of *o*,*o*′-dihalo-substituted deoxybenzoins,[14a] which discloses not only the coexistence of different mechanisms for this apparently simple nucleophilic substitution, but also the remarkable effect of ortho-substituents on the aryl groups.

On the other hand, it is noteworthy to say that naphthyl-α-aminonitrile **8e** underwent slow decomposition upon reacting with 2-iodo- and 2-bromobenzyl chloride, resulting in no deoxybenzoin formation, in contrast to the fast reaction of α-aminonitrile **8g** with naphthylmethyl bromide **10c**. The observed different behavior suggests that alkylation is specially sensitive to the steric hindrance at the reaction site. Conceivably, the presence of H-8 at the adjacent naphthyl ring obliges a constrained conformation of the aminocarbonitrile moiety flanked by the bulky sulfonate group, hindering the access of the electrophile.

To our surprise, acidic hydrolysis of intermediate amines **11** was thwarted by concomitant formation of the deprotected product, as evidenced by the isolation of **4j** (58% yield) in the case of deoxybenzoin **4a**, when performed at higher temperature than 90 °C (Scheme 4). This result is in concordance with the remarkable lability of ortho-formylated sulfonyl esters upon treatment with mineral acids, as reported by Bhatt.[28]

In parallel with this strategy, we also considered embarking on the synthesis of polymethoxylated deoxy-

(26) In our hands (see ref 14a), when using 2-iodobenzyl chloride as alkylating agent, inverse addition of the electrophile was necessary to optimize the yield of **4a**.

(27) Pairs of olefinic signals in the range of 5.3−5.6 and 146.1−150.4 ppm have respectively been recorded in the ^1H NMR and ^{13}C NMR spectra of the crude reaction, assignable to H-2 and C-1.

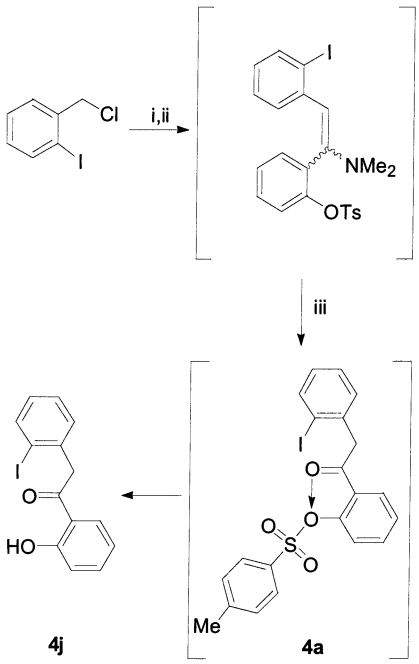
(28) Shashidhar, M.; Bhatt, M. V. *J. Chem. Soc., Chem. Commun.* **1987**, 654−656.

TABLE 3. Synthesis of Deoxybenzoins 4, Enamino Ketones 3, Protected 4,5-diarylpyrazoles 15 and *o,o′*-halohydroxy-4,5-diarylpyrazoles 2

R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	X^1	X^2	Y^1	Y^2	**2** (%)[a]	**3** (%)[a]	**4** (%)[a]	**15** (%)[a]
H	H	H	H	H	H	H	H	OTs	I	OH	I	**2a** (88)	**3a** (46)	**4a** (67)	**15a** (90)
H	H	H	H	H	H	Cl	H	I	OSO_2Ph	I	OH	**2b** (69)[b]	**3b** (58)[b]	**4b** (65)[b]	**15b** (63)
H	H	H	H	Cl	H	Cl	H	I	OSO_2Ph	I	OH	**2c** (82)	**3c** (41)[b]	**4c** (83)	**15b** (12)
H	OMe	OMe	H	H	H	H	H	I	OSO_2Ph	I	OH	**2d** (79)	**3d** (47)[b]	**4d** (72)	**15d** (94)
H	NEt_2	H	H	H	H	H	H	OSO_2Ph	I	OH	I	**2e** (64)[b]	**3e** (58)[b]	**4e** (54)	**15e** (91)
H	H	H	H	H	H			I	OSO_2Ph	I	OH	-	**3f** (45)[b]	**4f** (51)[b]	-[c]
OMe	OMe	H	H	H	OMe	OMe	H	OBz	Br	OH	Br	**2g** (81)	**3g** (81)	**4g** (88)[d]	**15g** (91)
OMe	OMe	H	H	H	OMe	OMe	H	OBz	I	OH	I	**2h** (98)	**3h** (58)	**4h** (91)[e]	**15h** (92)
H	OMe	H	OMe	H	OMe	OMe	H	OBz	I	OH	I	**2i** (95)	**3i** (58)	**4i** (95)[d]	**15i** (58)[f]

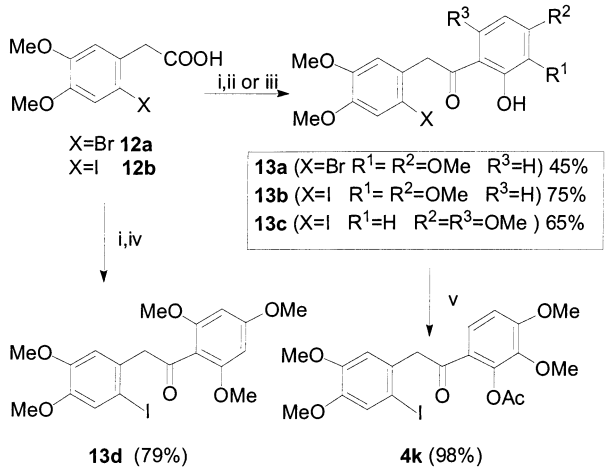
[a] Yield of pure crystallized compound. [b] Yield of pure chromatographed compound. [c] Target product was not detected. [d] Reaction was performed in THF. [e] Reaction was performed in 1,4-dioxane. [f] Combined yield of the *O*-protected pyrazole **15i** and debenzoylated pyrazole **2i** (85%).

SCHEME 4[a]



[a] Reagents and conditions: (i) NaH, DMF, −19 °C; (ii) **8a**, −19 °C to room temperature; (iii) concd HCl, MeOH, H_2O, 115 °C.

SCHEME 5[a]



[a] Reagents and conditions: (i) $SOCl_2$, PhMe, 140 °C; (ii) 1,2,3-(MeO)Ph, $AlCl_3$, DCM, 55 °C (for **13a,b**); (iii) 1,3,5-(MeO)Ph, $BF_3{\cdot}OEt_2$, PhMe, 140 °C (for **13c**); (iv) 1,3,5-(MeO)Ph, $AlCl_3$, PhMe, 55 °C (for **13d**); (v) AcCl, NaOH, TEBA (cat.) 1,4-dioxane, rt.

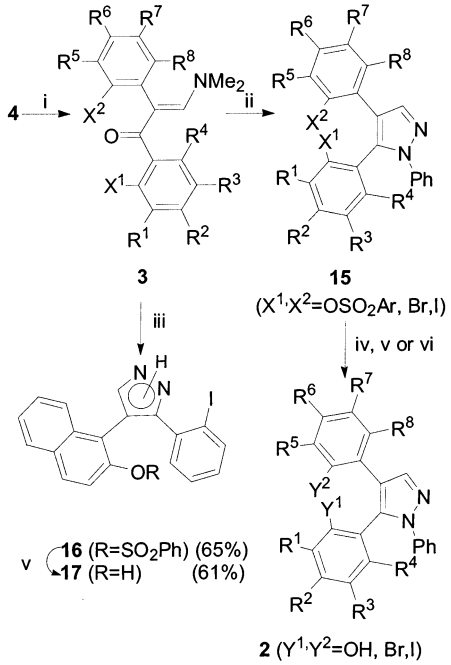
benzoins to have available a more complete set of substrates, regarding the electronic nature of the substituents. In this context, we considered the Friedel−Crafts (F−C) acylation of arenes with arylacetyl chlorides, a classical route to this type of deoxybenzoin.[29] In addition, there are some literature precedents related to the concomitant demethylation during this process of *o*-methoxy substituents to the carbonyl group, upon the action of a Lewis acid catalyst.[30] With this advantageous precedent in mind, we prepared 6-bromo- (**12a**) and 6-iodohomoveratric acid (**12b**) by direct bromination (Br_2) or iodination (ICl), respectively, in HOAc of the parent acid and assayed F−C acylation with some polymethoxylated arenes (Scheme 5). Reactions of acid chlorides of **12a,b** with 1,2,3-trimethoxybenzene in the presence of $AlCl_3$ as catalyst in dichloromethane (DCM) proceeded clearly to provide the *o,o′*-halohydroxy deoxybenzoins **13a,b** in fair to good yields (45−79%). Surprisingly, performing the acylation reaction on the acid chloride of **12b** with 1,3,5-trimethoxybenzene upon the same reaction conditions yielded the fully methoxylated compound **13d**. Forcing conditions gave rise to useless mixtures of polyhydroxylated compounds. However, the application of the less active Lewis catalyst $BF_3{\cdot}OEt_2$ allowed isolation of the desired compound **13c** in 65% yield. In contrast with iodo congener **13c**, the bromo analogue remained inaccessible, despite changes in solvent (THF, acetonitrile), catalysts ($TiCl_4$, $Sc(OTf)_3$)[31] (both in stoichiometric/substoichiometric quantities), or/and prolon-

(29) (a) Wähälä, K.; Hase, T. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3005−3008. (b) Anstead, G. M.; Katzenellenboguen, J. A. *J. Med. Chem.* **1988**, *31*, 1754−1761.

(30) Domínguez, E.; Lete, E.; Villa, M. J.; Iriondo, C. *Heterocycles* **1984**, *22*, 1217−1224.

(31) Scandium triflate has been reported as an excellent catalyst for F−C acylation, see: Tsuchimoto, T.; Tobita, K.; Hiyama, T.; Fukuzawa, S.-I. *J. Org. Chem.* **1997**, *62*, 6997−7005.

SCHEME 6[a]



[a] Reagents and conditions: (i) DMFDMA, PhMe, 90 °C. (ii) $PhNHNH_2$·HCl, H_2O, MeOH, NaOAc, HOAc, 140 °C. (iii) $NHNH_2$·2HCl, H_2O, MeOH, NaOAc, HOAc, 100 °C (for **3f**). (iv) NaOH, MeOH, H_2O, TEBA (cat.), 140 °C (sealed tube) (for **15a**). (v) K^{t}BuO, DMF, 0 °C (for **15b**−**e**, **16**). (vi) KOH, MeOH, H_2O, 70 °C, (for **15g**−**i**).

gation of reaction time/temperature. Importantly, this observation on the noticeably different reactivity of both substrates is consistent with the proposal of direct interaction of bromo substituent with the Lewis catalyst, which would impinge upon the subsequent demethylation.

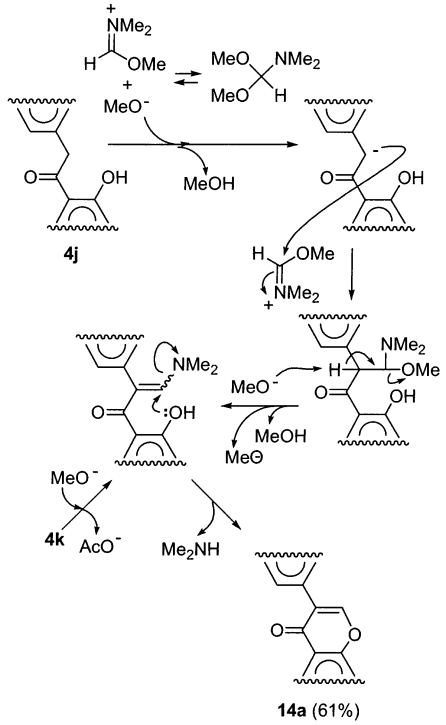
It is obvious that this result cannot be rationalized by invoking a mere steric effect of the halogens at the reaction site, since it would be considerably greater for the iodo derivative **12b**.

The reasoning that led to protection of phenolic deoxybenzoins **13a**−**c** as alkyl esters was based on the known resistance of this moiety to alkoxide-type bases and acidic media envisaged to apply in the remaining synthetic steps. Acetylation of **13b** upon the Schotten−Baumann protocol failed, probably due to the insolubility of the substrate in aqueous medium. Pefrorming a modified protocol of Illi for the esterification of phenols[32] (AcCl/NaOH) using triethylbenzylammonium chloride (TEBA) as catalyst furnished the acetate **4k** (98% yield) (Scheme 5). As will be discussed later, it was necessary to prepare benzoates **4g**−**i** (Table 3) using the aforementioned conditions (BzCl, NaOH), but the change of 1,4-dioxane for THF proved to be crucial to achieve an acceptable conversion degree for **4g** and **4i**.

2. Synthesis of *o,o′*-Halohydroxy-4,5-diarylpyrazoles. With *O*-protected deoxybenzoins **4** in hand, their enaminomethylated derivatives **3** were easily prepared by treatment with dimethyl formamide dimethyl acetal (DMFDMA) (Scheme 6. Table 3) in a Vilsmeier−Haack-type reaction. To our surprise, *O*-acetylated product **4j** afforded the isoflavone **14a** in a rapid and clean reaction at room temperature, as a consequence of the loss of acetyl group by the action of the methoxide ion coming from the imino derivative in equilibrium with DMFDMA in solution or generated in the aminomethylenation step, and subsequent displacement of NMe_2 group, as depicted in the proposed mechanistic pathway.[33] As we put forward previously and shown in Table 3, this unexpected deprotection process was sorted out by performing the reaction with benzoates **4g**−**i**, obtaining in this way the desired products **3** in moderate yield.[33]

Following our synthetic objectives, we next proceeded to convert enamino ketones **3** to the corresponding 4,5-diarylpyrazoles **15** by direct heterocyclization with phenylhydrazine in aqueous methanol (Scheme 6). Aside from the sterically impeded naphthoenamino ketone **3f**, which undergoes extensive decomposition, pyrazoles **15** were obtained regioselectively in excellent yields (Table 3), proving the efficiency of this approach to highly functionalized 4,5-diarylpyrazoles, even when bulky ortho-substituents were present. Thus, in striking contrast to Tupper's observations regarding a closely related heterocyclization,[34] we may infer the apparent insensitivity to the presence of bulky substituents at both ortho-positions on the aryl groups, which is supported by the production of the 3(5),4-naphthylarylpyrazole **16** (Scheme 6), wherein the substitution of phenylhydrazine by hydrazine itself and, consistently, the steric relief permitted the easy cyclization of naphthoenamino ketone **3f**. Nonetheless, we also found that this method was not independent of the nature of the enamino ketone used. Thus,

(33) Proposed synthetic pathway for the formation of isoflavone **14a**. The formation of isoflavones was suppressed by starting from benzoylated deoxybenzoins **13a**−**c**. All the same, the partial lability of this protecting group on deoxybenzoins **13b** and **13a** upon enaminomethylation conditions was made clear, as shown by the isolation of the corresponding isoflavones **14a,b** as minor products in 10 and 16% yield, respectively.



(32) Illi, V. O. *Tetrahedron Lett.* **1979**, *26*, 2431−2432.

(34) Tupper, D. E.; Ray, M. R. *Synthesis* **1997**, 337−341.

attempts conducted with substrates **3b,c** bearing chloro atoms in remote positions on the benzylic ring were not successful enough (61 and 12% yield, respectively), raising the concern that the number of electron-withdrawing substituents on the latter ring may be critical for the amine exchange/heterocyclization sequence.

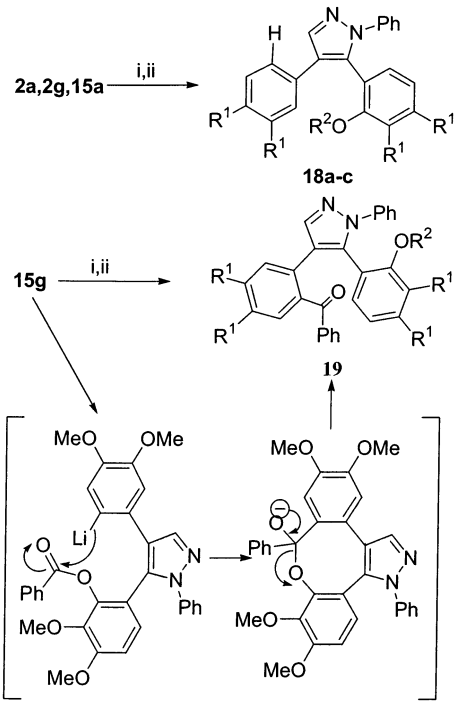
Finally, deprotection of sulfonates **15a−e** and **16** proved to be a troublesome task, due to the extreme robustness of the sulfonyl group to undergo basic hydrolysis under a wide range of conditions (NaOH/Me_2-CO, H_2O;[35a] KOH/MeOH;[35b] KOH/THF;[35c] KOH/DMF, MeOH;[35d] NaOMe/MeOH[35e]), which were too sluggish to afford pyrazoles **2** either in acceptable yield or conversion degree. However, a modification of the conditions of Moberg et al.[35f] using directly K^{t}BuO (Scheme 6) furnished phenolic pyrazoles through an instantaneous reaction in good yields (64−82% yield), as shown in Table 3. The difference in reactivity between sulfonates **15b−e, 16** and tosylate **15a** was somewhat perplexing, since this latter compound required comparatively stringent hydrolysis conditions (NaOH, MeOH, H_2O, 140 °C under pressure, TEBA (8 mol %)) to give the parent phenolic pyrazole **2a** (88% yield).

In clear contrast, benzoates **15g−i** were smoothly hydrolyzed upon standard basic conditions (KOH/ MeOH, H_2O), furnishing the corresponding phenolic pyrazoles in excellent yield (Scheme 6. Table 3).

3. Biaryl Ether Coupling Attempts via Boronic Acid Derivatives. Despite the considerable success to date reached by the introduction of the thallium(III)-mediated oxidative macrocyclization[36a] or the enzymatic oxidative phenolic coupling methodologies,[36b] widely applied in the synthesis of glycopeptide antibiotics such as vancomycin, by far, the difficult task of forming a C−O diaryl ether bond relies on (i) the classical Ullmann−ether synthesis,[17h] recently revitalized by modern and useful variations,[16a] (ii) S_NAr-based reactions on aryl fluorides, (iii) S_NAr-based reactions to arene−metal (Mn, Ru, and Fe mainly) π-complexes, (iv) to a much lesser extent, the recently introduced but not less promising Buchwald−Hartwig reaction of haloarenes and phenols,[16a,c] and (v) copper(II)-mediated coupling of boronic acids and phenols.[17d,f,37]

Attracted by the latter method, featuring the extremely mild conditions applied and the use of inexpensive catalysts, the preparation of the required boronic acid derivatives of selected *O*-protected and phenolic pyrazoles **15** and **2** was respectively undertaken (Scheme 7). All attempts at reacting aryllithium derivatives of the selected models with $B(OMe)_3$ or $B(O^iPr)_3$ met with failure, yielding the dehalogenated arenes **18** as the major isolable materials (Table 4).

SCHEME 7[a]



[a] Reagents and conditions: (i) *n*-BuLi, THF, TMEDA, −78 °C; (ii) (a) $B(OMe)_3$ or $B(O^iPr)_3$, −78 °C to room temperature; (b) H_3O^+.

TABLE 4. Metalation/Boronation Assays on 4,5-diarylpyrazoles

substrate	R_1	R_2	product (% yield)[a]
2a	H	H	**18a** (71)
2g	OMe	H	**18b** (44)
15a	H	Ts	**18c** (54)
15g	OMe	H	**19** (56)

[a] Isolated yields.

This result is in consonance with our earlier findings wherein an analogous behavior was exhibited by *o,o′*-dihaloaryl heterocycles,[14c] presumably ascribable to an unusually stable aggregation state of the organolithium intermediates generated. As shown in Scheme 7, it was noted that in the case of the benzoate **15g**, the sole isolated product was the pyrazole **19**, which, formally, had undergone debromination and intramolecular benzoyl group transfer. It is reasonable to assume that the product of the initial metal−bromine exchange might attack intramolecularly to the ester group, generating an oxepane-type intermediate (vide infra), which, after cleavage, would render the isolated product **19** with the benzoyl group located on the C-4 aryl ring. Spectrometric analysis (H^1 NMR and GC/MS) of the crude reaction revealed the absence of byproducts due to the direct attack of *n*-BuLi on the ester moiety, highlighting the rapidity of this process and reinforcing the hypothesis of its intramolecular nature.

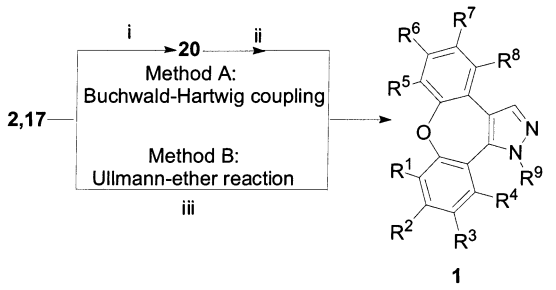
4. Palladium-Catalyzed Intramolecular O-Arylation of *o,o′*-Halohydroxy-4,5-diarylpyrazoles. In light of these results, we examined the feasibility of using the Buchwald−Hartwig reaction[16c,38] for access to the target tetracyclic system, encouraged by the wide application of this reaction, due in part, to the mild reaction condi-

(35) (a) Bordwell, F. G.; Boutan, P. J. *J. Am. Chem. Soc.* **1957**, *79*, 717−722. (b) Wolff, S.; Hoffmann, H. M. R. *Synthesis* **1988**, 760−763. (c) Civitello, E. R.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 3775−3782. (d) Theuns, H. G.; Lenting, H. B. M.; Salemink, C. A.; Tanaka, H.; Shibata, M. *Heterocycles* **1984**, *22*, 1995−2005. (e) Belanger, P. C.; Scheigetz, J.; Young, R. N. *Can. J. Chem.* **1983**, *61*, 2177−2182. (f) Levacher, V.; Adolfsson, H.; Moberg, C. *Acta Chem. Scand.* **1996**, *50*, 454−457.

(36) (a) Neuville, L.; Bois-Choussy, M.; Zhu, J. *Tetrahedron Lett.* **2000**, *41*, 1747−1751 and references therein. (b) Malnar, I.; Sih, C. J. *Tetrahedron Lett.* **2000**, *41*, 1901−1911.

(37) (a) Simon, J.; Salzbrunn, S.; Prakash, G. K. S.; Petasis, N. A.; Olah, G. A. *J. Org. Chem.* **2001**, *66*, 633−634. (b) Evans, D. E.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937−2940.

SCHEME 8[a]



[a] Reagents and conditions: (i) NaOH, PhMe, 135 °C; (ii) $Pd_2(dba)_3$/Ligand(4−9 mol %), PhMe, THF, 100 °C (sealed tube) (iii) CuBr·DMS, NaH, py, 120 °C.

tions and high functional group compatibility. Thus, by submitting phenolic pyrazoles **2a**, **2g** and **2h** as models to the conditions reported by Gingras (NaH, $Pd(PPh_3)_4$, *t*-BuOH, 100 °C) to prepare diaryl ether-based molecular wires,[39] only the dehalogenated products **18a,b** were obtained (64−71%). It is known that Pd-catalyzed C−O bond forming is a difficult task, due to the low nucleophilicity of the oxygen and, therefore, very slow reductive elimination from the arylpalladium alkoxo complex intermediate. Likewise, this process is strongly dependent on the steric features of the active catalytic system employed and alkali nature/concentration,[40d] in such a way that, until the introduction of bidentate (2,2′-bis-(diarylphosphino)-1,1′-binaphthyl-[17g] or 1,1′-(dialkylphosphino)ferrocene-type,[40b,c] mainly) or specifically designed monodentate dialkylphosphinobiphenyl ligands,[17a,b,40a,c] only electron-rich or -neutral aryl bromides could be applied. In this context, the obtained result with a first-generation ligand such as PPh_3 is fully consistent with literature precedents, proving that the use of such simple catalytic system may operate only in certain specific cases. To our delight, despite the fact that phenoxides are even less nucleophilic than alkoxides, when preformed sodium phenolates **20** derived from pyrazoles **2** and **17** (Scheme 8) were treated with $Pd_2(dba)_3$ in the presence of a bidentate ligand in a mixture of toluene and THF, after prolonged reaction times (17−21 h), the desired dibenzoxepines **1** were isolated in fair to moderate yields (Table 5). Slightly better yields were obtained when the catalytic system was based on the commercial ligands 1,1′-bis(diphenylphosphino)ferrocene (DPPF) rather than 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP),[41] requiring for the latter a greater ratio of catalyst (6.5−9 vs 4−7.5 mol %). In terms of the ability of the applied phosphines to promote the reductive elimination of the putative Pd−aryloxide intermediate, it is worth noting that DPPF, a ligand with a larger cone angle than BINAP, did give the optimal results.[42] The similar yields obtained from all the assayed pyrazoles **2** are highly relevant, which is in concert with Buchwald's previous observations of the apparent insensitivity of the Pd-catalyzed intramolecular formation of cyclic ethers to the electronic nature of the involved substituents.[43]

Thus, apart from the failed reactions of halophenol **2i** and halonaphthol **17** (probably due to the formidable steric interactions in the course of the formation of the alkoxo intermediate with the *N*-phenyl or H-3 on the pyrazole nucleus respectively), it is rather complicated from the inspection of Table 5 to unravel the various factors that contribute to facilitate the desired *O*-arylation. To our knowledge, only another efficient Pd-catalyzed etheration had been reported to date in a similar constrained system,[17c] expanding in some way the scope of this important transformation. On the other hand, it is also illustrative to verify the ability of iodo derivatives to promote this reaction, in contrast to the vast majoriy of previous reports that strongly recommend the use of bromoarenes as coupling partners. It is therefore tempting to speculate that the most plausible reasons why the Buchwald−Hartwig reaction worked on our starting halophenolic pyrazoles **2** are the thermodynamic stability of the ultimate heterocycle, along with the strain release on the supposed eight-membered palladacycle intermediate in the C−O bond formation.

5. Synthesis of Dibenzoxepino[4,5-*d*]pyrazoles via Ullmann−Ether Reaction. At this point of the research, the aim of a more efficient approach prompted us to seek an alternative method to achieve our goal by implementation of an intramolecular Ullmann−ether coupling to the oxepine ring. Toward this end, halophenolic pyrazoles **2a**, **2g**, **2h**, taken as models, were submitted to a selected survey of Ullmann−ether reaction conditions. Results of our screening studies involving the use of different copper species are listed in Table 6, wherein it can be discerned that many of the methods employed suffer from some drawbacks, such as longer reaction times and high temperatures, mainly due to the insolubility of copper reagents in the medium. In that respect, to overcome this apparent problem the use of completely soluble copper(I) complexes (entries 1, 7, 8) or CuO (entry 9) permitted increase of the reaction rate. It should be highlighted that the excellent performance of the novel protocol requires copper(I) triflate (entry 7) employed catalytically in the presence of Cs_2CO_3 as base[44] to furnish the target product at an unusual low temperature for this process (110 °C). Likewise, the use of copper(I) thiophenecarboxylate (CuTC) (entry 8), which has been reported to promote Ullmann−biaryl coupling at room temperature,[45] also worked efficiently but at a considerably higher temperature (145 °C), which had not been applied to the formation of a biaryl−ether linkage to date. Finally, copper(I) and -(II) oxides (entries 2,9), which usually are employed mixed with metallic copper

(38) (a) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852−860. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818.

(39) Pinchart, A.; Dallaire, C.; Gingras, M. *Tetrahedron Lett.* **1998**, *39*, 543−546.

(40) (a) Parrish, C. A.; S.-I.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2498−2500. (b) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224−3225. (c) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369−4378. (d) Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6787−6795.

(41) Control experiments were conducted in the same solvent mixture in the absence of a palladium catalyst, but none of the desired products were detected, and starting halide was completely recovered (>90%).

(42) Mann, G.; Hartwig, J. F. *Tetrahedron Lett.* **1997**, *38*, 8005−8008.

(43) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333−10334.

(44) Marcoux, J.-F.; Poye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10538−10540.

(45) Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312−2313.

TABLE 5. Results Obtained in the Synthesis of Dibenzoxepino[4,5-*d*]pyrazoles 1

Substrate	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Product[a]	1(%)[b,c,d]	1 (%)[e]
2a	H	H	H	H	H	H	H	H	**1a**	69 (51)	87
2b	H	H	H	H	Cl	H	H	H	**1b**	56 (44)	88
2c	H	H	H	H	Cl	H	Cl	H	**1c**	49 (41)	76
2d	H	OMe	OMe	H	H	H	H	H	**1d**	62 (51)	69
2e	H	NEt_2	H	H	H	H	H	H	**1e**	54 (44)	57 (89)[f]
17	H	H	H	H	H	H			**1f**	-[g]	-[g]
2g	OMe	OMe	H	H	H	OMe	OMe	H	**1g**	41 (24)	74
2h	OMe	OMe	H	H	H	OMe	OMe	H	**1g**	16 (21)	78
2i	H	OMe	H	OMe	H	OMe	OMe	H	**1h**	-[h]	72

[a] R^9=Ph (for **2a**−**i**). R^9=H (for **17**). [b] Isolated yield of chromatographed compound estimated to be of >95% purity, as indicated by ^{1}H NMR and GC/MS analyze. Yield calculated from the starting halophenolic pyrazoles **2**. [c] Yields obtained by method A (Buchwald−Hartwig reaction) when DPPF was used as ligand. Reactions were conducted with 4−7.5 mol % $Pd_2(dba)_3$ at 100 °C for 17−19 h. [d] Figures in parentheses refer to yields obtained when (*R*)-BINAP was used as ligand in method A. Reactions were conducted with 6.5−9 mol % $Pd_2(dba)_3$ at 100 °C for 17.5−48 h. [e] Yield of pure crystallized compound obtained by method B (Ullmann−ether synthesis). [f] Yield of pure chromatographed product. Yield in parentheses was determined by GC/MS with reference to an internal standard. Manipulation of product **1e** proved to be troublesome and induced a dramatic decrease in the isolated yield. [g] None of the tetracyclic product was detected. [h] Low yield of the expected product **1h** (12%) was measured by GC/MS with reference to an internal standard.

to promote Ullmann−ether reaction,[40,46] required unacceptable, prolonged heating periods. Interestingly, comparison of the results for substrates **2g** and **2h** in Table 6 reveals a slightly more efficient reactivity for the iodo-substituted pyrazole **2h** than the brominated analogue **2g**, both in terms of yield and reaction rate.

Once we had established the excellence of the CuBr·DMS reagent to accomplish the ultimate ring closure, halophenolic pyrazoles **2** were subjected to its action, resulting in the formation of the target tetracycles **1** in good yields. Table 5 illustrates the scope of this approach and permits us to state its convenience compared with the Pd-catalyzed C−O bond forming one, both in terms of yield and substitution range. As a matter of fact, compounds not obtainable by the Buchwald−Hartwig reaction, such as the constrained polymethoxylated dibenzoxepine **1h**, were isolated in a surprising good yield (72%). Additionally, it is of interest to note that the ortho-substituted dibenzoxepines around the ether linkage (**1c** and **1g**) did not suffer from lack of reactivity, in striking contrast to the literature precedents supporting the pernicious effect of substituents at that position on the Ullmann−ether reaction.[48] Despite the diverse substitution pattern, the isolated yields of dibenzoxepines **1** did not vary excessively, confirming the excellence of this protocol to carry out the dibenzoxepine ring closure, except in the case of diethylamino-substituted product **1e**. We surmise that, as occurred in previous precursors as well but to a larger extent, its low solubility in organic solvents and tendency to give gummy solids of troublesome manipulation may cause a significant loss of yield in the purification stage. We found that with a slight excess of the copper complex (8−12 mol % excess), the reaction proceeded readily to completion in sluggish substrates, in contrast with the deleterious effect of an increase of temperature. Disgracefully, and despite the fact of working with other systems under stringent conditions, insurmountable difficulty was encountered in attempting to utilize the naphthopyrazole **17**. In the light of the results obtained from more hindered substrates such as **1c**, **1g**, and **1h**, and taking into account the known ability of pyrazole nucleus to complex a wide range of transition metals,[49] we surmise that, once N-1 on the pyrazole ring has been deprotonated, complexation of the ring with the copper reagent might be responsible for the failure of further reaction rather than a virtual steric hindrance between the naphthyl substituent and H-3 in the transition state.

6. Preliminary Pharmacological Evaluation. Several selected dibenzoxepines **1** were evaluated for their affinity on a complete panel of peripheral and central nervous system receptors [serotonin (5-HT_{1A}, 5-HT_{2A}, 5-HT_3), serotonin uptake, dopamine (D_1, D_2), dopamine uptake, noradrenaline (α1, α2), noradrenaline uptake, and histamine H_1 and muscarinic receptors] by radioligand binding assays. As summarized in Table S1 (see Supporting Information), no assay exhibited a significant response (higher than 50% inhibition at 1 μM concentration) except for dibenzoxepine **1g**, which showed a limited binding affinity to D_2 dopamine receptors.

To our knowledge, a general, easily extensible technology for the construction of this novel structural family via the dibenzoxepine ring closure starting from 1,2-diarylethanones had not been described yet. Thus, and according to the previously shown discouraging pharmacological results, at present, further studies are underway to extend our novel ring closing tactic to enable development of versatile routes to other important classes of condensed *N*- and *O*-heteroaromatics that may exhibit the desired bioactivity.

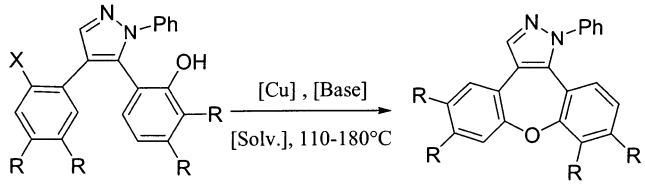
(46) Evans, D. A.; Ellmann, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1063−1072.

(47) It is commonly accepted that S_NAr mainly occurs with activated fluoro and chloroarenes; see: Paradisi, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: New York, 1991; Vol. 4, p 423. Control experiments were carried out in the absence of copper species (Table 6, entry 10), leading to the full recovery of starting phenolates, ruling out the operativity of this reaction pathway.

(48) Moroz, A. A.; Shvartsberg, M. S. *Russ. Chem. Rev.* **1974**, *43*, 679.

(49) Grimmett, M. R.; Iddon, B. *Heterocycles* **1994**, *37*, 2087−2149.

TABLE 6. Results from the Ullmann−Ether Coupling Assays on Halophenolic Pyrazoles 2a,g−i



2a R=H X=I
2g R=OMe X=Br
2h R=OMe X=I

1a R=H X=I
1g R=OMe X=Br

entry	substrate	reaction conditions	*t* (h)	**1** (% yield)[a,b]
1	**2a**	CuBr·DMS,[e] NaH, py, 120 °C	4	**1a** (87)*c*
	2g		6	**1g** (74)*c*
	2h		5,5	**1g** (78)*c*
2	**2a**	Cu_2O, NaH, py, 130−165 °C	6,5	**1a** (69)
	2g		24	**1g** (61)
	2h		19	**1g** (66)
3	**2a**	CuI,[d] K_2CO_3, py, 125−140 °C	6,5	**1a** (81)
	2g		18	**1g** (66)
	2h		14	**1g** (74)
4	**2a**	Cu, KI, DMSO, 180−200 °C	4	**1a** (42)
	2g		5	**1g** (46)
	2h		5	**1g** (41)
5	**2a**	CuCl, 18-crown-6, Na_2CO_3,	4	**1a** (55)
	2g	NMP, 150 °C	5	**1g** (59)
	2h		4,5	**1g** (51)
6	**2a**	CuBr, NaH, py, 150 °C	36	**1a** (9)
	2g		36	**1g** (11)
	2h		36	**1g** (16)
7	**2a**	$(CuOTf)_2$·PhH (5 mol %),	7	**1a** (71)
	2g	Cs_2CO_3, PhMe, 110 °C	9	**1g** (64)
	2h		7,5	**1g** (73)
8	**2a**	CuTC,[e] NaH, py, 145 °C	3	**1a** (74)
	2g		5	**1g** (62)
	2h		3	**1g** (68)
9	**2a**	CuO, K_2CO_3, py, 150 °C	22	**1a** (69)
	2g		92	**1g** (57)
	2h		54	**1g** (69)
10	**2a**	(1) NaOH, PhMe, 135 °C;	24	f,g
	2g	(2) DMF, 150 °C	24	
	2h		24	

[a] GC/MS with reference to an internal standard. [b] Reactions went to completion upon adding a slight excess (8−12 equiv mol %) of copper species. [c] Isolated yield of chromatographed compound estimated to be of >95% purity as indicated by ^{1}H NMR and GC analysis. [d] Initially, experiments were carried out by applying ultrasounds at 19−65 °C (see ref 50), but starting material was completely recovered. [e] CuBr·DMS, copper(I) bromide−dimethyl sulfide complex; CuTC, copper(I) thiophene carboxylate. [f] Recovery of the starting material (>90%). [g] See ref 47.

Conclusions

In summary, we have developed an operationally straightforward method for the preparation of the unreported dibenzoxepino[4,5-*d*]pyrazoles. Our protocol is amenable to construct multisubstituted electron-rich, -neutral, and -poor dibenzoxepino[4,5-*d*]pyrazoles that would not be easily obtained by other methods, from *o*,*o*′-halohydroxy-4,5-diarylpyrazoles by an efficient biaryl−ether coupling promoted by CuBr·DMS complex. Moreover, an alternative approach to the target dibenzoxepine derivatives relies on the Pd-catalyzed C−O bond formation of the biaryl−ether linkage, exhibiting limitations in terms of yield and steric demand of the generated compounds. In this approach, the use of a bidentate ligand (BINAP or preferably, DPPF) is crucial to reach the target compounds in reasonable yield.

Further, we have proved the validity of the amine exchange/heterocyclization sequence to prepare *o*,*o*′-haloarylsulfonyloxy- and *o*,*o*′-halobenzoyloxy-4,5-diarylpyrazoles. The strategically substituted aryl groups introduced on the 3-*N*,*N*-(dimethylamino)-*o*,*o*′-disubstituted-1,2-diarylpropenone precursors have shown the limitations imposed by electronically deactivated C-1 aryl groups or sterically demanding substituents at C-2.

Finally, preliminary pharmacological in vitro evaluation has shown the inability of the synthesized compounds to interact with the most common peripheral and central nervous system receptors.

Experimental Section

Instrumentation, General Procedures, and Materials. For general experimental details, see ref 14a.

Synthesis of Dibenzoxepino[4,5-*d*]pyrazoles (1).[51]

Method A (Ullmann−Ether Reaction). 1-Phenyldibenzo[2,3:6,7]oxepino[4,5-*d*]pyrazole (1a). Typical Procedure. NaH (95% in oil dispersion, 12.6 mg, 0.50 mmol) was added to a stirred solution of halophenolic pyrazole **2a** (0.2 g, 0.46 mmol) and CuBr·Me_2S (99%, 0.188 g, 0.91 mmol) in anhydrous pyridine (5 mL) under an atmosphere of Ar at ambient temperature. After stirring for 15 min, as the reaction mixture turned black, it was heated at 120 °C for 5.5 h, until consumption of starting material was confirmed by TLC (2% EtOAc/DCM). The mixture was allowed to cool, poured into 1.37 M HCl (40 mL), and extracted with DCM (5 × 10 mL). The organic layer was washed with 0.31 M $CuSO_4$ (1 × 5 mL), dried (anhyd Na_2SO_4), filtered off, and the solvent was removed in vacuo. The crude oil was absorbed on silica gel (1 g) and flash chromatographed eluting with the gradient 80→100% DCM/hexanes as eluant. The pure eluate was crystallized from MeOH affording dibenzoxepine **1a** (0.125 g, 87%) as a white powder: mp 171−173 °C (MeOH); R_f 0.82 (2% EtOAc/DCM); ^{1}H NMR ($CDCl_3$) δ 6.81 (1H, dd, J = 7.9, 1.6 Hz), 6.94 (1H, ddd, J = 8.1, 7.9, 1.6 Hz), 7.20−7.52 (10H, m), 7.57 (1H, dd, J = 6.9, 1.6 Hz), 8.01 (1H, s); ^{13}C NMR ($CDCl_3$) δ 120.3, 121.5, 122.3, 122.9, 124.7, 125.1, 125.5, 127.0, 127.9, 128.6, 128.7, 129.2, 130.2, 136.2, 137.9, 140.8, 155.9, 156.5; FTIR (neat film, cm^{-1}) 1597; EIMS (*m*/*z*, %) 310 (M+, 100), 281 (12), 206 (12), 77 (12). Anal. Calcd for $C_{21}H_{14}N_2O$: C, 81.27; H, 4.55; N, 9.03. Found: C, 81.39; H, 4.64; N, 9.17.

By using the same procedure and starting from the appropriate intermediate compound of preceding step, the following products were obtained.

5-Chloro-1-phenyldibenzo[2,3:6,7]oxepino[4,5-*d*]pyrazole (1b), after crystallization from EtOH: 88%, as an off-white powder; mp 199−201 °C (EtOH); R_f 0.47 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 6.79 (1H, dd, J = 7.1, 1.6 Hz), 6.94 (1H, ddd, J = 8.0, 7.5, 2.0 Hz), 7.25−7.52 (10H, m), 8.02 (1H, s); ^{13}C NMR ($CDCl_3$) δ 119.2, 122.2, 122.6, 122.7, 124.9, 125.1, 126.7, 127.2, 128.1, 128.3, 128.6, 129.2, 130.4, 130.6, 136.4, 137.8, 139.8, 154.3, 156.2; FTIR (neat film, cm^{-1}) 1597; EIMS (*m*/*z*, %) 346 (M + 2, 36), 344 (M+, 100), 308 (10), 281 (77), 77 (16). Anal. Calcd for $C_{21}H_{13}ClIN_2O$: C, 73.15; H, 3.80; N, 8.12. Found: C, 73.21; H, 3.94; N, 8.06.

(50) Bellón, R. F.; Carrasco, R.; Milián, V.; Rodés, L. *Synth. Commun.* **1995**, *25*, 1077−1083.

(51) Alternative substitutive nomenclature of dibenzoxepino[4,5-*d*]-pyrazoles **1** as azulene derivatives may also be accepted. According to this, the systematic names of the synthesized tetracycles **1** are as follows: **1a**, 1-phenyl-1*H*-8-oxa-1,2-diazadibenzo[*e*,*h*]azulene; **1b**, 7-chloro-1-phenyl-1*H*-8-oxa-1,2-diazadibenzo[*e*,*h*]azulene; **1c:** 5,7-dichloro-1-phenyl-1*H*-8-oxa-1,2-diazadibenzo[*e*,*h*]azulene; **1d**, 10,11-dimethoxy-1-phenyl-1*H*-8-oxa-1,2-diazadibenzo[*e*,*h*] azulene; **1e**, 10-diethylamino-1-phenyl-1*H*-8-oxa-1,2-diazadibenzo[*e*,*h*]azulene; **1g**, 1-phenyl-5,6,9,10-tetramethoxy-1*H*-8-oxa-1,2-diazadibenzo[*e*,*h*] azulene; **1h**, 1-phenyl-5,6,10,12-tetramethoxy-1*H*-8-oxa-1,2-diazadibenzo[*e*,*h*] azulene.

5,7-Dichloro-1-phenyldibenzo[2,3:6,7]oxepino[4,5-*d*]-pyrazole (1c), after crystallization from Et_2O: 76%, as an amber glassy solid; mp 105−107 °C (Et_2O); R_f 0.42 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 6.81 (1H, dd, J = 7.9, 1.6 Hz), 6.97 (1H, ddd, J = 7.9, 7.9, 2.0 Hz), 7.34 (1H, dd, J = 7.9, 1.6 Hz), 7.37−7.47 (6H, m), 7.58 (1H, d, J = 1.2 Hz), 7.61 (1H, d, J = 1.2 Hz), 8.03 (1H, s); ^{13}C NMR ($CDCl_3$) δ 122.5, 123.1, 125.2, 125.3, 127.8, 128.3, 128.5, 128.7, 129.3, 130.5, 130.6, 137.9, 139.7, 149.6, 155.9; FTIR (neat film, cm^{-1}) 1593; EIMS (*m*/*z*, %) 382 (M + 4, 13), 380 (M + 2, 71), 378 (M+, 100), 342 (12), 279 (14), 77 (36). Anal. Calcd for $C_{21}H_{12}Cl_2IN_2O$: C, 66.51; H, 3.19; N, 7.39. Found: C, 66.46; H, 3.45; N, 7.44.

10,11-Dimethoxy-1-phenyldibenzo[2,3:6,7]oxepino[4,5-*d*]pyrazole (1d), after crystallization from Et_2O: 69%, as a white powder; mp 166−167 °C (Et_2O), R_f 0.44 (2% EtOAc/DCM); ^{1}H NMR ($CDCl_3$) δ 3.30 (3H, s), 3.90 (3H, s), 6.20 (1H, s), 6,90 (1H, s), 7.20−7.27 (1H, m), 7.30 (1H, dd, J = 8.1, 1.5 Hz), 7.38−7.58 (7H, m), 8.03 (1H, s); ^{13}C NMR ($CDCl_3$) δ 55.4, 56.0, 105.5, 110.1, 113.9, 119.6, 121.3, 125.5, 125.7, 127.1, 128.0, 128.5, 129.2, 136.4, 137.8, 140.0, 145.6, 150.4, 155.9; FTIR (neat film, cm^{-1}) 1612; EIMS (*m*/*z*, %) 370 (M+, 100), 323 (15), 295 (24), 169 (13), 77 (17). Anal. Calcd for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.49; H, 4.96; N, 7.61.

10-*N*,*N*-Diethylamino-1-phenyldibenzo[2,3:6,7]oxepino-[4,5-*d*]pyrazole (1e), after purification by flash chromatography using 80% DCM/hexanes as eluant: 57%, as a yellow oil; R_f 0.64 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 1.15 (6H, t, J = 6.7 Hz), 3.34 (4H, q, J = 6.7 Hz), 6.22 (1H, dd, J = 8.9, 2.6 Hz), 6.60 (1H, d, J = 8.9 Hz), 6.61 (1H, d, J = 2.6 Hz), 7.20−7.46 (7H, m), 7.55 (2H, dd, J = 7.5, 1.6 Hz), 7.99 (1H, s); ^{13}C NMR ($CDCl_3$) δ 12.5, 44.4, 104.0, 107.8, 121.5, 125.1, 125.3, 127.0, 127.5, 128.2, 129.0, 129.2, 137.8, 140.7, 155.7, 158.2; FTIR (neat film, cm^{-1}) 1622; EIMS (*m*/*z*, %) 381 (M+, 81), 364 (100), 338 (20), 337 (38), 308 (8), 281 (8), 181 (20), 77 (24). Anal. Calcd for $C_{25}H_{23}N_3O$: C, 78.71; H, 6.08; N, 11.02. Found: C, 78.56; H, 6.20; N, 11.19.

1-Phenyl-5,6,9,10-tetramethoxydibenzo[2,3:6,7]oxepino-[4,5-*d*]pyrazole (1g), after crystallization from Et_2O: 78%, as a white powder; mp 187−189 °C (Et_2O); R_f 0.54 (2% EtOAc/DCM); ^{1}H NMR ($CDCl_3$) δ 3.82 (3H, s), 3.92 (6H, s), 4.08 (3H, s), 6.46 (1H, d, J = 9.1 Hz), 6.51 (1H, d, J = 9.1 Hz), 6.98 (1H, s), 7.05 (1H, s), 7.37−7.48 (3H, m), 7.52 (2H, dd, J = 8.7, 1.5 Hz), 7.99 (1H, s); ^{13}C NMR ($CDCl_3$) δ 56.0, 56.1, 56.3, 61.8, 105.9, 108.2, 108.7, 117.0, 117.4, 119.5, 122.9, 125.1, 127.7, 129.1, 135.8, 137.3, 140.2, 141.7, 149.1, 149.2, 150.5, 154.3; FTIR (neat film, cm^{-1}) 1600; EIMS (*m*/*z*, %) 430 (M+, 100), 415 (16), 387 (10), 77 (10). Anal. Calcd for $C_{25}H_{22}N_2O_5$: C, 69.76; H, 5.15; N, 6.51. Found: C, 69.94; H, 5.10; N, 6.67.

1-Phenyl-5,6,10,12-tetramethoxydibenzo[2,3:6,7]oxepino[4,5-*d*]pyrazole (1h), after purification by flash chromatography on silica gel eluting with the gradient 50→70% EtOAc/hexanes and subsequent crystallization of the pure eluate from EtOH: 72%, as a white powder; mp 151−153 °C (EtOH); R_f 0.43 (60% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 3.01 (3H, s), 3.84 (3H, s), 3.92 (6H, s), 6.09 (1H, d, J = 2.2 Hz), 6.56 (1H, d, J = 2.2 Hz), 7.24 (1H, d, J = 7.7 Hz), 7.36 (2H, dd, J = 7.7, 7.7 Hz), 7.45 (2H, d, J = 7.7 Hz), 7.97 (1H, s); ^{13}C NMR ($CDCl_3$) δ 54.3, 55.5, 56.1, 56.3, 95.9, 98.8, 105.2, 105.6, 109.1, 117.6, 120.0, 122.2, 126.6, 128.6, 134.0, 137.2, 142.7, 146.7, 149.0, 149.7, 156.4, 160.4, 162.3; FTIR (neat film, cm^{-1}) 1615; EIMS (*m*/*z*, %) 430 (M+, 100), 415 (17), 387 (9), 215 (10), 77 (15). Anal. Calcd for $C_{25}H_{22}N_2O_5$: C, 69.76; H, 5.15; N, 6.51. Found: C, 69.99; H, 5.21; N, 6.61.

Method B (Buchwald−Hartwig Reaction). 1-Phenyldibenzo[2,3:6,7]oxepino[4,5-*d*]pyrazole (1a). Typical Procedure. Ground NaOH (99%, 0.023 g, 0.56 mmol) was added to a stirred suspension of halophenolic pyrazole **2a** (0.22. g, 0.51 mmol) in anhydrous PhMe (14 mL) at ambient temperature under an atmosphere of Ar. The resultant mixture was heated to reflux for 30 min and allowed to cool without stirring. The supernatant orange solution containing the phenolate **20a** was transferred via cannula to an empty flask and was degassed by bubbling with Ar (20 min). A mixture of $Pd_2(dba)_3$ (99%, 16.5 mg, 17.9 μmol) and DPPF (97%, 40.9 mg, 71.6 μmol) in anhydrous and degassed THF (1.6 mL) was stirred for 20 min at ambient temperature under an atmosphere of Ar and added dropwise to the previously prepared solution of phenolate **20a**. The reaction mixture was heated at 100 °C for 17 h, until consumption of starting material was confirmed by TLC (2% EtOAc/DCM). After cooling to ambient temperature, the crude mixture was filtered through a pad of Celite and thoroughly washed with THF and the filtrate was evaporated under reduced pressure. The residue was flash chromatographed on silica gel eluting with the gradient 80→100% DCM/hexanes to give dibenzoxepine **1a** (0.11 g, 69%) as an off-white powder.

The application of this procedure on the appropriate halophenolic pyrazole **2** afforded the corresponding dibenzoxepine derivative **1** in the yield indicated in Table 5. The same protocol was followed when (*R*)-BINAP was used as ligand instead of DPPF. Catalyst ratio was increased in the case of deactivated substrates. In all cases, the purity of the obtained dibenzoxepines was >95% according to their spectroscopic (^{1}H NMR) and spectrometric (GC/MS) analyses.

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Supporting Information Available: Experimental procedures for the synthesis of precursors and intermediates (**2**−**17**); pharmacological results (Table S1) and the corresponding experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org

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