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Toward Safer Methodologies for the Synthesis of Polyheterocyclic Systems: Intramolecular Arylation of Arenes under Mizoroki–Heck Reaction Conditions

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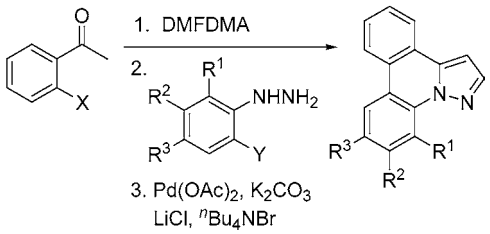
ABSTRACT



A straightforward synthesis of ibudilast-related pyrazolo[1,5-*f*]phenanthridines is accomplished by a tandem amine-exchange/heterocyclization of arylenaminones followed by an intramolecular biaryl coupling of the so-formed diarylpyrazoles. The direct, environmentally convenient ring-closure of the latter pyrazole intermediates, which show a close resemblance to the antiinflammatory drug celecoxib, is efficiently performed under Mizoroki–Heck reaction conditions.

Biaryl coupling methodologies constitute a fundamental tool in modern organic synthesis. Despite the number and high efficiency of widespread known cross-coupling procedures used in this field (Stille, Negishi, Suzuki−Miyaura, or Hiyama),[1] few examples of palladium-catalyzed direct arylation of aryl halides with arenes have been reported so far.[2] Indeed, Heck-type conditions applied to the arylation of arenes avoid classical transmetalation steps, thus making unnecessary the sometimes troublesome preparation[1a−c,3] and use of toxic[4] transmetallating agents. However, such advantageous arylation methodology, relatively well established in the heterocyclic fashion,[5] has been scarcely developed in arene chemistry.[2,6]

Toward a sustainable chemistry based on efficient waste effluent minimization procedures, the substitution of polluting processes that require stoichiometric amounts of metallic

(1) (a) *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds; Wiley: Bath, UK, 1998. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (c) De Frutos, O.; Atienza, C.; Echavarren, A. M. *Eur. J. Org. Chem.* **2001**, 163−171. (d) Xu, J.; Burton, D. J. *Tetrahedron Lett.* **2002**, *43*, 2877−2879.

(2) (a) Tsuji, J. *Transition Metal Reagents and Catalysts. Innovations in Organic Synthesis*; Wiley: Bath, UK, 2000, pp 94−95. (b) Kawamura, Y.; Satoh, T.; Miura, M.; Nomura, M. *Chem. Lett.* **1999**, 961−962. (c) Kametani, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2000**, *41*, 2655−2658. (d) Bringmann, G.; Heubes, M.; Breuning, M.; Göbel, L.; Ochse, M.; Schöner, B.; Schupp, O. *J. Org. Chem.* **2000**, *65*, 722−728.

(3) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73−78.

(4) (a) Dumartin, G.; Fouquet, E.; Pereyre, M.; Rabtier, M. *Appl. Organomet. Chem.* **1995**, *9*, 591−595. See also ref 6b, p 1404 and ref 13.

(5) Interesting examples of the so-called heteroaryl Heck reaction can be found in: (a) *Palladium in Heterocyclic Chemistry. A Guide for the Synthetic Chemist*; Li, J. J., Gribble, G. W., Eds; Elsevier: Oxford, UK, 2000. See also: (b) Penalva, V.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Appl. Catal.* **1999**, *182*, 399−405. (c) McClure, M. S.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M. H.; Roschangar, F. *Org. Lett.* **2001**, *3*, 1677−1680.

(6) (a) de Meijere, A.; Song, Z.-Z.; Lansky, A.; Hyuda, S.; Rauch, K.; Noltemeyer, M.; König, B.; Knieriem, B. *Eur. J. Org. Chem.* **1998**, 2289−2299. (b) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359−1469 and references cited therein.

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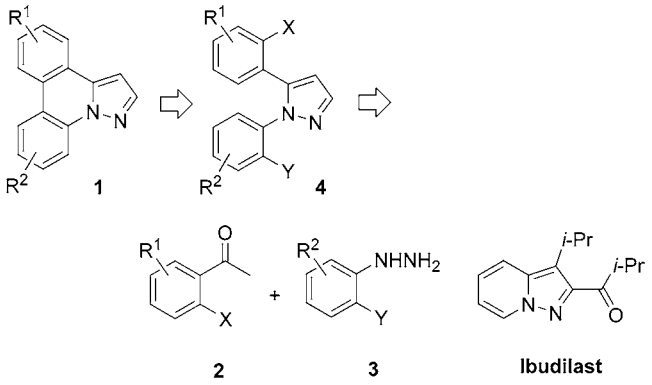
reagents by catalytic reactions has become a common trend in synthetic organic chemistry.[7] In this context, we wish to report a simple, straightforward strategy for the synthesis of a relatively complex tetracyclic system, pyrazolo[1,5-*f*]-phenanthridine **1**, using as the key step an intramolecular Heck-type coupling of arylbromide with arene moieties.

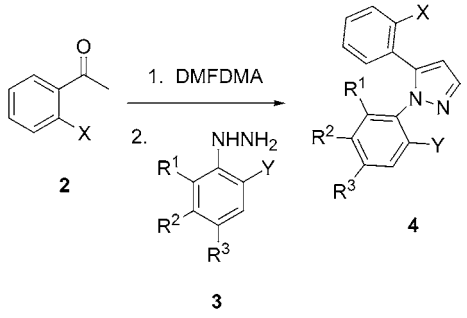
Phenanthridine fused heterocycles have attracted much attention mainly due to their electroluminescent properties, which make them a type of material suitable for discotic liquid crystals, single and multilayer devices, and organic diodes.[8a,b] In addition, the use of such compounds as potent antiviral agents and their interaction with DNA base pairs has been recently reported.[8c,d]

Interestingly, these prominent features have been excelled by the relevancy of the applications of pyrazolo[1,5]pyridines, pyrazolo[1,5](iso)quinolines, and even pyrazolo[1,5]-phenanthridines. In fact, besides the phosphodiesterase inhibitor ibudilast, a prostacyclin-mediated vasodilator and antiplatelet drug of choice for the treatment of diseases involving blood cells and vascular wall disorders,[9] other common uses of the above cited pyrazoloheterocycles include virucides for herpes virus infection[10a,b] or drugs for the treatment of Alzheimer's and Parkinson's diseases and dementia.[10c−e]



Our synthetic approach to the pyrazolo[1,5-*f*]phenanthridine tetracyclic system **1** started from commercially available acetophenones **2** and arylhydrazines **3**. Aminomethylenation of derivatives **2** was performed by using the Vilsmeier−Haack-type reagent dimethylformamide dimethyl acetal (DMFDMA), and the so-formed enaminoketones were reacted with hydrazines **3**, affording diarylpyrazoles **4** (Table 1), presumably by a tandem amine exchange/heterocyclization.[11]

Table 1. Prepared 1,5-Diarylpyrazoles **4**



entry	X	Y	R^1	R^2	R^3	**4** (%)[a]
1	Br	H	H	H	H	**4a** (92)
2	Br	H	Me	H	H	**4b** (89)
3	Br	H	H	H	Me	**4c** (88)
4	Br	H	Et	H	H	**4d** (88)
5	Br	H	H	H	^{t}Bu	**4e** (95)
6	Br	H	H	H	OMe	**4f** (89)
7	Br	H	H	CF_3	H	**4g** (91)
8	Br	Br	H	H	H	**4h** (87)
9	H	Br	H	H	H	**4i** (90)

[a] Isolated yield.

The key step, the intramolecular *o*,*o*′-biaryl coupling of diaryl derivatives **4**, was initially attempted by a well-established methodology previously used by our group in the synthesis of phenanthroheterocycles, the Stille−Kelly reaction.[12] Such ring closure was effected on *o*,*o*′-dibromo-derivative **4h**, thus providing target pyrazolo[1,5-*f*]phenanthridine **1a** with good yield (76%, Method A in Scheme 1).

Despite the excellent result for such a direct coupling, which features a clear step economy as no isolation of

(7) (a) Mukhopadhyay, S.; Rothenberg, G.; Gitis, D.; Sasson, Y. *J. Org. Chem.* **2000**, *65*, 3107−3110 and references therein. (b) Macquarrie, D. J.; Gotov, B.; Toma, S. *Platinum Metals Rev.* **2001**, *45*, 102−110.

(8) (a) Nakatsuka, M.; Shimamura, T. (Mitsui Chemical Industry Co.) JP2000311787, 2000 (*Chem. Abstr.* **2000**, *133*, 357083). (b) 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. (c) Casu, M.; Puligheddu, S.; Saba, G.; Marincola, F. C.; Orellana, G.; Lai, A. *J. Biomol. Struct. Dyn.* **1997**, *15*, 37−43. (d) Almerico, A. M.; Mingoia, F.; Diana, P.; Barraja, P.; Montalbano, A.; Lauria, A.; Loddo, R.; Sanna, L.; Delpiano, D.; Setzu, M. G.; Musiu, Ch. *Eur. J. Med. Chem.* **2002**, *37*, 3−10.

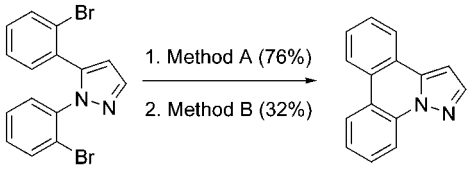
(9) (a) Kishi, Y.; Ohta, S.; Kasuya, N.; Sakita, S.; Ashikaga, T.; Isobe, M. *Cardiovasc. Drug Rev.* **2001**, *19*, 215−225. For recent applications of ibudilast in the therapy of other vascular wall disorders, such as erectile dysfunction and premature ejaculation, female arousal and ovulation disorders, and bronchial asthma, inter alia, see: (b) Palmer, S.; McKenna, S.; Tepper, M.; Eshkol, A.; MacNamee, M. C. US2002103106, 2002 (*Chem. Abstr.* **2002**, *137*, 135500). (c) Wilson, L. F.; Doherty, P. C.; Place, V. A.; Smith, W. L.; Abdel-Hamid, A. A. I. A. US20020037828, 2002 (*Chem. Abstr.* **2002**, *136*, 284433). (d) Takuma, K.; Lee, E.; Enomoto, R.; Mori, K.; Baba, A.; Matsuda, T. *Br. J. Pharmacol.* **2001**, *133*, 841−848. (e) Rile, G.; Yatomi, Y.; Qi, R.; Satoh, K.; Ozaki, Y. *Thromb. Res.* **2001**, *102*, 239−246.

(10) For pyrazolo[1,5-*a*]pyridines as antiviral agents, see: (a) Gudmundsson, K.; Johns, B. A. (Smi*thkl*ine Beecham Co.) WO0288124, 2002 (C. A. 137: 337887). (b) Alberti, M. J.; Chamberlain, S. D.; Chueng, M.; Gudmundsson, K.; Harris, P. A.; Johns, B. A.; Jung, D. K.; Peel, M. R.; Stanford, J. B. (Smithkline Beecham Co.) WO0278700, 2002 (*Chem. Abstr.* **2002**, *137*, 294953). Pyrazolopyridines, pyrazoloquinolines, and pyrazoloisoquinolines are reported as dopamine D4 and adenosine A1−A2 receptor antagonists or amyloidosis modulating agents. See for example: (c) Akahane, A.; Tanaka, A.; Minagawa, M.; Itani, H.; Ohtake, H. (Fujisawa Pharmaceutical Co.) WO0218382, 2002 (*Chem. Abstr.* **2002**, *136*, 232298). (d) Reiner, P. B.; Lam, F. C.-L. US20020037843, 2002 (*Chem. Abstr.* **2002**, *136*, 257275). See also: (e) Bettinetti, L.; Schlotter, K.; Huebner, H.; Gmeiner, P. *J. Med. Chem.* **2002**, *45*, 4594−4597.

(11) The strategy aminomethylenation/amine-exchange/heterocyclization has been previously exploited by our group. Although the mechanism of the tandem amine-exchange/heterocyclization is still unknown, several proposals have been made so far. See: (a) Domínguez, E.; Martínez de Marigorta, E.; Olivera, R.; SanMartin, R. *Synlett* **1995**, 955−956. (b) Olivera, R.; SanMartin, R.; Domínguez, E.; Solans, X.; Urtiaga, M. K.; Arriortua, M. I. *J. Org. Chem.* **2000**, *65*, 6398−6411.

(12) Olivera, R.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Tetrahedron* **2002**, *58*, 3021−3037 and references therein.

Scheme 1



4h **1a**

Method A: Me_6Sn_2, $Pd(PPh_3)_2Cl_2$, dioxane, 150°C, sealed tube

Method B: 10% $Pd(OAc)_2$, PPh_3, Cs_2CO_3, DMF, ↑↓

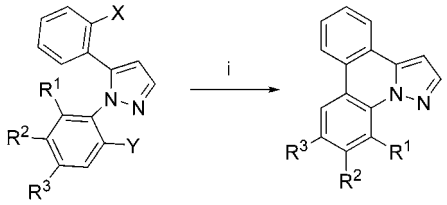
arylstannane intermediates was required, there still remained the problem of the toxicity of the employed hexamethylditin reagent and the trimethyltin bromide generated in the course of the reaction, both in stoichiometric amounts.[12] Furthermore, the complete removal of tin residues from reaction mixtures is still a matter of discussion/investigation, since most of the existent methodologies are highly dependent on the reaction conditions and cannot avoid some contamination, although to a low extent, of these harmful chemicals.[13]

Several procedures for the palladium-catalyzed reductive coupling of aryl halides have been reported in the last several years.[14] Such a coupling method, with a resemblance to the classic Ullmann reaction, has been conducted in its intermolecular fashion, whereas the intramolecular version is still to be developed.[15] However, encouraged by the potential environmental advantages involved, we assayed an array of experimental conditions[14b,c,16] to perform the latter "Ullmann-type" coupling on dibromoderivative **4h**, but only traces of target **1a** and partially debrominated compounds **4a** and **4i** were obtained. Surprisingly, a modification of our recently reported procedure for the palladium-catalyzed α-arylation of deoxybenzoins[17] provided tetracycle **1a**, although in a modest yield (Method B in Scheme 1).

The extension of the Heck reaction to the formation of biaryl bonds has been considered unlikely, since according to the classical mechanistic accounts regarding this process, the first step of the chemical pathway would involve a loss of aromaticity when performed on aromatic rings, and the last step, the *cis*-elimination, cannot be undergone by aromatic substrates.[6b] Nevertheless, new mechanistic proposals have been made,[18] and several examples of the substitution of hydrogen in (hetero)arenes by (hetero)aryl halides under Mizoroki−Heck reaction conditions have been reported,[2,5,6] therefore proving the existence of such a process.

Indeed, as shown in Table 2, when pyrazoles **4a**−**g** were submitted to Heck reaction conditions (10% $Pd(OAc)_2$, K_2CO_3, LiCl, $^nBu_4Br$, DMF, 110°C, sealed tube)[19] pyrazolo[1,5-*f*]phenanthridines **1** were obtained by an intramolecular direct arylation between the aryl halide and arene moieties.

Table 2. Synthesis of Pyrazolophenanthridines **1** by a Palladium-Catalyzed Coupling of Pyrazoles **4**



4 **1**

i: 10% $Pd(OAc)_2$, K_2CO_3, LiCl, $^nBu_4NBr$, DMF, 110°C, sealed tube

entry	X	Y	R^1	R^2	R^3	**1** (%)[a]
1	Br	H	H	H	H	**1a** (60)
2	Br	H	Me	H	H	**1b** (65)
3	Br	H	H	H	Me	**1c** (61)
4	Br	H	Et	H	H	**1d** (65)
5	Br	H	H	H	^{t}Bu	**1e** (62)
6	Br	H	H	H	OMe	**1f** (52)
7	Br	H	H	CF_3	H	**1g** (42)
8	H	Br	H	H	H	

[a] Yield of pure crystallized compound (MeOH).

To establish the influence of the electronic nature of the *N*-aryl substituents on the reaction results, we may establish that the reaction is tolerant of both electron-donating and electron-withdrawing groups attached to the *N*-aryl ring. However, we tentatively propose that, according to the data collected from Table 2, the presence of electron-donating groups promotes a slight activation of the *N*-aryl ring toward the palladation step leading to the key palladacycle-type intermediate.[20]

Although an additional advantage of such a Heck-type approach relies on the fact that only one of the coupling

(13) (a) Parsons, A. *Chem. Br.* **2002**, *38*, 42−44. (b) Savall, B. M.; Powell, N. A.; Roush, W. R. *Org. Lett.* **2001**, *3*, 3057−3060. (c) Newham, J.; Harwood, D.; Lomax, P. W. GB2350356, 2000 (*Chem. Abstr.* **2000**, *134*, 300262). (d) Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3072−3082. (e) Renaud, P.; Lacote, E.; Quaranta, L. *Tetrahedron Lett.* **1998**, *39*, 2123-2126.

(14) (a) Luo, F. T.; Jeevanandam, A.; Basu, M. K. *Tetrahedron Lett.* **1998**, *39*, 7939−7942. (b) Penalva, V.; Hassan, J.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron Lett.* **1998**, *39*, 2559−2560. (c) Boger, D. L.; Goldberg, J.; Anderson, C.-M. *J. Org. Chem.* **1999**, *64*, 2422−2426. (d) Hassan, J.; Hathroubi, C.; Gozzi, C.; Lemaire, M. *Tetrahedron* **2001**, *57*, 7845−7855.

(15) Very few examples of intramolecular reductive coupling of aryl halides with palladium can be found in the literature. See: Hennings, D.; Iwama, T.; Rawal, V. H. *Org. Lett.* **1999**, *1*, 1205−1208.

(16) (a) Hassan, J.; Penalva, V.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron* **1998**, *54*, 13793−13804. (b) Venkatraman, S.; Li, C.-J. *Tetrahedron Lett.* **2000**, *41*, 4831−4834.

(17) Churruca, F.; SanMartin, R.; Tellitu, I.; Dominguez, E. *Org. Lett.* **2002**, *4*, 1591−1594.

(18) New accounts about the critical role of anions and the real structure of the catalytic species in th Heck reaction have ruled out most textbook mechanisms, suggesting new catalytic cycles to be considered. See: Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314−321.

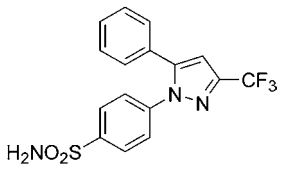
(19) **General Procedure:** Dry degassed DMF (15 mL) was added to an oven-dried heavy-wall pressure tube charged with $Pd(OAc)_2$ (0.18 mmol), K_2CO_3 (9.04 mmol), LiCl (2.71 mmol), $^nBu_4Br$ (1.82 mmol), and diaryl pyrazole **4** (1.80 mmol) under argon at room temperature. After the tube was closed, it was heated to 110 °C for 6−24 h until TLC showed the completion of the reaction. After cooling, the crude was poured onto an ice (5 g)/water (20 mL) mixture. The aqueous layer was extracted with diethyl ether (3 × 20 mL), and the combined organic layers were dried over anhydrous sodium sulfate and evaporated under reduced pressure to give a residue that was purified by flash chromatography on silicagel with 5−20% EtOAc/hexane as eluent.

partners must bear a halogen, care must be taken on choosing the suitable ring. In fact, only unreacted material was obtained from diaryl pyrazole **4i** (Table 2, entry 8), where, unlike substrates **4a**−**g**, the haloaryl moiety is attached to the *N*-1 position of the heterocycle.

The latter result fits in with the behavior observed in previous reports on intramolecular arylations under similar conditions, as the aryl halide moiety requires an *o*-carbonyl group attached to undergo the desired cyclization.[21] In our case the pyrazole C-5 atom plays a similar role to the above-mentioned carbonyl, essentially an electron-withdrawing effect that probably activates its attached coupling partner for the initial oxidative addition to the palladium catalyst. We therefore propose that the failure of the ring-closure from **4i** is in part due to the electron-donating nature of the *N*-1 atom to which the aryl halide moiety is attached. Besides, it also should be considered that after an initial oxidative addition step in **4i**, the so-formed palladium complex could form a stable 5-membered chelate with pyrazole *N*-2 nitrogen, thus preventing palladation with the aryl moiety attached to the C-5 position of the heterocycle.[22]

Another feature of the presented synthetic route to be outlined is the catalytic amount of the palladium salt $Pd(OAc)_2$ employed for the coupling of the aryl halide moiety onto a nonfunctionalized *ortho*-aromatic position, as previous procedures reported in this context often required 0.25−0.5 equiv of the catalysts or even stoichiometric amounts in some cases.[21a,c]

Finally, the relevance of the employed intermediates **4** cannot be underestimated, above all considering their resemblance to the recently marketed nonsteroidal antiinflammatory drug celecoxib.[23]



Celecoxib

To sum up, a three-step, high overall-yielding approach to the pyrazolo[1,5-*f*]phenanthridine framework from commercially available acetophenones and hydrazines is presented, featuring a tandem amine exchange/heterocyclization and an intramolecular palladium-catalyzed ring closure as the key transformations of the synthetic route. The latter arylation is performed under Heck reaction conditions, thus avoiding the use of stoichiometric amounts of transmetallating agents and the isolation of metalated intermediates. Therefore, the reported examples support the fact that the Heck reaction, one of the most versatile and powerful tools for the selective construction of carbon−carbon bonds from olefins, is becoming applicable to the coupling with aromatic rings.

We are presently investigating both the scope of the presented methodology and its extension to the synthesis of other polyheterocyclic systems.

Acknowledgment. This research was supported by the University of the Basque Country (Project UPV 41.310-13656) and the Spanish Ministry of Science and Technology (MCYT BQU2001-0313). Both institutions are gratefully acknowledged. S.H. also thanks the University of the Basque Country for a predoctoral scholarship.

Supporting Information Available: Characterization data for all unknown diarylpyrazoles **4a**−**h** and pyrazolophenanthridines **1b**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Although no detailed mechanism for this type of arylation has been proposed so far, reductive elimination of palladacycle intermediates is usually assumed as the last step of the mechanistic pathway. See ref 2a for more details.

(21) Normally such an aryl halide moiety is part of a benzamide or a benzoate framework. See, for example, refs 2c and 2d. See also: (a) Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1994**, *116*, 1004−1015. (b) Kitamura, M.; Ohmori, K.; Kawase, T.; Suzuki, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1229−1232. (c) Harayama, T.; Akiyama, T.; Nakano, Y.; Shibaike, K.; Akamatsu, H.; Hori, A.; Abe, H.; Takeuchi, Y. *Synthesis* **2002**, 237−241.

(22) Further mechanistic discussions about the role of the pyrazole nucleus and possible chelating effects will be published elsewhere.

(23) Celecoxib has been reported to be a selective cyclo-oxygenase-2 (COX-2) inhibitor, with remarkable antiinflammatory, analgesic, and antipyretic activities associated with a high degree of gastrointestinal safety. Other applications of this drug include the treatment of preterm labor, osteoarthritis and rheumatoid arthritis, inflammatory bowel disease, and duodenal polyposis in familial adenomatous polyposis, or preventing pain after otolaryngologic surgery. 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.; Schweer, 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.