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Dehydrative Synthesis of Functionalized Skipped Dienes from Stabilized Phosphonium Ylides and Allylic Alcohols in Water

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Abstract: A mild and extra activator-free dehydrative alkylation of stabilized phosphonium ylides with allylic alcohols in water is developed in the presence of [Pd(allyl)Cl]$_2$/dppf catalyst. A wide range of aryl, heteroaryl, alkyl and even allylic tertiary alcohols can readily react with stabilized phosphonium ylides with high regioselectivity for the efficient synthesis of functionalized skipped dienes in moderate to high yields. The role of water was investigated by means of a high-resolution mass spectrum and diffusion-ordered spectroscopy nuclear magnetic resonance, and the results revealed that water might play a crucial role in the formation of the л-allylpalladium complex via hydrogen bond. However, the present method is not suitable for water-sensitive phosphonium ylides.

Keywords: Skipped dienes; Dehydrative synthesis; Allylic alcohols; Water media; Hydrogen bond

Skipped dienes (also called 1,4-dienes) are important motifs in natural products and biologically active compounds showing unique antileukemia, antibiotic and anticancer properties.[1] Therefore, much attention has been paid for the synthesis of them.[2] They are traditionally prepared by transition metal (TM)-catalyzed allylic cross-couplings of alkenylmetal reagents with allylic partners under harsh conditions (Scheme 1A).[3] Recently, TM-catalyzed cross-couplings of simple alkenes[4] or dual functionalization of alkynes[5] have been developed as more preferable methods (Scheme 1B). However, these methods are mainly restricted to the synthesis of inner skipped dienes. To our best knowledge, reports on the synthesis of functionalized terminal skipped dienes are still rare.[6]

Phosphonium ylides are widely used in organic synthesis.[7] The groups of You and Tian have independently reported the allylic alkylation of phosphonium ylides with allylic esters or amines for the efficient synthesis of terminal functionalized skipped dienes (Scheme 1C).[8] Possibly owing to the poor leaving character of the hydroxy group, allylic alcohols, more easily-available, cheaper and stable, have not been employed to streamline the synthesis of functionalized terminal skipped dienes.[9]

With our continuous interests in alcohol-based alkylation[10] and aqueous media reactions,[11] herein, we wish to report a mild and activator-free dehydrative cross-couplings of stabilized phosphonium ylides with allylic alcohols in water media for the efficient synthesis of functionalized terminal skipped dienes (Scheme 1D). The method can also be applied to other common allylic alkylating reagents such as allylic ethers and esters under additive-free conditions.[12] Diffusion-ordered spectroscopy nuclear magnetic resonance (DOSY NMR) experiments suggested that hydrogen bond might be formed between water and allylic alcohol.[13]

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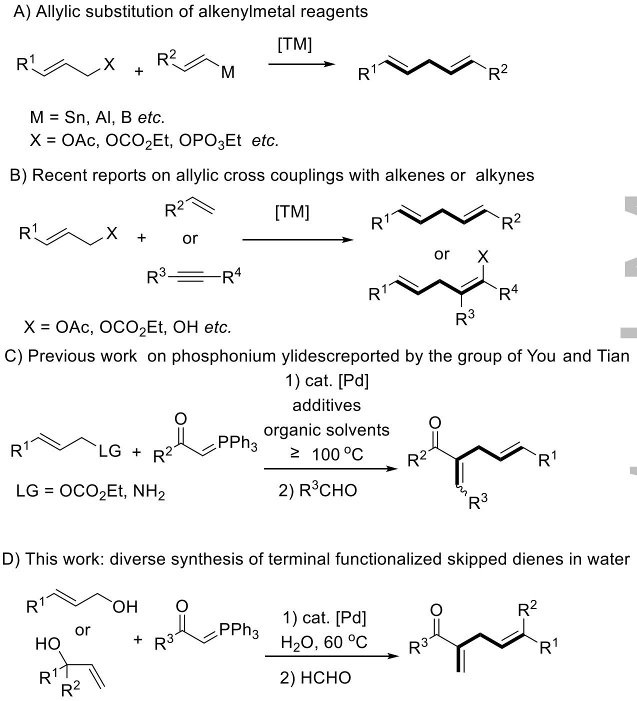
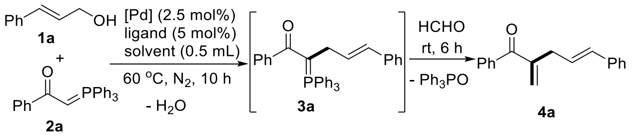


Scheme 1. Common methods for skipped diene synthesis

Noteworthy, possibly owing to that water media is theoretically disadvantageous to dehydrative reactions, the activator-free dehydrative couplings of allylic alcohols in water are much rare.[14-16]

Table 1. Optimization of the reaction conditions[a]

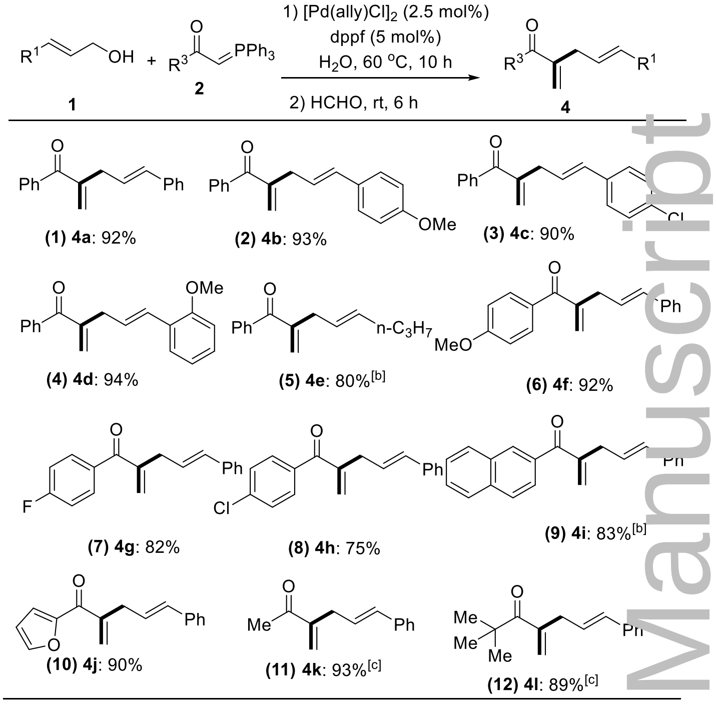


run	[Pd]	ligand	solvent	**4a**/%[b]
1	[Pd(allyl)Cl]$_2$	dppf	H_2O	92
2[c]	$Pd(OAc)_2$	dppf	H_2O	78
3 [c]	$PdCl_2$	dppf	H_2O	trace
4 [c]	$Pd(dba)_2$	dppf	H_2O	8
5	[Pd(allyl)Cl]$_2$	dppb	H_2O	45
6	[Pd(allyl)Cl]$_2$	binap	H_2O	trace
7	[Pd(allyl)Cl]$_2$	dppf	MeOH	65
8	[Pd(allyl)Cl]$_2$	dppf	EtOH	64
9	[Pd(allyl)Cl]$_2$	dppf	*i*-PrOH	60
10	[Pd(allyl)Cl]$_2$	dppf	$(CH_2OH)_2$	45
11	[Pd(allyl)Cl]$_2$	dppf	HFIP	trace
12[d]	[Pd(allyl)Cl]$_2$	dppf	H_2O	80

[a] Unless otherwise noted, the mixture of **1a** (0.36 mmol), **2a** (0.3 mmol), Pd catalyst (2.5 mol%), ligand (5 mol%) in a solvent (0.5 mL) was sealed under N_2 in a Schlenk tube, heated at 60 °C for 10 h, then HCHO (37% v/v in water, 3 equiv.) was added and stirred at rt for another 6 h and monitored by TLC and/or GC-MS. [b] isolated yield based on **2a**. [c] 5 mol% Pd catalyst was used. [d] under air.

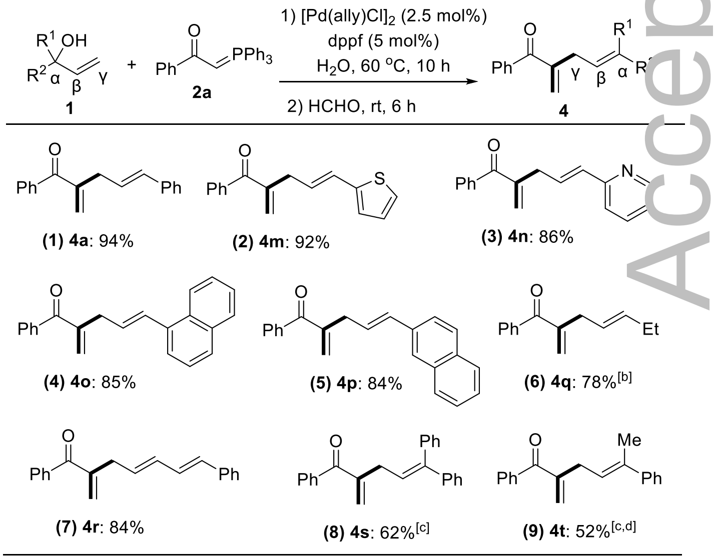
A mixture of cinnamyl alcohol **1a** and phosphonium ylide **2a** in water under a nitrogen atmosphere was heated at 60 °C for 10 h in the presence of [Pd(allyl)Cl]$_2$ (2.5 mol %) and dppf (5 mol), to our delight, a new phosphonium ylide **3a** was detected (Table 1, run 1).[17] Then a one-pot allylation/olefination was conducted, affording a skipped diene **4a** in a total isolated yield of 92% (run 1). Then other palladium catalysts were screened, but only low to moderate yields were obtained (runs 2-4). The ligands were also investigated, but dppf is still the best one (runs 5-6). Other protic solvents that were widely used as good hydrogen bond donors,[18] were also investigated, but the target **4a** were obtained only in low to moderate yields, showing that water is an indispensable solvent for the reaction (runs 7-11). Surprisingly, the reaction under air could also give the target **4a** in 80% isolated yield (run 12).
Various α-unbranched allylic alcohols and phosphonium ylides were then tested to extend the scope of the method. [19] As shown in table 2, as the model reaction, both electron-rich and -deficient cinnamyl alcohols including the sterically bulkier ortho-substituted ones reacted effectively with phosphonium ylide **2a** via a one-pot allylation/olefination sequence, affording high yields of the desired product **4a-d** (table 2, runs 1-4). [20] The reaction of alkyl substituted allylic alcohols, such as (*E*)-hex-2-en-1-ol could not give the desired products under standard conditions, but by extra adding 10 mol% TBAB, the target **4e** could be obtained in a moderate yield with specific α selectivity (run 5). On the other hand, the method could be successfully applied to aryl, heteroaryl, and alkyl ketone stabilized phosphonium ylides, affording the target skipped dienes **4f-l** in high yields (runs 6-12).

Table 2. Dehydrative synthesis of functionalized skipped dienes from stabilized phosphonium ylides and α-unbranched allylic alcohols in water [a]



[a] Unless otherwise noted, see run 1 of Table 1 for reaction conditions. Isolated yields of **4** were based on **2**. [b]10 mol% TBAB was added. [c] 70 °C

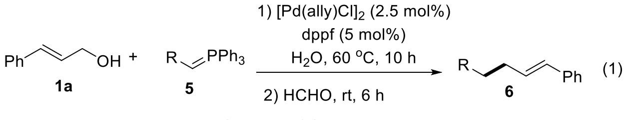
Table 3. Dehydrative synthesis of functionalized skipped dienes from stabilized phosphonium ylides and α-branched terminal allylic alcohols in water [a]



[a] Unless otherwise noted, see run 1 of Table 1 for reaction conditions. Isolated yields of **4** were based on **2a**. [b] 10 mol% TBAB was added. [c] 80 °C. [d] E/Z = 92/8^{GC}

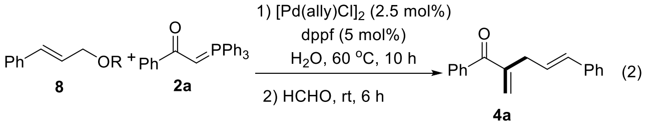
Then α-branched terminal allylic alcohols were also investigated. As shown in table 3, aryl, heteroaryl, alkyl and even allylic tertiary alcohols reacted smoothly with phosphonium ylide **2a**, specifically affording the target terminal skipped dienes in moderate to high yields with exclusive γ selectivity (table 3, runs 1-9).

The one-pot allylation/olefination sequence was then extended to ester-stabilized phosphonium ylides, but no desired skipped dienes could be obtained under standard conditions. Instead, an ester **6a** was obtained in 30% isolated yield (eq. 1A), Likewise, only trace amount of nitrile **6b** was obtained in the reaction of nitrile-stabilized phosphonium ylides (eq. 1B), which is quite different from the literature reports.[8] Interestingly, the ester **6a** could also be obtained in 30% isolated yield in the absence of formaldehyde (eq. 1C), revealing that **6a** might be generated from the hydrolysis of phosphonium ylide intermediates **7a** (*vide infra*),[21] suggesting that this new method is not suitable for water-sensitive phosphonium ylides.



A) 5a: R = CO$_2$Et, 6a, 30% yield
B) 5b: R = CN, 6b, trace
C) 5a: R = CO$_2$Et, without formaldehyde **6a,** 30% yield

Control experiments with other common allylic alkylating reagents, such as (*E*)-(3-ethoxyprop-1-en-1-yl)benzene **8a** and cinnamyl acetate **8b** were also investigated under standard conditions, interestingly, both reactions could give the desired product **4a** in high yields under additive-free conditions (eq. 2).

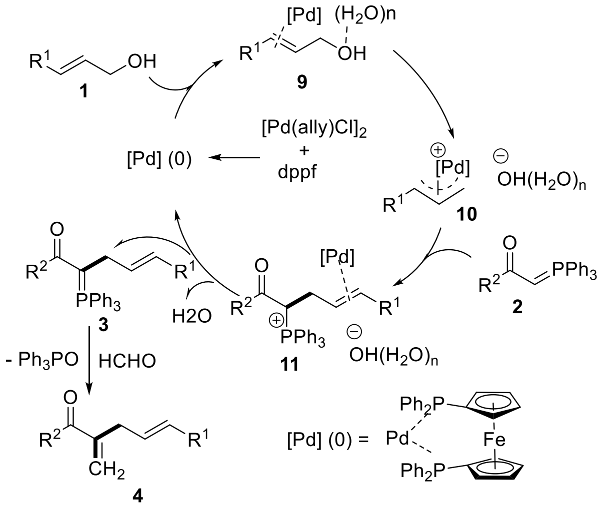


8a: R = Et, **4a:** 95% yield
8b: R = Ac, **4a:** 89% yield

ESI-high resolution mass spectrum (ESI-HRMS) analysis of the reaction mixture of cinnamyl alcohol **1a** and phosphonium ylide **2a** were carried out to probe the possible mechanism.[17] According to the high-resolution mass data, it can be concluded that $[Pd(CH_2CH{=}CHPh)(dppf)]^+$ may be the key intermediate,[17] suggesting that the C-O bond of the allylic alcohol is cleaved and an л-allylpalladium complex is formed during the reaction. Different from Len's report,[22] water may not serve as ligands of Pd species in our reactions.

The interaction of a water molecule with allylic alcohols was investigated by means of DOSY NMR.[23] The results revealed that hydrogen bond might be formed between water and allylic alcohol. Likely, other protic solvents such as methanol and HFIP were also investigated, showing that the interaction between water and allylic alcohol is much stronger than that between other two molecules and allylic alcohol.[17] Therefore, the reactions in water media are more efficient than that in other protic solvents.

Based on these control experiments and the literature reports, [8-9,22-24] a possible reaction mechanism was depicted in scheme 2. [Pd] (0), an active catalyst, is in situ generated from [Pd] (II) and phosphine ligand. Then the activation of OH group in allylic alcohol **1** by water via a hydrogen bond, followed by the cleavage of C-O bond gives π-allyl palladium **10**.[17] Then a nucleophilic attack of phosphonium ylide **2** to π-allyl palladium **10**, followed by a proton transfer of phosphonium salt **11** gives a new phosphonium ylide **3** and byproduct water,[17] meanwhile regenerates the active Pd (0) to continue the catalytic cycle. Finally, a one-pot Wittig reaction of phosphonium ylide **3** with formaldehyde affords the target skipped dienes **4**.



Scheme 2. The possible reaction mechanism

In conclusion, we developed a mild and extra activator-free dehydrative alkylation of stabilized phosphonium ylides with allylic alcohols in water for the efficient synthesis of functionalized terminal skipped dienes. The method can also be applied to other common allylic alkylating reagent such as allylic ethers and esters under additive-free conditions. DOSY NMR experiments and other studies suggested that hydrogen bond might be formed between water and allylic alcohol, and water might play a crucial role in the formation of the л-allylpalladium complex via hydrogen bond. The asymmetric synthesis using this novel method is under way.

Experimental Section

A mixture of allylic alcohol **1** (0.36 mmol), phosphonium ylide **2** (0.30 mmol), [Pd(ally)Cl]$_2$ (2.8 mg, 2.5 mol%), and dppf (8.3 mg, 5 mol%) in water (0.50 mL) was heated under nitrogen at 60 ºC for 10 h. After cooling down to room temperature, formalin (37% in water, w/w, 0.068 mL, 0.90 mmol) was added, and the resulting mixture was stirred for 6 h. Then the solvent was evaporated and the residue was purified by silica gel chromatography, eluting with ethyl acetate/petroleum ether (0/100~1/5), to give compound **4**.

Acknowledgements

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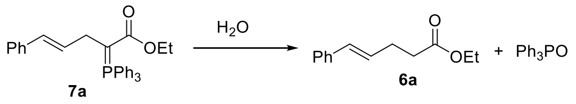
[19] Other aldehydes such as benzaldehyde was employed in the second olefination step, however, only trace amount of the desired 1,4-diene product was observed.

[20] As to β- substituted cinnamyl alcohols, such as (*E*)-2-methyl-3-phenylprop-2-en-1-ol, only trace amount of target product was observed.

[21] Possibly owing to that ester-stabilized phosphonium ylide intermediate (**7a**) is not stable enough under reaction conditions, it will be hydrolyzed to give the target **6a**.



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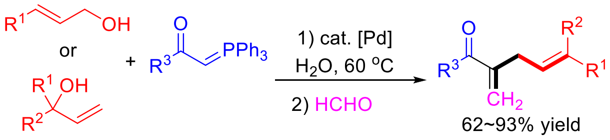
COMMUNICATION

Dehydrative Synthesis of Functionalized Skipped Dienes from Stabilized Phosphonium Ylides and Allylic Alcohols in Water



- mild and activator-free
- dehydrative coupling
- in water
- one-pot
- hydrogen bond activation
- DOSY-NMR

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

X. Ma,* J. Yu, C. Han, Q. Zhou, M. Ren, L. Li, L. Tang*