ARTICLE

Synthesis of bicyclic vinyl triazenes by Ficini-type reactions

Carl Thomas Bormann,[a] Farzaneh Fadaei-Tirani,[a] Rosario Scopelliti,[a] and Kay Severin[a]*

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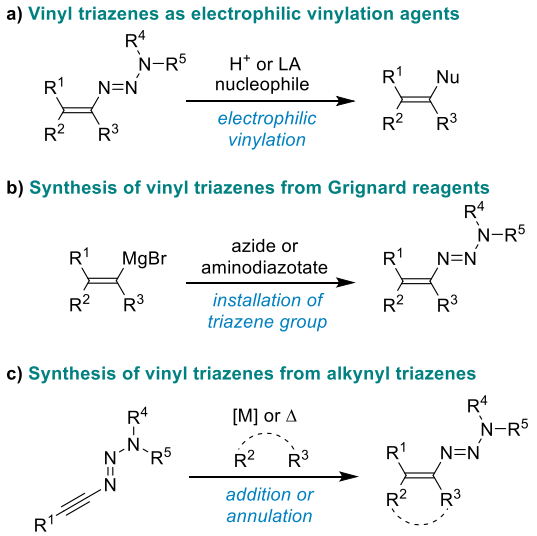
Cyclic olefins with triazene functions can display interesting reactivity, but synthetic access to these compounds is limited thus far. Herein, we describe the synthesis of cyclobutenyl triazenes fused to cyclopentanone or cyclohexanone rings. The bicyclic compounds are obtained by Lewis acid-catalyzed [2+2] cycloaddition reactions of 1-alkynyl triazenes and enones. In the presence of Me_2AlCl, bicyclic [4.2.0] triazenes rearrange into [3.2.1] ring systems. The triazene function in the latter can be used for further functionalizations. Notably, we show that vinyl triazenes can serve as substrates for Pd-catalyzed cross-coupling reactions with arylboronic acids.

Introduction

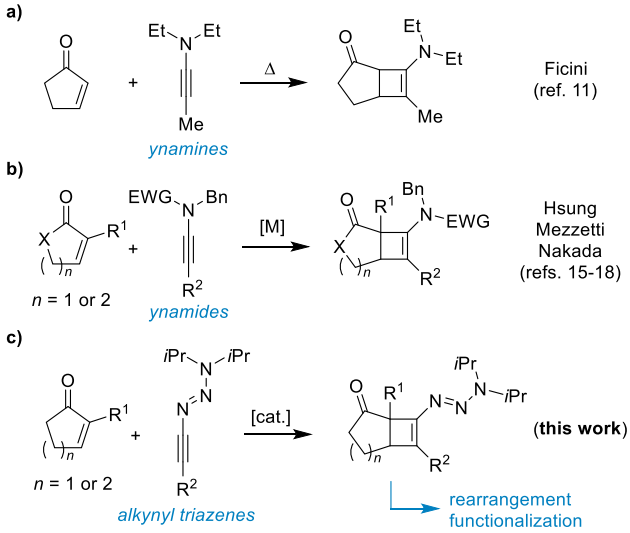
1-Vinyl triazenes are of interest in organic chemistry as bench-stable electrophilic vinylation agents.[1] The reactivity of vinyl triazenes is unleashed by Brønsted or Lewis acids, which promote cleavage of the triazene function and introduction of nucleophiles (Scheme 1a).



Scheme 1. Upon activation with Brønsted or Lewis acids (LA), vinyl triazenes serve as electrophilic vinylation reagents (**a**). Vinyl triazenes can be synthesized from vinyl Grignard reagents (**b**) or 1-alkynyl triazenes (**c**).

Vinyl triazenes can be obtained by reaction of vinyl Grignard reagents with azides[1–4] or aminodiazotates[5] (Scheme 1b). However, the use of those methods is limited by the low functional group tolerance of Grignard reagents. Alternatively, the synthesis of vinyl triazenes can be accomplished by addition reactions to the triple bond of 1-alkynyl triazenes (Scheme 1c).[1,6–10] Different types of reactions have been explored in this context, including Pd-catalyzed haloallylations, hydrogenations, and hydroarylations,[6] Ru-catalyzed [2+2] cycloaddition reactions with bicyclic alkenes,[7] Rh-catalyzed annulation reactions with functionalized aryl boronic acids,[8] and $Sc(OTf)_3$-catalyzed reactions with donor-acceptor-substituted cyclopropanes.[9] Furthermore, vinyl triazenes were obtained in thermal reactions between 1-alkynyl triazenes and ketenes or tetracyanoethylene.[9]

[2+2] Cycloaddition reactions between alkynes and enones can be achieved with highly nucleophilic ynamines. The coupling of cyclopentenone and N,N-diethylamino-1-propyne was first reported by Ficini and Krief in 1969 (Scheme 2a).[11] In subsequent studies, it was shown that other enones (e.g. cyclohexenones) are suited substrates as well.[12,13]



Scheme 2. [2+2] Cycloaddition reactions between enones and ynamines (**a**), ynamides (**b**), or 1-alkynyl triazenes (**c**).

[a] *Laboratory of Supramolecular Chemistry, EPFL SB ISIC LCS, BCH 3307 1015 Lausanne (Switzerland). E-mail: kay.severin@epfl.ch.*
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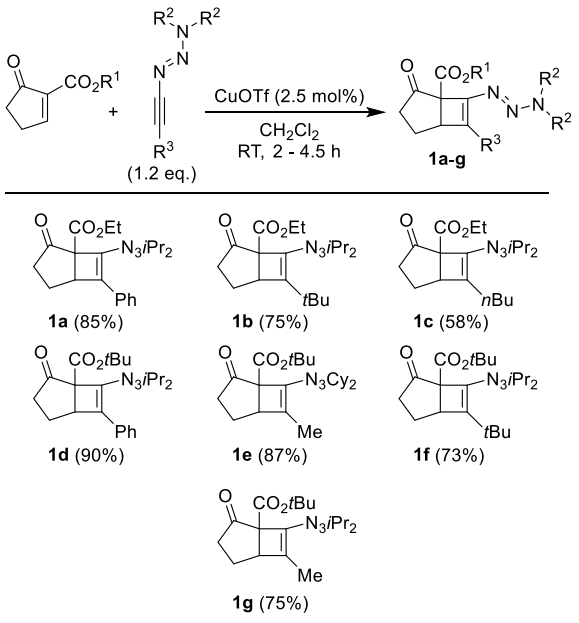
Due to the presence of an electron-withdrawing group, ynamides are less reactive than ynamines. The tamed reactivity facilitates synthesis, handling, and storage, and ynamides have become popular reagents in synthetic chemistry.[14] Ficini-type reactions with ynamides were first reported by Hsung and co-workers (Scheme 2b).[15] Thermally induced cycloadditions were not successful, but the reactions proceeded in the presence of catalytic $CuCl_2$ and $AgSbF_6$. When $AgNTf_2$ was used instead of $AgSbF_6$, the reaction could also be performed without $CuCl_2$.[16] The asymmetric synthesis of cyclobutenyl amides starting from α-unsaturated β-ketoesters was reported by the groups of Mezzetti[17] and Nakada.[18] As catalysts, chiral Ru(II) or Cu(II) complexes were employed. A catalyst-free cycloaddition of ynamides with highly activated enones (cyclic isoimidium salts) has also been described.[19]

Below, we show that Ficini-type reactions are possible with 1-alkynyl triazenes if appropriate Lewis acids are used as catalysts (Scheme 2c). The resulting cyclobutenyl triazenes can be rearranged under mild conditions into [3.2.1] bicyclooctenones, and the triazene group can be used for further functionalizations.

Results and Discussion

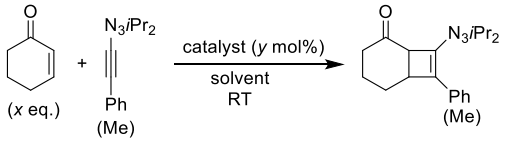
First, we investigated the reaction of ester-substituted cyclopentenones with 1-alkynyl triazenes. Using CuOTf as Lewis-acidic catalyst (2.5 mol%) and dichloromethane as solvent,[17] the desired cyclobutenyl triazenes were obtained in good yields (Scheme 3). Aliphatic and aromatic substituents on the alkyne were well tolerated. Changing from an ethyl to a more bulky *tert*-butyl ester did not adversely affect the yield.



Scheme 3. Synthesis of cyclobutenyl triazenes from ester-substituted cyclopentenones.

Proceeding to less activated, hence more challenging substrates, we turned to α,β-unsaturated ketones. Silver and copper salts, which are suitable catalysts for the analogous reaction with ynamides,[16,17] were ineffective (Table 1, entries 1 and 2). Traces of product were observed with $AgBF_4$ and a methyl-substituted triazene. However, synthetically useful amounts were not obtained. Instead, tris(pentafluorophenyl)borane (BCF) was found to be an effective catalyst (entry 3). A brief solvent screen revealed toluene as the most suitable solvent (entries 3–6). Lowering the catalyst concentration to from 5 to 2.5 mol% did benefit the yield (entry 7), but further reduction of the BCF concentration to 1 mol% led to a pronounced drop in yield (entry 8). Finally, a longer reaction time of 24 h slightly improved the yield (entry 9). Reducing the excess of cyclohexenone from 2.5 to 1.2 equivalents was possible, but the catalyst loading had to be increased to achieve an acceptable yield (entry 10).

Table 1. Optimization of the reaction between cyclohexenone and 1-alkynyl triazenes.



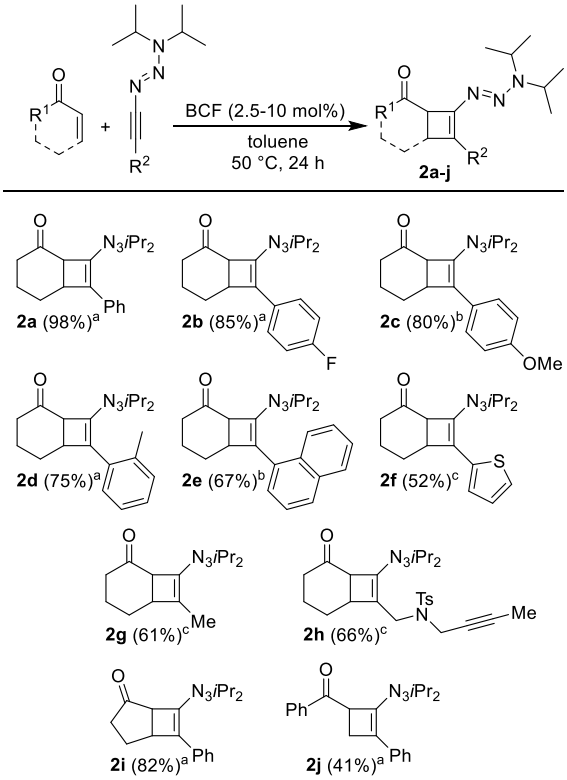
Entry	*x*	Catalyst	*y*	Solvent[a]	Time [h]	Yield [%][b]
1	1.2	CuOTf	4.5	DCM	3.5	n.d.[c]
2	1.2	$AgBF_4$	10	DCM	28	12[d]
3	2.5	BCF	5	DCM	16	65
4	2.5	BCF	5	Ph-Cl	16	72
5	2.5	BCF	5	DCE	16	71
6	2.5	BCF	5	Toluene	16	80
7	2.5	BCF	2.5	Toluene	16	90[e]
8	2.5	BCF	1	Toluene	16	16[e]
9	**2.5**	**BCF**	**2.5**	**Toluene**	**24**	**98[d,e]**
10	1.2	BCF	5	Toluene	24	88[e]

a) Concentration: 0.2 M. b) Determined by NMR spectroscopy using $MeNO_2$ as internal standard after filtration over silica and removal of volatiles under vacuum. c) Me instead of Ph substituent. d) Isolated yield. e) Filtered over alumina

With the optimized conditions at hand, we started to investigate the scope of the reaction (Scheme 4). Triazenes with aromatic, heteroaromatic, and alkyl substituents at the triple bond could be used as substrates for the reaction, providing cyclobutenyl triazenes in yields between 52 and 98% (**2a**–**2g**).

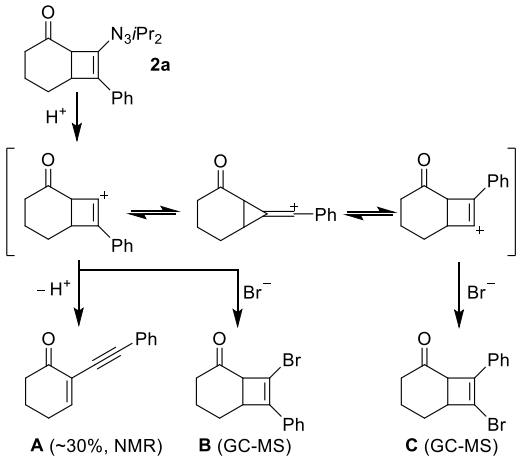
The importance of the triazene function as an activating group was evidenced by a reaction with a substrate featuring two alkyne groups, one with a methyl substituent and one with a N_3iPr_2 substituent. Only the triazene-activated alkyne was found to react with cyclohexanone, giving **2h** in 66% yield.

Using cyclopentenone instead of cyclohexanone gave the addition product **2i** in 82% yield. For cycloheptenone, on the other hand, no conversion was observed. In terms of acylic enones, we were able to convert phenyl vinyl ketone into a cyclobutenyl triazene, albeit with low yield (41%). No coupling reaction was observed for acrylate esters. It is worth noting that the BFC concentrations had to be adapted to the specific substrate.



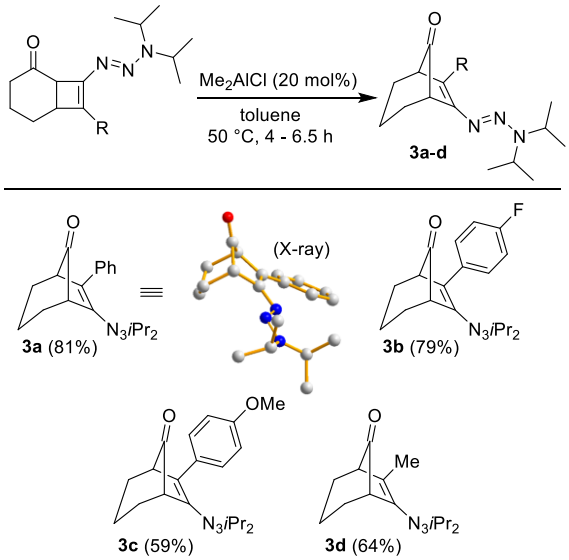
Scheme 4. Synthesis of cyclobutenyl triazenes from α,β-unsaturated ketones. a) 2.5 mol% BCF, b) 5 mol% BCF, c) 10 mol% BCF.

Previously, we had reported Ru-catalyzed [2+2] cycloaddition reactions of 1-alkynyl triazenes and strained alkenes (e.g. 1,4-dihydro-1,4-epoxynaphthalene).[7] Under acidic conditions, the triazene group in the resulting products could be replaced by a variety of different nucleophiles. Attempts to perform similar substitution reactions with the cyclobutenyl triazenes described herein were largely unsuccessful. The addition of acids to the triazenes resulted in a conversion, but a complex mixture of products was observed in all cases. Potential problems are acid-promoted ring-opening reactions of the cyclobutene ring.[11,12] For example, we have examined the reaction of **2a** with HBr (Scheme 5). GC-MS and ^{1}H-NMR analysis of the crude reaction mixture revealed a complex mixture of products, including alkyne **A**, originating from ring-opening of the cyclobutene. The formation of **A** is facilitated by the inherent strain of the cyclobutenyl ring[20] and by the acidity of the proton α to the carbonyl group. Furthermore, several species with the expected mass and isotope pattern of the desired brominated product were detected via GC-MS (two potential products, **B** and **C**, are shown in Scheme 5). This result suggests that the putative vinyl cation,[21] which is generated upon acidic cleavage of the triazene group, undergoes various rearrangements before being trapped by bromide.



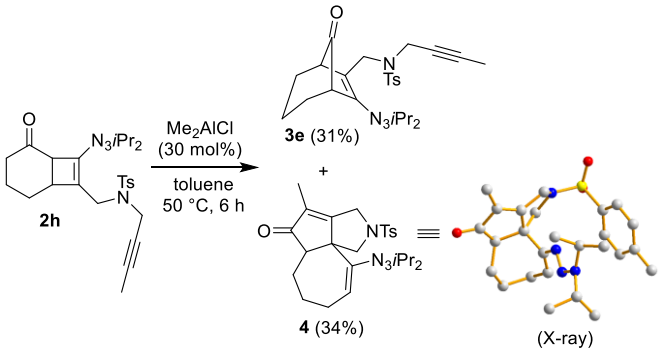
Scheme 5. Reaction of **2a** with HBr; Conditions: **2a** (1 eq.), HBr (6 eq.), Et_2O, 0 °C to RT, 3 h.

The results prompted us to explore if we could perform targeted rearrangements of cyclobutenyl triazenes. Hsung and co-workers have reported the $AlCl_3$-catalyzed conversion of fused cyclobutenyl amides into [3.2.1]-bicyclic ketones.[22] An analogous reaction could be realized with cyclobutenyl triazenes **2**. In the presence of catalytic amounts of Me_2AlCl (20 mol%), bicyclooctenonyl triazenes (**3a**–**3d**) were obtained in yields between 59 and 81% (Scheme 6). The structure of **3a** was confirmed by single-crystal X-ray analysis. It is worth noting that the rearrangements occurred under mild conditions when compared to what was reported by Hsung et al. (20 mol% Me_2AlCl vs. 40 mol% $AlCl_3$; 50 °C vs 105 °C).[22]



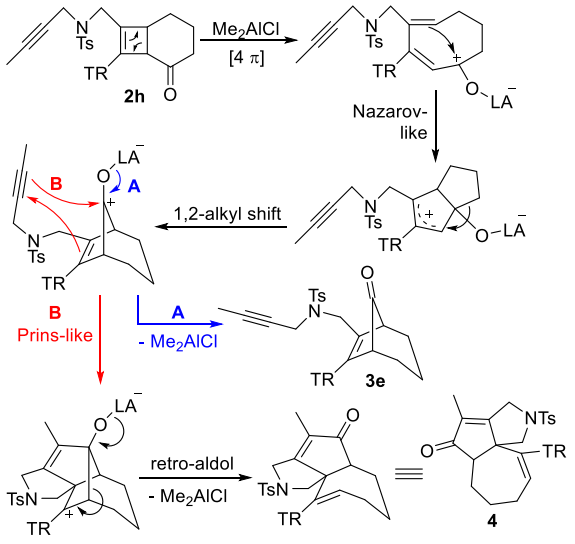
Scheme 6. Me_2AlCl-catalyzed rearrangement of cyclobutenyl triazenes.

In the case of **2h**, the tricyclic vinyl triazene **4** was obtained along with the expected [3.2.1]-bicyclic ketone **3e** in a 1.1:1 ratio (Scheme 7). The structure of **4** was confirmed by single-crystal X-ray analysis.



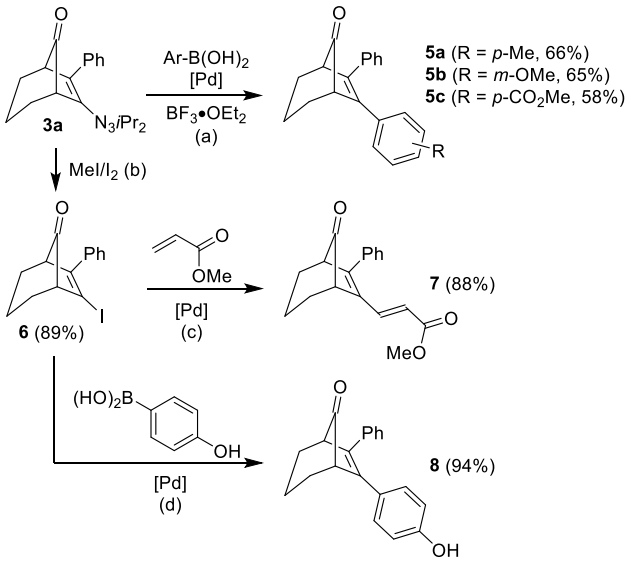
Scheme 7. Me_2AlCl-catalyzed rearrangement of **2h** gives a mixture of **3e** and **4**.

As suggested earlier[22], the mechanism of the formation of rearrangement products **3a–e** and **4** likely involves a common intermediate originating from the initial formation of a strained *cis*,*trans*-cyclooctadienone, subsequent Nazarov-like ring closure and a 1,2-alkyl shift. Dissociation of the Lewis acid leads to rearrangement products **3a**-**e** (Scheme 8, A). On the other hand, **4** could be formed by a Prins-like intramolecular reaction of the alkyne, followed by a retro-aldol reaction (Scheme 8, B).



Scheme 8. Proposed mechanism for the formation of **3e** (pathway A) and **4** (pathway B) from **2h**.[22] LA = Me_2AlCl, TR = 3,3-diisopropyltriaz-1-en-1-yl. The mechanism for the formation of **3e** and **3a**-**d** is assumed to be analogous.

Subsequently, we have examined the possibility of using the triazene function for further derivatizations. The reactions were performed with the bicyclic ketone **3a** as a representative example. Brønsted-acid induced cleavages were not successful, possibly because of the high ring strain of the putative cyclopentenyl cation intermediate.[23] However, a $BF_3{\cdot}OEt_2$-induced Suzuki-type reaction with arylboronic acids, as previously reported for aryltriazenes,[24] was successfully implemented to obtain substituted *Z*-stilbenes (Scheme 9a). By using a cross-coupling strategy, it is possible to obtain products with complete regioselectivity (**5a**), to override the inherent regioselectivity for electrophilic substitutions (**5b**), or to introduce arenes, which display low reactivity in cationic vinylations (**5c**).



Scheme 9. Derivatization of **3a;** a) Ar-$B(OH)_2$ (2 eq.), $Pd(PPh_3)_4$ (0.1 eq.), $BF_3{\cdot}OEt_2$ (2 eq.), DME, 4 h, RT. b) I_2 (0.2 eq.), MeI, 130 °C, 4 h. c) methylacrylate (1.5 eq.), $Pd(OAc)_2$ (0.1 eq.), NEt_3 (1.5 eq.), DMF, 50 °C, 14 h. d) Ar-$B(OH)_2$ (2 eq.), $Pd(OAc)_2$ (0.1 eq.), K_2CO_3 (2 eq.), DMF/H_2O 4:1, 85 °C, 6 h.

Conversion of the vinyl triazene **3a** to a vinyl iodide, **6**, was achieved in MeI in the presence of I_2 at elevated temperatures (Scheme 9b). This transformation could proceed via a radical pathway, as discussed for the iodination of aryl triazenes.[25,26] Vinyl iodide **6** was then used for Pd-catalyzed Heck- and Suzuki-reactions to give the coupling products **7** and **8** in high yields (Scheme 9c and 9d).

Conclusions

Cyclobutenyl triazenes fused to cyclopentanone or cyclohexanone rings were obtained by [2+2] cycloaddition reactions of 1-alkynyl triazenes and enones. Reactions with ester-substituted cyclopentenones are efficiently catalyzed by CuOTf, whereas cycloadditions with cyclohexenone are catalyzed by BCF. The bicyclic [4.2.0] triazenes derived from cyclohexenone can be rearranged into [3.2.1] ring systems. The triazene function in the latter enables further derivatizations. Notably, we demonstrate that vinyl triazenes can serve as substrates for Pd-catalyzed cross-coupling reactions with arylboronic acids.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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