Domino Reactions

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Heteroatom-Nucleophile-Induced C–C Fragmentations: Synthesis of Allenes and Entry to Domino Reactions**

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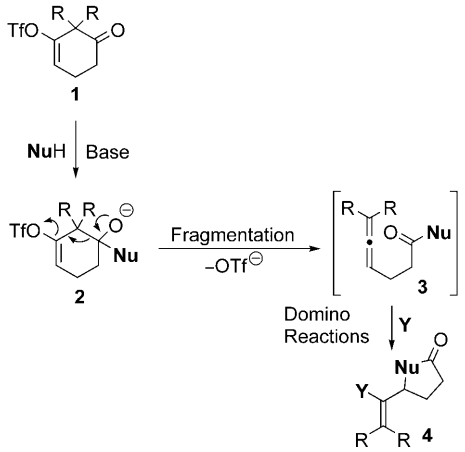
Dedicated to Professor Albert Eschenmoser on the occasion of his 85th birthday

Since their discovery by Burton and von Pechmann in 1887,[1] allenes have metamorphosed from a laboratory curiosity to a versatile and uniquely reactive functional group.[2] The C=C bond of allenes is around 10 kcal mol^{-1} less stable than that of simple alkenes,[3] rendering them significantly more reactive. In transition-metal-catalyzed reactions their reactivity is closer to that of alkynes than that of simple alkenes. Nonetheless, allenes display a distinct and complementary reactivity profile.[4] As consequence of their increasing synthetic importance, greater emphasis has been placed on the development of methods for their preparation.[5]

Owing to the seminal contribution from Eschenmoser in 1952[6] and subsequent studies by Grob,[7] carbonyl- and olefin-generating C–C bond fragmentations have found widespread applications in synthesis.[8] Nucleophile-induced Grob-type fragmentation reactions of vinylogous acyl triflates leading to ω-functionalized alkynes were developed by Dudley et al.[9] Recently, Williams and co-workers reported a related method for the synthesis of allenes from vinyl triflates such as **1**.[10] This method requires organolithium or organocerium carbon nucleophiles and leads to carbonyl moieties at the ketone or aldehyde oxidation level. In contrast, heteroatom nucleophiles failed to react or led to decomposition of the substrates. However, given their strong synthetic potential,[11] ω-heteroatom or carboxylic acid derivative functionalized allenes are the most valuable congeners. Thus a convenient and robust approach to this class of compounds is highly desirable.

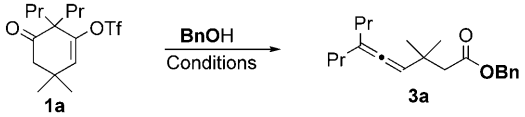
Herein we report a straightforward method for the heteroatom-induced Grob-type fragmentation of vinyl triflates **1** (Scheme 1). The reaction leads to trisubstituted allenes with a terminal carbonyl functionality at the oxidation level of a carboxylic acid. Furthermore, the resulting products **3** are amenable to a broad set of downstream reactions and can initiate domino reactions.



Scheme 1. C–C fragmentation of ketone **1** and potential domino reactions of the generated products **3**. Tf = trifluoromethanesulfonyl.

The fragmentation was initially examined with ketone **1a** and benzyl alcohol as the prototypical nucleophile (Table 1). The reactivity of **1a** is strongly dependent on the solvent. Even after prolonged heating, no conversion was observed in nonpolar solvents like dichloroethane or toluene (Table 1, entries 1 and 2), whereas fast conversions resulted in dipolar aprotic solvents (Table 1, entries 3–5). The employed base and its amount have a significant impact on the reactivity

Table 1: Optimization of the fragmentation reaction.[a]



Entry	*T* [°C]	*t* [h]	Base	Solvent[b]	Conversion [%][c]
1	50	6	Cs_2CO_3	DCE	0
2	50	6	Cs_2CO_3	toluene	0
3	50	2	Cs_2CO_3	DMSO	100
4	50	2	Cs_2CO_3	DMF	100
5	50	2	Cs_2CO_3	DMA	100
6	50	6	K_2CO_3	DMA	100
7	50	24	$NaHCO_3$	DMA	20
8	50	24	NEt_3	DMA	<5
9	50	24	–	DMA	<5
10[d]	23	7	Cs_2CO_3	DMA	100 (70%)[e]

[a] Conditions: 0.10 mmol **1a**, 5 equiv BnOH and base, 0.3 M; [b] DCE = dichloroethane, DMSO = dimethyl sulfoxide, DMA = *N*,*N*-dimethylacetamide. [c] Determined by NMR analysis. [d] 2 equiv BnOH and Cs_2CO_3. [d] Yield of isolated product in parentheses.

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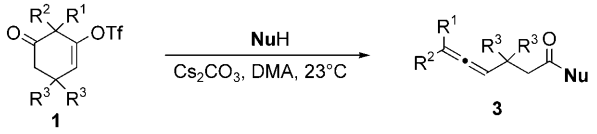
(Table 1, entries 5–9). The best results were obtained with cesium carbonate. Potassium carbonate displayed significant lower reactivity, and only very poor conversion was observed with sodium bicarbonate, with triethylamine, and in the absence of base. At ambient temperature, two equivalents of benzyl alcohol and cesium carbonate were sufficient for complete conversion, and benzyl ester **3a** was obtained in 70% yield (Table 1, entry 10).[12]

With these optimized conditions, we then explored the reactivity of different nucleophiles and ketones **1** (Table 2). In addition to benzyl alcohol and phenol, thiphenol also provided the corresponding allenes **3a**–**3g** (Table 2, entries 1–7). When the reaction was performed in wet DMA (40 equiv water), the free carboxylic acids **3h**–**3k** (Nu = OH) were obtained in excellent yields (Table 2, entries 8–11). Nitrogen nucleophiles like ammonia, anilines, primary and secondary amines, and sulfonyl amides also induce the fragmentation. However, they required reaction temperatures of 50 °C and the use of potassium carbonate to afford amides **3l**–**3t** in high yields (Table 2, entries 12–20).

Table 2: Scope of the fragmentation reaction.[a]



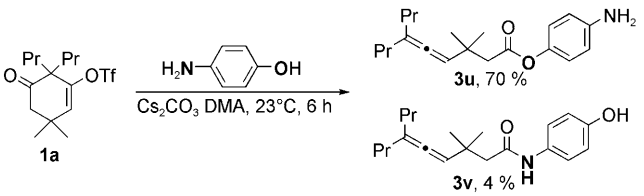
1 **3**

Entry	R^1	R^2	R^3	NuH	3	Yield [%][b]
1	Pr	Pr	Me	BnOH	**3a**	70
2	Me	Bn	H	BnOH	**3b**	65
3	Me	Me	H	BnOH	**3c**	51
4	allyl	allyl	Me	PhOH	**3d**	88
5	Pr	Pr	Me	PhOH	**3e**	92
6	allyl	Ph	H	PhOH	**3f**	56
7	allyl	allyl	Me	PhSH	**3g**	66
8[c]	allyl	Ph	H	H_2O	**3h**	86
9[c]	Pr	Pr	Me	H_2O	**3i**	99
10[c]	allyl	allyl	Me	H_2O	**3j**	99
11[c]	Me	Bn	H	H_2O	**3k**	90
12[d]	allyl	allyl	Me	NH_3	**3l**	94
13[c]	allyl	allyl	Me	$BnNH_2$	**3m**	96
14[c]	allyl	allyl	Me	$PhNH_2$	**3n**	84
15[c]	allyl	allyl	Me	Bn(Me)NH	**3o**	99
16[e]	allyl	allyl	Me	$TsNH_2$	**3p**	80
17[e]	Pr	Pr	Me	$TsNH_2$	**3q**	91
18[c]	allyl	allyl	Me	morpholine	**3r**	97
19[c]	Me	Bn	H	morpholine	**3s**	99
20[c]	Me	Me	H	morpholine	**3t**	72

[a] Conditions: 0.10 mmol **1**, 0.20 mmol NuH, 0.2 mmol Cs_2CO_3, 0.3 M in DMA, 23 °C, 7–12 h. [b] Yield of isolated product. [c] With 0.20 mmol K_2CO_3, 0.2 M in DMA, 50 °C, 20 h. [d] With 4 equiv NH_3 (0.5 M in dioxane), 32 h. [e] At 50 °C, 12 h.

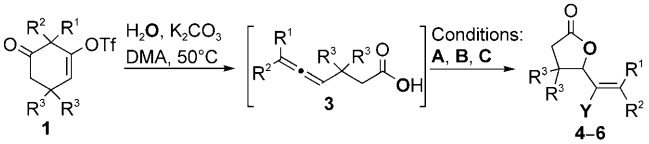
Remarkably, in the reaction with 4-aminophenol the phenolic hydroxy group reacts with high selectivity (Scheme 2). For instance, in the presence of cesium carbonate, aryl ester **3u** was formed in 70% yield, whereas amide **3v** was detected only in trace amounts.

The mild conditions and the broad spectrum of competent nucleophiles should make the fragmentation a suitable starting point for a range of subsequent reactions involving both formed functionalities. In this context, we explored the potential of the free carboxylic acids **3**, which are smoothly generated either in wet DMA or DMSO (Table 3). In the presence of trifluoroacetic acid, carboxylic acids **3** cyclized to give the corresponding five-membered allylic lactones **4a** and **4b** through protonation of the central carbon atom and trapping of the formed allylic carbenium ion (Table 3, entries 1 and 2). Another possibility is the addition of iodine upon completion of the fragmentation step. This iodolactonization led to the corresponding vinyl iodides **5**, which are amenable to further reactions, for example, cross-coupling (Table 3, entries 3–5).[13] It is also possible to directly obtain arylated tetrasubstituted olefins. In the presence of catalytic amounts of $[Pd(dba)_2]$ (dba = dibenzylideneacetone) and tricyclohexylphosphine, aryl iodides underwent arylative cyclization leading to **6a**–**6c** (Table 3, entries 6–8).[14] The reaction proceeded in good yields, though the stereoselectivity of the formed olefins was only modest when $R^1 \neq R^2$ (Table 3, entry 8).



Scheme 2. Selective reaction of *p*-aminophenol with ketone **1a**.

Table 3: Sequential reactions of carboxylic acids **3**.[a]



1 **3** **4–6**

Entry	Conditions	R^1	R^2	R^3	Y	4	Yield [%][b]
1	A	Pr	Pr	Me	H	**4a**	99
2	A	Me	Bn	H	H	**4b**	69[c]
3	B	Pr	Pr	Me	I	**5a**	78
4	B	Me	Bn	H	I	**5b**	83[d]
5	B	Me	Me	H	I	**5c**	72
6	C	Pr	Pr	Me	Ph	**6a**	83
7	C	Me	Me	H	Ph	**6b**	62
8	C	Me	Bn	H	Ph	**6c**	60[e]

[a] Conditions A: a) 0.10 mmol **1**, 3 equiv K_2CO_3, 40 equiv H_2O, 0.2 M in DMA, 50 °C, 20 h; b) CH_2Cl_2, TFA, 23 °C, 1 h; B: 0.10 mmol **1**, 3 equiv K_2CO_3, 40 equiv H_2O, 0.1 M in DMSO, 50 °C, 20 h, then 0.15 mmol I_2, 23 °C, 2 h; C: 0.10 mmol **1**, 3 equiv K_2CO_3, 40 equiv H_2O, 0.2 M in DMA, 60 °C, 20 h, then 0.15 mmol PhI, 5 mol% $[Pd(dba)_2]$, 7 mol% PCy_3, 10 h. [b] Yield of isolated product. [c] Z/E = 1:2.3. [d] Z/E = 1:1.3. [e] Z/E = 2.1:1.

When the fragmentation of **1a** was conducted in the presence of *N*-phenyl hydroxylamine, hydroxamic acid **3w** was obtained selectively (Scheme 3). Recently, the utility of N-substituted hydroxamic acids was shown for intramolecular

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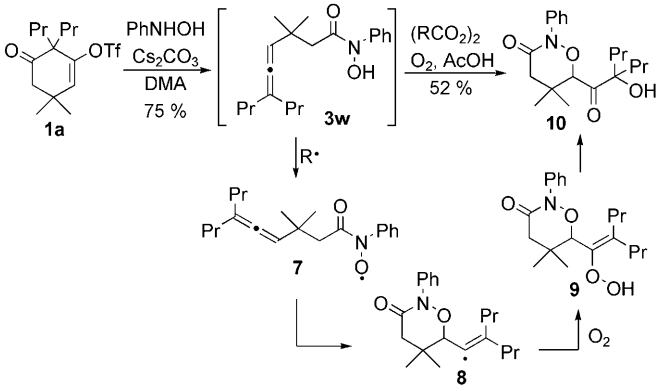
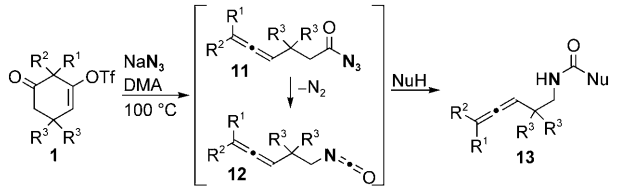


Scheme 3. Oxidative radical cyclization of allenic hydroxamic acid **3w**.

oxidative radical cyclizations of olefins with molecular oxygen.[15] Allenic hydroxamic acid **3w** was converted under comparable conditions (catalytic amounts of lauroyl peroxide in acetic acid under an atmosphere of oxygen) to the densely functionalized 1,2-oxazine **10**.[16] We assume that the initially formed oxygen-centered radical **7** cyclizes to give the vinyl radical **8**. The addition of molecular oxygen subsequently leads to the putative hydroperoxide **9**, which in turn, rearranges into hydroxyketone **10**, thus obviating reductive workup.[17]

We next tried to induce the fragmentation of **1** with the azide anion as a complementary nitrogen nucleophile. Our hypothesis was to generate acyl azide **11**, which under these reaction conditions should undergo a Curtius rearrangement to generate isocyanate **12** (Table 4). Indeed, heating **1** at 100 °C for one hour in the presence of sodium azide in DMA led to complete conversion of **1**.[18] When alcohols were added to the reaction mixture, the isocyanates **12** were intercepted and converted directly to carbamates **13a**–**13f** (Table 4, entries 1–6). Along the same lines, thiocarbamate (**13g**) and ureas (**13h**, **13i**) can be prepared (Table 4, entries 7–9). To avoid competition with the azide anion for the initial fragmentation and to suppress formation of the corresponding amides, amine and thiol nucleophiles had to be added after complete generation of **12**.

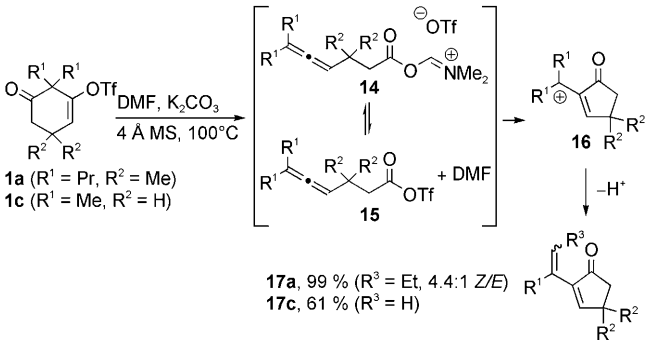
Table 4: Domino reaction consisting of fragmentation and Curtius reaction.[a]



Entry	R^1	R^2	R^3	NuH	**13**	Yield [%][b]
1	Pr	Pr	Me	BnOH	**13a**	77
2	Pr	Pr	Me	EtOH	**13b**	80
3	allyl	allyl	Me	BnOH	**13c**	75
4	Me	Me	H	BnOH	**13d**	54
5	Me	Bn	H	BnOH	**13e**	68
6	allyl	Ph	H	BnOH	**13f**	56
7[c]	Pr	Pr	Me	PhSH	**13g**	38
8[d]	Pr	Pr	Me	$BnNH_2$	**13h**	67
9[d]	Pr	Pr	Me	Me_2NH	**13i**	69

[a] Conditions: 0.10 mmol **1**, 3 equiv NaN_3, 5 equiv NuH, 0.1 M in DMA, 100–110 °C, 2–6 h. [b] Yield of isolated product. [c] 2 equiv PhSH and 0.1 equiv $(iPr)_2NEt$ were added after 1 h at 23 °C and the reaction mixture was then stirred for 14 h. [d] 2 equiv amine was added after 1 h at 100 °C and the reaction mixture was then stirred for 2 h.

Remarkably, when substrate **1a** was heated in the absence of nucleophile in dry DMF at 100 °C, enone **17** was obtained as the sole product in good yield (Scheme 4). This observation suggests that the solvent itself acts as the promoting



Scheme 4. Domino reaction consisting of a fragmentation and a Friedel–Crafts reaction.

nucleophile to induce the C–C bond fragmentation, thus generating either **14** or acyl triflate **15** as highly potent intermediates. However, neither of these intermediates could be detected, presumably because a rapid intramolecular Friedel–Crafts acylation leads via the putative allylic carbenium ion **16** to the final product, enone **17**.[19] At present, we do not know whether acyl azide **11** is formed by the direct attack of the azide anion, or whether the reaction proceeds via intermediates **14** or **15**.

In summary, we have developed a mild and operatively simple method the preparation of synthetically versatile ω-heteroatom-functionalized allenes through Grob-type fragmentations of 3-keto vinyl triflates **1**. The resulting products can be utilized for further functionalizations of both the allene and the carboxylic acid moieties, and they provide direct access to a range of structurally diverse structural motifs.

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Keywords: allenes · cyclization · domino reactions · fragmentation · radicals

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[18] Instead of isocyanate **12**, the symmetrical urea was obtained in virtually quantitative yield.
[19] Because **17c** is very volatile, its yield was determined by ^{1}H NMR spectroscopy.

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