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

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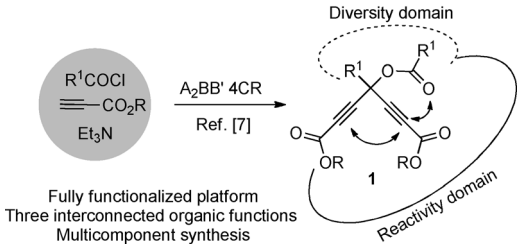
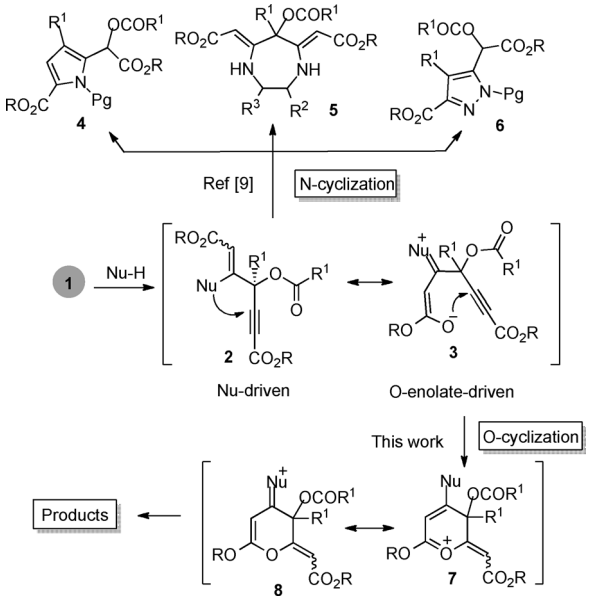
Domino reactions[1] constitute single-operation, multi-step processes able to generate two or more bonds under a constant set of reaction conditions. Usually, they transform simple starting materials into more complex chemical entities utilizing networks of construction reactions.[2] This property makes them excellent synthetic tools to carry out molecular construction with atom-,[3] redox-[4] and step-economy.[5] 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 motifs with biological relevance.[6] Skipped diynes **1**[7] constitute an example of such platforms (Scheme 1). They are conveniently synthesized in one step and on a multigram scale from alkyl propiolates and acid chlorides by a triethylamine-assisted multicomponent $A_2BB'4CR$.[8] 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[9] have shown how these C_7 units can be selectively transformed into polysubstituted pyrroles **4**,[9a] 1,4-diazepane derivatives **5**,[9b] or pyrazoles **6**,[9b] when they are made to react with primary amines, 1,2-diamines, and hydrazines, respectively (Scheme 2). These heterocycles are generated by N-cyclization of the corresponding enamine intermediates **2** (Nu = PgNH, $HNCH(R^2)CH(R^3)NH_2$, 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-



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



Scheme 2. Diverted domino reactivity of tertiary skipped diynes **1**.

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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 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_7 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 through 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,[10] 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, which possess 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. Table 1 summarizes the main experimental results,[11] 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 equiv) and pyrrolidine (**9a**; 1 equiv) in dichloromethane. After several assays, it was found that the reaction at room temperature for 16 h 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 (Table 1, entry 2). The structures of these two products,[12] which were unexpected, constituted experimental evidence of a reactivity shift in the diynic 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 a solvent allowed the diamine derivative **11aa** to be obtained in nearly quantitative yield (Table 1, entries 3–4). On the other hand, the reaction of diyne **1a** with dibenzylamine (**9b**) was shown 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%, Table 1, entry 5), the reaction in MeOH afforded the monoamine **10ab** (39%) and diamine **11ab** (53%, Table 1, entry 6).

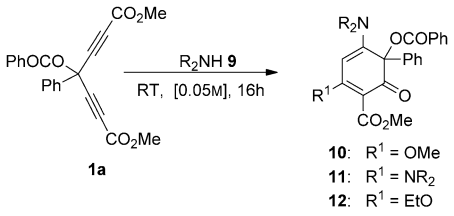
With these results at hand, it soon became evident that strong nucleophilic amines and/or less nucleophilic alcoholic solvents favored the formation of diamine derivatives **11**, whereas low nucleophilic amines and a stronger nucleophilic alcoholic solvent favored the formation of monoamine derivatives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

When dibenzylamine was used, the presence of product **12ab** with 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 the Supporting Information 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**, which share a similar steric environment at the nitrogen center but feature different electronic properties,[13] showed a clear relationship between the nucleophilicity of the amine and the ratio of monoamine **10**/diamine **11** in the reaction mixtures (Table 1, 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 the products and starting materials in the crude reaction mixture. 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

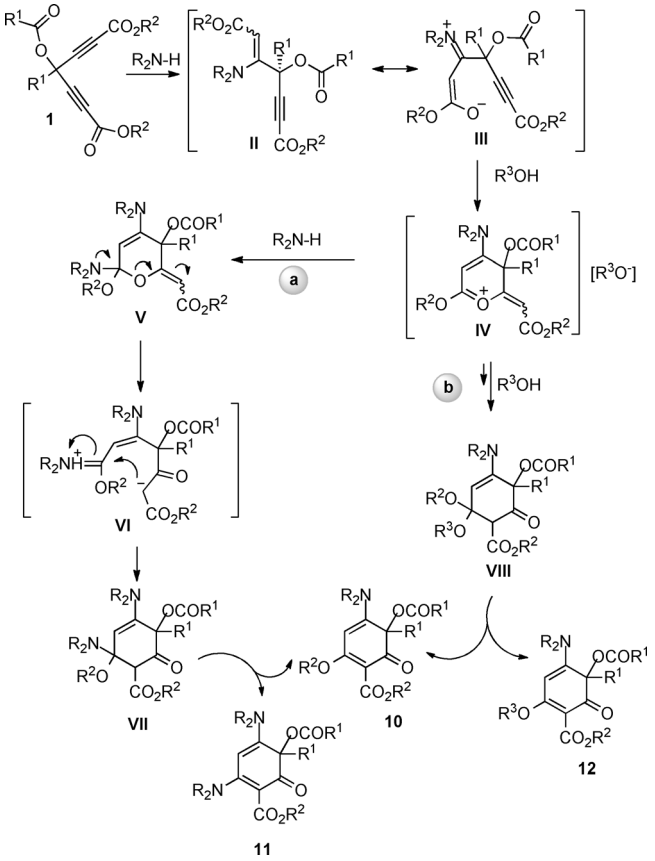
Table 1. Domino reaction of diyne **1a** and secondary amines **9a–d**.[a]



Entry	Solvent	Amine		10 [%]	11 [%]
1	CH_2Cl_2	C_4H_8NH[b]	**9a**	30	9
2	CH_2Cl_2	C_4H_8NH	**9a**	n.d.[c]	67
3	MeOH	C_4H_8NH	**9a**	n.d.	>99
4	EtOH	C_4H_8NH	**9a**	n.d.	>99
5	EtOH	Bn_2NH	**9b**	10[e]	86
6	MeOH	Bn_2NH	**9b**	39	53
7	MeOH[d]	Bn_2NH	**9b**	79	21
8	MeOH[d]	PMDBA[f]	**9c**	67	33
9	MeOH[d]	PNDBA[g]	**9d**	93[h]	7

[a] Reaction conditions: diyne (0.10 mmol), amine (0.22 mmol), solvent (2 mL). [b] 0.11 mmol. [c] n.d. = none detected. [d] 0.01 M. [e] Roughly equimolecular mixture of monoamides **11ab** and **12ab**. [f] PMDBA = bis(4-methoxyphenyl)methanamine. [g] PNDBA = bis(4-nitrophenyl)-methanamine. [h] 50% conversion (50% r.s.m).

Scheme 3. The scenario comprises two reaction pathways (**a** and **b**) diverging from a common intermediate **IV**. Pathway **a** is launched by the addition of a second amine unit on the

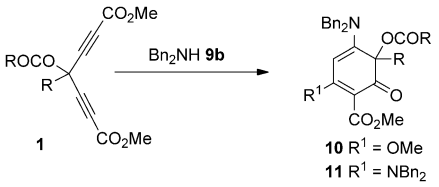


Scheme 3. O-enolate driven domino mechanistic proposal.

cyclic oxonium ion **IV** to give the orthoaminal **V**, which rearranges to aminal **VII** through the formation of the immonium-enolate **VI**. The elimination of R^2OH from **VII** delivers the diamino derivative **11**. The much less favored elimination of R_2NH 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 $= k_a$ [**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 a higher temperature. Whereas pyrrolidine (**9a**) meets the requirements of route **a** and it exclusively affords diamine derivative **11aa**[14] with independence of the reaction conditions, dibenzylamine (**9b**) can react following either of the two pathways, and the chemical outcome of the reaction will be 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 motifs 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**.

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 (0.01 M), 65 °C, 16 h) to afford monoamine **10ab** in 95% yield (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 alkynoate moiety. This steric effect resulted in a low-

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



Entry	R		Method	**10** [%][a]	**11** [%][a]
1	Ph	**1a**	A[b]	95	
2			B[c]		94
3			B[d]		91
4	2-ClC_6H_4	**1b**	A	84	
5			B		74
6	3-ClC_6H_4	**1c**	A	93	
7			B		86
8	4-ClC_6H_4	**1d**	A	92	
9			B		86
10	4-FC_6H_4	**1e**	A	95	
11			A[e]	94	
12			B		88
13	4-BiPh	**1f**	A	93	
14			B		80
15	4-MeC_6H_4	**1g**	A	96	
16			B		87
17	3-$MeOC_6H_4$	**1h**	A	93	
18			B		85
19	3,5-di$MeOC_6H_3$	**1i**	A	94	
20			B		81
21	*i*Pr	**1j**	A	85[f]	
22	C_6H_{11}	**1k**	A	84[f]	
23			B		40[g]

[a] Yields of isolated products. [b] Method A: diyne (0.10 mmol), dibenzylamine (0.11 mmol), MeOH (0.01 M), 65 °C, 16 h. [c] Method B: diyne (0.10 mmol), dibenzylamine (0.22 mmol), CH_2Cl_2/EtOH/H_2O (4:4:1), (0.0.5 M), RT, 16 h. [d] 15 mmol scale.[e] 7.5 mmol scale. [f] 3 days. [g] 1 week.

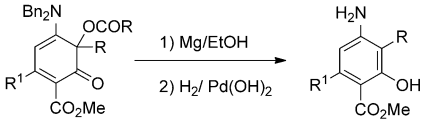
ering of the reactivity of aliphatic diynes **1j** and **1k**, which needed more forcing conditions (3 days) to be efficiently converted into their corresponding monoamine derivatives **10jb** and **10kb** (Table 2, entries 21 and 22).

With the monoamine derivatives **10ab–kb** at hand, we explored the selective formation of the corresponding diamine derivatives **11ab–kb**. Preliminary experiments had shown that the reaction of dibenzylamine (**9b**) and diyne **1a** in EtOH generated the diamine **11ab** in good yield (86%), however it was contaminated with significant amounts of monoamine derivatives **10–12ab** (10%, Table 1, entry 5). According to Scheme 3, 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.[15] Water was envisioned as a convenient co-solvent because it was expected that it would lower the nucleophilicity of EtOH through coordination, whereas it would increase the polarity of the reaction medium. After several experimental trials, we found that the mixture of EtOH/H_2O (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_2Cl_2 to the aqueous solvent cocktail brought the diynes **1a–k** into solution increasing the reaction efficiency without eroding the selectivity of the reaction. (Method B, Table 2). Under these conditions, aromatic diynes **1a–i** uniformly reacted with two equivalents 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^3 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 (Table 2, 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** (Table 3), which constitute valuable examples of salicylate derivatives[16] with a privileged biaryl[17] motif (R = Ar) and one (compound **13**) or two (compound **14**) amine groups in their structures. This transformation takes advantage of the presence of the tertiary aryloate group that is positioned α 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 aroylate group. The reduction of this hindered ketone was problematic but it was conveniently achieved using an excess of Mg in EtOH and heated to reflux to afford the corresponding phenol derivative in moderated to good yields (Table 3).[18] The amine deprotection under standard conditions (H_2–$Pd(OH)_2$) 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 (Table 3, entry 2).

Table 3. Synthesis of multivalent aromatic platforms **13** and **14**.[a]



10: R^1 = OMe
11: R^1 = NBn_2

13: R^1 = OMe
14: R^1 = NH_2

Entry	Starting material	R	Product	Yield [%][b]
1	**10ab**	Ph	**13a**	75
2	**10eb**	4-FC_6H_4	**13e**	68[c]
3	**10hb**	3-$MeOC_6H_4$	**13h**	62
4	**10ib**	3,5-di$MeOC_6H_3$	**13i**	75
5	**10kb**	C_6H_{11}	**13k**	48
6	**11ab**	Ph	**14a**	76
7	**11eb**	4-FC_6H_4	**14e**	74
8	**11fb**	4-BiPh	**14f**	50
9	**11gb**	4-MeC_6H_4	**14g**	75
10	**11hb**	3-$MeOC_6H_4$	**14h**	63
11	**11ib**	3,5-di$MeOC_6H_3$	**14i**	77

[a] See the Experimental Section. [b] Yield of isolated product. [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[19] and salicylate-based structures[20] 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.[21]

In summary, we have shown that tertiary skipped diynes **1** can be efficiently and selectively transformed into polysubstituted cyclohexadienones **10** and **11** by a divergent O-enolate-driven domino process. The manifold uses benzylamine as the secondary amine to generate up to four new bonds (2C–N, 1C–C, 1C=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;[22] such study is ongoing in our laboratory.

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_2Cl_2) to yield **10ab**. In certain cases it is useful to recrystallize the final product to remove small amounts of unreacted dibenzylamine (CH_2Cl_2 and 1.5% EtOAc/Hexane). Alternatively, 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_2Cl_2/H_2O (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_2Cl_2) 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, HCl (6 M) was added slowly. Once the methanol was evaporated under reduced pressure, the aqueous phase was extracted twice with CH_2Cl_2. After removing the solvent at reduced pressure, the crude products were dissolved in MeOH/CH_2Cl_2 (1:1, 100 mL). $Pd(OH)_2$/C (20%, 90 mg) was then added and the reaction mixture was hydrogenated with H_2 (1 atm) at room temperature for 16 h. 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

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Keywords: cyclization · cyclohexadienone · domino reactions · multicomponent reactions · skipped diynes

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[8] $A_2BB'4CRs$ refers to a four-component reaction that utilizes two different components (A and B) to give a product that 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, see: D. Tejedor, F. García-Tellado, *Chem. Soc. Rev.* **2007**, *36*, 484–491.

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[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 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.

[13] pK_a (Bn_2NH) = 8.76; pKa (PMDBA, **9c**) = 9.55; pK_a (PNDBA, **9d**) = 6.98 (Calculated using the ACD/pK_a 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 since only 47% of the desired product was isolated after 16 h.

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