

## Diverted Domino Reactivity in Tertiary Skipped Diynes. A Convenient Access to Polyfunctionalized Cyclohexadienones and Multivalent Aromatic Scaffolds.

David Tejedor,<sup>[a][b]\*</sup> Sara López-Tosco,<sup>[a][b]</sup> Javier González-Platas,<sup>[c]</sup> Fernando García-Tellado<sup>[a][b]\*</sup>

Domino reactions<sup>[1]</sup> constitute single-operation, multi-step processes able to generate two or more bonds under a constant set of reaction conditions. Usually, they transform simple starting materials into more complex chemical entities utilizing networks of construction reactions.<sup>[2]</sup> This property makes them excellent synthetic tools to carry out molecular construction with atom-,<sup>[3]</sup> redox-<sup>[4]</sup> and step-economy.<sup>[5]</sup> The sequential order by which these multi-step processes are performed (the reaction manifold) ultimately determines the chemical outcome of the process and therefore, the topology of the final product (the skeletal connectivity). In the last years, we have focused our efforts in the use of small, readily-accessible, densely functionalized platforms for the diversity-oriented domino generation of privileged structural motives with biological relevance.<sup>[6]</sup> Skipped diynes **1**<sup>[7]</sup> constitute an example of such platforms (Figure 1). They are conveniently synthesized in one step and multigram scale from alkyl propiolates and acid chlorides via a triethylamine assisted multicomponent  $A_2BB'$  4CR.<sup>[8]</sup> This modular origin ensures a convenient grade of functional diversity on the tertiary  $sp^3$ -center (diversity domain). The reactivity profile of the platform is defined by the two alkynoate units and the propargyl ester function (reactivity domain). Recent reports from our group<sup>[9]</sup> have shown how these  $C_7$ -units can be selectively transformed into polysubstituted pyrroles **4**,<sup>[9a]</sup> 1,4-diazepane derivatives **5**<sup>[9b]</sup> or pyrazoles **6**,<sup>[9b]</sup> when they are made to react with primary amines, 1,2-diamines and hydrazines respectively (Scheme 1).

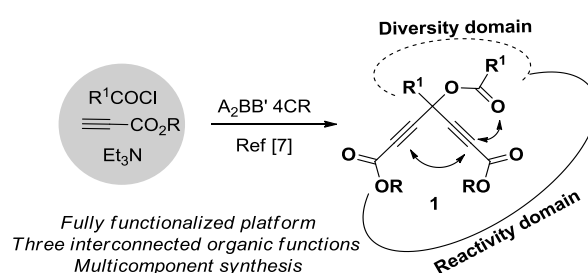
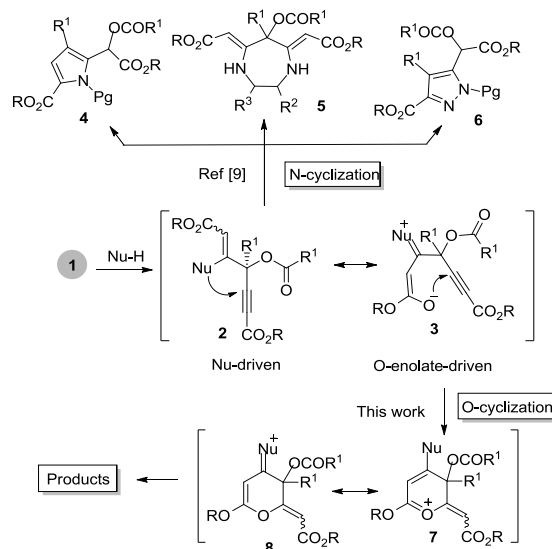


Figure 1. Synthesis and properties of skipped diynes **1**.

These heterocycles are generated by N-cyclization of the corresponding enamine intermediates **2** (Nu = PgNH, HNCH(R<sup>2</sup>)CH(R<sup>3</sup>)NH<sub>2</sub> and PgNH-NH respectively). Although the reactivity profile of enamine **2** can be characterized by the two canonical representations **2** (neutral) and **3** (zwitterionic), the N-cyclization controls the main domino reactivity pattern of this molecule (Nu-driven domino processes). We envisioned that an alternative O-enolate-driven domino reactivity pattern biased by the mesomeric form **3** could take place if this N-cyclization could be blocked. Under these conditions, the O-cyclization reaction of the enamine **2** would provide the cyclic oxonium ion **7**, which



Scheme 1. Diverted domino reactivity of tertiary skipped diynes **1**.

[a] Dr. D. Tejedor, Dr. S. López-Tosco, Dr. F. García-Tellado  
Instituto de Productos Naturales y Agrobiología  
Departamento de Química Biológica y Biotecnología  
Consejo Superior de Investigaciones Científicas  
Astrofísico Francisco Sánchez 3  
38206- La Laguna-Tenerife-Spain  
Fax: int-34922260135  
E-mail: [fgarcia@ipna.csic.es](mailto:fgarcia@ipna.csic.es); [dtejedor@ipna.csic.es](mailto:dtejedor@ipna.csic.es)  
Homepage: [www.ipna.csic.es/departamentos/qbb/qb](http://www.ipna.csic.es/departamentos/qbb/qb)

[b] Dr. D. Tejedor, Dr. S. López-Tosco, Dr. F. García-Tellado  
Instituto Canario de Investigación del Cáncer  
Homepage: [www.icic.es](http://www.icic.es)

[c] Dr. J. González-Platas (Crystallographer)  
Servicio de Difracción de Rayos X  
Departamento de Física Fundamental II  
Universidad de La Laguna  
Avda. Astrofísico Francisco Sánchez 2,  
38204 La Laguna, Tenerife, Spain.

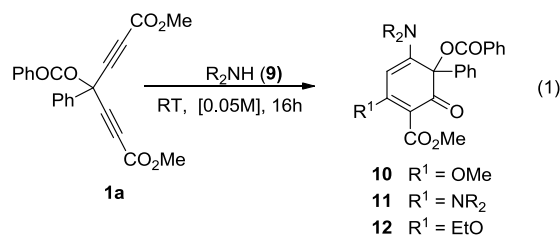
could be conveniently transformed into different products. This new scenario would enable the development of new domino processes and therefore, it would increase the synthetic power of these C<sub>7</sub>-platforms. The chemical accomplishment of this goal requires: 1) disfavoring the N-cyclization; 2) favoring the shift of the electronic density from the nitrogen to the oxygen atom; 3) stabilizing the cyclic oxonium ion **7** by a redistribution of the electronic deficiency via the canonical form **8** and 4) a polar and protic medium to favor the separation of charges produced going from **2** (neutral) to **3** (zwitterionic) and to assist in the acid-base quenching of the O-cyclization reaction. Whereas secondary amines could meet the first three requirements through the *interconversion* between their corresponding *iminium* and *enamine* forms,<sup>[10]</sup> alcohols would guarantee the fourth condition. In this communication we report the feasibility of this conceptual approach and we show how it can be implemented for the diversity-oriented synthesis of polysubstituted cyclohexadienones and multivalent aromatic scaffolds bearing a survey of valuable functionalities decorating the ring.

The hypothesis was assessed using the reaction of diyne **1a** with different secondary amines under different reaction conditions [Eq. (1)]. Table 1 summarizes the main experimental results,<sup>[11]</sup> using two representative secondary amines: pyrrolidine (**9a**), as a representative example of cyclic and highly nucleophilic secondary amines, and dibenzylamine (**9b**) as a representative example of acyclic, sterically demanding secondary amines with reduced nucleophilicity. We began this work studying the reaction of diyne **1a** (1 eq) and pyrrolidine (**9a**) (1 eq) in dichloromethane. After several assays, it was found that the reaction at room temperature for 16 hours afforded the mixture of cyclohexadienones derivatives **10aa** and **11aa** although in low yield (Table 1, entry 1). When the amount of pyrrolidine was doubled (to adjust the stoichiometry to the formation of **11aa**), the reaction exclusively generated the compound **11aa** in 67% yield (entry 2). The structures of these two products,<sup>[12]</sup> which were unexpected, constituted experimental evidence of a reactivity shift in the diyne platform, and they established the chemical outcome for the novel domino reaction pathway elicited from these platforms. According to our initial hypothesis, alcohols would be beneficial solvents for this domino reaction. It was gratifying to find that the use of MeOH or EtOH as solvent allowed obtaining the diamine derivative **11aa** in nearly quantitative yield (entries 3-4). On the other hand, the reaction of diyne **1a** with dibenzylamine (**9b**) showed to be solvent dependent. Whereas the reaction in EtOH generated the mixture of monoamines **10ab** (5%) and **12ab** (5%) together with the diamine **11ab** (86%) (entry 5), the reaction in MeOH afforded the monoamine **10ab** (39%) and diamine **11ab** (53%) (entry 6).

With these results at hand, it soon became evident that strong nucleophilic amines and/or less nucleophilic alcoholic solvents favored the formation of diamine derivatives **11**, while low nucleophilic amines and a stronger nucleophilic alcoholic solvent favored the formation of monoamine derivatives **10**.

When dibenzylamine was used, the presence of product **12ab** bearing an ethoxy group, revealed the participation of the solvent (EtOH), which was further confirmed by crossover experiments. Moreover, it was also confirmed that **10** and **12** did not interconvert under these reaction conditions (See SI for details). Interestingly, the dilution of the methanolic reaction increased the formation of the monoamine **10ab** up to 79% yield (entry 7). Further experiments with the dibenzylamine derivatives **9b-d**,

Table 1. Domino reaction of diyne **1a** and secondary amines **9a-d**.<sup>[a]</sup>



Entry	Solvent	Amine		<b>10</b> (%)	<b>11</b> (%)
1	CH <sub>2</sub> Cl <sub>2</sub>	C <sub>4</sub> H <sub>8</sub> NH <sup>[b]</sup>	<b>9a</b>	30	9
2	CH <sub>2</sub> Cl <sub>2</sub>	C <sub>4</sub> H <sub>8</sub> NH	“	n.d. <sup>[c]</sup>	67
3	MeOH	C <sub>4</sub> H <sub>8</sub> NH	“	n.d.	>99
4	EtOH	C <sub>4</sub> H <sub>8</sub> NH	“	n.d.	>99
5	EtOH	Bn <sub>2</sub> NH	<b>9b</b>	10 <sup>[e]</sup>	86
6	MeOH	Bn <sub>2</sub> NH	<b>9b</b>	39	53
7	MeOH <sup>[d]</sup>	Bn <sub>2</sub> NH	<b>9b</b>	79	21
8	MeOH <sup>[d]</sup>	PMDBA <sup>[f]</sup>	<b>9c</b>	67	33
9	MeOH <sup>[d]</sup>	PNDBA <sup>[g]</sup>	<b>9d</b>	93 <sup>[h]</sup>	7

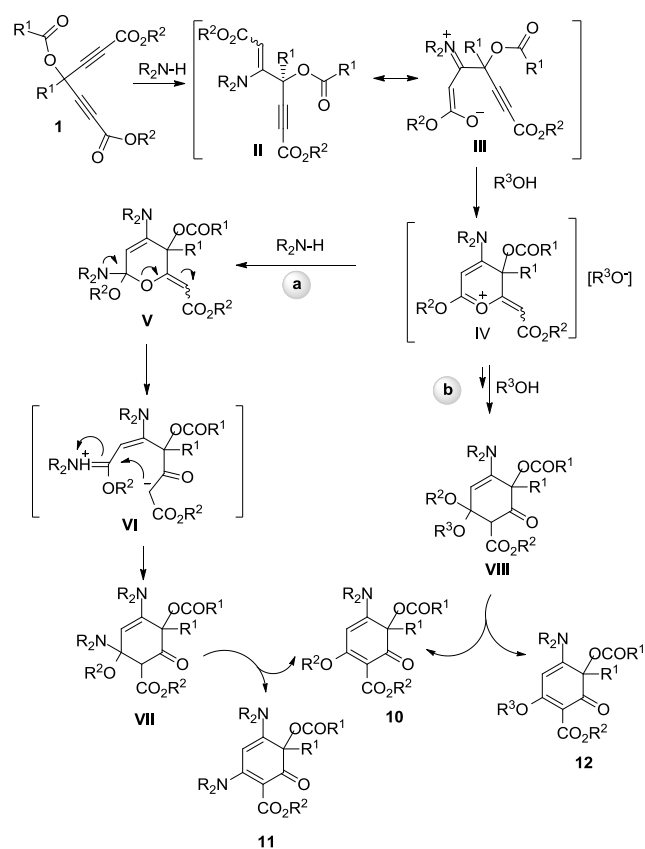
[a] Reaction conditions: diyne (0.10 mmol), amine (0.22 mmol), solvent (2 mL). [b] 0.11 mmol. [c] n.d. = non detected. [d] 0.01M. [e] Roughly equimolecular mixture of monoamines **11ab** and **12ab**. [f] PMDBA = bis(4-methoxyphenyl)methanamine. [g] PNDBA = bis(4-nitrophenyl)methanamine. [h] 50% conversion (50% r.s.m)

which share a similar steric environment at the nitrogen center but feature different electronic properties,<sup>[13]</sup> showed a clear relationship between the nucleophilicity of the amine and the ratio of monoamine **10**/diamine **11** in the reaction mixtures (entries 7-9). The reaction with amine **9d**, the worst nucleophile, was very slow and it afforded monoamine **10ad** in 47% yield (50% of conversion) after 7 days at room temperature. We did not observe other chemical entities different to products and starting materials in the reaction crude. This fact seems to point to an early rate limiting step in this domino reaction.

The chemical efficiency and the complexity generation power of this reaction exceeded all our expectations. *The reaction generated up to four new bonds (2 C-N, 1 C-C, 1 C=O) and one ring with excellent atom economy and an operationally simple protocol.*

The set of experimental data can be rationalized through the O-enolate driven domino manifold outlined in Scheme 2. The scenario comprises two reaction pathways (**a** and **b**) diverging from a common intermediate **IV**. The pathway **a** is launched by the addition of a second amine unit on the cyclic oxonium ion **IV** to give the orthoaminal **V**, which rearranges to aminal **VII** via the formation of the immonium-enolate **VI**. The elimination of R<sup>2</sup>OH from **VII** delivers the diamino derivative **11**. The much less favored elimination of R<sub>2</sub>NH would generate the monoamine derivative **10**. The pathway **b** is triggered by the addition of the solvent on **IV** to give the corresponding orthoester derivative (not shown), which rearranges to the mixed ketal **VIII**, which in turn eliminates alcohol to give the statistical mixture of monoamines **10** and **12**. Thus, whereas pathway **a** affords diamine **11** as the main compound, route **b** only delivers monoamine **10** (or **12** if methanol is not used as the alcoholic solvent). The pathway **a** is triggered by a bimolecular reaction (rate = *k<sub>a</sub>* [**IV**][amine]) and consequently, it would be benefited by high nucleophilic amines, high concentration, low nucleophilic solvents and low temperatures. On the other hand, route **b** is launched by a pseudo

first order reaction (rate =  $k_{ap}$  [IV],  $k_{ap} = k_b$  [solvent]) and it would be benefited by low nucleophilic amines, dilution, nucleophilic solvents and higher temperature. While pyrrolidine (**9a**) meets the requirements of route **a** and it exclusively affords diamine derivative **11aa**<sup>[14]</sup> with independence of the reaction conditions, dibenzylamine (**9b**) can react following either of the two pathways, and the chemical outcome of the reaction will come determined by the stoichiometry, solvent, concentration and temperature. Because tertiary dibenzylamines could be considered masked forms of primary amines (hydrogenolysis renders the free primary amine), the installation of these motives into the cyclohexadienones **10** and **11** would increase their synthetic value. With this idea in mind, we next undertook the selective transformation of diyne **1a** into cyclohexadienones **10ab** and **11ab**.

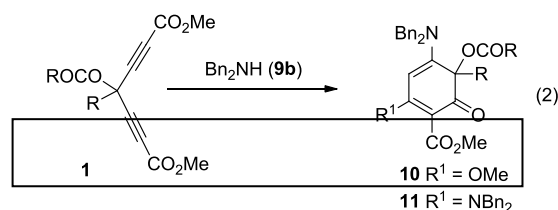


Scheme 2. O-enolate driven domino mechanistic proposal.

After some experimental work, we found that the reaction of diyne **1a** with one equivalent of dibenzylamine (**9b**) could be selectively funneled toward route **b** [MeOH (0.01M), 65°C, 16 h] to afford monoamine **10ab** in 95% yield (Eq. (2), method **A**) (Table 2, entry 1). The scope of this domino reaction was explored using the set of skipped diynes shown in Table 2. The reaction was tolerant with different functionalities decorating the diynes **1b-i**, rendering the corresponding monoamine derivatives **10bb-ib** in excellent yields. Although the tertiary  $sp^3$ -center on the skipped diyne does not participate directly in the reaction, it exerts steric hindrance on the alkyne moiety. This steric effect resulted in a lowering of the reactivity of aliphatic diynes **1j** and **1k** which needed more forcing conditions (3 days) to be

efficiently converted into their corresponding monoamine derivatives **10jb** and **10kb** (entries 21 and 22).

Table 2. Domino reaction of diyne **1** and dibenzyl amine (**9b**)



Method A: MeOH [0.01M], 65°C, 16h

Method B: CH<sub>2</sub>Cl<sub>2</sub>/EtOH/H<sub>2</sub>O/ (4/4/1), [0.05M], RT, 16h

Entry	R	Method	<b>10</b> (%) <sup>[a]</sup>	<b>11</b> (%) <sup>[a]</sup>
1	Ph	<b>A</b> <sup>[b]</sup>	95	
2		<b>B</b> <sup>[c]</sup>		94
3		<b>B</b> <sup>[d]</sup>		91
4	2-Cl-C <sub>6</sub> H <sub>4</sub>	<b>A</b>	84	
5		<b>B</b>		74
6	3-Cl-C <sub>6</sub> H <sub>4</sub>	<b>A</b>	93	
7		<b>B</b>		86
8	4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>A</b>	92	
9		<b>B</b>		86
10	4-F-C <sub>6</sub> H <sub>4</sub>	<b>A</b>	95	
11		<b>A</b> <sup>[e]</sup>	94	
12		<b>B</b>		88
13	4-BiPh	<b>A</b>	93	
14		<b>B</b>		80
15	4-Me-C <sub>6</sub> H <sub>4</sub>	<b>A</b>	96	
16		<b>B</b>		87
17	3-MeO-C <sub>6</sub> H <sub>4</sub>	<b>A</b>	93	
18		<b>B</b>		85
19	3,5-diMeO-C <sub>6</sub> H <sub>3</sub>	<b>A</b>	94	
20		<b>B</b>		81
21	<i>i</i> Pr	<b>A</b>	85 <sup>[f]</sup>	
22	C <sub>6</sub> H <sub>11</sub>	<b>A</b>	84 <sup>[f]</sup>	
23		<b>B</b>		40 <sup>[g]</sup>

[a] Isolated yields. [b] Method **A**: diyne (0.10 mmol), dibenzylamine (0.11 mmol). [c] Method **B**: diyne (0.10 mmol), dibenzylamine (0.22 mmol). [d] 15 mmol scale. [e] 7.5 mmol scale. [f] 3 days. [g] 1 week.

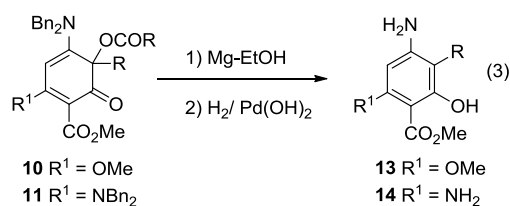
With the monoamine derivatives **10ab-kb** at hand, we explored the selective formation of the corresponding diamine derivatives **11ab-kb**. Preliminary experiments had showed that the reaction of dibenzylamine (**9b**) and diyne **1a** in EtOH generated the diamine **11ab** in good yield (86%) but contaminated with significant amounts of monoamine derivatives **10-12ab** (10%)(Table 1,entry 5). According to Scheme 2, it was apparent that if the nucleophilicity of the EtOH could be lowered then route **b** could be diminished and the yield of diamine **11** would be increased.<sup>[15]</sup> H<sub>2</sub>O was envisioned as a convenient co-solvent as it was expected that it would lower the nucleophilicity of EtOH through coordination while it would increase the polarity of the reaction medium. After several experimental trials, we found that the mixture of EtOH-H<sub>2</sub>O (4/1) was optimal for the selectivity of the reaction, but unfortunately, the low solubility of the lipophilic diynes **1b-k** in this aqueous media compromised the reaction efficiency. Fortunately, it was found that the addition of CH<sub>2</sub>Cl<sub>2</sub> to the aqueous solvent cocktail brought the diynes **1a-k** into solution increasing the reaction efficiency without eroding the

selectivity of the reaction. (Eq. (2), method **B**). Under these conditions, aromatic diynes **1a-i** uniformly reacted with two equivalent of dibenzylamine to give the corresponding diamine derivatives **11ab-ib** in good to excellent yields (Table 2). Aliphatic substituted diynes were not convenient substrates for this reaction. The steric hindrance exerted by the tertiary sp<sup>3</sup>-center on the alkynoate moiety comprised a kinetic barrier difficult to overcome. Under these conditions, diyne **1k** needed a week at room temperature to deliver the diamine **11ak** in only 40% yield (entry 23).

It is important to highlight that these reactions can be performed at multigram scales without significant erosion in the reaction efficiency (Table 2, entries 3 and 11).

Cyclohexadienones **10** and **11** represent densely functionalized building (synthetic) blocks with a polyvalent reactivity profile. Among the wide set of imaginable transformations that could be addressed on these platforms, we show herein their direct transformation into multivalent aromatic platforms **13** and **14** [Eq. (3)], which constitute valuable examples of salicylate derivatives<sup>[16]</sup> bearing a privileged biaryl<sup>[17]</sup> motive (R = Ar) and one (**13**) or two (**14**) amine groups in their structures. This transformation takes advantage of the presence of the tertiary aryloate group in  $\alpha$ -position to the non-enolizable carbonyl group. Reduction of this ketone to the corresponding alcohol would provide the corresponding phenol derivative by the concomitant elimination of the aryloate group. The reduction of this hindered ketone was problematic but it was conveniently achieved using an excess of Mg in refluxing EtOH to afford the corresponding phenol derivative in moderated to good yields [Eq. (3)].<sup>[18]</sup> The amine deprotection under standard conditions (H<sub>2</sub>-Pd(OH)<sub>2</sub>) rendered the corresponding amine-free aromatic scaffolds **13** and **14** in excellent yields. Gratifyingly, this two-step process could be efficiently performed without isolation of the phenol intermediate with a good overall efficiency for both platforms (Table 3). In addition, the whole transformation could be performed at multigram scale (entry 2).

Table 3. Synthesis of multivalent aromatic platforms **13** and **14**.<sup>[a]</sup>



Entry	St. material	R	Product	(%) <sup>[b]</sup>
1	<b>10ab</b>	Ph	<b>13a</b>	75
2	<b>10eb</b>	4-F-C <sub>6</sub> H <sub>4</sub>	<b>13e</b>	68 <sup>[c]</sup>
3	<b>10hb</b>	3-MeO-C <sub>6</sub> H <sub>4</sub>	<b>13h</b>	62
4	<b>10ib</b>	3,5-diMeO-C <sub>6</sub> H <sub>3</sub>	<b>13i</b>	75
5	<b>10kb</b>	C <sub>6</sub> H <sub>11</sub>	<b>13k</b>	48
6	<b>11ab</b>	Ph	<b>14a</b>	76
7	<b>11eb</b>	4-F-C <sub>6</sub> H <sub>4</sub>	<b>14e</b>	74
8	<b>11fb</b>	4-BiPh	<b>14f</b>	50
9	<b>11gb</b>	4-Me-C <sub>6</sub> H <sub>4</sub>	<b>14g</b>	75
10	<b>11hb</b>	3-MeO-C <sub>6</sub> H <sub>4</sub>	<b>14h</b>	63
11	<b>11ib</b>	3,5-diMeO-C <sub>6</sub> H <sub>3</sub>	<b>14i</b>	77

[a]See experimental section. [b] Isolated yields. [c] 7.0 mmol scale

It is important to note that the substitution pattern decorating structures **13** and **14** is not directly accessible by the established methodologies in the construction of biaryl<sup>[19]</sup> and salicylate-based structures<sup>[20]</sup> using simple and ready available precursors. In addition, the metal-free installation of two aromatic unprotected amine groups, which are relevant functional motifs in pharmacological and new materials research, is an appealing value of this methodology when compared with described metal catalyzed aminations.<sup>[21]</sup>

In summary, we have shown that tertiary skipped diynes **1** can be efficiently and selectively transformed into polysubstituted cyclohexadienones **10** and **11** via a divergent O-enolate driven novel domino process. The manifold uses benzylamine as the secondary amine to generate up to four new bonds (2 C-N, 1 C-C, 1 C=O) and one ring with excellent atom economy and an operationally simple protocol. Moreover, we have shown how these polysubstituted cyclohexadienones are suitable platforms for the access to multivalent aromatic scaffolds decorated with a rich functional pattern comprising: a biaryl (Ar, Ar), a salicylate (1,2-OH, COOH), an arylphenol (1,2-OH, Ar), a biarylamine (1,2-NH, Ar) and an anthranilate (1,2-NH,COOH). This substitution pattern is well suited for the generation of natural-product-like libraries throughout functional pairing strategies.<sup>[22]</sup> Such study is ongoing in our lab.

## Experimental Section

**General procedure for the synthesis of monoamines 10. Table 2, Method A.** Dibenzylamine (0.55 mmol) was added to a solution of diyne **1a** (188 mg, 0.50 mmol) in MeOH (50 mL) and the reaction mixture was stirred overnight at reflux. After removing the solvent under reduced pressure the products were purified by flash column chromatography (silica gel, EtOAc/CH<sub>2</sub>Cl<sub>2</sub>) to yield **10ab**. In certain cases it is useful to recrystallize the final product to remove small amounts of unreacted dibenzylamine (CH<sub>2</sub>Cl<sub>2</sub> and 1.5% EtOAc/Hexane). Alternatively, the chromatography can be avoided if the amount of subproduct cyclohexadienones **11** is not significant. Recrystallization typically affords the final product with yields similar to the reported ones in table 2.

**General procedure for the synthesis of monoamines 11. Table 2, Method B.** Dibenzylamine (1.05 mmol) was added to a solution of diyne **1a** (188 mg, 0.50 mmol) in a mixture of EtOH/CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O (4 mL/4 mL/1 mL) at room temperature. The reaction mixture was stirred overnight. After removing the solvent under reduced pressure the products were purified by flash column chromatography (silica gel, EtOAc/CH<sub>2</sub>Cl<sub>2</sub>) to yield **11ab**.

**General procedure for the synthesis of salicylates 13 and 14.** Cyclohexadienone **11ab** (738 mg, 1.00 mmol) was dissolved in MeOH (100 mL). Mg turnings (70 mmol) were added and the mixture was heated overnight at 65°C. After the reaction mixture was cooled to 0°C, 6M HCl was added slowly. Once the methanol was evaporated under reduced pressure, the aqueous phase was extracted twice with CH<sub>2</sub>Cl<sub>2</sub>. After removing the solvent at reduced pressure the crude products were dissolved in MeOH/CH<sub>2</sub>Cl<sub>2</sub> 1:1 (100 mL). 20% Pd(OH)<sub>2</sub>/C (90 mg) was added and the reaction mixture was hydrogenated with H<sub>2</sub> (1 atm) at room temperature for 16 hours. After filtration with celite and removal of the solvent under reduced pressure, the products were purified by flash column chromatography (silica gel, EtOAc/hexane) to afford **14a**.

## Acknowledgements

This research was supported by the Spanish MICINN and the European RDF (CTQ2008-06806-C02-02), the Spanish MSC ISCIII (RETICS RD06/0020/1046), FUNCIS (PI 43/09). S. L.-T. thanks Spanish MEC for a FPU grant. Authors thank technician Ms. Anna Jurado Varona for her experimental assistance.

**Keywords:** anthranilate • cyclohexadienone • domino • salicylate • skipped diynes.

[1] F. Tietze, G. Brasche, K. M. Gericke in *Domino reactions in Organic Synthesis*, Wiley-VCH: Weinheim, 2006.

- [2] *Construction reactions* are defined as those reactions that form skeletal bonds. See: a) J. B. Hendrickson, *J. Am. Chem. Soc.* **1975**, *97*, 5784-5800; b) T. Gaich, P. S. Baran, *J. Org. Chem.* **2010**, *75*, 4657-4673.
- [3] B. M. Trost, *Science* **1991**, *254*, 1471-1477.
- [4] N. Z. Burns, P. S. Baran, R. W. Hoffmann, *Angew. Chem.* **2009**, *121*, 2896-2910; *Angew. Chem. Int. Ed.* **2009**, *48*, 2854-2867.
- [5] P. A. Wender, V. A. Verma, T. J. Paxton and T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40-49.
- [6] For selected contributions, see: a) D. Tejedor, G. Méndez-Abt, L. Cotos, M. A. Ramirez, F. García-Tellado, *Chem. Eur. J.* **2011**, *17*, 3318-3321; b) L. León, C. Ríos-Luci, D. Tejedor, E. Pérez-Roth, J. C. Montero, A. Pandiella, F. García-Tellado, J. M. Padrón, *J. Med. Chem.* **2010**, *53*, 3835-3839; c) D. Tejedor, G. Méndez-Abt, F. García-Tellado, *Chem. Eur. J.* **2010**, *16*, 428-431; d) D. Tejedor, A. Santos-Expósito, F. García-Tellado, *Chem. Eur. J.* **2007**, *13*, 1201-1209; e) D. Tejedor, D. González-Cruz, A. Santos-Expósito, J. J. Marrero-Tellado, P. de Armas, F. García-Tellado, *Chem. Eur. J.* **2005**, *11*, 3502-3510; f) D. Tejedor, D. González-Cruz, F. García-Tellado, J. J. Marrero-Tellado, M. L. Rodríguez, *J. Am. Chem. Soc.* **2004**, *126*, 8390-8391; g) D. Tejedor, F. García-Tellado, J. J. Marrero-Tellado, P. de Armas, *Chem. Eur. J.* **2003**, *9*, 3122-3131.
- [7] D. Tejedor, S. López-Tosco, J. González-Platas, F. García-Tellado, *J. Org. Chem.* **2007**, *72*, 5454-5456.
- [8] A<sub>2</sub>BB' 4CRs refers to a four-component reaction that utilizes two different components (A and B) to give a product which incorporates into its structure two identical units of component A and two chemo-differentiated units of component B (B and B'). For full details and more examples of this type of multicomponent reactions: D. Tejedor, F. García-Tellado, *Chem. Soc. Rev.* **2007**, *36*, 484-491.
- [9] a) D. Tejedor, S. López-Tosco, J. González-Platas, F. García-Tellado, *Chem. Eur. J.* **2009**, *15*, 838-842; b) D. Tejedor, S. López-Tosco, J. González-Platas, F. García-Tellado, *Chem. Eur. J.* **2010**, *16*, 3276-3280.
- [10] For selected reviews, see: a) C. Grondal, M. Jeanty, D. Enders, *Nature Chem.* **2010**, *2*, 167-178; b) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590-1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570-1581.
- [11] From the large number of experimental results obtained from the reaction of diyne **1a** with different secondary amines under different reaction conditions, we have collected in Table 1 the most relevant and illustrating results related to this work.
- [12] The structures of these compounds were unambiguously assigned by single-crystal X-ray diffraction analysis. CCDC 820434 and CCDC 820435 contain the supplementary crystallographic data for the structures **10aa** and **11aa** respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
- [13] pKa (Bn<sub>2</sub>NH) = 8.76; pKa (PMDBA, **9c**) = 9.55; pKa (PNDBA, **9d**) = 6.98 (Calculated using the ACD/pKa dB program).
- [14] The reaction of pyrrolidine and related secondary amines with skipped diynes **1** in EtOH (or MeOH) presented a general scope with regard to the diyne. In all the assayed cases, the reactions afforded the corresponding diamine derivatives **11** in good to excellent yields. These results are not included in this work.
- [15] Although *i*PrOH, a less nucleophilic solvent, was selective in the formation of **11ab** (no **10ab** was detected) it was less efficient, as only 47% of the desired product was isolated after 16 hours.
- [16] Salicylates constitute core structures of pharmacologically important natural products. S. Bräse, A. Encinas, J. Keck, C. F. Nising, *Chem. Rev.* **2009**, *109*, 3903-3990.
- [17] D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893-930.
- [18] Cl-substituents at the aromatic ring were not tolerated. Mg/EtOH reduced the C<sub>sp<sup>2</sup></sub>-Cl to the corresponding C<sub>sp<sup>2</sup></sub>-H.
- [19] For selected reviews: a) J. A. Ashenhurst, *Chem. Soc. Rev.* **2010**, *39*, 540-548; b) R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461-1473; c) G. C. Fu, *Acc. Chem. Res.* **2008**, *41*, 1555-1564; d) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4516-4563; *Angew. Chem., Int. Ed.* **2005**, *44*, 4442-4489; e) J. Hassan, M. Sevignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359-1469.
- [20] a) M. Dai, Sarlah, M. Yu, S. J. Danishefsky, G. O. Jones, K. N. Houk, *J. Am. Chem. Soc.* **2007**, *129*, 645-657; b) H. Feist, P. Langer, *Synthesis* **2007**, 327-347.
- [21] J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534-1544.
- [22] For selected reviews see: a) T. E. Nilsen, S. L. Schreiber, *Angew. Chem.* **2008**, *120*, 52-61; *Angew. Chem. Int. Ed.* **2008**, *47*, 48-56; b) W. R. J. D. Galloway, A. Isidro-Llobet, D. R. Spring, *Nature Commun.* **2010**, *1*, doi:10.1038/ncomms1081; c) For a significant breakthrough in this area, see: D. Morton, S. Leach, C. Cordier, S. Warriner, A. Nelson, *Angew. Chem.* **2009**, *121*, 110-115; *Angew. Chem. Int. Ed.* **2009**, *48*, 104-109.

Received: ((will be filled in by the editorial staff))

Revised: ((will be filled in by the editorial staff))

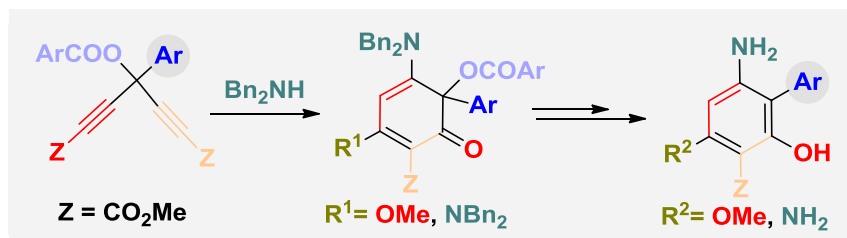
Published online: ((will be filled in by the editorial staff))

Entry for the Table of Contents (Please choose one layout only)

## Domino synthesis

David Tejedor\*, Sara López-Tosco,  
Javier González-Platas, Fernando  
García-Tellado\* .....Page – Page

**Diverted Domino Reactivity in  
Tertiary Skipped Diynes. A  
Convenient Access to  
Polyfunctionalized  
Cyclohexadienones and  
Multivalent Aromatic Scaffolds.**



**Diverting is the game!** A novel domino manifold has been implemented for the synthesis of cyclohexadienone based scaffolds from tertiary skipped diynes and secondary amines. The manifold takes

advantage of a novel O-enolate driven reactivity pattern discovered for these diynes. The scaffolds are conveniently transformed into the corresponding multivalent salicylate derivatives.