Published in final edited form as:

Angew Chem Int Ed Engl. 2011 November 25; 50(48): 11400–11404. doi:10.1002/anie.201104035.

Direct Arylation of 6-Phenylpurine and 6-Arylpurine Nucleosides by Ruthenium-Catalyzed C–H Bond Activation

Mahesh K. Lakshman*, Ashoke C. Deb, Raghu Ram Chamala, Padmanava Pradhan, and Ramendra Pratap

Department of Chemistry, The City College and The City University of New York, 160 Convent Avenue, New York, NY 10031-9198 (U.S.A.)

Abstract

One aryl or two? The title reaction predominantly gives monoarylation products with various amounts of diarylation product being observed in almost all cases (see scheme). Aryl iodides as well as aryl bromides were reactive under the optimized reaction conditions. The multiple nitrogen atoms in the purine, and oxygen atoms in the saccharide posed no problems in these transformations.

Keywords

arylation; C–H activation; homogenous catalysis; nucleosides; ruthenium

C–H bond activation represents an efficient approach to molecular functionalization.^[1,2] In the directed C–H bond activation, Lewis basic sites are exploited to draw the catalyst proximal to the reactive center. We have been interested in the C–H bond activation and arylation of nucleobases and nucleosides using the nitrogen atoms of the purine itself. In this context, 6-arylpurine has embedded 2-phenylpyridine and 4-phenylpyrimidine motifs. 2-Arylpyridines, and benzo[*h*]quinoline that contains a rigidified 2-phenylpyridine structure,

*Fax: (+) 01 212-650-6107, lakshman@sci.ccny.cuny.edu.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

have been the subject of C–H bond activation/arylation strategies using Pd, Ru, Rh and Fe.^[3–6] However, any metalcatalyzed conversion of purines and purine nucleosides is a challenging proposition owing to the presence of four nitrogen atoms in the nucleobases, plus additional oxygen atoms in the sugar unit; all of these heteroatoms could participate in metal sequestration and deactivation of catalytic processes.

As shown in Figure 1, the *N1* nitrogen atom of the purine is well positioned to direct C–H bond activation. Alternatively, *N7* can also function in a similar capacity. In order to gain preliminary insight, energy minimization was performed, using DFT at the B3LYP/6-311++G(2d,2p) level, on 2-phenylpyridine as well as 9-benzyl-6-phenyl-9*H*-purine. The distance between the metal-directing nitrogen atom and the *ortho*-hydrogen atom on the phenyl ring were calculated from the energy minimized structures, and are shown in Figure 2.

Consistent with known X-ray structures of 2-phenylpyridine derivatives,^[7] the aryl rings in 2-phenylpyridine are not coplanar. The pyridyl N to aryl *ortho*-H distance in this case is 2.49 Å. By comparison, in the energy-minimized structure of 9-benzyl-6-phenyl-9*H*-purine, the C6-aryl group is coplanar with the purine ring. We next compared the computed structure of 9-benzyl-6-phenyl-9*H*-purine to the crystallographic structures of 9-benzyl-6-phenyl-8-(*p*-tolyl)-9*H*-purine and 8,8'-bis(9-benzyl-6-phenyl)-9*H*-purine.^[8] In both compounds, the C6-phenyl group is coplanar with the purinyl system. We also evaluated the distance between *N1* and the *ortho*-hydrogen atom of the C-6 aryl group for these cases. In 9-benzyl-6-phenyl-8-(*p*-tolyl)-9*H*-purine, this distance is 2.43 Å whereas the distance to the *N7* is 2.34 Å. Similar distances of 2.43 Å and 2.36 Å, respectively, were obtained for 8,8'-bis(9-benzyl-6-phenyl)-9*H*-purine. These data closely match the DFT-derived distances for 9-benzyl-6-phenyl-9*H*-purine shown in Figure 2. Given the similar nitrogen atom to aryl hydrogen distances in 9-benzyl-6-phenyl-9*H*-purine and 2-phenylpyridine, we reasoned that C–H bond activation in purines and nucleosides should be feasible. In support of this hypothesis, serendipitously, undesired arylation of the C6-phenyl group has been observed in Pd/Cu-mediated C8 arylation of 9-benzyl-6-phenyl-9*H*-purine with iodobenzene or *p*-iodotoluene (2–10 equiv).^[8]

In initial experiments, [{RuCl₂(benzene)}₂] (**A**) and [{RuCl₂(*p*-cymene)}₂] (**B**) were selected as catalysts for assessing the C–H bond activation of 9-benzyl-6-phenyl-9*H*-purine (**1**), and 2 equivalents of iodobenzene were used to ensure complete consumption of **1**. Results from a preliminary screen of conditions are shown in Table 1. Notably, 5 mol% of catalyst **A** in combination with 40 mol% of PPh₃ resulted in full conversion (Table 1, entries 1–4), and catalyst **A** appeared marginally superior to catalyst **B** (compare entries 4 and 5). Replacement of K₂CO₃ with Cs₂CO₃ led to a slower reaction (entries 6 and 7), and the mono/diarylation ratio was substantially altered. This indicates an unknown, but crucial role of base in these C–H bond activation processes.

On the basis of the foregoing, we evaluated the use of aryl iodides and aryl bromides for the direct arylation of 9-benzyl-6-phenyl-9*H*-purine (**1**) under the optimal conditions developed in Table 1. Results from these experiments are shown in Table 2.

Results in Table 2 indicate that reactions can be accomplished with both aryl iodides and aryl bromides, in yields of 75–99% (combined for mono and diarylated products). Yields of reactions with aryl bromides were respectable (Table 2, entries 5–7) but a little lower than those with aryl iodides.

We next explored arylations of the more complex 2'-deoxynucleoside substrates, which are quite labile and prone to facile deglycosylation.^[9] The requisite 6-arylpurine 2'-deoxyribonucleosides (6-aryl 2'-deoxynebularines) are readily available via our previously

reported procedures.^[10] Results from the nucleoside arylation reactions are shown in Table 3.

The results in Table 3 indicate that the procedure is readily applicable to the sensitive 2'-deoxyribonucleoside substrates. However, 10 mol% of the Ru catalyst was needed to obtain complete consumption of the precursor. In contrast to the reactions of purine **1**, where a 1:8 ratio of Ru catalyst/PPh₃ was needed for complete reaction (Table 1 entry 4), use of a 1:4 or 1:8 ratio of the Ru catalyst/PPh₃ led to full conversion of **4a** (entries 1–4 in Table 3), but there were some differences. With iodobenzene, increased PPh₃ resulted in a better yield as well as mono/diarylation ratio (entry 1 versus 2). With *p*-iodotoluene, again a better ratio of mono/diarylation was observed with increased PPh₃, although the yield of the monoarylation remained almost the same (entry 3 versus 4). Electron-rich *p*-iodoanisole and electron-deficient *p*-iodoacetophenone both yielded successful arylation reactions (entries 5 and 6). Interestingly, for reasons currently unknown, when R = F or OPh (**4b**, **4c**), greater diarylation was observed in reactions with iodobenzene (entries 7 and 9). The same trend was also observed in the arylation of **4c** with iodobenzene using catalyst **B** (entry 10). With **4d** (R = OMe), greater monoarylation is again observed (entries 11 and 12). As in the case of purine **1**, aryl bromides were also reactive (entries 13 and 14).

Using catalyst **A**, we then examined C–H bond activation/arylation of *m*-nitrophenyl nucleoside derivative **7**^[10] and 2-amino-6-phenylpurine nucleoside **8**^[11] (Figure 3) with iodobenzene. In the case of **7**, no product formation was seen but some precursor decomposition occurred, thus indicating very electron-depleted aromatic rings, not surprisingly, are resistant to arylation (see mechanism in Scheme 1). Substrate **8** that is structurally similar to **4a**, but with an additional C-2 amino group, remained largely intact and showed no product formation. It appears therefore that presence of the amino group abolishes any reactivity.

Since in previous experiments 2 equivalents of aryl halide were used to achieve complete consumption of the purine or nucleoside precursor, we evaluated the arylation of **1** and **4a** with a variety of stoichiometries of iodobenzene; all other reaction conditions remained the same. These results are shown in Table 4. With purine **1**, incomplete reaction was observed with 1 equiv of iodobenzene, but substantially more monoarylated product **2a** was formed (entry 1). However, with 120 mol% of iodobenzene the result was nearly the same as that obtained with 200 mol% (compare entry 2 in Table 4 to entry 1 in Table 2). Increasing iodobenzene to 400 mol% yielded a greater proportion of diarylated product **3a**, but complete conversion to diarylated **3a** did not occur (entry 3). Doubling the reaction time did not increase diarylation either (entry 4). Stoichiometry of iodobenzene had very little effect on the mono/diarylation ratio of nucleoside precursor **4a** (entries 5–7 in Table 4 and entry 2 in Table 2), although a prolonged reaction time (60 h) was detrimental, and led to a lower yield (entry 7).

While this work was in progress, complementary Pd-catalyzed C–H bond activation of 6-arylpurines and three acetate-protected 6-arylpurine ribonucleosides has been reported.^[12] It is therefore reasonable to offer a comparison of the two approaches. In contrast to the reactions reported here, those catalyzed by Pd required 30 equiv of aryl iodides, with reaction times from 48 h (nucleosides) to 60 h (purines), at 120 °C.^[12] Thus, the present conditions are substantially more conservative on the aryl halide and generally provide faster reactions. Pd catalysis produces only monoarylation,^[12] plausibly due to slow reactions, whereas under Ru catalysis both mono and diaryl products are formed. Use of AcOH as solvent at 120 °C and N₂ atmosphere have been stated as crucial for the Pd-catalyzed reactions.^[12] Exposure to AcOH at elevated temperature may be unsuitable for acid-sensitive substrates such as the deoxyribonucleosides described here. Also, an inert

atmosphere is strictly necessary for Pd-catalyzed reactions. Plausibly, this is to suppress undesired dimerization of the purine, as dimerization has been observed previously when air was introduced into Pd-catalyzed arylation reactions.^[8] Most notably, as shown here, aryl bromides can be used in the Ru-catalyzed chemistry, whereas aryl bromides and chlorides were unreactive under Pd catalysis.^[12]

In analogy to reactions of 2-arylpyridines,^[4d] a possible mechanism involving the purinyl N1 nitrogen atom is depicted in Scheme 1. The monoarylated products could reenter the catalytic cycle resulting in diarylation. Consistent with an *N*-directed electrophilic attack by the aryl-Ru^{IV} complex onto the C-6 aryl ring, no reaction was observed with the *m*-nitrophenyl nucleoside derivative **7**. This is because reaction would have to occur at the electron deficient *para*- or *ortho*-positions to the nitro group.

Due to interest in oxidative C–H cross-coupling processes,^[3c,13–17] we evaluated whether purinyl nitrogen atom-directed C–H bond activation could be used to promote C–H cross coupling.^[18] This reaction gave dimerized 8,8'-bis(9-benzyl-6-phenyl)-9*H*-purine^[8] in ca. 20% yield, indicating a facile dimerization of **1** under oxidative conditions (50% of **1** was recovered).

We have demonstrated that Ru-catalyzed C–H bond activation/arylation can be accomplished with purines and deoxyribonucleosides. Both aryl iodides and aryl bromides are reactive, leading to densely functionalized products in relatively few steps. Metal-catalyzed approaches, such as that described here, provide facile routes to novel entities that are otherwise not easily accessed. This is important in the context of the high biological value placed on purine and nucleoside derivatives. Further work is currently ongoing in our laboratories on these and related chemical processes, including understanding the role of the purinyl N7, if any.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was partially supported by a PSC CUNY award to M.K.L. Infrastructural support at CCNY was provided by NIH RCMI Grant G12 RR03060. We thank Ms. Ona Liu (undergraduate research participant) for her contribution to this work, Frontier Scientific for generous samples of arylboronic acids, Dr. Bill Boggess and Nonka Sevova (University of Notre Dame) for HRMS analyses (NSF Grant CHE-0741793).

References

1. a) Dyker, G., editor. Handbook of C–H Transformations: Applications in Organic Synthesis. Vol. Vols. 1 and 2. Weinheim: Wiley-VCH; 2005. b) Kakiuchi, F.; Murai, S. Activation of Unreactive Bonds and Organic Synthesis. Murai, S., editor. Berlin: Springer-Verlag; 1999. p. 47–79.
2. Reviews: a) Lyons TW, Sanford MS. Chem. Rev. 2010; 110:1147–1169. [PubMed: 20078038] b) Ackerman L, Vicente R, Kapdi AR. Angew Chem. Int. Ed. 2009; 48:9792–9826. c) Chen X, Engle KM, Wang D-H, Yu J-Q. Angew. Chem. 2009; 121:5196–5217. Angew. Chem. Int. Ed. 2009; 48:5094–5115. d) Daugulis O, Do H-Q, Shabashov D. Acc. Chem. Res. 2009; 42:1074–1086. [PubMed: 19552413] e) Lewis JC, Bergman RG, Ellman JA. Acc. Chem. Res. 2008; 41:1013–1025. [PubMed: 18616300] f) Alberico D, Scott ME, Lautens M. Chem. Rev. 2007; 107:174–238. [PubMed: 17212475] g) Campeau L-C, Stuart DR, Fagnou K. Aldrichimica Acta. 2007; 40:35–41. h) Kalyani D, Sanford M. Top. Organomet. Chem. 2007; 24:85–116. i) Godula K, Sames D. Science. 2006; 312:67–72. [PubMed: 16601184] j) Hassan J, Sévignon M, Gozzi C, Schulz E, Lemaire M. Chem. Rev. 2002; 102:1359–1469. [PubMed: 11996540] k) Labinger JA, Bercaw JE. Nature. 2002; 417:507–514. [PubMed: 12037558] l) Jia C, Kitamura T, Fujiwara Y. Acc. Chem.

- Res. 2001; 34:633–639. [PubMed: 11513570] m) Shilov AE, Shul'pin GB. Chem. Rev. 1997; 97:2879–2932. [PubMed: 11851481]
3. For Pd catalysis, see: a) Shabashov D, Daugulis O. Org. Lett. 2009; 7:3657–3659. [PubMed: 16092843] b) Yu W-Y, Sit WN, Zhou Z, Chan AS-C. Org. Lett. 2009; 11:3174–3177. [PubMed: 19583200] c) Hull KL, Sanford MS. J. Am. Chem. Soc. 2007; 129:11904–11905. [PubMed: 17845047] d) Deprez NR, Sanford MS. Inorg. Chem. 2007; 46:1924–1935. [PubMed: 17348723] e) Hull KL, Lanni EL, Sanford MS. J. Am. Chem. Soc. 2006; 128:14047–14049. [PubMed: 17061885] f) Kalyani D, Deprez NR, Desai LV, Sanford MS. J. Am. Chem. Soc. 2005; 127:7330–7331. [PubMed: 15898779]
4. For Ru catalysis, see: a) Ackerman L, Althammer A, Born R. Tetrahedron. 2008; 64:6115–6124. b) Cheng K, Zhang Y, Zhao J, Xie C. Synlett. 2008:1325–1330. c) Özdemir I, Demir S, Çetinkaya B, Gourlaouen C, Maseras F, Bruneau C, Dixneuf PH. J. Am. Chem. Soc. 2008; 130:1156–1157. [PubMed: 18183987] d) Ackerman L. Org. Lett. 2005; 7:3123–3125. [PubMed: 15987221] e) Oi S, Fukita S, Hirata N, Watanuki N, Miyano S, Inoue Y. Org. Lett. 2001; 3:2579–2581. [PubMed: 11483065]
5. For Rh catalysis, see: a) Ye W, Luo N, Yu Z. Organometallics. 2010; 29:1049–1052. b) Zhao X, Yu Z. J. Am. Chem. Soc. 2008; 130:8136–8137. [PubMed: 18540607]
6. For Fe catalysis, see: Norinder J, Matsumoto A, Yoshikai N, Nakamura E. J. Am. Chem. Soc. 2008; 130:5858–5859. [PubMed: 18410099]
7. a) Lepeltier M, Lee TK-M, Lo KK-W, Toupet L, Le Bozec H, Guerchais V. Eur. J. Inorg. Chem. 2007:2734–2747. b) Sasaki I, Vendier L, Sournia-Saquet A, Lacroix PG. Eur. J. Inorg. Chem. 2006:3294–3302.
8. Čerňa I, Pohl R, Klepetářová B, Hocek M. Org. Lett. 2006; 8:5389–5392. [PubMed: 17078725]
9. Storr TE, Baumann CG, Thatcher RJ, De Ornellas S, Whitwood AC, Fairlamb IJS. J. Org. Chem. 2009; 74:5810–5821. [PubMed: 19630437]
10. Lakshman MK, Hilmer JH, Martin JQ, Keeler JC, Dinh YQV, Ngassa FN, Russon LM. J. Am. Chem. Soc. 2001; 123:7779–7787. [PubMed: 11493051]
11. Lakshman MK, Thomson PF, Nuqui MA, Hilmer JH, Sevova N, Boggess B. Org. Lett. 2002; 4:1479–1482. [PubMed: 11975608]
12. Guo HM, Jiang LL, Niu H-Y, Rao WH, Liang L, Mao R-Z, Li D-Y, Qu G-R. Org. Lett. 2011; 13:2008–2011. [PubMed: 21434677]
13. Itahara T. J. Org. Chem. 1985; 50:5272–5275.
14. Li R, Jiang L, Lu W. Organometallics. 2006; 25:5973–5975.
15. a) Stuart DR, Fagnou K. Science. 2007; 316:1172–1175. [PubMed: 17525334] b) Stuart DR, Villemure E, Fagnou K. J. Am. Chem. Soc. 2007; 129:12072–12073. [PubMed: 17880083]
16. Dwight TA, Rue NR, Charyk D, Josselyn R, DeBoef B. Org. Lett. 2007; 9:3137–3139. [PubMed: 17616203]
17. Xi P, Yang F, Qin S, Zhao D, Lan J, Gao G, Hu C, You J. J. Am. Chem. Soc. 2010; 132:1822–1824. [PubMed: 20102197]
18. Purine **1** was exposed to 10 mol% Pd(OAc)₂, 2 equiv of Ag₂CO₃, 0.5 mol equiv of 1,4-benzoquinone, 4 equiv of DMSO, and 53 equiv of benzene, at 100 °C for 24 h

9-Substituted purine:

R = substituent

Nucleoside: **Figure 1.**

N-directed C-H bond activation in 2-phenylpyridine, and two plausible modes of N-directed C-H bond activation in C6 arylpurines and nucleosides.

Figure 2. Energy minimized structures of 2-phenylpyridine (left) and 9-benzyl-6-phenyl-9*H*-purine (right).

Figure 3.
Nucleoside substrates that did not yield arylation products. TBDMS = *tert*-butyldimethylsilyl.

Scheme 1.

Possible mechanism for the C–H bond activation/arylation of 6-arylpyrimidine and 6-arylpyrimidine 2'-deoxyribonucleosides.

Table 1

Preliminary evaluation of the C–H bond activation process in 9-benzyl-6-phenyl-9*H*-purine (**1**).^[a]

Entry	Catalytic system ^[b]	Result ^[c]
1	A (2.5 mol%), PPh ₃ (20 mol%), K ₂ CO ₃ (3 equiv)	1/2a/3a = 83:15:2 ^[d]
2	B (2.5 mol%), PPh ₃ (20 mol%), K ₂ CO ₃ (3 equiv)	1/2a/3a = 83:15:2 ^[d]
3	A (5 mol%), PPh ₃ (20 mol%), K ₂ CO ₃ (3 equiv)	1/2a/3a = 63:34:3 ^[d]
4	A (5 mol%), PPh ₃ (40 mol%), K ₂ CO ₃ (3 equiv)	2a = 76% 3a = 17%
5	B (5 mol%), PPh ₃ (40 mol%), K ₂ CO ₃ (3 equiv)	1/2a/3a = 3:84:13 ^[d]
6	A (5 mol%), PPh ₃ (40 mol%), Cs ₂ CO ₃ (3 equiv)	1:2a:3a = 7:52:41 ^[d]
7 ^[e]	A (5 mol%), PPh ₃ (20 mol%), K ₂ CO ₃ (3 equiv)	2a = 56% 3a = 36%

^[a] Reaction conditions: **1** (0.2 M) in anhydrous NMP, iodobenzene (2 equiv), 120°C, 24 h.

^[b] **A** [{RuCl₂(benzene)}₂], **B** [{RuCl₂(*p*-cymene)}₂].

^[c] Yields are of isolated and purified products.

^[d] The reaction was incomplete. The ratio was determined from ¹H NMR spectra by the integration of the benzyl CH₂ resonances, which appear at δ = 5.49 ppm for **1**, 5.41 ppm for **2a**, and 5.32 ppm for **3a**. Bn = benzyl, NMP = *N*-methylpyrrolidone.

Table 2C–H bond activation/arylation of 9-benzyl-6-phenyl-9*H*-purine (**1**) with aryl iodides and aryl bromides.^[a]

Entry	Aryl halide	Yield [%] ^[b]	2/3
1		2a : 76 3a : 17	4.5:1
2		2b : 81 3b : 18	4.5:1
3 ^[c]		2c : 79 3c : 14	5.6:1
4		2d : 82 3d : trace	NA ^[d]
5		2a : 72 3a : 12	6:1
6		2b : 73 3b : 17	4.3:1
7		2d : 75 3d : trace	NA ^[d]

^[a] Reaction conditions: **1** (0.2 M) in anhydrous NMP, aryl halide (2 equiv), [{RuCl₂(benzene)}₂] (5 mol%), PPh₃ (40 mol%), K₂CO₃ (3 equiv), 120 °C.

^[b] Yields are of isolated and purified products.

^[c] The reaction was conducted using 10 mol% of [{RuCl₂(benzene)}₂] and 80 mol% of PPh₃.

^[d] Not applicable since only a trace of the diaryl product was detected.

Table 3

C–H bond activation/arylation of 3',5'-di-*O*-silyl 6-aryluracine 2'-deoxyribonucleosides (**4**) with aryl iodides and aryl bromides.

Entry	R =	Aryl halide	Yield [%] ^[a]	5/6
1 ^[b]	H		5a : 46	2:1
			6a : 23	
2 ^[c]	H		5a : 65	4.6:1
			6a : 14	
3 ^[b]	H		5b : 52	3.2:1
			6b : 16	
4 ^[c]	H		5b : 54	7.7:1
			6b : 7	
5 ^[c]	H		5c : 53 ^[d]	7.6:1
			6c : 7	
6 ^[c]	H		5d : 62	4.1:1
			6d : 15	
7 ^[c]	F		5e : 31	1:1.5
			6e : 44	
8 ^[c]	F		5f : 42	2.1:1
			6f : 20	
9 ^[c]	OPh		5g : 29	1:1.8
			6g : 53	
10 ^[e]	OPh		5g : 24	1:3
			6g : 72	
11 ^[c]	OMe		5h : 39	2.4:1
			6h : 16	
12 ^[c]	OMe		5i : 46	2.7:1
			6i : 17	
13 ^[c]	H		5a : 36	2:1
			6a : 18

Entry	R =	Aryl halide	Yield [%] ^[a]	5/6
14 ^[c]	H		5b: 57 6b: 18	3.2:1

^[a]Yields are of isolated and purified products.

^[b]Reaction conditions: **4a** (0.2 M) in anhydrous NMP, aryl halide (2 equiv), [{RuCl₂(benzene)}₂] (10 mol%), PPh₃ (40 mol%), K₂CO₃ (3 equiv), 120°C, 30 h.

^[c]Reaction conditions: **4a–d** (0.2 M) in anhydrous NMP, aryl halide (2 equiv), [{RuCl₂(benzene)}₂] (10 mol%), PPh₃ (80 mol%), K₂CO₃ (3 equiv), 120°C.

^[d]Owing to the close *R_f* values of products, a trace of the diarylated product was present.

^[e]Reaction conditions were the same as [c] except that [{RuCl₂(*p*-cymene)}₂] was used in place of [{RuCl₂(benzene)}₂].

Table 4Reactions of **1** and **4a** using various stoichiometries of iodobenzene.

Entry	Substrate	Mol% of Ph-I	t[h]	Yield [%] ^[a]	Mono/diaryl products
1 ^[b]	1	100	24	2a : 91% 3a : 2%	2a/3a = 45:1 ^[c]
2 ^[b]	1	120	24	2a : 80% 3a : 12%	2b/3b = 6.7:1
3 ^[b]	1	400	24	2a : 60% 3a : 30%	2b/3b = 2:1
4 ^[b]	1	400	48	2a : 59% 3a : 32%	2b/3b = 1.8:1
5 ^[d]	4a	120	30	5a : 62% 6a : 10%	5a/6a = 6.2:1
6 ^[d]	4a	400	30	5a : 62% 6a : 12%	5a/6a = 5.2:1
7 ^[d]	4a	400	60	5a : 53% 6a : 13%	5a/6a = 4.1:1

^[a]Yields are of isolated and purified products.^[b]Reaction conditions: **1** (0.2 M) in anhydrous NMP, PhI (see Table), [{RuCl₂(benzene)}₂] (5 mol%), PPh₃ (40 mol%), K₂CO₃ (3 equiv), 120°C.^[c]Reaction was incomplete, 4% of **1** was recovered.^[d]Reaction conditions: **4a** (0.2 M) in anhydrous NMP, PhI (see Table), [{RuCl₂(benzene)}₂] (10 mol%), PPh₃ (80 mol%), K₂CO₃ (3 equiv), 120°C.