Aqueous-Phase Heck Coupling of 5-Iodouridine and Alkenes under Phosphine-Free Conditions

Joon Hyung Cho, Kevin H. Shaughnessy*

Department of Chemistry, The University of Alabama, Tuscaloosa, AL 35487-0336, USA
Fax +1(205)3489104; E-mail: kshaughn@bama.ua.edu

Received 10 August 2011

Abstract: Palladium-catalyzed Heck couplings between 5-iodouridine and alkenes were carried out in aqueous media in the presence of triethylamine under phosphine-free conditions to give the desired products in high yields. In the absence of phosphine ligand, triethylamine appears to play a critical role in both generating the active catalyst species and serving as the base in the reaction.

Key words: aqueous phase, cross-coupling, Heck reaction, nucleosides, palladium

Nucleosides are central building blocks of all living systems. Because of this central role, there is extensive interest in methods to prepare modified nucleosides for use as pharmaceuticals and biochemical probes. Palladium-catalyzed reactions have proven to be effective ways to modify nucleosides through C–C or C–heteroatom bond-forming reactions.[1] All major classes of palladium-catalyzed coupling reactions have been used in nucleoside synthesis, including couplings with organometallic reagents (Suzuki, Stille, Hiyama), alkynylations (Sonogashira), alkenylations (Heck), and C–N bond formation (Buchwald–Hartwig).

Alkene-modified nucleosides have found important applications in medicine and biochemistry. 5-(*E*)-2-Bromoethenyl-2′-deoxyuridine (BVDU, Figure 1) is a highly potent and selective inhibitor of the herpes simplex and varicella-zoster viruses.[2] 5-Vinyluridine derivatives, such as 5-carboxyvinyl-2′-deoxyuridine (CVU), have also received significant interest as biochemical probes. CVU and related compounds are effective tools for photoligation in DNA and RNA.[3] The 5-vinyluridines undergo selective [2+2] photocyclization with the C5–C6 double bond of thymine. Alkene-modified purine nucleosides have received less attention, but have shown useful cytokinin, cytotoxic (**1**), and antimycobacterial activity.[4]

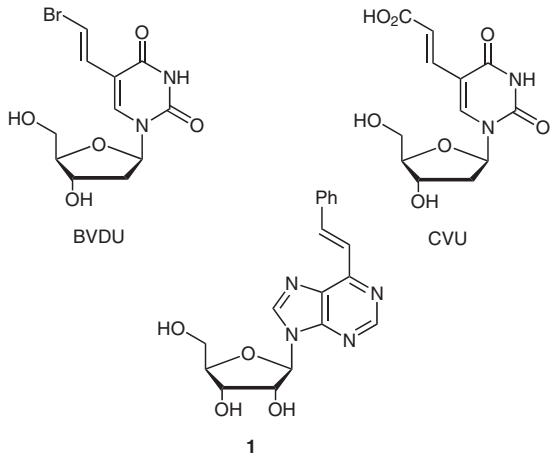


Figure 1 Examples of alkene-modified nucleosides with medical or biochemical applications

The Heck coupling is the most common method to introduce alkene substituents on the base of nucleosides. Early examples involved the palladium-catalyzed reaction of alkenes with mercuriated nucleosides.[5] The more accessible halonucleosides, such as 5-iodo-2′-deoxyuridine (5-IdU), are more widely used, however. The first practical large-scale preparation of BVDU used the $Pd(OAc)_2$/PPh_3-catalyzed coupling of 5-IdU and methyl acrylate in dioxane.[6] This methodology has been used in the synthesis of a variety of 5-alkenylated 2′-deoxyuridine derivatives.[7] DMF is often used as a solvent to provide improved solubility for the nucleoside.[8] Heck coupling of 6-halopurine nucleosides have been reported using $Pd_2(dba)_3$ under ligand-free conditions.[9] Lakshman has reported coupling of aryl iodides and 8-vinyladenosine using Pd/$P(o\text{-tol})_3$.[10] Heck couplings are also used in the synthesis of *C*-nucleosides.[11]

Water is an attractive solvent for organic synthesis due to its low toxicity, flammability, and environmental impact. In addition, aqueous biphasic catalysis offers the opportunity to separate water-soluble catalyst systems from organic product streams and recycle the aqueous-phase catalyst.[12] Hydrophilic catalysts offer the opportunity for homogeneous-phase coupling of water-soluble substrates, such as nucleosides. In this way, issues with low solubility of biomolecules in organic solvents can be avoided. The use of water-soluble catalysts based on monosulfonated triphenylphosphine (TPPMS) for cross-coupling of halonucleosides was first demonstrated by Casalnuovo.[13] Our group and others have extended this work to develop efficient methods for Suzuki[14] and Sonogashira[15] couplings of halonucleosides using palladium complexes of water-soluble ligands. These coupling reactions can be carried out on the unprotected nucleosides or nucleotides, thus avoiding wasteful protection/deprotection steps.

Although Heck couplings in aqueous solvents are well precedented,[16] there are no examples of the Heck coupling of nucleosides in water to our knowledge. Herein we re-

SYNLETT 2011, No. 20, pp 2963–2966
Advanced online publication: 11.11.2011
DOI: 10.1055/s-0031-1289886; Art ID: S07411ST

port that a catalyst derived from $Pd(OAc)_2$ alone or in the presence of a water-soluble ligand promotes the coupling of 5-IdU and alkenes in water under mild conditions.

To identify potential catalyst systems, the Heck coupling of 5-IdU and butyl acrylate (**2**) to make butyl (*E*)-3-(2′-deoxyurid-5-yl)propenoate (**3**) was performed in the presence of catalysts derived from $Pd(OAc)_2$ alone or in combination with tri(3-sulfonatophenyl)phosphine trisodium salt (TPPTS, Figure 2), sodium (2-cyclohexylphosphino)ethane sulfonate (DCPES), or tri(2,4-dimethyl-5-sulfonatophenyl) trisodium salt (TXPTS). The initial screening was performed in H_2O–MeCN (2:1) at 65 °C (Scheme 1). Conversion to adduct **3** was monitored using RP-HPLC (Figure 3). After 15 minutes, reactions catalyzed by $Pd(OAc)_2$ alone or in combination with TPPTS had proceeded to approximately 75% conversion. The DCPES-derived catalyst had given approximately 20% conversion, while no conversion had occurred with the TXPTS-derived catalyst. After one hour, both the ligand-free and TPPTS systems had reached nearly 100% conversion to product. The DCPES system required two hours to reach completion, while the TXPTS catalyst system showed no activity after three hours.

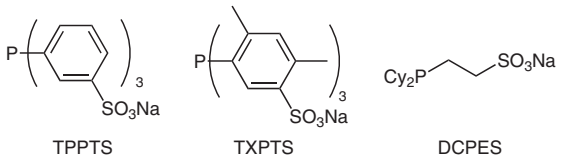
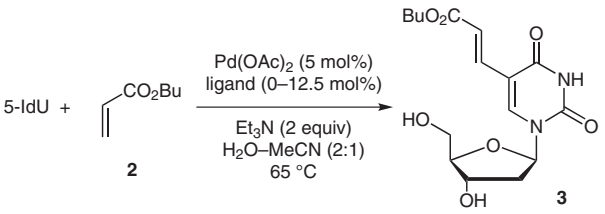


Figure 2 Water-soluble ligands screened for Heck coupling of 5-IdU



Scheme 1

Further optimization using $Pd(OAc)_2$ alone or with TPPTS was performed using the coupling of 5-IdU and 2-cyclohexen-1-one (**4**) in H_2O–MeCN (1:1) at 80 °C (Table 1). Reactions did not proceed in the absence of base (entries 1 and 2). Using sodium carbonate as the base gave no conversion in the absence of TPPTS, but complete conversion to product was observed when TPPTS was used with Na_2CO_3 (entries 3 and 4). In contrast, the ligand-free catalyst system did work when Et_3N was used as the base. At least one equivalent of the base was required for complete conversion (entries 5–7). Using TPPTS as ligand in the presence of Et_3N gave a similar rate of conversion to the ligand-free catalyst (entry 8).

These results show that the coupling can be accomplished without the use of phosphine ligand when Et_3N is used as the base. We hypothesized that Et_3N generates the catalytically active species. The phosphine-free coupling was then attempted using a catalytic amount of Et_3N and stoichiometric Na_2CO_3, but no conversion occurred (entries 9 and 10). Although Et_3N is capable of forming the active catalyst species and Na_2CO_3 is a competent base for the Heck coupling in the presence of TPPTS, the combination of bases provided an inactive catalyst system.

Based on these results, the coupling of 5-IdU with butyl acrylate (**2**), cyclohexenone (**4**), and styrene (**6**) was car-

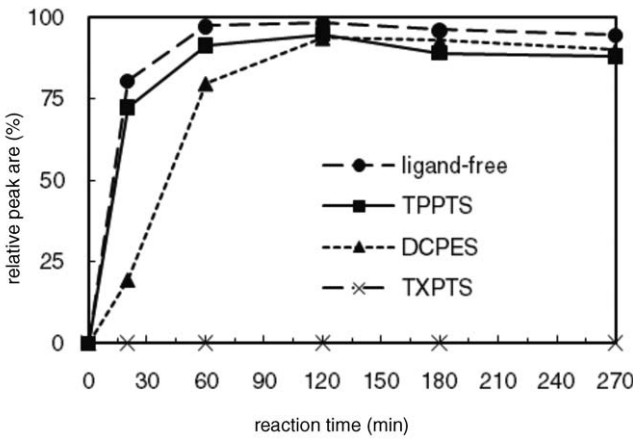
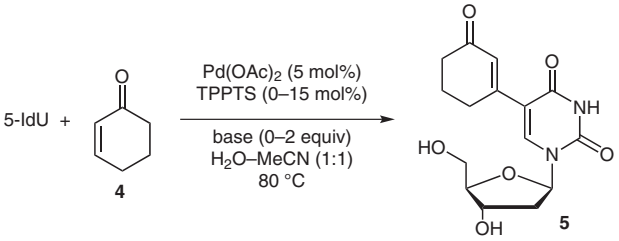


Figure 3 Reaction profile for coupling of 5-IdU and butyl acrylate using $Pd(OAc)_2$ alone or in combination with water-soluble phosphine ligands

Table 1 Optimization of the Coupling of 5-IdU and Cyclohexenone

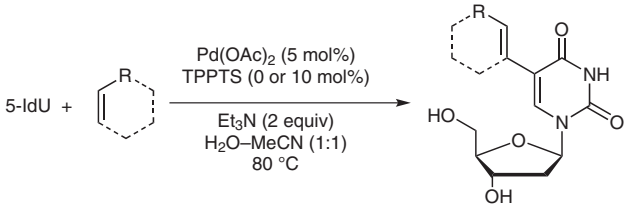


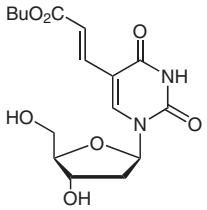
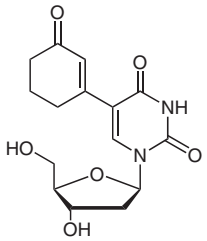
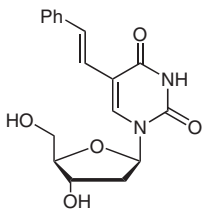
Entry	Ligand (mol%)	Base (equiv)	Time (h)	Ratio 5-IdU/**5**[a]
1	none	none	1	96:4
2	TPPTS (15)	none	1	96:3
3	none	Na_2CO_3 (2)	1.5	99:1
4	TPPTS (10)	Na_2CO_3 (2)	1	1:99
5	none	Et_3N (0.15)	1	80:20
6	none	Et_3N (1.2)	1	1:99
7	none	Et_3N (2)	0.5	1:99
8	TPPTS (10)	Et_3N (2)	0.5	1:99
9	none	Et_3N (0.15) Na_2CO_3 (2)	1	99:1
10	none	Et_3N (0.5) Na_2CO_3 (2)	1	99:1

[a] Determined by relative RP-HPLC peak area observed at λ = 287 nm.

ried out using the optimized conditions in the presence or absence of TPPTS (Table 2). The couplings were carried out in H_2O–MeCN (1:1) with two equivalents of Et_3N.[17] Coupling of 5-IdU with butyl acrylate in the absence of ligand gave the product **3** in 64% yield, while a higher yield (74%) was achieved when TPPTS was used as a ligand for this coupling. Compound **3** is a precursor to BVDU.[18] Cyclohexanone was coupled with 5-IdU to give **5** in 72% yield, which was identical to that achieved when TPPTS was used as a ligand. Coupling of 5-IdU with styrene to give **7** gave higher yields than were obtained with alkenes **2** and **4**. Again, the presence of TPPTS had no effect on the isolated yield of the coupled product.

Table 2 Heck Couplings of 5-IdU



Entry	Alkene	Ligand	Product	Yield (%)[a]
1	**2**	none		64
2		TPPTS		74
			3	
3	**4**	none		72
4		TPPTS		71
			5	
5	**6**	none		82
6		TPPTS		81
			7	

[a] Average isolated yield of two independent trials. All products were pure as determined by ^{1}H NMR and ^{13}C NMR spectroscopy.

Based on the successful results with 5-IdU, the Heck coupling of bromonucleosides was explored. Coupling of 5-bromo-2′-deoxyuridine (5-BrdU) with butyl acrylate gave only 25% conversion to **3** after two hours under the conditions optimized for 5-IdU. Longer reaction times did not improve the conversion to product. Heck couplings of 8-bromo-2′-deoxyguanosine (8-BrdG) and 8-bromo-2′-deoxyadenosine (8-BrdG) were also attempted, but only trace amounts of products were formed. Attempts to improve the conversion by changing reaction conditions, such as base (NaOAc, CsOH, Na_2CO_3), solvent ratios, temperatures (up to 120 °C), ligands (ligand-free, TPPTS, TXPTS, DCPES, *t*-Bu-Amphos), or additives (tetrabutylammonium halides) gave no improvement.

From results shown in Table 1 and Table 2, it was found that a phosphine ligand was not required when Et_3N was used as the base. In contrast, our previous studies on the Suzuki[14a] and Sonogashira[15b] couplings showed that water-soluble phosphine ligands were required to generate catalytically active species. Triethylamine appears to play two roles in the ligand-free system. In addition to acting as a base, Et_3N appears to reduce the Pd^{II} precatalyst to the Pd^0 active species. This activation would likely involve coordination of the amine followed by β-hydride elimination.[19] Deprotonation of the resulting palladium-hydride would give the Pd^0 active species. Under ligand-free conditions, the active species is likely colloidal palladium, possibly stabilized by coordination of the amine. Since little difference is seen between the yields obtained with and without TPPTS, it is likely that TPPTS does not play a significant role in the Et_3N-mediated reactions. When sodium carbonate is used as the base, TPPTS is required, however. TPPTS is known to reduce $Pd(OAc)_2$ to generate $Pd^0(TPPTS)_n$ and phosphine oxide.[20] Upon generation of this active species, sodium carbonate is a competent base for the coupling reactions.

Interestingly, using catalytic amounts of Et_3N relative to the 5-IdU in the presence of sodium carbonate as the stoichiometric base did not result in product formation. It is possible that a higher Et_3N/Pd ratio is required to generate or stabilize the active species. Alternatively, sodium carbonate may not be a competent base for the Et_3N-derived catalyst.

In conclusion, $Pd(OAc)_2$ in the presence of Et_3N provides an effective catalyst for the aqueous-phase Heck coupling of 5-IdU. Good yields were obtained with three prototypical Heck substrates, butyl acrylate, styrene, and cyclohexenone. The coupling could be carried out on the unprotected nucleoside. Attempts to extend this reaction to bromonucleosides were unsuccessful, however.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) (a) Lakshman, M. K. *J. Organomet. Chem.* **2002**, *653*, 234. (b) Agrofoglio, L. A.; Gillaizeau, I.; Saito, Y. *Chem. Rev.* **2003**, *103*, 1875. (c) Lakshman, M. K. *Curr. Org. Synth.* **2005**, *2*, 83.
(2) De Clercq, E. *Med. Res. Rev.* **2005**, *25*, 1.
(3) (a) Fujimoto, K.; Matsuda, S.; Takahashi, N.; Saito, I. *J. Am. Chem. Soc.* **2000**, *122*, 5646. (b) Yoshimura, Y.; Noguchi, Y.; Sato, H.; Fujimoto, K. *ChemBioChem* **2006**, *7*, 598.

(4) (a) Bråthe, A.; Gundersen, L.-L.; Rise, F.; Eriksen, A. B.; Vollsnes, A. V.; Wang, L. *Tetrahedron* **1999**, *55*, 211. (b) Bråthe, A.; Gundersen, L.-L.; Nissen-Meyer, J.; Rise, F.; Spilsberg, B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 877.
(5) Langer, P. R.; Waldrop, A. A.; Ward, D. C. *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 6633.
(6) Ashwell, M.; Jones, A. S.; Kumar, A.; Sayers, J. R.; Walker, R. T.; Sakuma, T.; De Clercq, E. *Tetrahedron* **1987**, *43*, 4601.
(7) (a) Whale, R. F.; Coe, P. L.; Walker, R. T. *Nucleosides Nucleotides* **1991**, *10*, 1615. (b) Ding, Y.; Girardet, J.-L.; Hong, Z.; Shaw, S. Z.; Yao, N. *Heterocycles* **2006**, *68*, 521. (c) Bartholomä, M. D.; Vortherms, A. R.; Hillier, S.; Ploier, B.; Joyal, J.; Babich, J.; Doyle, R. P.; Zubieta, J. *ChemMedChem* **2010**, *5*, 1513.
(8) (a) Garg, N. K.; Woodroofe, C. C.; Lacenere, C. J.; Quake, S. R.; Stoltz, B. M. *Chem. Commun.* **2005**, 4551. (b) Ding, H.; Greenberg, M. M. *J. Am. Chem. Soc.* **2007**, *129*, 772. (c) Ogino, M.; Taya, Y.; Fujimoto, K. *Org. Biomol. Chem.* **2009**, *7*, 3163. (d) Reddington, M. V.; Cunninghan-Bryant, D. *Tetrahedron Lett.* **2011**, *52*, 181.
(9) Tobrman, T.; Dvořák, D. *Eur. J. Org. Chem.* **2008**, 2923.
(10) Lagisetty, P.; Zhang, L.; Lakshman, M. K. *Adv. Synth. Catal.* **2008**, *350*, 602.
(11) Štambaský, J.; Hocek, M.; Kočovský, P. *Chem. Rev.* **2009**, *109*, 6729.
(12) Shaughnessy, K. H. *Chem. Rev.* **2009**, *109*, 643.
(13) Casalnuovo, A. L.; Calabrese, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4324.
(14) (a) Western, E. C.; Daft, J. R.; Johnson, E. M. II.; Gannett, P. M.; Shaughnessy, K. H. *J. Org. Chem.* **2003**, *68*, 6767. (b) Čapek, P.; Pohl, R.; Hocek, M. *Org. Biomol. Chem.* **2006**, *4*, 2278.
(15) (a) Thoresen, L. H.; Jiao, G.-S.; Haaland, W. C.; Metzker, M. L.; Burgess, K. *Chem. Eur. J.* **2003**, *9*, 4603. (b) Cho, J. H.; Prickett, C. D.; Shaughnessy, K. H. *Eur. J. Org. Chem.* **2010**, 3678.
(16) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771.
(17) **General Procedure for Heck Coupling of 5-IdU**: All reagents were purchased from commercial sources and used as received. 5-IdU (0.3 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), and TPPTS (17.1 mg, 0.03 mmol, if used) were placed in a round-bottomed flask under nitrogen. Deoxygenated H_2O–MeCN (1:1, 3 mL) was added to the reaction vessel, followed by the addition of the alkene (1.2 mmol) and Et_3N (61.0 mg, 0.600 mmol). The reaction was heated in an oil bath at 80 °C until RP-HPLC (C-18 column, eluted with a gradient ranging from 10% MeOH in H_2O to 100% MeOH in H_2O) or RP-TLC [C-18, H_2O–MeOH (1:2) eluent] showed complete conversion. The reaction mixture was diluted to 10 mL with H_2O–MeOH (1:1) and the pH was adjusted to 6–7 using 10% aq HCl. After removal of solvent, the crude product was purified by chromatography [RP-SiO_2, H_2O → MeOH–H_2O (60:40)].
Butyl (*E*)-3-(2′-Deoxyurid-5-yl)propenoate (3): With no phosphine. Yield: 75.0 mg (64%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.69 (s, 1 H), 8.45 (s, 1 H), 7.39 (d, *J* = 15.5 Hz, 1 H), 6.88 (d, *J* = 15.5 Hz, 1 H), 6.17 (dd, *J* = 6.5, 6.5 Hz, 1 H), 5.29 (d, *J* = 4.5 Hz, 1 H), 5.20 (t, *J* = 5.0 Hz, 1 H), 4.28–4.31 (m, 1 H), 4.14 (t, *J* = 6.8 Hz, 2 H), 3.84 (dd, *J* = 7.0, 3.5 Hz, 1 H), 3.60–3.72 (m, 2 H), 2.17–2.26 (m, 2 H), 1.60–1.66 (m, 2 H), 1.35–1.43 (m, 2 H), 0.94 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 166.7, 161.6, 149.1, 143.8, 137.8, 116.4, 108.1, 87.5, 84.7, 69.6, 63.4, 60.7, 39.9, 30.2, 18.6, 13.5.
(18) Jones, A. S.; Verhelst, G.; Walker, R. T. *Tetrahedron Lett.* **1979**, 4415.
(19) (a) Louie, J.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **1996**, *35*, 2359. (b) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 13978.
(20) Amatore, C.; Blart, E.; Genêt, J. P.; Jutand, A.; Lemaire-Audoire, S.; Savignac, M. *J. Org. Chem.* **1995**, *60*, 6829.