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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In memory of Professor Antonio González González

Abstract: The extremely mild and highly efficient catalytic generation of non-metalated, conjugated acetylides is reported. These acetylides are used to generate enol-protected functionalized propargylic alcohols **1**, 1,3-dioxolane compounds **2**, or 3,4,5-trisubstituted 4,5-dihydrofurans **4** through serial multibond-forming processes. The method calls for a nucleophile (a tertiary amine or phosphine) as a chemical activator, 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 nature of the nucleophile, the temperature, stoichiometry and solvent, and it can be tailored selectively by the appropriate choice of the experimental conditions.

Keywords: acetylides · autocatalysis · C–C coupling · conjugation · domino reactions

Introduction

Serial multibond-forming events (domino processes)[1, 2] constitute a very attractive approach to the development of new, efficient, synthetic methodologies using readily available and inexpensive starting materials allowing molecular complexity to be created quickly, with bond-forming efficiency and structural and atomic economy, in just one simple, safe, environmentally acceptable, and resource-effective operation; they are 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); the subsequent reaction takes place at the functionalities introduced in the previous transformation.[2c] When performed catalytically, this type of transformation constitutes a powerful and economical synthetic method of introducing chemical and structural complexity. Collections of small compounds with structural and functional diversity play important roles in the drug discovery process because they offer means for the structural identification of biologically active macromolecules[3] and also for identifying and optimizing new chemicals with small molecules that are able to interact specifically 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 (a tailored chemical outcome), atomic and structural 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

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bond-forming reaction. Substoichiometric amounts of base have been used by Knochel et al.[6] (10 mol% CsOH in DMSO) and Babler et al.[7] (10–20 mol% KO*t*Bu in DMSO), to catalyze 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 new, mild method for the in situ catalytic generation of reactive zinc acetylides which add to nitrones, imines, and aldehydes to give 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 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 depends strongly on the nature of the nucleophile, temperature, stoichiometry, 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 3,4,5-trisubstituted dihydrofurans **4** (Figure 1). The concurrent formation of up to three bonds

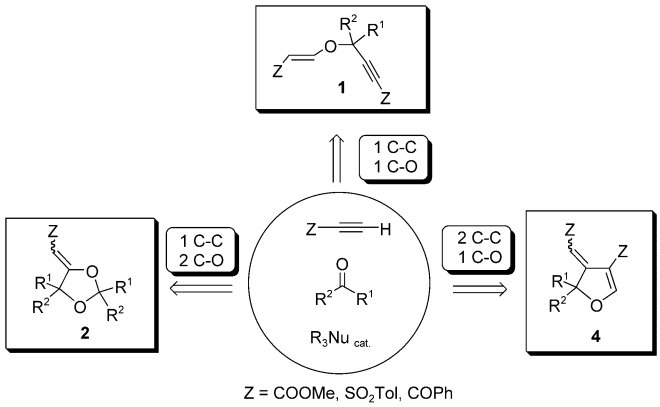


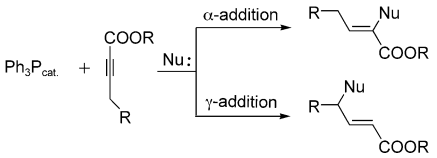
Figure 1. The three kinetically controlled domino processes based on the reaction of alkynoates and aldehydes or activated ketones triggered by a tertiary amine or phosphine.

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 4,5-dihdrofuranos 3,4,5-trisustituidos del tipo* ***4****. El método requiere un nucleófilo 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.*

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

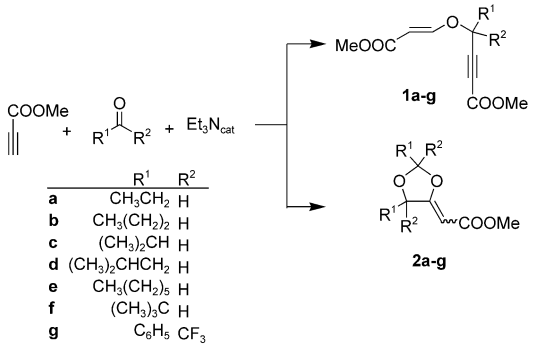
Conjugated acetylenes tend to give Michael addition in the presence of nucleophiles. There is a wide bibliographic precedent for this reaction in the literature.[10] Most Michael additions demand a nucleophile, a catalyst, and an electrophile, along with the conjugated alkyne.[11] Normally, the expected Michael adduct is formed when a conjugated alkyne reacts with a nucleophile. The tertiary phosphine catalyzed addition of nucleophiles to the triple bond of a conjugated alkynoate constitutes a remarkable exception (Scheme 1).



Scheme 1. Umpolung addition of nucleophiles to 2-alkynoates catalyzed by tertiary phosphines.

The chemical outcome of such 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 pK_a values of the terminal conjugated alkynoates (pK_a < 18.8),[14]



Scheme 2. Triethylamine-catalyzed reaction of methyl propiolate with aldehydes and activated ketones.

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 to 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:

1) It adds to the ammonium **II** to give the adduct **1**[15] and triethylamine to reinitiate the cycle **a**, or
2) It adds to another molecule of the electrophile to generate dioxolane **2** and ammonium acetylide **II** to reinitiate the cycle **b**.

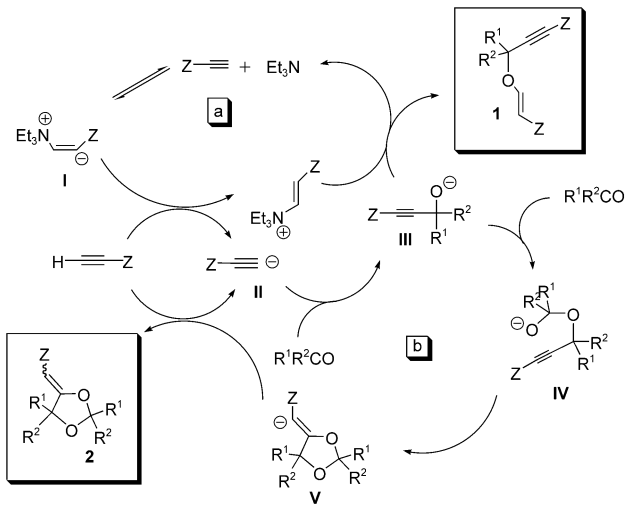
This cycle **b** constitutes an autocatalyzed synthesis of 1,3-dioxolanes **2**. The autocatalytic nature of this cycle is discussed further, below.

The stoichiometry and reaction temperature (Table 1) rule 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 products (entries 1–8). The chemical outcome of the reaction changed dramatically when the stoichiometry was reversed from 2:1 to 1:2 and the temperature was 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 dioxolanes **2** efficiently, independently of the stoichiometry and temperature used (entry 9).

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

Entry	Aldehyde/ ketone	Alkynoate/aldehyde 2:1 RT (%)[a]	2:1 0 °C (%)[a]	1:2 −78 °C (%)[b]
1	*n*-propanal	**1a** (79)	**1a** (87)	–
2	*n*-butanal	**1b** (80)	**1b** (85)	**1b** (4)
				2b (94)
3	isobutanal		**1c** (80)	**1c** (17)
				2c (70)
4	isobutanal			**1c** (6)[c]
				2c (84)
5	isopentanal		**1d** (75)	**1d** (3)
				2d (84)
6	*n*-heptanal		**1e** (76)	**1e** (5)
				2e (87)
7	pivaldehyde		**1f** (65)	**1f** (41)
				2f (13)
8	pivalaldehyde			**1f** (28)[c]
				2f (66)
9	trifluoroacetophenone		**1g** (0)	**1g** (0)
			2g (23)[d]	**2g** (90)

[a] Yield based on alkynoate. [b] Yields of 1,3-dioxolanes are referred to the mixture of the four diastereomers. [c] Alkynoate/aldehyde ratio 1:4. [d] 25% is the upper limit and corresponds to a 100% yield.



Scheme 3. Mechanism of the triethylamine-catalyzed reaction of methyl propiolate with aldehydes and activated ketones.

This multibond-forming process worked quite well even without a solvent. Thus, a smooth reaction occurred when methyl propiolate (1 equiv) was mixed with *n*-butanal (2 equiv) and triethylamine (10 mol%) at −78 °C, 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**.

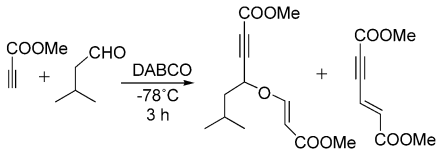
The nature of the tertiary amine was shown to be very important for the success of the reaction. The sterically demanding diisopropylethylamine did not show any catalytic activity. DBU and DBN behaved in a similar way. In contrast, DABCO, an extremely nucleophilic amine,[16] proved to be an extraordinary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

Table 2. DABCO-catalyzed reaction of methyl propiolate and aldehydes in dichloromethane.[a]

Entry	Aldehyde	Alkynoate/Aldehyde 2:1 −78 °C (%)[b]	1:2 −78 °C (%)
1	*n*-propanal	**1a** (84)	**1a** (87)
		3 (12)	**3** (3)
2	*n*-butanal	**1b** (82)	–
		3 (12)	
2	isobutanal	**1c** (83)	–
		3 (8)	
4	isopentanal	**1d** (70)	**1d** (80)
		3 (21)	**3** (6)
5	*n*-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.

Variable amounts of diester **3**[17] were also obtained as a side product in these DABCO-catalyzed reactions. The side reaction route affording diester **3** could only be minimized by using low temperatures and, with the less reactive aldehydes, 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, a solvent in which DABCO is scarcely soluble, the diester formation was minimized albeit at the expense of a severe reduction in the reaction rate. Mixtures of tetrahydrofuran and dichloromethane reduced the reaction time and also increased the ratio of **1**:**3** (Scheme 4).

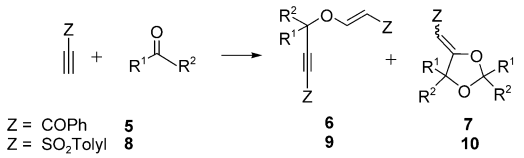


THF/CH_2Cl_2	**1d** [%]	**3** [%]
10:0	20	0
9:1	49	0
8:2	65	< 5
5:5	86	< 10
0:10	70	21

Scheme 4. DABCO-catalyzed reaction of methyl propiolate and isopentanal in THF/CH_2Cl_2 mixtures.

It is noticeable that no dioxolanes are obtained in these DABCO-catalyzed reactions, in sharp contrast with the triethylamine-catalyzed processes.

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



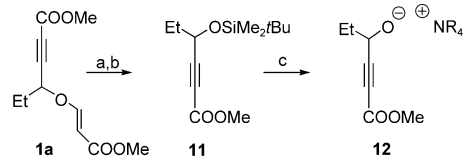
Scheme 5. Triethylamine-catalyzed reaction of alkyne sulfones and alkynones with aldehydes in dichloromethane.

Table 3. Triethylamine-catalyzed reaction of alkyne sulfones and alkynones with aldehydes in dichloromethane.

Entry	Alkyne	Aldehyde/ Ketone	Alkyne/Aldehyde 2:1 0 °C (%)[a,b]	1:2 −78 °C (%)
1	**5**	*n*-butanal	**6b** (0)[c] **7b** (19)	**7b** (82)
2	**5**	trifluoroacetophenone	**6g** (0)[c] **7g** (20)	**7g** (79)[d]
3	**8**	*n*-butanal	**9b** (56) **10b** (4)	**10b** (93)
4	**8**	trifluoroacetophenone	**9g** (0) **10g** (24)	**10g** (95)

[a] Yield based on alkynoate. [b] Yields of 1,3-dioxolanes are referred to the mixture of the four diastereomers. [c] A small amount of alkynone was recovered. [d] Allowed to warm to −30 °C, 6 h.

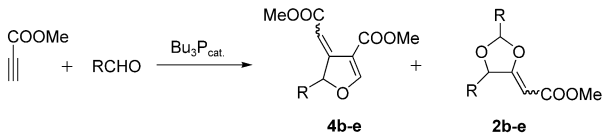
One consequence of the working mechanistic hypothesis outlined in Scheme 3 is the autocatalytic nature of the 1,3-dioxolane synthesis (cycle **b**). Once alkoxide **III** is generated, it catalyzes the acetylide formation through the intermediate **V**. Because alkoxide **III** is not easy to synthesize, the synthetically accessible ammonium alkoxide **12** was chosen as the catalyst. It was easily synthesized 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**



Scheme 6. Generation of the ammonium alkoxide intermediate **12**. a) CF_3CO_2H, 0 °C → RT, overnight; b) *t*$BuMe_2SiCl$, imidazole, DMF; c) Bu_4NF, THF.

catalyzed 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 but otherwise under the same conditions, the formation of 1,3-dioxolane **2a** was extremely sluggish. Addition of aldehyde (to the 2 equiv required for dioxolane formation) to this reaction mixture sped 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; they are more powerful nucleophiles and less basic than their nitrogen equivalent. Initial 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 to −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 mixture quickly turned black, indicating that polymeric material was being formed. When the temperature was lowered to −78 °C, the reaction mixture remained colorless for 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 as a mixture of diastereomers) (Scheme 7). The propargylic derivative **1b** was not observed. The yield and chemical outcome of this reaction were strongly dependent on the catalyst strength, stoichiometry, and the nature of the solvent (Table 4). When the alkynoate/aldehyde stoichiometry was changed from 2:1



Scheme 7. Tri-*n*-butylphosphine-catalyzed reaction of methyl propiolate with aldehydes.

Table 4. Tri-*n*-butylphosphine-catalyzed reaction of methyl propiolate with aldehydes in different solvents.

Entry	Solvent	T [°C]	Aldehyde	Alkynoate/Aldehyde 2:1 (%)[a]	3:1 (%)[a]	1:2 (%)[a]
1	CH_2Cl_2	−78	*n*-butanal	**4b** (25) **2b** (6)[b]		**2b** (73)
2	$CHCl_3$	−60	*n*-butanal	**4b** (38) **2b** (4)[b]	**4b** (44)	
3	$CHCl_3$	−60	isobutanal	**4c** (51)	**4c** (57)	
4	$CHCl_3$	−60	isopentanal	**4d** (43)	**4d** (48)	
5	$CHCl_3$	−60	4-pentenal	**4e** (25)	**4e** (38)	
6	$C_2H_4Cl_2$	−40	*n*-butanal	**4b** (22) **2b** (<2)[b]		
7	THF	−78	*n*-butanal	**2b** (20)		**2b** (77)
8	hexanes	−78	*n*-butanal	**2b** (24)		**2b** (83)
9	Et_2O	−78	*n*-butanal	**4b** (1.3) **2b** (23)		

[a] Calculated relative to the starting aldehyde. [b] Calculated relative to the starting alkynoate. The upper limit is 25%.

Table 5. Influence of the electronic nature of the phosphine catalyst on the formation of dihydrofuran: reaction of methyl propiolate and isobutanal catalyzed by tertiary phosphine in chloroform at −60 °C.

Entry	Phosphine	pK_a[a]	Alkynoate/Aldehyde 2:1 (%)	3:1 (%)	4:1 (%)
1	Bu_3P	8.43	**4c** (51)	**4c** (57)	**4c** (54)
2	Oct_3P[b]	–	**4c** (51)	**4c** (60)	
3	iBu_3P	7.97	**4c** (43)		
4	Bn_3P	–	**4c** (0)		
5	$Cyhex_3P$	9.70	**4c** (15)		
6	Me_2PhP	6.65	**4c** (7.4)		
7	$MePh_2P$	4.57	**4c** (0)		
8	Ph_3P	2.73	**4c** (0)		
9	$(MeO)_3P$	2.6	**4c** (0)		

[a] M. M. Rhaman, H.-Y. Liu, K. Eriks, A. Prock, W. P. Giering, *Organometallics* **1989**, *8*, 1–7. [b] Although we have not been able to find a pK_a value for tri-*n*-octylphosphine, it must be similar to that of tri-*n*-butyl phosphine.

to 1:2, the main products changed from dihydrofurans **4** to 1,3-dioxolanes **2** (entries 1, 7, 8). Surprisingly, only the halogenated solvents were suitable for dihydrofuran formation (entries 1–6). In non-halogenated solvents, only dioxolane compounds were formed (entries 7–9). Even when the stoichiometry was unfavorable, 1,3-dioxolane formation was a highly favored 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, although not in a linear manner. A large and variable amount of alkynoate was lost as polymeric material. When the stoichiometric ratio was changed from 2:1 to 1:2, 1,3-dioxolanes only were formed, in excellent yields. The polymerization was greatly minimized; polymerization is a serious problem only when the stoichiometry is favorable for dihydrofuran formation, and when it becomes a very significant route leading to loss of resources. Unfortunately, this polymerization side reaction could not be entirely eliminated. Lowering the tri-*n*-butylphosphine concentration from 40 to 10 mol% decreased the dihydrofuran yield dramatically, from 51 to 12%. Dilution did not prove to be more effective: a fourfold dilution reduced the yield from 34% ([alkynoate] = 1M) to 25% ([alkynoate] = 0.25M).

To minimize the polymerization route we explored the influence of the electronic nature of the phosphine on these reactions. Because isobutanal gave the best yields of dihydrofurans, it was chosen as the aldehyde partner in this study (Table 5). Tri-*n*-butylphosphine and tri-*n*-octylphosphine, which are exceptionally nucleophilic and weakly basic catalysts, gave the best yields of dihydrofurans (entries 1 and 2). Triisobutylphosphine 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 of ≈8–8.5, the lower the yield of dihydrofurans. Again, excess of alkynoate did not improve the yield to any considerable degree: an increment in yield of less than 10% 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 equiv) and isobutanal reacted with DABCO (20 mol%) and tri-*n*-butylphosphine (20 mol%) in dichloromethane at −60 °C for 1 h. 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 polymerization and heterocycle formation reactions.

Discussion

The enormous influence of the nature of the nucleophile, 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, **a**, **b**, and **c**, and two resource-wasteful 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 to 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 towards the diester **3** through an intramolecular Michael addition–elimination sequence of reactions with catalyst release (step 11), or
3) polymerize 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:

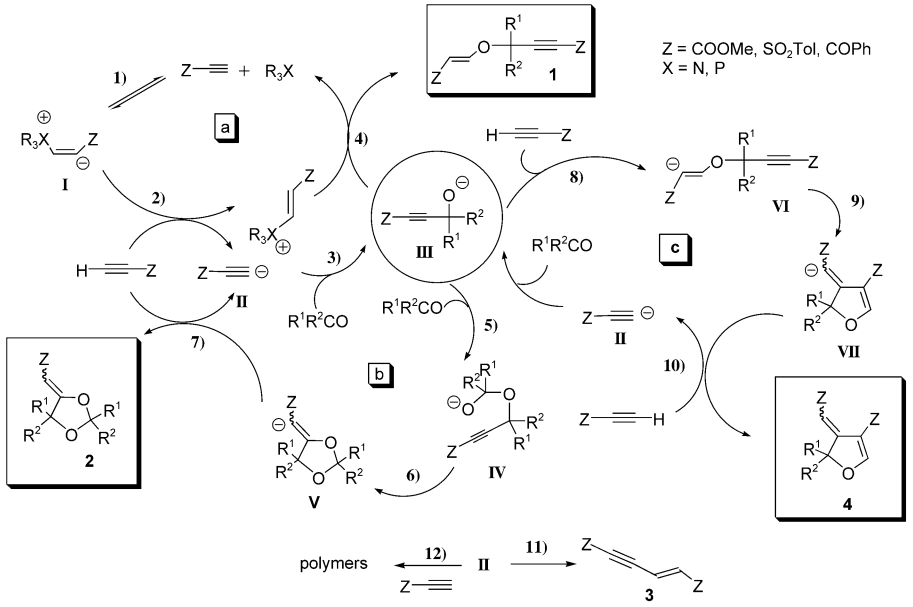
1) an intramolecular Michael addition on a β-ammonium acrylate to close cycle **a** (step 4),
2) an addition to the aldehyde or ketone to start cycle **b** (step 5), and
3) an intermolecular Michael addition to the reactant alkynoate to launch cycle **c** (step 8).

The rate of consumption of the available alkoxide **III** by each of these competing reactions will establish the amount of material delivered towards each of the three cycles **a**, **b**, or **c**, and therefore the chemical outcome of the process. Cycle **a** is kinetically the most favored because of the intramolecular nature of 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 towards 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 results in 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, their specific rate constants being independent. Under these conditions, the nature and concentration of the electrophilic partner are determinants directing the kinetic control of the entire process. However, 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 relative to aldehyde favors the bimolecular reactions in which this species is participating and such reactions will receive additional kinetic aid to compete with those others in which the aldehyde participates, and vice versa. Also, for the same reason, the formation of acetylide **II** is kinetically favored under these conditions.
3) *The electronic nature of the Michael acceptor species involved*: 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 phosphorus(III) atom to stabilize 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 basis for the umpolung effect described by Lu et al.[11a] and Trost et al.[12] in phosphine-catalyzed 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 catalyzed reaction: Hindered tertiary amines such as diisopropylethylamine, or good bases such as DBU and DBN, are not suitable catalysts for these reactions,[19] but triethylamine and DABCO show excellent catalytic activity, each with different selectivity. Thus, whereas triethylamine catalyzes the synthesis of both 1,3-dioxolanes **2** and enol-protected propargylic alcohols **1** in excellent yields (Table 1), DABCO catalyzes only the synthesis of compounds **1** (Table 2). The reason for this difference lies in the nucleophilic nature of both catalysts. The powerful nucleophile DABCO catalyzes the reaction exclusively through the kinetically favored cycle **a**. A high acetylide concentration and the high reactivity of the β-ammonium acrylate towards the Michael addition converge to the same kinetic result: amplification of cycle **a**, through a kinetically fast step 4), with kinetic inhibition of cycles **b** and **c**. Triethylamine, a poorer nucleophile, catalyzes 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 reaction 5) increases sufficiently to direct the transformation flow through cycle **b**, generating 1,3-dioxolanes **2** (Table 1). Under these unfavorable conditions, cycle **a** still survives and delivers compounds **1**, although



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.

in low yield. 4,5-Dihydrofuran derivatives **4** are clearly not synthesized in these tertiary amine catalyzed reactions.

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

Tertiary phosphine catalyzed reaction: Tertiary phosphines are more nucleophilic and less basic than the tertiary amines and they exhibit different catalytic behavior. Remarkably, they catalyze the synthesis of 4,5-dihydrofuran derivatives **4** and 1,3-dioxolanes **2** but they do not catalyze the synthesis of propargylic derivatives **1**. Their catalytic efficiency depends strongly on their electronic nature. Among the tertiary phosphines assayed, triisobutylphosphine, tri-*n*-octylphosphine and tri-*n*-butylphosphine behaved as suitable catalysts for these reactions (Table 5). Importantly, the synthesis of 4,5-dihydrofurans **4** called for a phosphine that was a good nucleophile ($pK_a \approx 8-8.5$), a halogenated solvent, a low temperature, and an excess of alkynoate, for it 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, polymerization of the starting alkynoate is highly wasteful in resources and this waste cannot be reduced 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 disfavored, and therefore cycle **a** is no longer the preferred transformation route. Nucleophile, temperature, stoichiometry, and nature of the solvent determine the kinetic course of the process. Halogenated solvents, good nucleophiles, and an excess of alkynoate favor reaction 8) and drive the transformation flow through cycle **c** to synthesis of 4,5-dihydrofurans. Non-halogenated solvents and a reversed stoichiometry dramatically increase the rate of 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 clear correlation between solvent properties and alkynoate reactivity. We believe that the effect of the halogenated solvents could be related to the stabilization 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 reaction 8). Although we have no definitive experimental answer, some features seem to confirm our hypothesis. Either coordinating (Et_2O, THF) or non-polar solvents (hexanes) strongly deactivate the 4,5-dihydrofuran synthesis and favor the production of 1,3-dioxolanes (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 minimizing formation of the dative complex. In the case of a non-polar solvent, the phosphonium ions should be tightly bonded to the anions generated and they should not be 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 may be responsible for the stability of these complexes.

Polymerization 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 minimized and it affects the yields of 4,5-dihydrofuran. A modest yield bonus can be accomplished by using an excess of alkynoate to feed both processes—cycle **c** and polymerization. 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 isobutanal (1 equiv) were allowed to react with a mixture of DABCO (20 mol%) and tri-*n*-butylphosphine (20 mol%) in dichloromethane at $-60\,^{\circ}C$ for 1 h, only the propargylic derivative **1c** (75%) was obtained. 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.

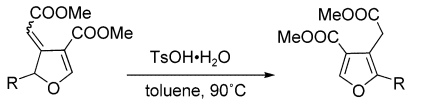
Autocatalysis: Tetrabutylammonium alkoxide **12** catalyzed the synthesis of 1,3-dioxolane **2a** in excellent yield (86%). The rate of the autocatalytic process depended strongly on the stoichiometry. Thus, whereas dioxolane **2a** was quickly synthesized using the optimum alkynoate/aldehyde ratio of 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 $0\,^{\circ}C$, no reaction took place. It is remarkable that whereas the triethylamine-catalyzed domino process can be performed at temperatures as low as $-78\,^{\circ}C$, autocatalysis needs thermal activation.

Influence of alkyne: Alkynone **5** and sulfone **8** were suitable partners in the triethylamine-catalyzed process (Table 3). The product distribution was governed by the nature of the electrophile and the alkyne reactivity. Dioxolane compounds were formed in all cases, regardless of the temperature and the alkyne/aldehyde ratio used. With the exception of **9b**, no other enol-protected propargylic compounds were produced. The good electrophilicity of the activated ketone and the low reactivity of alkynone **5** operate kinetically against cycle **a**, biasing the transformation towards cycle **b**.

Kinetic products and isomerization: 1,3-Dioxolanes **2** are obtained as a mixture of four diastereomers. The kinetic product is the *Z-syn* isomer, which appears with the highest yield in all cases. The thermodynamic product is the *E-anti*, which always appears with the lowest yield. On standing,

these products slowly isomerize towards the thermodynamic product, whereas in $CHCl_3$ solution the process is accelerated.[13]

4,5-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 also it mainly undergoes an aromatization to form the corresponding furan. This process can be accelerated to synthesize trisubstituted furans conveniently by way of stereoconvergent acid rearrangement of the two isomers (Scheme 9).



4b **13b** (92%)
4c **13c** (93%)
4d **13d** (91%)
4e **13e** (87%)

Scheme 9. Acid-catalyzed transformation of 4,5-dihydrofurans into furans.

Conclusion

We have reported here 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.[20]

Experimental Section

General: Melting points are uncorrected and were determined in a Reichter Thermovar apparatus. ^{1}H NMR and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded either at 200 and 50 MHz or at 500 and 125 MHz (Bruker AC200 and AMX500), respectively. FT-IR spectra were measured in chloroform solutions, with 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 EA1108 carbon, hydrogen, and nitrogen analyzer. Analytical thin-layer chromatography plates used were E. Merck Brinkman UV-active silica gel (Kieselgel 60F254) on aluminum. 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 text. Dichloromethane was distilled from CaH_2. Chloroform was distilled from anhydrous sodium sulfate. 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-{[(1*E*)-3-methoxy-3-oxo-1-propenyl]oxy}-2-hexynoate (1a): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.94$ (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); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 67.3$, 159.7, 152.8, 98.9, 82.6, 78.4, 71.3, 52.6, 50.9, 27.7, 8.8; IR ($CHCl_3$): $\tilde{\nu} = 2956.1$, 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 $C_{11}H_{14}O_5$: C 58.40, H 6.24; found: C 58.59, H 6.01.

Autocatalytic experiments: Trifluoroacetic acid (10 equiv) was added to a cooled (0 °C) solution of **2a** (2.12 mmol) in CH_2Cl_2 (5 mL) and the resulting mixture was allowed to warm up to room temperature and stirred for 16 h. The solution was washed with brine and with a saturated $NaHCO_3$ solution. The organic products were extracted with CH_2Cl_2 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. Et_2O was added and the organic layer was washed with water, dried over sodium sulfate, filtered 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). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 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); ^{13}C NMR (125 MHz, $CDCl_3$): $\Delta = 154.0$, 89.0, 75.7, 63.8, 52.6, 31.0, 25.7, 18.2, 9.4, −4.6, −5.2; IR ($CHCl_3$): $\tilde{\nu} = 2955.3$, 2237.0, 1714.8, 1435.7, 1257.6 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 227 (8.5) [$M^+ - C_2H_5$], 193 (54), 171 (16), 147 (68), 89 (100), 75 (20), 73 (27); elemental analysis calcd (%) for $C_{13}H_{24}O_3Si$: C 60.89, H 9.43; found: C 60.64, H 9.78.

A solution of **11** (0.10 mmol) in dry CH_2Cl_2 (3 mL) was stirred with Bu_4NF (1M THF, 0.10 mL, 0.10 mmol) at 0 °C until all starting material had 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 CH_2Cl_2 (2 mL) and the resulting mixture was stirred at 0 °C and allowed to warm up to RT for 2h. After the solvent had been removed 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 four diastereomers).

E*-*syn* *diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.98$ (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 data for the E-anti diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.27$ (s, 1H), 5.30 (m, 1H), 5.42 (t, ^3J(H,H) = 4.4 Hz, 1H).

Z*-*syn* *diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.00$ (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); ^{13}C NMR (500 MHz, $CDCl_3$) (major product): $\delta = 167.0$, 166.0, 109.1, 85.9, 81.1, 50.9, 26.5, 25.2, 8.8, 7.2; IR ($CHCl_3$): $\tilde{\nu} = 1709.8$, 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 $C_{10}H_{16}O_4$: C 59.98, H 8.05; found: C 59.89, H 8.35.

Characteristic data for the Z-anti diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.66$ (t, ^3J(H,H) = 6.4 Hz, 1H), 4.78 (s, 1H), 5.59 (t, ^3J(H,H) = 4.7 Hz, 1H).

Representative synthesis of a 3,4,5-trisubstituted-4,5-dihydrofuran: Tri-*n*-butylphosphine (0.96 mmol) was added to a cooled solution (−60 °C) of methyl propiolate (4.72 mmol) and isobutanal (2.36 mmol) in dry $CHCl_3$ (6.3 mL). The reaction mixture was stirred for 1.25 h and then quenched with 1M HCl (5 mL). After extraction with CH_2Cl_2 (3 × 10 mL), the organic layers were dried over anhydrous sodium sulfate. After the solvent had been removed 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 (*Z*/*E* 1:2.9). When left to stand this mixture is unstable and isomerizes slowly to the corresponding furan.

Methyl 4-(2-methoxy-2-oxoethylidene)-5-propyl-4,5-dihydro-3-furancarboxylate (4b)

***Z*-4b**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.94$ (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); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 168.0$, 167.4, 163.3, 157.8, 111.5, 105.1, 91.7, 51.2, 51.1, 36.6, 18.7, 13.6.

***E*-4b**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.94$ (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); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 166.5$, 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)

***Z*-4c**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.65$ (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); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 168.8$, 167.6, 163.1, 157.1, 112.3, 105.5, 95.7, 51.2, 51.1, 32.1, 20.1, 14.0.

***E*-4c**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.82$ (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, $CDCl_3$): $\delta = 166.5$, 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)

***Z*-4d**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.92$ (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); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 167.8$, 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**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.94$ (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, $CDCl_3$): $\delta = 166.5$, 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)

***Z*-4e**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.63–1.72$ (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), 7.89 (s, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 167.9$, 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**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.80–1.87$ (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, $CDCl_3$): $\delta = 166.4$, 165.2, 163.6, 151.2, 136.7, 115.9, 113.5, 104.5, 89.1, 51.6, 51.2, 35.0, 28.2.

Representative acid-catalyzed isomerization of 3,4,5-trisubstituted-4,5-dihydrofuran to 2,3,4-trisubstituted furans: A mixture of isomers of **4c** (213.8 mg, 0.937 mmol) and toluene-4-sulfonic acid monohydrate (0.2 equiv) were dissolved in toluene (5 mL) and the resulting solution was heated to 90 °C. The reaction was monitored by TLC until the conversion was complete. The reaction mixture was loaded directly into a silica gel column and eluted with *n*-hexane/EtOAc 90:10 to yield **13c** (198.8 mg, 93 %).

Methyl 4-(2-methoxy-2-oxoethyl)-5-propyl-3-furoate (13b): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.89$ (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, $CDCl_3$,): $\delta = 171.6$, 163.9, 155.2, 146.4, 118.3, 112.0, 51.9, 51.1, 29.2, 27.7, 21.4, 13.5; IR ($CHCl_3$): $\tilde{\nu} = 3024.4$, 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 $C_{12}H_{16}O_5$: C 59.99, H 6.71; found: C 60.05, H 6.73.

Methyl 5-isopropyl-4-(2-methoxy-2-oxoethyl)-3-furoate (13c): ^{1}H NMR (400 MHz, $CDCl_3$,): $\delta = 1.21$ (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); ^{13}C NMR (400 MHz, $CDCl_3$,): $\delta = 171.6$, 163.9, 159.4, 146.1, 118.2, 110.0, 51.9, 51.1, 29.0, 26.0, 21.0; IR ($CHCl_3$): $\tilde{\nu} = 3022.6$, 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 $C_{12}H_{16}O_5$: C 59.99, H 6.7; found: C 59.96; H 6.44.

Methyl 5-isobutyl-4-(2-methoxy-2-oxoethyl)-3-furoate (13d): ^{1}H NMR (400 MHz, $CDCl_3$,): $\delta = 0.87$ (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); ^{13}C NMR (400 MHz, $CDCl_3$,): $\delta = 171.5$, 163.9, 154.6, 146.4, 118.3, 112.7, 51.8, 51.1, 34.8, 29.3, 28.1, 22.1; IR ($CHCl_3$): $\tilde{\nu} = 3019.1$, 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 $C_{13}H_{18}O_5$: 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): ^{1}H NMR (400 MHz, $CDCl_3$,): $\delta = 2.30–2.36$ (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); ^{13}C NMR (400 MHz, $CDCl_3$,): $\delta = 171.5$, 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 ($CHCl_3$): $\tilde{\nu} = 3026.8$, 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 $C_{13}H_{16}O_5$: C 61.90, H 6.39; found: C 61.79, H 6.66.

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