

Synthesis of Densely Substituted $\alpha,\beta,\gamma,\delta$ -Dienones via the Pd^{II}-Catalyzed Allylation, H-Migration, and Aerobic Oxidative δ -Hydride Elimination Cascade

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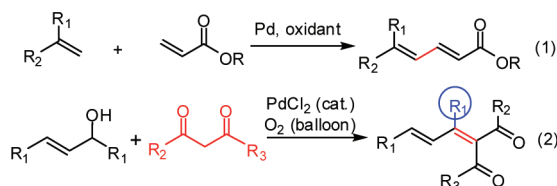
ABSTRACT



A novel protocol for the highly stereoselective synthesis of *E,E*- $\alpha,\beta,\gamma,\delta$ -unsaturated dicarbonyl compounds is presented. Starting from the readily available allylic alcohols and 1,3-diketones, an array of *E,E*- $\alpha,\beta,\gamma,\delta$ -dienones can be efficiently synthesized in high yields via Pd-catalyzed dehydrative allylation, H-migration, and aerobic oxidative δ -hydride elimination cascade. In addition to the novel reaction mechanism, the use of 1:1 allylic alcohol and 1,3-diketone as reactant, 5 mol % of PdCl₂ as catalyst, and 1 atm of environmentally benign O₂ as oxidant, as well as the generation of only H₂O byproduct, makes this protocol rapid, simple, atom-efficient, and clean.

$\alpha,\beta,\gamma,\delta$ -Unsaturated carbonyl compounds are important synthetic intermediates in a wide spectrum of chemical transformations. They are versatile precursors for 1,6- or 1,4-addition,¹ Diels–Alder reaction,² cycloaddition,³ and so forth. The most popular methods for the synthesis of $\alpha,\beta,\gamma,\delta$ -dienones relied mainly on the Knoevenagel condensation of α,β -unsaturated aldehyde with methylene

active compound⁴ and Horner–Wadsworth–Emmons olefination (HWE) of α,β -unsaturated phosphate with aldehyde.² However, the reactions of the corresponding ketone substrates were sluggish or produced Michael addition byproduct. Recently, some elegant protocols for the synthesis of $\alpha,\beta,\gamma,\delta$ -dienones via the Pd-⁵ and Rh-catalyzed⁶ direct cross-coupling of alkenes and acrylates have been reported (eq 1). However, a relatively high Pd catalyst loading (10–20 mol %) and inorganic salt as co-oxidants were required. Consequently, effective protocols for the synthesis of highly substituted (eq 2, R₁ ≠ H) $\alpha,\beta,\gamma,\delta$ -dienone derivatives are very rare.



To overcome this problem, we have initiated an investigation into the development of a novel protocol for the

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(1) For some examples of 1,6-addition, see: (a) Nishimura, T.; Yasuhara, Y.; Sawano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 7872. (b) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824. (c) den Hartog, T.; Harutyunyan, S. R.; Font, D.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 398. For examples of 1,4-addition, see: (d) Singh, R.; Ghosh, S. K. *Org. Lett.* **2007**, *9*, 5071 and references cited therein.

(2) For examples, see: Dockendorff, C.; Sahli, S.; Olsen, M.; Milhau, L.; Lautens, M. J. *Am. Chem. Soc.* **2005**, *127*, 15028 and references cited therein.

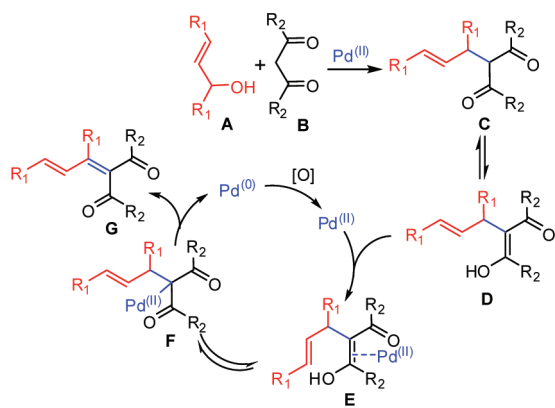
(3) Horie, H.; Kurahashi, T.; Matsubara, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 8956.

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synthesis of polysubstituted $\alpha,\beta,\gamma,\delta$ -unsaturated dicarbonyl compounds. Herein, we disclose that, starting from readily available allylic alcohols⁷ and 1,3-dicarbonyl compounds (eq 2), the synthesis of $\alpha,\beta,\gamma,\delta$ -unsaturated dicarbonyl compounds bearing substituents ($R_1 \neq H$) in the inner double bond could be achieved not only in high yields but also in *E,E*-form of selectivity via Pd^{II}-catalyzed tandem reactions, involving the dehydrative allylation, H-migration, and aerobic oxidative δ -hydride elimination. Moreover, the reaction proceeded smoothly in the presence of only 1:1 ratio of reactants, 5 mol % of PdCl₂ catalyst, and 1 atm of environmentally benign O₂ oxidant. In addition, only H₂O was generated as byproduct. These advantages make the new protocol highly efficient in terms of atom-economic and environmental impact.⁸ To the best of our knowledge, such a novel protocol has not been reported.

The initial synthetic strategy is illustrated in Scheme 1. Based on our recent experiences on Pd-catalyzed allylation reaction of heteroarenes and allylic acetates,⁹ as well as other reports on the Lewis acid-catalyzed allylic substitutions,^{10–13} we assumed that the Pd cation-catalyzed allylation of allylic alcohol **A** and 1,3-dicarbonyl compounds **B** would occur to afford **C**. Its tautomer **D** undergoes oxidative hydride elimination via the alkene-Pd coordination (**E**), C–Pd bond formation (**F**), and β -hydride elimination to produce the $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compound **G**.

Scheme 1. Tentatively Proposed Mechanism for the Pd^{II}-Catalyzed Synthesis of $\alpha,\beta,\gamma,\delta$ -Dienones



(5) (a) Hatamoto, Y.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **2004**, *6*, 4623. (b) Xu, Y.-H.; Lu, J.; Loh, T.-P. *J. Am. Chem. Soc.* **2009**, *131*, 1372. (c) Yu, H.; Jin, W.; Sun, C.; Chen, J.; Du, W.; He, S.; Yu, Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 5792. (d) Xu, Y.-H.; Wang, W.-J.; Wen, Z.-K.; Hartley, J. J.; Loh, T.-P. *Tetrahedron Lett.* **2010**, *51*, 3504. (e) Xu, Y.-H.; Chok, Y. K.; Loh, T.-P. *Chem. Sci.* **2011**, *2*, 1822.

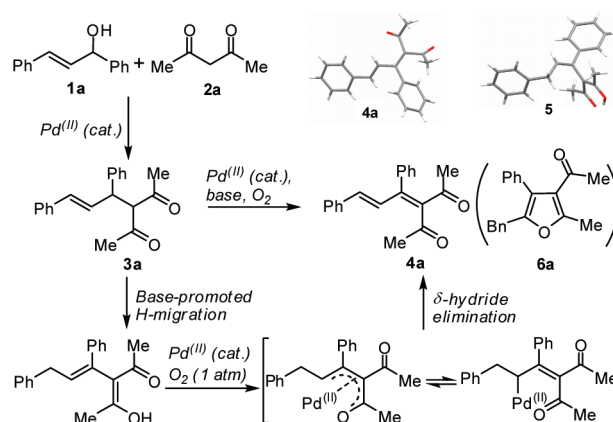
(6) Besset, T.; Kuhl, N.; Patureau, F. W.; Glorius, F. *Chem.—Eur. J.* **2011**, *17*, 7167.

(7) Allylic alcohols are commercially available or can be readily prepared according to the known methods; see: (a) Siddiqui, N.; Alam, P.; Ahsan, W. *Arch. Pharm. Chem. Life Sci.* **2009**, *342*, 173. (b) Crawford, J. J.; Henderson, K. W.; Kerr, W. J. *Org. Lett.* **2006**, *8*, 5073. (c) Ueda, M.; Miyaara, N. *J. Org. Chem.* **2000**, *65*, 4450.

(8) In modern organic synthesis, the combination of a multistep synthesis into a one-pot tandem operation or replacement of organic/

On the basis of the proposed mechanism, we screened the reaction parameters using allylic alcohol **1a** and 1,3-diketone **2a** as a model reaction (Scheme 2). Some important information was obtained after numerous experiments. Namely, the reaction is dramatically influenced by the basicity of the reaction system. We found that the Pd^{II}-catalyzed allylation of **1a** and **2a** proceeds smoothly to provide the allylated product **3a** in the absence of base but was suppressed completely when base was present. In contrast, base was indispensable for the formation of $\alpha,\beta,\gamma,\delta$ -dienone **4a** from **3a**. In addition, the conversion of **3a** to **4a** is accelerated remarkably by O₂ as compared to that under air and N₂ atmosphere.

Scheme 2. Real Pathway for the Pd^{II}-Catalyzed Synthesis of $\alpha,\beta,\gamma,\delta$ -Dienones



To clarify the reasons, we carried out some control experiments. The results revealed that in contrast to our initially proposed mechanism (Scheme 1), **3a** was indeed converted to dienol **5** very rapidly in the presence of base in almost quantitative yield. The structure of **5** was unambiguously determined by NMR and X-ray single-crystal analyses (see Scheme 2).¹⁴ Treatment of **5** in the presence of Pd^{II} and 1 atm of O₂ afforded *E,E*- $\alpha,\beta,\gamma,\delta$ -unsaturated dicarbonyl compound **4a** as a single stereoisomer whose structure was also clearly demonstrated by NMR and X-ray single-crystal analyses (see Scheme 2).¹⁴ These results

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(10) For AuCl₃-catalyzed reactions, see: Rao, W.; Chan, P. W. H. *Org. Biomol. Chem.* **2008**, *6*, 2426.

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(14) CCDC 847602 and 847601 contain the supplementary crystallographic data of compounds **4a** and **5**, respectively.

suggested that the real pathway for the formation of **4a** from **3a** proceeds indeed via a base-mediated enolization and 1,3-*H* migration to form **5**, followed by a Pd^{II}-catalyzed aerobic oxidative δ -hydride elimination.

Table 1. Optimization of the Reaction Conditions for the One-Pot Synthesis of **4a**^a

entry	catalyst (% mol)	additive	solvent	<i>t</i> ₁ / <i>t</i> ₂ ^b (h)	yield ^c (%)
1	PdCl ₂ (10)	K ₂ CO ₃	DMF	2/10	51
2	PdCl ₂ (10)	K ₂ CO ₃	dioxane	10/24	trace ^d
3	PdCl ₂ (10)	K ₂ CO ₃	toluene	9/24	trace
4	PdCl ₂ (10)	KHCO ₃	DMF	2/16	54
5	PdCl ₂ (10)	K ₃ PO ₄	DMF	2/20	49
6	PdCl ₂ (10)	K ₂ CO ₃ / 4 Å MS	DMF	2/6	61 ^e
7	PdCl ₂ (5)	K ₂ CO ₃ / 4 Å MS	DMF	2/8	59 ^e

^a Reaction conditions: allylic alcohol **1a** (0.5 mmol), 1,3-diketone **2a** (0.5 mmol, 1.0 equiv), O₂ at 1 atm, and PdCl₂ catalyst in solvent (3 mL) at 100 °C; then base (0.5 equiv) was recharged in situ and heated at 100 °C.

^b *t*₁ and *t*₂ stand for the reaction time for the formation of **3a** from **1a** and **2a** and the subsequent formation of **4a** from **3a**, respectively. ^c The yield of **4a** was determined by ¹H NMR spectroscopy because of the contamination of a small amount of furan byproduct **6a** (Scheme 2). ^d Monitored by TLC. ^e Isolated yield.

With these key reaction parameters as well as the reaction mechanism established, our efforts were devoted to optimizing the reaction conditions aimed at realizing the synthesis of $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds via a one-pot operation. Here, the key relies on an appropriate combination of catalyst, oxidant, and base that enables the tandem transformations to proceed efficiently without affecting the activity of the catalysts. Table 1 summarized some representative results. Extensive trials showed that PdCl₂ (10 mol %) was a highly active catalyst, affording the desired product **4a** in 51% yield in the presence of 1:1 molar ratio of **1a** and **2a** (Table 1, entry 1). In addition, a trace amount of furan derivative **6a** was formed (Scheme 2). A screening of solvents (entries 1–3) and bases (entries 1, 4, and 5) indicated that DMF and K₂CO₃ were better options. Further optimization toward lowering the catalyst loading revealed that, by adding 4 Å molecular sieves, the yield of **4a** could be improved to about 60% even by decreasing the catalyst loading from 10 mol % to 5 mol % (entries 6 vs 7). Thus, the optimized conditions for the synthesis of **4a** via the tandem procedure was a 1:1 molar ratio of **1a** and **2a**, 5 mol % of PdCl₂ catalyst, O₂ at 1 atm, and 4 Å MS (ca. 30 wt %) in DMF at 100 °C for 2 h, and then the reaction vessel was recharged in situ with K₂CO₃ (0.5 equiv) and further heated under an O₂ atmosphere at 1 atm for an additional 8 h. Under these conditions, **4a** was obtained in 59% isolated yield (entry 7). It should be mentioned that the moderate yield for **4a** resulted from the multistep column purification to remove the small amount byproduct **6a**. Thus, this protocol represents an efficient method for the synthesis of highly substituted $\alpha,\beta,\gamma,\delta$ -unsaturated dicarbonyl compounds in terms of the simple, rapid, clean, and atom-economic reaction process as well as the formation of only H₂O as byproduct.

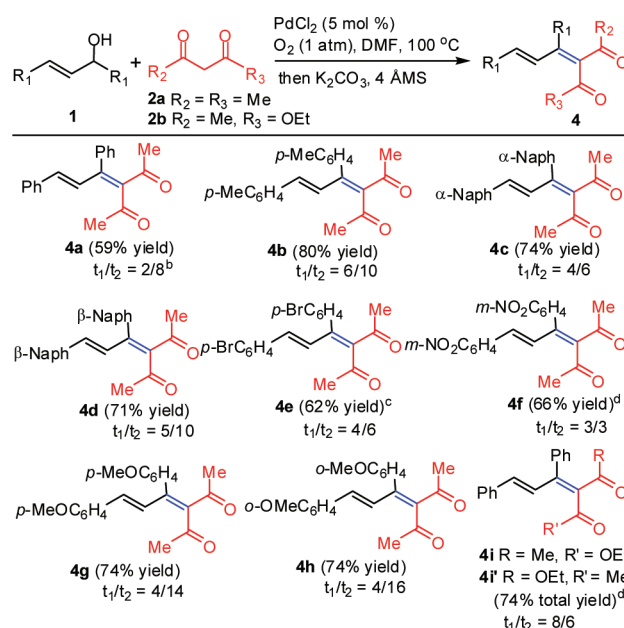


Figure 1. Synthesis of various $\alpha,\beta,\gamma,\delta$ -dienones from alkyl 1,3-dicarbonyl compounds. ^a Reaction conditions: allylic alcohol **1** (0.5 mmol), 1,3-diketone **2** (0.5 mmol, 1.0 equiv), O₂ at 1 atm, and PdCl₂ (5 mol %) in DMF (3 mL) at 100 °C; then K₂CO₃ (0.5 equiv) was recharged in situ and heated at 100 °C; isolated yield. ^b *t*₁ and *t*₂ stand for the reaction time of allylation and dienone formation, respectively. ^c Dienone formation was carried out at 60 °C. ^d The corresponding allylic acetate was used for allylation in CH₂Cl₂ catalyzed by Cu(OTf)₂, and dienone formation was carried out in DMF at 60 °C catalyzed by PdCl₂.

Having established the optimized conditions, we examined the general applicability of this protocol. An array of allylic alcohols reacted smoothly with the alkyl-substituted 1,3-diketone **2a** to afford the desired $\alpha,\beta,\gamma,\delta$ -unsaturated dicarbonyl compounds. As shown in Figure 1, allylic alcohols substituted by simple phenyl groups reacted well with **2a** to give **4a** and **4b** in good isolated yields. The fused aromatic systems such as α - and β -naphthyl substituents are also tolerated, delivering **4c** and **4d** in 74% and 71% yields, respectively. In addition, substrates either with electron-deficient Br and NO₂ or with electron-rich OMe functional groups in the phenyl ring periphery are also viable substrates as seen from the high yields of the corresponding products **4e–h**, although allylic acetate was shown to be more efficient for the allylation reaction of NO₂-substituted substrate (**4f**). Interestingly, bromides, which are well-known to be good leaving groups in Pd-catalyzed cross-couplings, remain intact under the reaction conditions. Moreover, the method is also applicable to acetyl acetate **2b**, affording the desired product **4i/4i'** (*E/Z* = 1.4/1) in 74% yield. Finally, it should also be mentioned that the method exhibits excellent stereoselectivity with the $\alpha,\beta,\gamma,\delta$ -diene moiety in the products assigned to be *E,E*.

Next, we extended the method to aryl 1,3-diketones as represented by **7a** and **7b** (Figure 2). It was found that various allylic alcohols decorated by simple phenyl (**8a–d**),

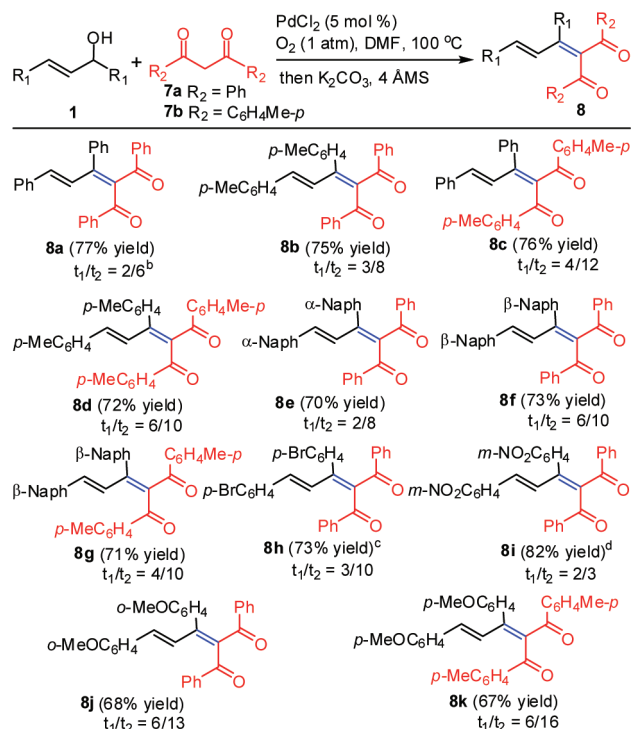


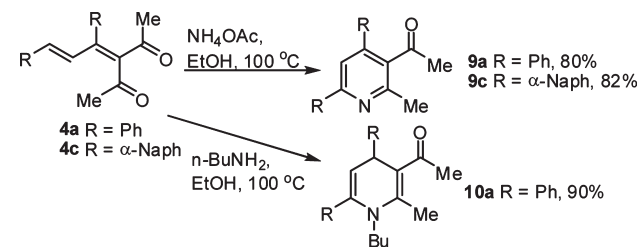
Figure 2. Synthesis of various $\alpha,\beta,\gamma,\delta$ -dienones from aryl 1,3-dicarbonyl compounds. ^aReaction conditions: allylic alcohol **1** (0.5 mmol), 1,3-diaryl diketone **7** (0.5 mmol, 1.0 equiv), O₂ at 1 atm, and PdCl₂ (5 mol %) in DMF (3 mL) at 100 °C; then K₂CO₃ (0.5 equiv) was recharged in situ and heated at 100 °C; isolated yield. ^bt₁ and t₂ stand for the reaction time of allylation and dienone formation, respectively. ^cThe dienone formation was carried out at 60 °C. ^dThe corresponding allylic acetate was used for allylation in CH₂Cl₂ catalyzed by Cu(OTf)₂, and dienone formation was carried out in DMF at 60 °C using PdCl₂ as catalyst.

fused naphthyl (**8e–g**), as well as electron-deficient and rich aryl groups (**8h–k**), underwent smooth transformation to afford the desired products both in high isolated yields and *E,E*-form of selectivity. In addition, the labile Br substituent in the phenyl ring is also tolerated (**8h**).

Finally, to probe the utility of the polysubstituted $\alpha,\beta,\gamma,\delta$ -unsaturated dicarbonyl compounds, the synthesis of 2,3,4,6-substituted pyridine derivatives was performed. As shown by several representative results in Scheme 3, **4a** and **4c** can be converted smoothly to the densely substituted pyridines **9a** and **9c** by simply heating with ammonium acetate in EtOH. In addition, *N*-alkyl-substituted 1,4-dihydropyridine derivatives, **10a**, for example, can also be readily obtained. These results provide an efficient pathway for the construction of highly substituted N-heterocycles, which are valuable structural motifs in nature

yet hard to synthesize. It should also be mentioned that, although the detailed results deserve further study, a preliminary observation showed that compounds **9** and **10**, whose structures feature a large delocalized system, exhibit interesting photoluminescent properties depending on the size of delocalization. These observations suggested that the polysubstituted pyridine derivatives can be potentially used as fluorescent probes or materials.

Scheme 3. Efficient Synthesis of Densely Substituted Pyridine Derivatives from $\alpha,\beta,\gamma,\delta$ -Unsaturated Dicarbonyl Compounds



In summary, we have developed a novel and efficient protocol for the synthesis of *E,E*- $\alpha,\beta,\gamma,\delta$ -unsaturated dicarbonyl compounds via the Pd-catalyzed tandem procedure involving allylation, H-migration, and aerobic oxidative δ -hydride elimination. The mechanism was elaborated by NMR and single X-ray analysis. In addition to the novel reaction mechanism, this method is atom-efficient, operationally rapid and simple, clean, and highly stereoselective and, therefore, would find extensive applications owing to the great importance of polysubstituted $\alpha,\beta,\gamma,\delta$ -dienone derivatives in numerous chemical transformations. The preliminary application of the polysubstituted $\alpha,\beta,\gamma,\delta$ -unsaturated dicarbonyl compounds has been elaborated by the construction of densely substituted pyridine derivatives. Investigations into the full substrate scope of this reaction, as well as the further downstream transformation aimed at investigating the relationship between the structure and luminescent properties are currently underway.

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Supporting Information Available. Experimental procedures, ¹H and ¹³C NMR and HRMS data, copies of ¹H and ¹³C NMR spectra, and X-ray data for compounds **4a** and **5** (CIF). This material is available free of charge via Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.