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Palladium-Catalysed Atom-Economical Synthesis of Conjugated Dienals from Terminal Acetylenes and Acrolein

Zoë Hearne and Chao-Jun Li*

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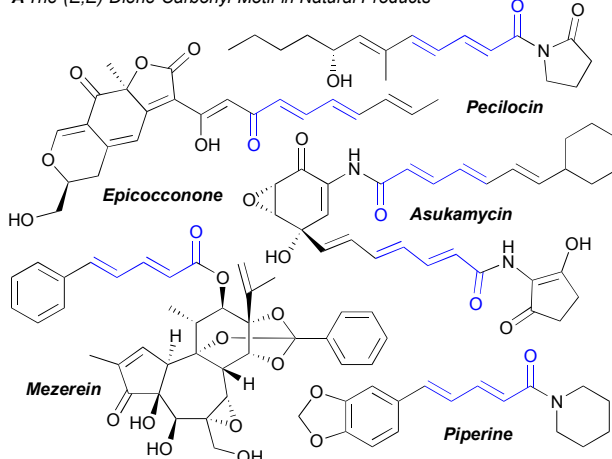
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Conjugated (*E,E*)-dienals are versatile synthetic intermediates owing to their trifunctional, electrophilic nature and the prevalence of the (*E,E*)-diene in a wide range of functional molecules. It is shown herein that (*E,E*)-dienals can be readily prepared in two palladium-catalysed steps from simple, unactivated starting materials; terminal acetylenes and acrolein can be coupled via conjugate addition, followed by alkyne isomerisation. This procedure provides a highly atom-economical, redox-neutral and practical method to prepare a range of conjugated (*E,E*)-dienals in good yields and diastereoselectivity.

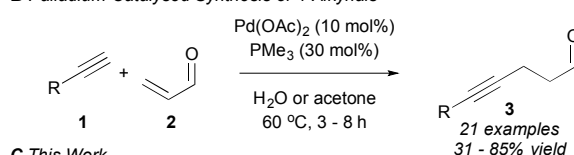
Conjugated (*E,E*)-dienals have demonstrated value as highly versatile synthetic intermediates en route to functional molecules. The (*E,E*)-diene component of their structure is one of the most commonly recurring motifs in natural products (Figure 1, A),¹ and they are valuable substrates as they can be readily derivatized owing to their trifunctional, electrophilic nature: featuring both an aldehyde and two conjugated alkenes. Studies on the manipulation of dienals for exclusive 1,2-,² 1,4-,³ or 1,6-addition⁴ draw attention to their flexible and tunable reactivity. Furthermore, dienals can be cyclised to access polycyclic indolines,⁵ cyclobutanones,⁶ chromans,⁴ cyclohexanones⁷ and isoxazolidines.⁸ Profiting from this synthetic versatility, conjugated (*E,E*)-dienals have featured in the synthesis of many functional molecules with varied applications, including pharmaceuticals,⁹ polyene pheromone natural products,¹⁰ and organic chromophores for technological applications (for example OLEDs and molecular wires).¹¹

Despite the broad utility of conjugated (*E,E*)-dienals, existing methods for their synthesis are not straightforward. Classical approaches such as Wittig¹² or Horner-Wadsworth-Emmons¹³ olefination reactions suffer from low atom economy, poor

A The (*E,E*)-Diene-Carbonyl Motif in Natural Products



B Palladium-Catalysed Synthesis of 4-Alkynals



C This Work

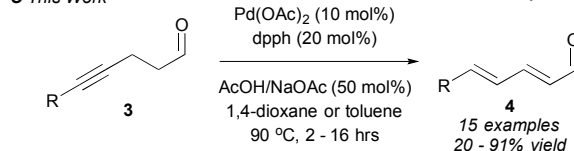


Figure 1: Ready access to a variety of natural products would be facilitated by a practical method to prepare versatile building blocks, such as conjugated (*E,E*)-dienals.

diastereoselectivity, and harsh reaction conditions. Recent contributions have offered elegant solutions to the challenge of preparing conjugated (*E,E*)-dienals, for example by propargyl vinyl ether¹⁴ or methylenecyclopropane rearrangements,¹⁵ organocatalytic oxidation,¹⁶ and other strategies.¹⁷ However, in such cases synthesis of the required starting materials require multiple steps and stoichiometric reagents, and many lack generality. To fully realise the potential of conjugated (*E,E*)-dienals

Department of Chemistry, FQRNT Centre for Green Chemistry and Catalysis, McGill University, 801 Sherbrooke Street West, Montréal, Québec H3A 0B8, Canada. E-mail: cj.li@mcgill.ca.

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in synthesis, the development of a practical, expedient and mild procedure for their formation would have great value. We were inspired by the literature concerning palladium-catalysed isomerisation reactions of alkynes to yield (*E,E*)-dienes,^{18, 19} a field launched by the groups of Trost,^{20, 21} Lu,²² and Imaizumi,²³ who first studied the transition-metal and organo-catalysed isomerisation of 4-alkynones to (*E,E*)-dienones. It was envisioned that just two palladium-catalysed steps could be used to access (*E,E*)-dienals; conjugate addition of terminal acetylenes (**1**) and acrolein (**2**) would return 4-alkynals (**3**, Figure 1, **B**), followed by isomerisation of the alkyne (Figure 1, **C**). This would provide a rapid and atom-economical access to conjugated (*E,E*)-dienals (**4**).

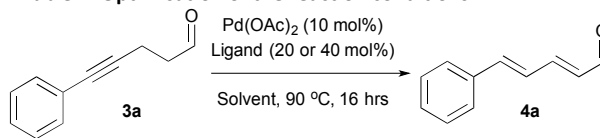
Having recently succeeded in developing a palladium-catalysed conjugated addition to prepare 4-alkynals,²⁴ herein is described the atom-economical and redox-neutral method for the diastereoselective isomerisation of a broad range of 4-alkynals (**3**) to conjugated (*E,E*)-dienals (**4**) in moderate to good yields. Relatively mild and operationally simple reaction conditions, combined with ready access to the alkyne substrates, make this approach advantageous for the synthesis of such versatile synthetic intermediates.

Studies began (Table 1) with testing conditions first reported by Trost and co-workers for the palladium-catalysed isomerisation of 2-alkynones to conjugated (*E,E*)-dienones.²⁰ A palladium catalyst was used, pre-formed from Pd(OAc)₂ (10 mol%) and triphenylphosphine (40 mol%) in THF solvent (0.2 M) under argon at room temperature for one hour. A 57% yield of the alkyne-isomerised product **4a** (entry 1) was obtained from substrate **3a** after stirring with the pre-formed catalyst for 16 hours at 90 °C. A survey of ligands revealed that bidentate phosphines were beneficial to this transformation (entries 2 – 6), particularly those with large bite-angles such as 1,1'-ferrocenediyl-bis(diphenylphosphine) (dppf, entry 5) and 1,6-bis(diphenylphosphino)hexane (dpph, entry 6). Catalyst pre-formation at 25 or 60 °C conferred little benefit (entries 6, 7 and 9), while stirring the catalyst components at 100 °C reduced the product yield to 59% (entry 8). Adding a sodium acetate/acetic acid buffer improves the yields slightly to 90% (entry 10). The solvent was changed from THF to 1,4-dioxane, the boiling point of which is higher than the reaction temperature, thus ensuring temperature consistency (entry 11). Control reactions, without palladium catalyst or phosphine ligand (entries 12 and 13, respectively) gave no product.

The scope of the reaction was tested using a range of aryl and aliphatic substrates (Figure 2). The phenyl-substituted substrate **3a** gave an excellent 95% yield, and aryl substrates bearing electron-rich (**3b** – **3d**) and electron-poor (**3f**, **3g**) substituents isomerised in good yields (62 – 81%). Aryl substrates with free-hydroxyl (**3e**), basic (**3h**) and heterocyclic (**3h** & **3i**) substituents isomerised in moderate yields (44 – 49%). The optimised reaction conditions were also successfully applied to 4-alkynones and 4-alkynoates, achieving very good yields of dienones (**4j**, 88%) and dienates (**4k**, 80%),

respectively. To demonstrate synthetic viability the reaction was scaled-up by applying slightly modified conditions to 800 mg (5.1 mmols) of **3a**. After stirring for 15 hours at 95 °C, a gratifying yield of 69% of **4a** was obtained. Diastereoselectivity of the process for the (*E,E*)-isomer was consistently high, with diastereomeric ratios (*dr*) ranging from 25(*E,E*):1(*Z,E*) to 67(*E,E*):1(*Z,E*). An exception was thiophenyl-substituted compound **4i**, which had reduced diastereoselectivity (*dr* = 11(*E,E*):1(*Z,E*):2(*E,Z*)). The (*E,E*)-stereochemistry of the major products was confirmed by single-crystal X-ray diffraction of representative compound **4h** (Figure 2).

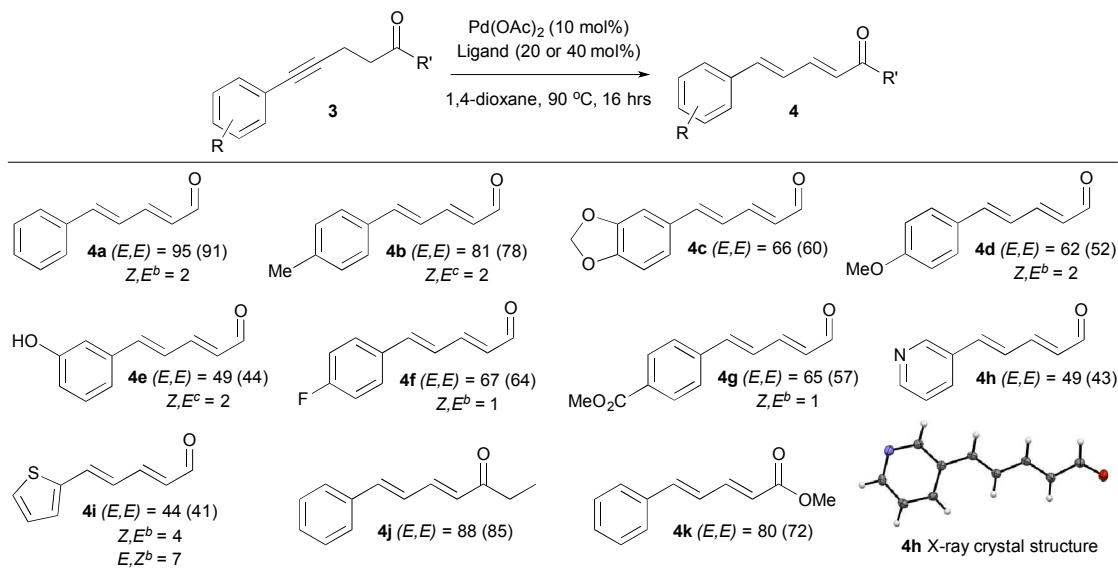
Table 1: Optimisation of the reaction conditions^a



Entry	Ligand	Pd/L Pre-Mix Temp (°C) ^b	Additive ^c	% Yield ^d
1	PPh ₃	25	none	57
2	dppp	25	none	23
3	dppb	25	none	40
4	dppe	25	none	68
5	dppf	25	none	69
6	dpph	25	none	81
7	dpph	60	none	80
8	dpph	100	none	59
9	dpph	None	none	75
10	dpph	None	AcOH/NaOAc	90
11 ^e	dpph	None	AcOH/NaOAc	95
12 ^e	none	None	AcOH/NaOAc	0
13 ^{e,f}	dpph	None	AcOH/NaOAc	0

^aReaction carried out with **3a** (0.2 mmol, 1.0 equiv.), Pd(OAc)₂ (0.02 mmol, 10 mol%), phosphine ligand (20 or 40 mol% for bidentate and monodentate phosphines, respectively), solvent (1 mL, 0.2 M), 90 °C for 16 hours. ^bCatalyst pre-formation: a mixture of the catalyst and ligand in THF (0.5 mL) was stirred under argon for one hour. ^c50 mol%. ^dYields calculated by ¹H NMR analysis of crude reaction mixtures using 1,3,5-trimethoxybenzene internal standard. ^e1,4-dioxane solvent. ^fNo Pd(OAc)₂ added.

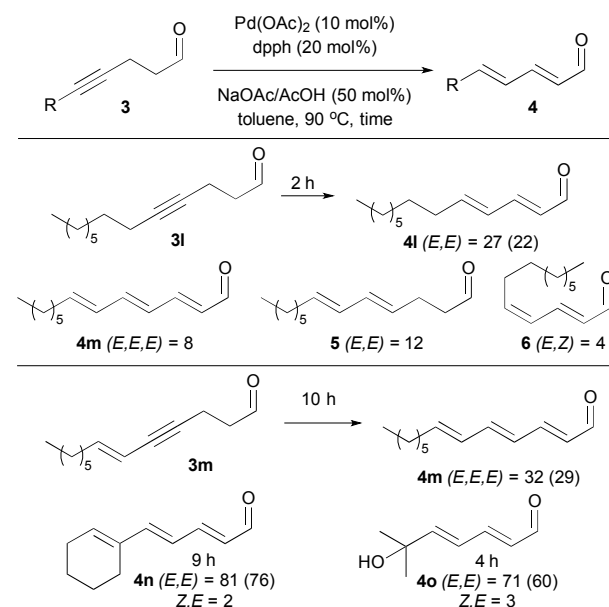
The reaction conditions for aliphatic substrates were optimised using octyl-substituted substrate **3l** (Figure 3). Reducing the reaction time and switching to toluene as the solvent increased the yield from 13% to 27%, but despite further optimisation the quantity of **4l** remained low. Efforts were hampered by poor regioselectivity; 4,6-dienal **5** forms in appreciable quantities. Regioselectivity was poor because unactivated, aliphatic alkynes such as **3l** have little electronic bias; the alkyne can isomerise in either direction, giving dienals **4l** and **5**. Side-product formation of the (*E,Z*)-stereoisomer **6** and trienal **4k** also reduced the yield of the desired product **4l**. Synthesis of a number of aliphatic dienals (**4o**) and trienals (**4m** and **4n**) was successfully realised using substrates which have sp³ α and β protons on only one side of the alkyne (Figure 3). Efforts to improve selectivity to favour the 2,4-dienal are underway in our laboratory.

Figure 2: Isomerisation of aromatic-substituted 4-alkynals catalysed by Pd(OAc)₂/dpph in 1,4-dioxane^a

^aAll reactions were carried out with **3** (0.2 mmol, 1.0 equiv.), Pd(OAc)₂ (0.02 mmol, 10 mol%), dpph (0.04 mmol, 20 mol%), NaOAc (0.1 mmol, 50 mol%), AcOH (0.1 mmol, 50 mol%), 1,4-dioxane (1 mL), 90 °C, 16 hours reaction time. NMR yields are shown, isolated yields are in parentheses. ^bNMR yield of minor isomer determined by ¹H NMR spectral analysis of crude reaction mixtures, and characterized by 1D selective-¹H TOCSY NMR, ^cNMR yield and characterisation of minor isomers by analogy to **4a**.

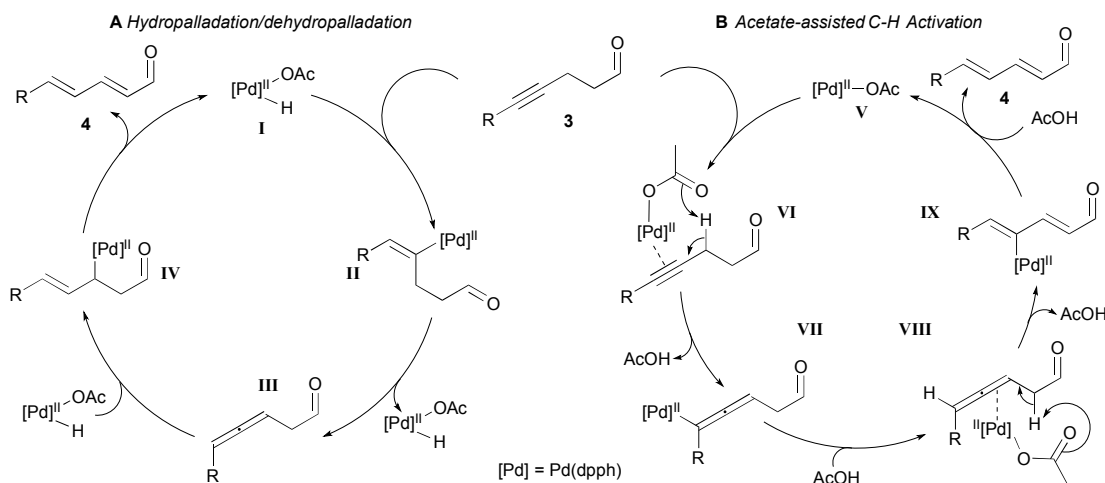
Two alternative mechanisms are proposed. The first (**A**, Figure 4) invokes a palladium-hydride as the active catalyst and proceeds by hydropalladation/dehydropalladation, while the second (**B**, Figure 4) involves an acetate-assisted C-H activation. Participation of a metal-hydride has been favoured in the literature for related transformations.^{18, 20} In this mechanism (Figure 4, **A**) palladium(0) forms by reduction of palladium(II) acetate with excess phosphine. The spontaneous nature of this process has been demonstrated for similar systems.²⁵ Oxidative addition of acetic acid generates a palladium(II) hydride (**I**), which adds to the alkyne (**7**) in a *syn* fashion to generate a vinyl palladium species (**II**). Dehydropalladation returns an allene intermediate (**III**). A second hydropalladation gives allylpalladium (**IV**) and β-hydride elimination returns the product (**4**) and re-generates the active palladium-hydride (**I**). Detection of either the metal-hydride or the allene was attempted by running the reaction in a sealed tube under argon using high-temperature NMR, but no resonances corresponding to either intermediate were observed. This does not exclude the involvement of a metal-hydride; the active-catalyst and allene may be too short-lived to be seen, or in the case of the allene may remain bound to palladium.

A second mechanism operating under the reaction conditions can also be envisioned (Figure 4, **B**), proceeding by acetate-assisted deprotonation in a similar fashion to the proposed mechanism for carboxylate-assisted C-H activation of arenes and enolates. Palladium(II) species bound to bidentate phosphine ligands are alkynophilic, and upon coordination can increase the electrophilicity of the alkyne,²⁶ increasing the acidity of the α-protons. Subsequent intra-molecular deprotonation by a bound acetate ligand (**VI**) might give a σ-allenyl palladium complex. Protiodepalladation of this intermediate gives an allene (**VIII**). A second iteration; acetate-

Figure 3: Isomerisation of aliphatic-substituted 4-alkynals catalysed by Pd(OAc)₂/dpph in 1,4-dioxane^a

^aAll reactions were carried out with **3** (0.2 mmol, 1.0 equiv.), Pd(OAc)₂ (0.02 mmol, 10 mol%), dpph (0.04 mmol, 20 mol%), NaOAc (0.1 mmol, 50 mol%), AcOH (0.1 mmol, 50 mol%), toluene (1 mL), 90 °C. Reaction time (in hours) is shown, followed by NMR yields, and isolated yields in parentheses. Minor products characterised by 2D NMR and/or 1D selective-¹H TOCSY NMR.

assisted deprotonation of the α-protons to give vinylpalladium **IX**, followed by protiodepalladation, returns the product (**4**).

Figure 4: Proposed mechanisms for the isomerisation of 4-alkynals to conjugated (*E,E*)-dienals

In conclusion, a practical and original method to access conjugated (*E,E*)-dienals via palladium-catalysed isomerisation of 4-alkynals has been realised. The highly atom-economical and redox-neutral process provides rapid access to conjugated (*E,E*)-dienals in moderate to good yields and broad scope. The products can be transformed into a variety of functional groups, and have been proven to be useful and versatile intermediates en route to a broad range of functional molecules. The synthetic method is a valuable addition to existing methods used to synthesise dienals, and employs readily accessible substrates, economical choices of catalyst and ligand, and a simple operation. Further efforts will be dedicated to understanding the reaction mechanism, and improving the substrate scope and yields.

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