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Toward Safer Processes for C−C Biaryl Bond Construction: Catalytic Direct C−H Arylation and Tin-Free Radical Coupling in the Synthesis of Pyrazolophenanthridines

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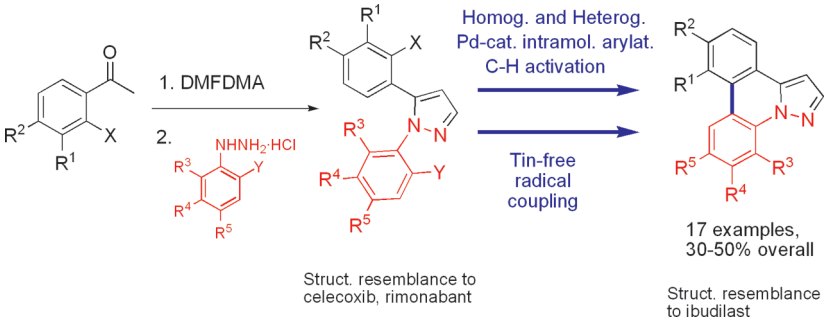

A series of pyrazolo[1,5-*f*]phenanthridine derivatives has been efficiently synthesized by a short, straightforward sequence. A tandem amine-exchange/heterocyclization of enaminones was successfully applied to the regioselective preparation of 1,5-diarylpyrazole intermediates with structure resemblance to relevant nonsteroidal anti-inflammatory drugs such as celecoxib or tepoxalin. The final key step, cyclization by intramolecular biaryl bond formation, was accomplished by two alternative methodologies: radical coupling and catalytic direct arylation via C−H activation. The scope and limitations of the two methodologies have been explored and their complementariness has been established. In addition, polymer-supported heterogeneous catalysts have been compared with homogeneous analogues. In the radical process, toxic tin derivatives have been avoided in order to employ environmentally safer protocols.

Introduction

Pyrazole derivatives, although scarcely found in nature, constitute an interesting family of heterocycles due to their application as pharmaceuticals[1] and in the agrochemical industry as herbicides and insecticides.[2] Among them, 1,5-diarylsubstituted derivatives[3] SC-558, tepoxalin, and celecoxib (currently marketed as Celebrex) have proved to be potent and selective inhibitors of cyclo-oxygenase-2 (COX-2) and, for this reason, these compounds have demonstrated

(1) See for example: (a) Madsen, U.; Slok, F. A.; Stensbol, T. B.; Brauner-Osborn, H.; Lutzhoft, H. C.; Poulsen, M. V.; Eriksen, L.; Krogsgaard-Larsen, P. *Eur. J. Med. Chem.* **2000**, *35*, 69–76. (b) Zhang, J.; Didierlaurent, S.; Fortin, M.; Lefrancois, D.; Uridat, E.; Vevert, J. P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1351–1355. (c) Mansour, A. K.; Eid, M. M.; Khalil, N. S. A. M. *Molecules* **2003**, *8*, 744–755. (d) Abunada, N. M.; Hassaneen, H. H.; Kandile, N. G.; Miqdad, O. A. *Molecules* **2008**, *13*, 1501–1517.

(2) See for example: (a) Lamberth, C. *Heterocycles* **2007**, *71*, 1467–1502. (b) Zheng, W.; Yates, S. R.; Papiernik, S. K. *J. Agric. Food Chem.* **2008**, *56*, 7367–7372.

(3) Diaryl heterocycles in general are a selective class of COX-2 inhibitors: Chavatte, P.; Yous, S.; Marot, C.; Baurin, N.; Lesieur, D. *J. Med. Chem.* **2001**, *44*, 3223–3230.

(4) (a) ÒConnor, J. P.; Lysz, T. *Drugs Today* **2008**, *44*, 693–709. (b) Taeuber, U. *Drugs Exp. Clin. Res.* **1990**, *16*, 7–15. (c) Argentieri, D.; Ritchi, D.; Tolman, E.; Ferro, M.; Watcher, M.; Mezick, J.; Capetola, R. *FASEB J. Antiinflammatory Agents*, 2, *4*, A369, **1988**. (d) Murray, W. V.; Hadden, S. K. *J. Org. Chem.* **1992**, *57*, 6662–6663. (e) Habeeb, A. G.; Praveen, P. N.; Knaus, E. E. *J. Med. Chem.* **2001**, *44*, 3039–3042. (f) Liu, H.; Huang, X.; Shen, J. M.; Luo, X.; Li, M.; Xiong, B.; Chen., G.; Shen, J.; Yang, Y.; Jiang, H.; Chen., K. *J. Med. Chem.* **2002**, *45*, 4816–4827. (g) Singh, S. K.; Vobbalareddy, S.; Shivaramakrishna, S.; Krishnamraju, A.; Rajjak, S. A.; Casturi, S. R.; Akhila, V.; Rao, Y. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1683–1688. (h) Weber, A.; Casini, A.; Heine, A.; Kuhn, D.; Sapuran, C. T.; Scozzafava, A.; Klebe, G. *J. Med. Chem.* **2004**, *47*, 550–557.

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remarkable anti-inflammatory, analgesic, and antipyretic activity, thus comprising a class of nonsteroidal anti-inflammatory drugs (NSAID).[4−7] Rimonabant was the first cannabinoid-1 receptor blocker with a 1,5-diarylpyrazol framework that was initially approved to treat obesity disorders and is currently assayed in the therapy of Parkinson′s disease (Figure 1).[7b] Similarly, compounds based on the pyrazolo[1,5-*a*]pyridine framework have shown interesting biological activity. In fact, this heterocyclic system is considered the most promising stable bioisostere of the indole nucleus avoiding problems related to the metabolic instability of indoles. The most relevant examples of this type of compounds are the well-known antiallergic and cerebroactive agent ibudilast, a potent leucotriene D4 antagonist,[8] the adenosine antagonist FK453,[8] and a series of highly selective D4 receptor ligands such us FAUC 113, FAUC 327, or FAUC 213[9] (Figure 2). In addition, among other attractive applications,[10] phenantridine moiety has been proposed as an effective pharmacophore in the class of DNA-intercalating antitumor agents.[11]

Following our investigations on the development of new methodologies for the access to novel polyheterocyclic derivatives, we planned the synthesis of a series of pyrazolophenanthridines **1** by cyclization of the corresponding 1, 5-diarylsubstituted pyrazoles **2** (Scheme 1). It is noteworthy the inherent interest of this appealing tetracyclic system derived from a sum of the features from the three heterocyclic moieties previously cited. Indeed, diaza derivatives **1**

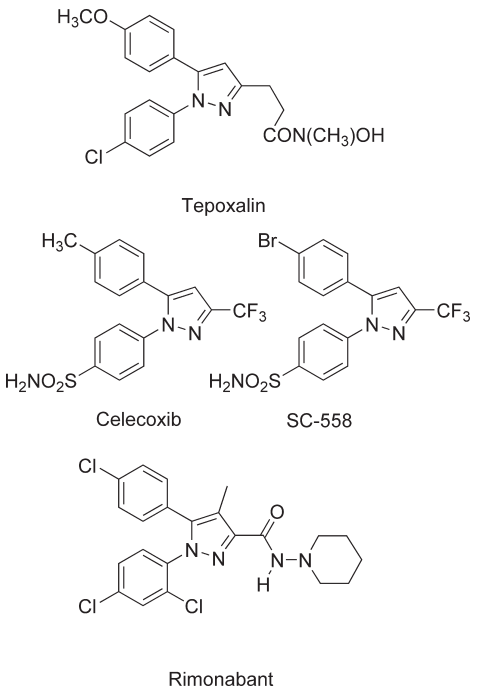


FIGURE 1. Some 1,5-diarylpyrazoles showing interesting pharmacological properties.

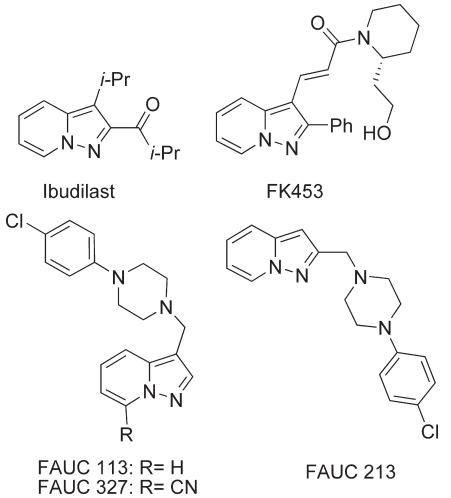
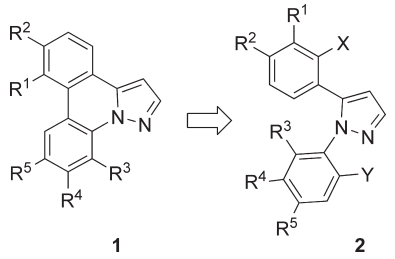


FIGURE 2. Selected examples of pyrazolo[1,5-*a*]pyridines of pharmacological significance.

SCHEME 1



can be considered as the rotationally constrained analogues of 1,5-diarylpyrazoles bearing a phenanthridine heterocycle

(5) DPC602, another 1,5-disubstituted pyrazole derivative, has been used as a powerful and orally bioavailable Xa factor inhibitor: Pruitt, J. R.; Pinto, D. J. P.; Galemmo, R. A.; Alexander, R. S.; Rossi, K. A.; Wells, B. L.; Drummond, S.; Bostrom, L. L.; Burdick, D.; Bruckner, R.; Chen, H.; Smallwood, A.; Wong, P. C.; Wright, M. R.; Bai, S.; Luettgen, J. M.; Knabb, R. M.; Lam, P. Y. S.; Wexler, R. R. *J. Med. Chem.* **2003**, *46*, 5298–5315.

(6) Other applications of celecoxib include the treatment of preterm labor, osteoarthritis and rheumatoid arthritis, inflammatory bowel disease, and duodenal polyposis in familial adenomatous polposis. See: (a) Stika, C. S.; Gross, G. A.; Leguizamon, G.; Gerber, S.; Levy, R.; Mathur, A.; Bernhard, L. M.; Nelson, D. M.; Sadovsky, Y. *Am. J. Obstet. Gynecol.* **2002**, *187*, 653–660. (b) Dilger, K.; Herrlinger, C.; Peters, J.; Seyberth, H. W.; Scheweer, H.; Klotz, U. J. *Clin. Pharmacol.* **2002**, *42*, 985–994. (c) Woessner, K. M.; Simon, R: A.; Stevenson, D. D. *Arthritis Rheum.* **2002**, *46*, 2201–2206.

(7) Another 1,5-diarylpyrazol is SR141716, a potent CB_1-selective cannabinoid antagonist: (a) Francisco, M. E. Y.; Burgués, J. P.; George, C.; Bailey, G. S.; William, A. F.; Seltzman, H. H.; Thomas, B. F. *Magn. Reson. Chem.* **2003**, *41*, 265–268. See also: (b) Kelsey, J.; Harris, O.; Cassin, J. *Behav. Brain Res.* **2009**, *203*, 304–307.

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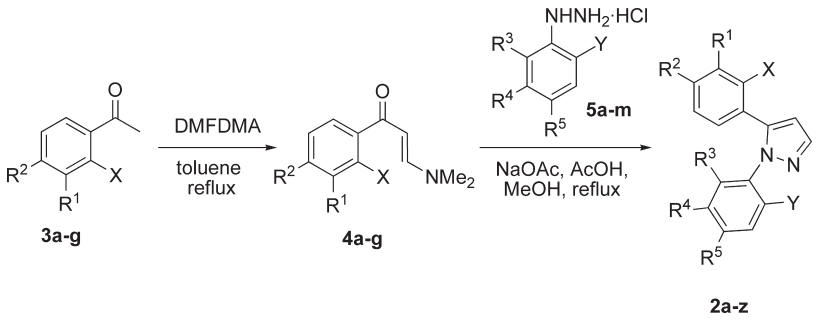
(10) Phenanthridine-fused heterocycles have attracted much attention mainly due to their electroluminiscent properties which make them a material suitable for discotic liquid crystals, single and multilayer devices, and organic diodes. See for example: (a) Twieg, R. J.; Gu, S.; Semyonov, A.; Sukhomlinova, L.; Malliaras, G. G.; Fan, R.; Singer, K.; Ostroverkhova, O.; Shiyanovskaya, I. *Polym. Mater.: Sci. Eng.* **2000**, *83*, 210–211. (b) Han, Y. S.; Kim, S. D.; Kwon, Y.; Choi, K.-H.; Park, L. S. *Mol. Cryst. Liq. Cryst.* **2006**, *459*, 119–128.

(11) (a) Aiello, E.; Dattolo, G.; Cirrincione, G.; Almerico, A. M.; Diana, P.; Grimaudo, S. *Farmaco* **1995**, *50*, 365–368. (b) Vrba, J.; Dolezel, P.; Vicar, J.; Ulrichova *J. Toxicol. in Vitro* **2009**, *23*, 580–588. (c) Toyoda, E.; Kagaya, S.; Cowell, I. G.; Kurosawa, A.; Kamoshita, K.; Nishikawa, K.; Iiizumi, S.; Koyama, H.; Austin, C. A.; Adachi, N. *J. Biol. Chem.* **2008**, *283*, 23711–23720.

TABLE 1. Synthesis of 1,5-Diarylsubstituted Pyrazoles 2a−z



entry	R^1	R^2	R^3	R^4	R^5	X	Y	**4**	**5**	**2** (%)
1	H	H	H	H	H	H	H	**4a**	**5a**	**2a** (69)
2	OMe	H	H	H	H	H	H	**4d**	**5a**	**2b** (55)
3	OMe	OMe	H	H	H	H	H	**4e**	**5a**	**2c** (84)
4	OMe	OMe	H	H	OMe	H	H	**4e**	**5f**	**2d** (75)
5	H	H	H	H	H	Br	H	**4f**	**5a**	**2e** (83)
6	H	H	Me	H	H	Br	H	**4f**	**5b**	**2f** (80)
7	H	H	Et	H	H	Br	H	**4f**	**5d**	**2g** (79)
8	H	H	H	CF_3	H	Br	H	**4f**	**5g**	**2h** (85)
9	H	H	H	H	Me	Br	H	**4f**	**5c**	**2i** (79)
10	H	H	H	H	OMe	Br	H	**4f**	**5f**	**2j** (81)
11	H	H	H	H	^{t}Bu	Br	H	**4f**	**5e**	**2k** (85)
12	H	H	H	H	CF_3	Br	H	**4f**	**5h**	**2l** (67)
13	H	F	H	H	H	Br	H	**4g**	**5a**	**2m** (91)
14	H	F	H	CF_3	H	Br	H	**4g**	**5g**	**2n** (82)
15	H	F	H	H	OMe	Br	H	**4g**	**5f**	**2o** (88)
16	H	F	H	H	^{t}Bu	Br	H	**4g**	**5e**	**2p** (86)
17	H	F	H	H	CF_3	Br	H	**4g**	**5h**	**2q** (86)
18	H	H	H	H	H	H	Br	**4a**	**5i**	**2r** (73)
19	OMe	H	H	H	H	H	Br	**4d**	**5i**	**2s** (53)
20	H	Me	H	H	H	H	Br	**4b**	**5i**	**2t** (64)
21	H	OMe	H	H	H	H	Br	**4c**	**5i**	**2u** (56)
22	OMe	OMe	H	H	H	H	Br	**4e**	**5i**	**2v** (83)
23	H	H	H	Me	H	H	Br	**4a**	**5l**	**2w** (60)
24	H	Me	H	Me	H	H	Br	**4b**	**5l**	**2x** (58)
25	H	H	H	CF_3	H	H	Br	**4a**	**5m**	**2y** (55)
26	H	Me	H	CF_3	H	H	Br	**4b**	**5m**	**2z** (66)

fused to the pyrazole ring, and this tetracyclic structure contains the pyrazole[1,5-*a*]pyridine framework.

Among the large variety of methodologies developed to biaryl bond construction, standard cross-coupling procedures (Suzuki−Miyaura,[12,13] Negishi,[14] Stille,[15] or Hiyama[16]) have demonstrated an outstanding efficiency. However, frequently, the preparation of the organometallic counterpart often constitutes a time-consuming and economically inefficient process in which toxic transmetallating agents are required.

For this reason, to carry out our synthetic target, we attempted more convenient protocols such as oxidative biaryl coupling, radical cyclization, or palladium-catalyzed direct arylation with the common feature of avoiding the transmetalation step.

Results and Discussion

1. Synthesis of 1,5-Diarylpyrazoles. As depicted in Table 1, our synthetic approach to 1,5-diarylpyrazole derivatives **2** started with the aminomethylenation of commercially available acetophenones **3** by means of the modified Vilsmeier−Haack reagent dimethylformamide dimethyl acetal (DMFDMA). The so-obtained enaminoketones **4** were reacted with a number of commercial or easily accessible hydrazines **5**[17] to afford a range of diarylpyrazoles **2a−z** via a tandem amine exchange/heterocyclation.[18] As shown in

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(17) Hydrazines **5j−m** were easily prepared by a diazotization/reduction sequence starting from the corresponding anilines. For experimental details see the Supporting Information.

(18) This tandem has been successfully applied by our group to the synthesis of different heterocycles: (a) Olivera, R.; SanMartin, R.; Domínguez, E.; Solans, X.; Urtiaga, M. K.; Arriortúa, M. I. *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.; Churruca, F.; Domínguez, E. *J. Org. Chem*. **2002**, *67*, 7215–7225. (d) Olivera, R.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Tetrahedron* **2002**, *58*, 3021–3037. (e) Hernández, S.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Org. Lett*. **2003**, *5*, 1095–1098.

Table 1 nonhalogenated pyrazoles (**2a**−**d**), derivatives bearing a bromoaryl group at the C-5 position of the pyrazole ring (**2e**−**q**) or bromoaryl group attached at N-1 of the pyrazole ring (**2r**−**z**), were successfully synthesized employing this facile methodology. It is noteworthy that pyrazoles **2** were obtained in all cases as single isomers. The complete regioselectivity of the process is presumably due to the higher nucleophilicity of the primary amine group compared to the secondary one in arylhydrazine derivatives.[19]

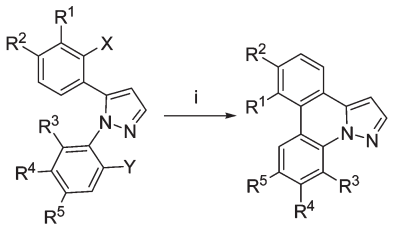
Once the series of intermediates **2** was prepared, different methodologies were explored in order to accomplish the key intramolecular biaryl bond formation.

2. Oxidative Coupling Experiments. This classical, and to some extent biomimetic procedure has been extensively used in the synthesis of a number of natural products.[20] Considering the principal advantages of this methodology, that is, no requirement for functionalization at the coupling positions and no serious limitations concerning substitution patterns in the substrates, this protocol has been successfully exploited by our group in the past years.[21] Therefore, we planned to explore the application of this methodology to the preparation of the tetracyclic pyrazolophenanthridine framework. Since previous studies in this context have demonstrated the beneficial effect of electron-donating substituents on the reaction course,[21b] trimethoxylated derivative **2d** was selected as the model substrate to carry out a set of initial assays. However, all attempts to promote cyclization employing different oxidizing agents such as $FeCl_3$,[22] VOF_3,[23] $MoCl_5$,[24] or the hypervalent iodine(III) reagent PIFA[25,21] resulted in the recovery of the starting material.

3. Palladium-Catalyzed Direct Arylation. The coupling of an aryl halide or pseudohalide with a simple arene has emerged as an excellent alternative to the above-mentioned cross-coupling methodologies, with the significant advantage of avoiding the requirement, and, consequently the preparation of the organometallic counterparts in stoichiometric amounts. However, in contrast with standard cross-coupling procedures, this approach to biaryls is far from general and more examples are needed to define a clear trend with regard to reaction conditions and favorable substrates.[26,27] Having in mind the good results afforded by this protocol in our preliminary work[28] we decided to exploit thoroughly the scope of this method in the synthesis of the pyrazolophenanthridine skeleton. Therefore, brominated diarylpyrazoles **2e**−**r** were submitted to the optimized reaction conditions (10% $Pd(OAc)_2$, K_2CO_3, LiCl, $^nBu_4NBr$, DMF, 110 °C, sealed tube, 5 h) (Table 2). The need for phase transfer catalyst TBAB is probably related to the stabilization of palladium nanoparticles, a possible active species in this kind of coupling.[26]

As depicted in Table 2, the use of such Jeffery's ligand-free conditions provided target tetracyclic compounds **1** in good yields when the *N*-aryl ring was activated with electron-donating substituents. Conversely, the presence of electron-withdrawing groups in the aromatic ring at N-1caused a substantial deactivation of the substrate, which was reflected in a poorer conversion even when more forcing reaction conditions were used (entries 4, 8, and 10). In contrast, a noteworthy improvement in the yield was observed with pyrazole derivatives **2** bearing an electron-withdrawing fluoride atom on the C-5 aromatic ring (entries

TABLE 2. Synthesis of Pyrazolo[1,5-*f*]phenanthridines by Direct Arylation



2 **1**

i. $Pd(OAc)_2$, K_2CO_3, LiCl, $^nBu_4NBr$, DMF, sealed tube

entry	R^1	R^2	R^3	R^4	R^5	X	Y	**2**	**1** (%)[a]
1	H	H	H	H	H	Br	H	**2e**	**1a** (60)
2	H	H	Me	H	H	Br	H	**2f**	**1b** (65)
3	H	H	Et	H	H	Br	H	**2g**	**1c** (65)
4	H	H	H	CF_3	H	Br	H	**2h**	**1d** (42)[b,c]
5	H	H	H	H	Me	Br	H	**2i**	**1e** (61)
6	H	H	H	H	OMe	Br	H	**2j**	**1f** (52)
7	H	H	H	H	^{t}Bu	Br	H	**2k**	**1g** (62)
8	H	H	H	H	CF_3	Br	H	**2l**	**1h** (14)[c]
9	H	F	H	H	H	Br	H	**2m**	**1i** (85)
10	H	F	H	CF_3	H	Br	H	**2n**	**1j** (46)[b,c]
11	H	F	H	H	OMe	Br	H	**2o**	**1k** (70)
12	H	F	H	H	^{t}Bu	Br	H	**2p**	**1***l* (77)
13	H	F	H	H	CF_3	Br	H	**2q**	**1m** (58)
14	H	H	H	H	H	H	Br	**2r**	**1a** (0)
15	H	Me	H	H	H	H	Br	**2t**	**1o** (0)
16	H	H	H	CF_3	H	H	Br	**2y**	**1d** (0)

[a]Isolated yield of chromatografically pure compound. [b]Single isomer was obtained. [c]The reaction was carried out at 130 °C.

(19) For more details about the mechanism of the tandem amine exchange/heterocyclization and the regioselectivity of the process with different dinucleophiles see: (a) Domínguez, E.; Ibeas, E.; Martinez de Marigorta, E.; Palacios, J. K.; SanMartin, R. *J. Org. Chem.* **1996**, *61*, 5435–5439. (b) Domínguez, E.; Martínez de Marigorta, E.; Olivera, R.; SanMartin, R. *Synlett* **1995**, 955–956.

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(26) Selected reviews: (a) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253–1264. (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (c) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 201–204.

(27) Several terms such as C−H bond activation, C−H bond functionalization, cross-dehalogenative coupling, or catalytic direct arylation have been used to identify the coupling of an aryl halide or pseudohalide with a simple arene being the former two are the most prevalent in the literature. See ref 26b. See also: (a) Bringmann, G.; Heubes, M.; Breuning, M.; Göbel, L.; Ochse, M.; Schöner, B.; Schupp, O. *J. Org. Chem.* **2000**, *65*, 722–728. (b) Harayama, T.; Akiyama, T.; Nakano, Y.; Shibaike, K.; Akamatsu, H.; Hori, A.; Abe, H.; Takeuchi, Y. *Synthesis* **2002**, 237–241. (c) Daugulis, O.; Hien-Quang Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074–1086.

(28) Initial results on the employment of the direct arylation of arenes under Mizoroki−Heck conditions to prepare pyrazolophenanthridines are reported in ref 18e.

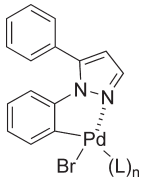


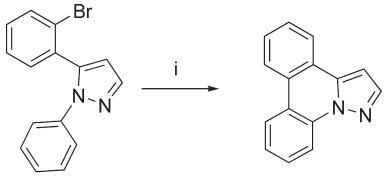
FIGURE 3. Possible intermediate from **2r**.

9−13). Concerning the regioselectivity of the coupling it is worth mentioning that unsymmetrically substituted diarylpyrazoles **2h** and **2n** afforded respectively tetracyclic derivatives **1d** and **1j** as the only isomers. On the other hand, when pyrazole **2r** was submitted to the same coupling conditions only unreacted substrate was obtained along with traces of the dehalogenated diarylpyrazole derivative **2a**. Similar results were obtained from other pyrazoles bearing the haloaryl moiety attached to the N-1 position (entries 14−16). An explanation for this behavior should be based on the donating nature of the pyrazole N-1 atom, which could deactivate the C_{aryl}−Br bond for oxidative addition. In addition, a relatively stable palladacycle probably formed by chelation with pyrazole N-2 nitrogen (Figure 3) that would hinder an effective palladation of the C-5 arene moiety by an electrophilic substitution-type process.[29] This proposal is in accordance with the above-mentioned positional effects and previous reports on the need for carbonyl groups ortho to the haloarene coupling partner.[27] It seems that the role of the pyrazol C-5 carbon is similar to that of a carbonyl group, thus activating the haloaryl moiety for the initial oxidative addition step. Finally, the need for phase transfer catalyst TBAB is probably related to the stabilization of palladium nanoparticles, possible active species in this kind of coupling.[26]

So, we can conclude that although care must be taken on choosing the appropriate brominated substrate, the direct catalytic arylation via the C−H activation approach is suitable for preparing the pyrazolo[1,5-*f*]phenanthridine framework in view of the efficiency and complete regioselectivity of this intramolecular biaryl bond formation.

4. Synthesis of the Pyrazolo[1,5-*f*]phenanthridine Framework by Heterogeneous Catalytic Direct Arylation. Several disadvantages often associated with homogeneous catalysis involve the difficulty of recycling the transition metal catalyst and, consequently, the loss of expensive metal, and the problems arising from the removal of potentially harmful metal traces from the final products. To circumvent these problems the immobilization of the catalyst onto a support is an appealing option that facilitates not only the isolation of the desired product by simple filtration, but also the recycling of the catalyst, thus providing a more sustainable process.[30] On the basis of the good results obtained in the homogeneous version, we decided to explore the same coupling-type using a polymer-supported palladium catalyst. We chose commercially available FibreCat 1001, FibreCat 1000-D7, and

TABLE 3. Selected Assays for the Heterogeneously Catalyzed Direct Arylation of Diarylpyrazol 2e



2e **1a**

entry	reaction conditions[a,b]	**1a** (%)[c]
1	10 mol % Pd/C, KOAc, NMP, 110 °C, 1 d	−[d]
2	10 mol % FC 1026, K_2CO_3, DMF, 110 °C, 1 d	−[d]
3	10 mol % FC 1001, Cs_2CO_3, toluene, 110 °C, 3 d	20
4	10 mol % FC 1001, K_2CO_3, DMF, 110 °C, 1 d	35
5	10 mol % FC 1001, K_2CO_3, DMF, 110 °C, 3 d	50
6	10 mol % FC 1000-D7, K_2CO_3, DMF, 110 °C, 1 d	40
7	10 mol % FC 1000-D7, K_2CO_3, DMF, 110 °C, 3 d	53
8	10 mol % $Pd(OAc)_2$, K_2CO_3, LiCl, $^nBu_4NBr$, DMF 110 °C,	60

[a]Reactions were carried out in a sealed tube. [b]The disclosed proportion of FC (%) refers to the relative amount of Pd metal from FC catalyst. [c]Isolated yield of chromatographically pure compound. [d]Starting material was recovered unchanged.

FibreCat 1026[31,32] due to our experience with the arylation of ketone enolates employing these catalysts,[33] and their fibrous nature that enables an ease of handling and good mechanical properties among other advantages.

As shown in Table 3, neither FC 1026 nor Pd/C, another typically employed heterogeneous system,[34] catalyzed the desired intramolecular coupling. Nevertheless, tetracycle **1a** was obtained by using FC 1001 and FC 1000-D7 catalysts (entries 5 and 7, respectively). In comparison with the aforementioned homogeneous catalytic system, both polymer-supported catalysts presented somewhat lower activities, a feature already observed in other C−C bond-forming reactions.[30] In fact, conversion rates did not match those obtained by the homogeneous system even by prolonging the reaction times.[35]

Accordingly, the optimized conditions from Table 3 (entry 7) were applied to a number of brominated derivatives **2** to provide a series of the corresponding pyrazolophenanthridine **1** with the results displayed in Table 4. The influence of the substituents of the aryl rings on the reaction outcome was identical with that observed in the homogeneous reaction. So, electron-withdrawing groups in the C-5 aryl ring

(29) Although the mechanism of the second step of the direct arylation is strongly dependent on several factors like the substrate, transition metal, base, solvent, and ligand, the first step is proposed to occur via oxidative addition of the transition metal into the aryl halide. This proposal is supported by the isolation of traces of the debrominated derivative.

(30) For a review about the use of heterogeneous palladium catalysts in C−C coupling reactions, see: Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133–173.

(31) The FibreCat 1000 series is commercialized by Johnson Matthey Chemicals. Futher information about FibreCat catalysts, including their application in Suzuki−Miyaura and Mizoroki−Heck coupling reactions, can be found at http://www.chemicals.matthey.com.

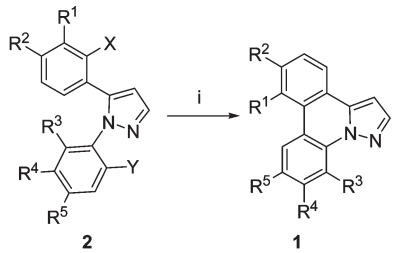
(32) Applications of this type of heterogeneous catalyst are reported in: (a) Colacot, T. J.; Gore, E. S.; Kuber, A. *Organometallics* **2002**, *21*, 3301–3304. (b) Colacot, T. J. *Top. Catal.* **2008**, *48*, 91–98. (c) Colacot, T. J.; Carole, W. A.; Neide, B. A.; Harad, A. *Organometallics* **2008**, *27*, 5605–4611.

(33) (a) Churruca, F.; SanMartin, R.; Carril, M.; Tellitu, I.; Domínguez, E. *Tetrahedron* **2004**, *60*, 2393–2408. (b) Churruca, F.; SanMartin, R.; Tellitu, I.; Dominguez, E. *Eur. J. Org. Chem.* **2005**, 2481–2490.

(34) The use of palladium supported on activated charcoal in cross-coupling reactions is described in: (a) Felpin, F.-X.; Fouquet, E.; Zakri, C. *Adv. Synth. Catal.* **2009**, *351*, 649–655. (b) Felpin, F.-X.; Fouquet, E.; Zakri, C. *Adv. Synth. Catal.* **2008**, *350*, 2559–2565. (c) Felpin, F.-X.; Ayad, T.; Mitra, S. *Eur. J. Org. Chem.* **2006**, 2679–2690. (d) Seki, M. *Synthesis* **2006**, 2975–2992.

(35) Reaction times longer than 3 days caused no improvement on the conversions.

TABLE 4. Synthesis of Pyrazolophenanthridines 1 by Direct Arylation Catalyzed by Heterogeneous FC 1000-D7



i. 10% FC 1000-D7, K_2CO_2, DMF, 110ºC, sealed tube

entry	R^1	R^2	R^3	R^4	R^5	X	Y	2	1 (%)[a]
1	H	H	H	H	H	Br	H	**2e**	**1a** (55)
2	H	H	H	H	OMe	Br	H	**2j**	**1f** (46)
3	H	H	Et	H	^{t}Bu	Br	H	**2k**	**1e** (45)
4	H	H	H	H	CF_3	Br	H	**2l**	**1h** (30)
5	H	F	H	H	H	Br	H	**2m**	**1i** (60)
6	H	F	H	H	OMe	Br	H	**2o**	**1k** (62)
7	H	F	H	H	^{t}Bu	Br	H	**2p**	**1*l*** (45)
8	H	F	H	H	CF_3	Br	H	**2q**	**1m** (38)

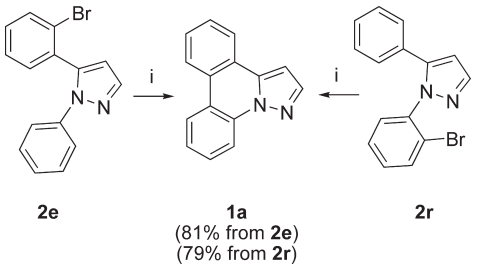
[a] ^{1}H NMR yields. Deoxybenzoin was used as internal standard.

improved the yield of the reaction, while the presence of such functionalities in the aryl moiety at N-1 produced significantly decreased conversions (entry 4). In contrast with the homogeneous version, ^{1}H NMR of the crudes revealed the presence of small (3−5%) amounts of dehalogenated pyrazoles **2**.

Regarding catalyst separation, it is noteworthy that a simple filtration from the reaction mixture provided polymer-supported FC 1000-D7 in quantitative amounts. After an easy treatment,[36] thusly recovered catalyst was reused in a further coupling but offered significantly lower conversions (21−25%) for product **1**. Taking into account that the limit of thermal stability of the FibreCat series is around 120 °C, it is likely that a partial leaching of Pd from polymer support due to the high temperatures and long reaction times provoked such diminished conversion rates.

5. Radical Coupling. Intramolecular aryl radical addition onto an aromatic ring has become a valuable methodology in organic synthesis because it allows mild and usually effective

SCHEME 2. Synthesis of 1a through Radical Coupling



cyclization protocols.[37] In this context, due to the nature of the weak Sn−H bond, tin hydrides have been reagents of choice as initiators of radical reactions. However, organotin derivatives show significant disadvantages such as the high toxicity or the difficult removal of the tin byproducts from the desired end products.[38] Among the several alternatives proposed to overcome these severe drawbacks,[39] the employment of silicon-based reagents has shown the most promise.[40] So, we decided to explore a tin-free biaryl radical coupling methodology for the access to pyrazolo[1,5-*f*]-phenanthridine skeleton employing tris(trimethysilyl)silane (TTMSS) and AIBN.[41] First of all, derivatives **2e** and **2r** bearing the haloaryl moiety at C-5 or N-1 positions respectively were reacted with the TTMSS/AIBN system. To our delight, in both cases tetracycle **1a** was obtained in good yields (Scheme 2).

These preliminary results suggested that this radical protocol might constitute a good alternative to the previously described metal-catalyzed approach to the target system. In contrast to the direct catalytic arylation process, this radical coupling seemed to present no limitations regarding the position of the halogenated counterpart. This peculiarity turned out to be quite convenient for us, since we were particularly interested in finding a reliable complementary method for the cyclization of N-1 bromoarylated intermediates **2r**−**z**. As shown in Table 5, reaction of the latter pyrazoles with the TTMSS/AIBN pair provided a series of pyrazolophenanthrinides and delimited the scope of the methodology.

Indeed, the coupling was successfully accomplished regardless of the electronic nature of the substituents. However, conversely to the previous described catalytic direct arylation coupling, in the radical protocol, when the C-5 aryl ring was unsymmetrically substituted the two possible isomers were obtained in identical yield reflecting the lack of regioselectivity of this process (Table 5, entries 3 and 6). The results of this environmentally safer protocol were compared to those obtained by the system Bu_3SnH/AIBN (Table 5, entries 2, 4, and 5). Considering the comparable yields, the lack of organotin traces in the final products, and other safety issues, we clearly opted for the above silicon-based

(36) After each reaction, the recovered catalyst was successively washed with aqueous 5% HCl, 10% Na_2CO_3, H_2O, THF, and a saturated solution of NaCl in CH_3CN. For more details see ref 33a. Unfortunately, ICP analysis of the filtrate after the initial filtration revealed the presence of a significant amount (>25%) of leached Pd. For a related work on the leaching of commercially available microencapsulated PdEnCat heterogeneous catalysts, see: Broadwater, S. J.; McQuade, D. T. *J. Org. Chem.* **2006**, *71*, 2131–2134.

(37) (a) Narasimhan, N. S.; Aidhhen, I. S. *Tetrahedron Lett.* **1988**, *29*, 2987–2988. (b) Lauk, U.; Dürst, D.; Fisher, W. *Tetrahedron Lett.* **1991**, *32*, 65–68. (c) Estévez, J. C.; Villaverde, M. C.; Estévez, R. J.; Castedo, L. *Tetrahedron* **1993**, *49*, 2787–2790. (d) Okita, T.; Isobe, M. *Tetrahedron* **1994**, *50*, 11143–11152. (e) Estévez, J. C.; Villaverde, M. C.; Estévez, R. J.; Castedo, L. *Tetrahedron* **1994**, *50*, 2107–2114. (f) Comins, D. L.; Hong, H.; Jianhua, G. *Tetrahedron Lett.* **1994**, *35*, 5331–5334. (g) Suzuki, H.; Aoyagi, S.; Kibayashi, C. T. *Tetrahedron Lett.* **1995**, *36*, 5331–5334. (h) Rosa, A. M.; Lob, A. M.; Branco, P. S.; Prabhakar, S.; Sá-da-Costa, M. *Tetrahedron* **1997**, *53*, 299–306. (i) Couture, A.; Deniau, E.; Grandclaudon, P.; Lebrun, S. *Synlett* **1997**, 1475–1477. (j) Ho, T. C. T.; Jones, K. *Tetrahedron* **1997**, *53*, 8287–8294. (k) Comins, D. L.; Thakker, P. M.; Baevsky, M. F.; Badawi, M. M. *Tetrahedron* **1997**, *53*, 16327–16340. (l) Nakanishi, T.; Suzuki, M.; Mashiba, A.; Ishikawa, K.; Yokotsuka, T. *J. Org. Chem.* **1998**, *63*, 4235–4239. (m) Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C. *J. Org. Chem.* **1998**, *63*, 3128–3132.

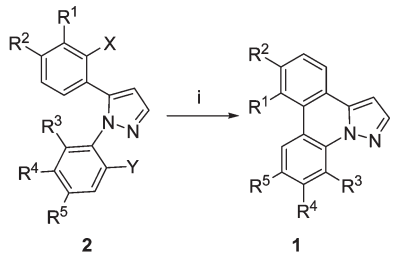
(38) Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3072–3082.

(39) Sibi, M. P.; Yang, Y.-H.; Lee, S. *Org. Lett.* **2008**, *10*, 5349−5352 and references cited therein.

(40) Chatgilialoglu, C. *Organosilanes in Radical Chemistry*; Wiley: Chichester, UK, 2004.

(41) For some examples about the employment of the TTMSS/AIBN system in radical reactions see: (a) Martínez-Barrasa, V.; García de Viedma, A.; Burgos, C.; Alvarez-Builla, J. *Org. Lett.* **2000**, *2*, 3933–3935. (b) Zhang, W.; Pugh, G. *Tetrahedron* **2003**, *59*, 3009–3018. (c) Allin, S. M.; Bowman, W. R.; Karim, R.; Rahman, S. S. *Tetrahedron* **2006**, *62*, 4306–4316.

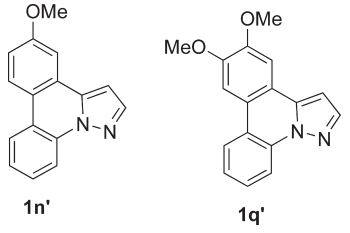
TABLE 5. Synthesis of Pyrazolophenanthridines 1 through Radical Coupling



i. TTMSS, AIBN, toluene, reflux

entry	R^1	R^2	R^3	R^4	R^5	X	Y	2	1 (%)[a]
1	H	H	H	H	H	Br	H	**2e**	**1a** (81)
2	H	H	H	H	H	H	Br	**2r**	**1a** (79) (81)[b]
3	OMe	H	H	H	H	H	Br	**2s**	**1n** (24)[c]
4	H	Me	H	H	H	H	Br	**2t**	**1o** (64) (82)[b]
5	H	OMe	H	H	H	H	Br	**2u**	**1p** (65) (83)[b]
6	OMe	OMe	H	H	H	H	Br	**2v**	**1q** (35)[d]
7	H	H	H	Me	H	H	Br	**2w**	**1r** (76)
8	H	Me	H	Me	H	H	Br	**2x**	**1s** (78)[c]
9	H	H	H	CF_3	H	H	Br	**2y**	**1d** (76)
10	H	Me	H	CF_3	H	H	Br	**2z**	**1t** (74)

[a]Isolated yield of chromatographically pure compound. [b]Isolated yield obtained by reaction with Bu_3SnH/AIBN. [c]Regiosomer **1n′** was obtained in identical yield. [d]Regiosomer **1q′** was obtained in identical yield



procedure as a complementary, safer entry to the target tetracycle.

Conclusions

In this paper we have described the synthesis of a series of pyrazolo[1,5-*f*]phenanthridines starting from readily available acetophenones and arylhydrazines. To accomplish the key intramolecular biaryl bond formation step, two complementary methodologies have been successfully employed: direct catalytic arylation and free-radical $S_{RN}1$ coupling. The former methodology, which avoids the requirement for transmetallating agents, has afforded the relatively complex tetracyclic systems in very good yields and with complete regioselectivities, providing that adequate substitution pattern in the aromatic rings is employed. The use of polymer-supported heterogeneous FibreCat catalyst makes this efficient methodology environmentally safer and cleaner as an effective removal of the catalyst is carried out with a simple filtration. In addition, a radical coupling has been accomplished employing the TTMSS/AIBN pair, which avoids the use of so toxic tin derivatives. In this case, although the process lacks regioselectivity, as expected for a radical method, the outcome of the reaction is not influenced by the nature of the substituents. Therefore, the complementariness of both protocols in this straightforward, high-yielding sequence (50% and 55% overall yield for **1a** by C−H arylation and TTMSS-mediated radical coupling, respectively) has been demonstrated.

Experimental Section

Synthesis of Pyrazolo[1,5-*f*]phenanthridines 1 through Catalytic Direct Arylation. General Procedure. Dry degassed DMF (15 mL) was added to an oven-dried heavy-walled pressure tube charged with $Pd(OAc)_2$ (0.18 mmol), K_2CO_3 (9.04 mmol), LiCl (2.71 mmol), $^nBu_4NBr$ (1.82 mmol), and diarylpyrazole **2** (1.80 mmol) under argon at room temperature. After the tube was closed, it was heated to 110 °C until TLC showed the completion of the reaction (6−24 h). After cooling, the crude was poured onto an ice/water mixture. The aqueous layer was extracted with diethyl ether (3 × 20 mL) and the combined organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The so-obtained residue was purified by flash chromatography on silica gel with EtOAc/hexanes as eluent.

9-Trifluoromethylpyrazolo[1,5-*f*]phenanthridine (1h): 14%, white powder, mp 135−139 °C (MeOH); ^1H NMR (250 MHz, $CDCl_3$) δ 7.01 (1H, d, J = 2.0 Hz), 7.61−7.67 (2H, m), 7.85−7.88 (1H, m), 8.02 (1H, d, J = 2.0 Hz), 8.04−8.08 (1H, m), 8.35−8.38 (1H, m), 8.61 (1H, s), 8.67 (1H, d, J = 8.7 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 99.9, 117.1, 121.0 (q, J = 3.6 Hz), 121.2, 122.9, 124.2 (q, J = 272.2 Hz), 124.3, 124.6, 125.6 (q, J = 3.6 Hz), 125.9, 127.1 (q, J = 32.1 Hz), 128.7, 129.0, 135.8, 137.8, 142.0; IR 1625 cm^{-1}; HRMS calcd for $C_{16}H_9F_3N_2$ 286.0718, found 286.0716.

Fluoropyrazolo[1,5-*f*]phenanthridine (1i): 85%, white powder, mp 135−138 °C (EtOH); ^1H NMR (250 MHz, $CDCl_3$) δ 6.90 (1H, d, J = 2.0 Hz), 7.23−7.30 (1H, m), 7.43−7.50 (1H, m), 7.63−7.69 (1H, m), 7.91−8.02 (3H, m), 8.19−8.22 (1H, m), 8.56−8.57 (1H, m); ^{13}C NMR (63 MHz, $CDCl_3$) δ 98.9, 108.7 (d, J = 23.3 Hz), 116.3 (d, J = 23.3 Hz),116.4, 120.4 (d, J = 5.4 Hz), 123.4, 125.0, 126.5 (d, J = 9.0 Hz), 128.8, 129.9, 134.0, 136.7, 141.1, 162.5 (d, J = 247.7 Hz); IR 1602 cm^{-1}; HRMS calcd for $C_{15}H_9FN_2$ 236.0750, found 236.0751.

10-Trifluoromethyl-6-fluoropyrazolo[1,5-*f*]phenanthridine (1j): 46%, white powder, mp 143−145 °C (EtOH); ^1H NMR (250 MHz, $CDCl_3$) δ 6.91 (1H, d, J = 2.0 Hz), 7.29−7.37 (1H, m), 7.65−7.69 (1H, m), 7.89−7.94 (1H, m), 7.98 (1H, d, J = 2.0 Hz), 7.97−8.02 (1H, m), 8.25−8.28 (1H, d, J = 8.3 Hz), 8.82 (1H, s); ^{13}C NMR (63 MHz, $CDCl_3$) δ 99.4, 109.1 (d, J = 23.3 Hz), 114.0 (q, J = 3.6 Hz), 117.5 (d, J = 23.3 Hz), 120,9, 121,1 (q, J = 3.6 Hz), 122.8, 123.6 (q, J = 272.9 Hz), 124.1, 126.6 (d, J = 9.0 Hz), 127.5 (d, J = 9.0 Hz), 131.5 (q, J = 34.1 Hz), 133.6, 136.7, 141.6, 162.4 (d, J = 249.5 Hz); IR 1617 cm^{-1}; HRMS calcd for $C_{16}H_8F_4N_2$ 304.0624, found 304.0619.

9-Methoxy-6-fluoropyrazolo[1,5-*f*]phenanthridine (1k): 70%, white powder, mp 187−190 °C (EtOH); ^1H NMR (250 MHz, $CDCl_3$) δ 3.97 (3H, s), 6.90 (1H, d, J = 2.0 Hz), 7.25−7.33 (2H, m), 7.64 (1H, d, J = 2.4 Hz), 7.88−7.94 (1H, m), 7.93 (1H, d, J = 2.4 Hz), 7.99−8.05 (1H, m), 8.49 (1H, d, J = 9.1 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 55.7, 98.6, 106.5, 108.7 (d, J = 23.3 Hz), 116.4 (d, J = 23.3 Hz), 117.5, 117.7, 120.8, 121.5, 126.6 (d, J = 9.0 Hz), 128.6 (d, J = 9.0 Hz), 136.0, 140.5, 157.0, 162.4 (d, J = 247.7 Hz); IR 1617 cm^{-1}; HRMS calcd for $C_{16}H_{11}FN_2O$ 266.0855, found 266.0865.

9-*terc*-Butyl-6-fluoropyrazolo[1,5-*f*]phenanthridine (1*l*): 77%, white powder, mp 166−169 °C (EtOH); ^1H NMR (250 MHz, $CDCl_3$) δ 1.47 (9H, s), 6.87 (1H, d, J = 2.4 Hz), 7.20−7.27 (1H, m), 7.73 (1H, dd, J = 8.7, 2.0 Hz), 7.93−8.00 (3H, m), 8.21 (1H, d, J = 1.6 Hz), 8.47 (1H, d, J = 8.7 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 31.4, 34.9, 98.6, 108.5 (d, J = 23.3 Hz), 116.0 (d, J = 23.3 Hz), 116.1, 119.4, 119.8 (d, J = 3.6 Hz), 120.5, 126.5 (d,

J = 9.0 Hz), 127.7, 129.1 (d, J = 9.0 Hz), 132.0, 136.5, 140.8, 147.9, 162.4 (d, J = 245.9 Hz); IR 1619 cm^{-1}; HRMS calcd for $C_{19}H_{17}FN_2$ 292.1376, found 292.1368.

9-Trifluoromethyl-6-fluoropyrazolo[1,5-*f*]phenanthridine (1m): 50%, white powder. mp 138−141 °C (EtOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.99 (1H, d, J = 2.0 Hz), 7.35−7.42 (1H, m), 7.92 (1H, dd, J = 8.7, 1.6 Hz), 8.02−8.13 (3H, m), 8.53 (1H, s), 8.71 (1H, d, J = 8.7 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 99.6, 109.0 (d, J = 23.3 Hz), 117.2, 117.3 (d, J = 23.3 Hz), 120.3 (d, J = 3.6 Hz), 121.0 (q, J = 3.6 Hz), 126.3, 126.7 (d, J = 9.0 Hz), 127.9 (d, J = 9.0 Hz), 135.8, 137.2, 142.1, 162.6 (d, J = 249.5 Hz); IR 1612 cm^{-1}; HRMS calcd for $C_{16}H_8F_4N_2$ 304.0624, found 304.0622.

Synthesis of Pyrazolo[1,5-*f*]phenanthridines 1 through Heterogeneous Catalytic Direct Arylation. General Procedure. Dry degassed DMF (6 mL) was added to an oven-dried reaction flask charged with 1,5-diarylpyrazol **2** (0.3 mmol) K_2CO_3 (1.7 mmol), and FibreCat 1000-D7 (0.03 mmol of Pd) at room temperature under argon. The stirred suspension was heated to 110 °C for 3 days. After cooling, the mixture was diluted with CH_2Cl_2, (30 mL) and filtered. The solvent was evaporated under reduced pressure and the so-obtained residue was purified by flash chromatography on silica gel with EtOAc/hexanes as eluent.

Synthesis of Pyrazolo[1,5-*f*]phenanthridines 1 through Radical Coupling. General procedure. A solution of TTMSS (0.2 mmol) and AIBN (0.5 mmol) in dry degassed toluene (4.5 mL) was added dropwise to a solution of 1,5-diarylpyrazole **2** (0.5 mmol) in the same solvent (6 mL). The mixture was heated at reflux for 7 h. After cooling, the solvent was evaporated under reduced pressure and the so-obtained residue was purified by flash chromatography on silica gel with EtOAc/hexanes as eluent.

5-Methoxypyrazolo[1,5-*f*]phenanthridine (1n): 24%, white needles, mp 111−114 °C (MeOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.97 (3H, s), 6.96 (1H, d, J = 1.6 Hz), 7.19 (1H, dd, J = 8.7, 2.4 Hz), 7.44−7.50 (2H, m), 7.57−7.63 (1H, m), 7.99 (1H, d, J = 1.6 Hz), 8.26−8.30 (2H, m), 8.56−8.59 (1H, m); ^{13}C NMR (63 MHz, $CDCl_3$) δ 55.5, 99.2, 106.4, 116.2, 116.9, 120,4. 121.3, 122.8, 124.4, 125.0, 125.2, 128.1, 133.0, 137.2, 140.8, 159.4; IR 1619 cm^{-1}; HRMS calcd for $C_{16}H_{12}N_2O$ 248.0950, found 248.0944.

7-Methoxypyrazolo[1,5-*f*]phenanthridine (1n′): 24%, white needles, mp 125−127 °C (MeOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.08 (3H, s), 6.96 (1H, d, J = 2.0 Hz), 7.08−7.11 (1H, m), 7.43−7.52 (2H, m), 7.61−7.72 (2H, m), 7.98 (1H, d, J = 2.0 Hz), 8.64−8.67 (1H, m), 9.37−9.41 (1H, m); ^{13}C NMR (63 MHz, $CDCl_3$) δ 55.7, 99.4, 110.4, 115.6, 116.6, 117.0, 121.2, 124.8, 125.9, 128.5, 129.3, 133.8, 137.2, 140.9, 158.4; IR 1602 cm^{-1}; HRMS calcd for $C_{16}H_{12}N_2O$ 248.0950, found 248.0962.

6-Methylpyrazolo[1,5-*f*]phenanthridine (1o): 64%, yellowish needles, mp 103−106 °C (MeOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.52 (3H, s), 6.91 (1H, d, J = 2.0 Hz), 7.30−7.33 (1H, m), 7.41−7.48 (1H, m), 7.60−7.67 (1H, m), 7.85 (1H, d, J = 7.9 Hz), 8.00 (1H, d, J = 2.0 Hz), 8.04 (1H, s), 8.27−8.31 (1H, m), 8.58 (1H, dd, J = 1.2, 8.3 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.8, 98.6, 116.1, 121.0, 121.4, 122.6, 123.2, 124.1, 124.7, 126.5, 128.9, 129.2, 133.8, 137.3, 138.0, 140.8; IR 1619 cm^{-1}; HRMS calcd for $C_{16}H_{12}N_2$ 232.1000, found 232.1006.

6-Methoxypyrazolo[1,5-*f*]phenanthridine (1p): 64%, white needles, mp 124−126 °C (MeOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.94 (3H, s), 6.82 (1H, d, J = 2.0 Hz), 7.09 (1H, dd, J 8.7, 2.4 Hz), 7.40−7.46 (1H, m), 7.59−7.65 (1H, m), 7.66 (1H, d, J = = 2.4 Hz), 7.88 (1H, d, J = 8.7 Hz), 7.94 (1H, d, J = 2.0 Hz), 8.21−8.24 (1H, m), 8.53−8.56 (1H, m); ^{13}C NMR (63 MHz, $CDCl_3$) δ 55.4, 98.0, 105.5, 116.2, 116.3, 117.8, 120.9, 123.2, 124.7, 125.8, 128.3, 129.2, 134.1, 137.3, 141.0, 159.5; IR 1621 cm^{-1}; HRMS calcd for $C_{16}H_{12}N_2O$ 248.0950, found 248.0939.

5,6-Dimethoxypyrazolo[1,5-*f*]phenanthridine (1q): 35%, white needles, mp 168−171 °C (MeOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.98 (3H, s), 4.00 (3H, s), 6.74 (1H, d, J = 1.6 Hz), 7.18 (1H, s), 7.36−7.42 (1H, m), 7.50 (1H, s), 7.51−7.57 (1H, m), 7.92 (1H, d, J = 1.6 Hz), 8.06−8.09 (1H, m), 8.47−8.51 (1H, m); ^{13}C NMR (63 MHz, $CDCl_3$) δ 55.8, 55.9, 97.7, 103.7, 104.9 116.1, 117.8, 120.5 120.8, 122.6, 124.6, 128.0, 133.0, 137.0, 140.7, 149.6; IR 1617 cm^{-1}; HRMS calcd for $C_{17}H_{14}N_2O_2$ 278.1055, found 278.1055.

6,7-Dimethoxypyrazolo[1,5-*f*]phenanthridine (1q′): 35%, white needles, mp 134−136 °C (MeOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.95 (3H, s), 4.00 (3H, s), 6.86 (1H, d, J = 2.0 Hz), 7.22 (1H, d, J = 8.7 Hz), 7.48 (1H, tdd, J = 8.3, 1.2 Hz), 7.65 (1H, tdd, J = 8.3, 1.2 Hz), 7.82 (1H, d, J = 8.7 Hz), 7.93 (1H, d, J = 2.0 Hz), 8.62 (1H, dd, J = 8.3, 1.2 Hz), 9.38 (1H, dd, J = 8.3, 1.2 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 56.2, 59.9, 98.3, 113.1, 115.9, 118.9, 120.6, 120.8, 121.2, 125.1, 128.5, 129.1, 134.1, 137.2, 141.0, 147.4, 153.1; IR 1612 cm^{-1}; HRMS calcd for $C_{17}H_{14}N_2O_2$ 278.1055, found 278.1058.

10-Methylpyrazolo[1,5-*f*]phenanthridine (1r): 76%, white powder, mp 87−90 °C (MeOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.52 (3H, s), 6.92 (1H, d, J = 2.0 Hz), 7.19−7.22 (1H, m), 7.44−7.53 (2H, m), 7.94−7.98 (1H, m), 7.96 (1H, d, J = 2.0 Hz), 8.12 (1H, d, J = 8.3 Hz), 8.19−8.23 (1H, m), 8.35 (1H, s); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.6, 99.0, 116.2, 118.7, 122.4, 123.1, 123.4, 124.2, 126.2, 126.8, 127.5, 128.0, 133.7, 137.4, 139.6, 140.8; IR 1625 cm^{-1}; HRMS calcd for $C_{16}H_{12}N_2$ 232.1000, found 232.1006.

6,10-Dimethylpyrazolo[1,5-*f*]phenanthridine (1s): 78%, white powder, mp 120−123 °C (MeOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.48 (3H, s), 2.52 (3H, s), 6.86 (1H, d, J = 2.4 Hz), 7.20 (1H, dd, J = 8.3, 1.2 Hz), 7.24−7.27 (1H, m), 7.81 (1H, d, J = 7.9 Hz), 7.94 (1H, d, J = 2.0 Hz), 7.97 (1H, s), 8.10 (1H, d, J = 8.2 Hz), 8.33 (1H, s); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.5, 21.8, 98.5, 116.1, 118.6, 121.0, 122.3, 123.0, 124.1, 126.0, 126.7, 128.7, 133.7, 137.5, 137.9, 139.4, 140.7; IR 1619 cm^{-1}; HRMS calcd for $C_{17}H_{14}N_2$ 246.1157, found 246.1147.

6-Methyl-10-trifluoromethylpyrazolo[1,5-*f*]phenanthridine (1t): 74% white powder, mp 195−199 °C (MeOH); ^{1}H NMR: (250 MHz, $CDCl_3$) δ 2.57 (3H, s), 6.94 (1H, d, J = 2.0 Hz), 7.43−7.46 (1H, m), 7.66−7.69 (1H, m), 7.92−7.95 (1H, m), 7.99 (1H, d, J = 2.0 Hz), 8.12 (1H, s), 8.42−8.45 (1H, m), 8.54 (1H, s); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.9, 99.2, 113.9, 121.0 (q, J = 3.6 Hz), 122.1, 123.1, 123.7, 123.8 (q, J = 271.1 Hz), 124.0, 124.4, 125.6, 130.6, 130.7 (q, J = 32.3 Hz), 133.6, 137.6, 138.6, 141.5; IR 1619 cm^{-1}; HRMS calcd for $C_{17}H_{11}F_3N_2$ 300.0874, found 300.0874.

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Supporting Information Available: Full experimental details, spectral data of all diarylpyrazoles and coupling products, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.