DOI: 10.1002/anie.200801987

Synthetic Methods

Acetylides from Alkyl Propiolates as Building Blocks for C_3 Homologation **

David Tejedor, Sara López-Tosco, Fabio Cruz-Acosta, Gabriela Méndez-Abt, and Fernando García-Tellado**

acetylides · asymmetric catalysis · C–C coupling · C_3 homologation · domino reactions

Dedicated to Professor George W. Kabalka on the occasion of his 65th birthday

Alkyl propiolates are reagents with a versatile reactivity profile that entirely remains in the C_3-homologated product for further elaboration. To be effective, this C_3 homologation requires suitable methods for the generation of the acetylide anion that are compatible with both the conjugated ester and the electrophilic partner. Recent advances include catalytic procedures for the in situ generation of these acetylides in the presence of suitable electrophiles. Whereas the organometallic methods have brought stereoselectivity to these reactions, the organocatalytic methods laid the ground for new efficient domino processes that generate complexity.

1. Introduction

Among the large number of C_3-homologation agents that are available,[1] alkyl propiolates ($HC{\equiv}C{-}CO_2R$)[2] maintain a privileged place in the light of the latest tendencies in drug research.[3] This C_3 unit has a rich reactivity profile (i.e., $\mathbf{d^0}$, $\mathbf{a^1}$, $\mathbf{a^2}$,[4] $\mathbf{a^3}$, $\mathbf{d^3}$, and $[\mathbf{a^3}+\mathbf{d^2}]$;[5] Figure 1 a) which entirely remains in the homologation product (with the obvious exception of $\mathbf{d^3}$). Among other applications, this chemically rich C_3 functionality can be used as handle for the generation of structural complexity and diversity in the homologated molecule (Figure 1 b).

Central to this issue is the development of suitable methods for a selective $\mathbf{d^3}$ reactivity, which requires the generation of a nucleophilic acetylide anion and its addition into the appropriate electrophile. Ideally, these acetylides would be generated catalytically in situ such that the nucleophilic addition is compatible with both the conjugated ester functionality and the electrophile. Under these conditions, the incorporated C_3 unit could be directly used in new homologating or complexity-generating reactions without requiring functionality reconstitution.

Classical methods have exploited the high acidity of the terminal acetylenic C–H bond ($pK_a \leq 18.8$) to form the metal

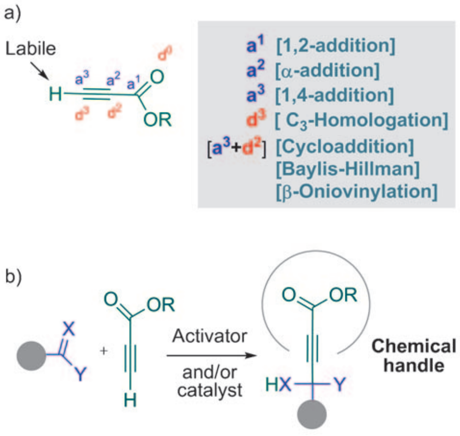


Figure 1. a) Versatile reactivity profile of alkyl propiolates; b) C_3 homologation reaction having $\mathbf{d^3}$ reactivity (green: C_3 homologating unit).

---

[*] Dr. D. Tejedor,[+] S. López-Tosco, F. Cruz-Acosta, G. Méndez-Abt, Dr. F. García-Tellado[+]
Instituto de Productos Naturales y Agrobiología-CSIC
Astrofísico Francisco Sánchez 3, 38206 La Laguna
Tenerife, Canary Islands (Spain)
Fax: (+34) 922-260135
E-mail: fgarcia@ipna.csic.es
dtejedor@ipna.csic.es
Homepage: http://www.ipna.csic.es/departamentos/qbb/qb/

[+] D.T. and F. G.-T. are associate researchers at the Instituto Canario de Investigación del Cáncer (www.icic.es).

[**] This research was supported by the Spanish Ministerio de Educación y Ciencia, the European Regional Development Fund (CTQ2005-09074-C02-02) and the Spanish MSC ISCIII (RETICS RD06/0020/1046), CSIC (Proyecto Intramural Especial 200719), and the Fundación Instituto Canario de Investigación del Cáncer (FICI-G.I.N°08/2007). S.L.-T. thanks MEC for a FPU grant, F.C.-A. thanks CSIC for a JAE predoc grant. We thank Dr. Tomás Martín and Dr. Pedro de Armas for helpful discussions and critical reading of this manuscript.

conjugated alkynylide by treatment with strong bases, such as *n*-butyllithium[6] or lithium diisopropylamide (LDA).[7] Although these procedures are compatible with alkyl propiolates, they cannot be performed in the presence of base-sensitive substrates such as aldehydes or ketones. This incompatibility means that the alkynoate deprotonation must be performed in a separate, preceding step to the C–C bond-forming reaction.

Other approaches that are in accord with the latest tendencies in organic synthesis[8] would be desirable to fully exploit the chemical advantages associated with these homologating building blocks. The design of new methods needs to overcome two difficulties associated with the electronic nature of these C_3 units: 1) the low nucleophilicity of these carbanions, and 2) the marked electrophilicity of the conjugated triple bond ($\mathbf{a}^3$ reactivity). The first difficulty limits both the scope of the electrophilic partner and the type of C–C bond-forming process in which they can participate, whereas the second restricts the nature of the metal and/or the base required to form the acetylide. Recent advances in this field include both metal and metal-free catalytic procedures for the in situ generation of the acetylide anions. Whereas the organometallic methods achieve stereoselectivity, metal-free procedures have laid the way for domino processes that generate complexity.

2. Metalated Acetylides of Alkyl Propiolates: Success in Asymmetric Catalysis

2.1. Lithium Acetylides: the Classical Homologating Agent for Substrate-Controlled Diastereoselective C_3 Homologation

Lithium salts of methyl or ethyl propiolates are the standard source of metalated acetylides ($\mathbf{d}^3$ reactivity). They are prepared by Midland's method[6] and are relatively stable if kept at low temperature (Scheme 1).[9] In spite of their weak nucleophilicity and the low temperatures required to obtain them, these acetylides add to aldehydes and ketones to give propargylic alcohols **1** in good yields.[10] Other electrophiles, such as nitrones,[11–13] acid chlorides,[14] Weinreb amides,[15,16] and acylpyridinium ions[17] are also accessible to these anions (Scheme 1). Less-active electrophiles require the use of coactivators or the replacement (transmetalation) of lithium with magnesium,[18] zinc,[19–22] cerium[23] or boron[24]). The stereoselectivity of these C_3 homologations is substrate-controlled, and good diastereoselectivity can be achieved by convenient combinations of chiral auxiliary and metal.[25]

2.2. Silver Acetylides: Bench-Stable Acetylides of Alkyl Propiolates

Koide and co-workers have reported the use of the bench-stable silver acetylide **6** as a synthetic alternative to the lithium salt of methyl propiolate. The acetylide is readily prepared from methyl propiolate in multigram quantities

From left to right: David Tejedor, Gabriela Méndez-Abt, Fabio Cruz-Acosta, Sara López-Tosco, Fernando García-Tellado

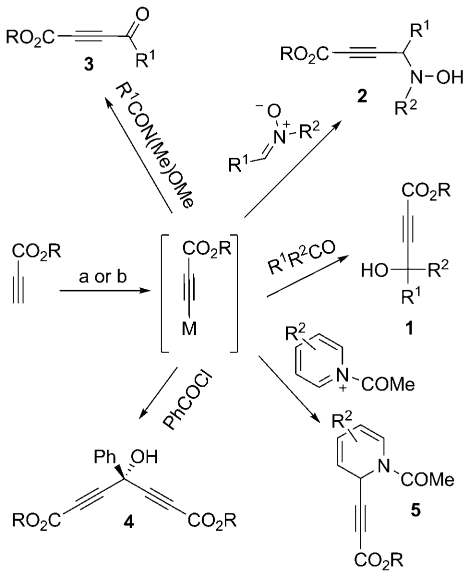
David Tejedor *was born in Madrid (Spain) in 1970. After moving to the United States and studying chemistry at the University of Nevada, he obtained his PhD under the supervision of Prof. G. W. Kabalka at the University of Tennessee in 1998. He moved back to Spain and between 2000 to 2007 he was a postdoctoral fellow in the group of F. Garcia-Tellado at the Instituto de Productos Naturales y Agrobiología. Since 2007, he has held a tenured scientist position at the Consejo Superior de Investigaciones Científicas.*

Gabriela Méndez-Abt *was born in Buenos Aires (Argentina) in 1983. She studied chemistry at the La Laguna University, and is a graduate student in the group of Dr. García-Tellado.*

Fabio Cruz-Acosta *was born in Santa Cruz de Tenerife (Spain) in 1980. He studied chemistry at the La Laguna University, and is a graduate student in the group of Dr. García-Tellado.*

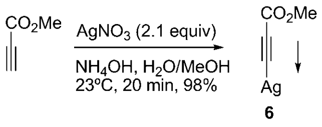
Sara López-Tosco *was born in Santa Cruz de Tenerife (Spain) in 1983. She studied Chemistry at the La Laguna University, and is a graduate student in the group of Dr. García-Tellado.*

Fernando García-Tellado *was born in Tenerife (Spain) in 1957. He studied chemistry at the University of La Laguna, where he later obtained his PhD in 1983 under the supervision of Prof. A. González González, Prof. B. M. Fraga, and Prof. M. García Hernández. After completing a postdoctoral work with Prof. J. R. Hanson at the University of Sussex, UK (1985–1986), he joined the Consejo Superior de Investigaciones Científicas as a tenured scientist in 1986. He was a Fulbright visiting researcher in Prof. A. D. Hamilton's group at the University of Pittsburg, USA (1989–1990). In 2008 he was promoted to Research Scientist. Since 2000, he has been also an associate researcher of the Instituto Canario de Investigación del Cáncer.*



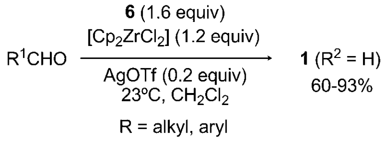
Scheme 1. Generation and addition of metal acetylides to electrophiles. a) *n*BuLi or LDA, THF, −78 °C (R = Et) or −100 °C (R = Me). b) Two steps: 1. see (a), 2. transmetalation.

(Scheme 2)[26] and it can be stored in a vial for months without special precautions.[27]



Scheme 2. Preparation of the bench-stable silver acetylide **6**.

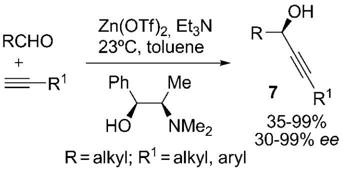
As expected for silver alkynyl compounds,[28] these acetylides have a low basicity and extreme mildness, requiring a stoichiometric amount of $[Cp_2ZrCl_2]$ and a catalytic amount of AgOTf to react with aldehydes (Scheme 3).[29,30] The benefits of this procedure have been demonstrated by Koide et al. in the synthesis of the antitumor agent FR901464.[31] A very recent report from this group has also extended this method to the synthesis of propargylic alcohols by a zirconium-promoted tandem epoxide rearrangement–alkynylation reaction.[27]



Scheme 3. $[Cp_2ZrCl_2]$/AgOTf-promoted addition of silver acetylides to aldehydes.

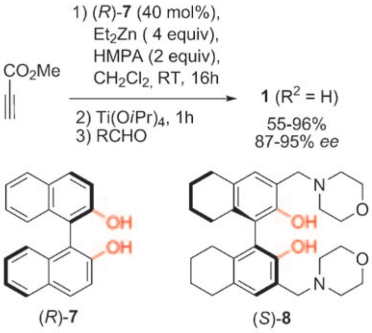
2.3. Zinc and Copper Acetylide Salts of Alkyl Propiolates: Catalytic Enantioselective C_3 Homologations

The catalytic generation of metal acetylides under conditions compatible with electrophilic reaction partners had long been an unresolved synthetic challenge.[32] A major breakthrough came from Carreira et al. with the first asymmetric addition of zinc acetylides to aldehydes (Scheme 4).[33]



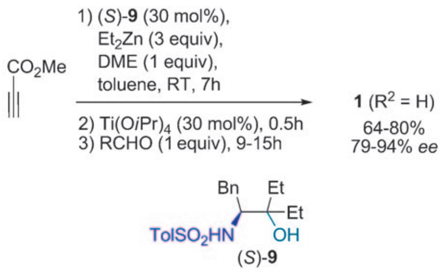
Scheme 4. Enantioselective addition of in situ generated zinc acetylides to aliphatic aldehydes.

Although the system works efficiently with a wide number of terminal alkynes, alkyl propiolates decompose if they are exposed to these reaction conditions. This drawback has been elegantly overcome by Pu and co-workers with the development of their binol–titanium catalytic system.[34] The reaction utilizes the chiral ligand (*R*)-1,1′-bi-2-naphthol ((*R*)-**7**), titanium tetraisopropoxide, ($Ti(OiPr)_4$) as a Lewis acid activator, and hexamethylphosphoramide (HMPA) as a Lewis base additive.[35] The catalytic system is performed in a one-pot manner and it involves two synthetically differentiated steps: 1) zinc acetylide formation, and 2) acetylide transfer to furnish the corresponding hydroxyalkyne product **1** in good yields (55–96 %) and high enantioselectivity (87–95 % *ee*; Scheme 5).

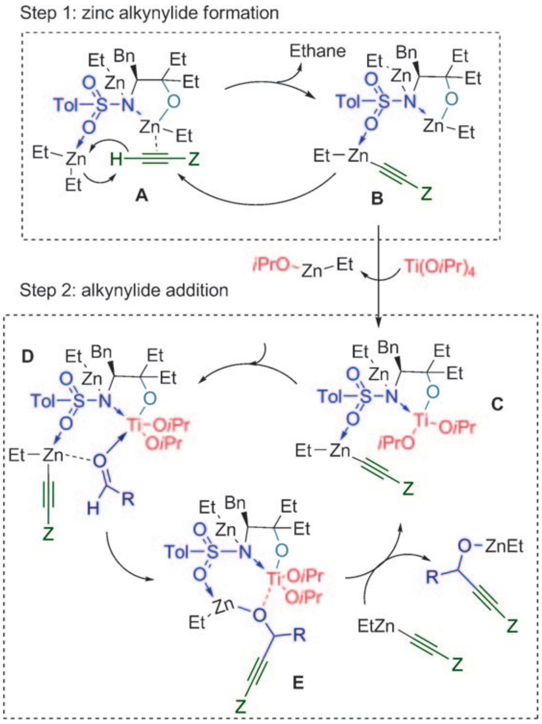


Scheme 5. Enantioselective addition of the zinc acetylide of methyl propiolate to aromatic and α,β-unsaturated aldehydes catalyzed by (*R*)-**7**/$Ti(OiPr)_4$/HMPA.

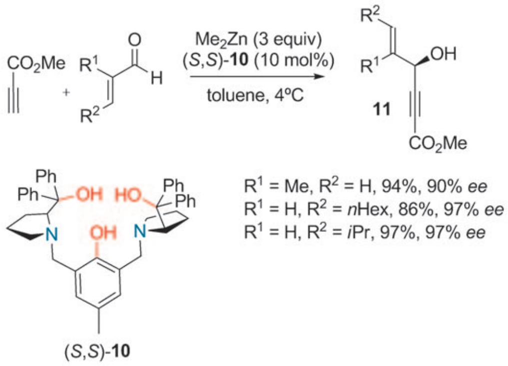
Incorporation of the Lewis base into the structure of the binol-based catalyst (in (*S*)-**8**, Scheme 5) improves the catalyst reactivity but not its chirality transfer efficiency.[36,37] On the other hand, the bifunctional β-sulfonamide alcohol (*S*)-**9** in combination with $Ti(OiPr)_4$ and 1,2-dimethoxyethane (DME) is an excellent catalyst for the 1,2-addition of propiolate to aldehydes (Scheme 6).[38] This catalytic system produces propargylic alcohol **1** in yields and optical purities similar to those of the (*R*)-**7**/Ti(O*i*Pr)$_4$/HMPA system, but the first step, zinc acetylide formation, is considerably faster (reaction time reduced from 16 to 7 h). Scheme 7 outlines the mechanistic proposal for this catalytic system.



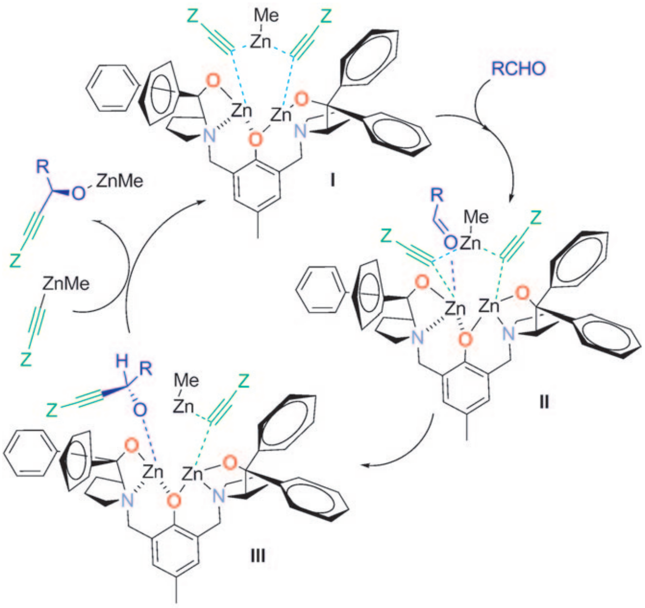
Scheme 6. Enantioselective addition of methyl propiolate to aldehydes catalyzed by β-sulfonamide alcohol (*S*)-**9**.



Scheme 7. Proposed catalytic cycle for the enantioselective addition of methyl propiolate to aldehydes using chiral β-sulfonamide alcohol ligands. Z = CO_2R.



Scheme 8. Enantioselective addition of methyl propiolate to α,β-unsaturated aldehydes using the proline-derived Trost binuclear zinc catalyst (*S*,*S*)-**10**.



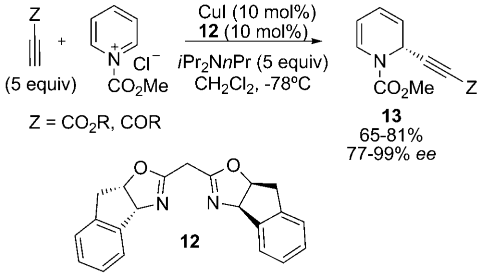
Scheme 9. Proposed catalytic cycle for the addition of methyl propiolate to α,β-unsaturated aldehydes using the bifunctional (*S*,*S*)-**10**. Z = CO_2R.

A highly enantioselective 1,2-addition of methyl and ethyl propiolate to aromatic and α,β-unsaturated aldehydes has been performed by Trost and co-workers using the bifunctional proline-derived binuclear zinc catalyst (*S*,*S*)-**10** (Scheme 8).[39] The proposed catalytic cycle accounts for the observed absolute stereochemistry of the propargylic alcohols **11** (Scheme 9). This procedure has been effectively applied in the first catalytic and enantioselective synthesis of the adociacetylene B, a polyacetylenic biologically active natural product.[40]

During the last two years, a few, significant advances in the metalation of propiolate esters using catalytic amounts of copper(I) have been reported. In a recent communication, Ma and co-workers describe the first asymmetric addition of alkyl propiolates and related conjugated terminal alkynes to 1-acylpyridinium salts catalyzed by a copper(I) complex of bis(oxazoline) **12** (Scheme 10).[41,42]

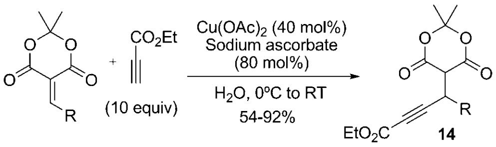
The reaction provides dihydropyridines **13** in good yields and excellent enantioselectivities (77–99 % *ee*). A copper(II)-catalyzed asymmetric addition of ethyl propiolate to aromatic nitrones that can be carried out in the presence of air has been recently described.[43]

Carreira and co-workers have successfully developed the first copper(I)-catalyzed conjugated addition of ethyl propiolate to acceptors derived from Meldrum's acid under mild and



Scheme 10. Enantioselective copper(I)-catalyzed addition of alkyl propiolate and related terminal conjugated alkynes to 1-acylpyridinium ions.

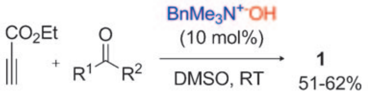
aqueous conditions (Scheme 11).[44] The conjugated addition presents two particular challenges: 1) the known property of acetylides to bind to copper as non-transferable ligands,[45] and 2) both the reagents and the products are good Michael acceptors. Despite these difficulties, the aqueous copper(I)-catalyzed 1,4-addition of ethyl propiolate to acceptors derived from Meldrum's acid generates the corresponding adducts **14** in good to excellent yields (54–92 %). The presence of a γ-oxygen functionality in the acceptor molecule accelerates the reaction and influences the stereochemical course of the conjugate addition (d.r. > 19:1). A copper(I)-catalyzed regioselective coupling of allylic halides and ethyl propiolate in the presence of weak inorganic bases has been recently described.[46] The reaction affords functionalized 1,4-enynes using environmentally neutral reagents and solvents without need for inert atmospheres.



Scheme 11. Copper(I)-catalyzed conjugated addition of ethyl propiolate to acceptors derived from Meldrum's acid.

3. Nonmetallic Acetylide Salts of Alkyl Propiolates: A Carousel of Acetylide-Driven Domino Processes

Nonmetalated acetylides are not easily accessible by conventional methods. Ishikawa and Saito have reported on the catalytic C_3 homologation of ketones and aliphatic aldehydes using ethyl propiolate and commercially available benzyltrimethylammonium hydroxide as a base (Scheme 12).[47] Although the method works well with robust aldehydes and ketones, the use of this strong base could be detrimental with other base-sensitive electrophiles.



Scheme 12. Organocatalyzed addition of propiolate to aldehydes and ketones.

A conceptually different, Lewis base-catalyzed domino approach has been developed by our group utilizing the strategy outlined in Figure 2.[48] Upon activation by a good nucleophile (tertiary amines or phosphines), alkyl propiolates launch a cascade of chemical events leading to the generation the amphiphilic salt **B**, which has a [$a^3 + d^3$] reactivity profile in the form of an acetylide ion (d^3 reactivity; C_3 homologating unit) and a β-activated acrylic ester (a^3 reactivity). In the presence of a suitable electrophile (**E**),[49] the acetylide generates the corresponding C_3-homologated adduct **C**, which can in turn react with any of the three electrophiles present in the reaction media (**$\mathrm{Nu^{+}{-}CH{=}CHCO_2R}$**, **E**, **$\mathrm{HC{\equiv}CCO_2R}$**) to generate the advanced intermediates **D**, **F**, or **G**. Each one of these intermediates generates products with different molecular structures whose topology and chemical complexity are defined by the own nature of the electrophile **E**. If the electrophile is an aliphatic aldehyde or an activated ketone, the densely functionalized molecular scaffolds **15–17** are generated (Figure 3).

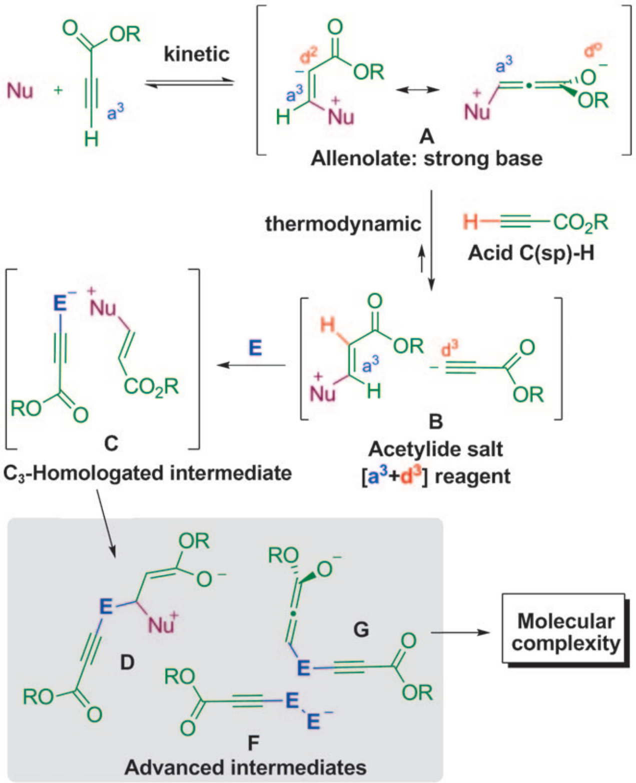


Figure 2. Nucleophile-triggered [$a^3 + d^3$] reactivity pattern of alkyl propiolates.

Each one of these molecular structures is generated selectively from a common C_3-homologated adduct **C** by a domino process that is selectively triggered by a particular catalyst, under a defined set of reaction conditions (temperature, stoichiometry, and solvent) and involving a particular reactivity profile of the alkynoate unit. Particular conditions

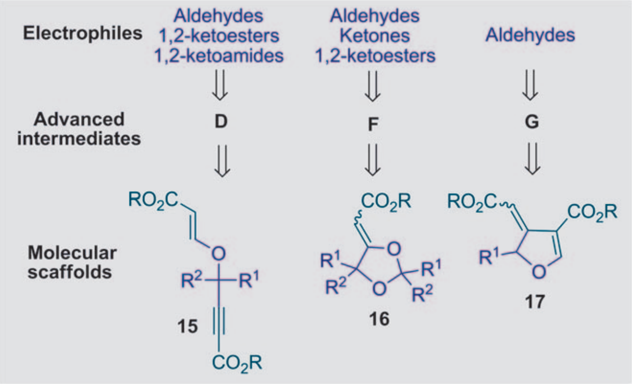
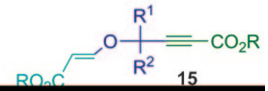


Figure 3. Molecular scaffolds generated from addition of alkyl propiolate to aldehydes and activated ketones.

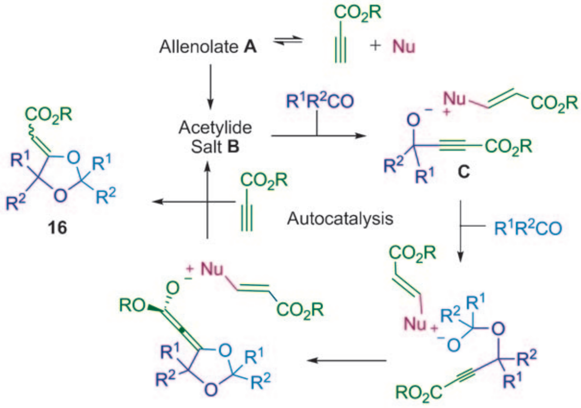
and reactivity profiles for each process are indicated in the corresponding Schemes 13–15.[50,51] These molecular structures are convenient building blocks for the building/coupling/pairing strategy in diversity-oriented synthesis (DOS).[3,52]

A common property of these three domino processes is the generation of molecular structures with functional and skeletal diversity by utilizing only two different reactants. Each one of the structures **15–17** incorporates two units of a reactant in the form of two differentiated chemical functions or structural motifs (this is graphically represented using two different tones of the same color). This remarkable property confers on the domino processes all of the synthetic advantages associated with three-component reactions (3CRs)—convergence, modularity, efficiency, and complexity—but using a simpler and easier to handle two-component synthetic manifold. Therefore, these domino reactions have been categorized as chemodifferentiating **ABB′** 3CRs to highlight: 1) their bimolecular nature (i.e., that two different species **A** and **B** are involved), 2) the dual role played by component **B** along the reaction pathway (**B** and **B′**), and 3) their three-component chemical outcome (3CRs).[54]

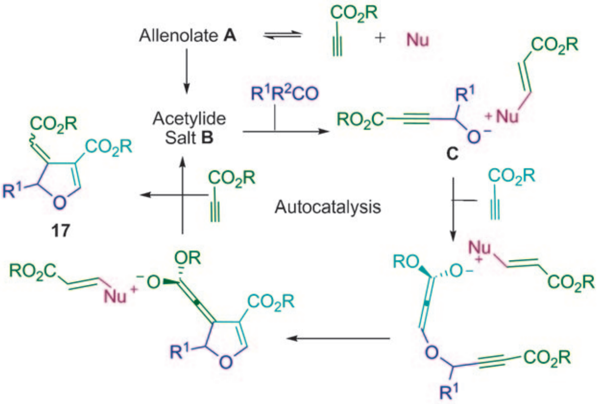


[redacted]

Scheme 13. Organocatalytic domino synthesis of propargylic enol ethers **15**. Propiolate reactivity: [a^3+d^3].
Catalyst: DABCO (−78 °C); electrophile: $R^1=H$, $R^2=$ alkyl; $R^1=$ *iso* or *sec* alkyl, $R^2=COOR^3$; various solvents; yield: 56–97%.
Catalyst: Et_3N (0 °C); electrophile: $R^1=H$, $R^2=$ alkyl; $R^1=$ alkyl, aryl, $R^2=CONR^3R^4$; various solvents; yield: 57–87%.
Catalyst: quinine (RT); electrophile: $R^1=H$, $R^2=$ alkyl; solvent: reagents suspended on water;[53] yield: 70–97%.

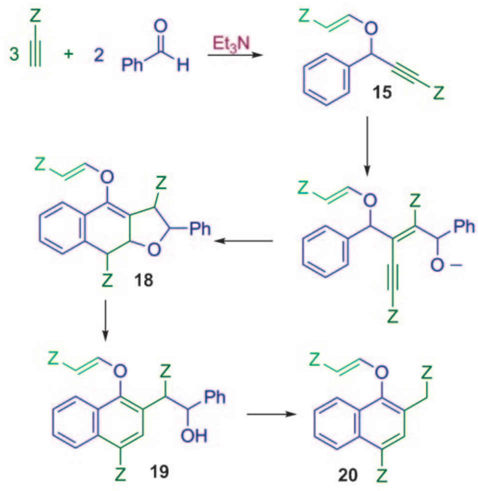


Scheme 14. Organocatalytic domino synthesis of 1,3-dioxolanes **16**. Propiolate reactivity: [a^3+d^3].
Catalyst: Et_3N/nBu_3P (−78 °C); electrophile: $R^1=H$, $R^2=$ alkyl; $R^1=$ alkyl, aryl, $R^2=CF_3$; various solvents; yield: 66–95%.
Catalyst: Et_3N (0 °C); electrophile: $R^1=$ aryl, *tert*-alkyl, $R^2=CO_2R^3$; various solvents; yield: 85–89%.



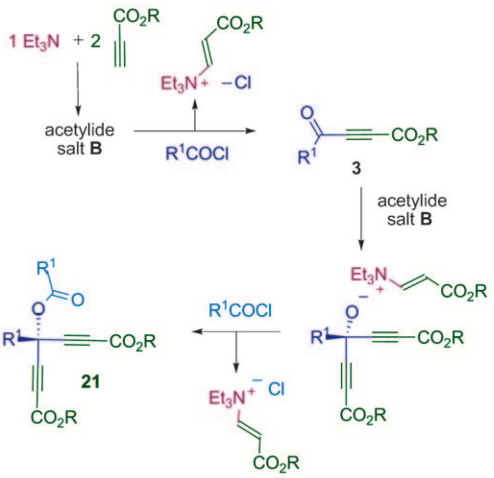
Scheme 15. nBu_3P-catalyzed synthesis of 4,5-dihydrofurans **17**. Propiolate reactivity: [$a^3+d^2+d^3$].
Catalyst: nBu_3P (−40 to −78 °C); electrophile: aliphatic aldehydes; halogenated solvents; yield: 38–57%.

An impressive example of a chemodifferentiation that is similar in origin has been described by Wang and co-workers (Scheme 16).[55] This $\mathbf{A_2B_2B'}$ 5CR domino process involves the formation of the enol-protected propargylic alcohol **15** ($R^1=Ph$, $R^2=H$) and its sequential transformation into the intermediate **18**, which in turn rearranges upon heating to form the naphthalene derivatives **19** or **20**. Overall, the reaction creates seven new bonds (5 × C–C and 2 × C–O) and two rings.



Scheme 16. Acetylide-driven chemodifferentiating $\mathbf{A_2B_2B'}$ 5CR. Z = CO_2R.

We have recently reported a triethylamine-promoted double C_3-homologation reaction utilizing acid chlorides as electrophiles.[14] The reaction generates fully substituted tertiary diynes **21** in good to excellent yields by chemodifferentiating $\mathbf{A_2BB'}$ 4CRs (Scheme 17). The synthetic approach requires a stoichiometric amount of the tertiary amine and an aromatic or branched aliphatic acid chloride to operate.

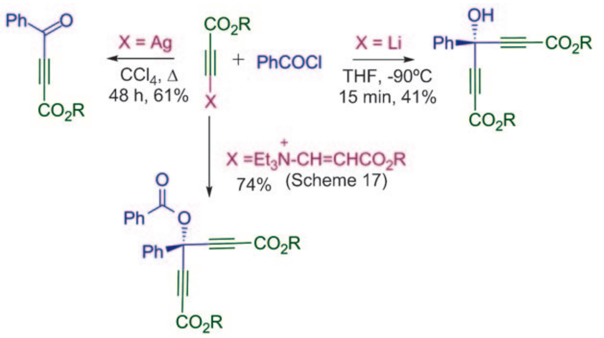


Scheme 17. Triethylamine-promoted double homologation. Synthesis of fully substituted tertiary 1,4-skipped diynes by $\mathbf{A_2BB'}$ 4CR.

The chemical efficiency of this metal-free approach is apparent when compared with its organometallic homologues (Scheme 18).

4. Summary and Outlook

In this Minireview, an overview is presented of the different methods that are suitable for the generation of acetylide anions of alkyl propiolates and their reactions with appropriate electrophiles.



Scheme 18. Organometallic versus organocatalytic C_3-homologation of benzoyl chlorides with alkyl propiolates.

Much effort has been devoted to the development of metal-catalyzed enantioselective C_3 homologation reactions, and during the last years, important procedures have been successfully implemented. Many of them have been also successfully applied to total synthesis. Despite these significant advances, more bench-friendly methods are desirable that can operate in the open atmosphere and be adapted to be incorporated in modular synthetic strategies. Furthermore, the metal-free methods covered herein have shown the strength of these base-free domino approaches to generate molecular diversity and complexity in a simple manner. Stereoselective procedures that generate skeletal and stereochemical diversity in a stereocontrolled manner remains an elusive challenge.

Received: April 28, 2008

---

[1] J. C. Stowell, *Chem. Rev.* **1984**, *84*, 409–435.
[2] For physicochemical properties and reactivity profiles of methyl and ethyl propiolate: G. C. Hirst in *Encyclopedia of Reagents for Organic Synthesis*, Vol. 5 (Ed.: L. A. Paquette), Wiley, New York, **1995**, pp. 3576–3578.
[3] T. E. Nielsen, S. L. Schreiber, *Angew. Chem.* **2008**, *120*, 52–61; *Angew. Chem. Int. Ed.* **2008**, *47*, 48–56.
[4] B. M. Trost, G. R. Dake, *J. Am. Chem. Soc.* **1997**, *119*, 7595–7596.
[5] a) For β-oniovinylations: R. Weiss, M. Bess, S. M. Huber, F. W. Heinemann, *J. Am. Chem. Soc.* **2008**, *130*, 4610–4617; b) for a recent review on Baylis–Hillman reactions, including terminal alkynoates: D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811–891.
[6] M. M. Midland, A. Tramontano, J. R. Cable, *J. Org. Chem.* **1980**, *45*, 28–29.
[7] K. Yamada, N. Miyaura, M. Itoh, A. Suzuki, *Synthesis* **1977**, 679–682.
[8] a) *Special issue*: "Frontiers in organic synthesis" (Ed.: P. A. Wender), *Chem. Rev.* **1996**, *96*, 1–600.
[9] Lithiated methyl propiolate decomposes at temperatures above −100 °C, whereas the ethyl ester is stable up −78 °C.
[10] For selected recent examples: a) W. He, J. Huang, X. Sun, A. J. Frontier, *J. Am. Chem. Soc.* **2008**, *130*, 300–308; b) T. Taniguchi, G. Tanabe, O. Muraoka, H. Ishibashi, *Org. Lett.* **2008**, *10*, 197–199; c) W. He, J. Huang, X. Sun, A. J. Frontier, *J. Am. Chem. Soc.*

2007, *129*, 498 – 499; d) C.-C. Li, C.-H. Wang, B. Liang, X.-H. Zhang, L.-J. Deng, S. Liang, J.-H. Chen, Y.-D. Wu, Z. Yang, *J. Org. Chem.* **2006**, *71*, 6892 – 6897; e) P. A. Roethle, D. Trauner, *Org. Lett.* **2006**, *8*, 345 – 347; f) D. Tejedor, A. Santos-Expósito, F. García-Tellado, *Synlett* **2006**, 1607 – 1609; g) B. M. Trost, M. L. Crawley, *J. Am. Chem. Soc.* **2002**, *124*, 9328 – 9329; h) Y.-G. Suh, J.-K. Jung, S.-Y. Seo, K.-H. Min, D.-Y. Shin, Y.-S. Lee, S.-H. Kim, H.-J. Park, *J. Org. Chem.* **2002**, *67*, 4127 – 4137; i) M. T. Crimmins, J. M. Pace, P. G. Nantermet, A. S. Kim-Meade, J. B. Thomas, S. H. Watterson, A. S. Wagman, *J. Am. Chem. Soc.* **2000**, *122*, 8453 – 8463.

[11] P. Merino, S. Franco, F. L. Mercham, T. Tejero, *Synlett* **2000**, 442 – 454 and references cited therein.

[12] a) S. K. Patel, K. Murat, S. Py, Y. Vallée, *Org. Lett.* **2003**, *5*, 4081 – 4084; b) J.-N. Denis, S. Tchertchian, A. Tomassini, Y. Vallée, *Tetrahedron Lett.* **1997**, *38*, 5503 – 5506.

[13] S. Hanessian, M. Bayrakdarian, X. Luo, *J. Am. Chem. Soc.* **2002**, *124*, 4716 – 4721.

[14] D. Tejedor, S. López-Tosco, J. González-Platas, F. García-Tellado, *J. Org. Chem.* **2007**, *72*, 5454 – 5456.

[15] B. M. Trost, M. L. Crawley, *Chem. Eur. J.* **2004**, *10*, 2237 – 2252.

[16] For an addition with a different outcome: T. Person, J. Nielsen, *Org. Lett.* **2006**, *8*, 3219 – 3222.

[17] D. L. Comins, S. Huang, C. L. McArdle, C. L. Ingalls, *Org. Lett.* **2001**, *3*, 469 – 471.

[18] For C_3-homologation of α-hydroxy aldehydes using magnesium acetylides: D. L. J. Clive, Y. Tao, Y. Bo, Y.-Z. Hu, N. Selvakumar, S. Sun, S. Daigneault, Y.-J. Wu, *Chem. Commun.* **2000**, 1341 – 1350.

[19] For the stereoselective addition of zinc acetylides to Garner's aldehyde: S. Hanessian, G. Yang, J.-M. Rondeau, U. Neumann, C. Betschart, M. Tintelnot-Blomley, *J. Med. Chem.* **2006**, *49*, 4544 – 4567.

[20] For the first palladium(0)-catalyzed $C(sp)-C(sp^2)$ coupling reaction of alkyl propiolates and aryl halides: a) L. Anastasia, E. Negishi, *Org. Lett.* **2001**, *3*, 3111 – 3113; b) K. Hiroya, S. Matsumoto, T. Sakamoto, *Org. Lett.* **2004**, *6*, 2953 – 2956.

[21] For an example of a palladium(0)-catalyzed cross-coupling reaction of methyl propiolate and α-iodoenamides: J. A. Mulder, K. C. Kurtz, R. P. Hsung, H. Coverdale, M. O. Frederick, L. Shen, C. A. Zificsak, *Org. Lett.* **2003**, *5*, 1547 – 1550.

[22] For a diastereoselective addition of methyl propiolate to chiral nitrones in the presence of catalytic amounts of Et_2Zn: a) S. K. Patel, S. Py, S. U. Pandya, P. Y. Chavant, Y. Vallée, *Tetrahedron: Asymmetry* **2003**, *14*, 525 – 528; b) S. Pinet, S U Pandya, P. Y. Chavant, A. Ayling, Y. Vallée, *Org. Lett.* **2002**, *4*, 1463 – 1466.

[23] For cerium acetylide additions to functionalized aldehydes: a) S. Hanessian, H. Yun, Y. Hou, M. Tintelnot-Blomley, *J. Org. Chem.* **2005**, *70*, 6746 – 6756; b) E. Vedjes, D. W. Piotrowski, F. C. Tucci, *J. Org. Chem.* **2000**, *65*, 5498 – 5505.

[24] For recent selected examples of boron-promoted epoxide opening with alkyl propiolates: a) C. D. Donner, *Tetrahedron Lett.* **2007**, *48*, 8888 – 8890; b) G. S. Kauffman, P. S. Watson, W. A. Nugent, *J. Org. Chem.* **2006**, *71*, 8975 – 8977; c) C. V. Ramana, B. Srinivas, V. G. Puranik, M. K. Gurjar, *J. Org. Chem.* **2005**, *70*, 8216 – 8219; d) M. Ball, A. Baron, B. Bradshaw, H. Omori, S. MacCormick, E. J. Thomas, *Tetrahedron Lett.* **2004**, *45*, 8737 – 8740; e) W. Zhu, D. Ma, *Org. Lett.* **2003**, *5*, 5063 – 5066; f) E. K. Dorling, E. Öhler, J. Mulzer, *Tetrahedron Lett.* **2000**, *41*, 6323 – 6326; g) for a study on the regioselectivity in the opening of β-hydroxy epoxides using different metal acetylides: B. M. Trost, J. P. N. Papillon, T. Nussbaumer, *J. Am. Chem. Soc.* **2005**, *127*, 17921 – 17937.

[25] A survey of good examples can be found in references [10–13,19,22,23].

[26] R. B. Davis, D. H. Scheiber, *J. Am. Chem. Soc.* **1956**, *78*, 1675 – 1678.

[27] B. J. Albert, K. Koide, *J. Org. Chem.* **2008**, *73*, 1093 – 1098.

[28] U. Halbes-Letinois, J.-M. Weibel, P. Pale, *Chem. Soc. Rev.* **2007**, *36*, 759 – 769.

[29] S. P. Shahi, K. Koide, *Angew. Chem.* **2004**, *116*, 2579 – 2581; *Angew. Chem. Int. Ed.* **2004**, *43*, 2525 – 2527.

[30] Silver acetylides react with acid chlorides to afford the corresponding propargylic ketones **3**. T. Naka, K. Koide, *Tetrahedron Lett.* **2003**, *44*, 443 – 445.

[31] B. J. Albert, A. Sivaramakrishnan, T. Naka, K. Koide, *J. Am. Chem. Soc.* **2006**, *128*, 2792 – 2793.

[32] For selected reviews: a) L. Pu, *Tetrahedron* **2003**, *59*, 9873 – 9886; b) P. Aschwanden, E. M. Carreira in *Acetylene Chemistry. Chemistry, Biology, and Material Science* (Eds.: F. Diederich, P. J. Stang, R. R. Tykwinski), Wiley-VCH, Weinheim, **2005**, pp. 101 – 138.

[33] a) N. K. Anand, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 9687 – 9688; b) D. E. Frantz, R. Fassler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806 – 1807; c) D. E. Frantz, R. Fassler, C. S. Tomoka, E. M. Carreira, *Acc. Chem. Res.* **2000**, *33*, 373 – 381.

[34] a) G. Gao, Q. Wang, X.-Q. Yu, R.-G. Xie, L. Pu, *Angew. Chem.* **2005**, *118*, 128 – 131; *Angew. Chem. Int. Ed.* **205**, *45*, 122 – 125; b) for a synthetic application: A. R. Rajaram, L. Pu, *Org. Lett.* **2006**, *8*, 2019 – 2021.

[35] a) G. Gao, R.-G. Xie, L. Pu, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5417 – 5420, and references cited therein.

[36] Y.-C. Qin, L. Liu, M. Sabat, L. Pu, *Tetrahedron* **2006**, *62*, 9335 – 9348.

[37] F. Yang, P. Xi, L. Yang, J. Lan, R. Xie, J. You, *J. Org. Chem.* **2007**, *72*, 5457 – 5460.

[38] L. Lin, X. Jiang, W. Liu, L. Qiu, Z. Xu, J. Xu, A. S. C. Chan, R. Wang, *Org. Lett.* **2007**, *9*, 2329 – 2332.

[39] B. M. Trost, A. H. Weiss, A. Jacobi von Wangelin, *J. Am. Chem. Soc.* **2006**, *128*, 8 – 9.

[40] B. M. Trost, A. H. Weiss, *Org. Lett.* **2006**, *8*, 4461 – 4464.

[41] Z. Sun, S. Yu, Z. Ding, D. Ma, *J. Am. Chem. Soc.* **2007**, *129*, 9300 – 9301.

[42] The procedure has been recently generalized to incorporate nonconjugated terminal alkynes and other pyridine-based heterocycles. D. A. Black, R. E. Beveridge, B. A. Arndtsen, *J. Org. Chem.* **2008**, *73*, 1906 – 1910.

[43] M.-C. Ye, J. Zhou, Y. Tang, *J. Org. Chem.* **2006**, *71*, 3576 – 3582.

[44] S. Fujimori, E. M. Carreira, *Angew. Chem.* **2007**, *119*, 5052 – 5055; *Angew. Chem. Int. Ed.* **2007**, *46*, 4964 – 4967.

[45] a) E. J. Corey, D. J. Beames, *J. Am. Chem. Soc.* **1972**, *94*, 7210 – 7211; b) H. O. House, W. F. Fischer, Jr., *J. Org. Chem.* **1969**, *34*, 3615 – 3618.

[46] L. W. Bieber, M. F. da Silva, *Tetrahedron Lett.* **2007**, *48*, 7088 – 7090.

[47] T. Ishikawa, T. Mizuta, K. Hagiwara, T. Aikawa, T. Kudo, S. Saito, *J. Org. Chem.* **2003**, *68*, 3702 – 3705.

[48] D. Tejedor, D. González-Cruz, A. Sántos-Expósito, J. J. Marrero-Tellado, P. Armas, F. García-Tellado, *Chem. Eur. J.* **2005**, *11*, 3502 – 3510.

[49] Electrophiles must be less acidic than the alkyl propiolate itself to allow the acetylide formation and consequently the corresponding domino processes. D. Tejedor, A. Santos-Expósito, F. García-Tellado, *Chem. Commun.* **2006**, 2667 – 2669.

[50] For domino reactions with alkyl propiolates and aldehydes or activated ketones: a) D. Tejedor, F. García-Tellado, J. J. Marrero-Tellado, P. de Armas, *Chem. Eur. J.* **2003**, *9*, 3122 – 3131; b) P. de Armas, F. García-Tellado, J. J. Marrero-Tellado, D. Tejedor, M. A. Maestro, J. González-Platas, *Org. Lett.* **2001**, *3*, 1905 – 1908.

[51] For domino reactions with alkyl propiolates and 1,2-ketoesters or 1,2-ketoamides: D. Tejedor, A. Santos-Expósito, F. García-Tellado, *Chem. Eur. J.* **2007**, *13*, 1201 – 1209.

[52] a) D. Tejedor, A. Santos-Expósito, D. González-Cruz, F. García-Tellado, J. J. Marrero-Tellado, *J. Org. Chem.* **2005**, *70*, 1042 – 1045; b) D. Tejedor, D. González-Cruz, F. García-Tellado, J. J. Marrero-Tellado, M. L. Rodríguez, *J. Am. Chem. Soc.* **2004**, *126*, 8390 – 8391; c) D. T. Aragón, G. V. López, F. García-Tellado, J. J. Marrero-Tellado, P. De Armas, D. Terrero, *J. Org. Chem.* **2003**, *68*, 3363 – 3365.

[53] Linear enol ethers **15** are obtained as their racemates in higher yields than in organic media using DABCO or Et_3N as catalysts. D. González-Cruz, D. Tejedor, P. de Armas, F. García-Tellado, *Chem. Eur. J.* **2007**, *13*, 4823 – 4832.

[54] For full details and more examples of this type of MCRs, see: D. Tejedor, F. García-Tellado, *Chem. Soc. Rev.* **2007**, *36*, 484 – 491.

[55] a) Y.-G. Wang, S.-L. Cui, X.-F. Lin, *Org. Lett.* **2006**, *8*, 1241 – 1244; b) S.-L. Cui, X.-F. Lin, Y.-G. Wang, *Eur. J. Org. Chem.* **2006**, 5174 – 5183.