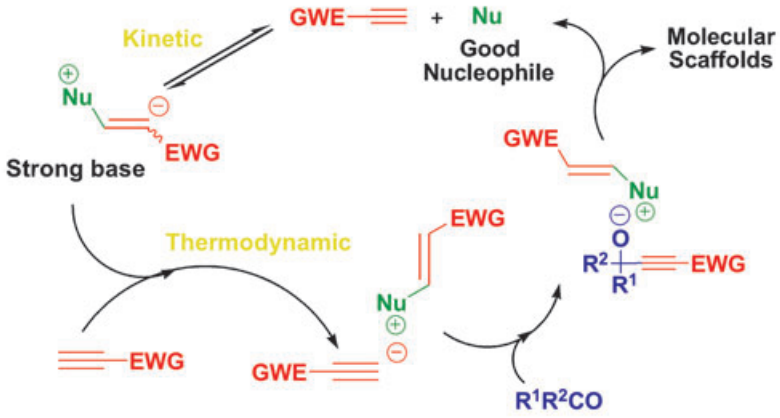
# From a Novel Reactivity Concept to Efficient Synthetic Manifolds for Diversity-Oriented Molecular Construction

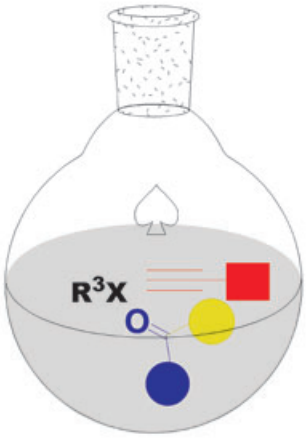
## The Reactivity Generation Concept

### Good Nucleophile Generates Strong Base



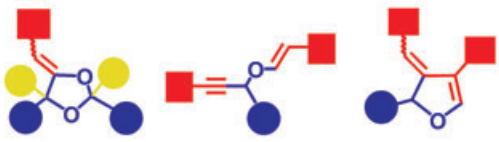

## The Synthetic Manifold for Diversity-Oriented Molecular Construction

### Catalytic Multicomponent Domino Process I

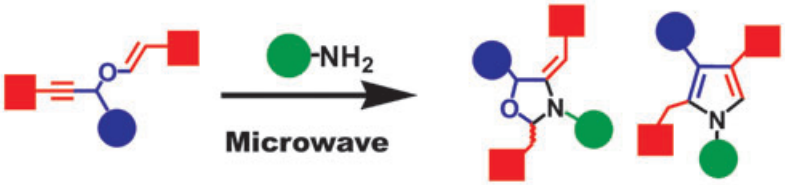



Alkyl, H
Alkyl
EWG
Alkyl, Ar
X N, P

**Highly Functionalized Molecular Scaffolds**



### Complexity-Generating Domino Process II




One-Pot Linked Domino Processes



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# Multicomponent Domino Processes Based on the Organocatalytic Generation of Conjugated Acetylides: Efficient Synthetic Manifolds for Diversity-Oriented Molecular Construction

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*Dedicated to Research Scientist Melchor García Hernández*

**Abstract:** The organocatalytic generation of a strong base by the action of a good nucleophile is the base for the in situ catalytic generation of conjugated acetylides in the presence of aldehydes or activated ketones. The method is affordable in a multicomponent, domino format able to generate a chemically diverse set of multifunctionalized adducts that are very well suited for diversity-oriented molecular construction. The domino process involves a nucleophile as catalyst and a terminal conjugated alkyne (**H−C≡C−Z**) and an aldehyde or activated ketone as building blocks. The chemical outcome of this process changes dramatically as a function of the nucleophile (tertiary amine or phosphine), temperature, stoichiometry, and solvent. These multicomponent domino processes achieve molecular construction with good atom economy and, very importantly, with an exquisite chemo-differentiating incorporation of identical starting units into the products (nondegenerated chemical output). These properties convert the **H−C≡C−Z** unit into a specific building block for diversity-oriented molecular construction. Applications to the modular and diversity-oriented synthesis of relevant heterocycles are discussed. A protocol involving two coupled domino processes linked in a one-pot manner will be discussed as an efficient synthetic manifold for the modular and diversity-oriented construction of multisubstituted nitrogen-containing heterocycles.

**Keywords:** alkynes · domino reactions · heterocycles · multicomponent reactions · nitrogen

## Introduction

The demand for new synthetic methodologies able to produce molecules in a highly effective manner has increased greatly in the last decades. This demand has fuelled an active search for new synthetic protocols addressing the modular and diversity-oriented construction of molecular complexity. Although the available arsenal of tools in synthetic organic chemistry is well suited to construct almost any imaginable molecule, this new scenario demands the continuous search for new reagents, catalysts, chemical transformations, and reaction-processing technologies. Efficient chemical syntheses not only need to be selective and high yielding, they also have to fulfill new intrinsic reaction values such as bond-forming efficiency and atom economy, as well as extrinsic ones such as economy and safety, in addition to being bench and environmentally friendly and resource-effective. Among the best known efficient chemical

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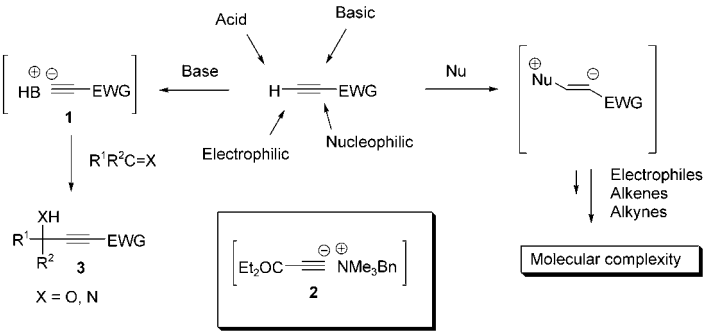
systems, multicomponent domino processes[1] occupy a privileged position. They accumulate an exceptional set of much-appreciated intrinsic and extrinsic reaction values that bring them closer to the concept of ideal synthesis. When performed in a catalytic manner, they constitute efficient synthetic manifolds for the modular and diversity-oriented construction of molecular complexity.

In this article we show the development and synthetic applications of new domino processes based on the organocatalytic generation of conjugated acetylides. This methodology relies on a novel concept of reactivity generation, that is, the organocatalytic generation of a strong base by the action of a good nucleophile.[2] The synthetic implementation of this concept allows the catalytic generation of conjugated acetylides in the presence of aldehydes or activated ketones to selectively produce a chemically diverse set of products as a function of the used nucleophile (a tertiary amine or phosphine), solvent, temperature, and stoichiometry. These products are excellent scaffolds for chemical-diversity generation.

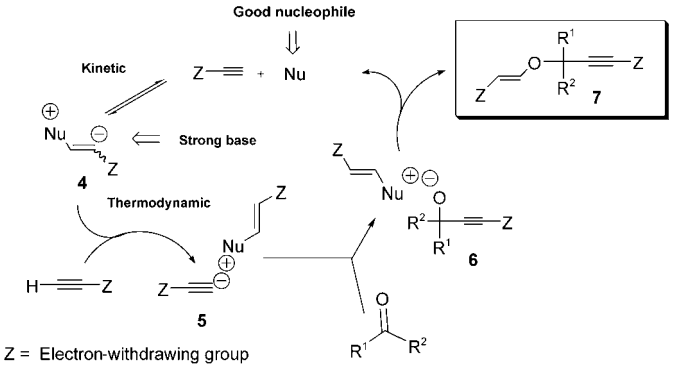
## Organocatalytic Generation of Conjugated Alkynylides

Nonmetalated conjugated alkynylides **1** (Scheme 1) are not easily accessible by conventional means.[3] Despite the several general approaches reported to the in situ catalytic generation of reactive metalated alkynylides,[4] there remains a paucity of non-metal-catalyzed generation of type **1** anions. Recently, Ishikawa and Saito reported on the organocatalytic generation of the ammonium acetylide **2** (Scheme 1).[5] The method utilizes a catalytic amount of benzyltrimethylammonium hydroxide in dimethyl sulfoxide to selectively deprotonate ethyl propiolate and other terminal alkynes in the presence of aldehydes and ketones to afford propargylic alcohols **3** (Scheme 1). Adducts **3**, incorporating a conjugated alkyne and a free hydroxyl group, constitute excellent building blocks for the productive construction of molecular complexity.[6] It would be more beneficial if these adducts could be generated in a domino format suitable for molecular diversity. Our approach to this challenge combines the two main chemical properties of terminal conjugated alkynes (Scheme 1): their relatively high acidity ($pK_a < 18.8$)[7] and their good Michael acceptor character.[8] This second property has been extensively exploited in heterocyclic construction through nucleophilic additions to conjugated triple bonds.[9] Our domino approach is outlined in Scheme 2.




Scheme 1. Reactivity pattern of terminal conjugated alkynes. EWG = electron-withdrawing group (also denoted by Z in further schemes).

The energetically-favoured nucleophilic addition to the terminal conjugated alkyne generates the zwitterionic intermediate **4** (kinetic reaction), which deprotonates the starting conjugated alkyne to generate the reactive acetylide salt **5** (thermodynamic reaction). Overall, a catalytic amount of a good nucleophile generates a catalytic amount of a strong base. Once formed, the reactive acetylide salt **5** adds to an




Scheme 2. Domino process based on the organocatalytic generation of conjugated alkynylides in the presence of aldehydes. A good nucleophile generates a strong base.

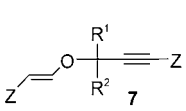
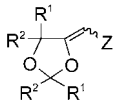
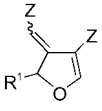
**Abstract in Spanish:** *La generación organocatalítica de una base fuerte por acción de un buen nucleófilo es la base para la generación in situ de aniones acetiluro conjugados en presencia tanto de aldehídos como de cetonas activadas. El método es abordable en un formato dominó multicomponente y genera un conjunto diverso de aductos altamente funcionalizados, muy adecuados para su utilización en construcción molecular orientada a la diversidad. El proceso dominó requiere un nucleófilo como catalizador y un alquino conjugado terminal (**H**−**C**≡**C**−**Z**) y un aldehído o cetona activada como elementos de construcción. El resultado de este proceso cambia dramáticamente en función del nucleófilo (aminas o fosfinas terciarias), la temperatura, la estequiometría y el disolvente. Estos procesos dominó multicomponente realizan construcciones moleculares con buena economía de átomo, y muy importante, con una exquisita quimio-diferenciada incorporación de idénticas unidades de reactivo en los productos finales (resultado químico no degenerado). Estas propiedades convierten a la unidad **H**−**C**≡**C**−**Z** en un elemento privilegiado de creación de diversidad molecular en procesos de construcción molecular orientados a la diversidad. Sus aplicaciones a la síntesis modular y orientada a la diversidad de moléculas heterocíclicas relevantes son discutidas. Un protocolo sintético constituido por dos procesos dominó acoplados y unidos en un formato monoetapa, se presenta como un modelo eficiente para la construcción modular y orientada a la diversidad de heterociclos nitrogenados polisustituidos.*

electrophile present in the reaction medium to give the expected addition products. Aldehydes or ketones bearing no protons with $pK_a < 18$ are good electrophiles and their adducts, propargylic alkoxides **6**, are themselves good nucleophiles for Michael addition to the reactive conjugated alkene counterion, affording enol-protected propargylic alcohol derivatives **7** and free nucleophile to restart the cycle.

Note the double role played by the catalyst in this domino process. It triggers the acetylide generation to launch the cycle and it catalyzes the Michael addition on the starting conjugated alkyne to terminate it. The catalyst performs both tasks through the formation of salt **5** (Scheme 2), which incorporates the two required reactive intermediates: the acetylide anion and the activated conjugated alkene counterion. The formation of this salt explains why terminal conjugated alkynes are not suitable substrates for catalytic Baylis–Hillman reactions.[10]

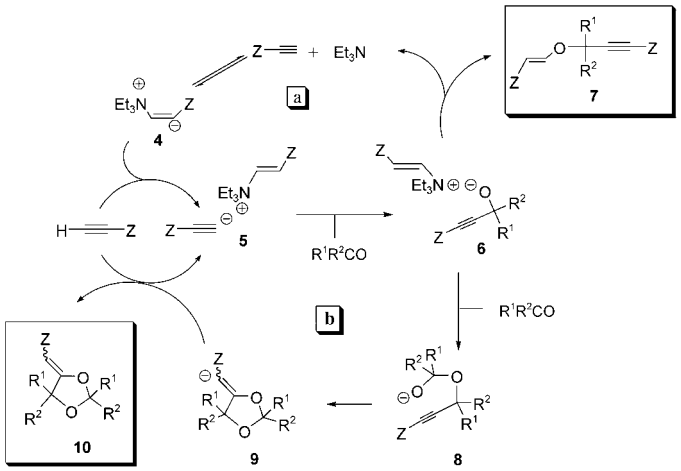
Pronucleophiles and aldehydes with $pK_a$ lower than 18 cannot be used under these conditions, because they inhibit the alkyne deprotonation, funnelling the chemical transformation toward the expected 1,4-nucleophilic addition (pronucleophile)[11] or aldolic reaction (aldehydes). We have successfully implemented this concept using trialkylamines or trialkylphosphines (organocatalysts) as the trigger nucleophile.[12]

Table 1. Intrinsic and extrinsic reaction values of domino processes **a**–**c**.[12]

| | Domino **a** | Domino **b** | | Domino **c** |
|---|---|---|---|---|
| |  **7** |  **10** | |  **16** |
| intrinsic reaction values | | | | |
| substrates | aldehydes | aldehydes | ketones | aldehydes |
| $R^1$ | alkyl | alkyl | Ph, $CF_3$ | alkyl |
| $R^2$ | H | H | 4-$CF_3$Ph | H |
| Z | COOR, $SO_2$Tol | COOR, COPh, $SO_2$Tol | | COOR |
| catalyst | DABCO, $Et_3N$ | $Et_3N$, $Bu_3P$ | | $R_3P$ ($pK_a \approx 8.5$) |
| solvent | wide tolerance | wide tolerance | | halogenated |
| selectivity | | 4 diastereoisomers | | regioselective |
| yield | 56–87 | 66–95 | | 40–70 |
| atom economy | high | high | | moderate |
| complexity | | 1 ring | | 1 ring |
| BFE[a] | 1 C–C, 1 C–O | 1 C–C, 2 C–O | | 2 C–C, 1 C–O |
| format | modular | modular | | modular |
| | diversity-oriented | diversity-oriented | | diversity-oriented |
| | multicomponent | multicomponent | | multicomponent |
| | | autocalytic | | |
| chemical inputs | degenerate | degenerate | | degenerate |
| | 2 HC≡C–EWG | 1 HC≡C–EWG | | 2 HC≡C–EWG |
| | 1 aldehyde | 2 aldehydes | | 1 aldehyde |
| | | (or 2 ketones) | | |
| chemical outputs | nondegenerate | nondegenerate | | nondegenerate |
| | chemo-differentiation | chemo-differentiation | | chemo-differentiation |
| extrinsic reaction values | | | | |
| solvent | technical grade | technical grade | | dry |
| atmosphere | air atmosphere | air atmosphere | | $N_2$ atmosphere |
| time | fast process | fast process | | fast process |
| cost | low | low | | low |
| waste | low | low | | low-moderate |
| processing | bench-friendly | bench-friendly | | bench-friendly |
| | simple | simple | | simple |
| | special precautions not required | | | |

[a] BFE = bond-forming efficiency.

**Different organocatalyst, different product**: 1,4-Diazabicyclo[2.2.2]octane (DABCO), a powerful amine nucleophile, catalyzes the reaction of aliphatic aldehydes with alkyl propiolates or alkynyl sulfones yielding enol-protected propargylic alcohols **7** with excellent atom economy (Table 1). Triethylamine, a milder amine nucleophile, also catalyzes this domino process efficiently affording a different set of products as a function of the reaction temperature and stoichiometry. At 0 °C, the expected compounds **7** are again formed with excellent atom economy. When temperature is lowered to −78 °C, a new domino process begins to operate funnelling the chemical transformation toward the formation of 1,3-dioxolane derivatives **10** (Scheme 3, cycle

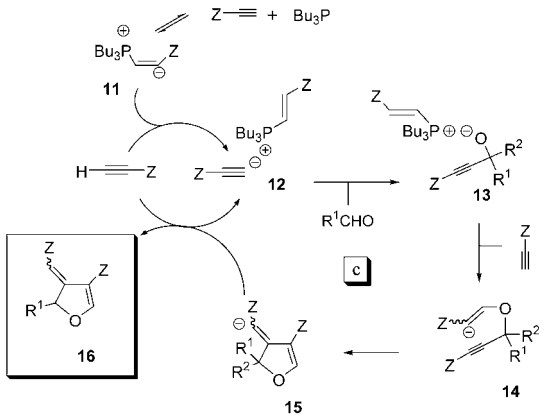



Scheme 3. Domino processes based on the organocatalytic generation of conjugated alkynylides in the presence of aldehydes and activated ketones. Changes in temperature and stoichiometry afford different sets of products.

**b**; see also Table 1). Dioxolanes are obtained in high yield as a mixture of the four possible diastereoisomers (*syn*/*anti*, *E*/*Z*). An interesting property of this new process is its autocatalytic nature: once alkoxide **6** is formed, it catalyzes its own synthesis by reaction with another molecule of aldehyde or ketone to give alkoxide **8**. Cyclization and alkyne deprotonation generates 1,3-dioxolane **10** and salt **5** to restart the cycle. In this set of reactions, the conjugated β-triethylammonium alkene displays a simple counterion function. Note that while triethylamine triggers the process, alkoxide **6** keeps it going.

Tertiary phosphines are more nucleophilic and less basic than their homologous tertiary amines and they exhibit different catalyst behavior. Remarkably, they catalyze the synthesis of 1,3-dioxolanes **10**, but they do not catalyze the synthesis of propargylic derivatives **7**. In non-halogenated solvents and at low temperature, tributylphosphine efficiently catalyzes the synthesis of 1,3-dioxolanes **10** (Scheme 3, $Bu_3P$ instead of $Et_3N$; also Table 1). Other trialkyl phosphines (isobutyl, *n*-octyl) are also suitable catalysts for this process. On the other hand, aromatic phoshines and phoshites do not show any catalyst activity. Remarkably, when the reactions are carried out in halogenated solvent, the chemical outcome of the process changes dramatically. A new domino process begins to operate funnelling the chemical transformation toward the formation of trisubstituted dihydrofurans **16** (Scheme 4, cycle **c**; Table 1). Note that in this




Scheme 4. Tributylphosphine-catalyzed domino synthesis of 2,3,4-trisubstituted dihydrofuranes from terminal conjugated alkynes and aldehydes.

process, the catalyst again performs two functions: triggering the domino process (generation of salt **12**) and activation of the starting alkynoate for Michael addition. The nature of this activation is unclear at the moment, but is strongly dependent on solvent and catalyst: only phosphines with $pK_a$ values around 8.5 are able to catalyze this process in halogenated solvents. Unfortunately, polymerization of the starting alkynoate is a resource-wasteful competitive reaction and it produces a deleterious effect on the overall yield.

**Chemo-differentiating incorporation of identical building blocks**: One remarkable property of these domino processes is the discrimination of identical starting materials through a chemo-differentiating incorporation into the products. In terms of diversity generation, it means that every domino process utilizes two identical starting units (degenerated chemical input) to construct highly functionalized products that contain a nondegenerated set of chemical functionalities. In other words: each chemical function incorporated into the product is chemically different from the other. This chemo-differentiating property converts the **H–C≡C–Z** unit into a specific building block for diversity-oriented molecular construction.

## Diversity-Oriented Molecular Construction

Compounds **7**, **10**, and **16** constitute highly functionalized molecular units that are well suited for using as scaffolds for diversity-oriented molecular construction (Figures 1 and 2).

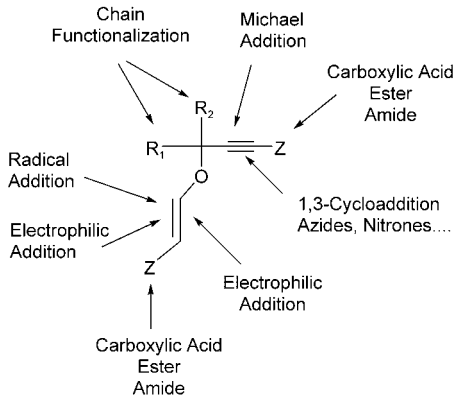



Figure 1. Reactivity pattern of the scaffolds **7**.

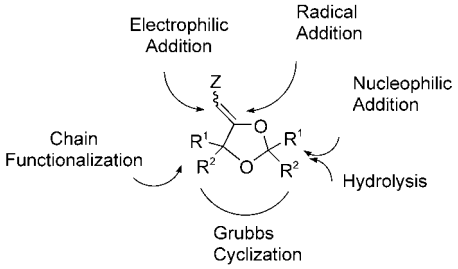
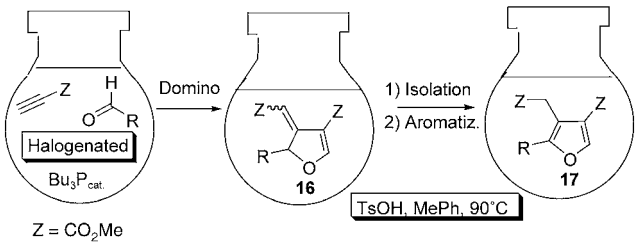



Figure 2. Reactivity pattern of the 1,3-dioxolanes **10**.

We have recently begun to explore the rich chemistry offered by these scaffolds. In particular, we have explored their use developing novel, metal-free, modular, and diversity-oriented synthesis of relevant heterocyclic scaffolds.

**Modular synthesis of 2,3,4-trisubstituted-furans**:[12a] Dihydrofurans **16** can be obtained as a mixture of *E*,*Z* isomers (Scheme 5) (Table 1). 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

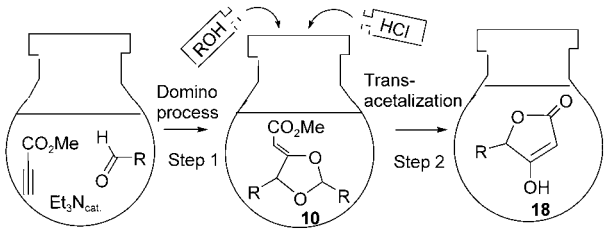



| R | Domino (%) | Aromatiz. (%) |
|---|---|---|
| *n*Pr | 44 | 92 |
| *i*Pr | 57 | 93 |
| *i*Bu | 48 | 91 |
| 3-Butenyl | 38 | 87 |

Scheme 5. Modular and diversity-oriented synthesis of 2,3,4-trisubsituted furans.

it mainly undergoes a slow aromatization to form the corresponding 2,3,4-trisubstituted furan **17**. This rearrangement is conveniently accelerated by acid treatment in hot toluene (Scheme 5). Overall, this procedure constitutes a metal-free, two-step, modular and diversity-oriented synthesis of 2,3,4-trisubstituted furans that are not easily obtained by other methods.[13,14] The chemical yields of these domino processes are not optimized, but they can be increased by using an excess of either aldehyde or alkynoate.[12a]

**Modular synthesis of 5-substituted tetronic acids**:[15] Acid-controlled trans-acetalization of 1,3-dioxolane derivatives **10** yields 5-substituted tetronic acids **18** in excellent yields. Linking this reaction to the organocatalyzed domino synthesis of 1,3-dioxolanes **10** allows us to obtain these molecules in a one-pot manner in good yields (Scheme 6). Linear, branched, and functionalized aldehydes are tolerated. In addition, the method is simple and bench-friendly. Once the domino process finishes, acid and alcohol are added to the same reaction flask and the reaction mixture is heated for 24 h to achieve complete trans-acetalization. Overall, it constitutes the first practical, metal-free, modular, and diversity-oriented one-pot synthesis of this family of biologically relevant molecules.[16]




| R | Tetronic acid (%) |
|---|---|
| Me | 69 |
| *n*Pr | 65 |
| *i*Pr | 65 |
| *t*Bu | 62 |
| 3-Butenyl | 58 |
| $BnOCH_2$ | 48 |

Scheme 6. Modular synthesis of 5-substituted tetronic acids (4-hydroxy-5H-furan-2-one).

**Coupling domino processes—an efficient approach to the modular construction of nitrogen-containing polysubstituted heterocycles**: We have approached this challenge through the development of coupled domino processes. Our design principle is based on the expected multiplicative effect on molecular complexity achieved by a chain of two or more coupled domino processes in the same reaction vessel. This approach requires the careful design of each of the participant domino processes. To be coupled in a chainlike manner, each domino process must generate a suitably functionalized molecule able to be simultaneously engaged in the subsequent complexity-generating domino process and so on. Experimentally, the transformation of this concept into a one-synthetic-step strategy is not a simple task due to the unattainable kinetic tuning of each of the numerous chemical reactions involved. A more feasible approach would consist in the transformation of this concept into a one-pot synthetic strategy. In this new scenario, the consecutive coupled domino processes should be performed one at a time and linked in a one-pot operation. We have successfully implemented this concept in a simple and practical experimental format. The syntheses of tetrasubstituted 1,3-oxazolidines **19** and tetrasubstituted pyrroles **20** constitute the first examples of this strategy.

**Tetrasubstituted 1,3-oxazolidines**:[17] 1,3-Oxazolidines **19** present a particular and interesting chemical topology. The molecule combines two biologically relevant structural motifs: an α,β-disubstituted 1,2-amino alcohol[18] and a latent β-substituted β-amino acid[19] (Figure 3). The masked

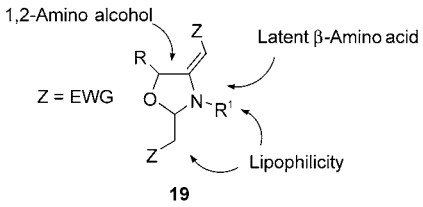
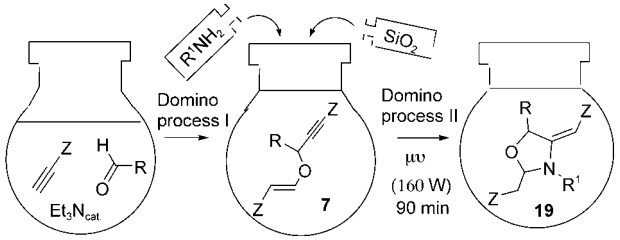



Figure 3. Biologically relevant structural motifs present in the 1,3-oxazolidines **19**.

form of this 1,2-amino alcohol functionality induces a lipophilicity enhancement that facilitates the drug delivery and, consequently, their favorable use as prodrugs.[20] Additionally, the heterocycle is an excellent platform to place pending chemical functionalities in an ordered three-dimensional array.

Our synthetic approach is outlined in Scheme 7. The protocol is composed of two coupled domino processes linked in a one-pot manner: an organocatalyzed domino synthesis of a propargylic scaffold **7** (domino I) and a microwave-assisted amine addition–cyclization domino process (domino II). The different chemical reactivity of the two α,β-unsaturated ester groups present in scaffold **7** addresses the se-




| Z | R | $R^1$ | μw (%) | $Yb^{3+}$ (%) |
|---|---|---|---|---|
| COOMe | Me | Bn | 60 | 71 |
| COOMe | Et | Bn | 58 | 70 |
| COOMe | Hex | Bn | 44 | 55 |
| COOMe | *i*Pr | Bn | 45 | 67 |
| COOMe | 4-Pentenyl | Bn | 49 | 54 |
| COOMe | *i*Pr | All | 36 | 65 |
| COOMe | *i*Pr | Bu | 30 | 68 |
| COOMe | Et | Ph | 45 | NR |
| COOMe | Et | *p*OMePh | 55 | NR |
| $SO_2$Tolyl | *i*Pr | Bn | | 54 |

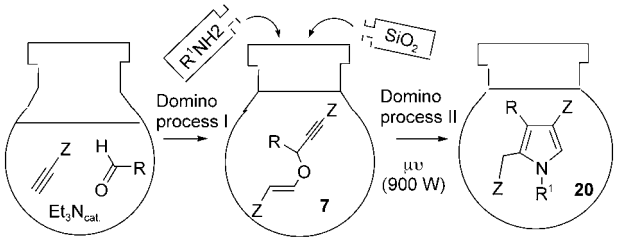
Scheme 7. Modular and diversity-oriented synthesis of tetrasubstitued 1,3-oxzolidines through two coupled domino processes.

lective 1,4-addition of the primary amine on the triple bond to launch the second domino process.

The synthetic protocol calls for an alkyl propiolate, an aliphatic aldehyde, and a primary amine. The method is mild enough to allow several functionalities on the aldehyde chain and it is quite general for the amine. Even aniline, a bad nucleophile, is able to produce the corresponding 1,3-oxazolidine **19** albeit with low atom efficiency: four equivalents of the amine are required to complete the reaction. Volatile amines are also tolerated, but they have to be used in excess to preclude material waste during the silica-gel absorption process. In these cases, the direct 1,2-addition of the amine on the ester function competes with the 1,4-addition on the triple bond, reducing the overall yield of the 1,3-oxazolidines. Overall, these two linked and coupled domino processes build up four new bonds and one ring in a very efficient manner and with a simple, bench and environmentally friendly reaction process. The first domino process does not require special caution with solvent or reagents; the microwave-assisted domino process is solvent-free. Once the first domino process is completed, silica gel and the primary amine are added to the reaction flask and the mixture is concentrated to dryness. The flask containing the solid mixture is placed in a domestic microwave oven and irradiated at 160 W for 90 min. Filtration and flash chromatography afford pure 1,3-oxazolidines **19**.

We have also developed a complementary version using a tandem Michael addition and ytterbium(III)-catalyzed cyclization reaction to transform linear scaffolds **7** in 1,3-oxazolidines **19**. The whole process is executed in a one-pot manner affording heterocycles **19** in higher yields than the microwave version (54–71%), although the amine versatility is reduced to aliphatic cases. In addition, ethynyl tolylsulfones are good substrates for this transformation and they afford 1,3-oxazolidines by simple heating of the respective propargylic derivative **7** and the primary amine.

**Tetrasubstituted pyrroles**:[21] Polysubstituted pyrroles are common pharmacophores of numerous natural antibiotics and alkaloids[22] and they have also found applications in the field of material chemistry.[23] Such properties are of considerable interest in the development of new efficient syntheses of these heterocycles. Among the plethora of methods available for pyrrole construction, metal-based strategies[24] and 1,3-dipolar cycloadditions[25] have received the most attention. In contrast, the number of examples reported in the literature dealing with metal-free, modular, and direct syntheses of these heterocycles is scarce.[26] A serendipitously discovered spontaneous rearrangement of 1,3-oxazolidines **19** to pyrroles **20** gave us the key for a novel modular and diversity-oriented synthesis of these important heterocycles. The protocol is outlined in Scheme 8. Microwave irradiation




| Z | R | $R^1$ | Pyrrol (%) |
|---|---|---|---|
| COOMe | Et | Bn | 44 |
| COOEt | Et | *p*OMePh | 53 |
| COOEt | Et | Bn | 51 |
| COOMe | Et | (*S*)-PHCHMe | 47 |
| COOEt | Et | Amino acid | 42 |
| COOEt | Hex | Bn | 47 |
| COOEt | 3-Butenyl | Bn | 41 |
| COOEt | Cit. | Bn | 49 |
| COOEt | *i*Pr | Bn | 46 |
| COOEt | *c*Pr | Bn | 46 |

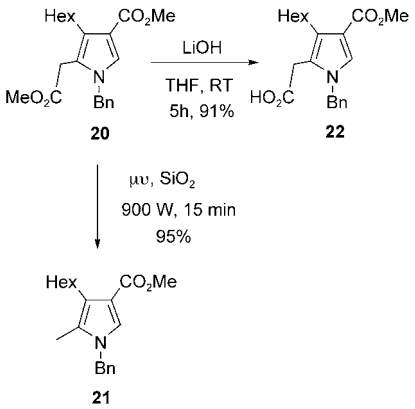
Amino acid = ethyl 3-aminobutyrate
Cit. = (*S*)-(–)-citronellal

Scheme 8. Modular and diversity-oriented synthesis of tetrasubstitued pyrroles through two coupled domino processes.

of a silica-gel-absorbed mixture of scaffold **7** and primary amine affords pyrroles **20** in good yields. Oxazolidines **19** are transient intermediates in this domino process. The method tolerates a wide scope in the primary amine (aromatic, aliphatic, amino acids, etc.) and it is sufficiently mild to allow a range of functionalities on the aldehyde chain.

Overall, these two linked and coupled domino processes build up two C–C bonds, two C–N bonds and an aromatic ring in a regioselective and efficient manner. The overall yields range from 44 to 53%, reflecting the high chemical efficiency of each of the reactions involved (at least nine reactions with a >90% average yield).

In addition, the aliphatic ester group of pyrroles **20** can be selectively submitted to a microwave-assisted reductive decarboxylation to give **21** or selectively hydrolyzed to the monoacid **22** to generate a new functional-diversity point on the molecule (Scheme 9).



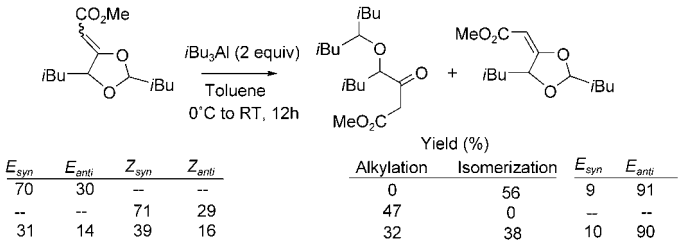

Scheme 9. Generation of a new functional-diversity point on the pyrrole molecule by microwave-assisted reductive decarboxylation or selective hydrolysis of the aliphatic ester group.

## Outlook

We have just begun to explore the vast chemical space accessible with this chemical methodology. The trees of chemical transformation outlined in Figure 1 show the large number of different chemical transformations we can assay with these scaffolds to cover unrevealed and/or biological coincident areas of the vast chemical space.

The asymmetric version of these catalytic domino processes remains to be implemented. It is expected that all the recent achievements in asymmetric organocatalysis and asymmetric phase-transfer catalysis can be applied here. Although our preliminary results are positive and encouraging, hard work remains to be done. In close connection, the role played by tributylphosphine in halogenated solvents catalyzing the synthesis of dihydrofurans **16** remains elusive. Our working hypothesis relies on the idea of a phosphonium-mediated activation of the triple bond, but other approaches have not been discarded.

We have shown how the chemo-differentiated incorporation of reagents into products converts the **H−C≡C−Z** unit into a specific building block for diversity-oriented molecular construction. This property is also inherent in domino processes type **b** (Scheme 3): two identical aldehydes (or ketones) units are incorporated into 1,3-dioxolanes **10** in the form of two chemo-differentiated ethers. Dioxolanes **10** are generated as a mixture of the four possible diastereomers (*syn*/*anti*, *E*/*Z*). Interestingly, the double-bond geometry controls the reactivity of the acetal center and can therefore be used as a control element in reactions involving this center. This geometrical property converts these dioxolanes into potential substrates for the development of skeletal-diversity-generating reactions.[27] Preliminary results are very encouraging. Scheme 10 shows an example of this idea.




| $E_{syn}$ | $E_{anti}$ | $Z_{syn}$ | $Z_{anti}$ |
|---|---|---|---|
| 70 | 30 | -- | -- |
| -- | -- | 71 | 29 |
| 31 | 14 | 39 | 16 |

| Yield (%) | | | |
|---|---|---|---|
| Alkylation | Isomerization | $E_{syn}$ | $E_{anti}$ |
| 0 | 56 | 9 | 91 |
| 47 | 0 | -- | -- |
| 32 | 38 | 10 | 90 |

Only the *Z* isomer participates in the reaction!!

Scheme 10. A mixture of four diastereoisomers exposed to the same reaction conditions is resolved into two structurally different products.

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