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Propargyl vinyl ethers and tertiary skipped diynes: two pluripotent molecular platforms for diversity-oriented synthesis.

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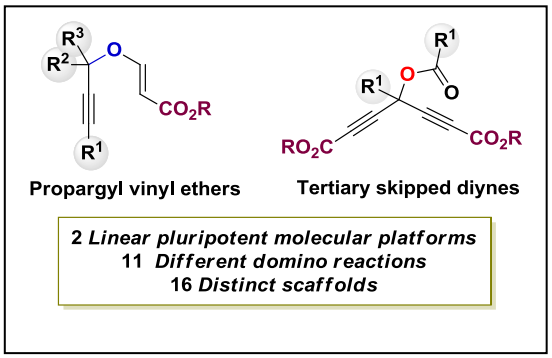


CONSPECTUS. During the last years, we have been involved in the development of a diversity-oriented synthetic strategy aimed to transform simple, linear and densely functionalized molecular platforms into collections of topologically diverse scaffolds incorporating biologically relevant structural motives such as N- and O- heterocycles, multifunctionalized aromatic rings, fused macrocycles, etc. The strategy merges the concepts of pluripotency (the property of an array of chemical functionalities to express different chemical outcomes under different chemical environments) and domino chemistry (chemistry based on

processes involving two or more bond-forming transformations that take place while the initial reaction conditions are maintained, with the subsequent reaction resulting as a consequence of the functionality installed in the previous one) to transform common multifunctional substrates into complex and diverse molecular frameworks. This designing concept constitutes the ethos of the so-called branching cascade strategy, a branched of diversity-oriented synthesis focused on the scaffold diversity generation. Two pluripotent molecular platforms have been extensively studied under this merging (branching) paradigm: C_4-O-C_3 propargyl vinyl ethers (PVEs)**1** and C_7 tertiary skipped diyne (TSDs) **2**. These are conveniently constructed from simple and commercially available raw materials (alkyl propiolate, ketones, aldehydes, acid chlorides) through multicomponent manifolds (ABB' three-component reaction for PVEs; A_2BB' four-component reaction for TSDs) or a simple two-step procedure (for PVEs). Their modular origin facilitates their structural/functional diversification without increasing the number of synthetic steps for their assembling. These two pluripotent molecular platforms accommodate a well-defined and dense array of through-bond/through-space interrelated functionalities on their structures, which defines their primary reactivity principles and establishes the reactivity profile. The PVEs are defined by the presence of an alkyne (alkynoate) function and a conjugated enol moiety and their mutual through-bond/through-space connectivity. This functional array accommodates a number of domino reactions launched either by a Michael addition on the alkynoate moiety (conjugated alkynes) or by a [3,3]-propargyl Claisen rearrangement (conjugated and nonconjugated alkynes). The reactivity profile of the TSDs is defined by the two connected alkynoate moieties (Michael addition) and the bispropargylic ester group ([3,3]-sigmatropic rearrangement). Using these first reactivity principles, each platform selectively delivers one unique and different skeleton (topology) from each domino transformation. Thus,

through the use of 11 instrumentally simple and scalable domino reactions, we have transformed these two linear (rod-symmetrical) pluripotent molecular platforms into 16 different scaffolds incorporating important structural motives and multifunctional decorative patterns. The generated scaffolds entail carbocycles, heterocycles, aromatics, β,γ-unsaturated esters and acids and fused polycycles. They can be transformed into more elaborated molecular skeletons by the use of chemical handles generated in the own domino reaction or by appending different functionalities to the pluripotent molecular platform (secondary reactivity principles).

1. Introduction

The generation of chemical libraries with skeletal (scaffold) and stereochemical diversity remains as one of the current challenges in diversity-oriented synthesis (DOS) programs.[1] During the past decade, several DOS strategies have been designed to overcome this huge task.[2] Among these, the most transited one is the so-called build/couple/pair (B/C/P) algorithm[3] which exploits the combination of simple building blocks to generate structurally diverse libraries of small molecules. The power of this strategy was elegantly demonstrated by Nelson and co-workers[4] in the synthesis of a library incorporating 84 different molecular skeletons. The B/C/P strategy incorporates other previously developed DOS approaches such as the so-called substrate-based (folding) and reagent-based (branching) approaches.[5] In the folding approach, different substrates are transformed into different products under the same reaction conditions. On the other hand, the reagent-based or branching approach relies on the transformation of a common substrate (building platform) into an array of diverse and distinct molecular architectures (skeletons) by application of either different reactants or different reaction conditions (reagent-based differentiation) (Figure 1). In general, the latter approach uses a densely functionalized

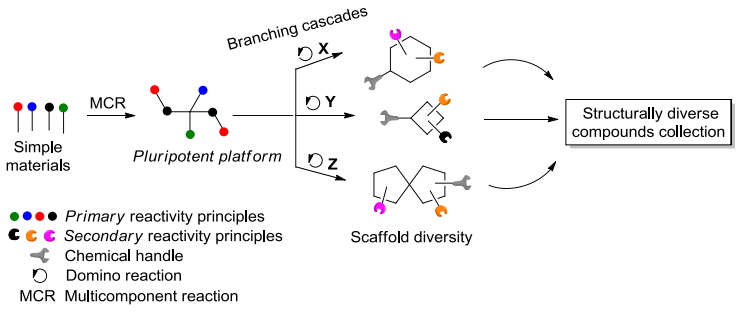


Figure 1. Pluripotent platforms in DOS

substrate (pluripotent molecular platform) to generate a set of distinct molecular frameworks, each equipped with a set of strategically placed functionalities for use in a new round of complexity-generating or branching reactions. Central to this approach is the design of the pluripotent molecular platform, which should ideally: (1) be well-suited for the development of domino chemistry, (2) support the maximum functionality on the minimum skeletal connectivity (high functional density), (3) provide simple, modular and direct access, (4) have a pluripotent reactivity profile able to afford different chemical outcomes under different chemical environments, (5) deliver a unique molecular skeleton per chemical outcome, and finally, (6) endow these skeletons with chemical handles for further generation of complexity and/or diversity. The design and synthesis of such platforms is not an easy task. Multicomponent reactions are very well suited to achieve this synthetic challenge, although their use in B/C/P strategies remains scarce.[6] Merging pluripotency with domino chemistry is a very appealing and powerful reagent-based DOS strategy that has been successfully used by different research groups (Figure 1).[7] This designing concept constitutes the ethos of the so-called branching cascade strategy,[8] a branched DOS process that utilizes cascade (domino) reaction sequences to transform a common multifunctional substrate into complex and diverse molecular frameworks. The synthetic power of this approach has been elegantly demonstrated by Stockman and co-

workers[9] who drove the transformation of the rod-symmetrical (2*E*,11*E*)-diethyl 7-oxotrideca-2,11-dienedioate platform in 12 different natural-product-like scaffolds using just 12 different tandem reactions. Kumar and co-workers[10] recently described a novel branching cascade approach to transform three simple acyclic substrates into 17 distinct scaffolds using domino chemistry and a two-phase building process.

During the past decade, we have been involved in a research program aimed at the domino transformation of acyclic pluripotent platforms **1** (propargyl vinyl ethers, PVEs) and **2** (tertiary skipped diynes, TSDs) into more complex scaffolds for library synthesis (Figure 2). Overall, we have generated 16 different scaffolds using 11 different domino reactions taking advantage of the reactivity profile encoded into these platforms (primary reactivity principles; Figure 3). The generated scaffolds entail carbocycles, heterocycles, aromatics, β,γ-unsaturated esters and acids and fused polycycles. Through the use of chemical handles generated in their own domino processes or by appending different orthogonal functionalities to the pluripotent platform (secondary reactivity principles), these scaffolds are susceptible to being transformed into more elaborated three-dimensional molecular skeletons, natural-product-like chemotypes, or privileged-pharmacophore structures featuring novel functionalization patterns adorning the structure (e.g. 3,5,8-trisubstituted coumarin derivatives[11]) (Figure 2; inset).

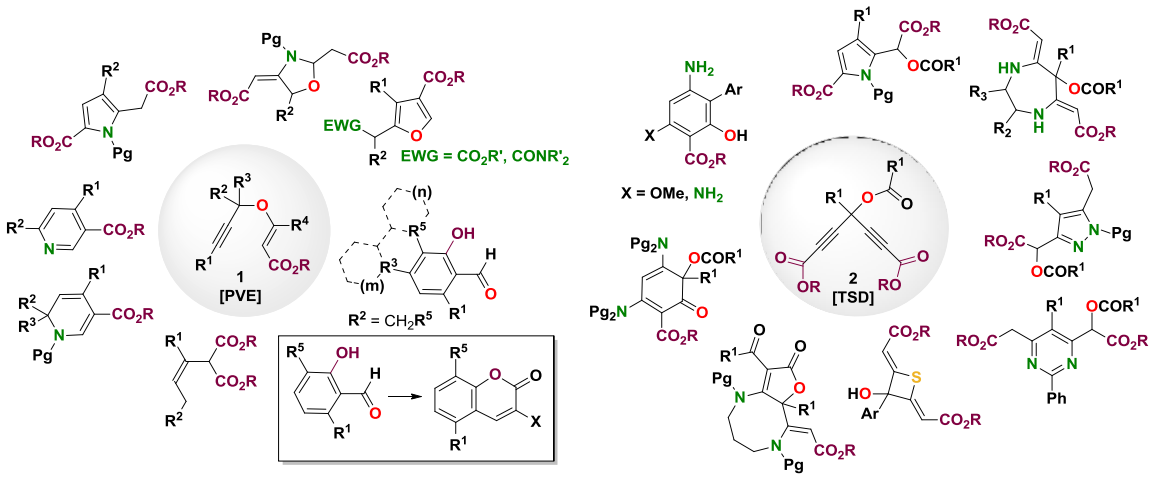
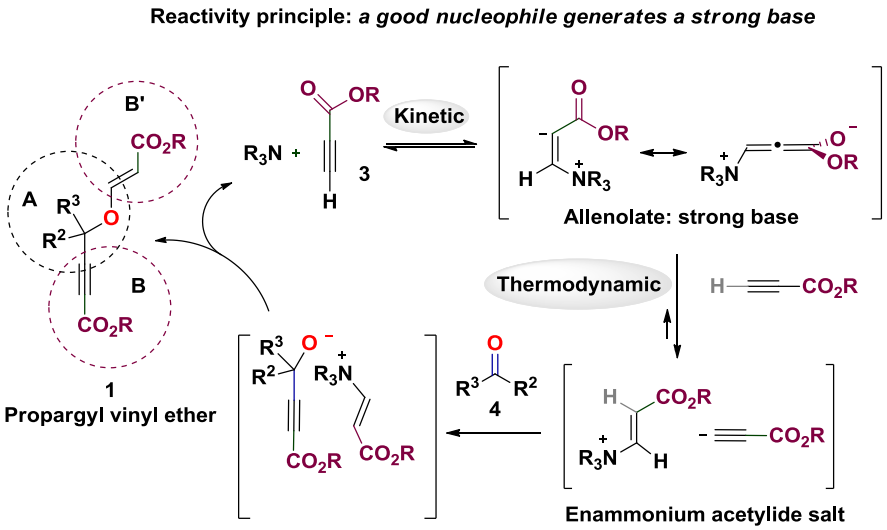


Figure 2. Transformations of pluripotent platforms **1** and **2**.

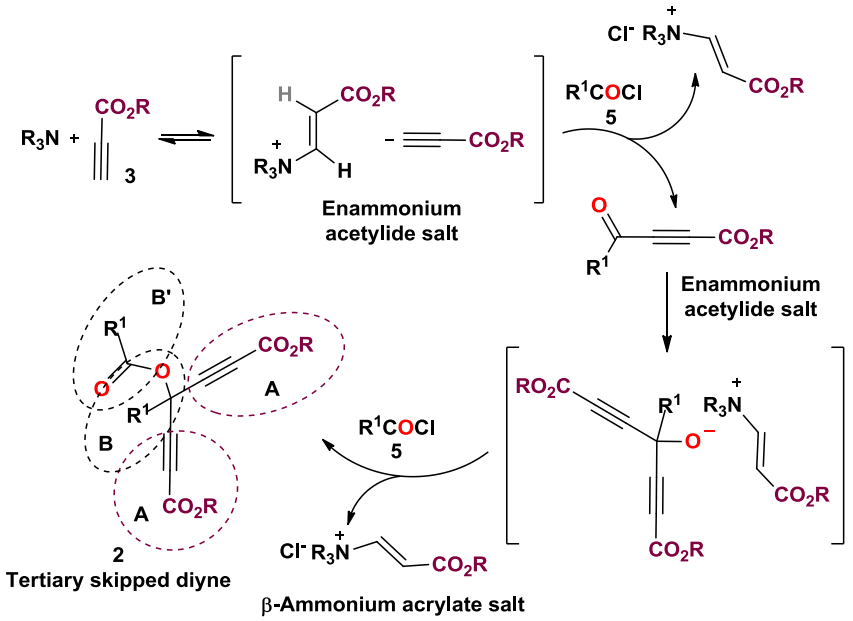
2. Synthesis and reactivity profile of PVEs and TSDs.

In 2003, we reported a novel domino process based on the in situ generation of a strong base (thermodynamic concept) by a good nucleophile (kinetic concept).[12] The domino manifold delivered PVEs **1** through the tertiary-amine-catalyzed coupling of two units of alkyl propiolate **3** and one unit of aldehyde **4** (or activated ketone) (Scheme 1).[13] The manifold was coined an ABB' three-component reaction (ABB' 3CR)[14] because one unit of aldehyde (component A) and two differentiated units of alkyl propiolate (components B and B') were incorporated into the final PVE **1**. The singularity of this reaction manifold relied on the chemodifferentiation of the two alkyl propiolate units via the formation of an enammonium acetylide salt.[15]

The reaction manifold could be extended to more highly oxidized carbonyl derivatives (i.e. acid chloride **5**) to deliver the corresponding TSDs **2** using the same reactivity principle but under noncatalytic conditions (A_2BB' 4CR, Scheme 2).[16] In these cases, the nucleophile cannot be regenerated along the reaction pathway and it remains in the reaction media in the form of a β-ammonium acrylate salt.



Scheme 1. ABB' 3MCR.



Scheme 2. AABB' 4MCR.

PVEs without the alkyne conjugation ($R^1 \neq CO_2R$; Figure 2) can be easily prepared by the DABCO-catalyzed addition of the corresponding propargyl alcohol on the alkyl propiolate (95-99% average yield).[17]

Both PVEs **1** and TSDs **2** accommodate a dense and interrelated functional array encoding a well-defined reactivity profile. For the PVE platforms, the profile is defined by the presence of an alkyne (alkynoate) function and a conjugated enol moiety and their through-bond/through-space connectivity (Figure 3a). A remarkable property of the PVEs armed with an alkynoate function is the orthogonal reactivity of the two unsaturated functionalities present in the platform: whereas the alkynoate behaves as an electron-deficient group, the conjugated enol acts as an electron-rich one. This allows the development of chemoselective chemistry on these structures using simple and standard chemistry (Michael additions, electrophilic additions). The ability of these C_4-O-C_3 functional arrays to afford [3,3]-propargyl Claisen rearrangements ([3,3]-PCRs) has been profusely demonstrated during the past decade,[18] and it constitutes the most important and versatile primary reactivity principle encoded in these platforms. With regard to the TSD platforms, the primary reactivity principles are defined by the expected Michael-acceptor character of the two alkynoate moieties, their through-bond/through-space connectivity, and the propensity of propargyl esters to carry out [3,3]-sigmatropic rearrangements (Figure 3b).[19] Using these primary reactivity principles, we have developed 11 different domino manifolds that have been categorized into two general types attending to the nature of the triggering reaction of the domino process:

(a) [$\mathbf{a^3}$]-triggered domino manifolds, which are launched by a Michael addition on the alkynoate moiety and can be performed on both platforms;

(b) [**PCR**]-triggered domino manifolds, which are triggered by the thermal [3,3]–propargyl Claisen rearrangement of the PVE platform.

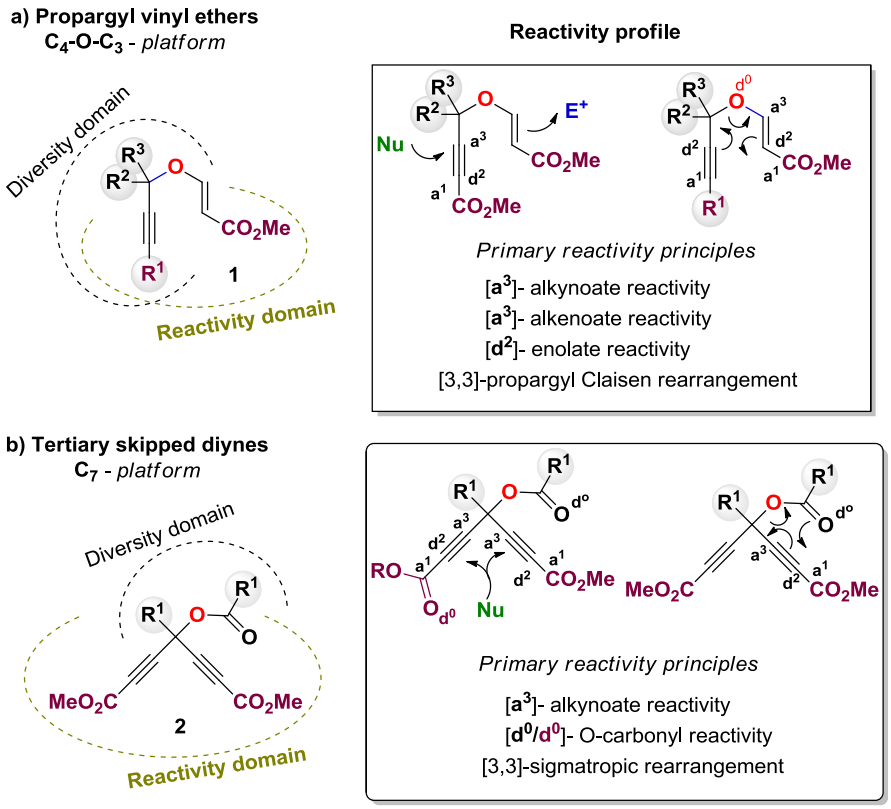


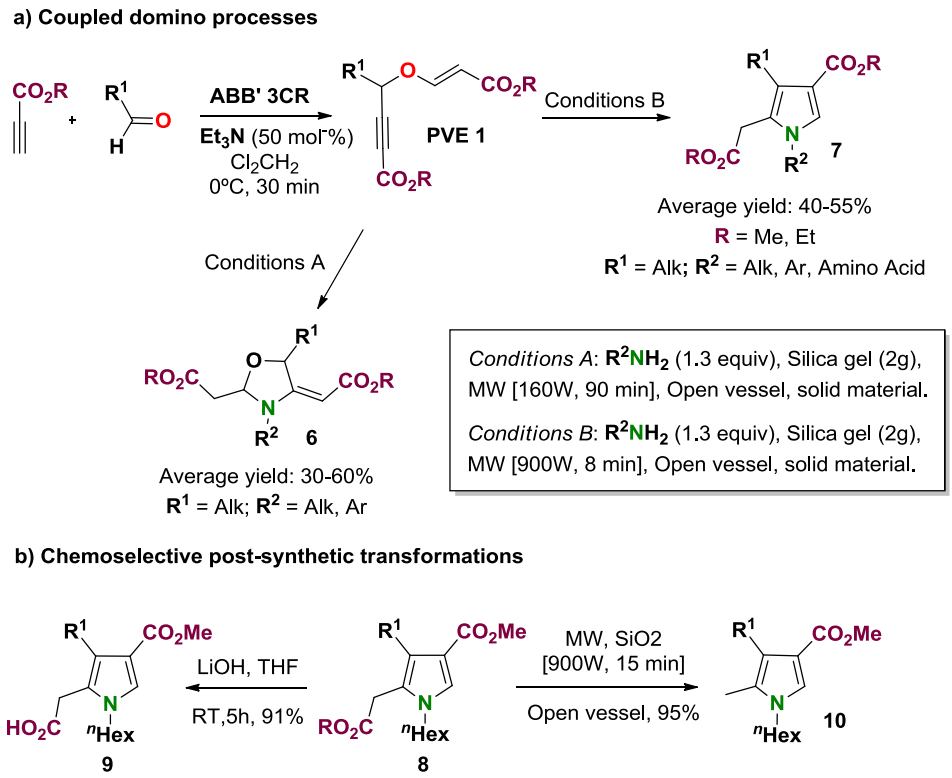
Figure 3. Reactivity profiles of pluripotent platforms **1** and **2**.

3. [a^3]-Triggered domino manifolds.

3.1 Coupled domino processes (Michael addition/cyclization/rearrangement): transforming PVEs into 1,3-oxazolidines and pyrroles.

Fully conjugated PVEs (R^1 = ester) reacted with primary amines under microwave (MW) heating to afford 1,3-oxazolidine derivatives **6**[20] or substituted pyrroles **7**.[21] The latter transformation was discovered by serendipity when samples of 1,3-oxazolidine derivatives **6** were transformed into the corresponding pyrrole derivatives **7** upon standing over long period of time. After a deep experimental study, we arrived at a domino manifold that could selectively deliver 1,3-oxazolidines **6** or the pyrroles **7** by a careful design of the experimental conditions. The protocol

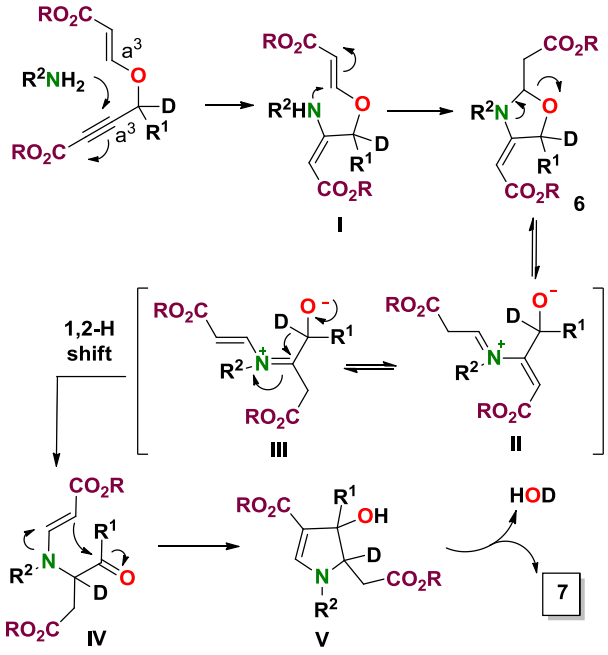
entailed two coupled domino processes performed in one-pot manner: first an ABB' 3CR to assemble the PVE platform from the corresponding aldehyde and alkyl propiolate and then a MW-assisted domino reaction of the PVE with a primary amine, both supported on silica gel. The coupled domino manifold selectively afforded 1,3-oxazolidine derivatives **6** or pyrrole derivatives **7** as a function of the power and extent of the MW irradiation (Scheme 3). While controlled heating of a silica-supported mixture of the PVE and the primary amine at 160 W (MW domestic oven, 90 min) afforded the corresponding 1,3-oxazolidine **6**,[20] stronger irradiation (900 W, 8 min) delivered the corresponding pyrrole **7**.[21a] The reaction showed a wide tolerance to both the primary amine and the aliphatic aldehyde (Scheme 3a). The reaction installed two chemically differentiated ester groups on the pyrrole ring (chemical handles, secondary reactivity principles) that could be submitted to selective hydrolysis or



Scheme 3. Synthesis of 1,3-oxazolidines **6** and pyrroles **7** from PVEs.

decarboxylation (Scheme 3b) using simple and standard chemistry in the former case or MW heating in the latter. These post-synthetic transformations allow the functional diversity of these derivatives to be increased and new reactivity motifs to be introduced for a subsequent round of complexity/diversity-generating reactions.

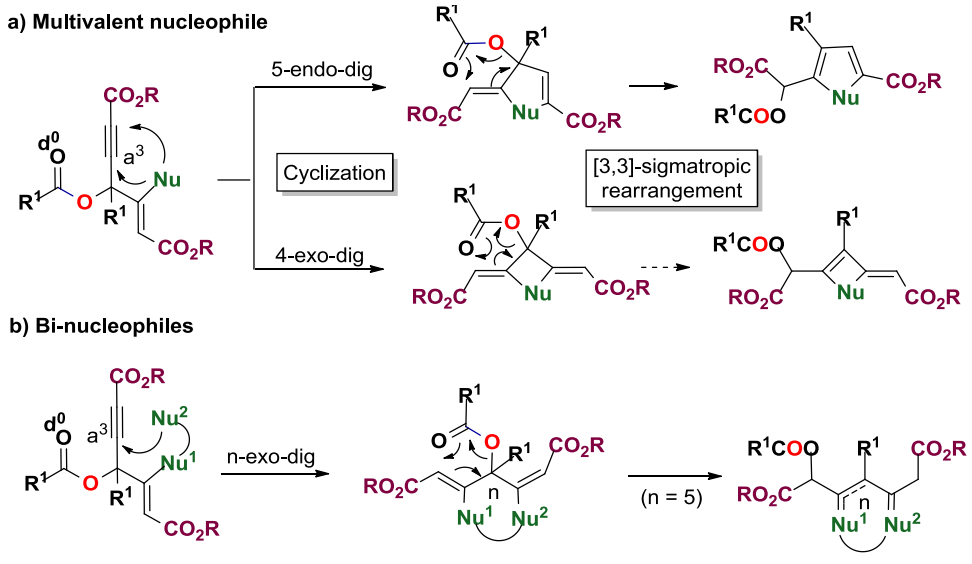
The mechanistic proposal for this rearrangement is outlined in Scheme 4. Once the 1,3-oxazolidine core forms (the nucleophilic addition on the $\mathbf{a}^3$-alkenoate position needs heating to proceed), it rearranges to pyrrole derivative **7** via enamine **IV**. The postulated [1,2]-hydride shift was confirmed by using d_4-acetaldehyde as the carbonyl component, which only incorporated only three deuterium labels at the methyl position of the pyrrole product ($R^1 = CD_3$). The fourth deuterium label was lost in the aromatization step, as it would be expected from the proposed mechanism.



Scheme 4. Mechanistic proposal for the formation of **7**.

3.2 Nucleophile-driven domino process (Michael addition/cyclization/[3,3]-sigmatropic rearrangement): transforming TSDs into a carousel of heterocyclic compounds.

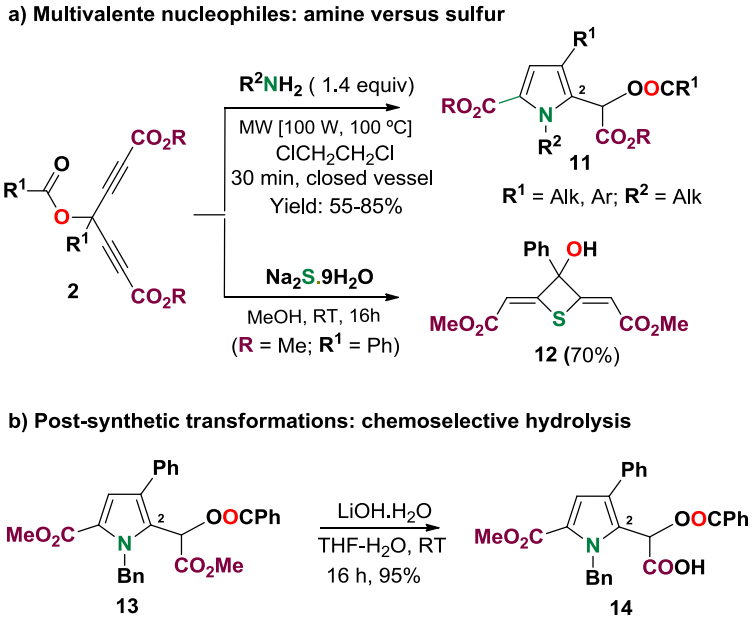
The chemical cartography of these domino processes is outlined in Scheme 5. For the case of multivalent nucleophiles (nucleophiles that can donate more than one pair of electrons; i.e., N, S) (Scheme 5a), once they add to the platform, they can perform a 4-exo-dig cyclization to construct a four-membered ring (entropically disfavored according to Baldwin´s rules), or the alternative 5-endo-dig cyclization (anti-Michael addition) to render the five-membererd ring (entropically favored but electronically disfavored). The latter one calls for the alkynoate deconjugation before the cyclization can proceed and requires energy (MW heating). The domino process concludes with a [3,3]-sigmatropic rearrangement of the allylic ester functionality, which generates an α-acyl(aroyl)oxy acetate chain and breaks the initial symmetry of the TSD platform. The driving force for this rearrangement is the generation of aromaticity in the final product.



Scheme 5. Domino reactions of TSDs with multivalent nucleophiles and binucleophiles.

When the nucleophilic entity entails two nucleophiles (binucleophile, **Nu^1-Nu^2**) (e.g., hydrazines, imidines, or 1,n-diamines) (Scheme 5b), then the second nucleophile executes the cyclization through a convenient and allowed *n*-exo-dig process (*n* = 5, 6 or 7) to deliver the corresponding *n*-membered heterocycle ring. The final [3,3]-sigmatropic rearrangement is observed only in those cases in which aromaticity is generated (*n* = 5 or 6).

Reaction with multivalent nucleophiles. The MW-assisted reaction of primary amines with TSDs **2** afforded the corresponding pyrroles **11** in good yields (55-85%) (Scheme 6).[22] As expected, the 5-endo-dig cyclization needed energy (MW heating) to proceed, being the rate-limiting step of the domino process (the cyclization requires alkynoate deconjugation). On the other hand, sodium sulfide, a larger and bivalent nucleophile, generated the corresponding thietane **12** in 70% yield at room temperature.[23] The larger size of sulfur compared to nitrogen enables this otherwise entropically disfavored cyclization. It is likely that basic hydrolysis of the

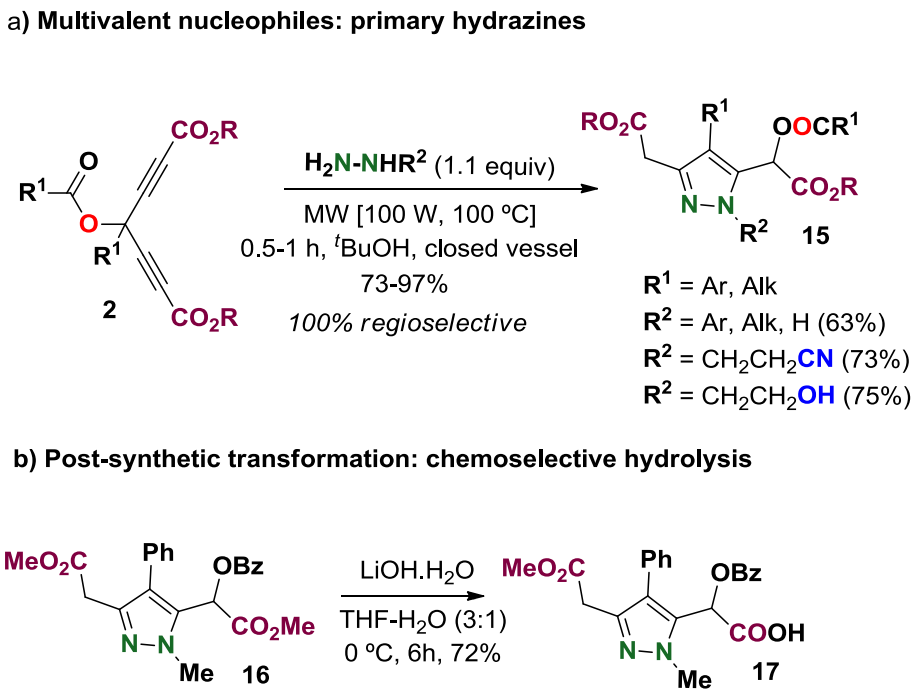


Scheme 6. Reactions of TSDs with multivalent nucleophiles.

allylic ester group delivers the corresponding alcohol and avoids the otherwise expected [3,3]-sigmatropic rearrangement.

Electronic effects allowed chemoselective hydrolysis of the aliphatic ester to give the carboxylic acid **14** (95%) under standard conditions (LiOH/THF-H_2O) (Scheme 6b). Monoacid **14** constitutes a good example of a substrate with a chemical handle for increasing the functional diversity (e.g., COOH → $COONR_2$) and/or optimization of its reactivity profile for further development of complexity-generating reactions.

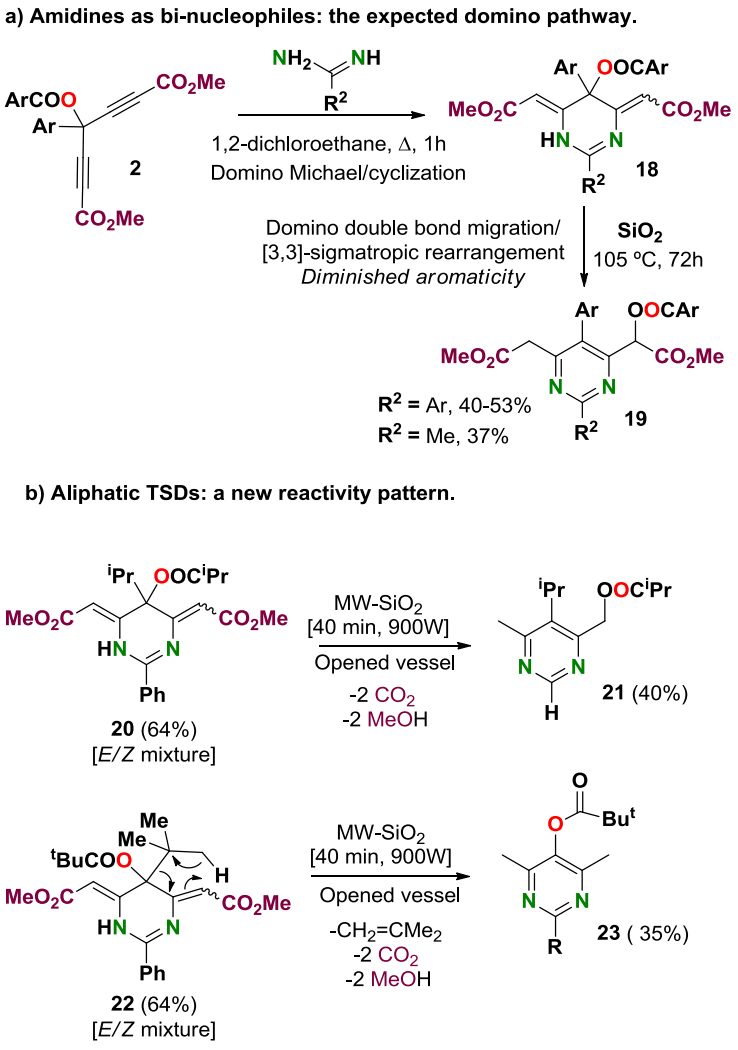
Reaction with bi-nucleophiles. When N-substituted hydrazines (**R^2NH-NH_2**) were used as the binucleophiles, the domino manifold delivered the pyrazoles **15** in good to excellent yields (73-97%) (Scheme 7a).[24] The diminished aromatic character of pyrazoles compared with pyrroles changed the rate limiting step of the domino process to the [3,3]-sigmatropic rearrangement (the non-rearranged N-substituted-4-aryl-4-aroyl-4,5-dihydro-1H-pyrazole intermediate could be isolated when the reaction was run at room temperature). The reaction proved to be completely regioselective (only the regioisomer with the α-substituted acetate chain in ortho position relative to the substituted nitrogen ring was obtained) and tolerant of a wide variety of substituents on both the hydrazine and the TSD. The derivatives armed with R^2 = CH_2CH_2**CN** and CH_2CH_2**OH** may be highlighted because they constitute well-suited candidates for pairing reactions with the substituted acetate chain. Selective hydrolysis of the methyl α-acyloxy (aroyloxy) acetate to give the corresponding monoacids (e.g. **17,** 72%) enabled the generation of an orthogonal chemical handle for further generation of diversity/complexity (Scheme 7b).



Scheme 7. Transformation of TSDs into pyrazoles **15**.

Unsubstituted amidines reacted with aromatic TSDs **2** (R^1 = Ar) to form the corresponding fully substituted pyrimidines **19**,[25] but the reduced aromaticity of the pyrimidine ring called for a one-pot coupled domino process (Scheme 8a). Once the six-membered ring was formed, the subsequent domino reaction (double bond migration and sigmatropic rearrangement) required acid assistance (silica gel), prolonged heating and solventless conditions to deliver the corresponding pyrimidine ring in 40-53% overall yield.

A novel reactivity pattern was uncovered in the reaction of alkyl-substituted TSDs **2** (R^1 = ^{i}Pr, ^{t}Bu) and benzimidamide (R^2 = Ph) (Scheme 8b). The MW irradiation of adduct **20** supported on silica gel (open vessel) generated the pyrimidine derivative **21** (40%) via a domino process

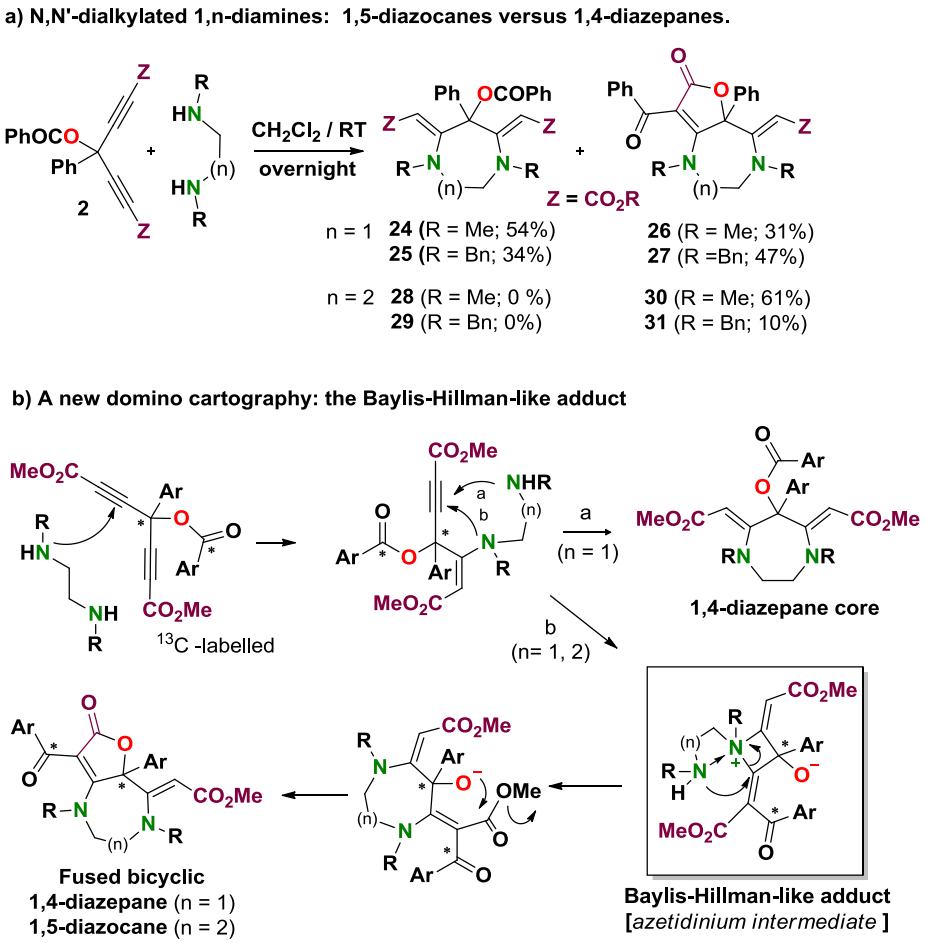


Scheme 8. Transformation of TSD into amidines **19**, **21** and **23**.

entailing two extra decarboxylation steps; on the other hand, when the same conditions were applied to the ^{t}Bu-containing derivative **22**, the 4,6-dimethyl substituted pyrimidine **23** was obtained in 35% yield. In this case, an unexpected aromatization process involving the loss of isobutene occurred instead of the expected [3,3]-sigmatropic rearrangement.

When an N,N'-dialkyl 1,2-diamines were used as the binucleophile (Scheme 9a; *n* =1), the reaction gave a mixture of expected 1,4-diazepane derivatives **24** (R = Me, 54%) or **25** (R = Bn; 34%) and the unexpected fused bicyclic scaffolds **26** (R = Me; 31%) or **27** (R = Bn; 47%).[26]

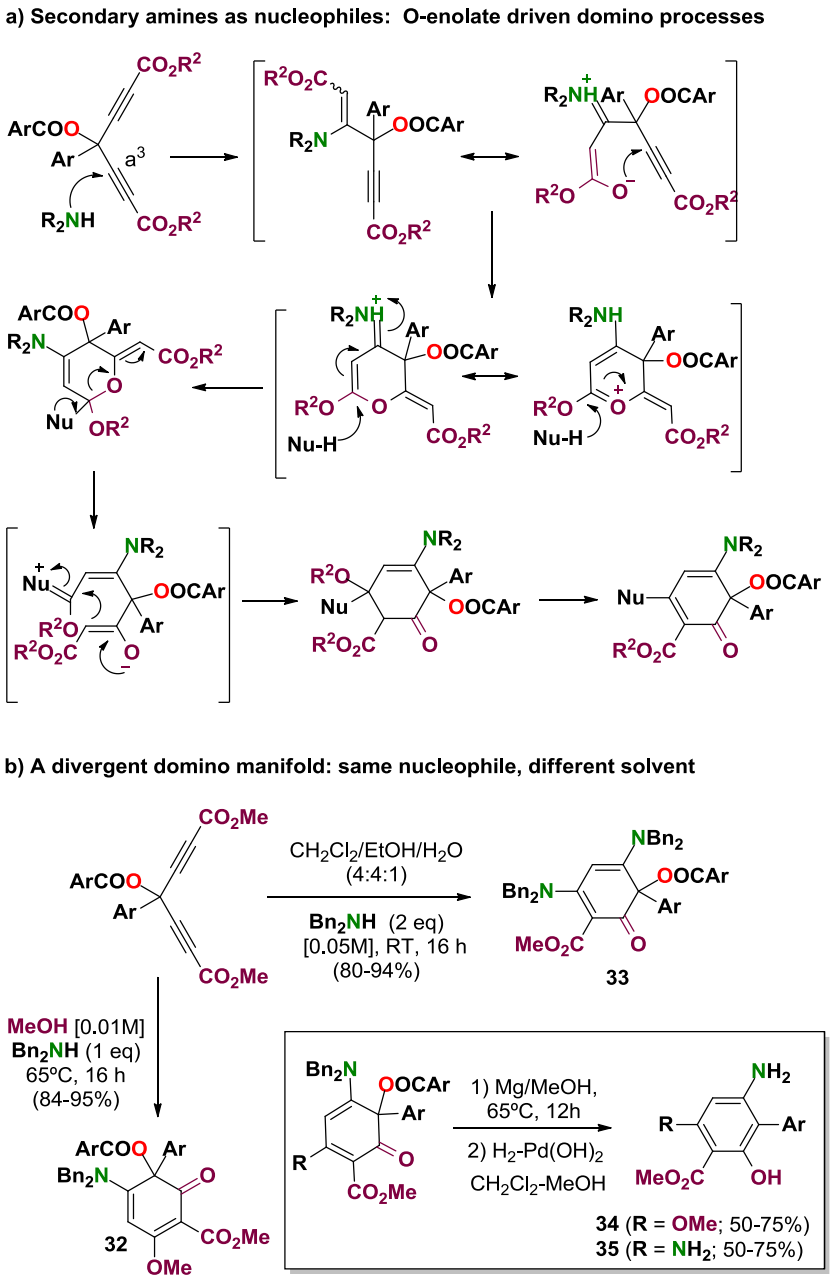
On the contrary, the use of an N,N'-dialkyl 1,3-diamine as the binucleophile (n = 2), selectively delivered the 1,5-diazocane derivatives **30** (R = Me; 61%) or **31** (R = Bn; 10%). The selective formation of the 1,5-diazocane **30** can be explained by the favored formation of a Baylis-Hillman-like adduct intermediate (azetidinium intermediate; Scheme 9b), which allows the formation of the otherwise kinetically disfavored eight-membered ring (the use of a doubly ^{13}C-labeled TSD derivative confirmed this rearrangement). A through-space electronic nitrogen-nitrogen interaction is thought to be responsible for the formation of this azetidinium intermediate. This interaction is strong enough to compete with the kinetically favored 7-exo-dig cyclization process (n = 1), delivering mixtures of **24**/**26 (**1.7/1) and **25**/**27** (0.7/1). The novel fused bicyclic 1,5-diazocane scaffold incorporates well appreciated pharmacophores into its structure (i.e., the butanolide ring and the 4-aminotetronic moiety). Although the synthetic scope of the reaction seems to be limited to N,N'-dimethyl (dibenzyl) 1,2-diamine and N,N'-dimethyl 1,3-diamine and aromatic TSDs (4-ClPh and 4-MePh afforded the corresponding fused bicyclic 1,5-diazocanes in 59 and 60% yields), the structure of the fused bicyclic scaffold and the novelty of the domino mechanism give importance to this chemical transformation. It is interesting to note that in these reaction manifolds, the [3,3]-sigmatropic rearrangement did not occur even when the 1,4-diazepane derivative was heated under MW irradiation. This fact confirmed that the sigmatropic rearrangement is driven by the final aromatization of the product.



Scheme 9. Reaction of TSDs with N,N'-dialkylated 1,*n*-diamines.

3.3 O-Enolate-driven domino processes: transforming TSDs into multisubstituted aromatic platforms.

The use of a secondary amine as the nucleophile traced a new domino pathway involving the [$\mathbf{d^0}$]-O-carbonyl reactivity of the TSD platform (Scheme 10a). We experimentally accomplished this new domino pathway in the form of a divergent reaction manifold (same intermediate, different products) using dibenzylamine as the secondary amine (dibenzylamine ensured reactivity and post-synthetic deprotection) and a polar and protic solvent (alcohol, alcohol-water)



Scheme 10. Secondary amines and TSDs: O-enolate driven domino processes.

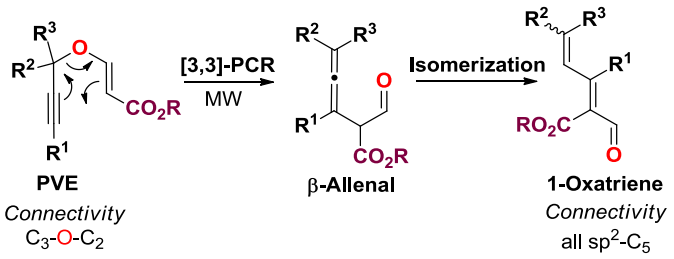
to stabilize the ionic intermediates formed during the process and to participate in the proton transfer reactions involved in it (Scheme 10b).[27] Two different experimental protocols were devised to selectively access cyclohexadienones **32** (Nu = OMe) and **33** (Nu = NBn_2). The use of diluted dibenzylamine (1 equiv) in hot methanol (0.01 M, 65 ºC) afforded cyclohexadienones **32**

in excellent yields (84-95%)(Scheme 10b). On the other hand, the use of dibenzylamine (2 equiv) in a 4:4:1 dichloromethane-ethanol-water mixture (0.05 M, RT) allowed us to obtain cyclohexadienones **33** in excellent yields (80-94%). The latter solvent cocktail was needed because the reaction called for a polar solvent and the TSD platforms showed to be highly insoluble in ethanol or ethanol-water mixtures at room temperature.

Cyclohexadienones **32** and **33** were further transformed into aromatic platforms **34** and **35**, respectively, through the two-step chromatography-free process outlined in the inset of Scheme 10b. Altogether, the process transforms TSDs **2** into multifunctional aromatic platforms entailing two differentiated hydroxyl groups, two amino groups supporting different chemical environments, an ester group and a biaryl motif. The domino process is divergent and can be selectively funneled toward either of the two products by a simple change of the solvent and fixing the amount of the amine to the stoichiometry of the process. The overall yield is good, the reaction manifold is easily scalable and the final aromatic platforms feature a set of secondary reactivity principles that are well-suited for further complexity generation.

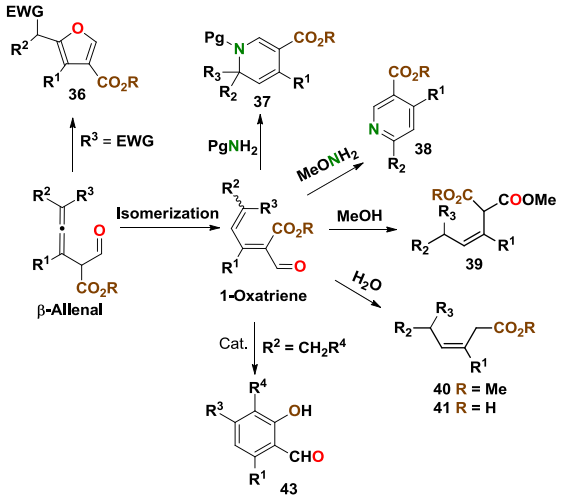
4. [PCR]-triggered domino manifolds.

The MW-assisted tandem propargyl Claisen rearrangement / 1,3-proton transfer reaction transforms PVEs **1** into the corresponding 1-oxatriene derivatives (Scheme 11).[18] Overall, this domino rearrangement transforms an easily assembled linear C_3-O-C_2 platform into a carbogenic C_5 all-sp^2 linear structure endowed with a reactive aldehyde, an ester function and a doubly conjugated trisubstituted diene. A plethora of domino reactions were hosted by this carbogenic platform to generate the array of scaffolds outlined in Scheme 12. Whereas products **43** were



Scheme 11. Tandem propargyl Claisen rearrangement / isomerization.

formed by the full rearrangement of the initial PVEs, products **36-41** were formed by the interception of the β-allenal or 1-oxatriene intermediates.

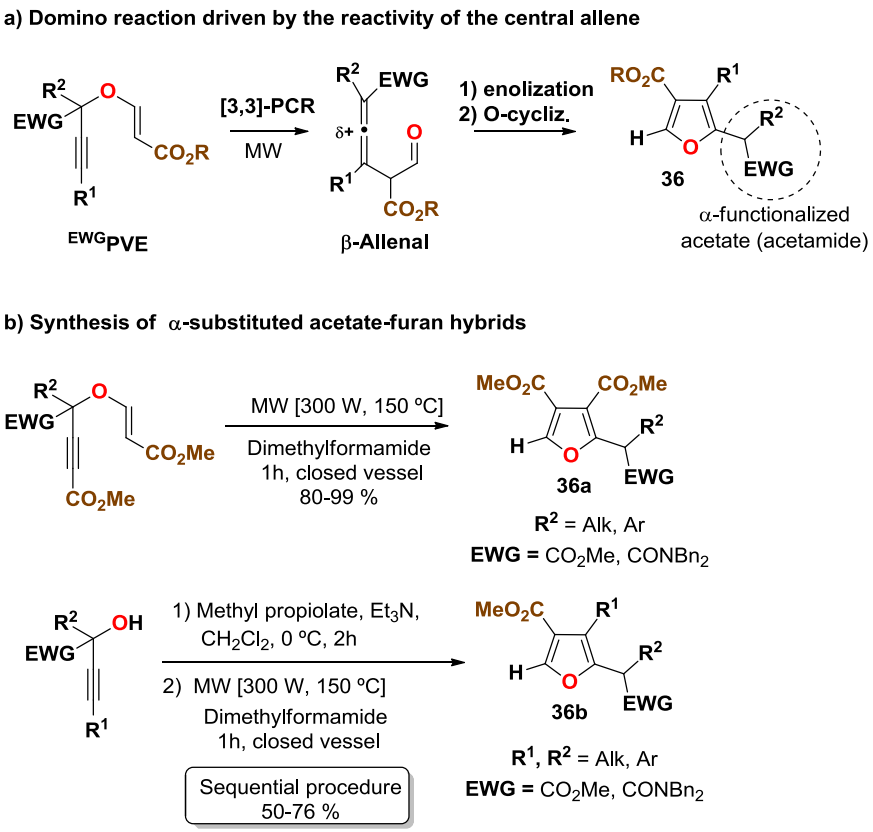


Scheme 12. Transformations of the 1-oxatriene scaffold.

4.1 [PCR]-driven domino processes of tertiary PVE bearing an electron-withdrawing group at the propargylic position: **transforming PVEs into furan derivatives.**

MW irradiation of PVEs armed with an electron withdrawing group (EWG) at the propargylic position (^{EWG}PVE)[28] led to furans **36** through a [**PCR**]-driven domino processes involving a tandem enolization / 5-exo-dig O-cyclization reaction of the β-allenal intermediate (Scheme 13a).[29] The presence of the EWG activated the central allenic position favoring this tandem

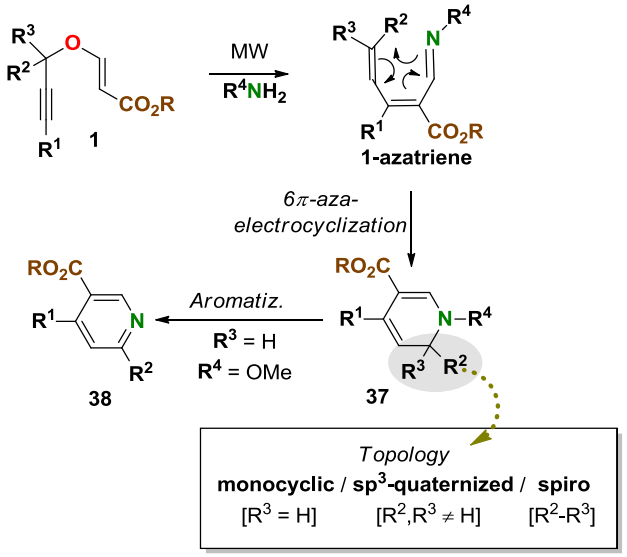
reaction over the [1,3]-H shift. The domino manifold required two different experimental procedures depending of the nature of the alkyne substituent (R^1) (Scheme 13b). In the case of methyl (alkyl) esters, the whole process could be performed in two steps (formation of the PVE and the subsequent domino rearrangement) to give **36a** in 80-99% yield or directly from the methyl (alkyl) propiolate and the 1,2-carbonyl compound without the isolation of the PVE intermediate (not shown) to give **36a** in 50-78% yield. When the substituent was an alkyl or aryl group, then the process was conveniently performed in a sequential manner from the propargyl alcohol without isolation of the intermediate PVE to give **36b** in 50-76 %.



Scheme 13. Transformation of PVEs into furans **36**.

4.2 [PCR]-driven domino processes in the presence of a primary amine: transforming PVEs into dihydropyridines and pyridines.

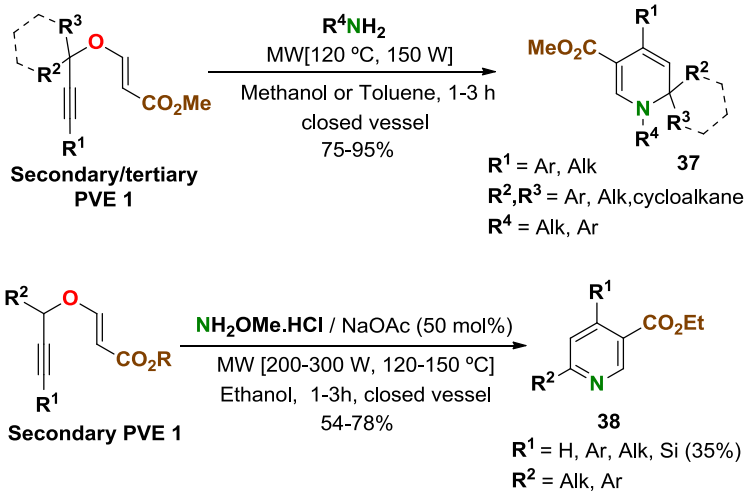
In the presence of a primary amine, the MW-assisted [PCR]-driven domino processes of PVEs **1** bearing a nonconjugated alkyne moiety ($R^1 \neq$ EWG) generated the corresponding 1,2-dihydropyridines **37**[30,31] or pyridines **38**[32] (Scheme 14). The domino transformation involved the condensation of the amine with the 1-oxatriene intermediate to form the corresponding 1-azatriene adduct which in turn performed a 6π-aza-electrocyclization to construct the 1,2-dihydropyridine ring. Because the nucleophilicity of the primary amine, the alkyne moiety of the PVE should be nonconjugated to avoid the formation of the corresponding 1,3-oxazolidines **6**[20] (Scheme 4) which would rearrange to pyrroles **7**.[21a]



Scheme 14. [PCR]-triggered domino manifold of PVEs in the presence of a primary amine.

The domino manifold is very efficient and operates with both secondary and tertiary PVEs and both aliphatic and aromatic primary amines to deliver the heterocyclic scaffold in good yields (~ 85% average yield) and decorated with a wide functional pattern including mono,

double or spiro substitution at the sp^3-position of the ring (Scheme 15). In addition, if the substituent of the amine is a good leaving group (e.g., R^4 = OMe), and one of the two R^2/R^3 substituents is hydrogen, then the domino process goes on to deliver the corresponding pyridine ring. In this case, the experimental protocol calls for the use of MeO-NH_2.HCl as the amine component and substoichiometric amounts of NaOAc as buffer to generate nicotinates **38** in good average yield (~65%)(Scheme 15).[32] The diversity-generating power of this protocol enables access to nicotinate derivatives featuring unusual substitution patterns (e.g., R^1 = Me_3Si, R^2 = Ph).

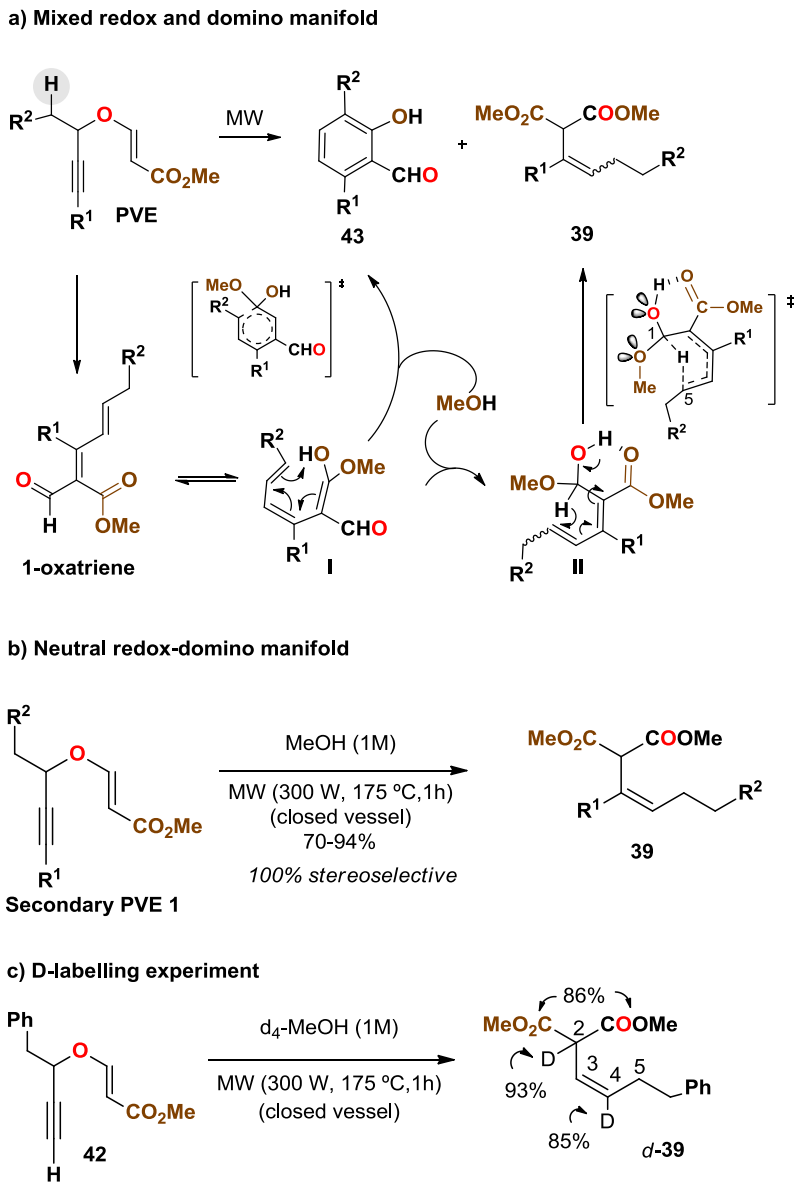


Scheme 15. Transformation of PVEs into 1,2-dihydropyridines **37** and pyridines **38**.

4.3 [PCR]-driven domino processes in the presence of an alcohol or water: transforming PVEs into di- and trisubstituted β,γ-unsaturated acids and esters.

During the course of our studies on the transformation of PVEs into 1,2-dihydropyridines, we discovered a new reactivity profile of secondary PVEs endowed with a methylene group attached to the propargylic position (Scheme 16a). It was observed that in the absence of nucleophiles, the

MW irradiation of these PVEs afforded roughly equimolar mixtures of β,γ-unsaturated esters **39** and salicylaldehydes **43**, with a predominance of the *E*-isomers (up to 100%) in the alkene products. It was hypothesized that these new scaffolds would be formed through a divergent domino process elicited by the formation of a common 1-oxatriene intermediate. The presence of a methylene group at the terminal position of the diene moiety should allow the generation of

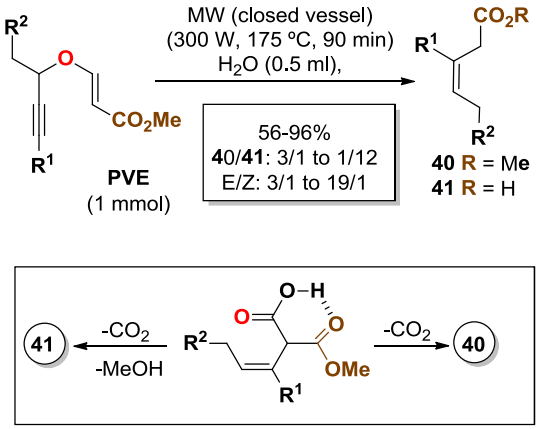


Scheme 16. Merging redox and domino chemistry: a neutral redox-domino manifold.

enol-diene intermediate **I,** which should trigger a tandem 6-π-electrocyclization/aromatization reaction to generate the salicylaldehyde core. This tandem reaction would release methanol to the reaction medium, which in turn would add to the 1-oxatriene intermediate to form the hemiacetal intermediate **II**. The formation of this hemiacetal would increase the hydricity of the adjacent C-H bond facilitating the required [1,5]-hydride shift to generate the β,γ-unsaturated ester **39** (the formation of an internal H-bond should further increase the n→σ* delocalization of the oxygen lone pair, rendering the geminal C-H bond much more hydridic). In this scenario, the formation of the enol intermediate **I** should be slower than the neutral redox rearrangement to allow for the coexistence of both domino processes. This fact was instrumentalized in the selective formation of the β,γ-unsaturated ester **39**. It was hypothesized that in the presence of an excess of methanol, the enolization pathway should be kinetically disfavored in favor of the redox one, funneling the whole process toward the formation of **39**. That was the case when the reaction was performed in methanol (Scheme 16b), affording the expected β,γ-unsaturated esters **39** in high yields (70-94%) with complete stereoselectivity (only the isomers with R^1 and R^2 in *trans* relationship were detected).[33] The postulated neutral redox rearrangement was confirmed by isotopic labelling experiments using d_4-methanol as the solvent (Scheme 16c). In accord with the mechanism outlined above, deuterium incorporation from the solvent was observed at the expected labile positions (esters and C_2 and C_4), but not at the allylic C_5 position. The absence of deuterium labeling at this position confirmed the direct hydride migration from the hemiacetalic position C_1 to the conjugated diene C_5 position ([1,5]-H shift).

This redox-domino reaction constitutes a nice example of stereoselective generation of trisubstituted olefins without the use of metal catalysis, which adds sustainability to this reaction. In order to increase the greenness of this approach, we next studied its extension to aqueous

conditions. Under these conditions, mixtures of β,γ-unsaturated monoester **40** and monoacid **41** were obtained in good yields (56-96%) and good stereoselectivity (E/Z ratios up to 19/1) (Scheme 17).[33] The ratio of **40/41** was found to be substrate-dependent, spanning from 3/1 (R^1 = H, R^2 = ^{n}Bu) to 1/12 (R^1 = CO_2Me, R^2 = ^{n}Pr). Fortunately, the mixture could be efficiently shifted either toward monoester **40** by acid-catalyzed esterification (H_2SO_4-MeOH) or toward monoacid **41** by alkaline hydrolysis (0.5 M NaOH in MeOH) without affecting the geometry and position of the double bond.

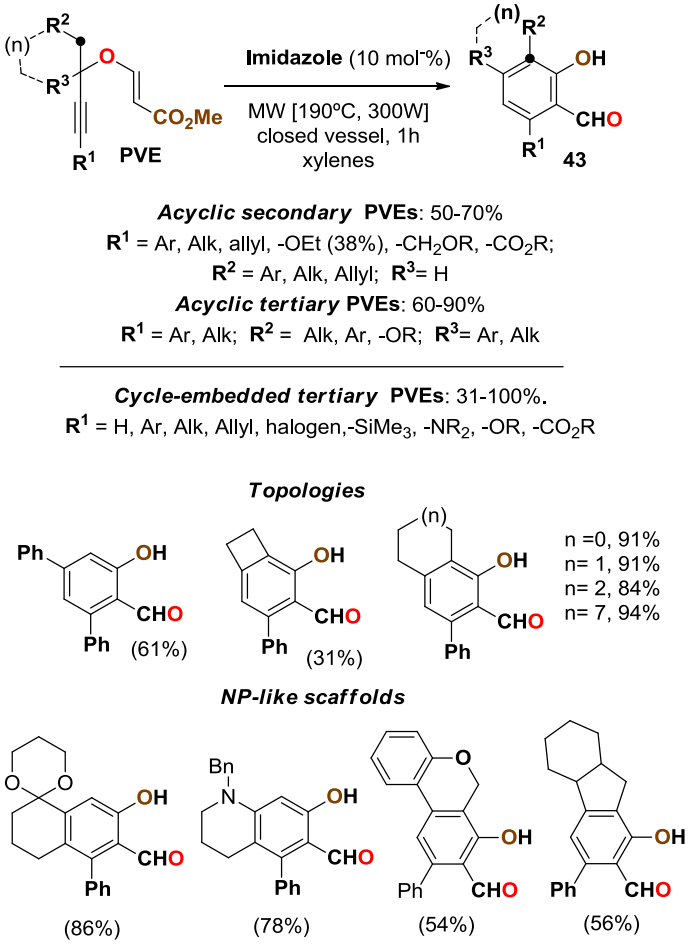


Scheme 17. MW-assisted rearrangement under aqueous conditions.

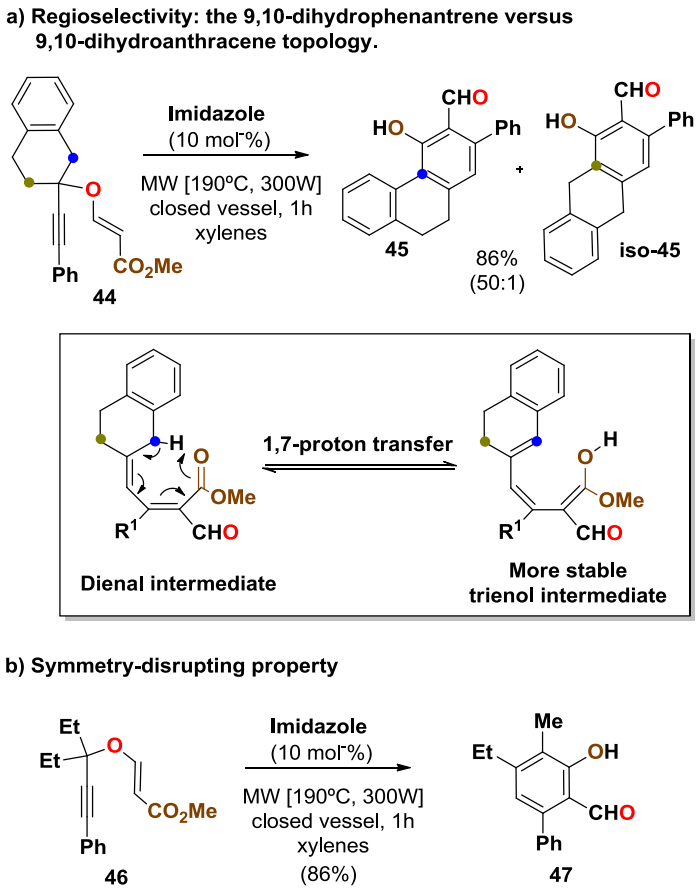
4.4 Organocatalyzed [PCR]-driven domino processes: transforming PVEs into salicylaldehydes.

The reversion of the domino manifold to the selective formation of salicylaldehyde derivatives **43** called for the use of an additive that can play the role of a catalyst for the enolization process (otherwise a high-energy step), a methanol scavenger to block the redox pathway, or both. After an intense experimental effort, we arrived at imidazole as a convenient catalyst for this transformation (Scheme 18).[34] Thus, MW irradiation of PVEs **1** in the presence of a catalytic

amount of imidazole (10 mol %) allowed us to obtain the corresponding salicylaldehyde derivatives **43** in good average yields and good tolerance with regard to the PVEs substitution pattern (aromatics, carbocycles, heterocycles, olefins, halogens, silicon, O- and N-radicals). In addition, the salicylaldehyde motif was supported on a wide set of topologies ranging from simple aromatic monocycles (acyclic secondary/tertiary PVEs) to complex fused polycyclic systems (tertiary PVEs). The reaction was also highly regioselective (Scheme 19a) and symmetry-disrupting: symmetrically substituted PVEs afforded asymmetrically substituted salicylaldehydes (Scheme 19b).

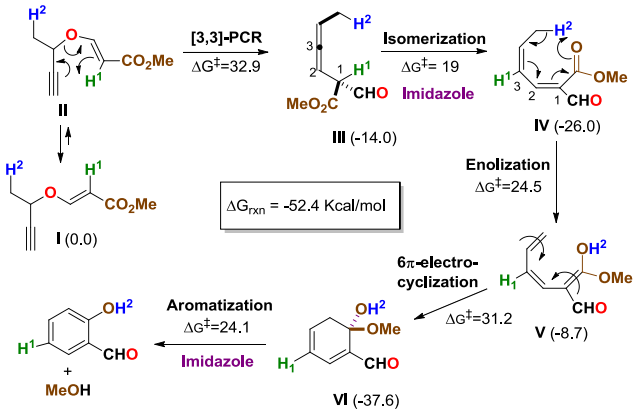


Scheme 18. Catalytic transformation of PVEs into salicylaldehydes **43.**



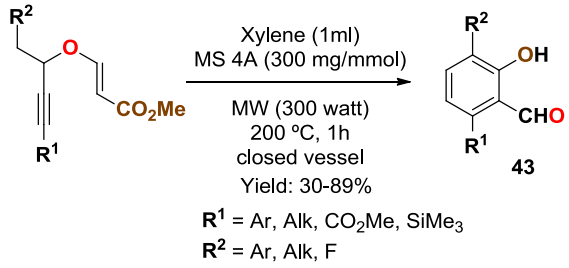
Scheme 19. Regioselectivity and symmetry disrupting properties of the catalytic reaction.

A computational DFT study was performed using a simplified model of PVE ($R^1 = R^2 = R^3 = H$).[34] The calculations underpinned an exergonic domino mechanism involving a sequential [3.3]-propargyl Claisen Rearrangement / isomerization / enolization / 6π-electrocyclization / aromatization set of reaction (Scheme 20). The catalytic role played by the imidazole was supported by these calculations, as it reduced the free energy of activation for the isomerization and the aromatization steps to 19 and 24.1 Kcal/mol respectively.



Scheme 20. DFT study of the reaction mechanism. Relative free energies are given in Kcal/mol.

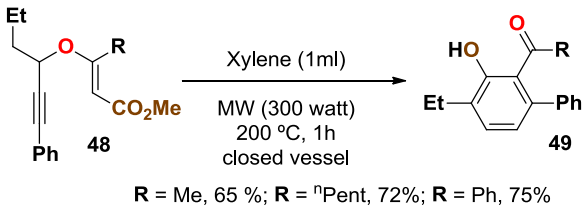
Molecular sieves 4Å (MS 4Å) also behaved as a convenient additive for this transformation[35] although its precise role remains unknown (MS can play the double role of a methanol scavenger and an enolization-assisting reagent[36]). Thus, the MW irradiation (300 W, 200 ºC, closed vessel, 1h) of a mixture of the secondary PVE and MS 4Å (300 mg/mmol of PVE) in xylenes (Scheme 21) delivered the salicylaldehydes **43** in moderate (30%; R^1 = Me_3Si; R^2 = Et; R^3 = H) to excellent (89%; R^1 = R^2 = Ph; R^3 = H) yields and with a varied substitution pattern at the ring. This transformation constitutes a valuable alternative to the catalytic procedure, especially when secondary PVEs need to be used.



Scheme 21. Non-catalytic transformation of secondary PVEs into salicylaldehydes **43**.

Interestingly, secondary PVEs **48**, armed with an extra substituent at the β-acrylate position delivered the corresponding phenolic ketones **49** in good yields (70% average yield) in

the absence of additive (the ketal intermediate cannot follow the redox pathway) (Scheme 22). Unfortunately, the tertiary PVE homologues are not easily accessible from the corresponding tertiary propargyl alcohols using the current methodology, so although they should be suitable substrates for this transformation, they could not be tested.



Scheme 22. Synthesis of phenolic ketones **49** from secondary PVEs **48**.

5. Conclusion.

In this Account we have described the use of PVEs **1** and TSDs **2** as pluripotent platforms for DOS strategies. A plethora of different scaffolds have been generated using the primary reactivity principles encoded into these two platforms through [$\mathbf{a^3}$]-triggered or [**PCR**]-triggered domino manifolds. The design of these pluripotent platforms have been discussed with especial emphasis in their synthesis and primary reactivity profiles. Eleven different domino processes have been implemented using these simple reactivity principles and a careful and rational control of the chemical reactivity. This methodology has found application in the fields of the diversity-oriented synthesis (coumarin library synthesis[11]) and target-oriented synthesis (total synthesis of the natural benzophenone metabolite morintrifolin B).[34] We hope that this Account serves to bring the attention of the synthetic community about the concept of pluripotent molecular platform and its productive implementation in DOS programs.

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