C–H Bond Activation

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Palladium-Catalyzed Cross-Coupling of Internal Alkenes with Terminal Alkenes to Functionalized 1,3-Butadienes Using C–H Bond Activation: Efficient Synthesis of Bicyclic Pyridones**

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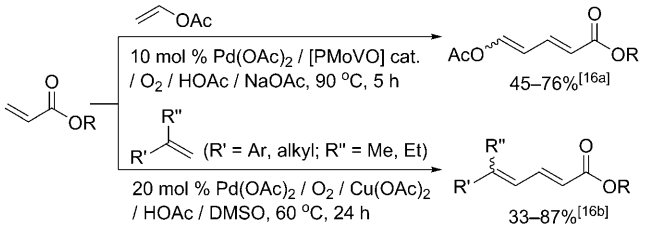
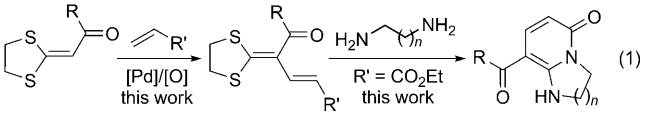
Transition-metal-catalyzed cross-coupling through C–H bond activation is emerging as one of the most important tools for carbon–carbon bond formation.[1] In general, vinylogous compounds can be synthesized by Wittig,[2] Heck,[3] and Suzuki[4] reactions, from the condensation of carbonyl compounds,[5] C–H addition to alkynes,[6] or by means of organometallic alkenyl compounds,[7] but direct alkenylation using C–H bond activation remains particularly attractive for constructing carbon–carbon double bonds owing to their synthetic simplicity and use of readily available reagents.[8] Vinylborates,[9] vinyl halides,[10] alkenyl acetates,[11] and cyclic 1,3-dicarbonyls[12] have been known for the direct alkenylation of arene and (hetero)arene C–H bonds. In a more simple and synthetically useful alkenylation, terminal alkenes have been applied as the coupling partners.[13–15] However, little attention has been paid to the direct alkenylation of alkenyl C–H bonds with an alkene as the coupling partner using C–H bond activation.[16]

1,3-Butadienes, as a class of versatile organic synthetic reagents,[17] have usually been prepared by indirect methods.[18] To date, only two reports have been documented for their direct synthesis, involving coupling two simple terminal alkenes, owing to the difficulty in activating two alkene substrates at the same time (Scheme 1).[16] Although two examples involving the reaction of 3-methyl-1*H*-indenes with *tert*-butyl acrylate were also reported,[16b] no work has been directed to the direct alkenylation of open-chain internal alkenes with another alkene as the coupling partner. In order to realize the direct cross-coupling of an internal alkene with a terminal alkene, the low reactivity of an internal alkenyl C–H bond should be overcome. We envisioned the introduction of a structural element that could increase the reactivity of an internal alkenyl C–H bond.[19] Thus, we hypothesized that a 1,2-dithiane group at the terminal position of an alkene should satisfy the requirement on activating an internal alkenyl C–H bond, and α-oxoketene dithioacetals[20] were chosen as the internal alkenes. Herein, we report the palladium(II)-catalyzed direct cross-coupling of α-oxoketene dithioacetals with terminal alkenes as well as the synthesis of bicyclic pyridones [Eq. (1)].



Scheme 1. Direct cross-coupling of two terminal alkenes.[16] Ac = acetate, DMSO = dimethyl sulfoxide.



The reaction of α-oxoketene dithioacetal **1a** with *tert*-butyl acrylate (**2a**) was explored to screen the reaction conditions (Table 1). With 10 mol% of $Pd(OAc)_2$ as the catalyst and in the presence of 2 equivalents of AgOAc, the reaction proceeded in *N*,*N*-dimethylformamide (DMF) at ambient temperature under an air atmosphere, forming the desired product, 1,3-buta-diene **3a**, in 49% yield within 40 hours (Table 1, entry 1). Increasing the temperature to 50 °C remarkably accelerated the reaction, while further elevating the reaction temperature did not obviously improve the reaction efficiency (Table 1, entries 2 and 3). Extending the reaction time deteriorated the yield of **3a** from 63% to 50%, owing to product decomposition (Table 1, entry 4). *N*,*N*-dimethylformamide seemed to be a suitable reaction solvent. An oxygen atmosphere did not promote the reaction,

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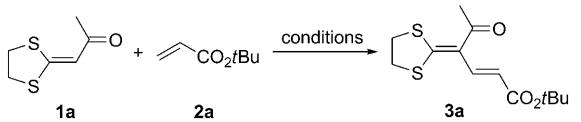
Table 1: Screening of reaction conditions for the direct cross-coupling of α-oxoketene dithioacetal **1a** with terminal alkene **2a**.[a]



1a **2a** **3a**

Entry	Catalyst (mol%)	Oxidant	Solvent	*T* [°C]	*t* [h]	Yield [%][b]
1	$Pd(OAc)_2$ (10)	AgOAc	DMF	RT	40	49 (39)[c]
2	$Pd(OAc)_2$ (10)	AgOAc	DMF	50	12	63
3	$Pd(OAc)_2$ (10)	AgOAc	DMF	70	12	64
4	$Pd(OAc)_2$ (10)	AgOAc	DMF	50	22	50
5	$Pd(OAc)_2$ (10)	AgOAc	DMSO	50	12	32
6	$Pd(OAc)_2$ (10)	AgOAc	toluene	50	12	15
7	$Pd(OAc)_2$ (10)	AgOAc	TFA	50	12	n.r.
8	$Pd(OAc)_2$ (10)	AgOAc	DMA	50	12	52
9	$Pd(OAc)_2$ (10)	AgOAc	THF	50	12	40
10	$Pd(OAc)_2$ (10)	O_2[d]	DMF	50	12	3
11	$Pd(OAc)_2$ (10)	AgOAc/O_2[d]	DMF	50	12	64
12	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$	DMF	50	12	11
13	$Pd(OAc)_2$ (10)	BQ	DMF	50	12	20
14	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$	DMF	50	12	n.r.
15	$PdCl_2$ (10)	AgOAc	DMF	50	12	15
16	$[Pd(PPh_3)_2Cl_2]$ (10)	AgOAc	DMF	50	12	6
17	$[Pd(PPh_3)_4]$ (10)	AgOAc	DMF	50	12	5
18	$Pd(OAc)_2$ (15)	AgOAc	DMF	50	8	75
19	$Pd(OAc)_2$ (20)	AgOAc	DMF	50	8	94 (86)[c]
20	$Pd(OAc)_2$ (20)	AgOAc[e]	DMF	50	8	74
21	$Pd(OAc)_2$ (20)	AgOAc[f]	DMF	50	8	81
22	$Pd(OAc)_2$ (20)	AgOAc[g]	DMF	50	8	90

[a] Conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), oxidant (1.0 mmol), solvent (2 mL), in air. [b] Determined by GC analysis. [c] Yield of isolated product given in parentheses. [d] Atmospheric O_2. [e] 1.0 equivalent. [f] 1.5 equivalents. [g] 3 equivalents. n.r. = no reaction, TFA = trifluoroacetic acid.

and $Cu(OAc)_2$, *para*-benzoquinone (BQ), and $PhI(OAc)_2$ were much less efficient oxidants than AgOAc. The use of $PdCl_2$, $[Pd(PPh_3)_2Cl_2]$, or $[Pd(PPh_3)_4]$ as the catalyst led to poor formation of the product (Table 1, entries 15–17). Increasing the catalyst loading from 10 to 20 mol% significantly increased the product yield from 63% to 94% (Table 1, entries 2, 18, and 19). It is noteworthy that 2 equivalents of AgOAc were necessary for a satisfactory conversion of **1a** (Table 1, entries 20–22).

Using these optimized conditions, the scope of the procedure was then examined (Table 2). The reactions of **1a** with electron-deficient terminal alkenes, i.e., alkyl acrylates and *N*,*N*-dimethylacrylamide **2a–d**, afforded 1,3-butadienes **3a–d** in 83–89% yield (Table 2, entries 1–4). With acrolein **2e**, product **3e** was obtained in only 45% yield (Table 2, entry 5). Treatment of **1a** with styrene (**2f**) generated the desired product **3f** (69%) and its isomer **3f′** (11%; Table 2, entry 6). In a similar fashion, the reaction of **1a** with 4-chlorostyrene (**2g**) also resulted in the separable isomers **3g** (73%) and **3g′** (10%; Table 2, entry 7). However, the reaction of **1a** and 4-methoxystyrene (**2h**) or 2-methylstyrene (**2i**) led to inseparable mixtures of isomers **3** and **3′** (Table 2, entries 8 and 9). Unexpectedly, the reaction of **1a** and allyl benzoate (**2j**) formed the allylation product **3j** in 56% yield. Vinyl acetate (**2k**) only exhibited a moderate reactivity. Allyl alcohol (**2l**) underwent the cross-coupling reaction with **1a** to afford 1,3-butadiene **3e** (37%), thus suggesting oxidation of the alcoholic hydroxyl during the reaction. The reactions of **1ba–c** with **2c** and **2d** produced the desired products **3l–o** in 54-67% yields (Table 2, entries 13–16), respectively, while the reactions of heteroaryl α-oxoketene dithioacetals **1bd** and **1be** with **2c** formed the desired major products **3p** (62%) and **3q** (60%) as well as the by-products **3p′** (7%) and **3q′** (7%) [Table 2, entries 17 and 18; Eq. (2)]. However, α-oxoketene

Table 2: Direct alkenylation of α-oxoketene dithioacetals **1a–d** with terminal alkenes **2**.[a]

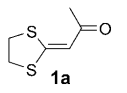
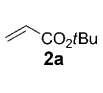
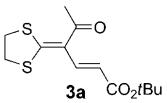
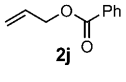
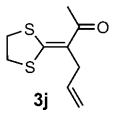
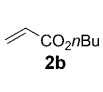
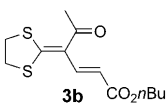
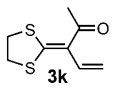
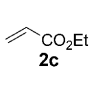
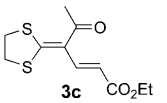
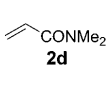
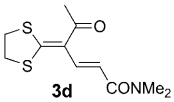
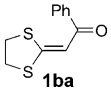
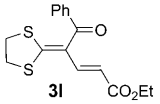
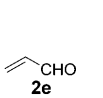
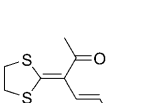
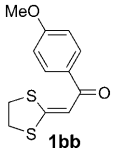
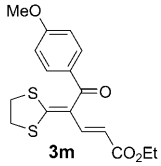
Entry	1	2	Product 3	Yield [%][b]	Entry	1	2	Product 3	Yield [%][b]
1	 **1a**	 **2a**	 **3a**	86	10[c]	**1a**	 **2j**	 **3j**	56
2	**1a**	 **2b**	 **3b**	83	11[c]	**1a**	 **2k**	 **3k**	35
3	**1a**	 **2c**	 **3c**	85	12[c]	**1a**	 **2l**	**3e**	37
4	**1a**	 **2d**	 **3d**	89	13	 **1ba**	**2c**	 **3l**	56
5[c]	**1a**	 **2e**	 **3e**	45	14	 **1bb**	**2c**	 **3m**	64

Table 2: (Continued)

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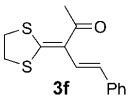
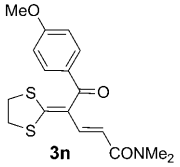
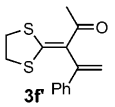
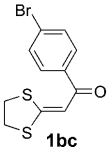
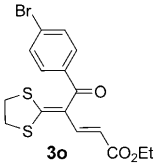
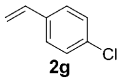
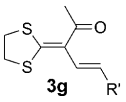
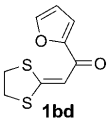
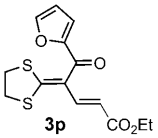
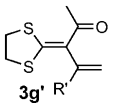
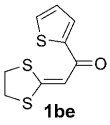
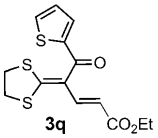
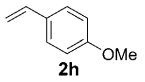
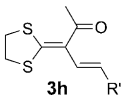
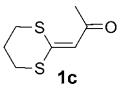
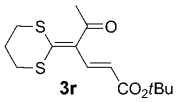
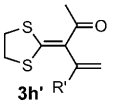
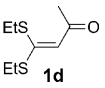
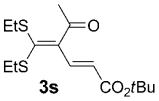
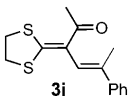
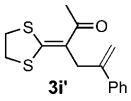
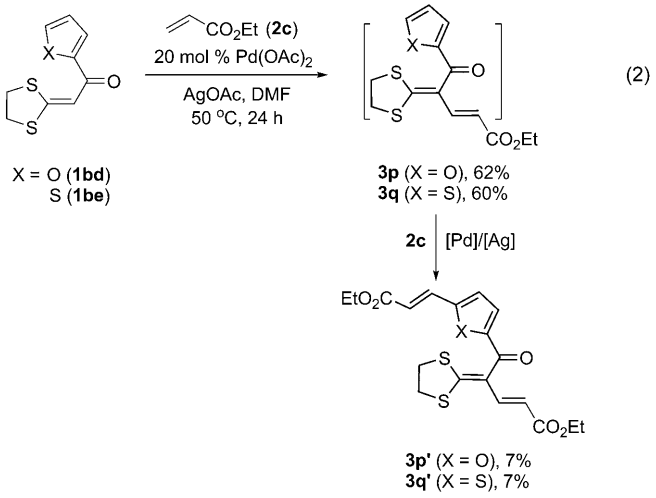
6[c]	1a	 2f	 3f	69	15	1bb	2d	 3n	67
			 3f'	11	16	 1bc	2c	 3o	54
7[c,d]	1a	 2g	 3g	73	17[g]	 1bd	2c	 3p	62
			 3g'	10	18[g]	 1be	2c	 3q	60
8[c,e]	1a	 2h	 3h	71 (3h/3h'=4:1)[f]	19	 1c	2a	 3r	38
			 3h'		20	 1d	2a	 3s	< 5
9[c]	1a	 2i	 3i	67 (3i/3i'=1:4)[f]					
			 3i'						

[a] Conditions: **1** (0.5 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (20 mol%), AgOAc (1.0 mmol), DMF (2 mL), 50°C, in air. Entries 1–4, 8 h; entries 5–8 and 10–12, 12 h; entries 9 and 13–18, 24 h. [b] Yield of isolated products. [c] **2** (2.5 mmol). [d] R′ = 4-ClC_6H_4. [e] R′ = 4-$MeOC_6H_4$. [f] Determined by ^1H NMR spectroscopy. [g] See Equation (2).

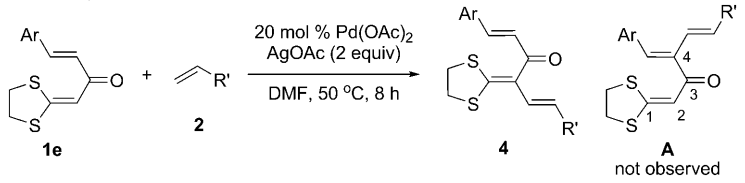
dithioacetals **1c** and **1d** only exhibited poor reactivity (Table 2, entries 19 and 20), thus revealing an obvious substituent effect of the alkylthio groups. The molecular structures of **3** were confirmed by the X-ray crystallographic structural determination of **3n**, in which the newly coupled carbon–carbon double bond exists in an *E* configuration (see the Supporting Information).

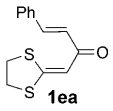
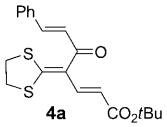
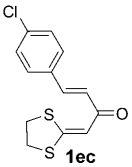
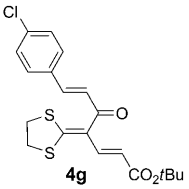
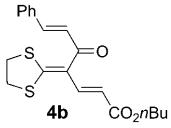
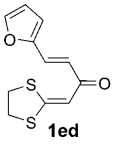
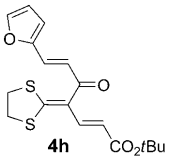
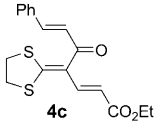
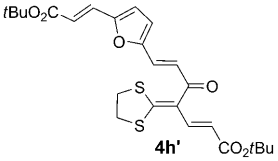
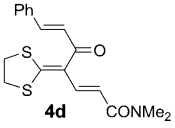
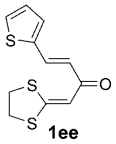
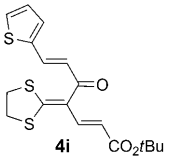
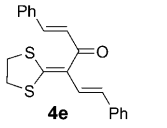
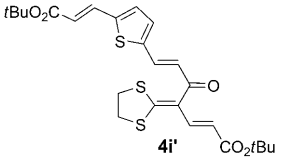
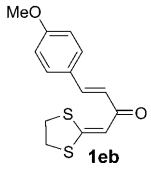
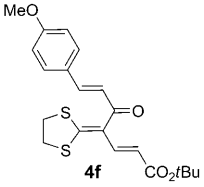
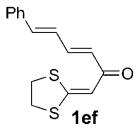
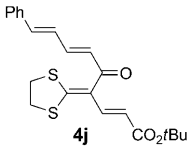
The cross-coupling reactions of α-cinnamoyl ketene dithioacetals **1ea** with alkenes **2a–d** gave ployene products **4a–d** in 71–82% yields (Table 3, entries 1–4). Using styrene **2f**, the desired product **4e** was obtained in 62% yield. Treatment of **1eb** and **1ec** with **2a** also efficiently afforded the desired products in 79% and 78% yields, respectively (Table 3, entries 6 and 7). Heteroaryl dithioacetals **1ed** and **1ee** were coupled with **2a** to afford **4h** and **4i** (60% and 62%, respectively) as well as the separable double alkenylation products **4h′** and **4i′** (8% and 10%, respectively; Table 3, entries 8 and 9). Triene **1ef** underwent the same reaction,



(2)

Table 3: Direct alkenylation of α-cinnamoyl ketene dithioacetals **1e** with terminal alkenes **2**.[a]



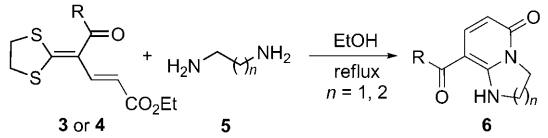
Entry	1	2	Product 4	Yield [%][b]	Entry	1	2	Product 4	Yield [%][b]
1	 **1ea**	**2a**	 **4a** CO_2tBu	82	7	 **1ec**	**2a**	 **4g** CO_2tBu	78
2	**1ea**	**2b**	 **4b** CO_2nBu	75	8	 **1ed**	**2a**	 **4h** CO_2tBu	60
3	**1ea**	**2c**	 **4c** CO_2Et	73				 **4h'** CO_2tBu	10
4	**1ea**	**2d**	 **4d** $CONMe_2$	71	9	 **1ee**	**2a**	 **4i** CO_2tBu	62
5[c]	**1ea**	**2f**	 **4e** Ph	62				 **4i'** CO_2tBu	8
6	 **1eb**	**2a**	 **4f** CO_2tBu	79	10	 **1ef**	**2a**	 **4j** CO_2tBu	59

[a] Conditions: **1e** (0.5 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (20 mol%), AgOAc (1.0 mmol), DMF (2 mL), 50°C, in air, 8 h. [b] Yield of isolated product. [c] **2f** (2.5 mmol).

forming tetraene **4j** (59%; Table 3, entry 10). Trienes of type **A** were not detected from the reactions, thus suggesting that the C(4)–H bond is much less reactive than the C(2)–H bond in **1e**. This observation is rationalized by the electronic nature of the carbon–carbon double bonds of **1e**, wherein polarization flows from the two electron-donating sulfur atoms to the electron-withdrawing carbonyl group[20] and makes C(2) more nucleophilic than C(4). Therefore, the C(2)–H bond in **1e** can be more easily activated to couple with terminal alkenes **2**. In addition, the C(5′)–H bond in 2′-furyl or 2′-thienyl substrates is also more reactive than the C(4)–H bond, so that double alkenylation occurred at C(5′) instead of C(4) in **1e**.

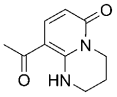
The reaction of **1** and **2** is presumably initiated by formation of the organometallic ketene species **B** from the electrophilic attack of the catalyst precursor $Pd(OAc)_2$ at C(2)–H bond of α-oxoketene dithioacetal **1** (Scheme 2). Coordination of terminal alkene **2** to the metal center, followed by insertion of the coordinated carbon–carbon double bond to the Pd–C bond forms species **C** which controls the stereochemical configuration of the products. β-Hydrogen elimination occurs to afford the desired 1,3-

Table 4: Synthesis of bicyclic pyridones **6**.[a,b]

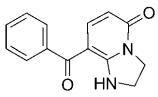


3 or **4** **5** **6**

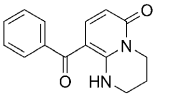
6a, 79%



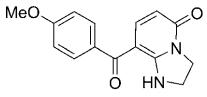
6b, 58%



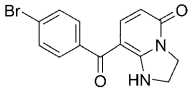
6c, 85%



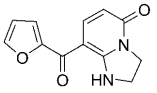
6d, 84%



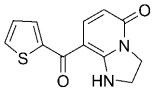
6e, 88%



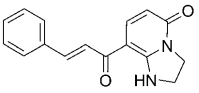
6f, 87%



6g, 74%

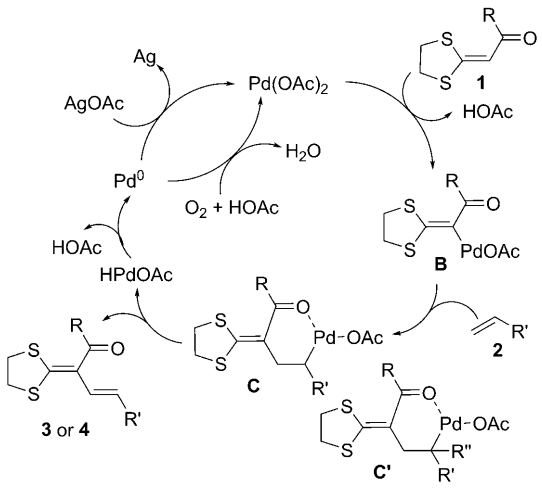


6h, 71%



6i, 63%[c]

[a] Conditions: **3** or **4** (0.25 mmol), diamine **5** (0.3 mmol), EtOH (2 mL), reflux, 14 h. [b] Yield of isolated product. [c] 100 °C.



Scheme 2. A proposed mechanism.

butadiene product **3** or **4** as well as a HPdOAc species which can be further reduced to palladium(0). Oxidation of the palladium(0) species regenerates $Pd(OAc)_2$ and finishes the catalytic cycle. Production of **3i′** and **3j** is presumably attributed to the formation of palladium(II) intermediate **C′**.

Pharmacologically active bicyclic pyridones[21] are usually synthesized by cyclocondensation of ketenaminals,[22] addition of diamines to thiomethyl pyridones,[23] intramolecular Mitsunobu reactions of 2,6-difluoropyridines,[24] and the functionalization of simple bicyclic pyridones.[25] Intrigued by the structural features, we reacted **3** and **4** with different diamines in ethanol at reflux, efficiently affording bicyclic pyridones **6** in 58–88% yields (Table 4). The molecular structures of **6** were further confirmed by X-ray crystallography of **6b** in which multiple hydrogen bonds are present (see the Supporting Information).

In summary, a novel palladium-catalyzed direct alkenylation of internal alkenes α-oxoketene dithioacetals with terminal alkenes has been successfully developed to synthesize functionalized 1,3-butadienes using C–H bond activation. Condensation of the resultant 1,3-butadienes with diamines efficiently afforded potentially bioactive bicyclic pyridones.

Experimental Section

Synthesis of **3a**: A mixture of **1a** (80 mg, 0.5 mmol), **2a** (128 mg, 1.0 mmol), $Pd(OAc)_2$ (23 mg, 0.1 mmol), and AgOAc (167 mg, 1.0 mmol) in DMF (2 mL) was stirred at 50 °C for 8 h. Water (30 mL) was then added, the solution was filtered, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and the volatile compounds were evaporated under reduced pressure. The resultant residue was purified by column chromatography on silica gel (petroleum ether (60–90 °C)/diethyl ether 9:1, v/v) to afford **3a** as a yellow solid (123 mg, 86%).

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Keywords: alkenes · alkenylation · C–H activation · heterocycles · palladium

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