JOC*Note*

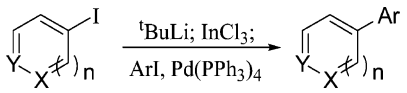
Indium-Mediated Synthesis of Heterobiaryls

Enrique Font-Sanchis, F. Javier Céspedes-Guirao, Ángela Sastre-Santos, and Fernando Fernández-Lázaro*

División de Química Orgánica, Instituto de Bioingeniería, Universidad Miguel Hernández, 03202 Elche, Spain

fdofdez@umh.es

Received December 22, 2006



The palladium-mediated coupling reaction between triorganoindium reagents and organic electrophiles is extended to the synthesis of heteroaromatic compounds. Both electron-rich and electron-poor heterocycles can act as the organic electrophile or as the organoindium derivative.

Compounds with a direct heterocycle−(hetero)cycle linkage are of widespread interest because of their ubiquitous applications. A great variety of such structures display biological activity. Thus, the alkaloid nicotine, the penicillin cloxacillin, the iron-chelating ligand desferrithiocin, the benzodiazepine bromazepam, and the angiotensin II receptor antagonist losartan are only a few examples of natural or synthetic drugs.[1] Other compounds are also used as ligands or dyes for different purposes.[2]

Different coupling procedures have been described to achieve a direct heteroaromatic−(hetero)aromatic linkage. Thus, for example, Stille and Suzuki couplings are useful approaches,[3] although yields are highly dependent on the choice of catalyst, ligands, solvent, and additives in the former.[4] Also, other metal-mediated couplings have been used.[5] However, we have paid attention to the palladium-catalyzed coupling reaction between triorganoindium reagents and organic electrophiles,[6] which is an atom-efficient process characterized by its high reactivity, efficiency, versatility, and chemoselectivity. An additional benefit of this reaction is the apparent low toxicity associated with indium, as opposed to tin, which is a major concern nowadays. In regard to aromatic couplings, this reaction has been confined to couplings in which one or both partners are phenyl or naphthyl rings. Only a few works used a heteroaromatic moiety, i.e., pyridine or thiophene, as the organic electrophile.[7]

Recently, a work has appeared dealing with indium-mediated biaryl formation, in which the preparation of symmetrical biaryls based on pyridine or thiophene is described.[8] Here, we wish to report the extension of this reaction to the one-pot cross-coupling between electron-rich and electron-poor heteroaromatics.

First, we decided to study the influence of the catalyst and the leaving group in the cross-coupling of heteroaromatics. As a reaction model we selected the coupling between tris(thienyl)-indium and a 3-substituted pyridine (Table 1). Tris(thienyl)-indium was prepared starting from commercially available thienyllithium by treatment with indium(III) chloride. Best results were obtained by using a slight excess (ca. 20%) of the electrophile, in accord with Sarandeses' finding that triorganoindium reagents efficiently transfer all three ligands. Entries 1−3 of Table 1 show that the best catalyst is tetrakis-(triphenylphosphine)palladium. Entries 3−5 indicate that the best leaving group is iodine. The low yield obtained with triflate-substituted pyridine is noteworthy. In this case, 2,2′-bisthienyl **2** (see Table 2), obtained by a homocoupling process, was also obtained in 47% yield.

With the previous results in mind, we have examined the coupling of tristhienylindium reagents with (hetero)aromatic electrophiles, obtaining the cross-coupled products in high yield (Table 2, entries 1−3), with the exception of 1-methyl-5-(2-thienyl)pyrazole **4** (entry 4). These results compare favorably

(1) See, for example: (a) Denton, T. T.; Zhang, X.; Cashman, J. R. *J. Med. Chem.* **2005**, *48*, 224. (b) Che, D.; Wegge, T.; Stubbs, M. T.; Seitz, G.; Meier, H.; Methfessel, C. *J. Med. Chem.* **2001**, *44*, 47. (c) Davies, J. R.; Kane, P. D.; Moody, C. J.; Slawin, A. M. Z. *J. Org. Chem.* **2005**, *70*, 5840. (d) Yang, C.-G.; Huang, H.; Jiang, B. *Curr. Org. Chem.* **2004**, *8*, 1691. (e) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1.

(2) (a) Katritzky, A. R.; Qi, M.; Feng, D.; Zhang, G.; Griffith, M. C.; Watson, K. *Org. Lett.* **1999**, *1*, 1189. (b) Nazeeruddin, M. K.; Péchy, P.; Renouard, T.; Zakeeruddin, S. M.; Humphry-Baker, R.; Comte, P.; Liska, P.; Cevey, L.; Costa, E.; Shklover, V.; Spiccia, L.; Deacon, G. B.; Bignozzi, C. A.; Grätzel, M. *J. Am. Chem. Soc.* **2001**, *123*, 1613. (c) Wu, P.-C.; Yu, J.-K.; Song, Y.-H.; Chi, Y.; Chou, P.-T.; Peng, S.-M.; Lee, G.-H. *Organometallics* **2003**, *22*, 4938. (d) Feng, K.; Hsu, F.-L.; Van DerVer, D.; Bota, K.; Bu, X. R. *J. Photochem. Photobiol. A. Chem.* **2004**, *165*, 223. (e) Velusamy, M.; Thomas, K. R. J.; Lin, J. T.; Hsu, Y.-C.; Ho, K.-C. *Org. Lett.* **2005**, *7*, 1899. (f) Bhor, S.; Anilkumar, G.; Tse, M. K.; Klawonn, M.; Döbler, C.; Bitterlich, B.; Grotevendt, A.; Beller, M. *Org. Lett.* **2005**, *7*, 3393. (g) Davis, J. M.; Truong, A.; Hamilton, A. D. *Org. Lett.* **2005**, *7*, 5405. (h) Newkome, G. R.; Patri, A. K.; Holder, E.; Schubert, U. S. *Eur. J. Org. Chem.* **2004**, 235.

(3) See, for example: (a) Echavarren, A. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3962. (b) Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704. (c) Baudoin, O. *Eur. J. Org. Chem.* **2005**, 4223. (d) Bai, L.; Wang, J. X. *Curr. Org. Chem.* **2005**, *9*, 535.

(4) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1132.

(5) See, for example: (a) Venkatraman, S.; Li, C.-J. *Org. Lett.* **1999**, *1*, 1133. (b) Bonnet, V.; Mongin, F.; Trécourt, F.; Breton, G.; Marsais, F.; Knochel, P.; Quéguiner, G. *Synlett* **2002**, *6*, 1008. (c) Gauthier, D. R., Jr.; Szumigala, R. H., Jr.; Dormer, P. G.; Armstrong, J. D., III; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 375. (d) Pierrat, P.; Gros, P.; Fort, Y. *Org. Lett.* **2005**, *7*, 697.

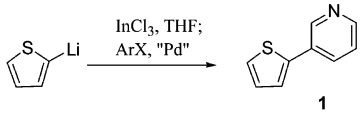
(6) (a) Pérez, I.; Pérez Sestelo, J.; Sarandeses, L. A. *Org. Lett.* **1999**, *1*, 1267. (b) Pérez, I.; Pérez Sestelo, J.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155. (c) Lee, P. H.; Sung, S.-Y.; Lee, K. *Org. Lett.* **2001**, *3*, 3201. (d) Lee, K.; Lee, J.; Lee, P. H. *J. Org. Chem.* **2002**, *67*, 8265. (e) Lehmann, U.; Awasthi, S.; Minehan, T. *Org. Lett.* **2003**, *5*, 2405. (f) Rodríguez, D.; Pérez Sestelo, J.; Sarandeses, L. A. *J. Org. Chem.* **2003**, *68*, 2518. (g) Baker, L.; Minehan, T. *J. Org. Chem.* **2004**, *69*, 3957.

(7) (a) Takami, K.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, *3*, 1997. (b) Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 2993. (c) Pena, M. A.; Pérez, I.; Pérez Sestelo, J.; Sarandeses, L. A. *Chem. Commun.* **2002**, 2246. (d) Lee, P. H.; Lee, S. W.; Lee, K. *Org. Lett.* **2003**, *5*, 1103. (e) Lee, P. H.; Lee, S. W.; Seomoon, D. *Org. Lett.* **2003**, *5*, 4963. (f) Takami, K.; Mikami, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2003**, *68*, 6627. (g) Sakai, N.; Annaka, K.; Konakahara, T. *Org. Lett.* **2004**, *6*, 1527. (h) Yanada, R.; Obika, S.; Oyama, M.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 2825. (i) Lee, S. W.; Lee, K.; Seomoon, D.; Kim, S.; Kim, H.; Kim, H.; Shim, E.; Lee, M.; Lee, S.; Kim, M.; Lee, P. H. *J. Org. Chem.* **2004**, *69*, 4852.

(8) Lee, P. H.; Seomoon, D.; Lee, K. *Org. Lett.* **2005**, *7*, 343.

10.1021/jo062638k CCC: $37.00
Published on Web 04/04/2007

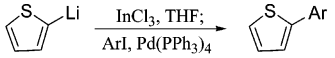
TABLE 1. Synthesis of Heterobiaryls: Effect of the Electrophile and the Catalyst



entry	aryl halide	Pd catalyst	yield[a] (%)
1		Pd/C	78
2		$Pd(PPh_3)_2Cl_2$	86
3		$Pd(PPh_3)_4$	98
4		$Pd(PPh_3)_4$	83
5		$Pd(PPh_3)_4$	41

[a] Isolated yield after column chromatography.

TABLE 2. Synthesis of Heterobiaryls Using Tristhienylindium



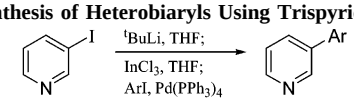
entry	aryl halide	product	yield[a] (%)
1		 **1**	98
2		 **2**	90
3		 **3**	84
4		 **4**	61

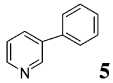
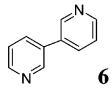
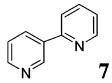
[a] Isolated yield after column chromatography.

with those obtained for other thiophene−thiophene[5a,9] or thiophene−pyridine couplings.[4,5b,10]

In a similar way, we have investigated the coupling of trispyridylindium with some halogenated (hetero)aromatics (Table 3). In this case, yields are somewhat lower than in the thiophene series. The high yield in the homocoupling process is noteworthy (entry 2).[5b,8] However, yields for cross-coupling are not so high (entries 1, 3, and 4). It is important to mention that in our hands the best conditions for lithium−chlorine exchange were using 2 equiv of *tert*-butyllithium according to a published procedure.[11] The use of butyllithium afforded somewhat lower yields.

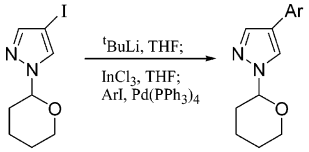
TABLE 3. Synthesis of Heterobiaryls Using Trispyridylindium

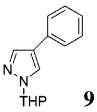
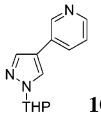
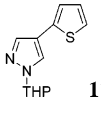


entry	aryl halide	product	yield[a] (%)
1		 **5**	66
2		 **6**	86
3		 **7**	50
4		 **1**	48

[a] Isolated yield after column chromatography.

TABLE 4. Synthesis of Heterobiaryls Using Tris(THP-protected pyrazol-4-yl)indium



entry	aryl halide	product	yield[a] (%)
1		 **9**	31
2		 **10**	27
3		 **11**	30

[a] Isolated yield after column chromatography.

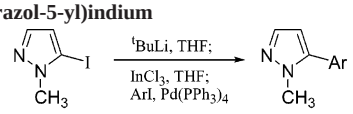
Finally, some couplings were conducted using two different trispyrazolylindium reagents. In the literature, there are only a few examples of $C_{sp2}-C_{sp2}$ coupling reactions involving pyrazole and either benzene, thiophene, or pyridine, with yields ranging from 12 to 90%.[12] In most of these cases, the pyrazole moiety acts as the electrophile. When the indium derivative from the THP-protected 4-iodopyrazole **8** is used, yields are very low

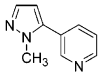
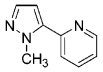
(9) See, for example: (a) Nising, C. F.; Schmid, U. K.; Nieger, M.; Bräse, S. *J. Org. Chem.* **2004**, *69*, 6830. (b) Andersen, N. G.; Maddaford, S. P.; Keay, B. A. *J. Org. Chem.* **1996**, *61*, 9556. (c) Albers, W. M.; Canters, G. W.; Reedijk, J. *Tetrahedron* **1995**, *51*, 3895. (d) Park, S. B.; Alper, H. *Tetrahedron Lett.* **2004**, *45*, 5515. (e) Su, W.; Urgaonkar, S.; McLaughlin, P. A.; Verkade, J. G. *J. Am. Chem. Soc.* **2004**, *126*, 16433.

(10) See, for example: (a) Cioffi, C. L.; Spencer, W. T.; Richards, J. J.; Herr, R. J. *J. Org. Chem.* **2004**, *69*, 2210. (b) Wolf, C.; Lerebours, R. *Org. Lett.* **2004**, *6*, 1147.

(11) Smith, A. P.; Savage, S. A.; Love, J. C.; Fraser, C. L. *Org. Synth.* **2002**, *78*, 51.

TABLE 5. Synthesis of Heterobiaryls Using Tris(1-methylpyrazol-5-yl)indium



entry	aryl halide	product	yield[a] (%)
1		 **12**	51
2		 **13**	48
3		 **14**	50
4		 **4**	55

[a] Isolated yield after column chromatography.

(Table 4), probably due to the acidic nature of the hemiaminal proton. Among the byproducts of these reactions we were not able to detect any homodimer species, only unreacted electrophiles and decomposition products from the pyrazole moiety with difficult to assign NMR spectra.

On the other hand, starting from 1-methyl-5-iodopyrazole[13] leads to moderate yields of cross-coupled products (Table 5). However, similar coupling yields have been described for reactions of 1-methylpyrazol-5-ylzinc[12a,c] and 1-methylpyrazol-5-yllithium,[14] pointing toward a lower reactivity of the 1-methylpyrazol-5-yl organometallics when compared with the thienyl analogues. Again, no homodimer species were detected.

In conclusion, the indium-mediated $C_{sp2}-C_{sp2}$ bond formation reaction has been extended to the cross-coupling of some electron-rich and electron-poor heterocycles in moderate to high yields in most cases. Further work is in progress to extend the process to other heterocyclic systems and to study the effect on coupling yields of electron-donating or electron-withdrawing substituents on either the aromatic rings of the electrophile or the organoindium reagent.[15]

Experimental Section

Preparation of Organolithium Compounds.[11] A commercial solution of *t*-BuLi in pentane (4.2 mmol, 1.7 M) was diluted with dry THF (10 mL) and cooled to −78 °C. To the resulting solution was slowly added the corresponding aryl iodide (2.1 mmol) in dry THF (2 mL). The mixture was stirred for 2 h.

Preparation of Organoindium Compounds. A 50 mL round-bottomed flask with indium(III) chloride (0.7 mmol) was dried under a positive argon pressure with a heat gun. After cooling, dry THF (10 mL) was added. The mixture was added to the previously described solution of the organolithium compound at −78 °C and stirred for 1 h, the cooling bath was removed, and the reaction mixture was warmed to room temperature.

Procedure for the Cross-Coupling Reaction. One-third of the previous solution of $(Ar)_3In$ (0.7 mmol) in dry THF was added to a refluxing mixture of the electrophile (2.5 mmol) and $Pd(PPh_3)_4$ (0.06 mmol) in dry THF (10 mL). The resulting mixture was refluxed under argon atmosphere overnight and the reaction quenched by addition of methanol. The mixture was concentrated, and diethyl ether (50 mL) was added. The organic phase was washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography.

Acknowledgment. Helpful comments and suggestions from the anonymous reviewers are gratefully acknowledged. Financial support from the Spanish Government-CICYT (Grant No. SAF2003-08140-C02-01) and Generalitat Valenciana (ACOMP06/057) is appreciated.

Supporting Information Available: Synthesis and characterization of compound **8**. Spectroscopic and analytical data for all new heterobiaryl compounds. Copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO062638K

(12) (a) Yagi, K.; Ogura, T.; Numata, A.; Ishii, S.; Arai, K. *Heterocycles* **1997**, *45*, 1463. (b) Eskildsen, J.; Kristensen, J.; Vedsø, P.; Begtrup, M. *J. Org. Chem.* **2001**, *66*, 8654. (c) Cottineau, B.; Chenault, J. *Synlett* **2002**, 769. (d) Majo, V. J.; Prabhakaran, J.; Mann, J. J.; Kumar, J. S. D. *Adv. Synth. Catal.* **2003**, *345*, 620. (e) Meegalla, S. K.; Doller, D.; Sha, D.; Soll, R.; Wisnewski, N.; Silver, G. M.; Dhanoa, D. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4949.

(13) Effenberger, F.; Krebs, A. *J. Org. Chem.* **1984**, *49*, 4687.

(14) Becht, J.-M.; Ngouela, S.; Wagner, A.; Mioskowski, C. *Tetrahedron* **2004**, *60*, 6853.

(15) During the peer review process, an article has appeared describing the use of indol- and pyridine-based triorganoindium reagents: Pena, M. A.; Pérez-Sestelo, J.; Sarandeses, L. A. *J. Org. Chem.* **2007**, *72*, 1271.