Acetylation of *N*-Heteroaryl Bromides via $PdCl_2$/(*o*-tolyl)$_3$P Catalyzed Heck Reactions

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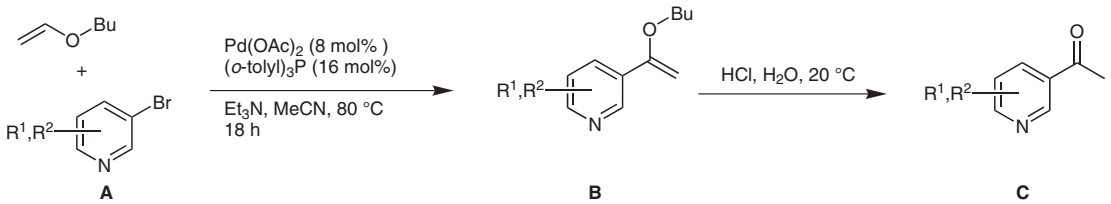
Abstract: A new user-friendly and convenient method for the acetylation of *N*-heteroaryl bromides is described. This process is based on the palladium-catalyzed olefination of an *N*-heteroaryl bromide with butyl vinyl ether, followed by acid hydrolysis of the intermediate heteroaryl vinyl ether in situ. Isopropanol at 85 °C, in the presence of $K_3PO_4 \cdot 3H_2O$ (2 equiv), $PdCl_2$ (2 mol%) and (*o*-tolyl)$_3$P (4 mol%), provided the best conditions, giving yields of *N*-heteroaryl bromides up to 75%.

Key words: acetylation, butyl vinyl ether, isopropanol, *N*-heteroaryl bromides

Heteroaryl methyl ketones are of significant interest in organic chemistry,[1–5] since versatile transformations of the acetyl function make them important intermediates in the synthesis of agrochemicals, pharmaceuticals and natural products.[6–10] In general, the introduction of the acetyl function is the most direct and versatile route through which to prepare functionalized heteroaryl methyl ketones. Wright et al. reported the first example of a palladium-catalyzed acetylation of heteroaryl bromides with butyl vinyl ether,[11] as outlined in Scheme 1.

The heteroaryl bromide A is transformed to intermediate heteroaryl vinyl ether B in a palladium-catalyzed Heck[12,13] olefinic coupling with butyl vinyl ether.[14] Acid hydrolysis of the intermediate furnishes the heteroaryl methyl ketone C. This process offers several advantages including mild reaction conditions that are tolerant of many functional groups, a two-step one-pot reaction, and acceptable yields. Nevertheless, some drawbacks still exist. For example, the chosen solvent, acetonitrile, is toxic and unfriendly to the environment. Moreover, the butyl vinyl ether is required to be present in five-fold greater amounts than the heteroaryl bromide, and the quantity of catalyst and ligand used is large. These two factors also make the method inconvenient and costly. Santelli et al.[15,16] developed an efficient catalytic system for the Heck olefinic coupling reaction, but the ligand they used, namely *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane, is difficult to obtain. The palladium-catalyzed Heck reaction of heteroaryl bromides with butyl vinyl ether in ionic liquids using 1,3-bis(diphenylphosphino)propane (dppp) as a ligand was reported.[17] *meso*-2,4-Bis(diphenylphosphino)pentane showed much better regioselectivity than dppp.[18] Regioselective and fast Pd(0)-catalyzed internal α-arylation of ethylene glycol vinyl ether with aryl halide has been accomplished in water.[19] Herein, we report a new, more convenient and eco-friendly palladium-catalyzed Heck olefinic coupling of heteroaryl bromides with vinyl ether, in the synthesis of heteroaryl methyl ketones.

We typically used the reaction described in Scheme 2 for optimization of the conditions. Initially we used Wright's conditions,[11] where the reaction was carried out with (5-bromopyridin-2-yl)dimethylamine (2.0 mmol) and butyl vinyl ether (10 mmol), using $Pd(OAc)_2$ (8 mol%) as catalyst and (*o*-tolyl)$_3$P (16 mol%) as ligand, triethylamine as base, and acetonitrile as solvent. However, even when the reaction was refluxed for ten hours under Ar, no product was produced. Since the $PdCl_2$/*i*-PrOH system was reported to catalyze the coupling reaction efficiently,[20] the reaction was then carried out with (5-bromopyridin-2-yl)dimethylamine (2.0 mmol) and butyl vinyl ether (2.4 mmol), with $PdCl_2$ (2 mol%) as catalyst, K_2CO_3 as base, and *i*-PrOH as solvent. The reaction mixture was refluxed for six hours under Ar but, again, no desired product was found (Table 1, entry 4), however, the addition of PPh_3 as ligand gave the desired product in 35% yield (Table 1, en-



Scheme 1

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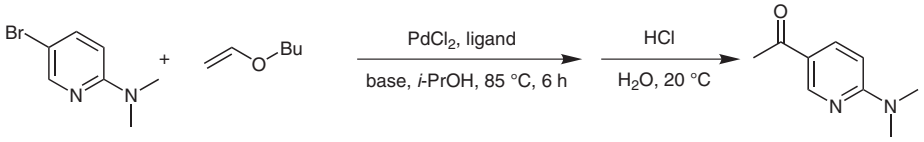


Scheme 2 The reaction used to optimize conditions

try 5). Therefore, we examined a series of bases containing potassium ions instead of K_2CO_3. KH_2PO_4, KOAc, and KOH failed completely, yielding no desired product; only starting material was recovered (Table 1, entries 9–11). $KF{\cdot}2H_2O$, *t*-BuOK, and K_2HPO_4 all gave the desired products, but the yields were low (Table 1, entries 6–8). Inspired by the different effects of KH_2PO_4 and K_2HPO_4 on the yields of the desired product, we used $K_3PO_4{\cdot}3H_2O$ as base in the reaction. To our delight, we isolated the desired product in 60% yield (Table 1, entry 2). Then we substituted $(o\text{-tolyl})_3P$ for PPh_3 and the isolated yield increased to 75% (Table 1, entry 1). However, chelated phosphine ligands, such as 1,2-bis(diphenylphosphino)ethane (dppe), gave a very low yield (Table 1, entry 3). This is in contrast with some recent reports where diphosphines have been used successfully.[16,18,19]

Table 1 Optimization of the Acetylation of 5-Bromo-2-dimethylaminopyridine with Butyl Vinyl Ether[a]

Entry	Ligand	Base (equiv)	Yield (%)[b]
1	$P(o\text{-}MeC_6H_4)_3$	$K_3PO_4{\cdot}3H_2O$ (2)	75
2	PPh_3	$K_3PO_4{\cdot}3H_2O$ (1.5)	60
3	dppe	$K_3PO_4{\cdot}3H_2O$ (1.5)	trace
4	none	K_2CO_3 (2)	0
5	PPh_3	K_2CO_3 (2)	35
6	PPh_3	$KF{\cdot}2H_2O$ (2)	27
7	PPh_3	*t*-BuOK (2)	15
8	PPh_3	$K_2HPO_4{\cdot}3H_2O$ (2)	25
9	PPh_3	KH_2PO_4 (2)	0
10	PPh_3	KOAc (2)	0
11	PPh_3	KOH (2)	0

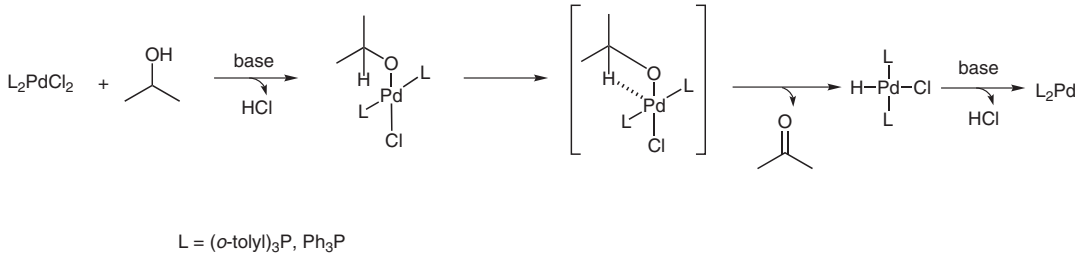
[a] Reactions were carried out in refluxing *i*-PrOH (5 mL) for 6 h under argon. The molecular ratio of *N*-heteroaryl halides, butyl vinyl ethers, $PdCl_2$, $(o\text{-tolyl})_3P$, and base was 1:1.2:0.02:0.04:1.5–2.0.
[b] Isolated yield.

The success of $K_3PO_4{\cdot}3H_2O$ as the base in the reaction is consistent with the recent proposal of 'ionic' versus 'neutral' mechanism in the Heck reaction of electron-rich olefins.[21] $K_3PO_4{\cdot}3H_2O$ must have less solubility than $K_2HPO_4{\cdot}3H_2O$ or KH_2PO_4, reducing the base's tendency to quench ionic intermediates during catalysis. This is in contrast with the anion-assisted Heck reaction reported by Jeffery et al.,[22] which was studied mechanistically by Amatore and Justand.[23] It has been reported that ionic liquid as solvent and ammonium salts that can act as hydrogen-bond donors, exert a remarkable accelerating effect on the rates of the regioselective arylation of electron-rich olefins by aryl halides.[24] The isopropanol used as solvent in our system may function analogously.

In most cases, the catalyst used in the Heck reaction is generated in situ. Various claims have been made about palladium(II/IV) catalytic cycles[25,26] and, indeed, some palladium(IV) species have been isolated.[21] However, all current evidence seems to point to a palladium(0/II) cycle. This means that the first step of the reaction is the reduction of the palladium(II) precursor into active palladium(0) species.

We propose a reasonable pathway for catalyst reduction in Scheme 3. L_2PdCl_2 reacts with isopropanol in the presence of base to generate a palladium isopropanolate intermediate.[27–30] Elimination of the β-H from the intermediate forms a L_2PdHCl species and acetone. Elimination of HCl from L_2PdHCl produces a $L_2Pd(0)$species, which is the proposed catalytic species for the reaction.

After optimizing the catalytic conditions, we evaluated the scope and limitations of the reaction. Generally, $PdCl_2$ (2 mol%), $(o\text{-tolyl})_3P$ (4 mol%), butyl vinyl ether (1.2 equiv), and $K_3PO_4{\cdot}3H_2O$ (2 equiv) were used, and the reaction was conducted in isopropanol at 85 °C for 6–10 hours. The results are summarized in Table 2. Substrates with primary amino groups gave low yields (Table 2, entries 3 and 6), however, when the amino groups of 5-bromo-2-aminopyridine and 5-bromo-2-aminopyrimidine were protected by methyl or acetyl groups, the yields increased significantly (Table 2, entries 1, 2, 4 and 5).



Scheme 3

5-Bromo-1-methylindoline, 5-bromo-1-acetylindoline, 4-bromoindole and 5-bromoindole also showed good reactivity, and the corresponding products were isolated in 55–63% yield (Table 2, entries 7–10).

Table 2 Heck Acetylation of Heteroaryl Halides with Butyl Vinyl Ethers[a]

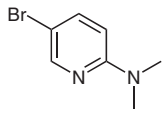
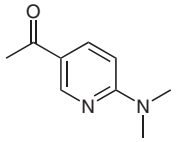
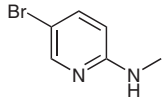
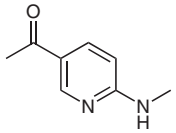
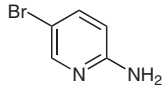
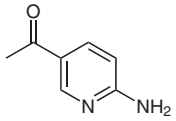
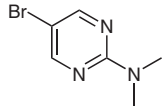
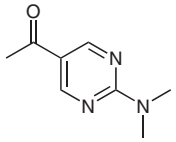
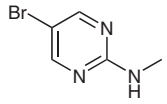
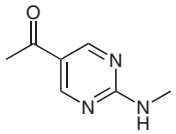
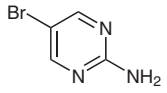
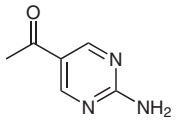
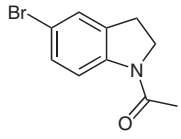
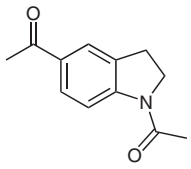
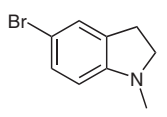
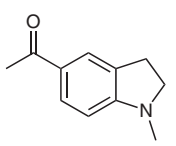
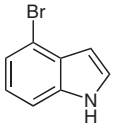
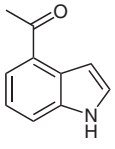
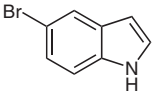
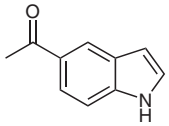
Entry	Substrate	Obtained or expected product	Time (h)	Yield (%)[b]
1		 **1**	6	75
2		 **2**	10	63
3		 **3**	10	trace
4		 **4**	6	75
5		 **5**	10	65
6		 **6**	10	trace
7		 **7**	8	62
8		 **8**	10	55

Table 2 Heck Acetylation of Heteroaryl Halides with Butyl Vinyl Ethers[a] (continued)

Entry	Substrate	Obtained or expected product	Time (h)	Yield (%)[b]
9		 **9**	6	63
10		 **10**	6	60

[a] Reactions were carried out in refluxing *i*-PrOH (5 mL), using heteroaryl halides (2.0 mmol), butyl vinyl ethers (2.4 mmol), $PdCl_2$ (0.04 mmol), $(o\text{-tolyl})_3P$ (0.08 mmol), and $K_3PO_4 \cdot 3H_2O$ (4.0 mmol) at 85 °C for 6–10 h under argon.
[b] Isolated yield.

In summary, we have developed a novel method for the acetylation of *N*-heteroaryl bromides. Using the catalytic system of $PdCl_2$/$(o\text{-tolyl})_3P$ in isopropanol, we have transformed *N*-heteroaryl bromides into *N*-heteroaryl methyl ketones in medium to high yields. Strongly coordinating groups, such as primary amino groups, are not tolerated. The use of isopropanol as solvent is very attractive in its cost and environmental friendliness.

All reagents and solvents were purchased from commercial sources and used without further purification. Products were purified by silica gel column chromatography. ^{1}H NMR spectra were recorded in $CDCl_3$ using a Bruker Avance 500 spectrometer at 500 MHz, with chemical shifts (δ) reported versus TMS as an internal standard. Melting points were obtained in open capillary tubes and are uncorrected.

Heck Coupling Reactions of Heteroaryl Bromides; 1-(6-Dimethylaminopyridin-3-yl)ethanone (1);[9] Typical Procedure

To a pre-dried Schlenk tube was added, sequentially, 5-bromo-2-dimethylaminopyridine (402 mg, 2.0 mmol), butyl vinyl ether (240 mg, 2.4 mmol), $PdCl_2$ (7 mg, 0.04 mmol), $(o\text{-tolyl})_3P$ (24 mg, 0.08 mmol), $K_3PO_4 \cdot 3H_2O$ (800 mg, 4.0 mmol) and anhydrous *i*-PrOH (5 mL). The mixture was stirred at reflux for 6–10 h; TLC analysis (petroleum ether–EtOAc, 10:1) showed complete conversion of 5-bromo-2-dimethylaminopyridine. The mixture was then cooled to r.t. and the solvent was recovered under vacuum. The residue was taken up in HCl (6 M, 5 mL) and stirred for 15 min. The mixture was then neutralized to pH 8 with aq NaOH (6 M). The product was extracted into EtOAc (3 × 10 mL) and the combined organic layers were washed with sat. brine (2 × 6 mL), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether–EtOAc, 10:1) to afford **1**.

Yield: 247 mg (75%); yellow solid; mp 63.8–64.2 °C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.5 (s, 3 H), 3.2 (s, 6 H), 6.5 (d, *J* = 9.1 Hz, 1 H), 8.0 (dd, *J* = 9.1, 2.2 Hz, 1 H), 8.8 (d, *J* = 2.2 Hz, 1 H).

1-(6-Methylaminopyridin-3-yl)ethanone (2)[9]
Mp 129.8–130.2 °C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.5 (s, 3 H), 3.0 (d, *J* = 4.5 Hz, 3 H), 5.3 (br s, 1 H), 6.4 (d, *J* = 8.8 Hz, 1 H), 8.0 (d, *J* = 8.8 Hz, 1 H), 8.7 (s, 1 H).

1-[2-(Dimethylamino)pyrimidin-5-yl]ethanone (4)[9]
Mp 92.0–92.9 °C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.5 (s, 3 H), 3.3 (s, 6 H), 8.8 (s, 2 H).

1-[2-(Methylamino)pyrimidin-5-yl]ethanone (5)
Mp 168.8–170.4 °C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.5 (s, 3 H), 3.1 (d, *J* = 5.1 Hz, 3 H), 5.9 (br s, 1 H), 8.8 (s, 1 H), 8.9 (s, 1 H).

1-(1-Acetylindolin-5-yl)ethanone (7)[31]
Mp 138.6–140.2 °C (Lit. 140–141 °C).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.3 (s, 3 H), 2.6 (s, 3 H), 3.2 (m, 2 H), 4.1 (m, 2 H), 7.8 (m, 2 H), 8.2 (d, *J* = 8.1 Hz, 1 H).

1-(1-Methylindolin-5-yl)ethanone (8)[27]
Mp 59.5–60.2 °C (Lit. 59.5–60 °C).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.5 (s, 3 H), 2.8 (s, 3 H), 3.0 (m, 2 H), 3.5 (m, 2 H), 6.3 (d, *J* = 8.3 Hz, 1 H), 7.7 (s, 1 H), 7.9 (m, 1 H).

1-Indol-4-ylethanone (9)[32]
Mp 161.5–162.4 °C (Lit. 163–164 °C).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.7 (s, 3 H), 7.3 (m, 1 H), 7.4 (d, *J* = 2.6 Hz, 2 H), 7.6 (d, *J* = 7.9 Hz, 1 H), 7.8 (d, *J* = 7.4 Hz, 1 H), 8.4 (br s, 1 H).

1-Indol-5-ylethanone (10)[33]
Mp 72.8–75.4 °C (Lit. 73–75 °C).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.7 (s, 3 H), 6.7 (s, 1 H), 7.3 (m, 1 H), 7.4 (d, *J* = 8.6 Hz, 1 H), 7.9 (d, *J* = 8.6 Hz, 1 H), 8.3 (s, 1 H), 8.5 (s, 1 H).

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