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Additions and Corrections

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Bengu Sezen and Dalibor Sames*

Cobalt-Catalyzed Arylation of Azole Heteroarenes via Direct C−H Bond Functionalization.

Page 3607. After the departure of the first author, the laboratory of the corresponding author (D. Sames) has not been able to reproduce the key results in this publication. Accordingly, the corresponding author withdraws this paper, and deeply regrets that the chemical community was misled by this publication.

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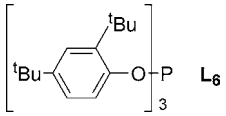
Volume 7, 2005

Juan Durán, Moisés Gulías, Luis Castedo, and José L. Mascareñas*

Ligand-Induced Acceleration of the Intramolecular [3 + 2] Cycloaddition between Alkynes and Alkylidenecyclopropanes.

Page 5693. The correct name for ligand **L**^{6} is tris(2,4-di-*tert*-butylphenyl)phosphite and the correct structure (Abstract and Figure 1) is the following:



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Cobalt-Catalyzed Arylation of Azole Heteroarenes via Direct C–H Bond Functionalization

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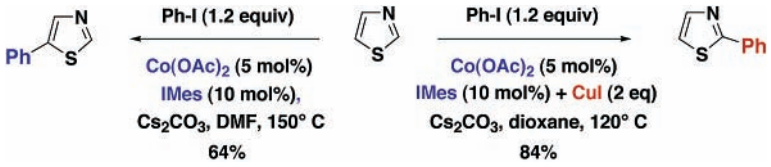
ABSTRACT



We herein report a new cobalt-catalyzed method for arylation of azole heteroarenes, including thiazole, oxazole, imidazole, benzothiazole, benzoxazole, and benzimidazole. The direct arylation of thiazole and oxazole was achieved both with iodo- and bromoarenes as the aryl donors in the presence of cobalt catalyst [$Co(OAc)_2$/IMes] and cesium carbonate, while imidazole required the use of zinc oxide as the base. A complete reversal of arylation from C-5 to C-2 was accomplished using the bimetallic Co/Cu/IMes system. A direct comparison of the new cobalt method and the previously developed palladium protocol revealed significant differences, in terms of both chemical yield and selectivity.

Heteroarenes represent structural units frequently found in a broad range of organic compounds, including natural products, pharmaceuticals, dyes, and other functional synthetics. Consequently, methods for direct functionalization and expansion of heterocyclic motifs would find enthusiastic users in various scientific disciplines. Current C−C bond-forming methods rely on establishing a reactive functionality (halogenation, metalation) prior to the cross-coupling reaction. In contrast, a more direct approach may not only eliminate the pre-functionalization step but may also prove in some cases complementary to traditional methods in terms of regiochemical outcome.[1]

Direct C-arylation of various heteroarenes has been previously demonstrated; however, these studies,[2] including our own,[3] have focused on the use of palladium catalysis. Although this choice is understandable in light of the unparalleled versatility of palladium in organic synthesis,[4] we became interested in the fundamental question of whether alternatives to palladium exist in this context. Out of nearly unlimited offerings of the periodic table, we focused on the metals of significantly lower cost compared to palladium.

Thus, we set out to explore a number of low-cost metal salts, including those of chromium, iron, cobalt, nickel, and copper, in the context of direct arylation of oxazole, thiazole, and imidazole. Interestingly, anhydrous $Co(OAc)_2$ proved to be a notable exception, providing promising early results while all other salts examined in this study were completely inactive. It is the aim of this paper to describe our preliminary results in this area.

The first substrate examined was thiazole **1** which had been reported to afford only mediocre yields of mono-arylation and bis-arylation products in the palladium-catalyzed arylation reaction.[2] In our hands, these claims were confirmed, and as shown in Table 1 (entry 5), palladium-catalyzed arylation with iodobenzene provided a mixture of products **2** and **4** in 42 and 15% yield, respectively. Upon addition of CuI, previously shown to promote arylation of acidic methylenes and methines (including the 2-position of thiazole

(1) Sezen, B.; Sames, D. *J. Am. Chem. Soc*. **2003**, *125*, 10580−10585.
(2) (a) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn*. **1998**, *71*, 467−473. (b) A review on arylation of arenes: Miura, M.; Nomura, M. *Top. Curr. Chem*. **2002**, *219*, 211−241.
(3) Sezen, B.; Sames, D. *J. Am. Chem. Soc*. **2003**, *125*, 5274−5275.
(4) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; John Wiley & Sons: New York, 1997.

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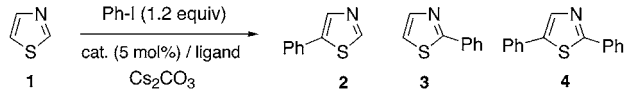
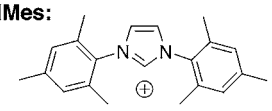
Published on Web 09/11/2003

Table 1. Cobalt-Catalyzed Arylation of Thiazole: A Comparison with Palladium-Based Methods



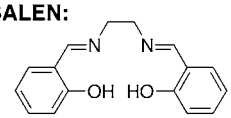
entry	conditions	yield
1	$Co(OAc)_2$, IMes (10 mol%), DMF, 150 °C, 12 h	64 / 0 / 0 % (42% with Ph-Br)
2	$Co(OAc)_2$, (+/-) Ph_3P (20 mol%), DMF, 150 °C, 12 h	traces
3	$Co(OAc)_2$, IMes (10 mol%), dioxane, 120 °C, 10 h + CuI (2 equiv)	0 / 84 / 0 %
4	$Co(OAc)_2$, SALEN (10 mol%), dioxane, 120 °C, 10 h + CuI (2 equiv)	0 / 87 / 0 % (76% with Ph-Br)
5	$Pd(OAc)_2$, Ph_3P (20 mol%), DMF, 150 °C, 12 h	42 / 0 / 15 %
6	$Pd(OAc)_2$, Ph_3P (20 mol%), DMF, 150 °C, 10 h + CuI (2 equiv)	0 / 18 / 37 %
7	control (no cat./ligand) + CuI (2 equiv)	0 / 11 / 0 %

IMes:



$Cl^{\ominus}$ / K_3PO_4

SALEN:



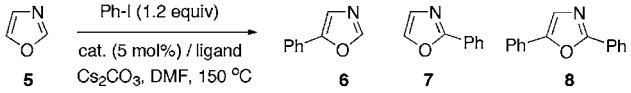
and *N*-methylimidazole),[5] a different mixture was obtained, containing products **3** and **4**, corresponding to mono- and bis-arylation at positions 2 and 5.[6]

We were encouraged to find that, in contrast to the palladium-based procedure, the cobalt-catalyzed method proved superior in terms of both yield and selectivity. Systematic optimization focused on the choice of cobalt source and ligand in addition to the usual parameters such as base, solvent, and temperature. 1,3-Bis-mesitylimidazolyl carbene (IMes)[7,8] proved to be the ligand of choice, together with anhydrous cobalt(II) acetate and cesium carbonate. Using these conditions,[9] the arylation reaction was selective, affording compound **2** as a single product in 64% yield (Table 1, entry 1). In the absence of the IMes ligand (or in the presence of triphenylphoshine), cobalt(II) acetate gave only a trace amount of the desired product (Table 1, entry 2). A complete switch from C-5 to C-2 selectivity was achieved by the addition of CuI, furnishing compound **3** exclusively in 84% yield. In addition to the IMes ligand, SALEN [ethylenebis-(salicylimine)] proved equally effective in this case (Table 1, entries 3 and 4). A control experiment examining cuprous iodide and cesium carbonate in the absence of cobalt and the ligand, produced C-2 arylation product, however, in low yield (11%, Table 1, entry 7), demonstrating the necessity of the bimetallic system. Noteworthy is the fact that bromobenzene also gave the corresponding arylated products, albeit at reduced yields in comparison to iodobenzene.

We were pleased that an attractive alternative to palladium was found. Furthermore, a direct comparison with the palladium method showed that the cobalt-based system proved superior both in terms of yield and selectivity. The cost of $Co(OAc)_2$ is $8.36 per gram which is significantly lower in comparison to $89.14 per gram of $Pd(OAc)_2$.[10] The availability and low cost of SALEN and IMes ligands further adds to the attractiveness of this protocol.

The conditions developed for thiazole were subsequently applied to oxazole. As in the previous case, palladium-catalyzed arylation was unselective yielding a mixture of three products **6**, **7**, and **8**, the last being the major one (Table 2). Although addition of CuI increased the yield of C-2 arylation, bis-arylation was still predominant, affording compound **8** in 42% yield as the major product along with 13% of compound **7**. Note that CuI itself provided C-2

Table 2. Cobalt-catalyzed Arylation of Oxazole: A Comparison with Palladium-Based Methods



entry	conditions	yield
1	$Co(OAc)_2$, IMes (10 mol%) DMF, 12 h	34 / 6 / 0 %
2	$Co(OAc)_2$, IMes (10 mol%), 100 °C, 10 h, + CuI (2 equiv)	0 / 73 / 0 % (58% with Ph-Br)
3	$Co(OAc)_2$, SALEN (10 mol%) dioxane, 10 h, + CuI (2 equiv)	0 / 53 / 8 %
4	$Pd(OAc)_2$, Ph_3P (20 mol%) DMF, 12 h	24 / 5 / 31 %
5	$Pd(OAc)_2$, Ph_3P (20 mol%) DMF, 10 h, + CuI (2 equiv)	0 / 13 / 42 %
6	control (no cat./ligand) + CuI (2 equiv)	0 / 27 / 0 %

(5) (a) Okuro, K.; Furuune, M.; Enna, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 4716−4721 and references therein. (b) See also ref 2a. (c) A discussion on possible roles of Cu(I) in Pd/Cu catalytic systems: Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359−5364.

(6) (a) Mori et al. have recently reported the use of fluoride salts in the Pd/Cu-catalyzed arylation of thiazole. Selective phenylation of 2-position was achieved at mild temperatures. Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700−1701. (b) For solid-phase-assisted selective arylation of azoles: Kondo, Y.; Komine, T.; Sakamoto, T. *Org. Lett.* **2000**, *2*, 3111−3113.

(7) (a) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1291−1309. (b) Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69−82.

(8) 1,3-Bis-mesitylimidazolium chloride is commercially available from Strem. It can also be prepared according to the procedure described in Arduengo, A. J., III (E. I. Du Pont de Nemours & Company), US 5.077.414 A2, 1992; WO 91/14678.

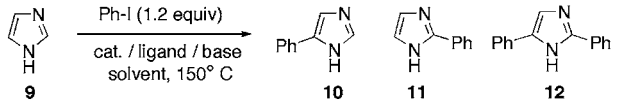
(9) In a typical procedure, anhydrous cobalt(II) acetate and the ligand were stirred at room temperature to form the active catalyst system, prior to the addition of the other reagents. This sequence of addition of ingredients proved to be important for the success of the method. For more detailed experimental procedures, see the Supporting Information.

(10) These prices are quoted from the Aldrich Catalog, Aldrich, Milwaukee, WI, 2003.

arylation product **7** exclusively, however, in low yield (27%, entry 6, Table 2). Although the $Co(OAc)_2$/IMes system was more selective, the yield was significantly lower than in the case of thiazole: C-5 arylation product **6** was obtained in 34% yield together with 6% of isomer **7**. Importantly, the C-2 selective method (Co/Cu/IMes) was quite successful, furnishing compound **7** exclusively in 73% yield. Currently, this appears to be the method of choice for the direct C-2 arylation of oxazole.[11] Thus, although the cobalt method was more selective, further optimization will be required to improve the yield of these reactions.

Subsequently, we posed the question of whether cobalt salts would be applicable to arylation of azole heterocyclic compounds containing a free N−H group. Recently, we developed a palladium-catalyzed method to effect direct C-arylation of free (NH)-azoles (e.g., pyrrole, indole, pyrazole, and imidazole).[3] The use of magnesium oxide (or zinc oxide) as the base was essential for the success of this method, and according to our proposal, the formation of magnesium *N*-azolyl salts takes place in situ. The salt not only protects the nitrogen but also promotes the reactivity of the heteroarene nucleus. In the case of imidazole, C-4(*5*) and C-2 arylation was carried out with excellent control of regioselectivity; namely, the Pd/Ph_3P/MgO system provided 72% yield of compound **10** as the exclusive product while the same protocol in the presence of CuI resulted in exclusive C-2 arylation, furnishing compound **11** in 83% yield (Table 3, entries 3 and 4). Next, we addressed the issue of whether

Table 3. C-Arylation of Imidazole: A Comparison of Cobalt- and Palladium-Based Methods

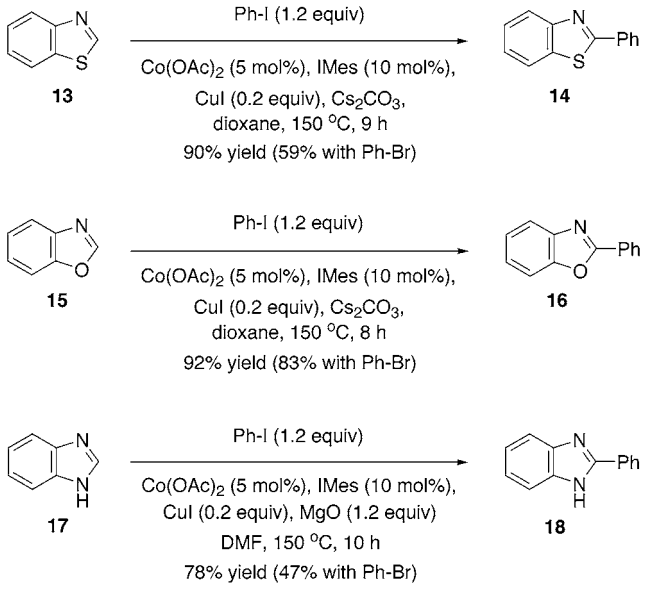


entry	conditions	yield
1	$Co(OAc)_2$ (5 mol%) IMes (10 mol%) ZnO (1.2 equiv), DMF, 12 h	41 / 0 / 0 %
2	$Co(OAc)_2$ (5 mol%) IMes (10 mol%) ZnO (1.2 equiv), DMF, 12 h + CuI (2 equiv)	0 / 78 / 0 %
3	$Pd(OAc)_2$ (5 mol%), Ph_3P (20 mol%) MgO (1.2 equiv), dioxane, 12 h	72 / 0 / 0 %
4	$Pd(OAc)_2$ (5 mol%), Ph_3P (20 mol%) MgO (1.2 equiv), dioxane, 12 h + CuI (2 equiv)	0 / 83 / 0 %

the cobalt system would be compatible with the magnesium azolyl salts. Although the $Co(OAc)_2$/IMes pair performed poorly in the presence of MgO (<20%), the use of zinc oxide led to a major improvement, affording a 41% yield of C-4(*5*) arylation product **10**. As in the previous cases, the addition of CuI resulted in the exclusive formation of the C-2 arylation product, namely compound **11** in 78% yield. While both palladium and cobalt systems proved highly selective for imidazole arylation (note that no *N*-arylation was detected in either case), the palladium method proved more efficient for C-4(*5*) phenylation (Table 3).

Finally, we explored benzothiazole, benzoxazole, and benzimidazole as substrates for the arylation conditions described above. We were pleased that the Co/Cu/IMes system converted benzothiazole **13** and benzoxazole **15** to the corresponding C-2 arylation products **14** and **16** in 90 and 92% yield, respectively (Scheme 1). Also, selective

Scheme 1. Cobalt-Catalyzed Arylation of Benzazoles



C-arylation of benzimidazole **17** was achieved by the protocol developed for imidazole, furnishing compound **18** as the sole product in 78% yield. In the case of benzothiazole and benzoxazole, the cobalt and palladium methods gave practically identical yields while the palladium system was more efficient in the arylation of benzimidazole (90% vs 78%, see the Supporting Information).

Although the mechanism of the cobalt-catalyzed arylation remains uncertain at this point, we wish to make a few points in the context of related cobalt-mediated/catalyzed processes.[12] Intramolecular Heck-type coupling of alkyl- and aryl iodides to alkenes have been promoted by stoichiometric amounts of Co(I) complexes [e.g., Na[Co(SALEN)]].[13] These reactions are usually formulated as free-radical reactions, and there is good evidence to support these claims.[14] More recently, cross-coupling of alkenyl, aryl, and alkyl halides with alkenes, Grignard compounds, and organozinc compounds have been catalyzed by Co(II) salts.[15] Co(I)/Co(III)

(11) The indirect methods require lithiation and transmetalation to zinc (to prevent oxazole ring cleavage) prior to cross-coupling. Anderson, B. A.; Harn, N. K. *Synthesis* **1996**, 583−585.

(12) The mechanistic picture for the palladium-catalyzed arylation of heteroarenes has not been elucidated either. For discussion and references on this topic, see ref 3.

(13) Bhandal, H.; Patel, V. F.; Pattenden, G.; Russell, J. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2691−2701.

(14) Clark, A. J.; Jones, K. *Tetrahedron Lett.* **1989**, *40*, 5485−5488.

or Co(0)/Co(II) catalytic cycles are usually invoked wherein the low-valent cobalt complex serves as an electron donor, which via single-electron transfer initiates the cleavage of the carbon−halide bond leading to a carbon-centered radical. Alternatively, oxidative addition of the organic halide to the low-valent cobalt may be envisioned, generating a homolysis prone carbon−cobalt bond. In accepting this view, the following mechanistic picture may be proposed for the direct arylation developed herein. Cobalt(II) salts are known to undergo disproportionation to Co(I) and Co(III) complexes. The former species may be transformed via oxidative addition to the aryl−Co(III) complex[16] which subsequently may act as an electrophile or a source of the aryl radical. The regioselectivity observed herein is not, however, consistent with a radical mechanism as free aryl radicals have shown preference for the 2-position of thiazole and 1-methylimidazole.[17] It may be argued that the presence of metal salts may strongly affect the regiochemical outcome. However, under acidic conditions, the C-2 preference of aryl radicals was even more pronounced; the same trend may be expected in the presence of Lewis acidic metal salts.[18] Thus, based on the observed regiochemistry, we propose that the heteroarene ring undergoes base promoted electrophilic metalation by an aryl−Co(III) complex, followed by reductive elimination. Different reactivity characteristics of the aryl−Co(III) species in comparison to the aryl−Pd(II) complex may account for higher regioselectivity of the cobalt-catalyzed arylation of thiazole and oxazole. The high C-2 selectivity observed in the presence of CuI may be rationalized by the propensity of Cu(I) salts to metalate acidic C−H bonds, in this instance, position C-2 of the 1,3-heteroazoles (followed by Cu−Co transmetalation and reductive elimination).[19]

In summary, the use of cobalt acetate represents a promising advance worthy of further exploration in the context of direct C−H bond arylation methods and possibly other C−C bond-forming reactions. Although the present study revealed clear parallels with established palladium catalysis, significant differences with respect to the chemical efficiency and degree of regioselectivity in C−H arylation reactions were observed. For example, in the case of thiazole, cobalt was clearly superior to the palladium system both in terms of yields and selectivity. Similarly, in the arylation of oxazole, the cobalt catalytic system proved more selective, although further optimization will be required to improve the yields of this process. Finally, although the cobalt-catalyzed arylation of imidazole and benzimidazole was highly selective, in this instance chemical yields were lower in comparison to the palladium system. Studies aimed at elucidation of the mechanism and scope of these reactions are currently underway in our laboratories.

Acknowledgment. Generous support for this work was provided by the National Institutes of Health (NIGMS), GlaxoSmithKline, Johnson & Johnson Pharmaceutical R & D, and Merck. D.S. is a recipient of the Alfred P. Sloan Fellowship and the Camille Dreyfus Teacher−Scholar Award. We thank Dr. J. B. Schwarz for editorial assistance.

Supporting Information Available: Experimental details and compound spectral characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) (a) Iyer, S. *J. Organomet. Chem*. **1995**, *490*, C27−C28. (b) Cahiez, G.; Avedissian, H. *Tetrahedron Lett*. **1998**, *39*, 6159−6162. (c) Avedissian, H.; Bérillon, L.; Cahiez, G.; Knochel, P. *Tetrahedron Lett*. **1998**, *39*, 6163−6166. (d) Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc*. **2001**, *123*, 5374−5375. (e) Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed*. **2002**, *41*, 4137−4139. Kneisel, F. F.; Monguchi, Y.; Knapp, K. M.; Zipse, H.; Knochel, P. *Tetrahedron Lett*. **2002**, *43*, 4875−4879.

(16) Ph-Co(III) complexes have been prepared via this route. Lampeka, J. D.; Jäger, E.-G.; Müller, K.; Schade, W. *Z. Chem.* **1988**, *28*, 70.

(17) (a) Metzger, J. V. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon: New York, 1984; Vol. 6, pp 263−266. (b) Grimmett, M. R. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon: New York, 1984; Vol. 5, pp 418−419.

(18) The effect of cobalt on the regiochemical course of intramolecular coupling between an aryl bromide and the pyridine ring has been observed. Harrowven, D. C.; Nunn, M. I. T.; Blumire, N. J.; Fenwick, D. R. *Tetrahedron Lett*. **2000**, *41*, 6681−6683.

(19) A metal−carbene intermediate should also be considered. For interesting reading on related topics, see: (a) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc*. **2002**, *124*, 3202−3203. (b) Gründemann, S.; Kovacevic, A.; Albrecht, M.; Faller, J. W.; Crabtree, R. H. *J. Am. Chem. Soc*. **2002**, *124*, 10473−10481.