Efficient Domino Process Based on the Catalytic Generation of Non-Metalated, Conjugated Acetylides in the Presence of Aldehydes or Activated Ketones

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To the memory of Professor Antonio González González

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Received (will be filled in by the editorial staff)

Abstract: We report on an extremely mild and highly efficient catalytic generation of non-metalated, conjugated acetylides. These non-metalated, conjugated acetylides are used to generate enol-protected functionalized propargylic alcohols **1**, 1,3-dioxolane compounds **2** or 2,3,4-trisubstituted 2,3-dihydrofurans **4** through serial multibond-forming processes. The method calls for a nucleophile as a chemical activator (a tertiary amine or phosphine), a conjugated terminal acetylene as the acetylide source and an aldehyde or activated ketone as the electrophilic partner. The chemical outcome of this process depends on the nucleophile nature, temperature, stoichiometry and solvent, and it can be tailored selectively by the proper selection of the experimental conditions.

Keywords: conjugated acetylides / catalytic generation / domino reactions / C-C coupling / autocatalysis

Introduction

The development of new efficient synthetic methodologies that using readily available and inexpensive starting materials allow molecular complexity to be created quickly, with bond-forming efficiency, structure-and atom-economy in just one simple, safe, environmentally acceptable and resource-effective operation is a hot topic in organic synthesis.^[1] Serial multibond-forming events (domino processes)^{[1],[2]} constitute a very appealing approach to these issues and a powerful tool for the synthesis of structurally complex small molecules. A domino reaction is defined as a process involving two or more bond-forming transformations under the same experimental conditions, that is, without the addition of additional reagents or catalysts, and in which the subsequent reaction takes place at the functionalities introduced in the previous transformation.^[2c] When they are performed in a catalytic manner this type of transformations constitute a powerful and economical synthetic way to introduce chemical and structural complexity. Collections of small compounds with structural and functional diversity play important roles in the drug discovery process because they offer the means for the structural identification of biologically active macromolecules^[3] and also, the means to identify and optimise new small-molecule chemical substances able to specifically interact with these macromolecules. Collections of these small polyfunctionalized molecules are now accessible through diversity-oriented syntheses,^[3d] which make use of complexity-generating reactions to append selected building blocks to a designed scaffold to lead to products with remarkably increased complexity and diversity. Domino reactions will be very good candidates for the creation of diversity-oriented libraries if they can be run with selectivity (tailored chemical outcome), atom and structure-economy (efficiency) and under polymer-supported conditions (simplified work-up and isolation).

We report here on an extremely mild and highly efficient serial multibond-forming process based on in situ catalytic generation of conjugated acetylides. The use of alkynilides as carbon nucleophiles for the formation of C-C bonds is valued in organic synthesis.^[4] These anions are commonly generated by the use of stoichiometric amounts of strong bases^[5] which are incompatible with the electrophilic partner of the C-C bond-forming reaction. Substoichiometric amounts of base have been used by Knochel et al.^[6] (10mol% CsOH in DMSO) and Babler et al.^[7] (10-20 mol% KO^tBu in DMSO) to catalyse the addition of terminal acetylides to aldehydes and ketones in the first case and ketones in the second. Carreira et al.^{[8],[9]} have developed a mild, new method for the in situ catalytic generation of reactive zinc acetylides which add to nitrones, imines and aldehydes to give the propargylic hydroxylamines, amines and alcohols, respectively. All of these methods fail when they are applied to terminal conjugated

acetylenes because of the known tendency of these compounds to form self-addition oligomers under basic conditions.^[11c] We have developed a protocol for the catalytic generation of these reactive, conjugated acetylides by the Michael addition of a tertiary amine or phosphine to the terminal conjugated alkynoate in the presence of an aldehyde or an activated ketone. This reversible reaction launches a kinetically controlled serial process whose chemical outcome strongly depends on the nucleophile nature, stoichiometry, temperature and solvent. Remarkably, the chemical outcome can be tailored at will to give selectively enol-protected functionalized propargylic alcohols **1**, 1,2,4-trisubstituted 1,3-dioxolanes **2** or 2,4,5-trisubstituted dihydrofurans **4** (Figure 1). The concurrent formation of up to three bonds yielding heterocycles or linear propargylic derivatives validates these reactions as a true catalytic domino process and makes them a very good choice for diversity-oriented synthesis.

Results

Conjugated acetylenes are prone to give Michael addition in the presence of nucleophiles. There is a wide bibliographic precedent for this reaction in the literature.^[10] Most of these reactions demand a nucleophile, a catalyst and an electrophile along with the conjugated alkyne.^[11] Normally, the expected Michael adduct is formed when a conjugated alkyne is reacted with a nucleophile. The tertiary phosphine catalysed addition of nucleophiles to the triple bond of a conjugated-alkynoate constitutes a remarkable exception (Scheme 1). The chemical outcome of these reactions reveals a change in the reactivity pattern of the triple bond redirecting the nucleophilic attack from the normal β -position to the abnormal γ -^[11a] or α -positions.^[12]

Recently, we have reported on a complementary chemical system formed by a terminal α,β -unsaturated alkynoate, an aldehyde as electrophile and triethylamine as a chemical activator (Scheme 2).^[13] The key to this system is the low pKa value of these terminal conjugated alkynoates (pKa<18.8)^[14] which makes them a very good proton source in the presence of suitable bases. The serial process is outlined in Scheme 3. In the absence of other proton sources, the terminal alkynoate is able to protonate the betaine **I** generated by the addition of the tertiary amine on the starting alkynoate liberating a very active terminal conjugated acetylide anion. This acetylide anion reacts with the electrophile (aldehyde or ketone) to give the alkoxide **III**, which evolves in two different ways:

- It adds to the ammonium **II** to give the adduct **1**^[15] and triethylamine to reinitiate the cycle **a**, or
- It adds to another molecule of the electrophile to generate dioxolane **2** and ammonium acetylide **II** to reinitiate the cycle **b**. This cycle **b** constitutes an autocatalysed synthesis of 1,3-dioxolane

compounds **2**. The autocatalytic nature of this cycle will be discussed further.

The stoichiometry and reaction temperature (Table 1) rules the whole serial multibond-forming process depicted in Scheme 3. Thus, it was found that for an alkynoate/aldehyde ratio of 2/1, the enol-protected propargylic alcohols **1** were formed at room temperature or 0°C, in good to excellent yields and as the sole compounds (Entries 1-8). The chemical outcome of the reaction dramatically changed when the stoichiometry was reversed from 2/1 to 1/2 and the temperature lowered to -78°C. Dioxolane compounds **2** were obtained in excellent yields and as a mixture of the four possible diastereomers (E-syn, E-anti, Z-syn and Z-anti). With sterically-demanding aldehydes, an excess of aldehyde had to be used in order to achieve better yields of dioxolane and to reduce the amount of the linear compound **1** (Entries 4 and 8). The case of trifluoroacetophenone was remarkable: it formed efficiently dioxolane compounds **2** with independence of the stoichiometry and temperature used (Entry 9).

We were delighted to observe that this multibond-forming process worked quite well even without a solvent. Thus, when methyl propiolate (1 equiv.) was mixed with n-butanal (2 equiv.) and triethylamine (10 mol%) at -78°C, a smooth reaction occurred furnishing dioxolane **2b** in 82-89% yield. At 0°C and using the inverse stoichiometry, the reaction gave a mixture of 1,3-dioxolane **2b** and propargylic derivative **1b**.

The nature of the tertiary amine was shown to be very important for the success of the reaction. The sterically demanding diisopropylethylamine did not show any catalytic activity. DBU and DBN behaved in a similar way. In contrast, DABCO, an extremely nucleophilic amine,^[16] proved to be an extraordinary catalyst for this reaction, yielding the enol-protected propargylic alcohol **1** in excellent yield (Table 2).

Variable amounts of diester **3**^[17] were also obtained as a side product in these DABCO-catalysed reactions. The side route affording diester **3** only could be minimised by the use of low temperatures and, with the less reactive aldehydes, by using an excess of the aldehyde (Entries 1, 4-6). Lowering the amount of DABCO did not improve the yield of the propargylic compounds **1**. When the reaction was carried out in tetrahydrofuran, solvent in which DABCO is scarcely soluble, the diester formation was minimised but at the expense of a severe reduction of the reaction rate. Mixtures of tetrahydrofuran and dichloromethane reduced the reaction time and also increased the **1/3** ratio (Scheme 4).

It is noticeable that no dioxolane compounds are obtained in these DABCO-catalysed reactions in sharp contrast with the triethylamine-catalysed processes.

The influence of the triple bond nature was examined using the commercially available alkynone **5** and alkyne sulphone **8** and triethylamine as catalyst (Scheme 5, Table 3). Only the sulphone **8** was able to furnish propargylic compounds **9** (Table 3, entry 3). Except in this case, dioxolane compounds were formed in all cases, regardless of the temperature and the alkyne/aldehyde ratio used.

One consequence of the working mechanistic hypothesis outlined in Scheme 3 is the autocatalytic nature of the 1,3-dioxolanes synthesis (cycle **b**). Once alkoxide **III** is generated, it catalyses the acetylide formation through the intermediate **V**. Because alkoxide **III** is not easy to synthesise, the synthetically accessible ammonium alkoxide **12** was chosen as the catalyst. It was easily synthesised from the propargylic enol ether **1a** by acid hydrolysis, followed by protection of the resulting propargylic alcohol as its tert-butyldimethylsilyl ether **11** and silyl-deprotection with tetrabutylammonium fluoride (Scheme 6). This salt was used as obtained directly in the autocatalysis experiments. As expected, the alkoxide **12** catalysed the formation of 1,3-dioxolanes. Seeding a mixture of methyl propiolate (1 equiv.) and *n*propanal (2 equiv.) in dichloromethane, at room temperature, with a catalytic amount of **12** (10 mol%) furnished the 1,3-dioxolane **2a** efficiently (86 %). No reaction could be observed at lower temperatures. Remarkably, when the stoichiometry was inverted, and under the same conditions, the formation of 1,3-dioxolane **2a** was extremely sluggish. Addition of aldehyde to this reaction mixture until completion of the 2 equivalents required for dioxolane formation speeded up the reaction yielding 1,3-dioxolane **2a** with high efficiency (71 %).

Since the nature of the nucleophile proved to have a notable influence on the chemical outcome of these domino reactions we next studied the use of phosphorus compounds as suitable catalysts for these processes. These are more powerful nucleophiles and less basic than their nitrogen equivalent. The first attempts using triphenylphosphine as the catalyst, methyl propiolate as the alkyne, *n*butanal as the electrophile and an alkynoate/aldehyde ratio of 2/1 were fruitless. The reaction mixture quickly turned black at room temperature affording oligomeric materials. When the temperature was lowered at -78°C, no reaction was observed. We then decided to change the catalyst to the more nucleophilic tri-*n*butylphosphine.^[18] Again, at room temperature the reaction quickly turned black indicating that polymeric material was being formed. When the temperature was lowered to -78°C, the reaction mixture remained colorless longer and a smooth reaction began to occur. Amazingly, 4,5-dihydrofuran **4b** was formed together with the expected 1,3-dioxolane compound **2b** (each one as a mixture of diastereomers) (Scheme 7). The propargylic derivative **1b** was not produced. The yield and chemical outcome of this reaction were strongly dependent on the catalyst strength, stoichiometry and the solvent nature (Table 4). Changing the stoichiometry from alkynoate/aldehyde: 2/1 to 1/2, the chemical outcome changed from dihydrofurans **4** to 1,3-dioxolanes **2** as the main compounds (Entries 1, 7, 8). Surprisingly, only the

halogenated solvents were suitable for the dihydrofuran formation (Entries 1-6). In non-halogenated solvents, only dioxolane compounds were formed (Entries 7-9). Even when the stoichiometry was unfavourable, the 1,3-dioxolane formation was a highly favoured process in these solvents (20-23%) (25% is the upper limit!). Increasing the alkynoate/aldehyde ratio from 2/1 to 3/1 increased the dihydrofuran yield, but not in a linear manner. A large and variable amount of alkynoate was missed as polymeric material. When the stoichiometric ratio was changed from 2/1 to 1/2, only 1,3-dioxolanes were formed in excellent yields: the polymerisation was highly minimised. The accompanying polymerisation is a serious problem only when the stoichiometry is favourable for dihydrofuran formation, and it becomes a very important missing route of resources. Unfortunately, this side reaction could not be eliminated. Lowering the tri-*n*-butylphosphine amount from 40 to 10 mol% dramatically decreased the dihydrofuran yield from 51 to 12%. Dilution did not prove to be more effective: a four times dilution reduced the yield from 34% ([alkynoate] = 1M) to 25% ([alkynoate] = 0.25M).

In order to minimise the polymerisation route we explored the influence of the electronic nature of the phosphine on these reactions. Because iso-butanal gave the best yields of dihydrofurans, it was chosen as the aldehyde partner in this study (Table 5). Tri-*n*butylphosphine and tri-*noctyl*phosphine, which are exceptionally nucleophilic and weakly basic catalysts, gave the best yields of dihydrofurans (Entries 1 and 2). Tri-*i*butylphosphine was a slightly worse catalyst (Entry 3). Although the yield of dihydrofurans does not correlate very well with the pK_a values (basicity) of the phosphines, it is clear that the further we move from the pK_a range ~8 – 8.5, the lower the yield of dihydrofurans. Again, excess of alkynoate did not improve the yield to any considerable degree: less than a 10% increment in yield was observed when the alkynoate/aldehyde ratio was increased from 2/1 to 3/1 or 4/1 (Entries 1 and 2).

An interesting result that shed some light on the reactivity pattern of this chemical system was obtained when the reaction was carried out in the presence of two nucleophiles. In this competitive experiment a mixture of methyl propiolate (2 equivalents) and *i*butanal was reacted with DABCO (20 mol%) and tri-*n*butylphosphine (20 mol%) in dichloromethane at –60°C for 1h. Under these conditions, neither heterocycles nor polymers were formed: only the propargylic derivative **1c** was obtained (75%). In spite of the excellent nucleophilicity of the tri-*n*butylphosphine, DABCO was a superior catalyst and suppressed almost completely both the polymerisation and heterocycle formation reactions.

Discussion

The enormous influence of the nucleophile nature, stoichiometry and temperature on the chemical outcome of these reactions points to a kinetically controlled serial multibond-forming event such as that outlined in Scheme 8. The overall process comprises three cycles, namely, cycles **a**, **b** and **c**, and two

resource-missing routes (11) and (12) affording diester **3** and polyenic polymers, respectively. Each cycle sets up a domino reaction delivering a single type of product. The serial process is triggered by the reversible 1,4-addition of the nucleophile on the conjugated triple bond (cycle **a**, step (1)). The zwitterionic intermediate **I** quickly deprotonates the acidic starting terminal alkynoate to give the corresponding ammonium or phosphonium acetylide salt **II** (cycle **a**, step (2)), which in turn, can:

1. React with a molecule of aldehyde to give the ammonium or phosphonium alkoxide **III** (cycle **a**, step (3)), or
2. Evolve toward the diester **3** through an intramolecular Michael addition-elimination sequence of reactions with catalyst release (Step (11)), or
3. Polymerise by reaction with starting alkynoate (Step (12)).

Alkoxide **III** is a common intermediate in the three cycles and it is consumed through three kinetically well-differentiated reactions, namely:

- An intramolecular Michael addition on a β -ammonium acrylate to close cycle **a** (step (4)),
- An addition to the aldehyde or ketone to start cycle **b** (step (5)) and
- An intermolecular Michael addition on the reactant alkynoate to launch cycle **c** (step (8)).

The consuming rate of the available alkoxide **III** by each one of these competing reactions will establish the amount of material delivered toward each one of the three cycles **a**, **b** or **c**, and therefore, the chemical outcome of the process. Cycle **a** is the most kinetically favoured due to the intramolecular nature of the reaction (4) and consequently, propargylic derivatives **1** must be the kinetically expected products. However, steps (5) and (8) are bimolecular reactions and their rates are strongly dependent on the concentrations of the participating species. Accordingly, if these bimolecular reactions can be accelerated, then the flow of substrate transformation can be diverted toward the synthesis of heterocyclic compounds **2** or **4** through cycles **b** and **c**.

Three factors rule the kinetic selectivity observed in these time-resolved events:

1. *The nucleophilic strength of the catalyst.* A poor nucleophile renders a slow reversible step (1) generating acetylide **II** in low concentration. In this scenario, the rates of all of the bimolecular reactions in which this anion is participating are reduced with independence of their specific rate constant values. Under these conditions, the nature and concentration of the electrophile partner are determinant to direct the kinetic control of the whole process. On the other hand, a good

nucleophile keeps the acetylide concentration sufficiently high to increase the rate of all the bimolecular reactions in which this anion is involved.

2. *The stoichiometry.* Excess of alkynoate with regard to aldehyde favours the bimolecular reactions in which this species is participating and they will receive an extra kinetic aid to compete with those others in which aldehyde participates and vice versa. Also, for the same reason, the formation of acetylide **II** is kinetically favoured under these conditions
3. *The electronic nature of the involved Michael acceptors species.* There are three classes of Michael acceptors in these processes: the starting alkynoate and the methyl β -ammonium or β -phosphonium acrylates. Here, the phosphines are clearly distinguished from the amines. The methyl β -ammonium acrylate is a good Michael acceptor because the electron withdrawing effect of the ammonium ion matches very well with the electronic distribution imposed by the ester. In the case of the phosphonium salt, the ability of the phosphorous atom to stabilise negative charges at the α -position reduces the electrophilic nature of this carbon atom and activates the other carbon of the double bond for the nucleophilic addition. This director effect mismatches with that imposed by the ester resulting in an overall reduction of reactivity. This is the base for the umpolung effect described by Lu et al.^[11a] and Trost et al.^[12] in the phosphine-catalysed nucleophilic addition to conjugated acetylenes. If we build a reactivity scale of Michael acceptors, the β -phosphonium acrylate would be the least reactive and the β -ammonium acrylate the most reactive, with the starting alkynoate in between.

Tertiary amine-catalysed reaction. Hindered tertiary amines such diisopropylethylamine, or good bases such as DBU and DBN are not suitable catalysts for these reactions.^[21] On the other hand, triethylamine and DABCO show excellent catalytic activity, each with different selectivity. Thus, while triethylamine catalyses both the synthesis of 1,3-dioxolane compounds **2** and enol-protected propargylic alcohols **1** in excellent yields (Table 1), DABCO only catalyses the synthesis of compounds **1** (Table 2). The reason for this different behaviour lies in the nucleophilic nature of both catalysts. The powerful nucleophile DABCO catalyses the reaction exclusively through the kinetically favoured cycle **a**. A high acetylide concentration and the high reactivity of the β -ammonium acrylate toward the Michael-addition converge to the same kinetic result: amplification of cycle **a**, through a kinetically fast step (4), with kinetic inhibition of the cycles **b** and **c**. Triethylamine, a poorer nucleophile, catalyses the reaction through cycle **a** only when alkynoate is in excess and the temperature is high (room temperature or 0°C). When the stoichiometry is reversed and the temperature is lowered to -78°C, the rate of the reaction (5) increases sufficiently to direct the transformation flow through cycle **b** generating 1,3-dioxolane

compounds **2** (Table 1). Under these unfavourable conditions, cycle **a** still survives and delivers compounds **1**, although in low yield. Obviously, 2,3-dihydrofuran derivatives **4** are not synthesised in these tertiary amine-catalysed reactions.

The absence of diester **3** and polymers in the triethylamine-catalysed processes indicates an inherently low rate constant associated to the reactions (11) and (12). This fact was exploited to reduce the amount of diester **3** in the DABCO-catalysed synthesis of propargylic derivatives **1** by using an aldehyde excess and low temperature (Table 2).

Tertiary phosphine-catalysed reaction. Tertiary phosphines are more nucleophilic and less basic than the tertiary amines and they present a different catalytic behaviour. Remarkably, they catalyse the synthesis of 2,3-dihydrofuran derivatives **4** and 1,3-dioxolane compounds **2** but they do not catalyse the synthesis of propargylic derivatives **1**. Their catalytic efficiency strongly depends on their electronic nature. Among the assayed tertiary phosphines, tri-*i*-butylphosphine, tri-*n*-octylphosphine and tri-*n*-butylphosphine behaved as suitable catalysts for these reactions (Table 5). Importantly, the synthesis of 2,3-dihydrofurans **4** called for a good nucleophilic phosphine ($pK_a \sim 8-8.5$), a halogenated solvent, low temperature and an alkynoate excess to proceed efficiently (Table 4). Non-halogenated solvents, low temperatures and reverse stoichiometry deliver 1,3-dioxolanes **2** in excellent yields. Contrary to the tertiary amine catalysis, polymerisation of the starting alkynoate is a highly wasteful route of resources and it can not be lightened in a simple manner.

The above-mentioned electronic deactivation of the β -phosphonium acrylates to the Michael addition creates a new kinetic scenario. Now, reaction (4) is kinetically disfavoured and therefore, cycle **a** is no longer the biased transformation route. Nucleophile, temperature, stoichiometry and solvent nature determine the kinetic course of the process. Halogenated solvents, good nucleophiles and alkynoate excess favour reaction (8) and drive the transformation flow through cycle **c** to 2,3-dihydrofurans synthesis. Non-halogenated solvents and a reversed stoichiometry dramatically increase the rate of the reaction (5) and all of the material is consumed through cycle **b** to deliver compounds **2**. What is the reason for this solvent-dependent alkynoate reactivity? We have no clear answer for this solvent effect. There is no apparently clear correlation between solvent properties and alkynoate reactivity. We believe that the effect of the halogenated solvents could be related to the stabilisation of a charge-dative complex between the starting alkynoate and the generated methyl β -phosphonium acrylate. The formation of this complex should augment the Michael acceptor character of the starting alkynoate and in consequence, it should also increase the value of the rate constant for the reaction (8). Although we have no definitive experimental answer, some features seem to confirm our hypothesis. Either

coordinating (Et₂O, THF) or non-polar solvents (hexanes) strongly deactivate the 2,3-dihydrofuran synthesis and favour the 1,3-dioxolanes production (Table 4, entries 7-9). These apparently controversial results can be explained on the basis of a dative complex between the alkynoate and the β -phosphonium acrylate. Thus, in a good coordinating solvent, the solvent itself competes with the alkynoate for the β -phosphonium coordination, disrupting, or at least minimising, the dative complex formation. In the case of a non polar solvent, the phosphonium ions should be tightly bounded to the generated anions and they should be not easily available for complexation with the alkynoate. In both cases, cycle **c** is not activated and it cannot compete with cycle **b** for the kinetic control of the process. Perhaps the role played by the halogenated solvents is related to their polarizability, which might be responsible for the stability of these complexes.

Polymerisation of the starting alkynoate through reaction (12) is also a solvent-dependent event and it is kinetically activated in halogenated solvents: activation of the starting alkynoate increases the rate of reaction (8), but also that of reaction (12). This reaction cannot be easily minimised and it has effects on the 2,3-dihydrofuran yields. A modest yield bonus can be accomplished by using an excess of alkynoate to feed both processes: cycle **c** and polymerisation. Under these conditions, synthetically reliable yields can be obtained (Table 5, entries 1 and 2).

In spite of the excellent nucleophilicity of the tri-*n*butylphosphine catalyst, DABCO proved to be the most active and most selective catalyst for these processes. Thus, when methyl propiolate (2 equiv.) and *i*butanal (1 equiv.) were allowed to react with a mixture of DABCO (20 mol%) and tri-*n*butylphosphine (20 mol%) in dichloromethane at -60°C for 1h, only the propargylic derivative **1c** was obtained (75%). DABCO launches cycle **a** in such a powerful kinetic manner that it inhibits all other possible reactions. β -Phosphonium acrylate, if formed, remains as a spectator.

Autocatalysis. Tetrabutylammonium alkoxide **12** catalysed the synthesis of 1,3-dioxolane **2a** in excellent yield (86%). The rate of the autocatalytic process displayed a strong stoichiometric dependence. Thus, while dioxolane **2a** was quickly synthesized using the optimum alkynoate/aldehyde ratio of 1/2, this process turned extremely sluggish when the stoichiometry was inverted. Also, the autocatalysis required temperature activation to proceed. When the temperature was lowered to 0°C no reaction took place. It is remarkable that while the triethylamine-catalysed domino process can be performed at temperatures as low as -78°C, autocatalysis needs a thermal activation.

Influence of alkyne. Alkynone **5** and sulphone **8** were suitable partners in the triethylamine-catalysed process (Table 3). The product distribution was governed by the nature of the electrophile and the alkyne reactivity. Dioxolane compounds were formed in all of the cases regardless the temperature and the

alkyne/aldehyde ratio used. Except **9b**, no other enol-protected propargylic compounds were produced. The good electrophilic nature of the activated ketone and the low reactivity of alkynone **5** kinetically operate against the cycle **a** biasing the transformation toward cycle **b**.

Kinetic products and isomerization. 1,3-Dioxolanes **2** are obtained as a mixture of 4 diastereomers. The kinetic product is the Z-syn isomer and it appears with the highest yield in all cases. The thermodynamic product is the E-anti and it always appears with the lowest yield. On standing, these products slowly isomerize towards the thermodynamic product while in a CHCl₃ solution the process is accelerated.^[13]

2,3-Dihydrofurans **4** are obtained as a mixture of two isomers. The E-isomer is the kinetic product and it appears with the highest yield in all cases. On standing, this isomer is not only converted into the Z-isomer, but it mainly undergoes an aromatization to form the corresponding furan. This process can be accelerated to conveniently synthesise trisubstituted furans by way of stereoconvergent acid-rearrangement of the two isomers (Scheme 9).

Conclusion

We have reported herein on an extremely mild and efficient domino process based on in situ selective catalytic generation of non-metalated, conjugated acetylides in the presence of activated electrophiles. Tertiary amines and tertiary alkyl phosphines proved to be good catalysts for these processes affording a different family of products in each case. The chemical outcome of these reactions can be tailored at will to give selectively enol-protected functionalized propargylic alcohols **1**, 1,2,4-trisubstituted 1,3-dioxolanes **2** or 2,4,5-trisubstituted dihydrofurans **4**. A mechanism is postulated to explain the experimentally observed influence of the nucleophile strength, temperature and stoichiometry on the kinetic course of these processes. These highly functionalized compounds can be of great significance in generating diversity in combinatorial libraries and in the development of multicomponent transformations.^[22]

Experimental Section

General remarks. Melting points are uncorrected and were determined in a Reichert Thermovar apparatus. ¹H NMR and ¹³C NMR spectra of CDCl₃ solutions were recorded either at 200 and 50 MHz or at 500 and 125 MHz (Bruker Ac 200 and AMX2-500), respectively. FT-IR spectra were measured in chloroform solutions using a Shimadzu IR-408 spectrophotometer. Mass spectra (low resolution) (EI/CI) were obtained with a Hewlett-Packard 5995 gas chromatograph/mass spectrometer. High-resolution mass spectra were recorded with a Micromass Autospec mass spectrometer. Microanalyses were

performed with a Fisons Instruments EA 1108 carbon, hydrogen, and nitrogen analyser. Analytical thin-layer chromatography plates used were E. Merck Brinkman UV-active silica gel (Kieselgel 60 F254) on aluminium. Flash column chromatography was carried out with E. Merck silica gel 60 (particle size less than 0.020 mm) using appropriate mixtures of ethyl acetate and hexanes as eluent. All reactions were performed in oven-dried glassware under nitrogen unless otherwise stated in the Dichloromethane was distilled from CaH₂. Chloroform was distilled from anhydrous sodium sulphate. Toluene was distilled from sodium/benzophenone. Triethylamine was distilled from potassium hydroxide pellets. All other materials were obtained from commercial suppliers and used as received.

Methyl 4-[(1E)-3-methoxy-3-oxo-1-propenyl]oxy}-2-hexynoate (1a): ¹H NMR (500 MHz, CDCl₃): δ = 0.94 (t, ³J (H,H) = 7.4 Hz, 3H), 1.77–1.84 (m, 2H), 3.57 (s, 3H), 3.66 (s, 3H), 4.52 (t, ³J (H,H) = 6.4 Hz, 1H), 5.24 (d, ³J (H,H) = 12.6 Hz, 1H), 7.43 (d, ³J (H,H) = 12.6 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃): δ = □□167.3, 159.7, 152.8, 98.9, 82.6, 78.4, 71.3, 52.6, 50.9, 27.7, 8.8. IR (CHCl₃) ν = 2956.1, 2243.2, 1717.9, 1646.5, 1626.5, 1255.2 cm⁻¹; MS (70 eV, EI): *m/z* (%) 226 (2.1) [M⁺], 125 (100), 93 (51), 79 (21), 65(27), 59 (25); elemental analysis calcd (%) for C₁₁H₁₄O₅: C 58.40, H 6.24; found: C 58.59, H 6.01.

Autocatalytic experiments: To a cooled (0 °C) solution of **2a** (2.12 mmol) in 5 ml of CH₂Cl₂ was added trifluoroacetic acid (10 equiv.) and the resulting mixture was allowed to warm up to room temperature and stirred for 16 hrs. The solution was washed with brine and with a saturated NaHCO₃ solution. The organic products were extracted with CH₂Cl₂ and passed through a short column (silica gel, n-hexane/EtOAc 60/40). The oil resulting from the evaporation of the solvents was dissolved in DMF (5 ml). TBDMSiCl (2.12 mmol) and imidazole (3 mmol) were added to the solution and the mixture was stirred overnight at room temperature. Ether was added and the organic layer was washed with water, dried over sodium sulphate, filtrated and concentrated at reduced pressure to give a gummy residue. Flash column chromatography (silica gel, n-hexane/EtOAc 97/3) gave pure derivative **11** (52% for the two steps). ¹H NMR (400 MHz, CDCl₃): δ = 0.10 (s, 3H), 0.13 (s, 3H), 0.89 (s, 9H), 0.98 (t, ³J (H,H) = 7.4 Hz, 3H), 1.69–1.76 (m, 2H), 3.76 (s, 3H), 4.38 (t, ³J (H,H) = 7.4 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ = □□154.0, 89.0, 75.7, 63.8, 52.6, 31.0, 25.7, 18.2, 9.4, -4.6, -5.2; IR (CHCl₃) ν 2955.3, 2237.0, 1714.8, 1435.7, 1257.6 cm⁻¹; MS (70 eV, EI): *m/z* (%) 227 (8.5) [M⁺-C₂H₅], 193 (54), 171 (16), 147 (68), 89 (100), 75 (20), 73 (27); elemental analysis calcd (%) for C₁₃H₂₄O₃Si: C 60.89, H 9.43; found: C 60.64, H 9.78.

A solution of **11** (0.10 mmol) in dry CH₂Cl₂ (3 ml) was stirred with Bu₄NF (1M THF, 0.10 ml, 0.10 mmol) at 0°C until all starting material disappeared (TLC). To this mixture was added dropwise a previously made solution containing methyl propiolate (0.089 ml, 1.0 mmol) and propanal (0.144 ml,

2.0 mmol) in dry CH₂Cl₂ (2 ml) and the resulting mixture was stirred at 0 °C and allowed to warm up to RT for 2 hrs. After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, n-hexane/EtOAc 90/10) to yield **2a** (86% as a mixture of 4 diastereomers). ¹H NMR (500 MHz, CDCl₃): **Esyn** δ = 0.98 (t, ³J (H,H) = 7.4 Hz, 3H), 0.99 (t, ³J (H,H) = 7.4 Hz, 3H), 1.64-1.84 (m, 4H), 3.66 (s, 3H), 5.09 (ddd, ³J (H,H) = 7.4, 2.7, 1.9 Hz, 1H), 5.27 (t, ³J (H,H) = 4.8 Hz, 1H), 5.36 (d, ³J (H,H) = 1.9 Hz, 1H); **Characteristic of Eanti** δ = 5.27 (s, 1H), 5.30 (m, 1H), 5.42 (t, ³J (H,H) = 4.4 Hz, 1H); **Zsyn** δ = 1.00 (t, ³J (H,H) = 7.4 Hz, 3H), 1.01 (t, ³J (H,H) = 7.4 Hz, 3H), 1.59–1.70 (m, 2H), 1.82-1.94 (m, 2H), 3.68 (s, 3H), 4.52 (dd, ³J (H,H) = 6.9, 3.4 Hz, 1H), 4.77 (d, ³J (H,H) = 1.1 Hz, 1H), 5.36 (t, ³J (H,H) = 4.5 Hz, 1H); **Characteristic of Zanti** δ = □4.66 (t, ³J (H,H) = 6.4 Hz, 1H), 4.78 (s, 1H), 5.59 (t, ³J (H,H) = 4.7 Hz, 1H); ¹³C NMR (50.3 MHz, CDCl₃): **Zsyn** (major product) δ = □□ □167.0, 166.0, 109.1, 85.9, 81.1, 50.9, 26.5, 25.2, 8.8, 7.2; IR (CHCl₃) ν = 1709.8, 1667.9. cm⁻¹; MS (70 eV, EI): *m/z* (%) 200 (47) [M⁺], 125 (30), 114 (77), 101 (43), 83 (28), 69 (100), 59 (21); elemental analysis calcd (%) for C₁₀H₁₆O₄: C 59.98, H 8.05; found: C 59.89, H 8.35.

Synthesis of 2,3,4-trisubstituted-2,3-dihydrofuran (representative example): To a cooled solution (-60 °C) of methyl propiolate (4.72 mmol) and iso-butyraldehyde (2.36 mmol) in dry CHCl₃ (6.3 ml) was added tri-n-butylphosphine (0.96 mmol). The reaction mixture was stirred for 1.25 hrs and then quenched with 1M HCl (5 ml). After extraction with CH₂Cl₂ (3x10 ml), the organic layers were dried over anhydrous sodium sulphate. After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, n-hexane/EtOAc 90/10) to yield **4c** (51%) as a separable mixture of isomers (1:2.9, Z:E). On standing this mixture is unstable and it isomerizes slowly to the corresponding furan.

Methyl 4-(2-methoxy-2-oxoethylidene)-5-propyl-4,5-dihydro-3-furancarboxylate (4b): ¹H NMR (400 MHz, CDCl₃): **Z-4b** δ = 0.94 (t, ³J (H,H) = 8.3 Hz, 3H), 1.48–1.69 (m, 3H), 1.93-2.03 (m, 1H), 3.70 (s, 3H), 3.77 (s, 3H), 5.97 (dt, ³J (H,H) = 8.4, 2.5 Hz, 1H), 6.43 (d, ³J (H,H) = 2.6 Hz, 1H), 7.89 (s, 1H); **E-4b** δ = 0.94 (t, ³J (H,H) = 7.4 Hz, 3H), 1.41–1.54 (m, 2H), 1.66-1.78 (m, 2H), 3.68 (s, 3H), 3.74 (s, 3H), 5.18-5.22 (m, 1H), 5.42 (s, 1H), 7.58 (s, 1H); ¹³C NMR (50.3 MHz, CDCl₃): **Z-4b** δ = □□ □168.0, 167.4, 163.3, 157.8, 111.5, 105.1, 91.7, 51.2, 51.1, 36.6, 18.7, 13.6; **E-4b** δ = 166.5, 165.3, 163.7, 151.5, 113.4, 104.2, 89.8, 51.5, 51.2, 37.8, 17.4, 13.7.

Methyl 5-isopropyl-4-(2-methoxy-2-oxoethylidene)-4,5-dihydro-3-furancarboxylate (4c): ¹H NMR (400 MHz, CDCl₃): **Z-4c** δ = 0.65 (d, ³J (H,H) = 6.9 Hz, 3H), 1.14 (d, ³J (H,H) = 6.9 Hz, 3H), 2.48-2.56 (m, 1H), 3.67 (s, 3H), 3.74 (s, 3H), 5.91 (dd, ³J (H,H) = 3.3, 2.9 Hz, 1H), 6.48 (d, ³J (H,H) = 2.9 Hz, 1H), 7.94 (s, 1H); **E-4c** δ = 0.82 (d, ³J (H,H) = 6.9 Hz, 3H), 1.10 (d, ³J (H,H) = 6.9 Hz, 3H), 1.92-

2.00 (m, 1H), 3.67 (s, 3H), 3.73(s, 3H), 5.08 (m, 1H), 5.44 (d, 3J (H,H) = 2.6 Hz, 1H), 7.61 (s, 1H).); ^{13}C NMR (50.3 MHz, CDCl_3): **Z-4c** δ = 168.8, 167.6, 163.1, 157.1, 112.3, 105.5, 95.7, 51.2, 51.1, 32.1, 20.1, 14.0; **E-4c** δ = 166.5, 165.7, 163.6, 150.6, 114.1, 104.5, 94.2, 51.5, 51.2, 34.2, 18.8, 14.2.

Methyl 5-isobutyl-4-(2-methoxy-2-oxoethylidene)-4,5-dihydro-3-furancarboxylate (4d): ^1H NMR (400 MHz, CDCl_3): **Z-4d** δ = 0.92 (d, 3J (H,H) = 6.9 Hz, 3H), 1.06 (d, 3J (H,H) = 6.6 Hz, 3H), 1.37-1.44 (m, 1H), 1.65-1.73 (s, 1H), 1.80-1.95 (s, 1H), 3.69 (s, 3H), 3.77(s, 3H), 6.00 (dd, 3J (H,H) = 10.3, 2.4 Hz, 1H), 6.41 (d, 3J (H,H) = 2.7 Hz, 1H), 7.87 (s, 1H); **E-4d** δ = 0.94 (d, 3J (H,H) = 6.6 Hz, 3H), 0.96 (d, 3J (H,H) = 6.6 Hz, 3H), 1.40-1.47 (m, 1H), 1.68-1.76 (s, 1H), 1.86-1.93 (s, 1H), 3.66 (s, 3H), 3.73(s, 3H), 5.20 (dd, 3J (H,H) = 10.1, 2.9 Hz, 1H), 5.38 (d, 3J (H,H) = 2.4 Hz, 1H), 7.56 (s, 1H); ^{13}C NMR (50.3 MHz, CDCl_3): **Z-4d** δ = 167.8, 167.3, 163.3, 158.2, 111.4, 105.0, 90.4, 51.3, 51.1, 43.8, 25.4, 23.4, 21.2; **E-4d** δ = 166.5, 165.2, 163.7, 151.1, 113.2, 104.2, 88.6, 51.5, 51.2, 45.3, 24.6, 23.2, 21.6.

Methyl-5-(3-butenyl)-4-(2-methoxy-2-oxoethylidene)-4,5-dihydro-3-furancarboxylate (4e): ^1H NMR (400 MHz, CDCl_3): **Z-4e** δ = 1.63-1.72 (m, 1H), 2.07-2.15 (s, 1H), 2.21-2.27 (s, 2H), 3.69 (s, 3H), 3.77(s, 3H), 4.97-5.09 (m, 2H), 5.78-5.88 (m, 1H), 5.97 (dt, 3J (H,H) = 8.7, 2.4 Hz, 1H), 6.44 (d, 3J (H,H) = 2.7 Hz, 1H). **E-4e** δ = 1.80-1.87 (m, 2H), 2.11-2.29 (s, 2H), 3.67 (s, 3H), 3.74(s, 3H), 4.98-5.07 (m, 2H), 5.21 (ddd, 3J (H,H) = 7.2, 4.5, 2.6 Hz, 1H), 5.42 (d, 3J (H,H) = 2.6 Hz, 1H), 5.75-5.83 (m, 1H), 7.57 (s, 1H); ^{13}C NMR (50.3 MHz, CDCl_3): **Z-4e** δ = 167.9, 167.4, 163.2, 157.4, 137.2, 115.5, 111.6, 105.4, 91.0, 51.3, 51.1, 33.6, 29.6; **E-4e** δ = 166.4, 165.2, 163.6, 151.2, 136.7, 115.9, 113.5, 104.5, 89.1, 51.6, 51.2, 35.0, 28.2.

Acid-catalyzed isomerization of 2,3,4-trisubstituted-2,3-dihydrofuran to 2,3,4-trisubstituted furans (representative example): **4c** (as a mixture of isomers, 213.8 mg, 0.937 mmol) and toluene-4-sulfonic acid monohydrate (0.2 eq.) was dissolved in toluene (5 ml) and the resulting solution was heated to 90°C. The reaction was monitored by TLC until the conversion was completed. The reaction mixture was directly loaded into a silica gel column and eluted with n-hexane/EtOAc: 90/10 to yield **13c** (93%).

Methyl 4-(2-methoxy-2-oxoethyl)-5-propyl-3-furoate (13b): ^1H NMR (400 MHz, CDCl_3): δ = 0.89 (t, 3J (H,H) = 7.4 Hz, 3H), 1.55–1.68 (m, 2H), 2.53 (t, 3J (H,H) = 7.3 Hz, 2H), 3.60 (s, 2H), 3.67 (s, 3H), 3.76 (s, 3H), 7.86 (s, 1H). ^{13}C NMR (400 MHz, CDCl_3): δ = 171.6, 163.9, 155.2, 146.4, 118.3, 112.0, 51.9, 51.1, 29.2, 27.7, 21.4, 13.5; IR (CHCl_3) ν = 3024.4, 2954.2, 1720.5, 1555.2 cm^{-1} ; MS (70 eV, EI): m/z (%) 240 (14) [M^+], 181 (30), 180 (100), 179 (20), 153 (16); elemental analysis calcd (%) for

C₁₂H₁₆O₅: C 59.99, H 6.71; found: C 60.05, H 6.73.

Methyl 5-isopropyl-4-(2-methoxy-2-oxoethyl)-3-furoate (13c): ¹H NMR (400 MHz, CDCl₃): δ = 1.21 (d, ³J (H,H) = 6.9 Hz, 6H), 2.91–2.98 (m, 2H), 3.62 (s, 2H), 3.66 (s, 3H), 3.75 (s, 3H), 7.84 (s, 1H); ¹³C NMR (400 MHz, CDCl₃): δ = 171.6, 163.9, 159.4, 146.1, 118.2, 110.0, 51.9, 51.1, 29.0, 26.0, 21.0; IR (CHCl₃) ν = 3022.6, 2972.6, 1721.5, 1555.5 cm⁻¹; MS (70 eV, EI): m/z (%) 240 (11) [M⁺], 193 (9.0), 181 (23), 180 (100), 165 (23), 149 (13), 77 (10); elemental analysis calcd (%) for C₁₂H₁₆O₅: C 59.99, H 6.7; found: C 59.96; H 6.44.

Methyl 5-isobutyl-4-(2-methoxy-2-oxoethyl)-3-furoate (13d): ¹H NMR (400 MHz, CDCl₃): δ = 0.87 (d, ³J (H,H) = 6.9 Hz, 6H), 1.88–1.99 (m, 1H), 2.41 (d, ³J (H,H) = 7.2 Hz, 2H), 3.58 (s, 2H), 3.66 (s, 3H), 3.75 (s, 3H), 7.85 (s, 1H); ¹³C NMR (400 MHz, CDCl₃): δ = 171.5, 163.9, 154.6, 146.4, 118.3, 112.7, 51.8, 51.1, 34.8, 29.3, 28.1, 22.1; IR (CHCl₃) ν = 3019.1, 2954.9, 1720.6, 1555.5 cm⁻¹; MS (70 eV, EI): m/z (%) 254 (24) [M⁺], 195 (49), 194 (100), 153 (64), 152 (30), 84 (38), 59 (40); elemental analysis calcd (%) for C₁₃H₁₈O₅: C 61.40, H 7.14; found: C 61.64; H 7.14.

Methyl 5-(3-butenyl)-4-(2-methoxy-2-oxoethyl)-3-furoate (13e): ¹H NMR (400 MHz, CDCl₃): δ = 2.30–2.36 (m, 2H), 2.64 (t, ³J (H,H) = 7.4 Hz, 2H), 3.59 (s, 2H), 3.66 (s, 3H), 3.75 (s, 3H), 4.95 (ddt, ³J (H,H) = 10.3, 1.9, 1.3 Hz, 1H), 4.99 (dq, ³J (H,H) = 17.0, 1.6 Hz, 1H), 5.76 (ddt, ³J (H,H) = 17.0, 10.1, 6.6 Hz, 1H), 7.86 (s, 1H); ¹³C NMR (400 MHz, CDCl₃): δ = 171.5, 163.8, 154.4, 146.5, 136.8, 118.4, 115.6, 112.2, 51.9, 51.1, 32.1, 29.2, 25.5; IR (CHCl₃) ν = 3026.8, 2953.2, 1720.5, 1555.4 cm⁻¹; MS (70 eV, EI): m/z (%) 252 (38) [M⁺], 211 (44), 193 (33), 192 (34), 179 (66), 153 (100), 86 (38), 84 (57); elemental analysis calcd (%) for C₁₃H₁₆O₅: C 61.90, H 6.39; found: C 61.79, H 6.66.

Acknowledgement. This research was supported by the Spanish Ministerio de Ciencia y Tecnología (PB98-0443-C02-02 and PPQ2002-04361-C04-03). FGT thanks to Professor Victor S. Martin for helpful discussions. DTA thanks to Instituto Canario de Investigación del Cáncer for a postdoctoral grant.

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- [20] Although we have not been able to find a pKa value for tri-*noctyl*phosphine, this must be similar to that of tri-*n*butyl phosphine.
- [21] This fact rules out the possibility of a thermodynamic formation of the acetylide ion by a direct acid-base reaction between the base and the terminal alkynoate. If this were the case, these basic amines would have been good or at least moderate catalysts for these reactions. This is not the case and their deficient catalyst ability is explained by their kinetic incapability to trigger these cascade processes.
- [22] We have recently accomplished an expeditious one-pot synthesis of 5-substituted tetronic acids (4-hydroxy-5H-furan-2-one) by the controlled acid hydrolysis of 1,3-dioxolane compounds **2**. D. Tejedor, G. V. López, F. García-Tellado, J. J. Marrero-Tellado, P. de Armas, D. Terrero, *J. Org. Chem.* (in press)

Figure 1. The three kinetically controlled domino processes based on the reaction of alkynoates and aldehydes or activated ketones triggered by a tertiary amine or phosphine.

Scheme 1. Umpolung addition of nucleophiles to

2-alkynoates catalysed by tertiary phosphines

Scheme 2. Triethylamine-catalysed reaction of methyl

propiolate with aldehydes and activated ketones

Scheme 3. Mechanism of the triethylamine-catalysed reaction of methyl

propiolate with aldehydes and activated ketones

Scheme 4. DABCO-catalysed reaction of methyl

propiolate and *ipentanal* in mixtures of THF- CH_2Cl_2

Scheme 5. Triethylamine-catalysed reaction of alkyne

sulphones and alkynones with aldehydes in dichloromethane

Scheme 6. Generation of the ammonium alkoxide intermediate **12**.

Scheme 7. Tri-*n*butylphosphine-catalysed reaction

of methyl propiolate with aldehydes.

Scheme 8. Proposed mechanism for the kinetically controlled serial multibond-forming process. The β -ammonium (or phosphonium) acrylate counter ions have been omitted for clarity.

Scheme 9. Acid-catalysed transformation of

2,3-dihydrofurans into furans.

Abstract in Spanish

En este trabajo se describe un método muy suave y eficiente para la generación catalítica de aniones acetiluro conjugados en ausencia de metales. Estos aniones acetiluros pueden generar selectivamente, mediante un proceso dominó catalítico, alcoholes propargílicos protegidos en la forma de su enol éter del tipo **1**, compuestos 1,3-dioxolánicos 1,2,4-trisustituidos del tipo **2** o compuestos 2,3-dihdrofuranos 2,3,4-trisustituidos del tipo **4**. El método requiere un nucleófilo actuando como iniciador químico (una amina o fosfina terciaria), un acetileno conjugado como fuente de aniones acetiluro y un aldehído o cetona

activada como especie electrofílica. La distribución de los productos depende marcadamente de la naturaleza del nucleófilo, la temperatura, la estequiometría y el tipo de disolvente utilizado, y puede ser dirigida selectivamente mediante la correcta elección de las condiciones experimentales.

Table 1. Triethylamine-catalysed reaction of methyl propiolate and aldehydes in dichloromethane.

Aldehyde (ketone)	Alkynoate/Aldehyde		
	2/1 rt (%) ^[a]	2/1 0°C (%) ^[a]	1/2 -78°C (%) ^[b]
1 <i>n</i> Propanal	1a (79)	1a (87)	--
2 <i>n</i> Butanal	1b (80)	1b (85)	1b (4) 2b (94)
3 <i>i</i> Butanal		1c (80)	1c (17) 2c (70)
4 "			1c (6) ^c 2c (84)
5 <i>i</i> pentanal		1d (75)	1d (3) 2d (84)
6 <i>n</i> Heptanal		1e (76)	1e (5) 2f (87)
7 Pivalaldehyde		1f (65)	1f (41) 2f (13)
8 "			1f (28) ^c 2f (66)
9 Trifluoroaceto-phenone		1g (0) 2g (23) ^d	1g (0) 2g (90)

^[a]Yield based on alkynoate. ^[b]Yields of 1,3-dioxolanes are

referred to the mixture of the 4 diastereomers. ^[c]Ratio

alkynoate/aldehyde:1/4. ^[d] 25% is the upper limit and it

corresponds to a 100% yield.

Table 2. DABCO-catalysed reaction of methyl

propiolate and aldehydes in dichloromethane.^[a]

		Alkynoate/Aldehyde	
		2/1	1/2
Aldehyde		-78°C (%) ^[b]	-78°C
1	<i>n</i> Propanal	1a (84)	1a (87)
		3 (12)	3 (3)
2	<i>n</i> Butanal	1b (82)	--
		3 (12)	
2	<i>i</i> Butanal	1c (83)	--
		3 (8)	
4	<i>i</i> Pentanal	1d (70)	1d (80)
		3 (21)	3 (6)
5	<i>n</i> Heptanal	1e (76)	1e (72)
		3 (12)	3 (3)
6	Pivalaldehyde	1f (67)	1f (80)
		3 (21)	3 (6)

^[a] 50 mol% of DABCO. ^[b] Yield based on alkynoate.

Table 3. Triethylamine-catalysed reaction of alkyne

sulphones and alkynones with aldehydes in dichloromethane.

			Alkyne/Aldehyde:	
		Aldehyde	2/1	1/2
Alkyne	(Ketone)		0°C (%) ^{[a],[b]}	-78°C
1	5	<i>n</i> Butanal	6b (0) ^[c]	7b (82)
			7b (19)	
2	5	Trifluoro- acetophenone	6g (0) ^[c]	7g (79) ^[d]
			7g (20)	
3	8	<i>n</i> Butanal	9b (56)	10b (93)
			10b (4)	
4	8	Trifluoro- acetophenone	9g (0)	10g (95)
			10g (24)	

^[a] Yield based on alkynoate. ^[b] Yields of 1,3-dioxolanes arereferred to the mixture of the 4 diastereomers. ^[c] Small amountof alkynone was recovered. ^[d] Allowed to warm to -30°C, 6h.Table 4. Tri-*n*butylphosphine-catalysed reaction of methyl

propiolate with aldehydes in different solvents.

	Solvent	Temp.	Aldehyde	Alkynoate/aldehyde		
				2/1(%) ^[a]	3/1	1/2
1	CH ₂ Cl ₂	-78°C	<i>n</i> Butanal	4b (25)		2b (73)
				2b (6) ^[b]		
2	CHCl ₃	-60°C	“	4b (38)	4b (44)	
				2b (4) ^[b]		
3	“	“	<i>i</i> Butanal	4c (51)	4c (57)	
4	“	“	<i>i</i> Pentanal	4d (43)	4d (48)	
5	“	“	4-Pentenal	4e (25)	4e (38)	
6	C ₂ H ₄ Cl ₂	-40°C	<i>n</i> Butanal	4b (22)		
				2b (<2) ^[b]		
7	THF	-78°C	“	2b (20)		2b (77)
8	Hexanes	-78°C	“	2b (24)		2b (83)
9	Et ₂ O	-78°C	“	4b (1.3)		
				2b (23)		

^[a] Calculated with regard to the starting aldehyde. ^[b] Calculated

with regard to the starting alkynoate. The upper limit is 25%

Table 5. The influence of the electronic nature of

the phosphine catalyst in the dihydrofuran formation

reaction. Reaction of methyl propiolate and isobutyral

catalysed by tertiary phosphine in chloroform at -60°C.

	Phosphine	pka ^[19]	Alkynoate/aldehyde		
			2/1 (%)	3/1	4/1
1	Bu ₃ P	8.43	4c (51)	4c (57)	4c (54)
2	Oct ₃ P ^[20]	-	4c (51)	4c (60)	
3	<i>i</i> Bu ₃ P	7.97	4c (43)		
4	Bn ₃ P	-	4c (0)		
5	Cyhex ₃ P	9.70	4c (15)		
6	Me ₂ PhP	6.65	4c (7.4)		
7	MePh ₂ P	4.57	4c (0)		
8	Ph ₃ P	2.73	4c (0)		
9	(MeO) ₃ P	2.6	4c (0)		

Table of Contents

Tertiary amines and tertiary alkyl phosphines catalyse an extremely mild and efficient domino process based on in situ selective catalytic generation of non-metalated, conjugated acetylides in the presence of activated electrophiles. The chemical outcome of these reactions can be tailored at will to give selectively enol-protected functionalized propargylic alcohols **1**, 1,2,4-trisubstituted 1,3-dioxolanes **2** or 2,4,5-trisubstituted dihydrofurans **4**. A mechanism is postulated to explain the experimentally observed influence of the nucleophile strength, temperature and stoichiometry on the kinetic course of these processes.

Figure 1

Scheme 1

Scheme 2

The diagram illustrates a catalytic cycle for the synthesis of cyclic enones and enynes. The cycle involves several key intermediates and reagents:

- Intermediate I:** A zwitterionic species, $\text{Et}_3\text{N}^+\text{C}^-\text{=CH-Z}$, which is the active catalyst.
- Reagents:**
 - $\text{Z-C}\equiv\text{C-H}$ (alkyne) and Et_3N (triethylamine) are added to regenerate the catalyst.
 - $\text{H-C}\equiv\text{C-Z}$ (alkyne) is used in the formation of cyclic enones.
 - $\text{R}_1\text{R}_2\text{CO}$ (ketone) is used in the formation of cyclic enynes.
- Intermediate II:** A zwitterionic species, $\text{Z-C}\equiv\text{C}^-\text{N}^+\text{Et}_3$, formed by the reaction of I with $\text{Z-C}\equiv\text{C-H}$.
- Intermediate III:** A species, $\text{Z-C}\equiv\text{C}(\text{O}^-\text{R}_2)\text{R}^1$, formed by the reaction of II with $\text{R}_1\text{R}_2\text{CO}$.
- Intermediate IV:** A cyclic enyne intermediate, $\text{R}^1\text{R}^2\text{C}(\text{O}^-\text{R}_2)\text{C}\equiv\text{C}(\text{Z})\text{CH}_2\text{CH}_2\text{O}$, formed by the cyclization of III.
- Intermediate V:** A cyclic enone intermediate, $\text{R}^1\text{R}^2\text{C}(\text{O}^-\text{R}_2)\text{C}(\text{Z})\text{CH}_2\text{CH}_2\text{O}$, formed by the cyclization of IV.
- Products:**
 - 2:** A cyclic enone, $\text{R}^1\text{R}^2\text{C}(\text{O}^-\text{R}_2)\text{C}(\text{Z})\text{CH}_2\text{CH}_2\text{O}$, formed by the reaction of V with $\text{H-C}\equiv\text{C-Z}$.
 - 1:** A cyclic enyne, $\text{R}^1\text{R}^2\text{C}(\text{O}^-\text{R}_2)\text{C}\equiv\text{C}(\text{Z})\text{CH}_2\text{CH}_2\text{O}$, formed by the reaction of V with $\text{Z-C}\equiv\text{C-H}$.

Scheme 4

THF/ CH_2Cl_2	1d	3
10 / 0	20%	0%
9 / 1	49%	0%
8 / 2	65%	< 5%
5 / 5	86%	< 10%
0/10	70%	21%

Scheme 5

Scheme 6

(a) CF₃CO₂H, 0°C → rt, overnight; (b) *t*BuMe₂SiCl, Imidazole, DMF; (c) Bu₄NF, THF.

Scheme 7

Scheme 8

Scheme 9

TOC