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Bifunctional Titanocene Catalysis in Multicomponent Couplings: A Convergent Assembly of β-Alkynyl Ketones

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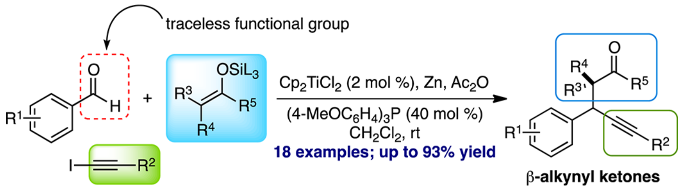
ABSTRACT



Herein is described a titanium-catalyzed three-component coupling to assemble β-alkynyl ketones in a single operation. Treatment of an aryl aldehyde with an acetylide and silyl enol ether in the presence of a bifunctional titanocene catalyst enables the highly convergent assembly of β-alkynyl ketones in good to excellent yields.

The development of new transformations that rely on relay catalysis and cascade bond formations has enabled the rapid and convergent construction of highly versatile synthetic building blocks.[1] However, despite recent interest in aryl-substituted β-alkynyl carbonyl derivatives for pyran, furan, and pyrrole construction,[2] most strategies for their assembly employ linear sequences that rely on sequential C−C bond formations. Two common methods involve either an enolate alkylation using a prefunctionalized propargylic electrophile[2d,3] or the conjugate addition of an acetylide to an α,β-unsaturated carbonyl (Scheme 1a).[4] Our recent work in multifunctional titanocene catalysis[5] led us to speculate that a multicomponent coupling of an aryl aldehyde **1**, acetylide precursor **3**, and silyl enol ether **2** would result in a significantly more convergent approach to the synthetically valuable aryl-substituted β-alkynyl ketones **4** (Scheme 1b). The aryl-substituted oxygen heterocycles bearing tertiary all-carbon centers is a prevalent structural motif in nature, as exemplified by calyxin L (**5**), epicalyxin F (**6**),[6] brainin B (**7**),[7] and

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(1) (a) Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Acc. Chem. Res.* **2012**, *45*, 1278. (b) Ramachary, D. B.; Jain, S. *Org. Biomol. Chem.* **2011**, *9*, 1277. (c) Ambrosini, L. M.; Lambert, T. H. *ChemCatChem* **2010**, *2*, 1373. (d) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993. (e) Davies, H.; Sorensen, E. *Chem. Soc. Rev.* **2009**, *38*, 2981. (f) Felpin, F.-X.; Fouquet, E. *ChemSusChem* **2008**, *1*, 718. (g) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (h) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (i) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195. (j) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed.* **1993**, *32*, 131.

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(4) (a) Shibata, I.; Kano, T.; Kanazawa, N.; Fukuoka, S.; Baba, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1389. (b) Yamaguchi, M.; Hayashi, A.; Hirama, M. *Chem. Lett.* **1992**, *21*, 2479. (c) Fujishima, H.; Takada, E.-i.; Kara, S.; Suzuki, A. *Chem. Lett.* **1992**, *21*, 695.

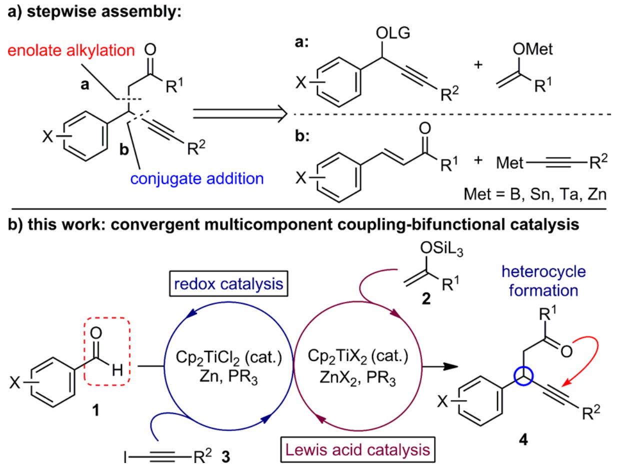
(5) (a) Fleury, L. M.; Kosal, A. D.; Masters, J. T.; Ashfeld, B. L. *J. Org. Chem.* **2013**, *78*, 253. (b) Gianino, J. B.; Ashfeld, B. L. *J. Am. Chem. Soc.* **2012**, *134*, 18217. (c) Campos, C. A.; Gianino, J. B.; Pinkerton, D. M.; Ashfeld, B. L. *Org. Lett.* **2011**, *13*, 5680. (d) Fleury, L. M.; Ashfeld, B. L. *Tetrahedron Lett.* **2010**, *51*, 2427. (e) Fleury, L. M.; Ashfeld, B. L. *Org. Lett.* **2009**, *11*, 5670.

(6) (a) Washio, T.; Nambu, H.; Anada, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **2007**, *18*, 2606. (b) Tian, X.; Rychnovsky, S. D. *Org. Lett.* **2007**, *9*, 4955. (c) Tian, X.; Jaber, J. J.; Rychnovsky, S. D. *J. Org. Chem.* **2006**, *71*, 3176. (d) Tezuka, Y.; Gewali, M. B.; Ali, M. S.; Banskota, A. H.; Kadota, S. *J. Nat. Prod.* **2001**, *64*, 208. (e) Gewali, M. B.; Tezuka, Y.; Banskota, A. H.; Ali, M. S.; Saiki, I.; Dong, H.; Kadota, S. *Org. Lett.* **1999**, *1*, 1733.

(7) Yang, M.; Cai, L.; Shen, X.; Zhao, M.; Yin, T.; Ding, Z. *Chin. J. Chem* . **2012**, *30*, 1323.

10.1021/ol400943a

Scheme 1. Approaches toward β-Alkynyl Ketones



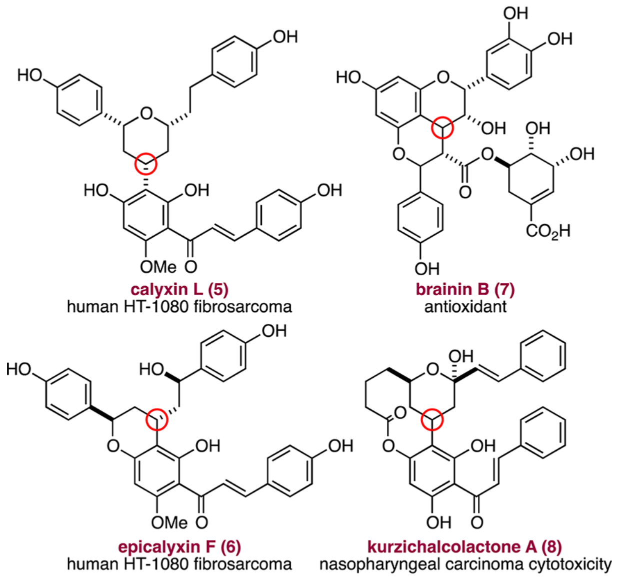
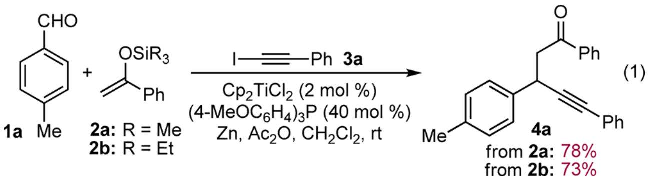


Figure 1. Biologically active heterocyclic natural products.

kurzichalcolactone A (**8**)[8] (Figure 1). The intriguing biological properties associated with these natural products make this architectural subunit an important target for synthesis. A multicomponent coupling approach toward aryl-substituted β-alkynyl carbonyl construction results in a flexible and modular assembly of this heterocyclic motif. Additionally, the alkyne and carbonyl subunits are versatile functional handles for a wide array of secondary transformations. By using a single low-valent titanocene catalyst to facilitate consecutive redox- and Lewis acid-catalyzed transformations, we can access new C–C bonds to efficiently assemble this molecular architecture.[9] Herein, we report a highly convergent assembly of β-aryl γ-ynones that exploits the redox and Lewis acidic properties of low-valent titanocene using an aryl aldehyde as a traceless dielectrophilic functionality.

Although our previous work[5b,c] on titanocene-catalyzed multicomponent couplings indicates that the addition of an enolate derivative would provide direct access to aryl-substituted β-alkynyl ketones, the use of pregenerated metal enolates is complicated by competitive formation of aldol and aldol condensation products under the Lewis acidic conditions of the coupling reaction. Acylation resulting from attack of the intermediate propargylic acetate by the enolate anion could hinder the desired coupling event. Therefore, we began our studies by examining silyl enol ethers as enolate surrogates, speculating that their temperate reactivity would afford the desired three-component coupling adduct. Gratifyingly, treatment of aldehyde **1a**, iodoalkyne **3a**, and either TMS-enol ether **2a** or TES-enol ether **2b** with Cp_2TiCl_2 (2 mol %), zinc dust, $(4\text{-}MeOC_6H_4)_3P$ (40 mol %), and Ac_2O provided ketone **4a** in 78% and 73% yield, respectively (eq 1). With these conditions in hand, we focused our attention on establishing functional group compatibility in the titanocene-catalyzed multicomponent coupling reaction.



Aldehyde and iodoalkyne variability was examined by coupling **1**, **2a**–**c**, and **3** using our optimized conditions (Table 1). Generally, good yields of the corresponding ketones **4** were obtained for a diverse assortment of aryl aldehydes and substituted iodoalkynes. The presence of an aryl halide in aldehydes **1b** and **1c** did not negatively affect the formation of ketones **4b** and **4c** (entries 1 and 2). Electron-rich aryl aldehyde **1d** also provided the corresponding ketone **4d** in 78% yield (entry 3). TIPS silyl enol ether **2c** and thiophene **1e** proved effective in the titanocene-catalyzed coupling with **3a** to give ketone **4e** in 75% yield (entry 4). Aryl- and alkyl-substituted alkynyliodides **3b**, **3c**, and **3d** reacted efficiently with aldehydes **1a** and **1f**, respectively, to yield ketones **4f**–**h** (entries 5–7). It is particularly noteworthy that the primary propargylic acetate in **3e** remained intact throughout the coupling to give ketone **4i** indicating exceptional chemoselectivity for alkylation of the more substituted secondary acetate intermediate (entry 8). Finally, employing the acetylene surrogate, TIPS-iodoalkyne **3f**, yielded ketone **4j** in 66% yield (entry 9).

To establish the functional variability of the silyl enol ether component, aldehydes **1a** and **1d** were treated with

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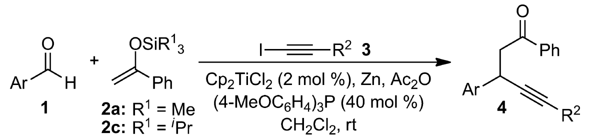
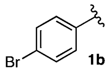
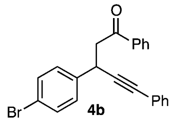
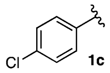
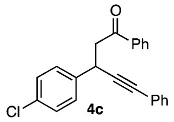
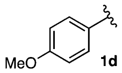
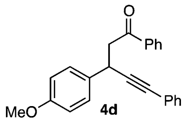
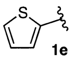
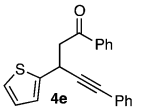
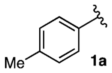
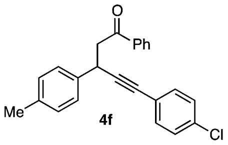
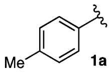
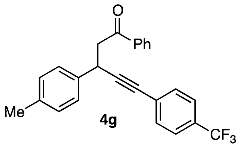
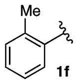
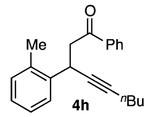
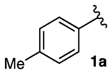
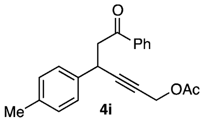
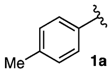
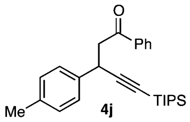
(8) Dumontet, V.; Hung, N. V.; Adeline, M.-T.; Riche, C.; Chiaroni, A.; Sévenet, T.; Guéritte, F. *J. Nat. Prod.* **2004**, *67*, 858.

(9) (a) Gansäuer, A.; Behlendorf, M.; von Laufenberg, D.; Fleckhaus, A.; Kube, C.; Sadasivam, D. V.; Flowers, R. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 4739. (b) Kosal, A. D.; Ashfeld, B. L. *Org. Lett.* **2010**, *12*, 44. (c) Justicia, J.; Sancho-Sanz, I.; Álvarez-Manzaneda, E.; Oltra, J. E.; Cuerva, J. M. *Adv. Synth. Catal.* **2009**, *351*, 2295. (d) Yang, F.; Zhao, G.; Ding, Y.; Zhao, Z.; Zheng, Y. *Tetrahedron Lett.* **2002**, *43*, 1289. (e) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849. (f) Dang, Y.; Geise, H. J. *J. Organomet. Chem.* **1991**, *405*, 1. (g) McMurry, J. E. *Acc. Chem. Res.* **1974**, *7*, 281.

Table 1. Aldehyde and Iodoalkyne Compatibility[a]

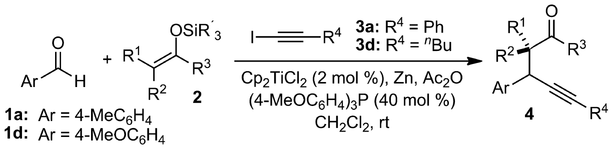


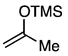
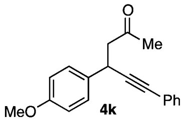
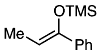
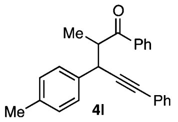
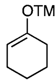
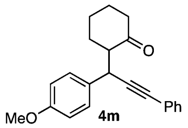
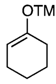
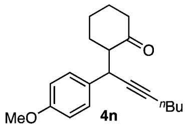
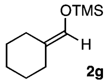
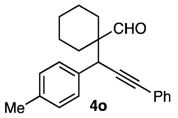
entry	Ar	R²	product[b]	
1[c]	 **1b**	Ph (**3a**)	 **4b**	93%
2	 **1c**	Ph (**3a**)	 **4c**	61%
3	 **1d**	Ph (**3a**)	 **4d**	78%
4[d]	 **1e**	Ph (**3a**)	 **4e**	75%
5[e]	 **1a**	4-Cl-C$_6$H$_4$ (**3b**)	 **4f**	67%
6	 **1a**	4-F$_3$C-C$_6$H$_4$ (**3c**)	 **4g**	71%
7	 **1f**	^{n}Bu (**3d**)	 **4h**	72%
8	 **1a**	AcOCH$_2$ (**3e**)	 **4i**	62%
9	 **1a**	TIPS (**3f**)	 **4j**	66%

[a] Conditions: **1** (0.5 mmol), **2a** (0.65 mmol), **3** (0.6 mmol), Cp$_2$TiCl$_2$ (2 mol %), Zn (1.05 mmol), (4-MeOC$_6$H$_4$)$_3$P (40 mol %), Ac$_2$O (0.55 mmol). [b] Isolated yields. [c] 25 mol % (4-MeOC$_6$H$_4$)$_3$P used. [d] Enol ether **2c** (0.6 mmol) employed. [e] 80 mol % (4-MeOC$_6$H$_4$)$_3$P used.

either iodoalkyne **3a** or **3d** and silyl enol ethers **2** to provide the corresponding β-alkynyl ketones **4** in good yields (Table 2). Enol ether **2d** derived from acetone proved effective in the formation of ketone **4k** (entry 1). Silyl enol ethers bearing substituents at the α-position were also tolerated in the coupling reaction. Both the *Z*-enol ether **2e** and *E*-enol ether **2f** reacted with aldehydes **1a** and **1d** respectively, to yield the corresponding ketones **4l** and **4m** in 67% yield as a 1:1 mixture of diastereomers (entries 2 and 3). Employing the alkyl-substituted iodoalkyne **3d** did not adversely affect the yield of ketone **4n** formation (entry 4). Additionally, the aldehyde-derived silyl enol ether **2g** underwent alkylation with aldehyde **1a** and iodoalkyne **3a** to yield adduct **4o** in 78% yield (entry 5). It is particularly noteworthy that none of the corresponding aldol product resulting from addition of residual enol ether **2g** to aldehyde **4o** was observed in the reaction. Attempts at subjecting silyl ketene acetals to the reaction conditions resulted in formation of a complex mixture of compounds with no desired ester product detectable.

Table 2. Silyl Enol Ether Variability[a]



entry	1	2	3	product[b]	
1	**1d**	 **2d**	**3a**	 **4k**	49%
2[c]	**1a**	 **2e**	**3a**	 **4l**	67%
3[c]	**1d**	 **2f**	**3a**	 **4m**	67%
4[c]	**1d**	 **2f**	**3d**	 **4n**	68%
5[d]	**1a**	 **2g**	**3a**	 **4o**	78%

[a] Conditions: same as in Table 1. [b] Isolated yields. [c] Product obtained as a 1:1 mixture of diastereomers. [d] 80 mol % (4-MeOC$_6$H$_4$)$_3$P used.

Although silyl enol ethers **2a**–**g** participated in the multicomponent coupling to yield products resulting from α-C-alkylation, vinylogous enol ethers underwent exclusive γ-alkylation. For example, the titanocene-catalyzed coupling of silyloxy furan **2h** with aldehyde **1f** and

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(10) (a) Ogata, A.; Nemoto, M.; Kobayashi, K.; Tsubouchi, A.; Takeda, T. *Chem.—Eur. J.* **2007**, *13*, 1320. (b) Gansäuer, A.; Barchuk, A.; Keller, F.; Schmitt, M.; Grimme, S.; Gerenkamp, M.; Muck-Lichtenfeld, C.; Daasbjerg, K.; Svith, H. *J. Am. Chem. Soc.* **2007**, *129*, 1359. (c) Gansäuer, A.; Narayan, S. *Adv. Synth. Catal.* **2002**, *344*, 465.

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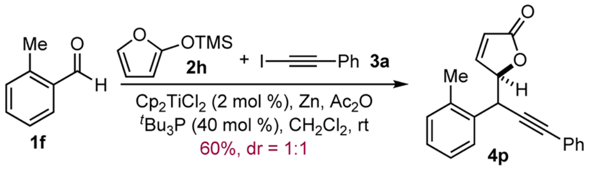
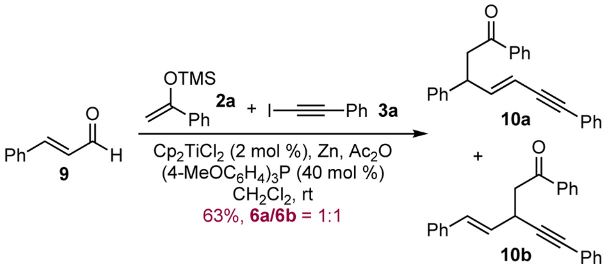
(12) (a) Eisch, J.; Boleslawski, M. *J. Organomet. Chem.* **1987**, *334*, C1. (b) Eisch, J.; Manfre, R. *Fundam. Res. Homogeneous Catal.* **1979**, *3*, 397. (c) Martin, H.; Jellinek, F. *J. Organomet. Chem.* **1967**, *8*, 115. (d) Brintzinger, H. *J. Am. Chem. Soc.* **1967**, *89*, 6871.

iodoalkyne **3a** provided butenolide **4p** in 60% yield as a 1:1 mixture of diastereomers (eq 2).



(2)

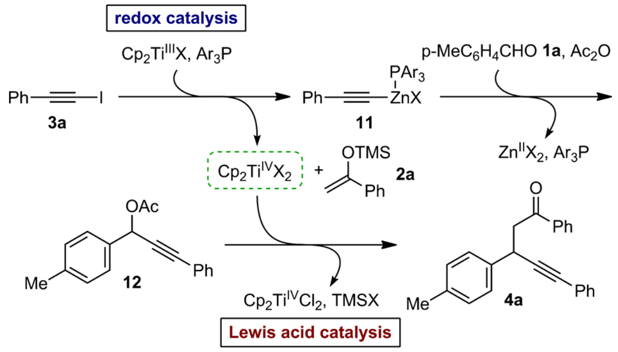
α,β-Unsaturated aldehydes were also effective substrates in the multicomponent assembly of β-disubstituted ketones. Coupling enal **9**, enol ether **2a**, and iodoalkyne **3a** under our optimized conditions afforded isomeric ketones **10a** and **10b** in a 1:1 ratio (eq 3). The lack of regioselectivity in the enol ether alkylation indicates the possibility of an electrophilic allyl intermediate where there is little to no preference for alkylation at either allylic terminus.



(3)

Consistent with our previously reported studies,[5] there appears to be a synergistic effect of Cp_2TiCl_2, Zn^0, and $^tBu_3P$ in both C–C bond-forming steps.[9e,10] Omission of both Cp_2TiCl_2 and Zn^0 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), subsequent silyl enol ether alkylation was not observed. Perhaps most interesting was the effect of phosphine concentration on the reaction outcome. Our empirical observations point to phosphine having a positive impact on the initial iodoalkyne metalation and carbonyl addition steps, while higher concentrations of phosphine hindered the subsequent enol ether alkylation. For example, in the coupling of aldehyde **1a**, enol ether **2a**, and iodoalkyne **3c**, increasing the concentration of phosphine (80 mol %) had an adverse effect leading to 41% yield of **4g** and 47% of the corresponding propargylic acetate intermediate. This is consistent with our hypothesis that the presence of phosphine promotes iodoalkyne metal–halogen exchange and addition to the aldehyde through an unusual Zn–P ligation.[11] However, an abundance of phosphine can lead to saturation of the Ti^{IV} complexes and Zn^{II} salts present, ultimately hindering the Lewis acid-catalyzed propargylic ionization step necessary for enol ether alkylation. Although PPh_3 successfully provided **4a** in 74% yield, other phosphines failed to approach the efficiencies observed with $(4\text{-}MeOC_6H_4)_3P$. The exact role of phosphine is the subject of current investigation and will be reported in due course.

Scheme 2. Relay Catalysis in C–C Bond Formations



On the basis of these results, a possible relay mechanism for the three-component coupling involves initial $Cp_2Ti^{III}X$-catalyzed zincation of iodoalkyne **3a** to yield zinc acetylide **11** and $Cp_2Ti^{IV}X_2$ (Scheme 2).[12] Addition of **11** to aldehyde **1a** followed by in situ acylation with Ac_2O provides propargylic acetate **12**. Activation of **12** by Lewis acidic $Cp_2Ti^{IV}X_2$ results in propargylation of silyl enol ether **2a** most likely via a cationic open transition state. It is important to note that the $Zn^{II}X_2$ salts generated in the metalation–carbonyl addition event may also participate in the Lewis acid-mediated propargylic substitution. However, an alternative mechanism formation of a propargylic titanocene intermediate from acetate **12** followed by a reductive coupling with silyl enol ether **2** cannot be ruled out.

In summary, we have developed a titanocene-catalyzed multicomponent coupling approach toward the highly convergent assembly of β-alkynyl ketones from readily available aldehydes, silyl enol ethers, and iodoalkynes. Through consecutive C–X/C–O activations facilitated by a bifunctional titanocene catalyst, two new C–C bonds are generated in a single operation using aldehydes as a traceless, dielectrophilic functionality. The resulting β-alkynyl ketones are known to be versatile building blocks in the construction of heterocyclic architectures prevalent in natural products. Mechanistic studies and the application of this method in total synthesis are currently being pursued and will be reported in due course.

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

The authors declare no competing financial interest.