Efficient Preparation of Functionalized (*E,Z*) Dienes Using Acetylene as the Building Block

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(*E,Z*)-Diene structures spread widely in the scope of not only important bioactive natural products,[1] but also useful chemicals applicable in the perfume industry and other fields.[2] The characteristic (*E,Z*) double-bond configuration of the molecules, which is usually responsible for the special functions,[3] meanwhile poses great challenges for their stereoselective synthesis. The advent solutions mainly reside in the range of Wittig-type olefination[4] or transition-metal-mediated coupling reactions of deliberately functionalized precursors.[5] While the methods of both classes have been successfully used in a good number of laboratory syntheses, their intrinsic drawback of low atom economy causing poor mass conversion greatly limited their application in large-scale preparations.

A naive retrosynthetic analysis suggests that two acetylene molecules can be added together to form the (*E,Z*) double bonds, provided the addition reaction occurs in a stereoselective manner. Indeed, from the well-documented organometallic elementary reactions, we could infer that a tandem addition incorporating two molecules of acetylene may lead to (*E,Z*)-conjugated diene structure (Scheme 1).
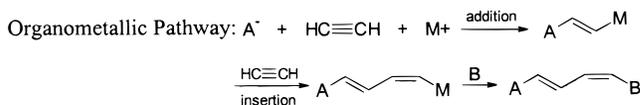
In this sequence, the stereochemical requirements of trans-addition and cis-insertion (carbometalation) helped to establish the otherwise hard-to-access conjugate (*E,Z*) double-bond configuration. Despite the extreme efficiency this sequence may bring about, there was only one precedent in the literature realizing such a concept: The Pd-catalyzed cotrimerization reaction of acetylene and allyl chloride developed by Kaneda et al.,[6] but the reaction gave in low yield a mixture of codimer and cotrimer and the stereochemistry of the cotrimer was not established (Scheme 2).

Recently, we have developed the facile synthesis of γ,δ-unsaturated carbonyl compounds in which a halide-assisted protonolysis efficiently recycles Pd(II)-catalytic species,[7] thus effecting the tandem addition reaction of halide, an alkyne, and an α,β-unsaturated carbonyl. In this context, we attempted the reaction of acetylene with α,β-unsaturated electron-deficient alkenes in the presence of palladium catalyst to explore the possibility of developing new methods for (*E,Z*)-diene synthesis.
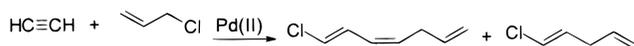
Acrolein was first selected to react with acetylene under the catalysis of Pd(OAc)$_2$. We first used acrolein as solvent
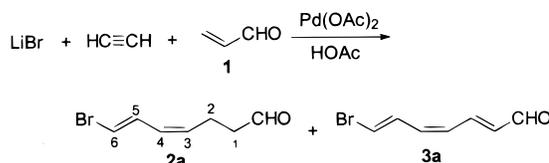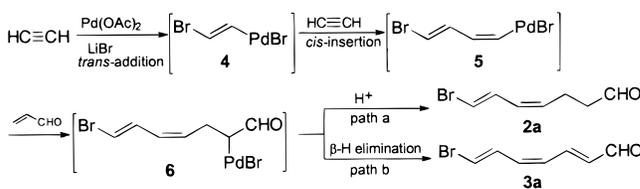
Scheme 1

Scheme 2

Scheme 3

Scheme 4

to avoid the excessive polymerization of acetylene. When acetylene was passed through a mixture of acrolein **1** (20 mL), HOAc (50 mmol), Pd(OAc)$_2$ (0.5 mmol), and LiBr (5 mmol) at 15 °C for 2 h, rapid formation of palladium black was observed. The reaction afforded the expected dienal **2a** together with the α,β-unsaturated trienal **3a** in 220% and 80% yield, respectively (yields are calculated on the basis of Pd(OAc)$_2$) (Scheme 3).[8] Pure **2a** could be purified carefully by column chromatography. The geometry of the two double bonds in **2a** was established by the coupling constants in ^{1}H NMR between related vinylic protons. Thus, $J(H^6-H^7)$ of 14 Hz and $J(H^4-H^5)$ of 11 Hz manifest the (6*E*) and (4*Z*) double bonds, respectively. Further evidence from NOESY studies of the chloro derivative **2b** unambiguously shows the (*E,Z*)-configuration of the molecule.[9]

The formation of **2a** and **3a** could be explained by Scheme 4, which also rationalizes the stereoselectivity. First, trans-halopalladation of acetylene gives the (*E*)-vinylpalladium intermediate **4**, which is inserted by a second molecule of acetylene to form (*E,Z*)-dienylpalladium **5**; after the insertion of acrolein, the (2-oxoalkyl)palladium intermediate undergoes protonolysis (path a) or β-hydride elimination (path b) to afford **2a** or **3a**, respectively.

Our previous studies reveal that excess coordinating halide inhibits β-H elimination and facilitates protonolysis in acidic conditions.[7] A number of reaction conditions were screened. The results were summarized in Table 1.

Preliminary results showed that polar solvents, high acetylene and halide concentration, and low temperature favor the yield of **2a**. In most cases, using HOAc as a solvent and passing acetylene rapidly into the reaction mixture, **2a** was isolated as the main product after chromatography (entries 3–5, Table 1). A codimerization byproduct of acetylene and acrolein,[10] which could be removed after purification, could be detected in some cases by ^{1}H NMR spectra.

We found that the LiBr–Pd(OAc)$_2$ ratio has a great impact on the reaction: when the LiBr–Pd(OAc)$_2$ ratio was in-

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(8) The ratio of **2a** to **3a** was determined by the ^{1}H NMR spectra of the product mixture. The presence of the trienal product **3a** was further supported by GC–MS analysis and UV spectra.
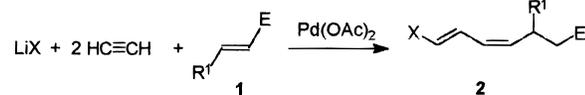
(9) There is a strong NOE effect between H^6 and H^3 and no cross-peak between H^5 and H^3.

Table 1. Pd(II)-Catalyzed Coupling Reaction of Halide, Acetylene, and Acrolein[a]

entry	Pd(OAc)$_2$ (equiv)	LiBr (equiv)	acrolein (equiv)	solvent (20 mL)	yield[b] (%) 2a	3a
1	1	10	as solvent	acrolein[c]	210	80[c]
2	1	10	50	MeCN[c]		
3	1	10	50	HOAc	550 (11)[b]	
4	1	80	100	HOAc	2500 (25)[b]	
5	1	200	300	HOAc	3980 (13)[b]	
6	1	200	300	HOAc−H$_2$O[d]	7720 (26)[b]	
7[e]	1	600	450	HOAc−H$_2$O[d]	19500 (43)[b]	

[a] Pd(OAc)$_2$ (0.5 mmol), <15 °C, 5 h. [b] Yields based on Pd(OAc)$_2$; figures in parentheses represent the yields calculated on the basis of acrolein used. [c] HOAc (50 mmol) was used. [d] HOAc−H$_2$O (5:1, v:v) mixture solvent was used. [e] A 10-g scale experiment.

Table 2. Pd(II)-Catalyzed Coupling Reaction of Halides, Acetylene, and Electron-Deficient Alkenes[a]

$$\text{LiX} + 2\ \text{HC}\equiv\text{CH} + \underset{\mathbf{1}}{\overset{E}{\diagdown}} \xrightarrow{\text{Pd(OAc)}_2} \underset{\mathbf{2}}{X\diagup\diagdown\diagup\diagdown\diagup E}^{R^1}$$

entry	X	1 R^1	1 E	time (h)	product 2	yield[b] (%)
1	Cl	H	CHO	24	**2b**	1720 (6) 3460 (12)[c]
2	Br	Me	CHO	24	**2c**	850 (3)
3	Cl	Me	CHO	24	**2d**	320 (1)
4[d]	Br	H	COMe	5	**2e**	1240 (4)
5	Br	H	COBu	5	**2f**	820 (41)[e]
6	Br	H	COPh	4	**2g**	570 (29)[e]
7	Br	H	NO$_2$	5	**2h**	550 (28)[e]
8	Cl	H	NO$_2$	6	**2i**	200 (10)[e]

[a] Pd(OAc)$_2$ (0.05 mmol), LiX (10 mmol), alkene (15 mmol), HOAc (5 mL), rt. [b] Yields based on Pd(OAc)$_2$; figures in parentheses represent the yields calculated on the basis of alkenes used. [c] HOAc (5 mL)−H$_2$O (1 mL). [d] Pd(OAc)$_2$ (0.5 mmol), LiBr (40 mmol), HOAc (20 mL). [e] Alkene (1 mmol).

creased from 10:1 to 200:1, the catalyst activity was dramatically enhanced and the reaction yield went up from 550% to 3980% (based on palladium), respectively (entries 3 and 5, Table 1). This can be accounted for by the predominant complexation of halide ion on palladium, which favors protonolysis over β-H elimination. The solvent effect is also remarkable: changing HOAc to a HOAc−H$_2$O mixture (5:1, v:v) increased the yield by 1-fold (entry 6 vs 5, Table 1). The reason for the beneficial effect of adding water is not clear yet. In a 10-g-scale experiment, a further increase of LiBr amount in HOAc−H$_2$O system returned

(10) 5-Bromo-4(E)-pentenal was obtained as the codimer in less than 10% yield on the basis of the ^{1}H NMR analysis of the crude product.
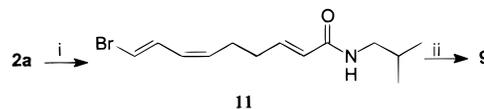
(11) The low reactivity of iodide may be due to the strong coordination between iodide and Pd(II) and the covalent characteristic of the Pd−I bond. Gabriele, B.; Costa, M.; Salerno, G.; Chiusoli, G. P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 83.

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(15) In a typical reaction, acetylene (passed successively through water, chromic acid, and concentrated sulfuric acid) was passed through a mixture of Pd(OAc)$_2$ (0.05 mmol), LiBr (10 mmol), and acrolein **1a** (15 mmol) in HOAc (5 mL) at <15 °C for 24 h. Ether (100 mL) was added, and the mixture was washed with water (5 mL × 2). The organic layer was dried (Na$_2$SO$_4$) and concentrated, and the residue was subjected to column chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 1:20) to give the cotrimerization product **2a**.

Scheme 5[a]

$$\mathbf{2a} \xrightarrow{i} \underset{\mathbf{11}}{Br\diagdown\diagup\diagdown\diagup\diagdown\diagup\overset{O}{\underset{H}{\diagdown N}}\diagup\diagdown} \xrightarrow{ii} \mathbf{9}$$

[a] Reaction conditions: (i) Ph$_3$PCH$_2$CONHCH$_2$CHMe$_2$$^+Br^-$, LDA, THF, 62%; (ii) MeZnCl, Pd(OAc)$_2$, THF, 89%.

nearly 200 turnovers (43% yield based on acrolein), following the same trend as in HOAc solvent (entry 7, Table 1).

The clean reaction, high catalytic efficiency, and high stereoselectivity encouraged us to explore the acetylene−alkene tandem addition reactions of other electron-deficient alkenes and lithium halides (Table 2). Preliminary results showed that different α,β-unsaturated carbonyl compounds all gave (E,Z) cotrimerization products in high stereoselectivity. Relative lower yields were obtained for sterically hindered substrates (entries 2 and 3, Table 2). LiCl and LiBr gave comparable yields of halogenodienic carbonyl compounds, while iodide showed much lower reactivity[11] and iodo-substituted analogue was not isolated in pure form.

Alkenes with weaker electron-withdrawing groups such as acrylonitrile and methyl acrylate failed to give cotrimerization product. However, nitroethylene was found to be an effective electrophile to afford the corresponding nitro-substituted diene. Thus, with the abundant transformations related to vinyl halide, carbonyl, and nitro groups, the present reaction provides sound precursors to a wide range of unsaturated compounds with (E,Z) diene structures.

A number of biologically active natural products and insecticides have an (E,Z)-diene subunit, e.g., insect pheromones[1c,d] and lipid amides such as spilanthol (**7**).[13,14]

$$\underset{\mathbf{7}}{\diagup\diagdown\diagup\diagdown\diagup\diagdown\diagup\overset{O}{\diagdown}\underset{H}{N}\diagup\diagdown}$$
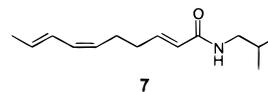
Also known as afinin, spilanthol was isolated from *Spilanthes oleraceae* Jacq. and is the most insecticidally active and stable of the natural isobutylamides thus far isolated and identified.[13b] The synthesis of spilanthol was reported by several groups in multistep and low overall yields.[13b,14] The utility of our method can be demonstrated by the concise synthesis of spilanthol. Starting from the (E,Z) dienal **2a** prepared from acetylene−acrolein cotrimerization,[15] Wittig olefination of the aldehyde followed by the palladium-catalyzed coupling of MeZnCl with the vinylic bromide afforded **7** in 55% overall yield (Scheme 5). The ^{1}H NMR and ^{13}C NMR spectra of the synthetic product are consistent with the reported data.[14b,d]

In summary, we have developed an efficient synthetic method for (E,Z)-diene compounds based on acetylene−alkene cooligomerization.[15] Through halopalladation, tandem acetylene−olefin insertion, and halide-assisted protonolysis, halide, two molecules of acetylene, and an electron-deficient alkene are assembled to give functionalized (E,Z) dienes in one step in high stereoselectivity. The high stereoselectivity, simplicity of operation, and possible application to large-scale preparation suggest its potential practical use.

Supporting Information Available: Characterization data for new compounds and ^{1}H NMR spectra for compounds **2a−d,f−i**, **7**, and **8**, NOESY spectra for **2b**, and ^{13}C NMR spectra for **7** (14 pages).