C−C Bond Fragmentation

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Sequential 1,4-/1,2-Addition of Lithium(trimethylsilyl)diazomethane onto Cyclic Enones to Induce C−C Fragmentation and N−Li Insertion

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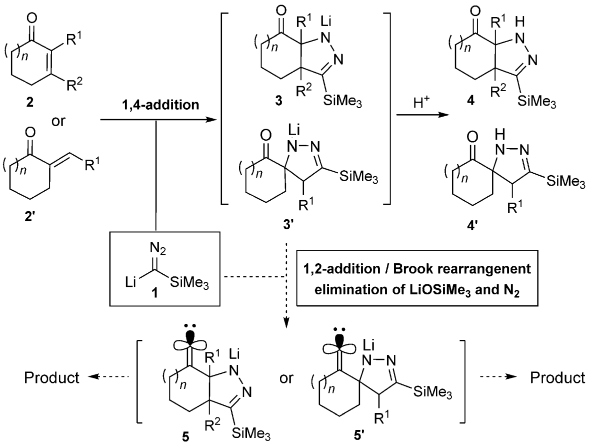
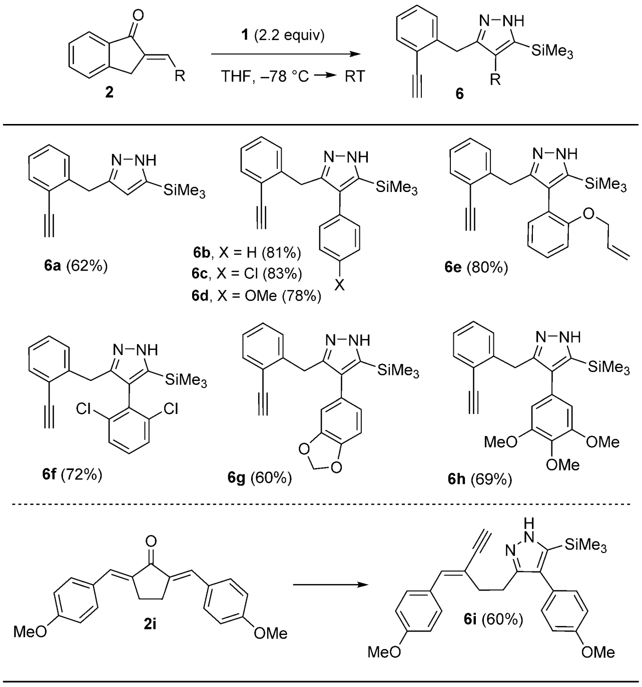
Abstract: *α,β-Unsaturated ketones generally undergo addition reactions with nucleophiles with a preference for either 1,2- or 1,4-addition, but rarely both. However, the right combination of reagents allows for consecutive 1,4- and 1,2-additions to occur: Cyclic α,β-unsaturated ketones undergo double additions with lithium(trimethylsilyl)diazomethane, effectively generating various molecular frameworks with complexity and diversity. Owing to the sequential generation of several intermediates of multifaceted reactivity, including diazoalkane derivatives and alkylidene carbenes, it is possible to induce novel Grob-type C−C fragmentations, alkylidene carbene mediated Li−N insertions, and dipolar cycloadditions by controlling the reaction parameters.*

Reactions involving two consecutive additions of strong nucleophiles to α,β-unsaturated ketones (enones) are rare[1] as the first reaction in 1,2-addition or 1,4-addition mode would convert the electrophilic starting enone into the corresponding alkoxide or enolate, respectively. For consecutive double additions to be feasible, the first addition must occur in 1,4-fashion, and the resulting 1,4-adduct should be present in its keto, and not in its enolate, form. However, under typical reaction conditions, in situ conversion of the enolate into the corresponding keto form is not feasible owing to the incompatibility of typical electrophiles with strong nucleophiles.[2] Considering this reactivity requirement, lithium(trimethylsilyl)diazomethane (LTMSD, **1**)[3,4] has ideal characteristics for 1,4/1,2-double addition to enones because it can act as a strong nucleophile during the first addition, and the enone carbonyl group will then be regenerated by trapping of the enolate intermediate by the diazo moiety of the adduct.



Scheme 1. Sequential 1,4-/1,2-addition of **1** to cyclic ketones with an endo- or an exocyclic double bond.

Table 1: Pyrazoles by 1,4/1,2-addition of **1** followed by sequential elimination and Grob-type fragmentation.



On the basis of the known reaction between **1** and cyclic enones **2**/**2′** to generate pyrazolines **4**/**4′**,[5] most likely by protonation of putative intermediate **3**/**3′**, we envisioned that these intermediates could further react with **1** when two equivalents of LTMSD are employed from the start of the reaction (Scheme 1). Once 1,2-addition between **1** and **3**/**3′** has occurred, the resulting alkoxide of the 1,2-adduct would induce a C→O silyl migration (1,3-Brook rearrangement)[6] to generate a new intermediate, **5**/**5′**. We expected that depending on the structural characteristics of the carbon skeleton of these intermediates and the reaction conditions, these intermediates would lead to different end products by Li−N insertion[7] or Grob-type fragmentation[8] pathways. Herein, we report the formation of various novel hetero-

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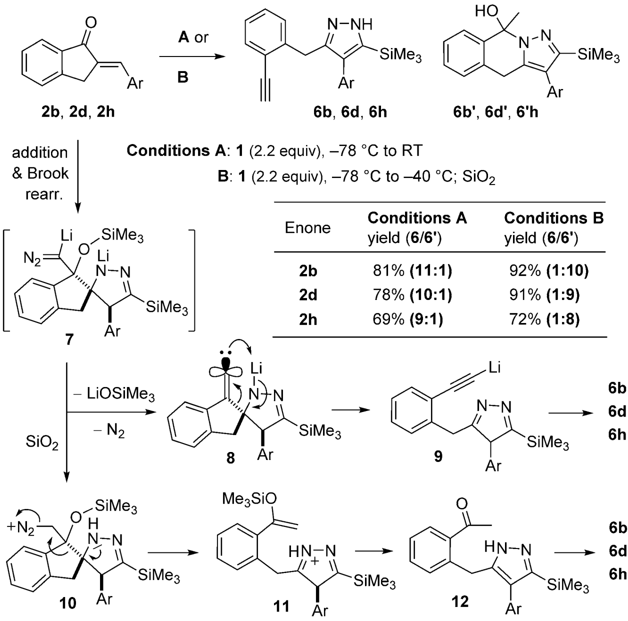
cycles[9] from these putative intermediates, which were in turn derived from the 1,4/1,2-double addition of **1** to exo- and endocyclic α,β-unsaturated ketones.

The feasibility of the proposed double 1,4/1,2-addition-based multistep transformation was first examined with benzylidene indanones (Table 1). Treatment of methylidene indanone (**2a**, R = H) with **1** (2.2 equiv) at −78 °C followed by slow warming to room temperature provided pyrazole **6a** in 62 % yield. Benzylidene indanone (**2b**, R = Ph) provided pyrazole **6b** in 81 % yield under identical conditions. Similarly, 4-chloro- and 4-methoxy-substituted benzylidene indanones (**2c** and **2d**) provided pyrazoles **6c** and **6d** in 83 % and 78 % yield, respectively. Furthermore, benzylidene indanones with 1-allyloxy, 1,6-dichloro, 3,4-methylenedioxy, and 2,3,4-trimethoxy substituents (**2e**–**2g**) afforded the corresponding pyrazoles **6e**–**6g** in yields of 60–80 %. This fragmentation reaction is not limited to the indanone system. Under the same conditions, bis(benzylidene) cyclopentanone **2i** delivered enyne **6i** in 60 % yield.

Having achieved this novel pyrazole formation that proceeds by tandem 1,4/1,2-addition, we expected that the reaction path leading to pyrazoles could be diverted to generate different final products. This assumption was based on the predicted multiple chelation of the putative 1,4/1,2-adduct, where the elimination of lithium silanolate ($LiOSiMe_3$) could be modulated by temperature, time, additives, and solvent (Scheme 2). As expected, depending on the reaction conditions, benzylidene indanones **2b**, **2d**, and **2h** afforded pyrazoles **6b**, **6d**, and **6h** and/or different pyrazoles **6b′**, **6d′**, and **6d′** upon treatment with **1** (2.2 equiv). When the reaction mixture was slowly warmed to room temperature after the addition of **1**, pyrazoles **6b**, **6d**, and **6h** were predominantly observed; however, quenching the reaction with silica gel at about −40 °C before warming up yielded the pyrazoles **6b′**, **6d′**, and **6d′** as the major products. The yields and ratios of these structurally different pyrazoles are strongly dependent on the temperature and the timing of the SiO_2 quench. Under optimized conditions, excellent yields and ratios of **6b**/**6b′**, **6d**/**6d′**, and **6h**/**6h′** were achieved. The identity of these pyrazoles was unambiguously established by X-ray diffraction.[10]

The reactions of six- and seven-membered cyclic ketones with a conjugated exocyclic double bond and **1** (2.2 equiv, −78 °C→25 °C) provided completely different products compared to those of the corresponding five-membered counterparts (Table 2). The reaction of pulegone (**2j**) afforded bicyclic 4*H*-1,2-diazepine derivative **6j** in excellent yield (entry 1), which is the result of N−Li insertion to form **7a′** (Scheme 3). However, under the same conditions, **2k** afforded cyanohydrin **6k** in 67 % yield by 1,2-addition followed by oxidative deamination (entry 2),[11] whereas the corresponding tetralone derivative **2l** exclusively afforded Grob fragmentation product **6l** (entry 3). Furthermore, the reaction of benzylidene cycloheptanone (**2m**) afforded 4*H*-1,2-diazepine derivative **6m** in slightly lower yield (entry 4).



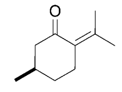
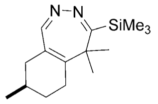
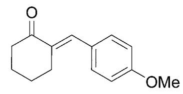
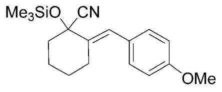
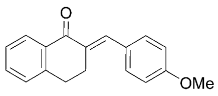
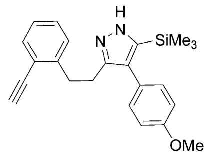
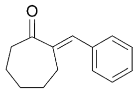
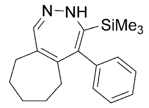
Conditions A: **1** (2.2 equiv), –78 °C to RT

B: **1** (2.2 equiv), –78 °C to –40 °C; SiO_2

Enone	Conditions A yield (**6**/**6′**)	Conditions B yield (**6**/**6′**)
2b	81% (**11:1**)	92% (**1:10**)
2d	78% (**10:1**)	91% (**1:9**)
2h	69% (**9:1**)	72% (**1:8**)

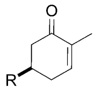
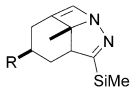
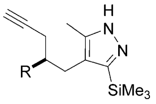
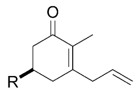
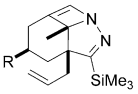
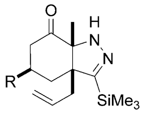
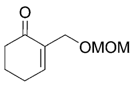
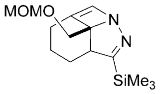
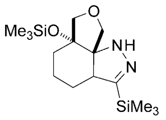
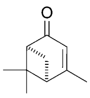
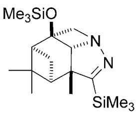
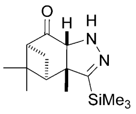
Scheme 2. Mechanisms of different C−C fragmentations.

Table 2: 1,4/1,2-Additions of **1** with cyclohexenone derivatives.

Entry	Enone	Product	Yield [%]
1	 **2j**	 **6j**	89
2	 **2k**	 **6k**	67
3	 **2l**	 **6l**	65
4	 **2m**	 **6m**	51

In stark contrast, cyclohexenone derivatives with an endocyclic double bond can form various products depending on their substituents (Table 3). Carvone (**2n**) and dihydrocarvone (**2o**) produced mixtures of the carbene-inserted pyrazole and Grob fragmentation products in 87 % (**6n**/**6n′** = 5:1) and 75 % (**6o**/**6o′** = 3:1) yield, respectively (entries 1 and 2). Compound **2p**, which contains an isopropenyl substituent

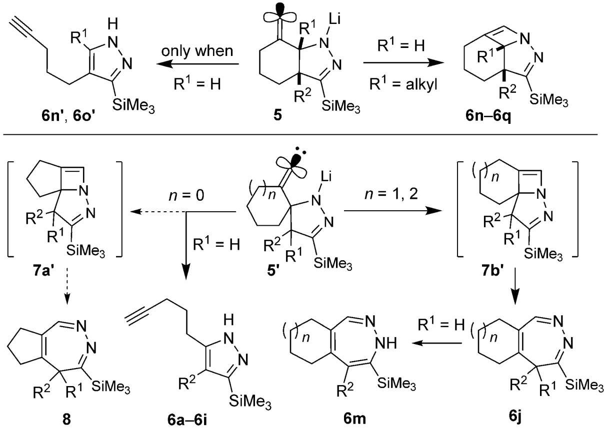
Table 3: 1,4/1,2-Additions of **1** with cyclohexenone derivatives.

Entry	Enone	Products			Yield [%]
			+		
1	**2n**, R = 	**6n**	(5:1)	**6n′**	87
2	**2o**, R = 	**6o**	(3:1)	**6o′**	75
			+		
3	**2p**, R = 	**6p**	(1:0)	**6p′**	72
4	**2q**, R = H	**6q**	(3:1)	**6q′**	87
			+		
5	**2r**	**6r**	(1:1)	**6r′**	81
			+		
6	**2s**	**6s**	(3:1)	**6s′**	82

at the 4-position, provided **6p** as the sole product (entry 3), whereas **2q**, which is devoid of the isopropenyl group, afforded a mixture of **6q** and monoadduct **6q′** in a 3:1 ratio (entry 4). 2-Cyclohexenone **2r**, which features a methoxymethyl (MOM) protected hydroxymethyl group, delivered two products, namely insertion product **6r** and tetrahydrofuran **6r′** in 81 % yield and a 1:1 ratio (entry 5). The formation of **6r′** is the consequence of slow elimination of LiOSiMe$_3$ from the bisadduct of **1** owing to strong chelation of the C–Li moiety by the MOM group. The reaction of verbenone (**2s**) provided **6s** and **6s′** in 87 % yield and a 1:1 ratio (entry 6). The sterically hindered nature of the monoadduct of **2s** with **1** slowed down both the second addition of **1** and the elimination of LiOSiMe$_3$ from the bisadduct.

From the reactions in Table 2 and Table 3, a general trend can be identified (Scheme 3). Alkylidene carbene **5** of a six-membered fused bicycle can undergo either fragmentation or insertion into the N–Li bond to generate **6n′** and **6o′** or **6n**–**6q**, respectively. The Grob-type fragmentation of **5** only occurred when R′ = H, otherwise N–Li insertion is more favorable. This may imply that the aromatization to form a pyrazole is the ultimate driving force for C–C bond cleavage. On the other hand, the fate of alkylidene carbene **5′** of five- and six-membered spirobicycles depend on its ring size. From [4.4] spirocycle **5′** ($n = 0$), only fragmentation occurred to generate **6a**–**6i**, whereas product **8**, which would be obtained via putative intermediate **7a′**, was not formed, which is most likely due to the high strain of **7a′**. For [4.5] spirocycle **5′** ($n = 1$), both C–C fragmentation and N–Li insertion occurred to generate **6l** and **7b′**, and the cycloreversion of the latter afforded **6j** and **6k** (after tautomerization). In the case of [4.6] spirocycle **5′** ($n = 2$), only N–Li insertion occurred to generate **6m**.

In conclusion, we have revealed the sequential 1,4-/1,2-addition of LTMSD (**1**) to exo- and endocyclic enones followed by subsequent Grob-type C–C fragmentation or alkylidene carbene mediated Li–N insertion depending on the reaction conditions and quenching procedures. These domino processes were enabled by the unique reactivity of LTMSD, which selectivity undergoes 1,4-addition, leaving the free carbonyl group for the subsequent 1,2-addition untouched. The fate of the lithiated diazomethane moiety with an α-silyloxy group at different stages of the overall process can be controlled by adjusting the temperature and its protonation states. By choosing the right combination of these two reaction parameters in combination with substrates with specific structural characteristics, various unique molecular structures could be synthesized in a single operational step from terpene derivatives.



Scheme 3. General trends observed for consecutive 1,4-/1,2-addition followed by C–C fragmentation and Li–N insertion.

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Keywords: carbenes · C–C cleavage · 1,3-dipolar cycloaddition · pyrazoles · unsaturated ketones

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[10] CCDC 1433828 (**6f**) and 1433827 (**6b′**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[11] The reasons for the favorable 1,2-addition over 1,4-addition for this enone and the mechanism of the oxidative deamination to form the cyano group from the corresponding diazo moiety are not known.

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