JOC Note

# Metal-Free Access to Fully Substituted Skipped Diynes. An Efficient Chemodifferentiating $A_2BB'$ 4CR Manifold

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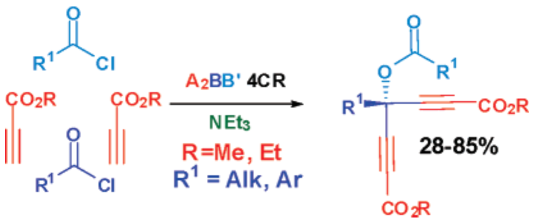

A metal-free chemodifferentiating $A_2BB'$ 4CR manifold for the modular synthesis of tertiary skipped diynes is described. The manifold performs a triethylamine triggered reaction of alkyl propiolates and acid chlorides to assemble two units of each component in the form of two propargylic alkynoates, a tertiary alcohol, and an ester. A differentiated incorporation of the two acid chloride components ensures functional diversity in the final structure. In addition, the presence of two connected propargylic alkynoates provides a reactive platform for complexity generation.

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Skipped diynes are linear $C_5$ structural units composed of two triple bonds connected by an $sp^3$ carbon center (Figure 1a). This naturally occurring structural motif[1] is a very well appreciated synthon for the construction of novel carbon-rich structures[2,3]— as well as a valuable precursor of the 1,4-*cis*,*cis*-diene units present in many bioorganic relevant molecules.[4] The main synthetic approaches to these systems rely on the cross-coupling reactions of metal−alkynylides and propargylic electrophiles.[5] A plethora of structurally diverse 1,4-diynes have been obtained by using this well-established strategy.[6] Although this methodology is general and with wide scope, a complementary metal-free access to these structures in accordance with the more environmentally friendly tendencies in organic synthesis should be desirable. Herein we report on our results on the design and development of a metal-free $A_2BB'$ 4CR approach to these systems.[7] This synthetic manifold constructs tertiary skipped diynes by a triethylamine triggered reaction of terminal conjugated alkynes and acid chlorides in a modular and efficient manner (Figure 1b). The resulting tertiary 1,4-diynes incorporate two identical units of the alkynoate ($A_2$) and two chemodifferentiated units of the acid chloride (B and B′) in their structure. While the conjugated character of the two alkyne units offers an additional reactivity profile to these scaffolds (reactivity domain), the chemodifferentiated incorporation of the two units of acid chloride introduces a convenient degree of diversity in the final structure (diversity domain).

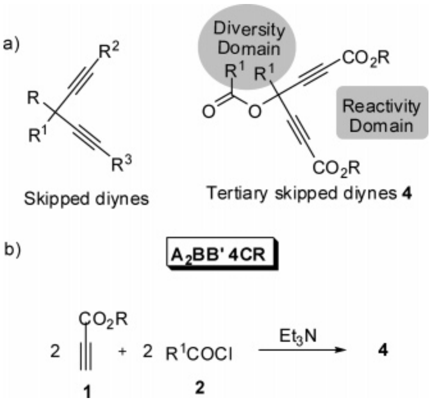

**FIGURE 1.** (a) General structure of skipped diynes (1,4-diynes) and tertiary skipped diynes **4**. (b) $A_2BB'$ 4CR manifold for the synthesis of tertiary skipped diynes **4**. A, B = components; B′ = component B incorporated in a differentiated manner; 4CR = four-component reaction.

In the last 5 years, we have been involved in the design and development of new ABB′ 3CRs based on the catalytic

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§ Universidad de La Laguna.

[1] For some examples, see: (a) Lim, Y. J.; Lee, C.-O.; Hong, J.; Kim, D.-K.; Im, K. S.; Jung, J. H. *J. Nat. Prod.* **2001**, *64*, 1565−1566. (b) Chill, L.; Miroz, A.; Kashman, Y. *J. Nat. Prod.* **2000**, *63*, 523−526. (c) Lim, Y. J.; Kim, J. S.; Im, K. S.; Jung, J. H.; Lee, C.-O.; Hong, J.; Kim, D.-K. *J. Nat. Prod.* **1999**, *62*, 1215−1217. (d) Kim, J. S.; Lim, Y. J.; Im, K. S.; Jung, J. H.; Shim, C. J.; Lee, C.-O.; Hong, J.; Lee, H. *J. Nat. Prod.* **1999**, *62*, 554−559.

[2] For selected examples, see: (a) Livingston, R.; Cox, L. R.; Odermatt, S.; Diederich, F. *Helv. Chim. Acta* **2002**, *85*, 3052−3077. (b) Livingston, R. C.; Cox, L. R.; Gramlich, V.; Diederich, F. *Angew. Chem., Int. Ed.* **2001**, *40*, 2334−2337. (c) Maurette, L.; Godard, C.; Frau, S.; Lepetit, C.; Soleilhavoup, M.; Chauvin, R. *Chem.-Eur. J.* **2001**, *7*, 1165−1170. (d) Van Ornum, S. G.; Bruendl, M. M.; Cao, H.; Reddy, M.; Grubisha, D. S.; Bennet, D. W.; Cook, J. M. *J. Org. Chem.* **2000**, *65*, 1957−1971. (e) An, Y.-Z.; Rubbin, Y.; Schaller, C.; McElvany, S. W. *J. Org. Chem.* **1994**, *59*, 2927−2929.

[3] For selected reviews, see: (a) de Meijere, A.; Kozhushkov, S. I. *Top. Curr. Chem.* **1999**, *201*, 1−42. (b) Diederich, F.; Gobbi, L. *Top. Curr. Chem.* **1999**, *201*, 44−79. (c) Scott, L. T.; Cooney, M. J. Macrocyclic Homoconjugated Polyacetylenes. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, Germany, 1995; Chapter 9, pp 321.

[4] For a review, see: Durand, S.; Parrain, J.-L.; Santelli, M. *J. Chem. Soc., Perkin Trans. I* **2000**, 253−273.

[5] For selected recent examples, see: (a) Kessabi, J.; Beaudegnies, R.; Jung, P. M. J.; Martin, B.; Montel, F.; Wendeborn, S. *Org. Lett.* **2006**, *8*, 5629−5632. (b) Montel, F.; Beaudegnies, R.; Kessabi, J.; Martin, B.; Muller, E.; Wendeborn, S.; Jung, P. M. J. *Org. Lett.* **2006**, *8*, 1905−1908.

[6] For a review, see: Tedeschi, C.; Saccavini, C.; Maurette, L.; Soleilhavoup, M.; Chauvin, R. *J. Organomet. Chem.* **2003**, *670*, 151−169.

[7] Multicomponent reactions designated as $A_2BB'$ 4CR are defined as bimolecular processes that, using only two different starting materials (A and B), are able to generate a product whose structure incorporates two identical units of component A and two chemodifferentiated units of component B. For a tutorial review, see: Tejedor, D.; García-Tellado, F. *Chem. Soc. Rev.* **2007**, *36*, 484−491.

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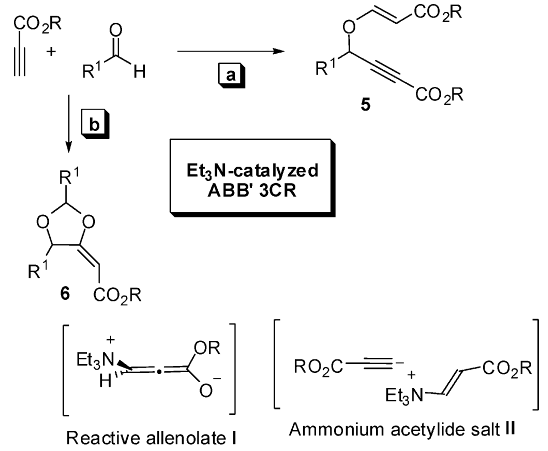
**SCHEME 1. Triethylamine-Catalyzed ABB′ 3CRs Based on the Organocatalytic Generation of Reactive Allenolates I**



generation of allenolate **I** by reaction of triethyl amine (catalyst) on a terminal alkynoate (Scheme 1).[8] In the presence of aliphatic aldehydes, allenolate **I** launches two different acetylide-driven domino reactions affording selectively propargylic enol ethers **5** (path a) or 1,3-dioxolane derivatives **6** (path b) as a function of temperature, catalyst, and stoichiometry. The low p$K_a$[9] values of alkyl propiolates allow the selective generation of acetylides **II** from allenolate **I** in the presence of an enolizable aliphatic aldehyde.

We envisioned that tertiary skipped diynes such as **4** could be synthesized in a modular manner through these multicomponent processes if an acid chloride could be used instead of the aldehyde. The idea is outlined in Scheme 2. In this new scenario, the addition of the first equivalent of the acetylide **II** onto the acid chloride would afford the $\alpha,\beta$-alkynyl ketone intermediate **3**. This would be followed by the addition of a second equivalent of the acetylide to afford the tertiary alkoxide **IV**. Finally, the alkoxide would react with the acid chloride, the hardest electrophile present in the medium, to give the expected acylated 1,4-diyne **4**. Two chemical limitations must be overcome for the practical development of this system: (a) the limited nucleophicity of the ammonium acetylides **II**,[10] and (b) the release of free triethylamine (catalyst) from salt **III**. Fortunately, the former could be overcome by the intrinsic high electrophicity of the acid chloride and the intermediate $\alpha,\beta$-alkynyl ketone **3**.[4,6] The latter did not have a simple chemical solution and it forced us to use stoichiometric amounts of triethylamine and an excess of alkynoate to compensate for the unproductive formation of salt **III**.

**SCHEME 2. Triethylamine-Triggered Chemodifferentiating $A_2BB'$ 4CR Synthetic Manifold Involving Terminal Alkynoates and Acid Chlorides**

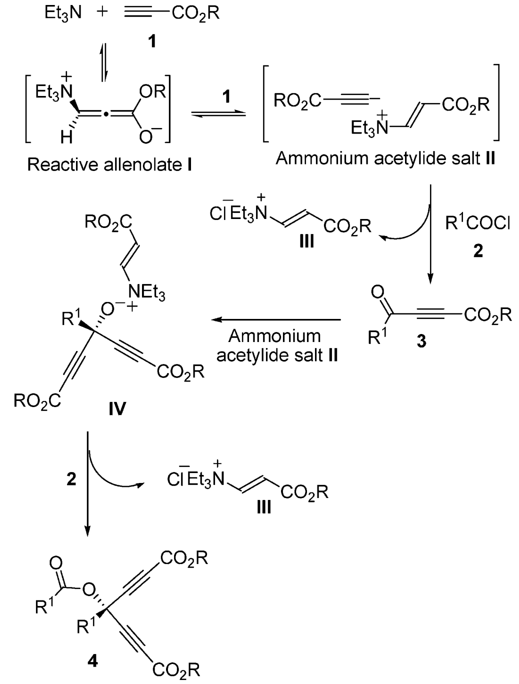
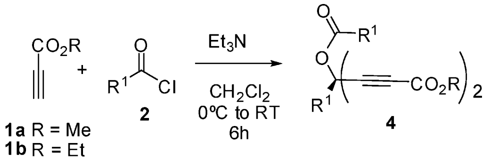


**TABLE 1. $A_2BB'$ 4CR Synthesis of Tertiary Skipped Diynes 4[a]**



| entry | propiolate | acid chloride | product (%)[b] | |
|---|---|---|---|---|
| 1 | **1a** | Ph | **2a** | **4aa** (74) |
| 2 | **1b** | Ph | **2a** | **4ba** (83) |
| 3 | **1a** | 4,4′-biphenyl | **2b** | **4ab** (81) |
| 4 | **1b** | 4,4′-bipheny | **2b** | **4bb** (85) |
| 5 | **1a** | 2-Cl-Ph | **2c** | **4ac** (77) |
| 6 | **1a** | 4-Cl-Ph | **2d** | **4ad** (75) |
| 7 | **1a** | 3-Me-Ph | **2e** | **4ae** (76) |
| 8 | **1a** | 4-Me-Ph | **2f** | **4af** (69) |
| 9 | **1a** | 4-F-Ph | **2g** | **4ag** (81) |
| 10 | **1a** | 4-OMe-Ph | **2h** | **4ah** (34) |
| 11 | **1a** | iPr | **2i** | **4ai** (56) |
| 12 | **1b** | iPr | **2i** | **4bi** (47) |
| 13 | **1a** | cHex | **2j** | **4aj** (47) |
| 14 | **1a** | tBu | **2k** | **4ak** (28) |
| 15 | **1a** | nPr | **2*l*** | **4a*l*** (0) |

[a] Reagents and conditions: (1) Alkyl propiolate (2.2 mmol), acid chloride (1.0 mmol), $CH_2Cl_2$ (3 mL), 0 °C, 5 min. (2) Triethylamine (1.05 mmol), 0 °C to rt, 6 h (or until the acid chloride is consumed) [b] Isolated yields.

The synthetic manifold was implemented by using the reaction of benzoyl chloride with methyl propiolate in the presence of triethylamine. After some experimentation it was found that the reaction of an excess of methyl propiolate (2.2 equiv) with benzoyl chloride (1 equiv) and triethylamine (1 equiv) afforded skipped diyne **4aa** in 74% yield (Table 1, entry 1). Other nucleophiles such as DABCO or tri-*n*-butylphosphine were not efficient triggers for these 4CRs. Once an experimental protocol was established, it was applied to the set of acid chlorides shown in Table 1. In general, aromatic acid chlorides uniformly reacted with methyl or ethyl propiolate to afford the 1,4-diynes **4aa**−**ag**, **4ba**, and **4bb** in moderate to good yields (Table 1, entries 1−9). Even the highly deactivated 4-methoxybenzoyl chloride (**2h**) could be transformed into the corresponding diyne **4ah** in a modest 34% yield (entry 10).

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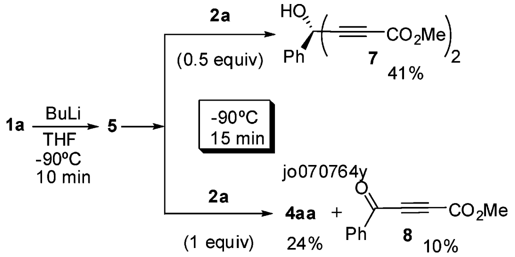
(8) (a) Tejedor, D.; Santos-Expósito, A.; García-Tellado, F. *Chem. Commun.* **2006**, 2667−2669. (b) Tejedor, D.; González-Cruz, D.; Sántos-Expósito, A.; Marrero-Tellado, J. J.; Armas, P.; García-Tellado, F. *Chem.-Eur. J.* **2005**, *11*, 3502−3510. (c) Tejedor, D.; García-Tellado, F.; Marrero-Tellado, J. J.; de Armas, P. *Chem.-Eur. J.* **2003**, *9*, 3122−3131. (d) de Armas, P.; García-Tellado, F.; Marrero-Tellado, J. J.; Tejedor, D.; Maestro, M. A.; González-Platas, J. *Org. Lett.* **2001**, *3*, 1905−1908.

(9) Kresge, A. J.; Pruszynski, P. *J. Org. Chem.* **1991**, *56*, 4808−4811.

(10) We have found that these acetylides do not react with normal ketones, nonactivated aromatic aldehydes, or simple esters under the reaction conditions used in these manifolds. Unpublished results.

**SCHEME 3. Organometallic Synthetic Manifold**



The well-known base-catalyzed formation of highly reactive ketenes from aliphatic acid chlorides is a serious and competitive side reaction in these manifolds. Therefore, and as could be predicted, acid chlorides bearing linear alkyl chains cannot be used due to the increased acidity of their α-hydrogens (entry 15). On the other hand, aliphatic acid chlorides bearing no α-hydrogens (entry 14) or aliphatic acid chlorides whose α-hydrogens are less acidic (entries 11−13) afforded the expected products although in lower yields (28−56%).

Overall, the whole process consumes 2 equiv of alkyl propiolate and 1 equiv of triethylamine to generate 1 equiv of acetylide **II**. Excess of base and alkynoate are accumulated in the form of the salt **III**, which can be easily removed and recovered by simple filtration of the reaction mixture, or productively used in a subsequent complexity-generating reaction (Scheme 2).[11]

The chemical efficiency of this metal-free manifold is highlighted when it is compared with its organometallic homologue (Scheme 3). In our hands, the reaction of 1 equiv of benzoyl chloride with 2 equiv of lithium acetylide **5** afforded the corresponding 1,4-diyne **7** in a modest 41%. On the other hand, the stoichiometric reaction gave a 2:1 mixture of skipped diyne **4aa** and propargylic ketone **8** in a low combined yield of 34%.

In summary, we have developed a metal-free $A_2BB'$ 4CR manifold for the modular synthesis of tertiary skipped diynes. The manifold constructs the linear $C_5$ structural motif by using two units of propiolate and one unit of acid chloride. A second unit of the acid chloride is incorporated as an ester function ensuring a grade of diversity in the structure. In addition, the presence of two connected propargylic alkynoates in these scaffolds provides a handle for further reactions and complexity generation.[12] This issue is currently under study in our lab.

## Experimental Section

**Experimental Details for the Synthesis of Skipped Diynes (4): Representative Example:** Methyl propiolate (2.2 mmol) and benzoyl chloride (1.0 mmol) were dissolved in 3 mL of $CH_2Cl_2$. After the mixture was cooled to 0 °C, triethylamine (1.05 mmol) was added and the reaction mixture was stirred and allowed to reach room temperature for 6 h (or until the acid chloride is consumed). The reaction mixture was filtered and the solvent and excess reagents were then removed under reduced pressure. Product was isolated by flash column chromatography (silica gel, *n*-hexane/EtOAc 90/10 or 80/20).

**Dimethyl 4-(benzoyloxy)-4-phenylhepta-2,5-diynedioate (4aa):** $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.78 (s, 6H), 7.42−7.47 (m, 5H), 7.57−7.61 (m, 1H), 7.81−7.84 (m, 2H), 8.01−8.04 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 53.0, 67.8, 78.9, 80.6, 126.5, 128.5, 128.7, 129.0, 129.95, 130.00, 133.8, 135.9, 152.9, 163.4. IR ($CHCl_3$, cm$^{-1}$) 2246, 1724, 1452, 1436, 1258, 1084, 1063. Anal. Calcd for $C_{22}H_{16}O_6$: C, 70.21; H, 4.29. Found: C, 70.00; H, 4.42. MS, *m/z* (rel intensities) 376 ($M^+$, 3.5), 255 (18), 197 (17), 105 (100), 77 (44), 51 (23).

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**Supporting Information Available:** General experimental and characterization data for compounds **4ab**−**ak**, **4ba**, **4bb**, and **4bi** and X-ray data for the derivative **4ak**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] This research is in progress in our lab. For example, we have recently shown that these salts are good substrates for certain cycloadditions. (a) Gonzalez-Cruz, D.; Tejedor, D.; de Armas, P.; Garcia-Tellado, F. *Chem. Eur. J.* **2007**, *13*, 4823−4832. (b) Gonzalez-Cruz, D.; Tejedor, D.; de Armas, P.; Morales, E. Q.; Garcia-Tellado, F. *Chem. Commun.* **2006**, 2798−2800.

[12] (a) For a recent highlight article dealing with gold-catalyzed reactions involving propargylic esters as a source of diversity, see: Marion, N.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2−5. (b) For a review including palladium-catalyzed additions to $\gamma$-hydroxy alkynoates, see: Lewandowska, E. *Tetrahedron* **2006**, *63*, 2107−2122. For selected recent examples, see: (c) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 985−988 and references cited therein. (d) Kato, K.; Teraguchi, R.; Yamamura, S.; Mochida, T.; Akita, H.; Peganova, T. A.; Vologdin, N. V.; Gusev, O. V. *Synlett* **2007**, 638−642. (e) Kato, K.; Teraguchi, R.; Kusakabe, T.; Motodate, S.; Yamamura, S.; Mochida, T.; Akita, H. *Synlett* **2007**, 63−66. (f) Prasad, B. A. B.; Yoshimoto, F. K.; Sarpong, R. *J. Am. Chem. Soc.* **2005**, *127*, 12468−12469. (g) Jung, C.-K.; Wang, J.-C.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4118−4119. (h) Suzuki, T.; Ohmori, K.; Suzuki, K. *Org. Lett.* **2001**, *3*, 1741−1744. (i) Frey, L. F.; Tillyer, R. D.; Ouellet, S. G.; Reamer, R. A.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Chem. Soc.* **2000**, *122*, 1215−1216.