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TIPS-Diazoacetone Aldol Addition: Mechanistic Aspects and Contribution to the Synthesis

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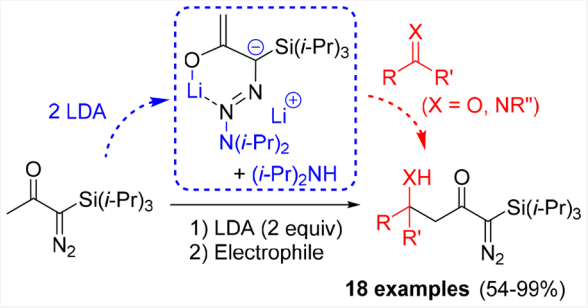
ABSTRACT: Aldol addition of α-triisopropylsilyl-α-diazoacetone (TIPS-diazoacetone), promoted by excess lithium diisopropylamide (LDA), was developed and applied to the synthesis of original *C*-TIPS diazoaldols, *C*-TIPS diazoketols, and a related Mannich-type product. An unprecedented mechanistic pathway has been proposed, involving a lithiated triazene intermediate resulting from the nucleophilic addition of LDA on the diazo moiety, supported by experimental results and DFT calculations.



INTRODUCTION

The synthetic transformations that may be conceived on α-diazocarbonyl compounds constitute a vast area of exploration for organic chemists. Indeed, decomposition of the C=N$_2$ function into carbene is a gateway to chemical diversity via numerous processes such as insertions, cyclopropanations, Wolff, and sigmatropic rearrangements.[1] α-Diazocarbonyl compounds are thus high-value intermediates in organic synthesis, and numerous efforts have been devoted to studying how the generated carbene can evolve in order to create original scaffolds.[2] Conversely, the design of methods to elaborate functionalized α-diazocarbonyl compounds while keeping the diazo functionality intact has been less explored, although constituting an important source of diversity downstream. In this field, a widespread strategy to access diversely substituted diazocarbonyl compounds **B** is the electrophilic substitution at the diazo carbon atom of (diazomethyl) carbonyl precursors **A** with various electrophiles[1,3] (Scheme 1a). The intrinsic nucleophilicity of the diazotated carbon, which can be enhanced by deprotonation with a large array of bases, accounts for the efficiency of this "diazo-side" approach. A "methyl-side" carbon chain extension has also been studied, however, to a lesser extent, mainly on the methyl ketone moiety of diazodicarbonyl precursors **C** (Scheme 1b). Aldol-type and Mannich-type additions, involving boron,[4a] lithium,[4b] titanium enolates,[4c−f] or Lewis acid-catalyzed Mukaiyama procedures from silyl enol ethers,[4g,h] proved successful to provide scaffolds **D**. Besides, the use of α-triethylsilyl-α-diazoacetone (TES-diazoacetone) **E** was developed in our team as a three-carbon building block allowing convergent access to functionalized carbon chains **F**[5] (Scheme 1c). Protection of the more reactive diazo carbon was required to achieve lithium diisopropylamide (LDA)-induced "methyl-side" aldol addition in a first step so that the stable diazoaldol intermediate resulting from *C*-desilylation could cleanly undergo LDA-induced "diazo-side" addition in a second step. This methodology was successfully applied to hindered and acid-sensitive aldehydes during the function-oriented synthesis of peloruside A analogues.[6]

In the diazo strategy implemented on TES-diazoacetone **E** (Scheme 1c), the triethylsilyl-protecting group on the diazo carbon was sufficiently labile to be partially removed during hydrolysis of the "methyl-side" aldol addition, and simple methanolysis efficiently completed the deprotection before "diazo-side" addition. Beyond this role of temporary protection, trialkylsilyl groups attached to the diazo carbon of diazocarbonyl scaffolds have proved useful to generate original silyl-substituted scaffolds upon the transformation of the diazo function via Wolff rearrangement[7] or upon silicium 1,3-(C → O) migration, followed by either 1,3-dipolar cycloadditions[8] or diazo loss, inducing C−H insertion[9] or rearrangement to siloxyalkyne.[10] On the other hand, trialkylsilyl groups of TES-diazoacetone **E** and α-triisopropylsilyl-α-diazoacetone (TIPS-diazoacetone) **1** (Scheme 2) behaved as efficient activating groups to allow mild TBAF-triggered aldol additions.[11]

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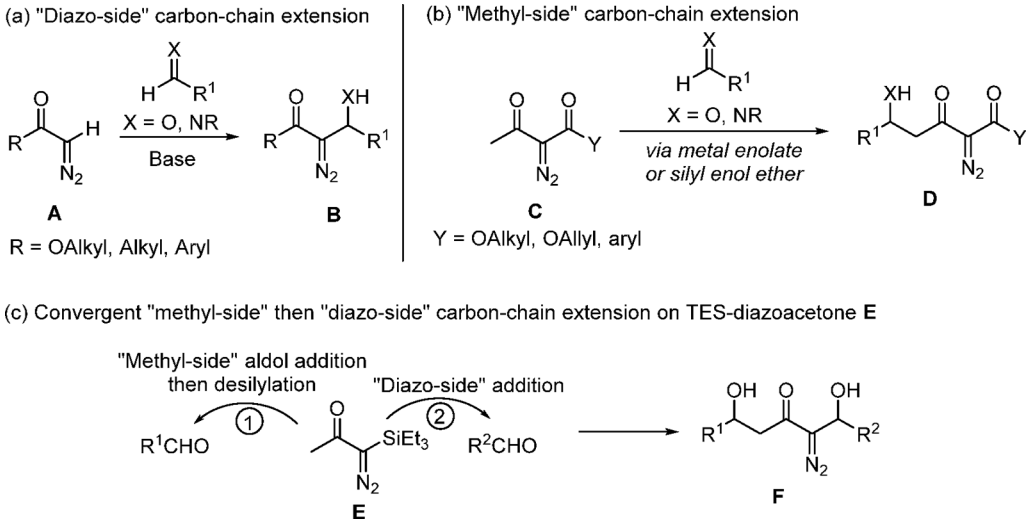
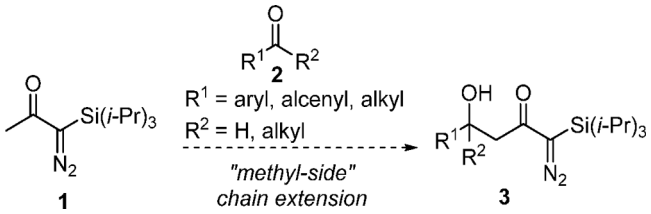
Scheme 1. Elaboration of Functionalized Diazocarbonyl Compounds by Aldol and Mannich-Type Methodologies



Scheme 2. This Work: "Methyl-Side" Aldol Addition on TIPS-Diazoacetone 1



To date, only simple α-trialkylsilyl α-diazocarbonyl substrates have been involved in the above-mentioned processes, prepared by late *C*-silylation of the corresponding (diazomethyl) carbonyl scaffold using silyltrifate/iPr$_2$NEt, just before the diazo transformation.[9,7d,e] A methodology able to widen the scope of the functional diversity that can be achieved on these α-diazo-α-trialkylsilyl scaffolds would be valuable in this field of research. For such purpose, the "methyl-side" aldol addition of TIPS-diazoacetone **1** will be investigated here (Scheme 2). Mechanistic aspects of this unexplored reaction, providing stable original *C*-TIPS diazoaldols, will be unveiled and discussed.

RESULTS AND DISCUSSION

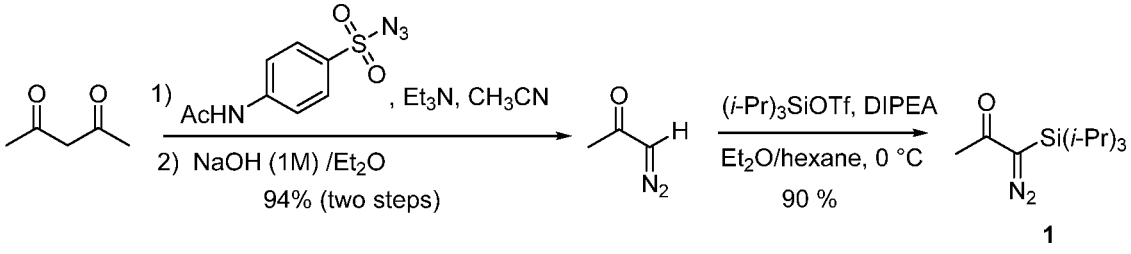
TIPS-Diazoacetone Synthesis. The TIPS-protecting group was selected in this work in order to avoid the uncontrolled deprotection previously observed with TES-diazoacetone **E** during "methyl-side" aldol addition,[5] and considering the propensity for hydrolysis of TBS-diazoacetone,[9] which was observed by our group in preliminary assays. TIPS-diazoacetone **1** was easily prepared on a multigram scale in three steps[11a,b] via a Regitz diazo transfer[12] from 4-acetamidobenzenesulfonyl azide (*p*-ABSA)[13,14] as a safer surrogate to TsN_3 (Scheme 3). Pure TIPS-diazoacetone **1** could be stored in the freezer for several months without noticeable decomposition.[15]

"Methyl-Side" Aldol Addition of TIPS-Diazoacetone. While it has been well established that diazodicarbonyl structures like **C** (Scheme 1b) are sufficiently stabilized to generate diverse metal enolates,[4] less stabilized simple diazoacetyl substrates, although synthetically useful, have been left aside. The only examples of "methyl-side" aldol additions from α-alkyl-α-diazoacetones like **G** were reported by Taber's team (Scheme 4a), constituting a key step in their elegant strategy dedicated to the synthesis of isoprostanes.[16] Potassium enolate of the methylketone was generated using KHMDS, and TESCl was necessary to activate the electrophile. Our group extended this methodology to the aldol addition of α-triethylsilyl-α-diazoacetone (TES-diazoacetone, **E**) (Scheme 4b), from which the lithium enolate was efficiently formed using excess LDA and reacted with a range of aldehydes.[5]

Based on these results, aldol addition between TIPS-diazoacetone **1** and benzaldehyde was first investigated using LDA as the base. The influence of the temperature and the amount of LDA was first studied (Table 1).

The optimal conditions set up previously for the aldol addition of TES-diazoacetone **E** consisted of reacting it with 2 equiv of LDA at −50 °C (T_1), followed by the addition of the electrophile at −100 °C (T_2) (Scheme 4). These conditions, applied to TIPS-diazoacetone **1**, led to the expected diazoaldol

Scheme 3. Preparation of TIPS-Diazoacetone 1



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Scheme 4. Methyl-Side Aldol Addition on α-Alkyl-α-diazoacetones and α-Triethylsilyl-α-diazoacetone

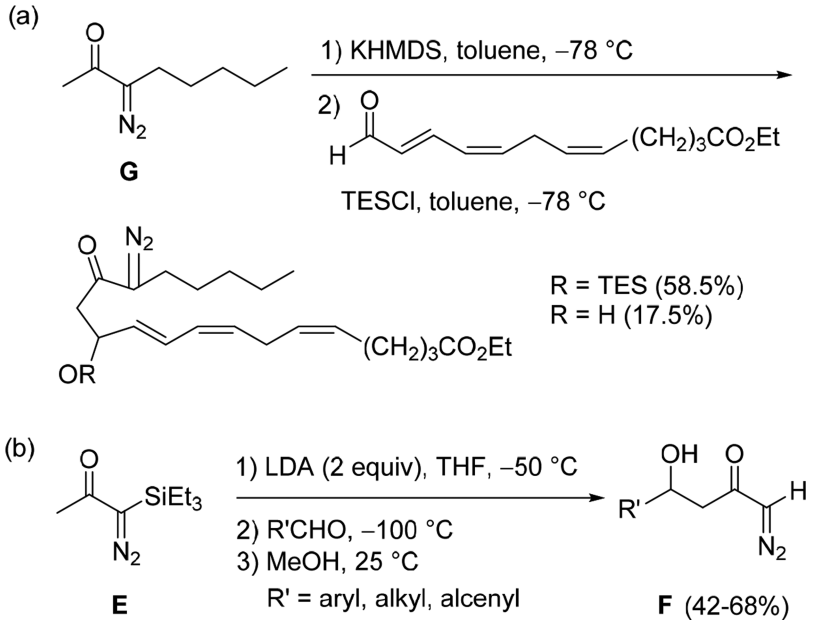
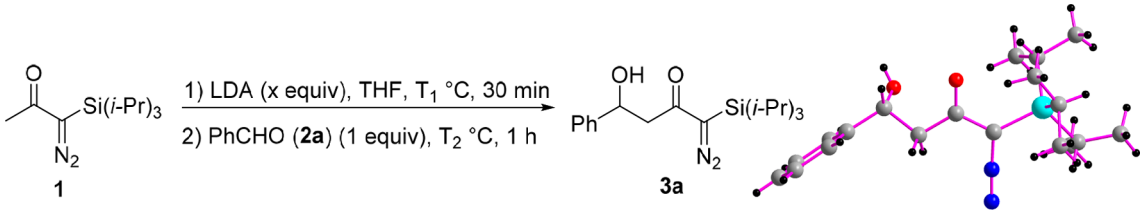


Table 1. Aldol Addition between TIPS-Diazoacetone 1 and Benzaldehyde using LDA



entry	LDA (*x* equiv)	T_1 (°C)	T_2 (°C)	isolated yield (%) **3a**[a]
1	2	−50	−100	64[b]
2	2	−25	−100	85
3	2	−25	−78	83
4	2	−25[c]	−78	71−86[d]
5	2.2	−25[c]	−78	84
6	2.2	−25[c]	−25	70[b]
7	1.75	−25	−100	73
8	1.5	−25[c]	−78	77
9	0.95−1.25	−25[c]	−78	0−85[b,e]
10	1 + HMPA (1 equiv)	−25[c]	−78	0−31[b]
11	1 + HMPA (2 equiv)	−25[c]	−78	0[b]
12	1 + LiBr (1 equiv)	−25[c]	−78	0[b]

[a]Reactions performed on a 0.5−1 mmol scale. [b]Conversion, based on the integration of the CH_3 signal of **1** and the CH_2 signals of **3a** on the ^1H NMR spectrum of the crude product. [c]T_1 was maintained for 1 h. [d]Range of yields obtained from 8 experiments. [e]Highly unreproducible results, based on 10 experiments.

3a as a unique product, albeit with a moderate 64% conversion (Table 1, entry 1). When T_1 was increased to −25 °C, the nearly complete conversion was observed, and the aldol addition product **3a** was isolated in a high 85% yield (Table 1, entry 2). Similar yields were obtained when T_2 was increased from −100 °C to −78 °C (Table 1, entry 3) or when the contact time with LDA at −25 °C (T_1) was extended from 30 min to 1 h (Table 1, entry 4). Performing the reaction with 2.2 equiv of LDA did not influence the yield (Table 1, entry 5). However, increasing T_2 from −78 °C to −25 °C was detrimental to the reaction, resulting in a moderate 70% conversion (Table 1, entry 6). An additional assay, carried out under Barbier conditions at −78 °C, using 2 equiv of LDA, led to a disappointing 23% yield. Attempts were then carried out to decrease the amount of LDA used to generate the enolate. While a small decrease of the isolated yield was observed with 1.5 or 1.75 equiv of LDA (Table 1, entries 7 and 8), surprisingly, unreproducible results were observed when the amount of LDA used was in the range of 0.95−1.25 equiv (Table 1, entry 9). Inconsistent conversions from 0% to 85% were typically obtained with a given set of conditions. When LiBr[17] or HMPA,[18] known to modify the aggregation state of LDA and enolates complexes, were added to the THF solution of LDA, no or low conversion was observed (Table 1, entries 10−12). Eventually, the use of 2 equiv of LDA and proper control of the temperature after the addition of the electrophile

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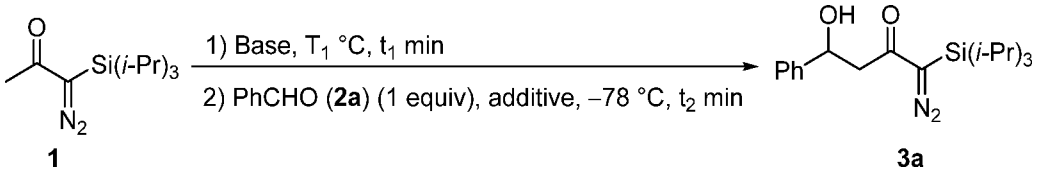
Table 2. Influence of the Nature of the Base on the Aldol Addition of TIPS-Diazoacetone 1



1 3a

entry	base (x equiv)[a]	T_1 (°C)	t_1 (min)	additive (x equiv)	t_2 (min)	products formed	isolated yield (%)
1	LTMP (1)	−25	60		60	**3a**	0[b]
2	LTMP (2)	−25	60		60	**3a**	49[b]
3	LiHMDS (1)	−25	60		60	**3a**	37−81[c]
4	LiHMDS (2)	−25	60		60	**3a**	76−83[d]
5	KHMDS (1)	−25	60		60	**3a**/**4a**/**1** = 6:55:39[e]	*f*
6	KHMDS (1.1)[g]	−78	40		60	**3a**/**4a** = 75:25[e]	**3a** (38), **4a** (12)
7	KHMDS (1.1)[g]	−78	40	LiBr (1.3)	60	**3a**	58−79[h]
8	KHMDS (1.05)[i]	−78	20	TESCl (1.2)	15	complex mixture[j]	**3a** (22), **5a** (36)

[a]KHMDS and LiHMDS were used as a 0.5 M solution in toluene. Solvent: THF for entries 1−7; toluene for entry 8. [b]Conversion based on the ^{1}H NMR of the crude product. [c]Range of yields obtained from 4 experiments. [d]Range of yields obtained from 3 experiments. [e]Ratio based on the ^{1}H NMR spectrum of the crude product. [f]Not purified. [g]0.9 equiv of benzaldehyde **2a** was used. [h]Based on 4 assays. [i]1.2 equiv of benzaldehyde **2a** was used. [j]Diazoaldols **3a** and **5a** were formed, along with other silylated products.

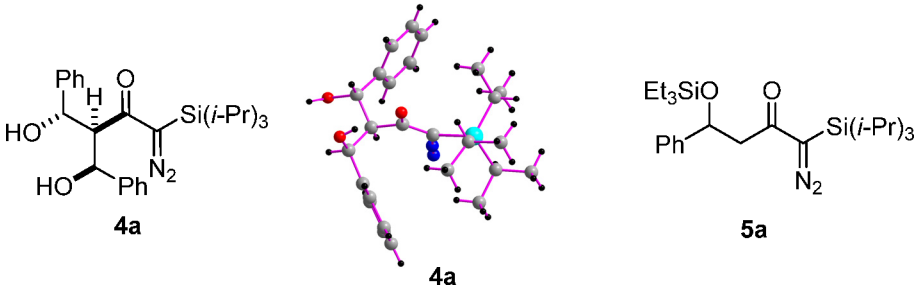


Figure 1. Byproducts formed during the aldol addition between TIPS-diazoacetone **1** and benzaldehyde **2a**.

(−78 °C) constituted the best conditions to ensure reproducible and high yields of diazoaldol **3a**.[19] The stability of this new *C*-TIPS diazoaldol is worth noticing.[20] No desilylated aldol was detected on the proton NMR spectrum of the crude product, and purification by chromatography using Et_3N-neutralized silica gel induced the formation of a few percent of the corresponding desilylated aldol.[21] The structure of diazoaldol **3a** was confirmed by X-ray diffraction analysis.[22]

The unreproducible results obtained when the aldolisation was conducted with 0.95−1.25 equiv of LDA suggested that a pathway, competitive to deprotonation, could operate with this lithium amide. In an attempt to rationalize these intriguing results, the influence of the nature of the amide anion was investigated (Table 2, entries 1−4).

At first, LDA was replaced by other lithium amides, more hindered like lithium tetramethylpiperidide (LTMP), or less basic like lithium bis(trimethylsilyl)amide (LiHMDS). With LTMP, under the same reaction conditions as LDA, the same trend was observed: no conversion was detected with 1 equiv of LTMP while the reaction proceeded, although with a lower conversion than with LDA, using 2 equiv (Table 2, entries 1 and 2). Contrary to LDA and LTMP, the use of 1 equiv of LiHMDS consistently led to the expected aldol, although fluctuating yields were obtained, from modest 37% to high 81% yield (Table 2, entry 3). On the other hand, good and homogeneous yields, similar to those obtained with 2 equiv of LDA, were achieved with 2 equiv of LiHMDS (Table 2, entry 4).

In order to assess the influence of the countercation, the aldolisation of TIPS-diazoacetone **1** was next carried out with potassium bis(trimethylsilyl)amide (KHMDS) (Table 2, entries 5−8). Under the same conditions of temperature as with LiHMDS, the use of a stoichiometric amount of KHMDS led mainly to the formation of the bis-aldol **4a** (Table 2, entry 5), the structure of which was confirmed by X-ray diffraction[22] (Figure 1).

Decreasing the temperature of the enolate formation from −25 °C to −78 °C favored the formation of the expected diazoaldol **3a** over the unwanted bis-aldol **4a** but led to diazoaldol **3a** in a low 38% yield (Table 2, entry 6). The only examples of aldol addition of diazoketones, described by Taber's team (Scheme 4a),[16] systematically involved the formation of the potassium enolate with KHMDS associated with the activation of the aldehyde by adding either LiBr[16a] or TESCl.[16b] Correlating these conditions and our previous observations, it made clear that activation of the aldehyde was necessary when using KHMDS, as a result of its lower pK_a compared with LDA, and its softer K^+ countercation compared to Li^+.[23] Thus, in order to prevent the double aldol addition to proceed and to shift the equilibrium of the aldol addition reaction, a mixture of benzaldehyde **2a** and LiBr in THF was added to the reaction mixture of TIPS-diazoacetone **1** and KHMDS (1.1 equiv), following Taber's procedure[16a] (Table 2, entry 7). Indeed, these conditions inhibited the formation of the bis-aldol **4a**, and diazoaldol **3a** was obtained in homogeneous and reproducible yields (58−79%). In contrast, when replacing LiBr by TESCl, as recommended by Taber's

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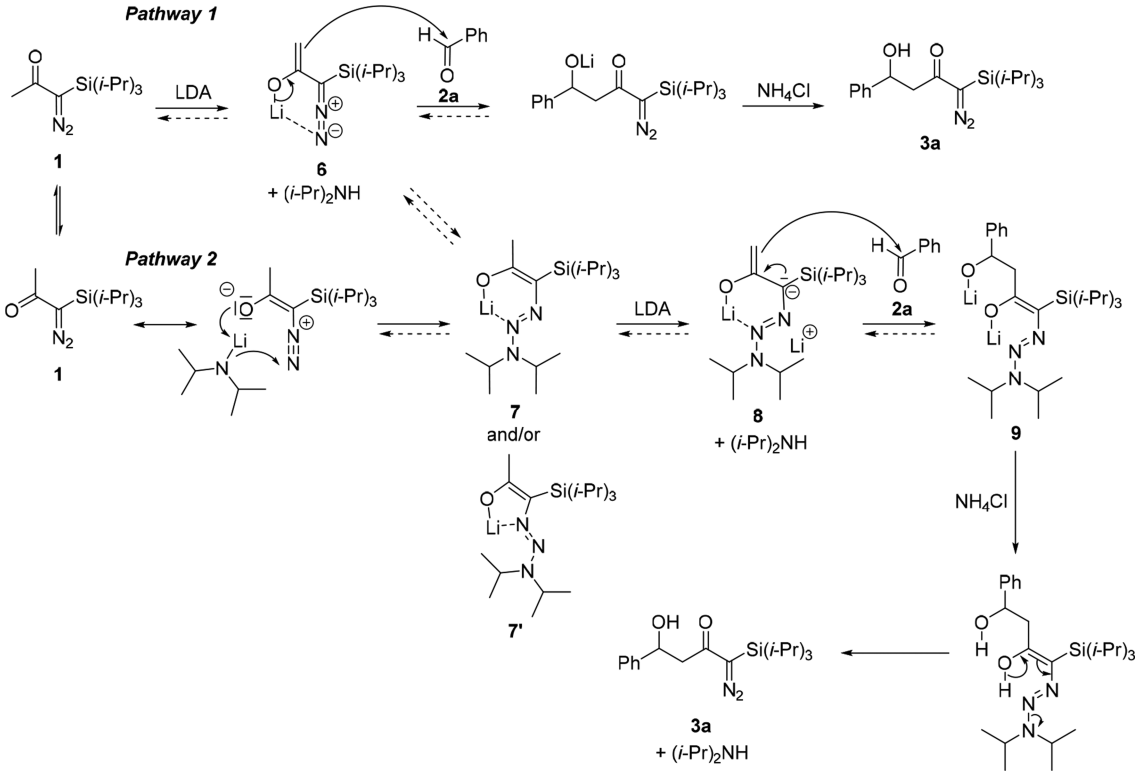
Scheme 5. Proposed Mechanism for the LDA-Induced Aldol Addition of TIPS-Diazoacetone 1



team in order to overcome the lack of reproducibility noticed with the former conditions,[16b] the expected diazoaldol **3a** and TES-protected diazoaldol **5a** (Figure 1) were isolated in moderate yields from a complex mixture (Table 2, entry 8).

The above study highlighted the influence of the nature of the base on the outcome of the aldol addition between TIPS-diazoacetone **1** and benzaldehyde **2a**. A stoichiometric amount of bis(trimethylsilyl) amides allowed the reaction to proceed. With KHMDS, acceptable and reproducible yields were obtained as soon as LiBr was added to the aldehyde, whereas with LiHMDS, the reaction consistently occurred, albeit with fluctuating isolated yields. In contrast, dialkylamides like LDA and LTMP share the same trend: the stoichiometric amount of base led to no conversion at all or highly unreproducible conversions. However, high and reproducible yields of diazoaldol **3a** were achieved by using 2 equiv of LDA, constituting the optimal aldol addition conditions for our system.

Mechanistic Proposal. From the above results, two hypotheses emerged, which could explain the highly unreproducible results obtained with LDA. First, as LDA is much more basic than bis(trimethylsilyl)amides, it could be envisioned that LDA is able to competitively deprotonate another position on the substrate. However, TIPS-diazoacetone **1** does not bear another acidic hydrogen, which precluded this hypothesis. A second hypothesis was that LDA could, competitively to its role of the base toward the methyl ketone, play the role of a nucleophile toward the electrophilic terminal nitrogen of the diazo function. Indeed, the dual mechanism (deprotonation/nucleophilic addition) induced by LDA in THF at a low temperature has been highlighted on α,β-ethylenic esters and thoroughly investigated.[24] Moreover, the addition of PPh_3,[25] $Ge[N(SiMe_3)_2]_2$,[26] or a carbon nucleophile[27] on the diazo function of diazodicarbonyl moieties as well as the addition of Et_3N on the diazo function of diazomalodinitrile[28] have been well-documented. In the light of these examples, an original mechanistic rationale was proposed to explain the outcome of the aldolisation between TIPS-diazoacetone **1** and benzaldehyde **2a** in the presence of LDA (Scheme 5).

In this mechanism, the reaction between LDA and TIPS-diazoacetone **1** could follow two competitive pathways, depending on whether LDA first acts as a base to deprotonate the substrate (pathway 1, Scheme 5) or acts as a nucleophile, which adds to the electrophilic diazo function (pathway 2, Scheme 5). Deprotonation by LDA would generate, through pathway 1, the expected lithium enolate **6**, leading to aldol **3a** after aldol addition and hydrolysis. In a competitive way, TIPS-diazoacetone **1**, for which the diazonium enolate resonance structure could be favored by complexation with the lithium cation, could undergo, through pathway 2, the nucleophilic addition of LDA. A lithiated triazene could thus be generated, stabilized through the six-membered chelate **7** or through the five-membered chelate **7′**. Though inert toward benzaldehyde **2a**, the lithiated triazene could undergo deprotonation by a second molecule of LDA to produce lithiated carbanion **8**, stabilized by the silicon atom in the α-position. Lithiated carbanion **8** would undergo aldol addition with benzaldehyde **2a** to afford the triazene aldolate species **9**. The latter should decompose under NH_4Cl hydrolysis to yield the expected aldol **3a** and diisopropylamine. The proposed mechanism, involving two competitive pathways and most probably reversible steps, may explain the dramatic lack of reproducibility of the aldol addition conducted with 1 equiv of LDA. The outcome of the reaction (nucleophilic addition versus enolization) could indeed be greatly affected by aggregation/deaggregation rates of LDA in the medium, highly dependent on the salts concentration like LiCl potentially present.[24b] The absence of

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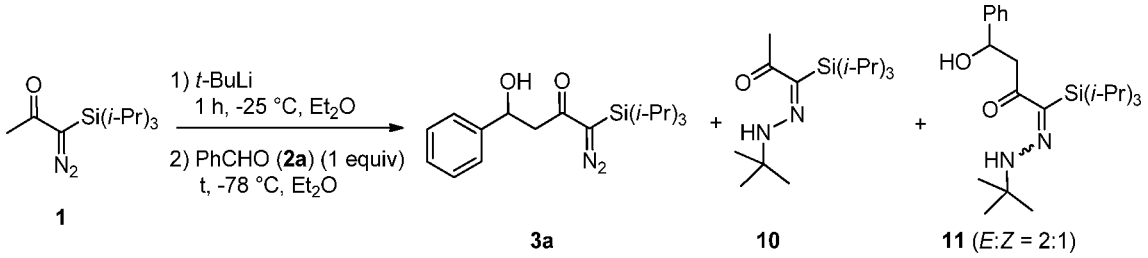
Table 3. Aldol Addition of TIPS-Diazoacetone with *t*-BuLi



entry	*t*-BuLi (*x* equiv)	reaction time *t* (h)	isolated yield (%) **3a**	isolated yield (%) **10**	isolated yield (%) **11**
1	1	1	13	42	13
2	2	1	*a*	46	23
3	2	5	*a*	23	53

[a]Not observed.

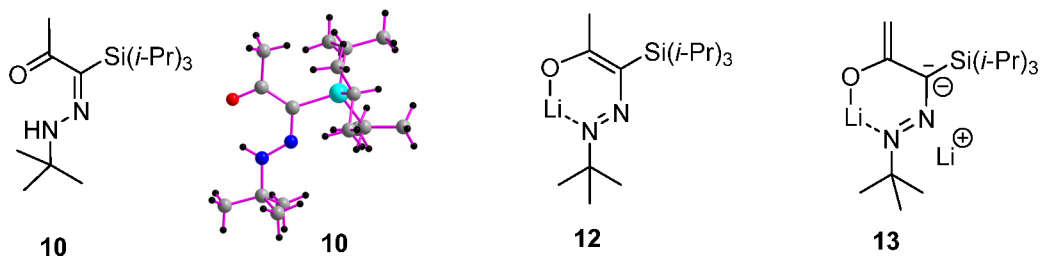


Figure 2. ORTEP diagram of α-keto hydrazone **10** and structures of the postulated intermediates **12** and **13**.

conversion surprisingly observed in several experiments conducted with 1 equiv of LDA could be rationalized by the quantitative formation of lithiated triazene **7** or **7′**, inert to benzaldehyde. On the contrary, the use of 2 equiv of LDA would allow the aldol addition to proceed in a reproducible way, via the formation of the lithiated carbanion **8** and/or the lithium enolate **6**. The fact that LTMP showed the same trend than LDA suggested that, though hindered, this amide could also add to the linear electrophilic diazo function, particularly free from steric hindrance.[29]

Contrary to dialkylamides, bis(trimethylsilylamides) are intrinsically not nucleophilic species due to electronic delocalization on the d orbitals of the silicon atoms. Therefore, the nucleophilic addition of KHMDS or LiHMDS to the diazo function through pathway 2 is not conceivable, and only deprotonation should proceed with these bases, resulting in aldol **3a** via the unique pathway 1. The requirement for an excess of LiHMDS to obtain a good and homogeneous yield of aldol **3a** (Table 2, entry 4) could be rationalized by the fact that bis(trimethylsilylamides) are much less basic than dialkylamides, requiring the displacement of the aldol addition equilibrium.

Experimental results in favor of the above mechanistic proposal were obtained when the aldol addition was carried out with *t*-BuLi (Table 3).

Indeed, with 1 equiv of *t*-BuLi, under the same conditions of temperature than used with LDA, using diethyl ether as the solvent,[30] the reaction led to the formation of three products (Table 3, entry 1). Although deprotonation toward lithium enolate **6** was expected to be favored with highly basic *t*-BuLi, diazoaldol **3a** was isolated as the minor product in only 13% yield. Besides, α-keto hydrazone **10**, whose structure was confirmed by X-ray analysis (Figure 2), and aldol hydrazone **11** were isolated in 42% and 13% yields, respectively. α-Keto hydrazone **10** clearly resulted from the addition of *t*-BuLi on the diazo moiety, generating lithium diazoenolate **12** (Figure 2), which was then hydrolyzed. Aldol hydrazone **11**, obtained as a 2:1 mixture of (*E*)/(*Z*) diastereoisomers, would be formed via deprotonation of the lithium diazoenolate **12** by *t*-BuLi and subsequent aldol addition of the generated stabilized carbanion **13** (Figure 2).

Results obtained with 2 equiv of *t*-BuLi did corroborate this hypothesis (Table 3, entries 2 and 3). When the reaction mixture was stirred for 1 h after the addition of benzaldehyde **2a**, diazoaldol **3a** was not observed, and compounds **10** and **11** were isolated in 46% and 23% yields, respectively (Table 3, entry 2). Extending the reaction time from 1 to 5 h led to a similar global yield of compounds **10** and **11**, but the ratio of these two products was roughly exchanged with a 23% isolated yield of α-keto hydrazone **10** and a 53% isolated yield of aldol hydrazone **11** (Table 3, entry 3). These results confirm that intermediate **13**, the precursor of aldol **11**, should result from deprotonation of lithium diazoenolate **12** by excess *t*-BuLi. Overall, the outcome of the assays carried out with *t*-BuLi proved in accordance with the mechanistic proposal suggested earlier for dialkylamide-induced aldol addition (Scheme 5), involving a competition between pathways 1 and 2. However, contrary to the N−N bond in the lithiated triazene intermediates **7**, **7′**, and **9** (Scheme 5), the C−N bond resulting from the addition of *t*-BuLi on the diazo function could not be broken during hydrolysis. In that respect, the identification of hydrazones **10** and **11** allowed to elucidate the mechanism involved with *t*-BuLi, while providing support for the proposed mechanism with dialkylamides.

In order to provide additional support to the mechanism postulated with LDA, the intermediates were calculated by DFT calculations at the M06-2X/6-311+G(d,p) SMD (THF) level of theory,[31] using TIPS-diazoacetone **1** and 2 molecules

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Table 4. Relative Electronic Energy ($\Delta\Delta E$), Enthalpy ($\Delta\Delta H^0_{248}$), and Free Energies ($\Delta\Delta G^0_{248}$) of the Intermediates Involved in the Postulated Mechanism with LDA at the M06-2X/6-311+G(d,p) SMD (THF) Level in kJ/mol

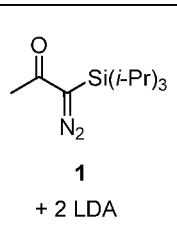
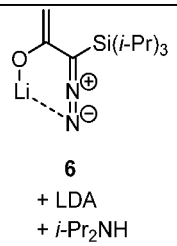
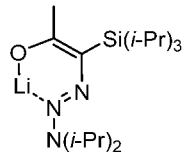
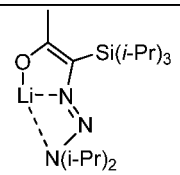
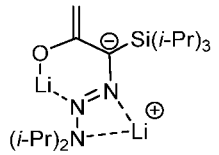
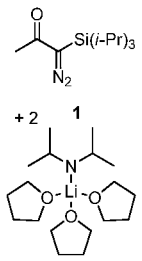
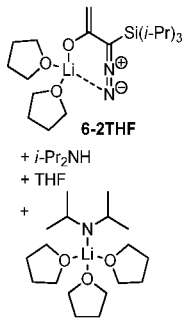
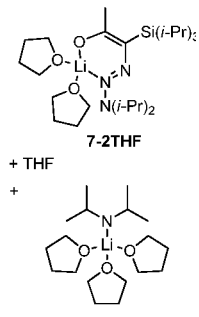
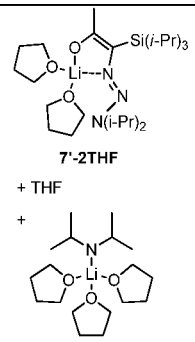
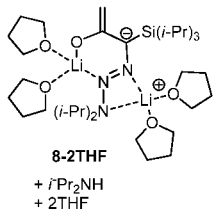
Structure	 **1** + 2 LDA	 **6** + LDA + *i*-Pr_2NH	 **7** + LDA	 **7'** + LDA	 **8** + *i*-Pr_2NH
$\Delta\Delta E$	0.0	−34.9	−107.4	−118.1	−161.2
$\Delta\Delta H^0_{248}$	0.0	−28.8	−93.9	−103.6	−143.6
$\Delta\Delta G^0_{248}$	0.0	−25.5	−39.4	−46.3	−82.4

Table 5. Relative Electronic Energy ($\Delta\Delta E$) and Enthalpy ($\Delta\Delta H^0_{248}$) of the Postulated Intermediates with LDA as THF Chelates at the M06-2X/6-311+G(d,p) SMD (THF) Level in kJ/mol

Structure	 + 2 **1**	 **6-2THF** + *i*-Pr_2NH + THF +	 **7-2THF** + THF +	 **7'-2THF** + THF +	 **8-2THF** + *i*-Pr_2NH + 2THF
$\Delta\Delta E$	0.0	−56.1	−92.9	−100.6	−104.3
$\Delta\Delta H^0_{248}$	0.0	−57.1	−86.6	−93.4	−97.5

of LDA as the reference (Table 4). Enthalpy and Gibbs free energies are calculated at 248 K (−25 °C). Intermediates **7** and **7′**, resulting from the addition of LDA to the diazo function, proved more stable than the lithium enolate intermediate **6** resulting from deprotonation ($\Delta\Delta G^0_{248}$ = −13.9 and −20.8 kJ/mol, respectively). Noteworthy is the higher stability of the five-membered chelate **7′** compared to the six-membered chelate **7** ($\Delta\Delta G^0_{248}$ = −6.9 kJ/mol). As expected, stabilized carbanion **8** was identified as the most stable intermediate by far, stabilized by −36.1 kJ/mol as compared with triazene **7′** (Table 4).

Overall, the $\Delta\Delta G^0_{248}$ values between the different intermediates are consistent with (i) the competitive formation of intermediates **6**, **7**, and **7′** in favor of **7′** in the presence of 1 equiv of LDA and (ii) the formation of stabilized carbanion **8** from lithiated triazenes **7** and/or **7′** (Scheme 5) in the presence of 2 equiv of LDA. With the purpose of evaluating the real influence of the solvent on these intermediates, THF molecules were introduced in order to position the lithium cation in a tetrahedral coordinate sphere, and the corresponding chelates were calculated at the same level as previously. In order to focus on the electronic effect induced by the presence of the THF on these molecules, the relative electronic energy ($\Delta\Delta E$) and the enthalpy ($\Delta\Delta H^0_{248}$) are given below (Table 5).

These results are very instructive as they show that the intermediate that will most benefit from the stabilization by the solvent is lithium enolate **6**. The relatively low energy differences between enolate **6** and lithiated triazenes **7** and **7′** bring support to the hypothesis of two competitive pathways (deprotonation/nucleophilic addition), accounting for the random reactivity observed with 1 equiv of LDA.

Furthermore, decomposition of the triazenes by breaking of the N−N bond during hydrolysis proved consistent with the high $\Delta\Delta G^0_{248}$ values calculated between enol structures **14** and **14′** on the one hand (postulated through hydrolysis of intermediates **7** and **7′**, respectively) and TIPS-diazoacetone **1** + *i*-Pr_2NH on the other hand (Table 6). Indeed, a high stabilization was gained through the decomposition of the hydrolyzed triazenes **14** and **14′** to form diazoacetone **1**, by −111,7 kJ/mol and −75 kJ/mol, respectively. This result can explain why no triazene could be observed or isolated experimentally, whereas *t*-BuLi adduct **10** could be isolated (Figure 2), since breaking of the C−N bond is not possible due to the high basicity of *t*-BuLi and the stability of the C−N bond formed.

Aldol Addition of TIPS-Diazoacetone: Scope of the Reaction. With reproducible and high-yielding conditions in our hands to perform the aldol addition between TIPS-diazoacetone **1** and benzaldehyde **2a**, we extended the method to a range of aldehydes, ketones, and an imine. The conditions implemented with 2 equiv of LDA were applied (Scheme 6).

Aromatic and heteroaromatic aldehydes behaved well in those conditions, providing original *C*-TIPS-diazoaldols **3a**−**3f**

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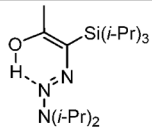
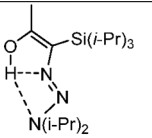
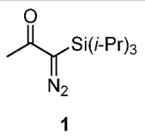
Table 6. Relative Electronic Energy ($\Delta\Delta E$), Enthalpy ($\Delta\Delta H^0_{248}$), and Free Energies of the Corresponding Enols 14 and 14′ Compared to the Starting Materials at the M06-2X/6-311+G(d,p) SMD(THF) Level in kJ/mol

Structure	 **14**	 **14′**	 **1** + *i*-Pr_2NH
$\Delta\Delta E$	0.0	−40.2	−50.1
$\Delta\Delta H^0_{248}$	0.0	−38.2	−64.1
$\Delta\Delta G^0_{248}$	0.0	−36.7	−111.7

in yields ranging from 54 to 88%. Good yields of diazoaldols **3g**−**3k** were also achieved from hindered and/or enolizable or even functionalized alkyl aldehydes (54−99%). α,β-Unsaturated aldehydes proved good substrates as well, leading to diazoaldols **3l**−**3o** in homogeneous yields (61−78%). Among those, diazoaldol **3o** was obtained as a mixture of diastereoisomers from a highly functionalized enantiopure aldehyde previously synthesized in our group as a key fragment in total synthesis.[6] Ketones like acetophenone and 1,1,1-trifluoroacetone proceeded well in the reaction with TIPS-diazoacetone **1**, leading to the expected products in 77% and 80% yields, respectively. Finally, the Mannich-type reaction proved feasible with *N*-benzylidene-*p*-toluene sulfonimine,[32] affording the corresponding Mannich adduct in 71% isolated yield. It should be noticed that while no desilylation occurred during the aldol addition process, a few percent yields of several *C*-desilylated diazoaldols **3′** were formed during chromatography and isolated[21] (Scheme 6). Pleasingly, X-ray diffraction could be performed on diazoaldols **3b** and **3e** as proofs of their structure.[22]

OUTLOOKS AND CONCLUSION

The "methyl-side" aldol addition of TIPS-diazoacetone **1** has been developed as a convergent way to synthesize diversely functionalized stable *C*-TIPS diazoaldols. Through the investigation of different bases, the use of 2 equiv of LDA turned up to constitute the appropriate conditions to achieve the aldol addition in good and reproducible yields. These conditions were successfully applied to 15 aldehydes, 2 ketones, and an imine. A novel mechanism was proposed to rationalize the requirement of 2 equiv of the base in order to achieve reproducible yields in the dialkylamide-promoted aldol addition of TIPS-diazoacetone **1**. Dialkylamides like LDA were suggested to add to the terminal nitrogen atom of the diazo function, made highly electrophilic due to very low bulkiness of this group, competitively to their expected role of the base toward the methyl ketone. The resulting lithiated triazene could, in turn, undergo deprotonation by LDA and add to the electrophile, eventually leading to the expected *C*-TIPS diazoaldol after hydrolysis. Experimental results obtained with *t*-Buli supported this hypothesis, as well as DFT calculations of the postulated intermediates. The knowledge of the specific reactivity of α-trialkylsilyl-α-diazoacetones toward lithium amides, usually known for their non-nucleophilic basic behavior, is crucial to explore further the synthetic potential of these hardly explored versatile 3-carbon building blocks. The library of stable *C*-TIPS diazoaldols synthesized here illustrates their value to access complex silylated diazocarbonyl scaffolds, potential precursors to wide molecular diversity through diazo transformation. Investigation of the asymmetric extension of the "methyl-side" aldol addition of α-trialkylsilyl-α-diazoacetones is underway, for which the use of chiral lithium amides is naturally constituting a privileged direction.

EXPERIMENTAL SECTION

Caution: Although we never had any trouble with the handling of the diazo compounds described in this study, diazo compounds are potentially explosive and should be handled with care in a well-ventilated fumehood. Aqueous layers containing azides traces should undergo adequate treatment before discarding.[33]

General Information. All air- and moisture-sensitive reactions were carried out under argon with anhydrous solvents using oven-dried glassware (90 °C). Et_2O and THF were dried through activated alumina columns (Glass Technology GTS 100). DIPEA, 2,2,6,6-tetramethylpiperidine, and CH_3CN were distilled over CaH_2. Et_3N was distilled over KOH. Commercial aldehydes and ketones were distilled or recrystallized before use. Reactions at −25 °C and −78 °C were performed using a bath cooled by the cryogenic flow. Commercial LDA (2 M/THF) was titrated with menthol, and 1,10-phenanthroline.[34] *n*-BuLi,[35] *t*-BuLi,[36] LiHMDS,[35] and KHMDS[37] were titrated just before use. Melting points were measured with a Kofler Heating Bench System Wagner & Munz.

Purifications by flash column chromatography were carried out using Merck Kieselgel 60 silica gel (particle size: 32−63 μm). Column chromatography was performed using 60 μm silica gel. Thin-layer chromatography (TLC) was performed with SIL G/UV254 plates, and products were detected by UV light or vanillin ethanolic solution. High-performance thin-layer chromatography (HPTLC) was performed with 1000 μm Silica Gel GF/UV254 20 cm × 20 cm plates. ^{1}H NMR (200 or 400 MHz), ^{13}C NMR (100.6 MHz), and ^{19}F NMR (188.3 MHz) spectra were recorded on a BRUKER DPX 200 or on a BRUKER Advance AC 400 spectrometer. Chemical shifts, δ ,were reported as parts per million (ppm) relative to Me_4Si. Coupling constants (J) were expressed in hertz (Hz), and splitting patterns were expressed as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sep (septet), m (multiplet), bs (broad singlet), or combinations of these. Proton and carbon assignments were established using COSY, HSQC, HMBC, and DEPT-Q. Infrared spectra (IR) were recorded on a PerkinElmer FT-IR Spectrum One spectrometer equipped with an ATR unit. The wavenumbers of representative absorption peaks were given in cm^{-1}. High-resolution mass spectra were recorded on a Bruker MicroTOF-QIII, ESI mode.

Preparation of TIPS-Diazoacetone (1). *1-Diazo-1-(triisopropylsilyl)propan-2-one (TIPS-Diazoacetone)*[9] *(1).* To a stirred solution of diazoacetone[13,11a] (1.8 g; 21 mmol) in a 1:1 mixture of anhydrous Et_2O/hexane (260 mL) at 0 °C were added diisopropylethylamine (4.9 mL; 28 mmol) and triisopropylsilyl trifluoromethanesulfonate (63.5 mL; 24 mmol). After 90 min of stirring at 0 °C under an argon atmosphere, the reaction mixture was hydrolyzed by the addition of a saturated aqueous $NaHCO_3$ solution (100 mL). The organic layer was washed with saturated aqueous NH_4Cl (2 × 50 mL) and brine (100 mL), dried over Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. The oily residue was purified by flash column chromatography (silica gel, petroleum ether/diethyl ether = 99:1) to afford TIPS-diazoacetone (**1**) as an orange oil (4.6 g, 90% yield):[15] R_f = 0.33 (petroleum ether/ethyl acetate = 99:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 2.30 (s, 3H), 1.45−1.21 (m, 3H), 1.10 (d, 18H, J = 6.9 Hz).

"Methyl-Side" Aldol Addition on TIPS-Diazoacetone (1) with LDA. *Protocol P1.* To a stirred solution of freshly titrated LDA[34] (2 M/THF, 2.0 equiv) in anhydrous THF (4.8 mL/mmol of TIPS-diazoacetone (**1**)), cooled at −25 °C, was added a solution of TIPS-diazoacetone (**1**) (1.0 equiv) in anhydrous THF (4.8 mL/mmol of (**1**)). After 1 h of stirring at −25 °C, the reaction mixture was cooled to −78 °C, and a solution of aldehyde (**2**) (1 equiv) in

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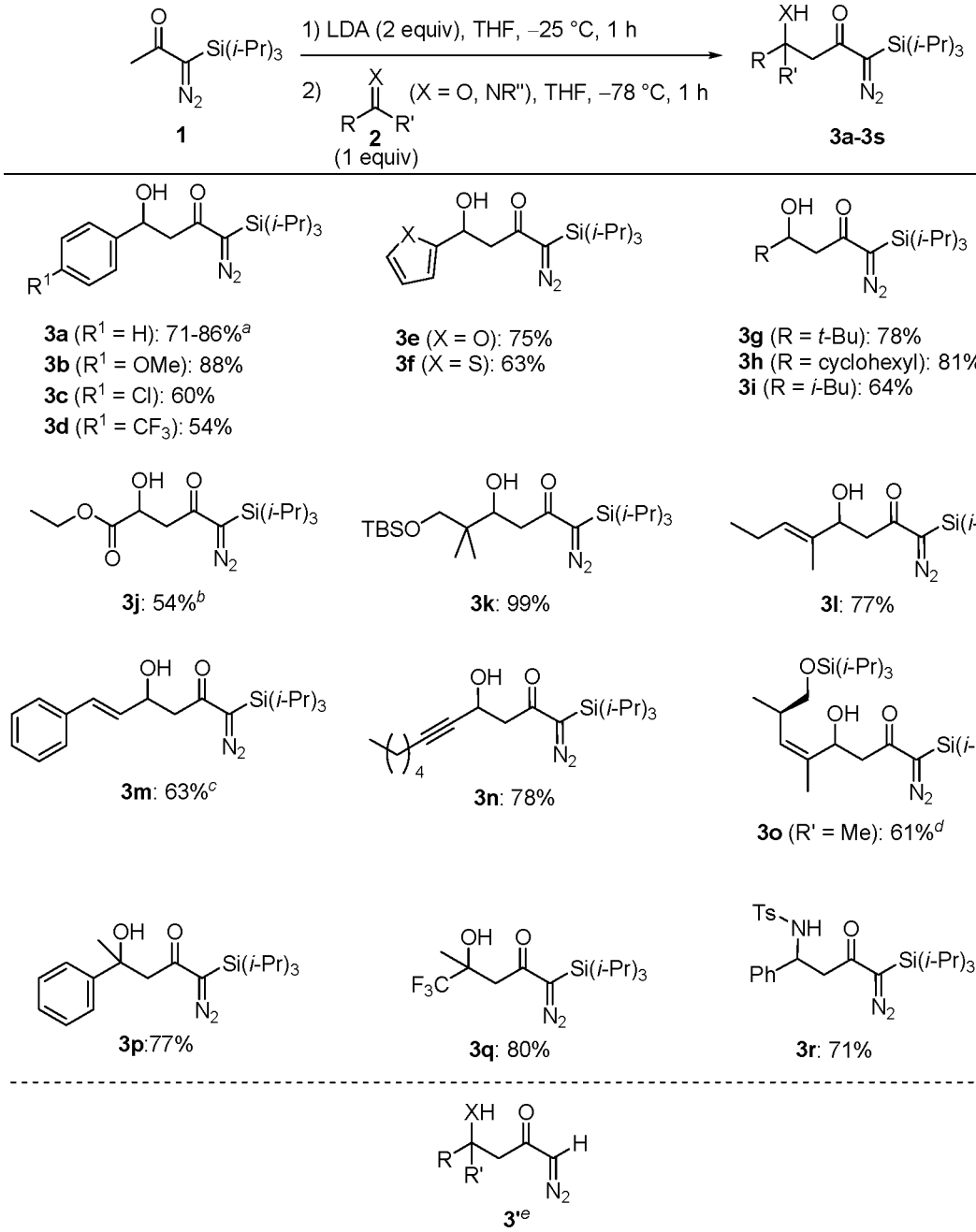
Scheme 6. Extension of the LDA-Induced Aldol Addition of TIPS-Diazoacetone 1 to a Range of Electrophiles



[a]On a 0.5−1 mmol scale; 67% yield on a 5 mmol scale. [b]2 equiv of ethyl glyoxylate was used. [c]Diazoaldol **3m** proved unstable in $CDCl_3$, and degradation was observed upon storage. [d]$T°$ = −100 °C instead of −78 °C. [e]Traces of several desilylated diazoaldols **3′** were formed during chromatographic purification and could be isolated, as detailed in the Experimental Section.

anhydrous THF (4.8 mL/mmol of aldehyde) was added dropwise. After an additional 1 h of stirring at −78 °C, accurately maintained,[19] the reaction mixture was hydrolyzed with saturated aqueous NH_4Cl and slowly warmed to rt. The aqueous layer was extracted with Et_2O (× 3). The combined organic layer was washed with brine, dried (Na_2SO_4), and filtered, and the filtrate was concentrated under reduced pressure. The residue was chromatographed (silica gel neutralized with 2% of NEt_3; petroleum ether/ethyl acetate = 10:0 to 5:5) to afford the corresponding diazoaldol (**3**).

*1-Diazo-4-hydroxy-4-phenyl-1-(triisopropylsilyl)butan-2-one (**3a**).* This compound was prepared from TIPS-diazoacetone (**1**)(232 mg, 1 mmol) and benzaldehyde (**2a**) (102 μL, 1 mmol) according to protocol P1. Diazoaldol (**3a**) was obtained after column chromatography as a yellow solid (288 mg, 86% yield), along with a small amount of the corresponding *C*-deprotected aldol (**3a′**)[5] (17 mg, 9% yield) isolated as an orange oil. Diazoaldol (**3a**): mp = 86 °C; R_f = 0.65 (petroleum ether/ethyl acetate = 90:10); IR (neat) ν_{max} (cm^{-1}) 3419 (ν_{O-H}), 2064 ($\nu_{N=N}$), 1627 ($\nu_{C=O}$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.39−7.32 (m, 4H), 7.28−7.24 (m, 1H), 5.18−5.15 (m, 1H), 3.89 (d, 1H, J = 2.8 Hz), 2.99−2.87 (m, 2H), 1.33 (sep, 3H, J = 7.4 Hz), 1.08 (d, 9H, J = 7.5 Hz), 1.07 (d, 9H, J = 7.5 Hz); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$) δ (ppm) 198.3 (C), 142.9 (C), 128.6 (2 CH), 127.7 (CH), 125.8 (2 CH), 70.6 (CH), 53.7 (C), 47.0 (CH_2), 18.4 (6 CH_3), 11.5 (3 CH); HRMS (ESI/Q-TOF) m/z [M + Na]$^+$ calcd for $C_{19}H_{30}N_2O_2SiNa$ 369.1969, found 369.1962. 1-Diazo-4-hydroxy-4-phenylbutan-2-one (**3a′**):[5] R_f = 0.10 (cyclohexane/ethyl acetate = 70:30); ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.46−7.28

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(m, 5H), 5.28 (bs, 1H), 5.18 (dd, 1H, J = 8.1, 4.4 Hz), 2.88−2.52 (m, 2H).

When prepared from TIPS-diazoacetone (**1**) (1.20 g, 5 mmol) and benzaldehyde (**2a**) (510 μL, 5 mmol) according to protocol P1, diazoaldol (**3a**) was obtained in 67% yield (1.16 g) after column chromatography.

*1-Diazo-4-hydroxy-4-(4-methoxyphenyl)-1-(triisopropylsilyl)-butan-2-one (**3b**).* This compound was prepared from TIPS-diazoacetone (**1**) (144 mg, 0.6 mmol) and 4-methoxybenzaldehyde (**2b**) (76 μL, 0.6 mmol) according to protocol P1. Diazoaldol (**3b**) was obtained after column chromatography as an orange solid (198 mg, 88% yield), along with a small amount of the corresponding *C*-deprotected aldol (**3b′**)[5] (3 mg, 4% yield) isolated as an orange oil. Diazoaldol (**3b**): mp = 80 °C; R_f = 0.31 (petroleum ether/ethyl acetate = 90:10); IR (neat) ν_{max} (cm^{-1}) 3409 (ν_{O-H}), 2064 ($\nu_{N=N}$), 1620 ($\nu_{C=O}$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.31 (d, 2H, J = 8.7 Hz), 6.89 (d, 2H, J = 8.7 Hz), 5.15−5.11 (m, 1H), 3.80 (s, 3H), 3.75 (d, 1H, J = 2.9 Hz), 2.98−2.86 (m, 2H), 1.33 (sep, 3H, J = 7.3 Hz), 1.09 (d, 9H, J = 7.5 Hz), 1.08 (d, 9H, J = 7.5 Hz); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$) δ (ppm) 198.5 (C), 159.3 (C), 135.1 (C), 127.1 (2 CH), 114.1 (2 CH), 70.3 (CH), 55.4 (CH_3), 53.7 (C), 47.0 (CH_2), 18.5 (6 CH_3), 11.6 (3 CH); HRMS (ESI/Q-TOF) m/z $[M + Na]^+$ calcd for $C_{20}H_{32}N_2O_3SiNa$ 399.2074, found 399.2069. 1-Diazo-4-hydroxy-4-(4-methoxyphenyl)butan-2-one (**3b′**):[5] R_f = 0.11 (cyclohexane/ethyl acetate = 70:30); ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.29 (d, 2H, J = 8.7 Hz), 6.88 (d, 2H, J = 8.7 Hz), 5.28 (bs, 1H), 5.12 (dd, 1H, J = 8.3, 3.6 Hz), 3.80 (s, 3H), 3.49 (bs, 1H), 2.86−2.55 (m, 2H).

*4-(4-Chlorophenyl)-1-diazo-4-hydroxy-1-(triisopropylsilyl)butan-2-one (**3c**).* This compound was prepared from TIPS-diazoacetone (**1**) (149 mg, 0.6 mmol) and 4-chlorobenzaldehyde (**2c**) (88 mg, 0.6 mmol) according to protocol P1. Diazoaldol (**3c**) was obtained after column chromatography as a yellow solid (142 mg, 60% yield). Diazoaldol (**3c**): mp = 100 °C; R_f = 0.48 (petroleum ether/ethyl acetate = 90:10); IR (neat) ν_{max} (cm^{-1}) 3411 (ν_{O-H}), 2064 ($\nu_{N=N}$), 1622 ($\nu_{C=O}$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.31 (s, 4H), 5.14 (t, 1H, J = 6.0 Hz), 3.99 (bs, 1H), 2.94−2.86 (m, 2H), 1.32 (sep, 3H, J = 7.5 Hz), 1.08 (d, 9H, J = 7.5 Hz), 1.07 (d, 9H, J = 7.5 Hz); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$) δ (ppm) 198.1 (C), 141.4 (C), 133.4 (C), 128.7 (2 CH), 127.2 (2 CH), 70.0 (CH), 53.9 (C), 46.8 (CH_2), 18.4 (6 CH_3), 11.5 (3 CH); HRMS (ESI/Q-TOF) m/z $[M + Na]^+$ calcd for $C_{19}H_{29}ClN_2O_2SiNa$ 403.1579, found 403.1563.

*1-Diazo-4-hydroxy-4-(4-(trifluoromethyl)phenyl)-1-(triisopropylsilyl)butan-2-one (**3d**).* This compound was prepared from TIPS-diazoacetone (**1**) (241 mg, 1 mmol) and 4-trifluoromethylbenzaldehyde (**2d**) (137 μL, 1 mmol) according to protocol P1. Diazoaldol (**3d**) was obtained after column chromatography as an orange solid (223 mg, 54% yield). Diazoaldol (**3d**): mp = 75 °C; R_f = 0.48 (petroleum ether/ethyl acetate = 90:10); IR (neat) ν_{max} (cm^{-1}) 3415 (ν_{O-H}), 2067 ($\nu_{N=N}$), 1619 ($\nu_{C=O}$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.62 (d, 2H, J = 8.2 Hz), 7.52 (d, 2H, J = 8.2 Hz), 5.26−5.22 (m, 1H), 4.02 (bs, 1H), 2.97−2.89 (m, 2H), 1.33 (sep, 3H, J = 7.5 Hz), 1.08 (d, 9H, J = 7.5 Hz), 1.07 (d, 9H, J = 7.5 Hz); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$) δ (ppm) 198.1 (C), 146.9 (C), 130.0 (q, J = 32.4 Hz, C), 126.1 (2 CH), 125.6 (q, J = 3.7 Hz, 2 CH), 124.2 (q, J = 272.5 Hz, C), 70.1 (CH), 54.0 (C), 46.6 (CH_2), 18.4 (6 CH_3), 11.5 (3 CH); ^{19}F NMR (188.3 MHz, $CDCl_3$) δ (ppm) −62.47; HRMS (ESI/Q-TOF) m/z $[M + Na]^+$ calcd for $C_{20}H_{29}F_3N_2O_2SiNa$ 437.1843, found 437.1833.

*1-Diazo-4-(furan-2-yl)-4-hydroxy-1-(triisopropylsilyl)butan-2-one (**3e**).* This compound was prepared from TIPS-diazoacetone (**1**) (148 mg, 0.6 mmol) and furfural (**2e**) (51 μL, 0.6 mmol) according to protocol P1. Diazoaldol (**3e**) was obtained after column chromatography as an orange solid (155 mg, 75% yield). Diazoaldol (**3e**): mp = 58 °C; R_f = 0.45 (petroleum ether/ethyl acetate = 90:10); IR (neat) ν_{max} (cm^{-1}) 3434 (ν_{O-H}), 2084 ($\nu_{N=N}$), 1599 ($\nu_{C=O}$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34 (dd, 1H, J = 1.8, 0.8 Hz), 6.31 (dd, 1H, J = 3.2, 1.8 Hz), 6.26 (dt, 1H, J = 3.2, 0.8 Hz), 5.17−5.15 (m, 1H), 3.88 (bs, 1H), 3.14 (dd, 1H, J = 16.2, 8.4 Hz), 3.00 (dd, 1H, J = 16.2, 3.7 Hz), 1.32 (sep, 3H, J = 7.5 Hz), 1.07 (d, 9H, J = 7.5 Hz), 1.06 (d, 9H, J = 7.5 Hz); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$) δ (ppm) 197.7 (C), 155.2 (C), 142.1 (CH), 110.4 (CH), 106.4 (CH), 64.7 (CH), 53.8 (C), 43.1 (CH_2), 18.4 (6 CH_3), 11.5 (3 CH); HRMS (ESI/Q-TOF) m/z $[M + Na]^+$ calcd for $C_{17}H_{28}N_2O_3SiNa$ 359.1761, found 359.1752.

*1-Diazo-4-hydroxy-4-(thiophen-2-yl)-1-(triisopropylsilyl)butan-2-one (**3f**).* This compound was prepared from TIPS-diazoacetone (**1**) (240 mg, 1 mmol) and 2-thiophenecarboxaldehyde (**2f**) (93 μL, 1 mmol) according to protocol P1. Diazoaldol (**3f**) was obtained after column chromatography as a brown solid (222 mg, 63% yield). Diazoaldol (**3f**): mp = 84 °C; R_f = 0.23 (petroleum ether/ethyl acetate = 95:5); IR (film) ν_{max} (cm^{-1}) 3395 (ν_{O-H}), 2090 ($\nu_{N=N}$), 1602 ($\nu_{C=O}$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.24 (dd, 1H, J = 4.9, 1.5 Hz), 6.99−6.95 (m, 2H), 5.42 (dd, 1H, J = 8.0, 3.8 Hz), 4.10 (bs, 1H), 3.09 (dd, 1H, J = 16.3, 8.0 Hz), 3.02 (dd, 1H, J = 16.3, 3.8 Hz), 1.33 (sep, 3H, J = 7.5 Hz), 1.08 (d, 9H, J = 7.5 Hz), 1.07 (d, 9H, J = 7.5 Hz); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$) δ (ppm) 197.8 (C), 146.7 (C), 126.8 (CH), 124.7 (CH), 123.5 (CH), 67.1 (CH), 53.9 (C), 46.7 (CH_2), 18.4 (6 CH_3), 11.5 (3 CH); HRMS (ESI/Q-TOF) m/z $[M + Na]^+$ calcd for $C_{17}H_{28}N_2O_2SSiNa$ 375.1533, found 375.1529.

*1-Diazo-4-hydroxy-5,5-dimethyl-1-(triisopropylsilyl)hexan-2-one (**3g**).* This compound was prepared from TIPS-diazoacetone (**1**) (224 mg, 0.9 mmol) and pivalaldehyde (**2g**) (109 μL, 0.9 mmol) according to protocol P1. Diazoaldol **3g** was obtained after column chromatography as a yellow oil (236 mg, 78% yield). Diazoaldol (**3g**): R_f = 0.56 (petroleum ether/ethyl acetate = 90:10); IR (film) ν_{max} (cm^{-1}) 3461 (ν_{O-H}), 2065 ($\nu_{N=N}$), 1620 ($\nu_{C=O}$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.73 (ddd, 1H, J = 10.4, 3.0, 1.9 Hz), 3.21 (bs, 1H), 2.75 (dd, 1H, J = 15.8, 1.9 Hz), 2.55 (dd, 1H, J = 15.8, 10.4 Hz), 1.34 (sep, 3H, J = 7.5 Hz), 1.09 (d, 9H, J = 7.5 Hz), 1.08 (d, 9H, J = 7.5 Hz), 0.93 (s, 9H); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$) δ (ppm) 199.7 (C), 75.7 (CH), 53.6 (C), 40.1 (CH_2), 34.6 (C), 25.9 (3 CH_3), 18.5 (3 CH_3), 18.5 (3 CH_3), 11.6 (3 CH); HRMS (ESI/Q-TOF) m/z $[M + Na]^+$ calcd for $C_{17}H_{34}N_2O_2SiNa$ 349.2282, found 349.2281.

*4-Cyclohexyl-1-diazo-4-hydroxy-1-(triisopropylsilyl)butan-2-one (**3h**).* This compound was prepared from TIPS-diazoacetone (**1**) (239 mg, 1 mmol) and cyclohexane carbaldehyde (**2h**) (121 μL, 1 mmol) according to protocol P1. Diazoaldol (**3h**) was obtained after column chromatography as an orange oil (283 mg, 81% yield), along with a small amount of the *C*-deprotected aldol (**3h′**)[5] (14 mg, 7% yield) isolated as an orange oil. Diazoaldol (**3h**): R_f = 0.59 (petroleum ether/ethyl acetate = 90:10); IR (neat) ν_{max} (cm^{-1}) 3446 (ν_{O-H}), 2065 ($\nu_{N=N}$), 1623 ($\nu_{C=O}$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.85−3.79 (m, 1H), 3.28 (d, 1H, J = 3.2 Hz), 2.75 (dd, 1H, J = 16.2, 2.6 Hz), 2.64 (dd, 1H, J = 16.2, 9.3 Hz), 1.90−1.08 (m, 11H), 1.34 (sep, 3H,J = 7.5 Hz), 1.09 (d, 18H, J = 7.5 Hz); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$) δ (ppm) 199.6 (C), 72.4 (CH), 53.5 (C), 43.2 (CH), 42.0 (CH_2), 29.1 (CH_2), 28.5 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 18.5 (6 CH_3), 11.6 (3 CH); HRMS (ESI/Q-TOF) m/z $[M + Na]^+$ calcd for $C_{19}H_{36}N_2O_2SiNa$ 375.2438, found 375.2428. 4-Cyclohexyl-1-diazo-4-hydroxybutan-2-one (**3h′**):[5] R_f = 0.12 (cyclohexane/ethyl acetate = 70:30); ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 5.31 (bs, 1H), 3.95−3.73 (m, 1H), 3.16 (bs, 1H), 2.54−2.38 (m, 2H), 1.91−1.46 and 1.44−0.76 (2 m, 11H).

*1-Diazo-4-hydroxy-6-methyl-1-(triisopropylsilyl)heptan-2-one (**3i**).* This compound was prepared from TIPS-diazoacetone (**1**) (141 mg, 0.6 mmol) and isovaleraldehyde (**2i**) (67 μL, 0.6 mmol) according to protocol P1. Diazoaldol (**3i**) was obtained after column chromatography as a yellow oil (122 mg, 64% yield), along with a small amount of the *C*-deprotected aldol (**3i′**)[5] (5 mg, 5% yield) isolated as an orange oil. Diazoaldol (**3i**): R_f = 0.44 (petroleum ether/ethyl acetate = 90:10); IR (film) ν_{max} (cm^{-1}) 3458 (ν_{O-H}), 2068 ($\nu_{N=N}$), 1623 ($\nu_{C=O}$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.17−4.11 (m, 1H), 3.32 (d, 1H, J = 2.8 Hz), 2.71 (dd, 1H, J = 16.3, 2.8 Hz), 2.61 (dd, 1H, J = 16.3, 8.8 Hz), 1.87−1.76 (m, 1H), 1.54−1.47 (m, 1H), 1.33 (sep, 3H, J = 7.5 Hz), 1.21−1.19 (m, 1H), 1.10 (d, 9H, J = 7.5 Hz), 1.09 (d, 9H, J = 7.5 Hz), 0.93 (d, 6H, J = 6.6 Hz); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$) δ (ppm) 199.3 (C), 66.4 (CH),

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53.4 (C), 45.7 (CH_2), 45.4 (CH_2), 24.6 (CH), 23.5 (CH_3), 22.2 (CH_3), 18.5 (6 CH_3), 11.6 (3 CH); HRMS (ESI/Q-TOF) m/z [M + Na]$^+$ calcd for $C_{17}H_{34}N_2O_2SiNa$ 349.2282, found 349.2274. 1-Diazo-4-hydroxy-6-methylheptan-2-one (**3i′**):[5] R_f = 0.10 (cyclohexane/ethyl acetate = 70:30); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.29 (bs, 1H), 4.26−4.03 (m, 1H), 2.57−2.33 (m, 2H), 1.93−1.67 (m, 1H), 1.60−1.38 (m, 1H), 1.14−1.02 (m, 1H), 0.92 (d, 6H, J = 6.7 Hz).

*Ethyl 5-Diazo-2-hydroxy-4-oxo-5-(triisopropylsilyl)pentanoate (**3j**).* This compound was prepared from TIPS-diazoacetone (**1**) (150 mg, 0.6 mmol) and ethyl 2-oxoacetate (**2j**) (47 wt % in toluene, 264 μL, 1.2 mmol) according to protocol P1. Diazoaldol (**3j**) was obtained after column chromatography as a yellow oil (115 mg, 54% yield). Diazoaldol (**3j**): R_f = 0.30 (petroleum ether/ethyl acetate = 90:10); IR (film) ν_{max} (cm^{-1}) 3467 (ν_{O-H}), 2065 ($\nu_{N=N}$), 1737 ($\nu_{C=Oester}$), 1632 ($\nu_{C=Oketone}$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.50 (dt, 1H, J = 6.1, 5.0 Hz), 4.24 (q, 2H, J = 7.1 Hz), 3.44 (d, 1H, J = 6.1 Hz), 3.07 (d, 2H, J = 5.0 Hz), 1.33 (sep, 3H, J = 7.5 Hz), 1.29 (t, 3H, J = 7.1 Hz), 1.09 (d, 9H, J = 7.5 Hz), 1.08 (d, 9H, J = 7.5 Hz); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ (ppm) 195.7 (C), 173.6 (C), 67.8 (CH), 61.9 (CH_2), 53.5 (C), 42.1 (CH_2), 18.4 (3 CH_3), 18.4 (3 CH_3), 14.2 (CH_3), 11.5 (3 CH); HRMS (ESI/Q-TOF) m/z [M + Na]$^+$ calcd for $C_{16}H_{30}N_2O_4SiNa$ 365.1867, found 365.1872.

*6-((tert-Butyldimethylsilyl)oxy)-1-diazo-4-hydroxy-5,5-dimethyl-1-(triisopropylsilyl)hexan-2-one (**3k**).* This compound was prepared from TIPS-diazoacetone (**1**) (142 mg, 0.6 mmol) and 3-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethylpropanal (**2k**) (136 mg, 0.6 mmol) according to protocol P1. Diazoaldol (**3k**) was obtained after column chromatography as a yellow oil (269 mg, 99% yield): R_f = 0.68 (petroleum ether/ethyl acetate = 90:10); IR (film) ν_{max} (cm^{-1}) 3495 (ν_{O-H}), 2065 ($\nu_{N=N}$), 1626 ($\nu_{C=O}$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.98 (ddd, 1H, J = 9.8, 3.5, 2.8 Hz), 3.63 (d, 1H, J = 3.5 Hz), 3.48 (d, 1H, J = 9.7 Hz), 3.45 (d, 1H, J = 9.7 Hz), 2.72 (dd, 1H, J = 15.0, 9.8 Hz), 2.64 (dd, 1H, J = 15.0, 2.8 Hz), 1.40−1.29 (m, 3H), 1.09 (d, 18H, J = 7.4 Hz), 0.90 (s, 3H), 0.89 (s, 9H), 0.87 (s, 3H), 0.05 (s, 6H); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ (ppm) 199.1 (C), 74.7 (CH), 71.5 (CH_2), 53.4 (C), 41.1 (CH_2), 38.8 (C), 26.0 (3 CH_3), 21.9 (CH_3), 19.9 (CH_3), 18.5 (3 CH_3), 18.5 (3 CH_3), 18.4 (C), 11.6 (3 CH), −5.5 (2 CH_3); HRMS (ESI/Q-TOF) m/z [M + Na]$^+$ calcd for $C_{23}H_{48}N_2O_3Si_2Na$ 479.3096, found 479.3097.

*(E)-1-Diazo-4-hydroxy-5-methyl-1-(triisopropylsilyl)oct-5-en-2-one (**3l**).* This compound was prepared from TIPS-diazoacetone (**1**) (99 mg, 0.4 mmol) and (*E*)-2-methylpent-2-enal (**2l**) (48 μL, 0.4 mmol) according to protocol P1. Diazoaldol (**3l**) was obtained after column chromatography as a yellow oil (107 mg, 77% yield), along with a small amount of the *C*-deprotected aldol (**3l′**)[5] (9 mg, 12% yield) isolated as an orange oil. Diazoaldol (**3l**): R_f = 0.30 (petroleum ether/ethyl acetate = 90:10); IR (film) ν_{max} (cm^{-1}) 3413 (ν_{O-H}), 2063 ($\nu_{N=N}$), 1620 ($\nu_{C=O}$); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 5−51−5.44 (m, 1H), 4.50−4.43 (m, 1H), 3.34 (d, 1H, J = 2.9 Hz), 2.87−2.69 (m, 2H), 2.11−1.96 (m, 2H), 1.65 (s, 3H), 1.38−1.24 (m, 3H), 1.09 (d, 18H, J = 7.0 Hz), 0.96 (t, 3H, J = 7.6 Hz); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ (ppm) 198.8 (C), 134.8 (C), 128.6 (CH), 73.6 (CH), 53.5 (C), 43.7 (CH_2), 20.9 (CH_2), 18.4 (6 CH_3), 14.0 (CH_3), 12.0 (CH_3), 11.5 (3 CH); HRMS (ESI/Q-TOF) m/z [M + Na]$^+$ calcd for $C_{18}H_{34}N_2O_2SiNa$ 361.2282, found 361.2271. (*E*)-1-Diazo-4-hydroxy-5-methyloct-5-en-2-one (**3l′**):[5] R_f = 0.12 (cyclohexane/ethyl acetate = 70:30); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 5.47 (t, 1H, J = 7.2 Hz), 5.32 (bs, 1H), 4.45 (dd, 1H, J = 8.9, 3.6 Hz), 2.68−2.40 (m, 2H), 2.03 (quint, 1H, J = 7.2 Hz), 1.62 (s, 3H), 0.96 (t, 3H, J = 7.5 Hz).

*(E)-1-Diazo-4-hydroxy-6-phenyl-1-(triisopropylsilyl)hex-5-en-2-one (**3m**).* This compound was prepared from TIPS-diazoacetone (**1**) (240 mg, 1 mmol) and cinnamaldehyde (**2m**) (126 μL, 1 mmol) according to protocol P1. Diazoaldol (**3m**) was obtained after column chromatography as an orange oil (236 mg, 63% yield), which proved unstable in $CDCl_3$ and upon storage, along with a small amount of the *C*-deprotected aldol (**3m′**)[5] (5 mg, 2% yield) isolated as an orange oil. Diazoaldol (**3m**): R_f = 0.44 (petroleum ether/ethyl acetate = 90:10); IR (film) ν_{max} (cm^{-1}) 3413 (ν_{O-H}), 2065 ($\nu_{N=N}$), 1629 ($\nu_{C=O}$); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.41−7.23 (m, 5H), 6.67 (dd, 1H, J = 16.0, 1.1 Hz), 6.24 (dd, 1H, J = 16.0, 6.0 Hz), 4.80−4.78 (m, 1H), 3.68 (d, 1H, J = 3.0 Hz), 2.96−2.76 (m, 2H), 1.42−1.27 (m, 3H), 1.09 (d, 18H, J = 7.0 Hz); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ (ppm) 198.3 (C), 136.7 (C), 130.6 (CH), 130.2 (CH), 128.6 (2 CH), 127.8 (CH), 126.6 (2 CH), 69.2 (CH), 53.8 (C), 45.0 (CH_2), 18.4 (6 CH_3), 11.5 (3 CH); HRMS (ESI/Q-TOF) m/z [M + Na]$^+$ calcd for $C_{21}H_{32}N_2O_2SiNa$ 395.2125, found 359.2114. (E)-1-Diazo-4-hydroxy-6-phenylhex-5-en-2-one (**3m′**):[5] R_f = 0.13 (cyclohexane/ethyl acetate = 70:30); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.45−7.22 (m, 5H), 6.66 (d, 1H, J = 16.0 Hz), 6.21 (dd, 1H, J = 16.0, 6.1 Hz), 5.33 (bs, 1H), 4.88−4.67 (m, 1H), 3.37 (bs, 1H), 2.73−2.54 (m, 2H).

*1-Diazo-4-hydroxy-1-(triisopropylsilyl)undec-5-yn-2-one (**3n**).* This compound was prepared from TIPS-diazoacetone (**1**) (220 mg, 0.9 mmol) and 2-octynal (**2n**) (130 μL, 0.9 mmol) according to protocol P1. Diazoaldol (**3n**) was obtained after column chromatography as an orange oil (261 mg, 78% yield). Diazoaldol (**3n**): R_f = 0.32 (petroleum ether/ethyl acetate = 90:10); IR (film) ν_{max} (cm^{-1}) 3402 (ν_{O-H}), 2065 ($\nu_{N=N}$), 2104 ($\nu_{C\equiv C}$), 1626 ($\nu_{C=O}$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.81−4.77 (m, 1H), 3.51 (d, 1H, J = 5.3 Hz), 2.99 (dd, 1H, J = 16.0, 7.4 Hz), 2.88 (dd, 1H, J = 16.0, 4.0 Hz), 2.18 (td, 2H, J = 7.2, 2.0 Hz), 1.53−1.46 (m, 2H), 1.38−1.30 (m, 7H), 1.09 (d, 18H, J = 7.4 Hz), 0.89 (t, 3H, J = 7.2 Hz); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ (ppm) 197.3 (C), 85.6 (C), 79.6 (C), 59.3 (CH), 53.7 (C), 45.4 (CH_2), 31.1 (CH_2), 28.3 (CH_2), 22.2 (CH_2), 18.7 (CH_2), 18.3 (6 CH_3), 14.0 (CH_3), 11.5 (3 CH); HRMS (ESI/Q-TOF) m/z [M + Na]$^+$ calcd for $C_{20}H_{36}N_2O_2SiNa$ 387.2438, found 387.2436.

*(7R,Z)-1-Diazo-4-hydroxy-5,7-dimethyl-1-(triisopropylsilyl)-8-((triisopropylsilyl)oxy)oct-5-en-2-one (**3o**).* This compound was prepared from TIPS-diazoacetone (**1**) (149 mg, 0.6 mmol) and (*R,Z*)-2,4-dimethyl-5-((triisopropylsilyl)oxy)pent-2-enal (**2o**)[6] (178 mg, 0.6 mmol) according to protocol P1. Diazoaldol (**3o**) was obtained as a mixture of diastereoisomers after column chromatography as an orange oil (196 mg, 61% yield). For analytical purpose, diastereoisomers (**3o$_{d1}$**) and (**3o$_{d2}$**) were separated on HPTLC neutralized with 2% of NEt_3; petroleum ether/ethyl acetate = 98/2). Diazoaldol (**3o$_{d1}$**): R_f = 0.70 (petroleum ether/ethyl acetate = 90:10); IR (film) ν_{max} (cm^{-1}) 3449 (ν_{O-H}), 2062 ($\nu_{N=N}$), 1630 ($\nu_{C=O}$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.06−5.00 (m, 2H), 3.56−3.43 (m, 2H), 3.15 (bs, 1H), 2.94 (dd, 1H, J = 15.5, 9.4 Hz), 2.78−2.70 (m, 1H), 2.56 (dd, 1H, J = 15.5, 3.5 Hz), 1.74 (d, 3H, J = 1.4 Hz), 1.35 (sep, 3H, J = 7.5 Hz), 1.11−1.04 (m, 39H), 0.93 (d, 3H, J = 6.6 Hz); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ (ppm) 198.2 (C), 136.5 (C), 131.8 (CH), 68.4 (CH_2), 66.5 (CH), 53.5 (C), 43.4 (CH_2), 35.0 (CH), 18.5 (6 CH_3), 18.4 (CH_3), 18.1 (6 CH_3), 17.6 (CH_3), 12.1 (3 CH), 11.6 (3 CH). Diazoaldol (**3o$_{d2}$**): R_f = 0.64 (petroleum ether/ethyl acetate = 90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.05−4.97 (m, 2H), 3.52−3.39 (m, 3H), 2.90 (dd, 1H, J = 16.2, 10.1 Hz), 2.82−2.74 (m, 1H), 2.63 (dd, 1H, J = 16.2, 2.5 Hz), 1.74 (d, 3H, J = 1.4 Hz), 1.35 (sep, 3H, J = 7.5 Hz), 1.11−1.04 (m, 39H), 0.94 (d, 3H, J = 6.6 Hz); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ (ppm) 198.7 (C), 136.0 (C), 131.4 (CH), 68.7 (CH_2), 67.4 (CH), 53.5 (C), 44.1 (CH_2), 35.2 (CH), 19.0 (CH_3), 18.5 (6 CH_3), 18.1 (6 CH_3), 17.8 (CH_3), 12.1 (3 CH), 11.6 (3 CH). HRMS (ESI/Q-TOF) m/z [M + Na]$^+$ calcd for $C_{28}H_{56}N_2O_3Si_2Na$ 547.3722, found 547.3719.

*1-Diazo-4-hydroxy-4-phenyl-1-(triisopropylsilyl)pentan-2-one (**3p**).* This compound was prepared from TIPS-diazoacetone (**1**) (239 mg, 1 mmol) and acetophenone (**2p**) (117 μL, 1 mmol) according to protocol P1. Diazoketol (**3p**) was obtained after column chromatography as a yellow solid (275 mg, 77% yield): mp = 66 °C; R_f = 0.53 (petroleum ether/ethyl acetate = 90:10); IR (neat) ν_{max} (cm^{-1}) 3276 (ν_{O-H}), 2075 ($\nu_{N=N}$), 1600 ($\nu_{C=O}$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.45−7.43 (m, 2H), 7.34−7.29 (m, 2H), 7.22−7.18 (m, 1H), 5.17 (s, 1H), 3.32 (d, 1H, J = 15.2 Hz), 2.78 (d, 1H, J = 15.2 Hz), 1.56 (s, 3H), 1.22 (sep, 3H, J = 7.5 Hz), 0.96 (d, 9H, J = 7.5 Hz), 0.92 (d, 9H, J = 7.5 Hz); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ (ppm) 199.5 (C), 147.2 (C), 128.4 (2 CH), 126.8 (CH), 124.5 (2 CH), 74.1 (C), 54.7 (C), 48.4 (CH_2), 31.0 (CH_3), 18.2 (3 CH_3), 18.2 (3 CH_3),

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11.4 (3 CH); HRMS (ESI/Q-TOF) m/z [M + Na]$^+$ calcd for $C_{20}H_{32}N_2O_2SiNa$ 383.2125, found 383.2115.

*1-Diazo-5,5,5-trifluoro-4-hydroxy-4-methyl-1-(triisopropylsilyl)-pentan-2-one (**3q**).* This compound was prepared from TIPS-diazoacetone (**1**) (238 mg, 1 mmol) and 1,1,1-trifluoroacetone (**2q**) (89 μL, 1 mmol) according to protocol P1. Diazoketol (**3q**) was obtained after column chromatography as a white solid (279 mg, 80% yield): mp = 60 °C; R_f = 0.36 (petroleum ether/ethyl acetate = 95:5); IR (neat) ν_{max} (cm^{-1}) 3362 (ν_{O-H}), 2070 ($\nu_{N=N}$), 1606 ($\nu_{C=O}$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.63 (bs, 1H), 3.03 (d, 1H, J = 15.5 Hz), 2.64 (d, 1H, J = 15.5 Hz), 1.43 (s, 3H), 1.35 (sep, 3H, J = 7.5 Hz), 1.09 (d, 18H, J = 7.5 Hz); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ (ppm) 197.6 (C), 125.9 (q, J = 286.0 Hz, C), 73.5 (q, J = 29.2 Hz, C), 55.6 (C), 40.1 (CH_2), 22.2 (m, CH_3), 18.3 (3 CH_3), 18.3 (3 CH_3), 11.5 (3 CH); ^{19}F NMR (188.3 MHz, $CDCl_3$) δ (ppm) −82.32; HRMS (ESI/Q-TOF) m/z [M + Na]$^+$ calcd for $C_{15}H_{27}F_3N_2O_2SiNa$ 375.1686, found 375.1682.

*N-(4-Diazo-3-oxo-1-phenyl-4-(triisopropylsilyl)butyl)-4-methylbenzenesulfonamide (**3r**).* This compound was prepared from TIPS-diazoacetone (**1**) (149 mg, 0.6 mmol) and (*E*)-*N*-benzylidene-4-methylbenzenesulfonamide (**2r**)[32] (162 mg, 0.6 mmol) according to protocol P1. Mannich adduct (**3r**) was obtained after column chromatography as a yellow solid (222 mg, 71% yield). Compound **3r**: mp = 121 °C; R_f = 0.24 (petroleum ether/ethyl acetate = 90:10); IR (neat) ν_{max} (cm^{-1}) 3272 (ν_{N-H}), 2067 ($\nu_{N=N}$), 1629 ($\nu_{C=O}$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.62 (d, 2H, J = 8.3 Hz), 7.18−7.15 (m, 5H), 7.14−7.11 (m, 2H), 6.20−6.17 (m, 1H), 4.77−4.72 (m, 1H), 3.09 (dd, 1H, J = 15.5, 5.2 Hz), 2.86 (dd, 1H, J = 15.5, 5.9 Hz), 2.37 (s, 3H), 1.21 (sep, 3H, J = 7.5 Hz), 0.96 (d, 9H, J = 7.5 Hz), 0.95 (d, 9H, J = 7.5 Hz); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ (ppm) 196.1 (C), 143.1 (C), 139.6 (C), 137.7 (C), 129.5 (2 CH), 128.5 (2 CH), 127.6 (CH), 127.2 (2 CH), 126.6 (2 CH), 55.0 (CH), 53.9 (C), 43.9 (CH_2), 21.5 (CH_3), 18.2 (6 CH_3), 11.4 (3 CH); HRMS (ESI/Q-TOF) m/z [M + Na]$^+$ calcd for $C_{26}H_{37}N_3O_3SSiNa$ 522.2217, found 522.2213.

"Methyl-Side" Aldol Addition on TIPS-Diazoacetone (1) with 2 Equiv of LTMP. To a stirred solution of LTMP (1.35 M, 1.48 mL, 2.0 mmol, 2 equiv) prepared from 2,2,6,6-tetramethylpiperidine, freshly distilled over CaH_2, and *n*-BuLi (freshly titrated,[35] 1.35 M/hexane) in anhydrous THF (4.8 mL) at −25 °C was added a solution of α-triisopropylsilyl-α-diazoacetone (**1**) (0.240 g, 1.0 mmol, 1.0 equiv) in anhydrous THF (4.8 mL). After 1 h of stirring at the same temperature, the reaction mixture was cooled to −78 °C, and a solution of benzaldehyde (**2a**) (0.102 mL, 1.0 mmol, 1 equiv) in anhydrous THF (4.8 mL) was added dropwise. After an additional 1 h of stirring at −78 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl and slowly warmed to rt. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layer was washed with brine (20 mL), dried (Na_2SO_4), and filtered, and the filtrate was concentrated under reduced pressure. A conversion of 49% into diazoaldol (**3a**) was observed on the ^{1}H NMR spectrum of this crude product.

"Methyl-Side" Aldol Addition on TIPS-Diazoacetone (1) with LiHMDS. To a stirred solution of LiHMDS (freshly titrated,[35] 1 M/THF, 2.0 equiv) in anhydrous THF (2 mL) at −25 °C was added a solution of α-triisopropylsilyl-α-diazoacetone (**1**) (100 mg, 0.42 mmol, 1 equiv) in anhydrous THF (2 mL). After 1 h of stirring at the same temperature, the reaction mixture was cooled to −78 °C, and a solution of aldehyde (42 μL, 0.42 mmol, 1.0 equiv) in anhydrous THF (2 mL) was added dropwise. After an additional 1 h of stirring at −78 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl and slowly warmed to rt. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layer was washed with brine (20 mL), dried (Na_2SO_4), and filtered, and the filtrate was concentrated under reduced pressure. The residue was chromatographed (silica gel neutralized with 2% of NEt_3; petroleum ether/ethyl acetate = 10:0 to 5:5) to afford the corresponding diazoaldol (**3a**) in yields ranging from 76 to 83% on 3 assays.

"Methyl-Side" Aldol Addition on TIPS-Diazoacetone (1) with KHMDS. *Procedure without an Additive.* To a solution of KHMDS (freshly titrated,[37] 0.5 M/toluene, 0.92 mL, 0.45 mmol, 1.1 equiv) in anhydrous THF (4.2 mL) at −78 °C under argon was added a solution of TIPS-diazoacetone (**1**) (99 mg, 0.41 mmol, 1.0 equiv) in anhydrous THF (2.1 mL) over 10 min. The mixture was stirred for 40 min at −78 °C, after which a solution of benzaldehyde (**2a**) (38 μL, 0.37 mmol, 0.9 equiv) in anhydrous THF (2.1 mL) was added over 5 min. This mixture was stirred for 60 min at −78 °C, after which 10 mL of saturated NH_4Cl solution was added, and the mixture was warmed to rt. The mixture was then partitioned between ethyl acetate and, sequentially, water (20 mL) and brine (20 mL). The combined organic layer was dried (Na_2SO_4) and filtered, and the filtrate was concentrated under reduced pressure. The residue was chromatographed (silica gel neutralized with 2% of NEt_3; petroleum ether/ethyl acetate = 10:0 to 5:5) to afford the corresponding diazoaldol (**3a**) (50 mg, 38% yield) and bis-aldol (**4a**) (21 mg, 12% yield) as an orange solid.

*1-Diazo-4-hydroxy-3-(hydroxy(phenyl)methyl)-4-phenyl-1-(triisopropylsilyl)butan-2-one (**4a**):* mp = 145 °C; R_f = 0.67 (petroleum ether/ethyl acetate = 70:30); IR (neat) ν_{max} (cm^{-1}) 3382 (ν_{O-H}), 3351 (ν_{O-H}), 2077 ($\nu_{N=N}$), 1593 ($\nu_{C=O}$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.44−7.42 (m, 2H), 7.38−7.27 (m, 7H), 7.22−7.18 (m, 1H), 5.47−5.46 (m, 1H), 5.25 (d, 1H, J = 9.2 Hz), 4.74 (d, 1H, J = 9.2 Hz), 3.64 (dd, 1H, J = 9.2, 2.7 Hz), 3.24 (bs, 1H), 0.99 (sep, 3H, J = 7.5 Hz), 0.70 (d, 9H, J = 7.5 Hz), 0.70 (d, 9H, J = 7.5 Hz); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ (ppm) 200.5 (C), 142.7 (C), 141.7 (C), 128.9 (2 CH), 128.6 (2 CH), 128.5 (CH), 127.2 (CH), 126.9 (2 CH), 125.0 (2 CH), 73.4 (CH), 71.8 (CH), 59.6 (CH), 56.7 (C), 17.9 (6 CH_3), 11.2 (3 CH);HRMS (ESI/Q-TOF) m/z [M + Na]$^+$ calcd for $C_{26}H_{36}N_2O_3SiNa$ 475.2387, found 475.2375.

Procedure with LiBr as an Additive. To a solution of KHMDS (freshly titrated,[37] 0.5 M/toluene, 0.92 mL, 0.46 mmol, 1.1 equiv) in anhydrous THF (4.2 mL) at −78 °C under argon was added a solution of TIPS-diazoacetone (**1**) (100 mg, 0.42 mmol, 1.0 equiv) in anhydrous THF (2.1 mL) over 10 min. The mixture was stirred for 40 min at −78 °C, after which a solution of dry LiBr (47 mg, 0.54 mmol, 1.3 equiv) and benzaldehyde (**2a**) (38 μL, 0.38 mmol, 0.9 equiv) in anhydrous THF (2.1 mL) was added over 5 min. This mixture was stirred for 60 min at −78 °C, after which 10 mL of saturated NH_4Cl solution was added, and the mixture was warmed to rt. The mixture was then partitioned between ethyl acetate and, sequentially, water (20 mL) and brine (20 mL). The combined organic layer was dried (Na_2SO_4) and filtered, and the filtrate was concentrated under reduced pressure. The residue was chromatographed (silica gel neutralized with 2% of NEt_3, petroleum ether/ethyl acetate = 10:0 to 5:5) to afford the corresponding diazoaldol (**3a**) in yields ranging from 58 to 79% on 4 assays.

Procedure with TESCl as an Additive. To a stirred solution of TIPS-diazoacetone (**1**) (100 mg, 0.42 mmol, 1 equiv) in anhydrous toluene (8.5 mL) at −78 °C was added dropwise KHMDS (freshly titrated,[37] 0.5 M/toluene, 0.87 mL, 0.44 mmol, 1.05 equiv) over 15 min. After 5 min of stirring, a solution of benzaldehyde (**2a**) (51 μL, 0.5 mmol, 1.2 equiv) and TESCl (83 μL, 0.5 mmol, 1.2 equiv) in anhydrous toluene (1.8 mL) was added. After 15 min of stirring at −78 °C, the reaction mixture was partitioned between EtOAc and, sequentially, saturated aqueous NH_4Cl (20 mL) and brine (20 mL). The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed (silica gel neutralized with 2% of NEt_3, petroleum ether/ethyl acetate = 10:0 to 5:5), and two products were isolated from a complex mixture: (**3a**) as a yellow solid (30 mg, 22% yield) and (**5a**) as an orange oil (66 mg, 36% yield).

*1-Diazo-4-phenyl-4-((triethylsilyl)oxy)-1-(triisopropylsilyl)butan-2-one (**5a**):* R_f = 0.90 (petroleum ether/diethyl ether = 90:10, phosphomolybdic acid stain); IR (film) ν_{max} (cm^{-1}) 2068 ($\nu_{N=N}$), 1622 ($\nu_{C=O}$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36−7.28 (m, 4H), 7.25−7.21 (m, 1H), 5.20 (dd, 1H, J = 7.7, 5.3 Hz), 3.04 (dd, 1H, J = 14.3, 7.7 Hz), 2.74 (dd, 1H, J = 14.3, 5.3 Hz), 1.35−1.27 (m, 3H), 1.05 (d, 18H, J = 7.4 Hz), 0.85 (t, 9H, J = 8.0 Hz), 0.53−0.46 (m, 6H); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ (ppm) 196.1 (C), 144.6 (C), 128.4 (2 CH), 127.6 (CH), 126.1 (2 CH), 72.3 (CH),

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53.6 (C), 50.0 (CH_2), 18.5 (6 CH_3), 11.6 (3 CH), 6.9 (3 CH_3), 4.9 (3 CH_2); HRMS (ESI/Q-TOF) m/z $[M + Na]^+$ calcd for $C_{25}H_{44}N_2O_2Si_2Na$ 483.2834, found 483.2823.

"Methyl-Side" Aldol Addition on TIPS-Diazoacetone (1) with *t*-BuLi. To a stirred solution of *t*-BuLi (freshly titrated,[36] 1.5 M/pentane, 0.84 mL, 1.26 mmol, 2.0 equiv) in anhydrous Et_2O (3 mL) at −25 °C was added a solution of α-triisopropylsilyl-α-diazoacetone (**1**) (151 mg, 0.63 mmol, 1.0 equiv) in anhydrous Et_2O (3 mL). After 1 h of stirring at the same temperature, the reaction mixture was cooled to −78 °C, and a solution of benzaldehyde (**2a**) (64 μL, 0.63 mmol, 1 equiv) in anhydrous Et_2O (3 mL) was added dropwise. After an additional 5 h of stirring at −78 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl and slowly warmed to rt. The aqueous layer was extracted with Et_2O (3 × 4 mL). The combined organic layer was washed with brine (20 mL), dried (Na_2SO_4), and filtered, and the filtrate was concentrated under reduced pressure. The residue was chromatographed (silica gel neutralized with 2% of NEt_3, petroleum ether/ethyl acetate = 10:0 to 5:5) to afford α-ketohydrazone (*E*)-(**10**) as a yellow solid (43 mg, 23% yield) and α-ketohydrazone (**11**) as a mixture of diastereoisomers ((*E*)-**11**/(*Z*)-**11** = 2:1) as a yellow liquid (135 mg, 53% yield).

*(E)-1-(2-(tert-Butyl)hydrazono)-1-(triisopropylsilyl)propan-2-one (**10**):* mp = 76 °C; R_f = 0.80 (petroleum ether/ethyl acetate = 90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 13.55 (bs, 1H), 2.19 (s, 3H), 1.36 (sep, 3H, J = 7.5 Hz), 1.30 (s, 9H), 1.09 (d, 18H, J = 7.5 Hz); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$) δ (ppm) 197.5 (C), 131.0 (C), 55.8 (C), 29.5 (CH_3), 28.9 (3 CH_3), 19.1 (6 CH_3), 12.6 (3 CH); HRMS (ESI/Q-TOF) m/z $[M + Na]^+$ calcd for $C_{16}H_{34}N_2OSiNa$ 321.2333, found 321.2322.

*1-(2-(tert-Butyl)hydrazono)-4-hydroxy-4-phenyl-1-(triisopropylsilyl)butan-2-one (**11**):* IR (neat) ν_{max} (cm^{-1}) 3449, 2943, 2864, 1643, 1582, 1463, 1389, 1364, 1182, 1118, 1057, 1017, 917, 881. Major diastereoisomer (*E*)-**11**: R_f = 0.50 (petroleum ether/ethyl acetate = 90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 13.61 (bs, 1H), 7.42−7.35 (m, 5H), 5.16 (dd, 1H, J = 9.5, 2.6 Hz), 4.27 (bs, 1H), 2.88 (dd, 1H, J = 16.7, 2.6 Hz), 2.78 (dd, 1H, J = 16.7, 9.5 Hz), 1.33 (s, 9H), 1.31−1.25 (m, 3H), 1.06 (d, 18H, J = 7.4 Hz); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$) δ (ppm) 199.0 (C), 143.5 (C), 130.9 (C), 128.7 (2 CH), 127.6 (CH), 125.8 (2 CH), 71.1 (CH), 56.4 (C), 48.6 (CH_2), 28.9 (3 CH_3), 19.1 (6 CH_3), 12.6 (3 CH). Minor diastereoisomer (*Z*)-**11**: R_f = 0.44 (petroleum ether/ethyl acetate = 90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.33−7.22 (m, 5H), 7.20 (bs, 1H), 5.11 (dd, 1H, J = 9.6, 2.8 Hz), 4.15 (bs, 1H), 3.33 (dd, 1H, J = 16.6, 2.8 Hz), 3.08 (dd, 1H, J = 16.6, 9.6 Hz), 1.43 (sep, 3H, J = 7.5 Hz), 1.26 (s, 9H), 1.07 (d, 9H, J = 7.5 Hz), 1.07 (d, 9H, J = 7.5 Hz); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$) δ (ppm) 205.1 (C), 144.2 (C), 130.9 (C), 128.4 (2 CH), 127.2 (CH), 126.0 (2 CH), 71.3 (CH), 55.8 (C), 45.8 (CH_2), 28.9 (3 CH_3), 19.1 (6 CH_3), 12.9 (3 CH); HRMS (ESI/Q-TOF) m/z $[M + Na]^+$ calcd for $C_{23}H_{40}N_2O_2SiNa$ 427.2751, found 427.2751.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02725.

^{1}H and ^{13}C NMR spectra for all new products; single-crystal X-ray diffraction data for structures **3a**, **3b**, **3e**, **4a**, and **10**; computational methods and data (PDF)

Accession Codes

CCDC 2008880−2008884 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. Modern Organic Synthesis with α-Diazocarbonyl Compounds. *Chem. Rev.* **2015**, *115*, 9981−10080. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998.

(2) (a) Ferreira, V. F. Synthesis of Heterocyclic Compounds by Carbenoid Transfer Reactions. *Curr. Org. Chem.* **2007**, *11*, 177−193. (b) Murphy, G. K.; Stewart, C.; West, F. G. Intramolecular generation

and rearrangement of oxonium ylides: methodology studies and their application in synthesis. *Tetrahedron* **2013**, *69*, 2667−2686. (c) Gillingham, D.; Fei, N. Catalytic X-H insertion reactions based on carbenoids. *Chem. Soc. Rev.* **2013**, *42*, 4918−4931. (d) Burtoloso, A. C. B.; Dias, R. M. P.; Bernardim, B. α,β-Unsaturated Diazoketones as Useful Platforms in the Synthesis of Nitrogen Heterocycles. *Acc. Chem. Res.* **2015**, *48*, 921−934. (e) Ciszewski, L. W.; Rybicka-Jasińska, K.; Gryko, D. Recent developments in photochemical reactions of diazo compounds. *Org. Biomol. Chem.* **2019**, *17*, 432−448.

(3) Zhang, Y.; Wang, J. Recent development of reactions with α-diazocarbonyl compounds as nucleophiles. *Chem. Commun.* **2009**, 5350−5361.

(4) (a) Calter, M. A.; Sugathapala, P. M.; Zhu, C. Aldol-Cyclization Reaction Sequence for the Synthesis of Tetrahydrofurans. *Tetrahedron Lett.* **1997**, *38*, 3837−3840. (b) Dong, C.; Mo, F.; Wang, J. Highly Diastereoselective Addition of the Lithium Enolate of α-Diazoacetoacetate to *N*-Sulfinyl Imines: Enantioselective Synthesis of 2-Oxo and 3-Oxo Pyrrolidines. *J. Org. Chem.* **2008**, *73*, 1971−1974. (c) Calter, M. A.; Zhu, C. De Novo Syntheses of Racemic Deoxy-C-nucleosides. *J. Org. Chem.* **1999**, *64*, 1415−1419. (d) Bel Abed, H.; Mammoliti, O.; Bande, O.; Van Lommen, G.; Herdewijn, P. Strategy for the Synthesis of Pyridazine Heterocycles and Their Derivatives. *J. Org. Chem.* **2013**, *78*, 7845−7858. (e) Deng, G.; Jiang, N.; Ma, Z.; Wang, J. $Rh_2(OAc)_4$-Mediated Diazo Decomposition of δ-(*N*-Tosyl)amino-β-keto-α-diazo Carbonyl Compounds: A Novel Approach to Pyrrole Derivatives. *Synlett* **2002**, *2002*, 1913−1915. (f) Dong, C.; Deng, G.; Wang, J. New Approaches to Polysubstituted Pyrroles and γ-Lactams Based on Nucleophilic Addition of Ti(IV) Enolates Derived from α-Diazo-β-keto Carbonyl Compounds to *N*-Tosylimines. *J. Org. Chem.* **2006**, *71*, 5560−5564. (g) Doyle, M. P.; Kundu, K.; Russell, A. E. Catalytic Addition Methods for the Synthesis of Functionalized Diazoacetoacetates and Application to the Construction of Highly Substituted Cyclobutanones. *Org. Lett.* **2005**, *7*, 5171−5174. (h) Kundu, K.; Doyle, M. P. Constructing chiral diazoacetoacetates by enantioselective catalytic Mukaiyama aldol reactions. *Tetrahedron: Asymmetry* **2006**, *17*, 574−577.

(5) Lancou, A.; Haroun, H.; Kundu, U. K.; Legros, F.; Zimmermann, N.; Mathé-Allainmat, M.; Lebreton, J.; Dujardin, G.; Gaulon-Nourry, C.; Gosselin, P. α-Triethylsilyl-α-diazoacetone in double cross-aldolisation: convenient acetone equivalent toward 5-hydroxy-1,3-diketones. *Tetrahedron* **2012**, *68*, 9652−9657.

(6) Chany, A.-C.; Legros, F.; Haroun, H.; Kundu, U. K.; Biletskyi, B.; Torlak, S.; Mathe-Allainmat, M.; Lebreton, J.; Mace, A.; Carboni, B.; Renoux, B.; Gosselin, P.; Dujardin, G.; Gaulon-Nourry, C. Function-Oriented Synthesis toward Peloruside A Analogues. *Org. Lett.* **2019**, *21*, 2988−2992.

(7) (a) Brückmann, R.; Schneider, K.; Maas, G. Wolff Rearrangement of (l-Diazo-2-oxoalkyl) silanes. *Tetrahedron* **1989**, *45*, 5517−5530. (b) Loebach, J. L.; Bennett, D. M.; Danheiser, R. L. (Trialkylsilyl)vinylketenes: Synthesis and Application as Diene Components in Diels-Alder Cycloadditions. *J. Org. Chem.* **1998**, *63*, 8380−8389. (c) Marsden, S. P.; Pang, W.-K. Efficient, general synthesis of silylketenes *via* an unusual rhodium mediated Wolff rearrangement. *Chem. Commun.* **1999**, 1199−1200. (d) Marsden, S. P.; Ducept, P. C. Synthesis of highly substituted allenylsilanes by alkylidenation of silylketenes. *Beilstein J. Org. Chem.* **2005**, *1*, 1−6. (e) Bucher, S. M.; Brückmann, R.; Maas, G. Aryl Trialkylsilyl Ketenes: Acid-Catalyzed Synthesis from 1-Aryl-2-diazo-2-trialkylsilylethanones and Their Conversion into 3-Silyl-1-silyloxyallenes. *Eur. J. Org. Chem.* **2008**, 4426−4433. (f) Marsden, S. P.; Steer, J. T.; Orlek, B. S. Synthesis of α-silylalkylbenzoxazoles and oxazoles from stable silylketenes. *Tetrahedron* **2009**, *65*, 5503−5512.

(8) (a) Munschauer, B. R.; Maas, G. 1,3-(C→O) Silyl Shift in α-Diazo α-Silyl Ketones: Cycloaddition Reactions and Kinetic Proof for the β-Siloxydiazoalkene Intermediate. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 306−308. (b) Kerth, J.; Jikyo, T.; Maas, G. Cycloaddition Behavior of 1,2-Thiaphospholes: Reactions with Diazocumulenes and with Cyclopentadiene. *Eur. J. Org. Chem.* **2003**, 1894−1903. (c) Jikyo, T.; Schatz, J.; Maas, G. Reactivity of heterophospholes toward 1,3-dipolar cycloaddition of diazo compounds-an FMO analysis. *J. Phys. Org. Chem.* **2003**, *16*, 504−512.

(9) Brückmann, R.; Maas, G. Thermal Decomposition of α-Diazo-α-(trialkylsilyl)alkanones - Intramolecular C/H Insertion of Siloxyalkylidenecarbene Intermediates. *Chem. Ber.* **1987**, *120*, 635−641.

(10) Maas, G.; Brueckmann, R. Preparation of l-Aryl-2-siloxyalkynes from Silylated α-Diazo Carbonyl Compounds. *J. Org. Chem.* **1985**, *50*, 2801−2802.

(11) (a) Abid, I.; Gosselin, P.; Mathé-Allainmat, M.; Abid, S.; Dujardin, G.; Gaulon-Nourry, C. TBAF-Triggered Aldol-Type Addition of α-Triethylsilyl-α-diazoacetone. *J. Org. Chem.* **2015**, *80*, 9980−9988. (b) Abid, I.; Gavelle, S.; Chany, A.-C.; Legros, F.; Gosselin, P.; Abid, S.; Dujardin, G.; Gaulon-Nourry, C. Advances in the TBAF-induced aldol-type addition of α-trialkylsilyl-α-diazoacetones: TIPS versus TES. *C. R. Chim.* **2017**, *20*, 595−600. (c) Kanemasa, S.; Araki, T.; Kanai, T.; Wada, E. Fluoride-Catalyzed Aldol Reaction of Ethyl Trimethylsilyidiazoacetate with Aldehydes Leading to Ethyl α-Diazo-β-Hydroxy Esters and Rhodium Catalyzed Decarboxylative Rearrangement of Diazo Urethanes Leading to β-Amino Acrylates. *Tetrahedron Lett.* **1999**, *40*, 5059−5062.

(12) Regitz, M. Eine neue Synthese für α-Diazo-β-dicarbonyl-verbindungen aus Benzolsulfonylaziden und β-Diketonen. *Justus Liebigs Ann. Chem.* **1964**, *676*, 101−109.

(13) Sharpe, R. J.; Malinowski, J. T.; Johnson, J. F. Asymmetric Synthesis of the Aminocyclitol Pactamycin, a Universal Translocation Inhibitor. *J. Am. Chem. Soc.* **2013**, *135*, 17990−17998.

(14) Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. Diazotransfer Reactions with *p*-Acetamidobenzenesulfonyl Azide. *Synth. Commun.* **1987**, *17*, 1709−1716.

(15) TIPS-diazoacetone **1** should be carefully purified by column chromatography as contamination with silylated residues would (1) induce its desilylation upon storage and (2) decrease the efficiency of the following base-induced aldol addition.

(16) (a) Taber, D. F.; Herr, R. J.; Gleave, D. M. Diastereoselective Synthesis of an Isoprostane: (±)-8-*epi*-$PGF_{2\alpha}$ Ethyl Ester. *J. Org. Chem.* **1997**, *62*, 194−198. (b) Taber, D. F.; Kanai, K. Synthesis of the four enantiomerically-pure isomers of 15-F_{2t}-isoprostane. *Tetrahedron* **1998**, *54*, 11767−11782. (c) Taber, D. F.; Jiang, Q. Total Synthesis of the Four Enantiomerically Pure Diastereomers of 8-F_{2t}-Isoprostane. *J. Org. Chem.* **2001**, *66*, 1876−1884.

(17) (a) Polt, R.; Seebach, D. Stereoselective Alkylation of Glycine Units in Dipeptide Derivatives: "Chirality Transfer" via a Pivalaldehyde *N*,*N*-Acetal Center. *J. Am. Chem. Soc.* **1989**, *111*, 2622−2632. (b) Henderson, K. W.; Dorigo, A. E.; Liu, Q.-Y.; Williard, P. G.; Schleyer, P. v. R.; Bernstein, P. R. Structural Consequences of the Addition of Lithium Halides in Enolization and Aldol Reactions. *J. Am. Chem. Soc.* **1996**, *118*, 1339−1347.

(18) (a) Collum, D. B.; McNeil, A. J.; Ramirez, A. Lithium Diisopropylamide: Solution Kinetics and Implications for Organic Synthesis. *Angew. Chem., Int. Ed.* **2007**, *46*, 3002−3017. (b) Ma, Y.; Collum, D. B. Lithium Diisopropylamide-Mediated Reactions of Imines, Unsaturated Esters, Epoxides, and Aryl Carbamates: Influence of Hexamethylphosphoramide and Ethereal Cosolvents on Reaction Mechanisms. *J. Am. Chem. Soc.* **2007**, *129*, 14818−14825.

(19) When the temperature was not efficiently controlled, a minor amount of bis-aldol **4a** was formed (Figure 1), leading to a sensitive decrease of the yield.

(20) Pure diazoaldol **3a** proved stable when stored in the freezer.

(21) See Experimental Section for details.

(22) The CIF file is provided in the Supporting Information for each X-ray crystallographic structure determination.

(23) Mulvey, R. E.; Robertson, S. D. Synthetically Important Alkali-Metal Utility Amides: Lithium, Sodium, and Potassium Hexamethyldisilazides, Diisopropylamides, and Tetramethylpiperidides. *Angew. Chem., Int. Ed.* **2013**, *52*, 11470−11487.

(24) (a) Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. Deconjugative alkylation of the enolate anion derived from ethyl crotonate. *Tetrahedron Lett.* **1973**, *14*, 2433−2436. (b) Ma, Y.;

https://doi.org/10.1021/acs.joc.0c02725
J. Org. Chem. 2021, 86, 4917−4931

Hoepker, A. C.; Gupta, L.; Faggin, M. F.; Collum, D. B. 1,4-Addition of Lithium Diisopropylamide to Unsaturated Esters: Role of Rate-Limiting Deaggregation, Autocatalysis, Lithium Chloride Catalysis, and Other Mixed Aggregation Effects. *J. Am. Chem. Soc.* **2010**, *132*, 15610−15623.
(25) (a) Bel Abed, H.; Mammoliti, O.; Van Lommen, G.; Herdewijn, P. A short and convenient strategy for the synthesis of pyridazines via Diaza-Wittig reaction. *Tetrahedron Lett.* **2012**, *53*, 6489−6491. (b) Bel Abed, H.; Mammoliti, O.; Bande, O.; Van Lommen, G.; Herdewijn, P. Strategy for the Synthesis of Pyridazine Heterocycles and Their Derivatives. *J. Org. Chem.* **2013**, *78*, 7845−7858.
(26) Glidewell, C.; Lloyd, D.; Lumbard, K. W. Formation of Germanium-Nitrogen Double Bonds in Reactions of the Electronrich Germylene Bis[bis(trimethylsilyl)amido]germanium(II) with a Range of Diazo-compounds. *J. Chem. Soc., Dalton Trans.* **1987**, 501−508.
(27) (a) Sachse, A.; Penkova, L.; Noël, G.; Dechert, S.; Varzatskii, O. A.; Fritsky, I. O.; Meyer, F. Efficient Syntheses of Some Versatile 3,5-Bifunctional Pyrazole Building Blocks. *Synthesis* **2008**, *5*, 800−806. (b) Outirite, M.; Bentiss, F.; Buisine, E.; Capet, F.; Lagrenée, M. Synthesis and Crystal Structure of 3,5-Diacetyl-4-methylpyrazole. *J. Heterocyclic Chem.* **2010**, *47*, 1025−1030.
(28) Regitz, M. New Methods of Preparative Organic Chemistry. Transfer of Diazo Groups. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 733−749.
(29) Whereas LDA used in this study was from the commercial source, tending to be LiCl-free, LTMP was formed from tetramethylpiperidine and commercial BuLi, containing various amounts of LiCl. The presence of such salt could influence the aggregation state and thus the course of the reaction.
(30) Et_2O solvent was preferred over THF as *t*-BuLi was shown to deprotonate THF in those conditions.
(31) For additional informations, see the Supporting Information.
(32) Morales, S.; Guijarro, F. G.; García Ruano, J. L.; Cid, M. B. A General Aminocatalytic Method for the Synthesis of Aldimines. *J. Am. Chem. Soc.* **2014**, *136*, 1082−1089.
(33) (a) Deadman, B. J.; O'Mahony, R. M.; Lynch, D.; Crowley, D. C.; Collins, S. G.; Maguire, A. R. Taming tosyl azide: the development of a scalable continuous diazo transfer process. *Org. Biomol. Chem.* **2016**, *14*, 3423−3431. (b) Archibald, T. Managing Hazardous Reactions and Compounds in Process Chemistry, *ACS Symposium Series*; Vol. *1181*; Chapter 3, pp 87−109.
(34) Vedejs, E.; Engler, D. A.; Telschow, J. E. Transition-Metal Peroxide Reactions. Synthesis of α-Hydroxycarbonyl Compounds from Enolates. *J. Org. Chem.* **1978**, *43*, 188−196.
(35) Love, B. E.; Jones, E. G. The Use of Salicylaldehyde Phenylhydrazone as an Indicator for the Titration of Organometallic Reagents. *J. Org. Chem.* **1999**, *64*, 3755−3756.
(36) Burchat, A. F.; Chong, J. M.; Nielsen, N. Titration of alkyllithiums with a simple reagent to a blue endpoint. *J. Organomet. Chem.* **1997**, *542*, 281−283.
(37) Duhamel, L.; Plaquevent, J.-C. 4-Phenylbenzylidene benzylamine: a new and convenient reagent for the titration of solutions of lithium alkyls and metal amides. *J. Organomet. Chem.* **1993**, *448*, 1−3.

https://doi.org/10.1021/acs.joc.0c02725
J. Org. Chem. 2021, 86, 4917−4931