Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 8869–8871

TETRAHEDRON LETTERS

A highly active catalyst system for the heteroarylation of acetone

Ping Liu,* Thomas J. Lanza, Jr., James P. Jewell, Carrie P. Jones, William K. Hagmann and Linus S. Lin

Department of Medicinal Chemistry, Merck Research Laboratories, Merck & Co., Inc., PO Box 2000, Rahway, NJ 07065, USA

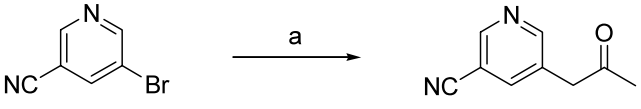
Received 4 September 2003; revised 18 September 2003; accepted 19 September 2003

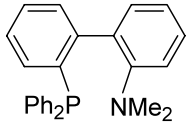
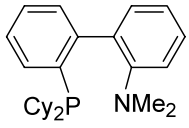
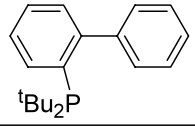
Abstract—A highly active catalyst system for the heteroarylation of acetone has been identified. The coupling between the in situ generated tributyltin enolate of acetone and a variety of heteroaromatic bromides, chlorides, and triflates in the presence of this catalyst system provided arylacetones in good yields.

The palladium-catalyzed coupling of aryl halides with ketone enolates to form sp^2-sp^3 C–C bonds has emerged as an extremely useful method for the synthesis of α-aryl ketones.[1] Buchwald, Hartwig, and others have developed new catalyst systems that rendered this reaction quite general for a wide range of carbonyl substrates.[2] Recently, the enantioselective construction of quaternary centers by α-arylation of ketone enolates has also been realized.[3] Although a lot of advances have been made in this area, to the best of our knowledge there has been only one report of α-arylation reaction of acetone.[4,5] Herein, we report a highly active catalyst system for the palladium-catalyzed heteroarylation of acetone that provides an array of α-heteroaryl acetones.

During our research we required a convenient preparation of α-heteroaryl acetones from commercially available heteroaromatic halides. The attempt to convert 5-bromopyridine-3-carbonitrile to the corresponding methyl ketone using the literature procedure ($PdCl_2$(*o*-$Tol_3P)_2$ as the catalyst)[4] did not provide synthetically useful yields (<10%). The effect of phosphine ligands on this palladium-catalyzed heteroarylation of acetone was then investigated and the results are summarized in Table 1. Little or no product in the presence of triphenylphosphine and tri(*o*-tolyl)phosphine (entries 1 and 2) was observed; but modest yields of products in the presence of DPPF and Xantphos (entries 3 and 4), and much improved yields in the presence of

Table 1. Effects of phosphine on the palladium-catalyzed heteroarylation of acetone



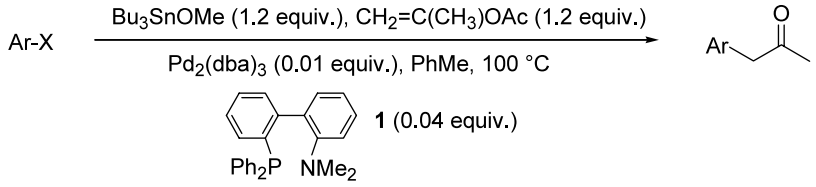
Entry	Phosphine		Yield (%)[c]
1	Ph_3P[b]		0
2	P(o-Tol)$_3$		<10
3	dppf		35
4	Xantphos		52
5		**1**	81
6		**2**	58
7		**3**	60

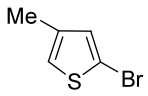
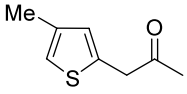
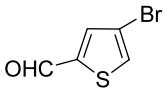
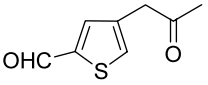
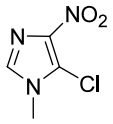
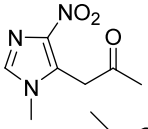
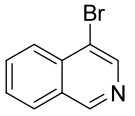
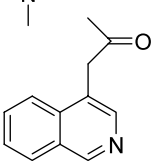
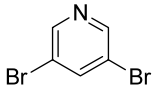
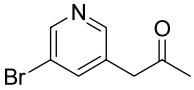
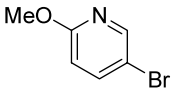
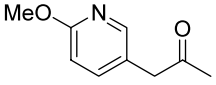
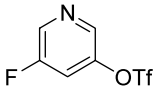
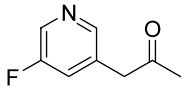
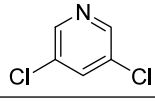
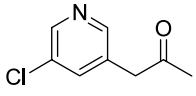
[a] Reaction conditions: ArX (1 equiv.), Bu_3SnOMe (1.2 equiv.), isopropenyl acetate (1.2 equiv.), phosphine (0.04 equiv.), $Pd_2(dba)_3$ (0.01 equiv.), PhMe, 100 °C.
[b] $Pd(PPh_3)_4$ was used. [c] Isolated yield.

* Corresponding author. Tel.: +1-732-594-0321; fax: +1-732-594-2210; e-mail: ping_liu2@merck.com

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.09.176

Table 2. Scope of the palladium-catalyzed heteroarylation of acetone



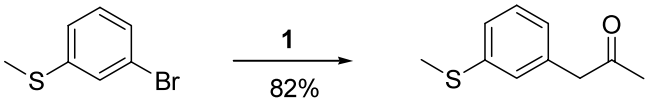
Entry	Ar-X	Product[a]	Yield[b]
1			86%
2			88%
3			77%
4			90%
5			35%
6			<10%
7			57%
8[c]			55%

[a] All products gave satisfactory NMR and MS data.
[b] Isolated yield after column chromatography on silica. [c] Phosphine **3** was used.

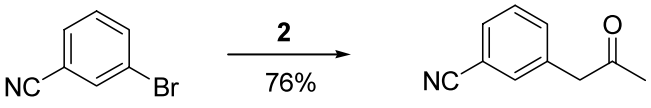
Buchwald's *o*-biphenyl phosphines (entries 5–7) were obtained.[6] 2-Dimethylamino-2′-diphenylphosphino-1,1′-biphenyl (**1**) was found to be the best among the phosphines surveyed thus far, which provided the desired α-pyridyl acetone in 81% yield.

A wide array of electronically and structurally diverse heteroaromatic substrates were converted to the corresponding methyl ketones using this catalyst system (Table 2).[7] This reaction tolerates electron-donating groups on the aromatic ring (entry 1) as well as electron-withdrawing groups (entries 2 and 3). Yields for a few substrates including 3-bromo-6-methoxy pyridine (entry 6) remain low (<10%) for unknown reasons. Heteroaromatic bromide, chloride, and triflate[8] are all suitable substrates for this synthetically useful transformation. In terms of the scope of the heterocycles, this reaction is also quite general. Thiophenes, imidazoles, pyridines, as well as other heterocycles are all suitable substrates.[9]

This palladium-catalyzed arylation of acetone also works quite well on phenyl halide substrates (Eqs. (1) and (2)).[6] Interestingly, with an electron-donating group (CH_3S) on the phenyl ring, biphenyl ligand **1** gave optimal results; while with an electron-withdrawing group (CN) on the phenyl ring, biphenyl **2** gave the optimal results.



(1)



(2)

The mechanistic details of the arylation reaction are not yet fully understood. Presumably, in a pathway similar to that described by Buchwald and Palucki, a tin enolate is generated in situ from tributyltin methoxide and isopropenyl acetate, which undergoes transmetallation and coupling to the aryl partner to deliver the α-aryl acetone.[1a] Since the reaction conditions are essentially neutral, polyarylation and enolate mediated condensation are not significant pathways. In comparison, both side reactions were observed in the presence of a base.[2a]

In summary, we have identified a highly active catalyst system for heteroarylation of acetone that converts various heteroaromatic bromides, chlorides, and triflates to the corresponding α-aryl acetones in good yields.

References

1. (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108–11109; (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382–12383; (c) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740–1742.
2. For leading references, see: (a) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360–1370; (b) Gaertzen, O.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 465–475; (c) Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410–8411; (d) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473–1478; (e) Terao, Y.; Fukuoka, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2002**, *43*, 101–104.
3. (a) Spielvogel, D. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 3500–3501; (b) Hamada, T.; Chieffi, A.; Ahman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261–1268; (c) Ahman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918–1919.
4. Kosugi, M.; Suzuki, M.; Hagiwara, I.; Goto, K.; Saitoh, K.; Migita, T. *Chem. Lett.* **1982**, 939–940.
5. Hartwig observed the α-arylation of acetone during studies of catalytic amination in acetone solvent but no yields were reported, see: Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234–245. Direct heteroarylation of acetone with the Buchwald protocol[2a] as well as the Hartwig protocol[2d] was attempted, but in our hands none of them gave the synthetically useful yield of the desired products.
6. The *o*-biphenyl phosphines were purchased from Strem Chemical Co.
7. General experimental conditions: ArX (0.5 mmol), Bu_3SnOMe (173 μL, 0.6 mmol), isopropenyl acetate (66 μL, 0.6 mmol), and the biphenyl ligand (**1**, **2**, or **3**, 0.02 mmol), were dissolved in PhMe (1.5 mL), to which was added $Pd_2(dba)_3$ (5 mg, 0.05 mmol). The reaction mixture was heated at 100°C and monitored by TLC (2–14 h depending on substrates). Then the reaction mixture was subjected to column chromatography to obtain the α-aryl acetones.
8. All the starting materials in Table 2 are commercially available except for entry 7 where the triflate was prepared from 5-fluoro-3-pyridinol.
9. For a new substrate, a quick screen of the catalyst using biphenyl phosphines **1**, **2**, or **3** might be needed.