Ambiphilic allenes: synthesis and reactivity[†]

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Ambiphilic allenes are generated by an organocatalyzed domino reaction of alkyl propiolates and aromatic 1,2-diketones; in the absence of any external chemical agent, these allenes perform a thermally-driven dimerization reaction to generate the corresponding fully-substituted cyclobutanes in a regio- and highly stereoselective manner.

The search for organic molecules expressing ambiphilic reactivity is a sought-after challenge in organic chemistry.¹ Isocyanides constitute a paradigmatic example with a carbon atom able to react with both electrophiles and nucleophiles.² Allenes armed with an e-donating group and an e-acceptor group at the C3- π system (1,3-relationship) are expected to express this property at the C2 position (Fig. 1). Allene reactivity is regulated to a large extent by the substitution pattern adorning the C3- π system.³ In this sense, although the individual effects of e-donating (EDG) and e-withdrawing groups (EWG) on allene reactivity are well established (Fig. 1), 3a,4 the overall effect when they operate in a 1,3-assonant manner remains to be evaluated. With these precedents we have initiated a research program aimed at the synthesis and study of 1,3-bifunctional allenes as synthetically relevant ambiphilic reactants for the development of novel domino and multicomponent reactions. For experimental reasons related to our previous work on the chemistry of non-metallic conjugated acetylides,⁵ we selected the allenic esters 1 as the target bifunctional allene for these studies.6

We envisioned that these allenic esters could be synthesized by a tertiary amine-catalyzed domino reaction involving 1,2-diketones and terminal conjugated acetylides (Scheme 1). The manifold was devised on the basis of our previous studies on the organocatalyzed generation of conjugated acetylides I and their reactivity against different types of electrophiles.⁷ It was hypothesized that the intermediate II, obtained from the nucleophilic addition of I onto the 1,2-diketone, should suffer



Fig. 1 Substituent effect on allene reactivity.



Scheme 1 Tertiary amine-catalyzed domino-based manifold.

a rearrangement that would lead to the rupture of the more labile CO–CO bond (BE \approx 70 kcal mol⁻¹) *via* epoxide III.⁸ Interestingly, and in accordance with our previous experiences, in the process to form the desired allene 1, intermediate IV would be basic enough to generate more acetylide and regenerate the nucleophile from its β -ammonium acrylate resting state, and thus, keep the catalytic cycle going.

To test this proposal, we chose the Et_3N -catalyzed reaction of benzil (2a) and methyl propiolate (3a) as the model reaction (Scheme 2). It was found that when a solution of both reactants in dichloromethane was treated at 0 °C with Et_3N (10 mol%), a smooth reaction occurred affording a major product which slowly transformed into other products. Interestingly, this intermediate could be detected by TLC but it could not be isolated for characterization. A more detailed study of the reaction showed that after 10 min at 0 °C the

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Scheme 2 Et₃N-catalyzed reaction of benzil and methyl propiolate.

practical totality of the starting benzil had been transformed into this new compound. Ouenching the reaction at this time with pyrrolidine afforded enamine 4 (77%) which could be isolated and further hydrolyzed to ketone 5. Because enamine 4 is the expected addition compound on an allene such as **1aa**. we assigned this structure to the main reaction intermediate, thus verifying the postulated cascade of events shown in Scheme 1. This assignment was further corroborated by running the reaction in an NMR tube using CDCl₃ as solvent. ¹³C-NMR analysis of the reaction mixture at different times showed that the quaternary allene peak at 210 ppm,^{6c} clearly visible just minutes after setting the reaction, totally disappeared when the reaction was completed. In a separate experiment, the reaction was allowed to progress overnight at room temperature and under these conditions, allene laa was fully transformed into the mixture of cyclobutanes 6aa-7aa and cyclobutene 8aa (80%) (Scheme 2). Prolonged treatment of this mixture with Et₃N (1 equiv.; 24 h) generated the mixture of cyclobutanes 6aa and cyclobutenes 8aa via quantitative transformation of 7aa into 8aa. Structures of cyclobutane 6aa and cyclobutene 8aa were unambiguously confirmed by X-ray crystallographic analyses.[†] To the best of our knowledge, this protocol constitutes the first example of a synthesis of allenes involving a rearrangement of 1,2-diarylketones.

Cyclobutanes **6aa** and **7aa** constitute therefore the chemical picture of the allene's basal reactivity which is expressed as a stereoselective and self-biased formal [2 + 2]-cycloaddition. Due to the novelty and functional complexity of these cyclobutanic products, we undertook a study of the synthetic scope of this transformation (Table 1‡). The reaction proved to be general with regard to both the alkyl propiolate (entries 1–5) and the electronic nature of the aromatic 1,2-diketones (entries 1, 6–10) affording a combined yield of cyclic products

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 Table 1
 Et₃N-catalyzed reaction of 1,2-diketones 2 with alkynoates 3

Entry	2	Ar =	3		6 (dr) ^{<i>a</i>}	8	Rsm ^b
1	а	Ph	а	Me	54 (97:3)	26	10
2	а	Ph	а	Me	$47(97:3)^{c}$	21	
3	а	Ph	b	Et	48 (96:4)	21	13
4	а	Ph	с	tBu	40 (9:1)	28	23
5	а	Ph	d	Bn	43 (97:3)	20	22
6	b	4-Me-C ₆ H ₄	а	Me	51 (97:3)	20	13
7	с	$4 - F - C_6 H_4$	а	Me	$55 (\geq 99)$	17	14
8	d	4-MeO-C ₆ H ₄	а	Me	50 (97:3)	14	24
9	e	3-MeO-C ₆ H ₄	а	Me	42 (96:4)	18	14
10	f	$2 = (2 - FurylCO)_2$	а	Me	22 (≥99)	6	20
^a Trans ¹ H-NM	s : 1R s	<i>cis</i> ratio determined ignals. ^b Recovered 1,	l by 2-di	integ ketone	gration of re . ^c 100 mmol	eprese scale	entative

6 and **8** typically of 60–75%. Although relatively small amounts of 1,2-diketone starting materials were always recovered, use of excess propiolate did not increase the conversion. In all of the cases, cyclobutanes **6** were obtained as the major products with an impressive high *trans*-diastereoselectivity (more interesting C_2 -symmetry), while minor cyclobutenes **8** were generated as single geometric isomers. The regioselectivity of the formal [2 + 2]-cycloaddition is moderate and it remains practically unchanged in the -78° to 20 °C temperature range. Finally, and not less importantly for practical purposes, the reaction could be easily scaled up to 100 mmol with a similar chemical efficiency (68% of combined yield) (entry 2).

Cyclic acenaphthenequinone **2g** afforded spiro-1,3dioxolane derivatives **9** and a small amount of **6ga** (Scheme 3).⁷ Observe that in this case, the CO–CO σ -bond is strong enough to inhibit the rearrangement and the transformation is funnelled toward the 1,3-dioxolane **9** formation through an **ABB**' three-component acetylide-driven process.⁹ When fixing the stoichiometry to that required for this process (2:1), the yield of **9** goes up to 70% (mixture of isomers) and **6ga** is not produced.

A preliminary DFT study at the B3LYP/6-31G* level showed a HOMO–LUMO gap of 0.17030 eV for allene **1aa**, a magnitude sufficiently small to allow an ambiphilic reactivity profile (Table 2).¹⁰ This property also explains the observed smooth tendency for dimerization and the complete observed regioselectivity. Table 2 highlights the activating effect exercised by both the Ph and OBz groups allocated at C_3 and the opposite effect played by the ester group at C_1 . Although a widely accepted stepwise mechanism involving a perpendicular bisallyl diradical¹¹ would explain the observed



Scheme 3 Acetylide-driven 1,3-dioxolane 9 formation.

Table 2 HOMO-LUMO energies (eV) for R^1R^2C C=CHR^3

\mathbb{R}^1	\mathbb{R}^2	R ³	НОМО	LUMO	ΔE
Н	Н	Н	-0.26297	0.02065	0.28362
Ph	Н	Н	-0.21846	-0.02670	0.19176
OBz	Н	Н	-0.24221	-0.05275	0.18946
Н	Н	CO_2Me	-0.26746	-0.03807	0.22939
Ph	OBz	Н	-0.21814	-0.04983	0.16831
Ph	OBz	CO ₂ Me	-0.22733	-0.05703	0.17030

regio- and stereoselectivity, a concerted mechanism cannot be ruled out. $^{\rm 12}$

In summary, we have reported a novel and efficient organocatalytic synthetic manifold to gain access to bifunctional allenes 1 from readily available starting materials, under mild reaction conditions and in very short periods of time. In the absence of other chemical reactants, these allenes suffer a remarkably smooth thermally-driven dimerization to form the functionalized complex cyclobutanes 6 and cyclobutenes **8**. Overall, the reaction mainly generates one C_2 -symmetric cyclobutane ring featuring two quaternary aromatic esters, two exocyclic conjugated aliphatic esters, and thus, a (Z,Z)-1,3-diene function. Interestingly, the reaction network forms two C-O and four C-C bonds, while it breaks only two C-C bonds. Finally, and not less important, the in situ generation of these allenes is mild enough to be compatible with a large number of organic functionalities and it constitutes an excellent workbench for the discovery of new complexity generating processes. The efficient formation of enamine 4 is a good example of this property. This issue is being developed in our lab.

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Notes and references

‡ **Representative procedure:** 1,2-diketone **2a** (3.00 mmol) and methyl propiolate (**3a**) (3.00 mmol) are dissolved in CH₂Cl₂ (5 mL) and the solution is cooled to 0 °C in an ice bath. Et₃N (0.30 mmol) is added and the reaction is allowed to react overnight without further cooling. Et₃N (3 mmol) is added and the reaction is allowed to react for one additional day (this step simplifies the isolation of **6aa** while **7aa** *cis/trans* transforms into **8aa**. Purification of products **6aa** *trans/cis* and **8aa** was carried out by flash column chromatography (silica gel, *n*-hexane–EtOAc 80 : 20 to 60 : 40). Cyclobutane **6aa** *trans*-isomer (major): white solid, mp = 181.0–182.6 °C; ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 3.37 (s, 6H), 6.86 (s, 2H), 7.16–7.29 (m, 10H),

7.41 (tt, J = 7.4 and 1.3 Hz, 2H), 7.56 (m, 4H), 7.69 (m, 4H), ¹³C NMR (100 MHz, CDCl₃, 25 °C): $\delta = 51.5$, 92.4, 117.8, 127.6, 128.0, 128.1, 128.2, 129.2, 129.9, 132.5, 134.8, 151.2, 163.3, 164.7; IR (HCCl₃): $\tilde{\nu} = 3027.8$, 1730.3, 1449.9, 1436.1, 1343.8, 1268.1, 1222.3, 1108.6 cm⁻¹; anal. calc. for C₃₆H₂₈O₈: C, 73.46; H, 4.79. Found: C, 73.47; H, 4.71%; m/z (%): 588 (0.3) [M⁺], 362 (8.4), 162 (28), 130 (19), 105 (100), 77 (32). **Cyclobutene 8aa**: yellow solid, mp = 156.5–157.9 °C; ¹H NMR (400 MHz, CDCl₃, 25 °C): $\delta = 3.32$ (s, 3H), 3.38 (s, 3H), 6.08 (s, 1H), 7.33–7.41 (m, 6H), 7.46–7.54 (m, 6H), 7.65 (tt, J = 7.5 and 1.3 Hz, 2H), 8.19 (m, 2H); ¹³C NMR (100 MHz, CDCl₃, 25 °C): $\delta = 51.0$, 51.5, 110.4, 126.5, 127.5, 127.9, 128.0, 128.6, 128.77, 128.79, 129.0, 129.5, 130.1, 131.1, 133.9, 134.4, 136.5, 142.2, 149.5, 156.6, 161.5, 164.6, 165.4; IR (HCCl₃): $\tilde{\nu} = 3028.2, 2953.0, 1731.6, 1435.9, 1258.0, 1063.4$ cm⁻¹; anal. calc. for C₂₉H₂₂O₆: C, 74.67; H, 4.75. Found: C, 74.77; H, 5.00%; m/z (%): 466 (24) [M⁺], 330 (10), 215 (17), 106 (19), 105 (100), 77 (60).

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