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Modulation of the Electronic Properties of Non-innocent (*E*,*E*)-Dibenzylideneacetone for Palladium(0)-Mediated Heck Alkenylation of 5-Iodo-2′-deoxyuridine and Scale-Up Studies

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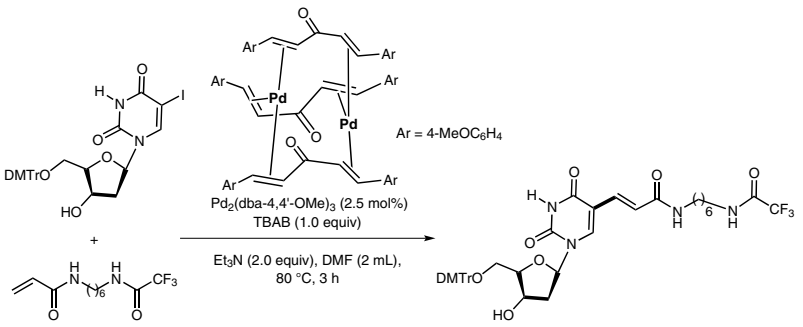
Dedicated to Professor Richard K. Taylor on his 65th birthday



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Abstract Subtle modulation of the electronic properties of the dibenzylideneacetone (dba) ligand allows the development of an efficient protocol for the Heck alkenylation of 5-iodo-2′-deoxyuridine. This protocol enables the large-scale synthesis of commercially important nucleoside building blocks. The isolation of one key molecule was accomplished under column-free conditions on a 10-gram scale.

Key words Heck alkenylation, dibenzylideneacetone, scale-up, nucleosides, 5-iodo-2′-deoxyuridine

Palladium-catalyzed cross-coupling reactions are powerful carbon–carbon (C–C) and carbon–heteroatom bond-forming reactions that have found applications in a variety of fields. These processes, in particular Suzuki–Miyaura,[1] Stille,[2] Sonogashira,[3] Buchwald–Hartwig[4] amination, and Heck[5] alkenylation reactions, have commonly been used to test the range of application of novel palladium catalysts/precatalysts. The employment of strongly σ-donating ligands in combination with common palladium precursors has allowed researchers to develop efficient catalytic systems to address synthetically challenging problems. One of the most commonly applicable phosphine-free palladium(0) precursors is the air-stable complex [Pd_2dba-H_3] first reported by Ishii.[6–9] Elaborate studies to understand the effect of 'non-innocent' dba-H on the catalytic activity of different cross-coupling reactions have been systematically carried out by Fairlamb and co-workers.[10,11] Amatore and Jutand, through their studies involving cyclic voltammetry, chronoamperometry, and UV spectroscopic experiments have also provided support for the involvement of the dba-H ligand in catalytic cycles of these processes.[12]

In recent years several examples have also emerged in the literature that support the rate-enhancing effect exerted by simple modulation of the electronic properties of the dibenzylideneacetone ligand.[13,14] Fu and co-workers have demonstrated, through their work on the intramolecular Heck reactions of unactivated alkyl halides, that instead of employing [Pd_2(dba-4,4′-$H)_3$], the use of [Pd_2(dba-4,4′-$OMe)_3$] provided better selectivity towards the formation of cyclized product.[15] Similar observations were also reported by Fairlamb and co-workers for the C–H bond arylation of unprotected adenine nucleosides where significant improvements in yields were observed with changes in the electronic properties of the dibenzylideneacetone ligand.[16] Therefore, we were inspired to develop a more efficient C–C bond-forming protocol for the synthesis of modified nucleosides by careful modulation of the electronic properties of the dibenzylideneacetone ligand.

Modified nucleosides are important biomolecules and their assembly via metal-mediated cross-coupling has become an attractive alternative to the classical synthetic approach in recent years. In particular, palladium-catalyzed cross-coupling reactions such as Suzuki–Miyaura, Stille, and Heck reactions have become an indispensable synthetic tool due to ease of handling.[17]

Derivatization of different nucleosides using these types of C–C bond-forming technologies has been routinely performed under relatively mild conditions.[18,19] One such molecule is the 2′-deoxyuridine-linker **1** (Figure 1) that has attracted much attention due to its application for post-synthesis conjugation of diagnostic oligonucleotides useful as a fluorescent tag or an affinity probe. The only reported synthesis for obtaining molecule **1** involved the cross-coupling of the toxic mercuric salt of 2′-deoxyuridine with a substituted acrylamide linker in low yield.[20] It is therefore of importance to develop a more efficient synthetic protocol with scale-up possibility. In this regard, we herein report

our findings on the effect of modulation of the electronic properties of the dibenzylideneacetone ligand on the catalytic activity of Heck alkenylation reaction of 5-iodo-2′-deoxyuridine with different linkers providing an easy access to compounds analogous to molecule **1**, and in the process develop a more efficient protocol for accessing molecule **1**. Scale-up studies of molecule **1** have also been performed with a column-free protocol for purification of the nucleoside as one of the unique features of the new processes reported herein.

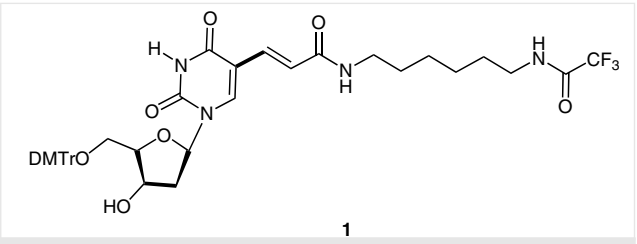

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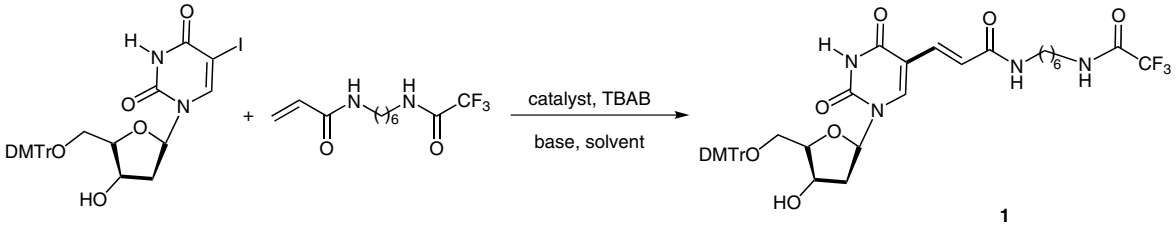
Figure 1 2′-Deoxyuridine-based C5-linker molecule; DMTr = 4,4′-dimethoxytrityl

Heck alkenylation of 5-iodo-2′-deoxyuridine with different linkers has been routinely performed under palladium-catalyzed conditions using phosphine as the ligand.[21] Although the reactivity of these catalytic systems towards such transformations has been high, the phosphine-based byproducts make the overall process synthetically less attractive. To overcome this problem we envisaged the possibility of employing easily accessible [Pd_2(dba-4,4′-H)$_3$] as a ligand-free[22] palladium(0) precursor for the Heck reaction of DMTr-protected 5-iodo-2′-deoxyuridine with different linkers and set about performing screening studies.

At the outset of our screening studies (Table 1), variation in solvent (entries 1–5) revealed that *N*,*N*-dimethylformamide was the only solvent giving any kind of reactivity under the given conditions. Although lower concentrations of catalyst loading would be beneficial for the synthesis of nucleosides, 2.5 mol% was found to be the optimum catalyst concentration to obtain better yields of the product (entries 6–10). Changes in the amount of base, solvent, or additive (TBAB) brought about a slight improvement in yield. To study the catalyst, several different palladium(0) and palladium(II) phosphine free precursors were employed (entries 23–29). Most of the palladium(II) precursors failed to furnish the desired product, while an interesting effect was observed in the case of substituted [Pd_2(dba-4,4′-X)$_3$] complexes. Interestingly, increasing the electron-density using a methoxy substituent on the dibenzylideneacetone ligand brought about an appreciable improvement in yield (entry 28), whereas a retarding effect was observed with an electron-withdrawing substituent (CF_3) on the dibenzylideneacetone (entry 29). To the best of our knowledge this is the first report of any such enhancement being observed for the Heck alkenylation of nucleosides brought about by simple modulation of the electronic properties of the dibenzylideneacetone ligand. Drastic improvement in the yield as well as reduction in reaction time was observed when a soluble base triethylamine was employed instead of sodium acetate (entries 30 and 31). This resulted in the reduction of reaction time from 18 hours to only 3, making this protocol synthetically attractive. From all these results it was decided to employ [Pd_2(dba-4,4′-OMe)$_3$] as the catalyst in the presence of triethylamine as the soluble base in *N*,*N*-dimethylformamide.

Table 1 Optimization Study for Heck Reaction of 5′-*O*-DMTr-5-iodo-2′-deoxyuridine



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Entry	Catalyst	Catalyst (mol%)	TBAB (equiv)	Base (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)
Solvent screening study								
1	[Pd_2(dba-4,4′-H)$_3$]	2.5	1.0	NaOAc (2.5)	DMF (2 mL)	80	18	28
2	[Pd_2(dba-4,4′-H)$_3$]	2.5	1.0	NaOAc (2.5)	NMP (2 mL)	80	18	–[a]
3	[Pd_2(dba-4,4′-H)$_3$]	2.5	1.0	NaOAc (2.5)	toluene (2 mL)	80	18	–[a]
4	[Pd_2(dba-4,4′-H)$_3$]	2.5	1.0	NaOAc (2.5)	xylene (2 mL)	80	18	–[a]
5	[Pd_2(dba-4,4′-H)$_3$]	2.5	1.0	NaOAc (2.5)	dioxane (2 mL)	80	18	–[a]

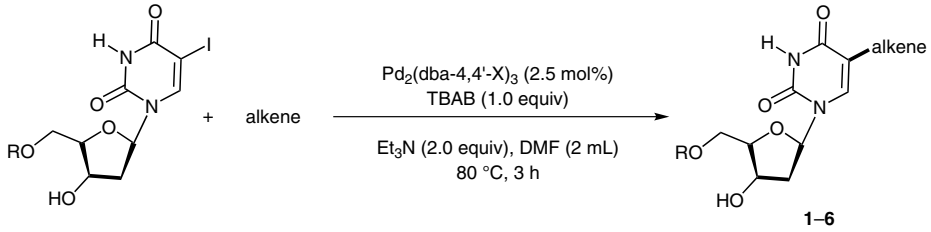
Table 1 (continued)

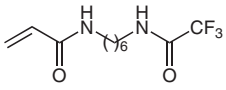
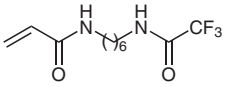
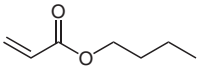
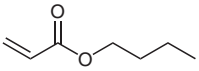
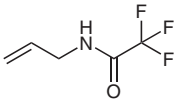
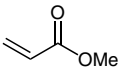
Entry	Catalyst	Catalyst (mol%)	TBAB (equiv)	Base (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)
Effect of catalyst concentration								
6	$[Pd_2(dba\text{-}4,4'\text{-}H)_3]$	2.5	1.0	NaOAc (2.5)	DMF (2 mL)	80	18	28
7	$[Pd_2(dba\text{-}4,4'\text{-}H)_3]$	1.5	1.0	NaOAc (2.5)	DMF (2 mL)	80	18	26
8	$[Pd_2(dba\text{-}4,4'\text{-}H)_3]$	1.0	1.0	NaOAc (2.5)	DMF (2 mL)	80	18	<10
9	$[Pd_2(dba\text{-}4,4'\text{-}H)_3]$	0.75	1.0	NaOAc (2.5)	DMF (2 mL)	80	48	<10
10	$[Pd_2(dba\text{-}4,4'\text{-}H)_3]$	0.25	1.0	NaOAc (2.5)	DMF (2 mL)	80	48	<10
Impact of base (equiv)								
11	$[Pd_2(dba\text{-}4,4'\text{-}H)_3]$	2.5	1.0	NaOAc (2.0)	DMF (2 mL)	80	18	28
12	$[Pd_2(dba\text{-}4,4'\text{-}H)_3]$	2.5	1.0	NaOAc (2.5)	DMF (2 mL)	80	18	28
13	$[Pd_2(dba\text{-}4,4'\text{-}H)_3]$	2.5	1.0	NaOAc (3.0)	DMF (2 mL)	80	18	38
14	$[Pd_2(dba\text{-}4,4'\text{-}H)_3]$	2.5	1.0	NaOAc (3.5)	DMF (2 mL)	80	18	37
15	$[Pd_2(dba\text{-}4,4'\text{-}H)_3]$	2.5	1.0	NaOAc (4.0)	DMF (2 mL)	80	18	34
Impact of concentration								
16	$[Pd_2(dba\text{-}4,4'\text{-}H)_3]$	2.5	1.0	NaOAc (3.0)	DMF (1 mL)	80	18	25
17	$[Pd_2(dba\text{-}4,4'\text{-}H)_3]$	2.5	1.0	NaOAc (3.0)	DMF (2 mL)	80	18	38
18	$[Pd_2(dba\text{-}4,4'\text{-}H)_3]$	2.5	1.0	NaOAc (3.0)	DMF (4 mL)	80	18	28
Impact of TBAB (equiv)								
19	$[Pd_2(dba\text{-}4,4'\text{-}H)_3]$	2.5	0	NaOAc (3.0)	DMF (2 mL)	80	18	5
20	$[Pd_2(dba\text{-}4,4'\text{-}H)_3]$	2.5	0.5	NaOAc (3.0)	DMF (2 mL)	80	18	34
21	$[Pd_2(dba\text{-}4,4'\text{-}H)_3]$	2.5	1.0	NaOAc (3.0)	DMF (2 mL)	80	18	38
22	$[Pd_2(dba\text{-}4,4'\text{-}H)_3]$	2.5	2.0	NaOAc (3.0)	DMF (2 mL)	80	18	36
Catalyst screening study								
23	$[Pd_2(dba\text{-}4,4'\text{-}H)_3]$	2.5	1.0	NaOAc (3.0)	DMF (2 mL)	80	18	38
24	$PdCl_2$	5.0	1.0	NaOAc (3.0)	DMF (2 mL)	80	18	–[a]
25	$[K_2PdCl_4]$	5.0	1.0	NaOAc (3.0)	DMF (2 mL)	80	18	–[a]
26	$Pd(OAc)_2$	5.0	1.0	NaOAc (3.0)	DMF (2 mL)	80	18	–[a]
27	Pd/C	5.0	1.0	NaOAc (3.0)	DMF (2 mL)	80	18	–[a]
28	$[Pd_2(dba\text{-}4,4'\text{-}OMe)_3]$	2.5	1.0	NaOAc (3.0)	DMF (2 mL)	80	18	49
29	$[Pd_2(dba\text{-}4,4'\text{-}CF_3)_3]$	2.5	1.0	NaOAc (3.0)	DMF (2 mL)	80	18	8
Selection of base								
30	$[Pd_2(dba\text{-}4,4'\text{-}OMe)_3]$	2.5	1.0	NaOAc (3.0)	DMF (2 mL)	80	18	49
31	$[Pd_2(dba\text{-}4,4'\text{-}OMe)_3]$	2.5	1.0	Et_3N (2.0)	DMF (2 mL)	80	3	64
Impact of reaction temperature								
32	$[Pd_2(dba\text{-}4,4'\text{-}OMe)_3]$	2.5	1.0	Et_3N (2.0)	DMF (2 mL)	80	3	64
33	$[Pd_2(dba\text{-}4,4'\text{-}OMe)_3]$	2.5	1.0	Et_3N (2.0)	DMF (2 mL)	60	8	57
34	$[Pd_2(dba\text{-}4,4'\text{-}OMe)_3]$	2.5	1.0	Et_3N (2.0)	DMF (2 mL)	40	18	48

[a] No reaction.

Our next focus was to further study the effect of change in electronic properties of the dibenzylideneacetone ligand on the Heck alkenylation of DMTr-protected and unprotected 5-iodo-2′-deoxyuridine with different linkers (Table 2). To assess the generality of the observed rate differences in Heck alkenylation, three palladium(0) precursors were employed, namely $[Pd_2(dba\text{-}4,4'\text{-}H)_3]$, $[Pd_2(dba\text{-}4,4'\text{-}OMe)_3]$, and $[Pd_2(dba\text{-}4,4'\text{-}CF_3)_3]$. First, we investigated this reaction under the given set of conditions using triethylamine as the base.

Table 2 Effect of Modulation of Electronic Properties on Heck Reaction of 5-Iodo-2′-deoxyuridine



Entry	Alkene	R	Yield (%) with catalyst employed		
			$[Pd_2(dba\text{-}4,4'\text{-}H)_3]$	$[Pd_2(dba\text{-}4,4'\text{-}OMe)_3]$	$[Pd_2(dba\text{-}4,4'\text{-}CF_3)_3]$
1		DMTr (**1**)	30	64	13
2		H (**2**)	25	75	10
3		DMTr (**3**)	57	71	31
4		H (**4**)	63	77	45
5		H (**5**)	51	62	39
6		H (**6**)	69	88	27

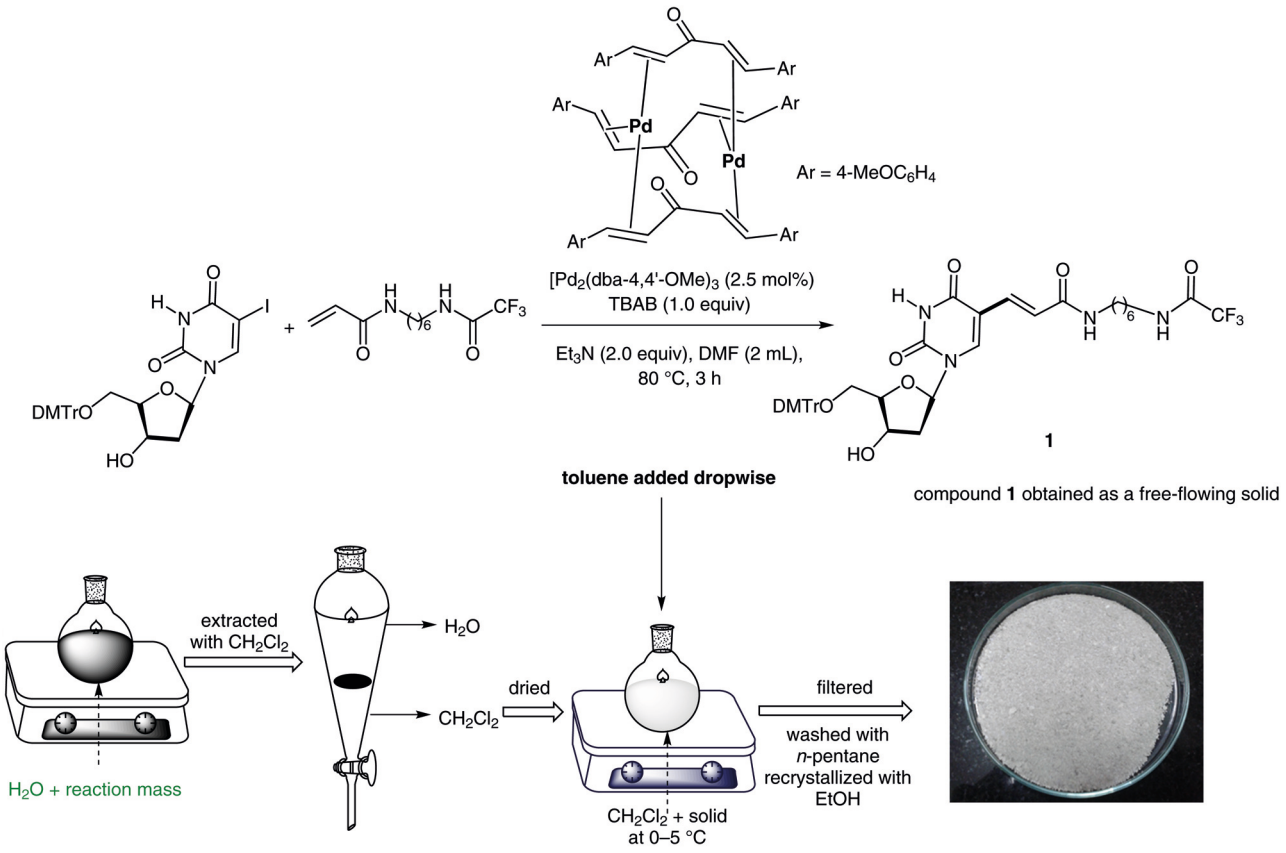
It is apparent that dba-4,4′-X ligands play a major role in determining the reactivity of the catalytic system. In most cases, appreciable differences in reactivity were observed with the $[Pd_2(dba\text{-}4,4'\text{-}OMe)_3]$ complex, outperforming all others irrespective of the substrate (DMTr-protected or unprotected 5-iodo-2′-deoxyuridine). Although, with increase in chain length of the linker a more pronounced effect could be observed. It is, at present, difficult to predict the exact reason for such an observation, however a nanoparticular pathway (similar to the ones reported by Jeffrey[22c] and de Vries[22a] for phosphine-free Heck reactions) seems more of a possibility. Although, the involvement of substituted dba-4,4′-X ligands could be directly involved in the rate-determining oxidative addition step.[10c] This process could be accelerated by the donating properties of the dba-4,4′-X ligands.

These results encouraged us to explore the possibility of developing an efficient and more importantly a column-free protocol for the synthesis of fully protected nucleoside **1**. The reaction conditions developed herein were employed to carry out the catalytic cross-coupling reaction of the 5-iodo-2′-deoxyuridine with the 6-acryloyl-*N*′-trifluoroacetyl-1,6-diaminohexane linker[23] on a 5.0-mmol (3.28 g) scale using $[Pd_2(dba\text{-}4,4'\text{-}OMe)_3]$ as the catalyst (Table 3).

For the purification of the cross-coupled product **1**, a liquid antisolvent purification method[24,25] was viewed as a viable option for the isolation of the nucleoside as it is less energy intensive and ideal for scale-up processes, it has improved handling, and it is contaminant free. The crude product on dissolution in dichloromethane was stirred at 0–5 °C and slow addition of toluene as the antisolvent resulted in the precipitation of compound **1**, which was filtered, washed with pentane resulting in 61% of pure isolated product (confirmed by LCMS, NMR, and HPLC). Excellent reproducibility was observed when the reaction was repeated on a 5.0- and 15-mmol scale (Table 3).

To the best of our knowledge, this is most efficient, high-yielding nonchromatographic protocol for the synthesis of DMTr-protected nucleoside **1**. It should also be mentioned that the process for C–C bond formation developed herein is mild enough to sustain an acid-labile (DMTr) and a base-labile (TFA) group during this reaction.

Table 3 Scale-Up Synthesis of DMTr-Protected Nucleoside **1** (Column-Free Purification Protocol by Liquid Antisolvent Precipitation)



Scale-up	Amount					Solvent (mL)	Yield (%) (Weight)
	Nucleoside	Alkene	Catalyst	TBAB	Et_3N		
1st	5.0 mmol (3.28 g)	5.0 mmol (1.33 g)	0.12 mmol (0.14 g)	5.0 mmol (1.61 g)	10 mmol (1.01 g)	DMF (10)	61% (2.42 g)
2nd	5.0 mmol (3.28 g)	5.0 mmol (1.33 g)	0.12 mmol (0.14 g)	5.0 mmol (1.61 g)	10 mmol (1.01 g)	DMF (10)	61% (2.48 g)
3rd	7.61 mmol (5.0 g)	7.61 mmol (2.02 g)	0.19 mmol (0.21 g)	7.61 mmol (2.45 g)	15.22 mmol (1.54 g)	DMF (15)	61% (3.7 g)
4th	15.23 mmol (10.0 g)	15.23 mmol (4.04 g)	0.38 mmol (0.42 g)	15.23 mmol (4.90 g)	30.44 mmol (3.08 g)	DMF (30)	60% (7.3 g)

An efficient and environmentally friendly protocol for the large-scale synthesis of DMTr-protected C5-modified nucleosides has been made possible through the simple modulation of the electronic properties of the dibenzylideneacetone ligand in the phosphine-free palladium(0) precursor [Pd_2(dba-4,4′-X)$_3$]. The electron-donating substituent (OMe) on the dibenzylideneacetone ligand [Pd_2(dba-4,4′-OMe)$_3$] significantly improved the product yield over its electron-withdrawing (CF_3) substituent during cross-coupling reactions of nucleosides. Scale-up of the synthetic process for compound **1** was also demonstrated with 10 grams of substrate with excellent reproducibility. Furthermore, the product isolation without chromatography makes this protocol very attractive for further scale-up and applicable to the synthesis of other nucleoside analogues.

NMR data (^1H or ^{13}C) were recorded on Bruker Avance 400 spectrometers. HPCL-MS analyses were performed on a Shimadzu Prominence spectrometer. The ionization mechanism used was electrospray in positive and negative ion full scan mode using MeCN as solvent and N_2 gas for desolvation. IR spectra were recorded on a Perkin-Elmer spectrophotometer 16F PC FTIR, by preparing KBr pellets. C, H and N analyses were carried out with a Carlo Erba instrument.

Heck Alkenylation of 5-Iodo-2'-deoxyuridine; General Procedure

A solution of precatalyst [Pd_2(dba-4,4′-OMe)$_3$] (2.5 mol%) in anhyd DMF (1.0 mL) was stirred for 5 min at r.t. under N_2. Then, nucleoside (0.5 mmol) along with TBAB (0.5 mmol) were added and the solution stirred for 5 min at 80 °C. Thereafter, Et_3N (1.0 mmol) and alkene linker (0.5 mmol) were also added with DMF (1.0 mL). The resulting solution was then stirred at 80 °C for 3.0 h. When the reaction was complete, the solvent was removed under vacuo and the resultant residue obtained was purified by column chromatography (CH_2Cl_2–MeOH, 96:4) to afford the desired product as a white solid. Spectroscopic data matched those for previously reported compounds in the literature: **1**,[20] **4**,[26] **5**,[27] and **6**.[28]

(*E*)-3-[1-(5-{[Bis(4-methoxyphenyl)(phenyl)methoxy]methyl}-4-hydroxytetrahydrofuran-2-yl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl]-*N*-[6-(2,2,2-trifluoroacetamido)hexyl]acrylamide (1)[20]

Yield: 0.258 g (64%).

IR (KBr): 3424, 3080, 2934, 1705, 1609, 1508, 1251, 1178, 1033, 829 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.55 (s, 1 H), 9.40 (s, 1 H), 8.03–8.01 (m, 2 H), 7.34–7.17 (m, 8 H), 7.09–6.84 (m, 5 H), 6.18–6.15 (m, 1 H), 5.29 (s, 1 H), 4.23 (s, 1 H), 3.89–3.86 (m, 1 H), 3.72 (s, 3 H), 3.70 (s, 3 H), 3.22–3.09 (m, 6 H), 2.35–2.14 (m, 2 H), 1.52–1.39 (m, 5 H), 1.32–1.25 (m, 5 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 165.7, 162.1, 158.2, 156.4 (q, J = 38 Hz, $COCF_3$), 149.5, 145.0, 142.8, 135.7, 132.3, 129.8, 127.9, 127.8, 126.7, 122.1, 117.5 (q, J = 288 Hz, CF_3), 113.3, 109.5, 85.6, 85.5, 84.6, 70.2, 63.9, 54.9, 29.0, 28.2, 26.0, 25.9.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –77.09.

MS (ESI): m/z = 795 [M + H$^+$].

Anal. Calcd for $C_{41}H_{45}F_3N_4O_9$: C, 61.96; H, 5.71; N, 7.05. Found: C, 61.82; H, 5.63; N, 6.95.

(*E*)-3-{1-[4-Hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl}-*N*-[6-(2,2,2-trifluoroacetamido)hexyl]acrylamide (2)

Yield: 0.184 g (75%).

IR (KBr): 3439, 2942, 1721, 1671, 1556, 1477, 1294, 988 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.56 (s, 1 H), 9.41 (s, 1 H), 8.27 (s, 1 H), 8.06 (s, 1 H), 7.12–6.98 (m, 4 H), 6.17–6.13 (m, 1 H), 5.27–5.25 (m, 1 H), 5.16–5.14 (m, 1 H), 4.27 (s, 1 H), 3.80 (s, 1 H), 3.68–3.55 (m, 2 H), 3.17–3.10 (m, 4 H), 2.17–2.13 (m, 2 H), 1.48–1.43 (m, 4 H), 1.29–1.22 (m, 4 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 165.6, 162.0, 156.8 (q, J = 39 Hz, $COCF_3$), 149.4, 142.5, 132.1, 121.7, 117.5 (q, J = 289 Hz, CF_3), 109.2, 87.6, 84.6, 70.0, 61.0, 29.0, 28.1, 26.0, 25.9.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –77.10.

MS (ESI): m/z = 493 [M + H$^+$].

Anal. Calcd for $C_{20}H_{27}F_3N_4O_7$: C, 48.78; H, 5.53; N, 11.38. Found: C, 48.61; H, 5.39; N, 11.45.

Butyl (*E*)-3-[1-(5-{[Bis(4-methoxyphenyl)(phenyl)methoxy]methyl}-4-hydroxytetrahydrofuran-2-yl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl]acrylate

Yield: 0.227 g (71%).

IR (KBr): 3452, 2923, 1699, 1510, 1250, 1097 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (s, 1 H), 7.41–7.39 (m, 2 H), 7.31–7.22 (m, 8 H), 6.98–6.83 (m, 6 H), 6.28–6.25 (m, 1 H), 4.50–4.48 (m, 1 H), 4.11–4.05 (m, 3 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.43–3.40 (m, 2 H), 2.57–2.54 (m, 1 H), 2.31–2.26 (m, 1 H), 1.57–1.53 (m, 2 H), 1.34–1.26 (m, 3 H), 0.91–0.87 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.3, 161.4, 158.6, 149.4, 144.2, 141.5, 135.8, 135.4, 135.3, 129.9, 127.9, 127.0, 119.8, 113.2, 110.0, 86.8, 86.5, 86.0, 72.0, 64.1, 55.1, 41.2, 30.4, 18.9, 13.5.

MS (ESI, –): m/z = 655 [M – H$^+$].

Anal. Calcd for $C_{37}H_{40}N_2O_9$: C, 67.67; H, 6.14; N, 4.27. Found: C, 67.54; H, 6.01; N, 4.13.

Large-Scale Heck Alkenylation of 5-Iodo-2′-deoxyuridine via Column-Free Protocol; General Procedure

A solution of precatalyst [Pd_2(dba-4,4′-OMe)$_3$] (2.5 mol%) in anhyd DMF (5 mL) was stirred for 5 min at r.t. under N_2. Then, nucleoside (5 mmol) along with TBAB (5 mmol) were added and the solution stirred for 5 min at 80 °C. Thereafter, Et_3N (10 mmol) and alkene linker (5 mmol) were also added with DMF (5 mL). The resulting solution was then stirred at 80 °C for 3.0 h. The mixture was poured into ice-cold water (500 mL) and the resultant mixture was stirred vigorously for 30 min. This solution was then extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic layer was evaporated in vacuo to give a solid residue. The solid obtained was subsequently dissolved in CH_2Cl_2 (50 mL). The solution was cooled with ice and stirred on a magnetic stirrer. To this solution was slowly added toluene to precipitate out the desired product **1** which was later recrystallized (EtOH, 20 mL) to provide pure product (2.42 g, 61%) identical to that reported by Lyttle and co-workers.[20]

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Supporting Information

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