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Aryl Aldehydes as Traceless Dielectrophiles in Bifunctional Titanocene-Catalyzed Propargylic C−X Activations

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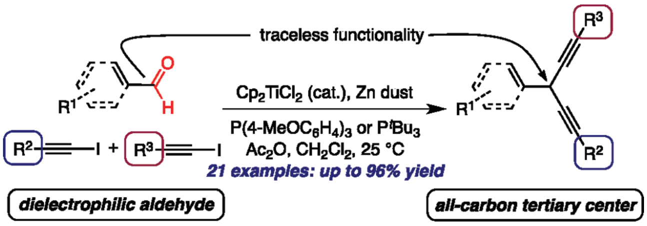
ABSTRACT



The titanocene-catalyzed construction of all-carbon substituted tertiary centers directly from aromatic aldehydes is described. The starting aldehyde behaves as a traceless functionality in the formation of multiple carbon−carbon bonds through consecutive carbon−heteroatom bond activations. The sequential addition of a metal acetylide and a second carbon nucleophile to the dielectrophilic aldehyde enables the construction of symmetrical and unsymmetrical 1,4-diynes in good yields.

Aldehydes are one of the most widely recognized electrophilic functional groups in organic synthesis. However, their use as a traceless functional handle for *multiple C−C bond formations* is generally limited to sequential, acid-mediated Friedel−Crafts-type arylations[1] and Michael additions to in situ generated Knoevenagel condensation products.[2] The synthetic utility of this ubiquitous functional group would be greatly expanded if construction of an all-carbon substituted tertiary center could be achieved through *sequential, direct nucleophilic substitutions of a dielectrophilic aldehyde*. Contrary to conventional carbonyl reactivity, conditions that render an aldehyde dielectrophilic ultimately generate a tertiary, all-alkyl substituted carbon center through two distinct nucleophilic additions in a one-pot procedure. Based on our previous work with titanocene-catalyzed C−C bond formations,[3] we reasoned that the redox and oxophilic properties of titanocene[4] could be harnessed to facilitate the initial addition of a carbon-based nucleophile *and* activate the resulting alkoxide for a second C−C bond formation. These sequential C−X/C−O bond activations lead to a net double alkylation that rapidly installs *two functional handles*.

Based on the documented ability of titanocene to reduce propargyl alcohol derivatives,[5] we chose to begin our

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(1) For selected references on the hydroxyarylation of aldehydes, see: (a) Zhu, Z.-B.; Wei, Y.; Shi, M. *Chem.—Eur. J.* **2009**, *15*, 7543. (b) Prakash, G. K. S.; Panja, C.; Shakhmin, A.; Shah, E.; Mathew, T.; Olah, G. A. *J. Org. Chem.* **2009**, *74*, 8659. (c) Prakash, G. K. S.; Paknia, F.; Chacko, S.; Mathew, T.; Olah, G. A. *Heterocycles* **2008**, *76*, 783. (d) Saito, S.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 11081. (e) Olah, G. A.; Rasul, G.; York, C.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1995**, *117*, 11211. (f) Griepentrog, H. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 1876.

(2) For selected references pertaining to one-pot condensation−Michael additions to aldehydes, see: (a) Scroggins, S. T.; Chi, Y.; Fréchet, J. M. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 2393. (b) Renzetti, A.; Dardennes, E.; Fontana, A.; Maria, P. D.; Sapi, J.; Gerard, S. *J. Org. Chem.* **2008**, *73*, 6824. (c) Wang, Y.-G.; Cui, S.-L.; Lin, X.-F. *Org. Lett.* **2006**, *8*, 1241.

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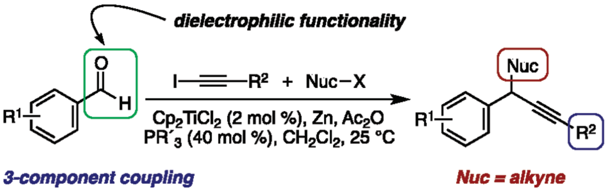
studies by examining metal acetylides as the first nucleophilic component in our dialkylation sequence. We envisioned that a multifunctional catalyst could be used to directly assemble an all-carbon substituted tertiary center via the controlled addition of an acetylide and a second carbon nucleophile to an aromatic aldehyde (eq 1).[6] This cascade design would greatly enhance synthetic efficiency[7] by streamlining the C–C bond-forming process.[8] Herein, we report the implementation of this concept toward the successful *construction of symmetrical and unsymmetrical 1,4-diynes directly from dielectrophilic aldehydes.*

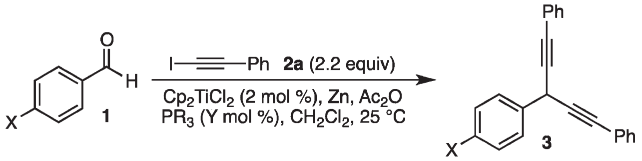


(1)

Although the metal-catalyzed addition of acetylides to aldehydes is well established,[9] introduction of two acetylenes to yield 1,4-diynes, a synthetically versatile subunit that allows access to polyunsaturated fatty acids, leukotrienes, and prostaglandins[10] is less precedented.[11,12] Therefore, we began our studies by examining the addition of two alkynes to a dielectrophilic aldehyde as a means of assembling this architectural motif. Treatment of aldehyde **1a** and iodoalkyne **2a** with Cp_2TiCl_2 (5 mol %), Zn(0), and TMSCl in CH_2Cl_2 provided diyne **3a** in only 12% yield (Table 1, entry 1).[13] However, replacement of TMSCl with Ac_2O increased the yield of **3a** to 65% yield (entry 2).[14] The addition of Ac_2O is likely facilitating propargylic C–O activation.

In light of our previous finding that phosphine additives dramatically affect titanocene-catalyzed C–C bond formations, we examined this phenomenon in the formation of 1,4-diynes.[3] Gratifyingly, the addition of (4-MeO-$C_6H_4)_3P$ (20 mol %) effectively increased the yield of **3a** to 83% (entries 3). A similar effect was observed with benzaldehyde (**1b**) wherein the addition of phosphine increased the yield of 1,4-diyne **3b** from 20% to 66% (entries 4 and 5).[15] Upon further investigation, we discovered that the yield of 1,4-diyne **3** was highly dependent on the nature and amount of phosphine employed. Tributylphosphine and triphenylphosphite gave <5% of **3b** (entries 6 and 7), and electron-rich aryl phosphines failed to improve the yield of **3b** (entry 8). These results indicate that the relative size and basicity of added phosphine profoundly affects the amount of 1,4-diyne obtained. Lowering the amount of (4-MeO-$C_6H_4)_3P$ from 20 to 10 mol % led to a modest decrease in the yield of **3b** (entry 9). However, increasing the amount of (4-MeO-$C_6H_4)_3P$ to 40 mol % provided **3b** in an improved 80% yield (entry 10). Interestingly, when the amount of phosphine exceeded 40 mol %, little improvement was observed.

Table 1. Optimized 1,4-Diyne Formation[a]



entry	X	additive	R	Y mol %	yield (%)[b]
1	OMe (**1a**)	Ac_2O	no phosphine	–	12 (**3a**)
2	OMe (**1a**)	Ac_2O	no phosphine	–	65 (**3a**)
3	OMe (**1a**)	Ac_2O	4-MeO-C_6H_4	20	83 (**3a**)
4	H (**1b**)	Ac_2O	no phosphine	–	20 (**3b**)
5	H (**1b**)	Ac_2O	4-MeO-C_6H_4	20	66 (**3b**)
6	H (**1b**)	Ac_2O	*n*-Bu	20	0 (**3b**)
7	H (**1b**)	Ac_2O	OPh	20	<5 (**3b**)
8	H (**1b**)	Ac_2O	2,4,6-MeO-C_6H_4	20	34[c] (**3b**)
9	H (**1b**)	Ac_2O	4-MeO-C_6H_4	10	58[c] (**3b**)
10	H (**1b**)	Ac_2O	4-MeO-C_6H_4	40	80 (**3b**)

[a] Reaction conditions: **1** (0.40 mmol), **2a** (0.96 mmol), Cp_2TiCl_2 (2.0 mol %), Zn (0.84 mmol), TMSCl or Ac_2O (0.80 mmol), and phosphine at 0.1 M for 2 h at rt. [b] Isolated yields. [c] Yields determined by 500 MHz ^1H NMR.

With optimized conditions in hand, we examined a series of aldehydes in the formation of symmetrical 1,4-diynes (Table 2). In general, electron-rich benzaldehyde derivatives provided 1,4-diynes in good to excellent yields (entries

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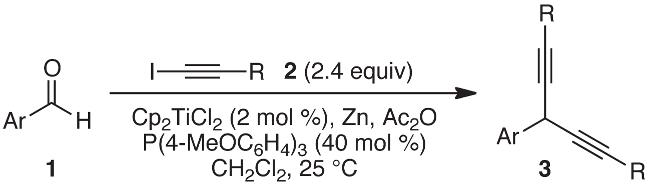
(15) The remaining material was recovered as unreacted benzaldehyde.

1–5). The *bis*-alkynylation reaction appears insensitive to *ortho* substitution and iodoalkyne substitution (entries 1 and 4). Aliphatic iodoalkynes are tolerated, as exemplified by the conversion of propargyl ether **2e** and *n*-butyl iodoalkyne **2f** to 1,4-diynes **3g** and **3h** respectively (entries 5 and 6). Silylacetylene **2g** also provided the corresponding symmetrical 1,4-diyne **3i**, although in diminished yield (entry 7). The presence of an aryl halide in aldehydes **1d** and **1e** did not hinder 1,4-diyne formation (entries 8 and 9). Likewise, ester-substituted aldehyde **1f** gave diyne **3l** (entry 10). However, the more electron-deficient p-CF_3 and p-NO_2 substituted benzaldehyde derivatives showed negligible overall reactivity. Analogous reactions with heteroaromatic aldehydes proceeded in excellent yield as exemplified by the reaction of thiophene **1g** to yield 1,4-diyne **3m** (entry 11).

Table 2. Synthesis of Symmetrical 1,4-Diynes[a]



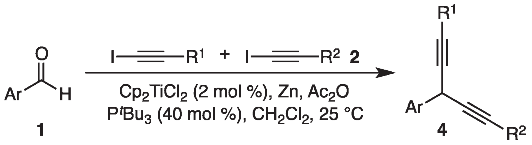
entry	Ar	R	product	yield (%)[b]
1	2-Me-C_6H_4 (**1c**)	Ph (**2a**)	**3c**	93
2	4-MeO-C_6H_4 (**1a**)	4-Cl-C_6H_4 (**2b**)	**3d**	88
3	4-MeO-C_6H_4 (**1a**)	4-MeO-C_6H_4 (**2c**)	**3e**	59
4	2-Me-C_6H_4 (1c)	4-F_3C-C_6H_4 (**2d**)	**3f**	76
5	4-MeO-C_6H_4 (**1a**)	CH_2OEt (**2e**)	**3g**	60
6	4-MeO-C_6H_4 (**1a**)	^{n}Bu (**2f**)	**3h**	56
7	4-MeO-C_6H_4 (**1a**)	Si(^{i}Pr)$_3$ (**2g**)	**3i**	25
8	4-Cl-C_6H_4 (**1d**)	Ph (**2a**)	**3j**	96
9	4-F-C_6H_4 (**1e**)	Ph (**2a**)	**3k**	80
10	4-MeO_2C-C_6H_4 (**1f**)	Ph (**2a**)	**3l**	50
11	2-thiophene (**1g**)	Ph (**2a**)	**3m**	92

[a] Same conditions as those in Table 1. [b] Isolated yields.

Efforts to apply this protocol directly to the concurrent addition of two different alkyne components resulted in statistical mixtures of symmetrical and unsymmetrical 1,4-diynes. After extensive optimization, it was discovered that the symmetrical products could be relegated to trace amounts (< 10%) if the second alkyne component was added after alkoxide formation and followed by the slow addition of Ac_2O over 11 h (Table 3). Additionally, switching from (4-MeO-C_6H_4)$_3$P to ^{t}Bu$_3$P provided slightly better yields of the unsymmetrical 1,4-diynes. In general, electron-rich and -poor aryl substituents on the aldehyde and iodoalkyne components gave diynes **4** in good yields. To the best of our knowledge, this represents the first example of an unsymmetrical 1,4-diyne synthesis using a one-pot, three-component, intermolecular coupling strategy.

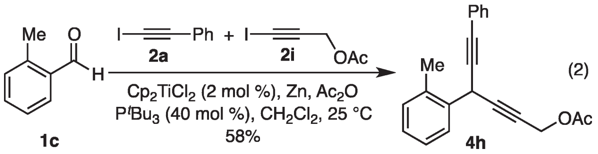
The formation of the second carbon–carbon bond proved chemoselective for the alkoxide derivative that arose as a result of the initial acetylide addition to the aldehyde. Specifically, sequential treatment of aldehyde **1c** with iodoalkyne **2a** followed by propargyl acetate **2i** provided diyne **4h** in good yield, while leaving the primary propargylic acetate intact (eq 2). The observed chemoselectivity would indicate that the propargylic C–X activation event is governed by the electronic influence of the aromatic aldehyde and not primarily dictated by the steric environment around the resulting alkoxide derivative.

Table 3. Synthesis of Unsymmetrical 1,4-Diynes[a]



entry	Ar	R^1	R^2	product	yield (%)[b]
1	2-Me-C_6H_4 (**1c**)	2-Me-C_6H_4 (**2h**)	**2a**	**4a**	52
2	**1c**	4-Cl-C_6H_4 (**2b**)	**2a**	**4b**	56
3	**1c**	4-F_3C-C_6H_4 (**2d**)	**2a**	**4c**	50
4	**1c**	**2d**	**2c**	**4d**	57
5	4-MeO-C_6H_4 (**1a**)	Ph (**2a**)	**2c**	**4e**	53
6	4-Cl-C_6H_4 (**1d**)	4-MeO-C_6H_4 (**2c**)	**2a**	**4f**	55
7	**1d**	**2b**	**2a**	**4g**	50

[a] Same as those in Table 1 with the exception that the second alkynyliodide and Ac_2O were added after formation of the intermediate propargylic alkoxide was observed. [b] Isolated yields.



While examining the Ti-catalyzed formation of unsymmetrical 1,4-diynes, we observed two instances where 1,5-diyne **5** was generated as a significant byproduct of the reaction (eq 3).[5a,16,17] Treatment of aldehyde **1b** with iodoalkyne **2a** followed by **2d** in the presence of P^{t}Bu$_3$ yielded 1,5-diyne **5a** in 38% as a 1:1 mixture of *meso* and *dl* diastereomers. Likewise, the addition of iodoalkyne **2e** to aldehyde **1c** provided a 1:1 diastereomeric mixture of 1,5-diyne **5b** in 20% yield.[18] Postulating that the 1,4- and 1,5-diynes arise from a configurationally unstable propargyltitanocene intermediate, treatment of enantiomerically enriched acetate **6**[19] with iodoalkyne **2c**,

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[16] 1,5-Diynes were typically observed in ≤5% yield during 1,4-diyne synthesis.

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[18] The remaining material consisted of a complex mixture containing allenes, unreacted starting material, and unidentified coupling products.

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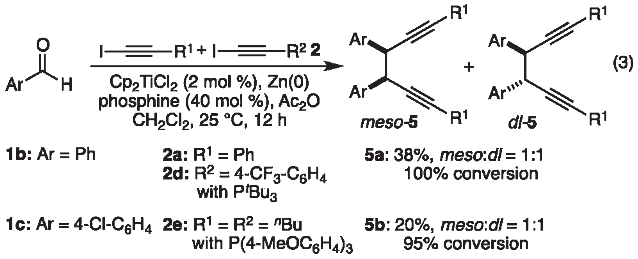
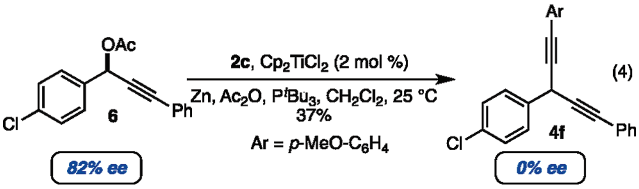
Cp_2TiCl_2, Zn(0), ${}^tBu_3P$, and Ac_2O generated 1,4-diyne **4f** with complete loss of optical activity (eq 4). The combination of these results supports a mechanism involving the reduction of an intermediate propargylic acetate by low valent titanocene in the construction of 1,4-diynes.[5b,20,21]

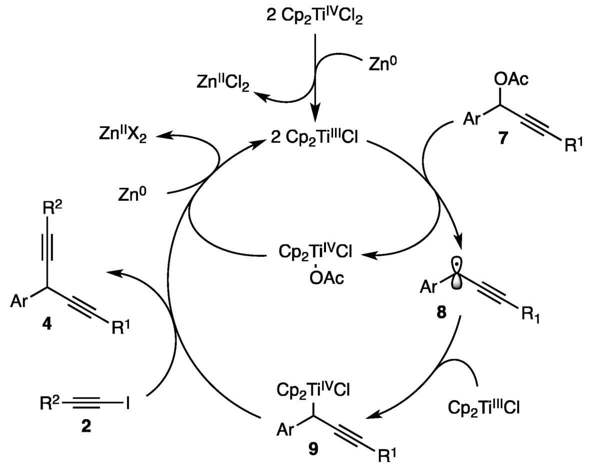




In an effort to gain further mechanistic insight into the titanocene-catalyzed synthesis of 1,4-diynes, the conversion of aldehyde **1b** to diyne **3b** was examined. The need for Cp_2TiCl_2 and Zn(0) was confirmed by the observation that omission of either reagent led to recovered aldehyde **1b** after 2 h at rt. Although the presence of Zn(0) and phosphine in the absence of Cp_2TiCl_2 provided the intermediate propargylic alcohol after extended periods of time (> 24 h), the presence of Cp_2TiCl_2 has an obvious impact on alkoxide formation. Substitution of Cp_2TiCl_2 for $BF_3{\bullet}OEt_2$ failed to provide either the propargylic alcohol or diyne **3b**, indicating that titanium is likely not merely acting as a Lewis acid in the second alkynylation event.

Our composite results point to a synergistic effect of catalytic Cp_2TiCl_2, zinc dust, and phosphine in both formation of the initial propargyl alcohol derivative and acetate displacement in the generation of 1,4-diynes. While the details of the initial metal acetylide addition are as yet unknown, a possible mechanism for the second C$-$C bond-forming event begins with the reduction of acetate **7** by $Cp_2Ti^{III}Cl$ to yield propargyl radical **8** (Scheme 1).[5a] A second single electron transfer provides propargyltitanocene **9**, which undergoes coupling with a second equivalent of alkynyliodide **2**. Alternatively, the introduction of the second alkyne equivalent may involve the zinc or titanocene acetylide derivative of **2**, both of which are possible under the reaction conditions. Finally, reduction of the resulting Ti(IV) complex by zinc dust completes the catalytic cycle. Although the exact role of phosphine is the subject of current investigation, we hypothesize that it may stabilize low valent titanocene complexes generated while also increasing the reactivity of organozinc intermediates through an unusual P$-$Zn ligation.[22]

Scheme 1. Proposed Catalytic Cycle for 1,4-Diyne Formation



In summary, we have developed a unique three-component coupling reaction to access 1,4-diynes in a remarkably mild and efficient process that relies on the multifunctional capabilities of titanocene. The use of commercially available and inexpensive Cp_2TiCl_2 makes this process attractive from a practical standpoint in comparison to alternative methods. Mechanistic studies and efforts toward expanding the scope of dielectrophilic aldehydes using various carbon nucleophiles are underway. The results of these, and subsequent studies, will be reported in due course.

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Supporting Information Available. Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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