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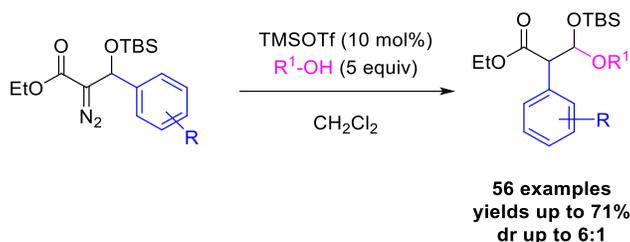
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Acid-catalyzed decomposition of *O*-silylated α -diazo- β -hydroxy esters: access to mixed monosilyl acetals

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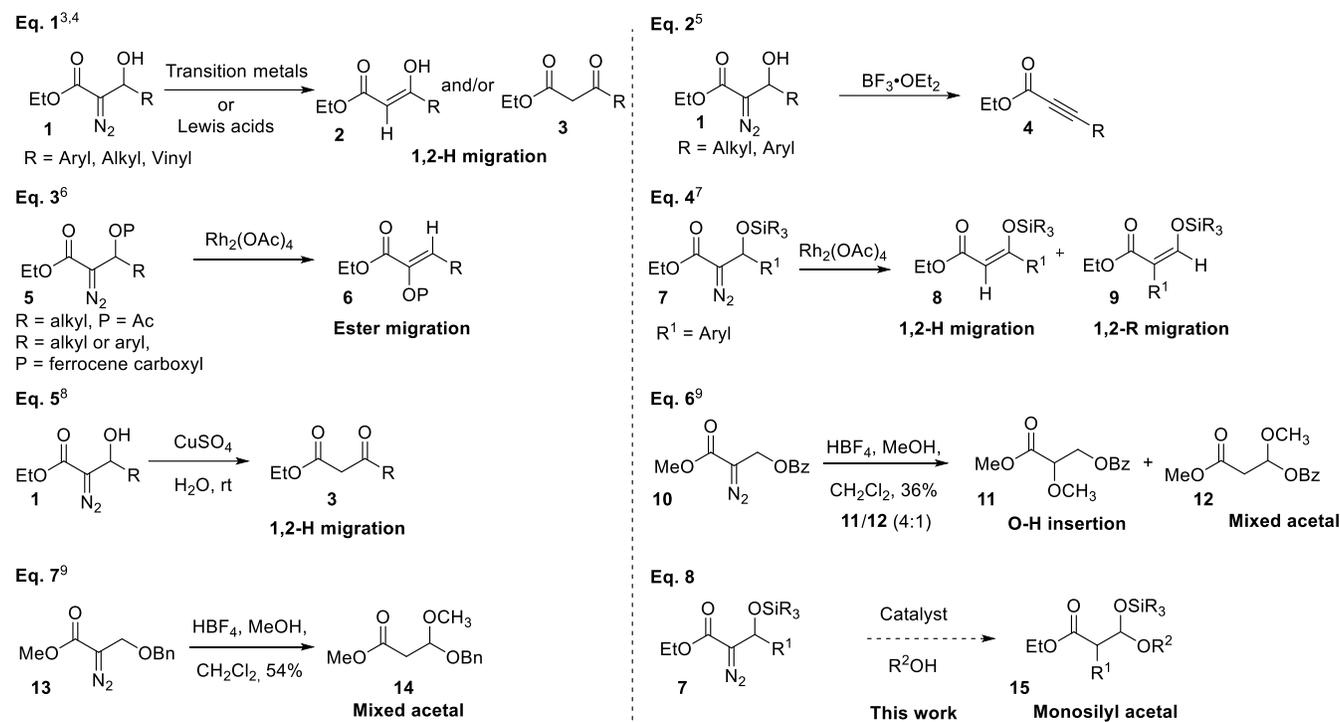
ABSTRACT: Acid-catalyzed decomposition of diazocarbonyl compounds triggers a wide range of transformations leading to synthetically useful building blocks with high diversity. In this field, the chemistry of α -diazo- β -hydroxyester substrates is largely dominated by migration processes. We describe herein a new approach to original mixed monosilyl acetals from *O*-protected α -diazo- β -hydroxy- β -aryl esters and alcohols, catalyzed by TMSOTf. The ratio between these original mixed acetals, the symmetric acetals and the migration products fluctuates, depending on the catalyst, the nature of the alcohols and the substituent on the aromatic ring. Fifty-six examples are reported herein with yields up to 71% and diastereoselectivity up to 6:1. Such mixed monosilyl acetals constitute a synthetic equivalent of α -substituted β -oxoesters with high potential for further transformations.

INTRODUCTION

Diazocarbonyl compounds have been used for decades in a wide range of transformations (including C-H insertion, X-H insertion, migration, cyclopropanation) in order to generate functional diversity.¹ In this field, while the synthesis of α -diazo- β -hydroxy esters is well described in the literature,² few studies have been conducted on the transformation of the diazo moiety, despite the synthetic potential of these compounds. Diazo decomposition induced by transition metals (Rh, Cu, Pd...), in the absence of a nucleophile (RX-H), has been performed on α -diazo- β -hydroxy esters **1** bearing β -aryl, β -alkyl or β -vinyl groups. A fast 1,2-H migration occurred, affording enol **2** or the corresponding β -ketoester **3** in good yields (**Scheme 1, Eq. 1**).³ Besides, Lewis acids have been reported to mediate the 1,2-H migration,⁴ except for $\text{BF}_3 \cdot \text{OEt}_2$ which led predominantly to alkyne **4** (**Scheme 1, Eq. 2**).⁵ Studies of diazo decomposition have also been conducted on *O*-protected substrates and the influence of the protecting group on the migration was evaluated. When an acetoxy or a ferrocenecarboxyl group was used as a protection, $\text{Rh}_2(\text{OAc})_4$ -catalyzed diazo decomposition of **5** led to the migration of the ester moiety (**Scheme 1, Eq. 3**).⁶ Additionally, the effect of a silyl protecting group on a β -aryl substituted substrate has been briefly examined by Wang (**Scheme 1, Eq. 4**).⁷ This study, which was restricted to the use of Rh(II) catalysts, showed that the silyl ether favored the 1,2-Ar over the 1,2-H migration in most cases. This migration selectivity may result from steric effects overriding electronic effects of the silyloxy substituent.

On the other hand, the diazo decomposition of α -diazo- β -hydroxyesters in the presence of a R-XH nucleophile has been hardly explored. The transition metal-promoted decomposition of α -diazo- β -hydroxy ester **1** in the presence of water has been studied by Wang (**Scheme 1, Eq. 5**), affording efficiently 1,2-H migration product when the reaction was catalyzed by CuSO_4 without any trace of O-H insertion product.⁸ Exposure of the benzoate-protected diazo substrate **10** to methanol containing HBF_4 led to a 4:1 mixture of the insertion product **11** and mixed acetal (OCH₃, OBz) **12** in 36% global yield (**Scheme 1, Eq. 6**). When the benzoate protecting group was replaced by a benzyl group on this specific primary alcohol, the mixed acetal (OCH₃, OBn) **14** was the sole product formed in 54% yield (**Scheme 1, Eq. 7**).⁹

Scheme 1. Diazo decomposition of α -diazo- β -hydroxyesters



To the best of our knowledge, the diazo decomposition of *O*-silylated α -diazo- β -hydroxy esters **7** in the presence of an alcohol under transition metal or Lewis acid catalysis has not been reported so far.

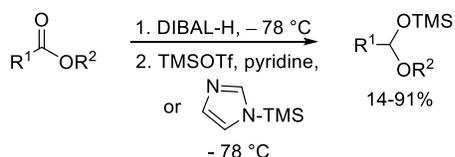
Inspired by the reports described above, we conceived that monosilyl acetals **15** may be synthesized through the diazo decomposition of substrates **7** in the presence of an alcohol (**Scheme 1, Eq. 8**). The synthetic potential of this stable and original silylated function moiety lies in its easy transformation into the versatile aldehyde function,^{10,11} and its use in Mukaiyama aldol^{12,13,14} and Hosomi-Sakurai reactions.^{15,16} Besides α -iodo mixed TBS-acetals proved efficient intermediates to access allyl vinyl ethers stereoselectively.¹⁷ Despite its synthetic potential, few methods have been reported so far for the synthesis of this building block and to date, monosilyl acetals have been primarily prepared from esters or aldehydes.

TMS-monosilyl acetals have been synthesized by DIBAL-H reduction of an ester followed by trapping of the intermediate with either TMSOTf/pyridine¹⁸ or TMS-imidazole (**Scheme 2, Eq. 1**).¹⁵ However, this method is not suited to access ester-containing mixed silyl acetals. An alternative method was later developed from aldehydes using NaOtBu and TMSN_3 or TBSCN (**Scheme 2, Eq. 2**),¹⁴ but in this case the alkoxy group of monosilyl acetal was restricted to *tert*-butoxy. Access to other trialkylsilyl monosilyl acetals was made possible by the development of

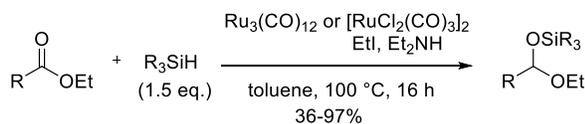
the hydrosilylation of esters, catalyzed by a ruthenium-,¹⁰ a manganese- or a rhenium-based complex,¹¹ using various trialkylsilanes (Et_3SiH , $t\text{-BuMe}_2\text{SiH}$, PhMe_2SiH) (**Scheme 2, Eq. 3 and 4**). Although efficient, this method does not tolerate any other ester function on the substrate and uses expensive catalysts. In addition, α -iodo mixed TBS-acetals could be generated by the action of NIS on the corresponding silyl enol ether in the presence of an alcohol^{16,17,19} (**Scheme 2, eq. 5**) or by oxidative cleavage of vicinal monoprotected diols under photochemical conditions (**Scheme 2, Eq. 6**).²⁰

Scheme 2. Monosilylated mixed acetal synthesis

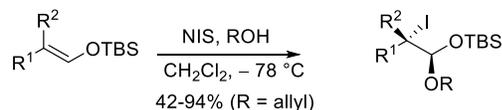
Eq. 1^{15,18}



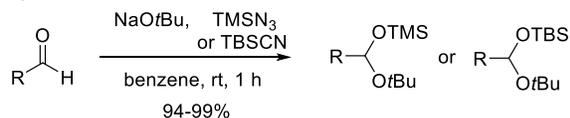
Eq. 3¹⁰



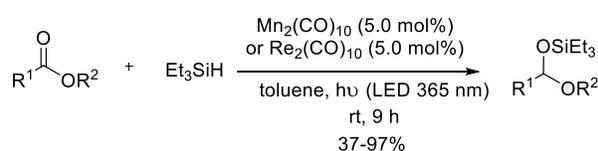
Eq. 5^{16,17,19}



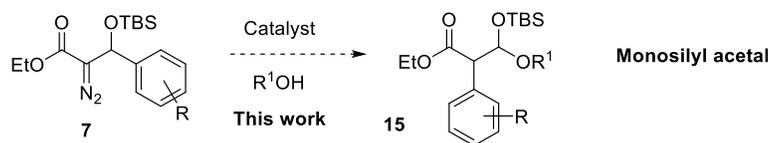
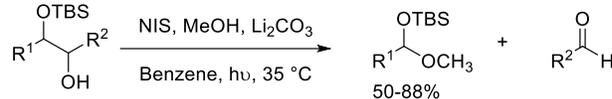
Eq. 2¹⁴



Eq. 4¹¹



Eq. 6²⁰



Considering the synthetic potential of the mixed silyl acetal function moiety but also the limitations highlighted in the previous methods, a new approach allowing to achieve a wider functional diversity would be of high value, particularly in order to reach ester-containing mixed monosilyl acetals. To this aim, we wish to report here the TMSOTf-catalyzed formation of functionalized original stable monosilyl acetals **15** from OTBS-protected α -diazo- β -hydroxy esters and alcohols.

RESULTS

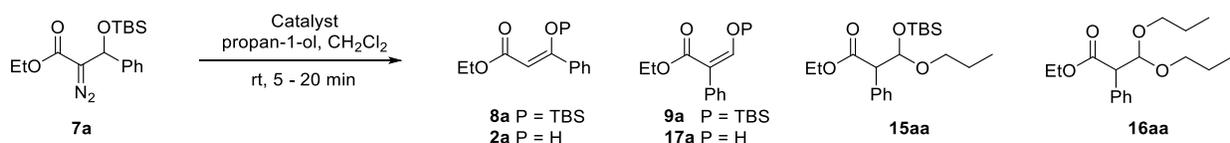
The initial investigations were performed on *O*-TBS protected α -diazo- β -hydroxy- β -phenyl-ester **7a** and propan-1-ol as the external nucleophile (**Table 1**). The *tert*-butyldimethylsilyl protecting group was selected for this study as a good compromise between stability and steric hindrance. Compound **7a** was prepared by nucleophilic addition of ethyl lithiodiazoacetate on benzaldehyde, followed by a silyl ether protection of the corresponding hydroxyl group under the classical TBSCl/Imidazole/DMAP conditions (See Supporting Information, Scheme S2).^{2,5b,21,22} The first experiments were conducted at room temperature in dichloromethane with propan-1-ol as co-solvent and the influence of various catalytic systems was explored.

The use of $\text{Rh}_2(\text{OAc})_4$ and $\text{Rh}_2(\text{oct})_4$ gave exclusively the 1,2-H and 1,2-Ar migration products **8a** and **9a**, which is in line with the results obtained by Wang in the absence of alcohol (**Table 1, entries 1 and 2**).⁷ With this transition metal, the preference for the 1,2-Ar migration might result from the bulkiness of the TBS protecting group. Several

silver (I) salts were then evaluated (AgClO_4 , AgBF_4 and AgOTf , **Table 1, entries 3 to 5**). Only 1,2-H/Ar migration products were observed and, contrary to rhodium (II) catalysts, a high selectivity for the 1,2-H migration occurred. Assays were then carried out with copper (I) and copper (II) salts.

With copper (I) salts, the 1,2-H migration product **8a** was also formed as the main product (**Table 1, entries 6 and 7**). In contrast, while no conversion was observed with the copper (II) salts $\text{Cu}(\text{OAc})_2$ and $\text{Cu}(\text{acac})_2$, copper (II) triflate led to the formation of the expected mixed monosilyl acetal **15aa** (36% yield, dr = 1.5:1) and acetal **16aa** (20% yield) in addition to deprotected 1,2-H and 1,2-Ar migration compounds **2a** and **17a** (**Table 1, entry 8**). Considering the encouraging results obtained with copper (II) triflate, behaving as both a carbene generator and a Lewis acid, we decided to test other Lewis acids like $\text{Yb}(\text{OTf})_3$, $\text{In}(\text{OTf})_3$, $\text{Sc}(\text{OTf})_3$, SnCl_4 and TMSOTf (**Table 1, entries 9-13**). All the investigated Lewis acids gave mixed acetal **15aa** as the major compound, along with minor amounts of acetal **16aa** and deprotected migration products **2a**.²³ It is worth noting that the O-H insertion product has never been detected in the crude. Best yields of **15aa**, around 50%, were obtained with $\text{Sc}(\text{OTf})_3$ and TMSOTf (**entries 11 and 13**). However at this point, TMSOTf , far less expensive than $\text{Sc}(\text{OTf})_3$, was the preferred candidate for this study. In the presence of alcohol, TMSOTf is undoubtedly generating TfOH *in situ*. Therefore, the latter was evaluated, as well as HBF_4 . However, although their use also provided acetal **15aa** in similar ratios, additional unidentified side products were observed. We therefore decided to generate *in situ* a clean source of TfOH and TMSOTf was selected to push forward this study.

Table 1. Screening of catalysts for the reaction of diazo derivative 7a with propan-1-ol

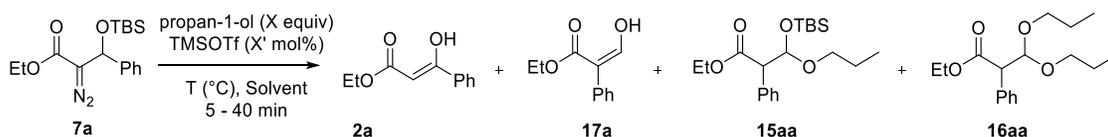


entry	Cat. (mol %)	Time (min)	Compound Ratio ^a				Yield (%) ^d		
			8a or 2a ^b	9a or 17a ^c	15aa	16aa	Migration ^e	15aa	16aa
1	$\text{Rh}_2(\text{OAc})_4$ (1)	20	0.2	1	0	0	90 ^f	0	0
2	$\text{Rh}_2(\text{Oct})_4$ (1)	15	0.1	1	0	0	95 ^f	0	0
3	AgClO_4 (10)	5	1	0.15	0	0	72 ^f	0	0
4	AgBF_4 (10)	5	1	0.1	0	0	72 ^f	0	0
5	AgOTf (10)	5	1	0.1	0	0	94 ^f	0	0
6	$\text{Cu}(\text{MeCN})_4\text{BF}_4$ (10)	5	1	0.2	0	0	98 ^f	0	0
7	$\text{Cu}(\text{MeCN})_4\text{PF}_6$ (10)	5	1	0.2	0	0	96 ^f	0	0
8	$\text{Cu}(\text{OTf})_2$ (10)	60	0.5	0.05	1	0.4	31	36 ^g	20
9	$\text{Yb}(\text{OTf})_3$ (5)	120	0.3	-	1	0.55	12	46 ^g	18
10	$\text{In}(\text{OTf})_3$ (5)	60	0.4	-	1	0.5	23	46 ^g	26
11	$\text{Sc}(\text{OTf})_3$ (5)	120	0.3	-	1	0.4	17	49	19
12	SnCl_4 (10)	240	0.35	-	1	0.6	4	40 ^g	7
13	TMSOTf (10)	40	0.35	0.05	1	0.4	17	50	16

^a Ratio determined by ¹H NMR analysis of the crude product. ^b **8a** for entries 1 to 7 and **2a** for entries 8 to 13. ^c **9a** for entries 1 to 7 and **17a** for entries 8 to 13. ^d Unless otherwise stated, yields were estimated by ¹H NMR spectroscopy, after silica gel chromatography, from fractions containing a mixture of migration products, monosilyl acetal **15aa** and acetal **16aa**.^e The yield refers to the total amount of migration products isolated: (**8a+9a**) when the reaction was conducted with rhodium catalysts, silver salts or copper (I) catalysts; (**2a+17a**) in the other cases. ^f Conversion estimated from the ¹H NMR spectrum of the crude product. ^g Isolated yield.

The influence of the amount of propan-1-ol, the catalyst loading and the nature of the solvent on the product distribution was then evaluated. In the previous experiments, propan-1-ol was used as a co-solvent. Decreasing gradually the amount of propan-1-ol from 65 equiv to 1.1 equiv proved detrimental to the formation of the mixed monosilyl acetal **15aa**, while the proportions of migration products (**2a+17a**) and acetal **16aa** increased (**entries 1-3**). Nevertheless, using 5 equiv of propan-1-ol appeared to be a good compromise with the prospect of extending the methodology to various alcohols (**entry 2**) and the optimization went on with this amount of alcohol.

Table 2. Optimization of the reaction conditions for the formation of the mixed monosilyl acetal 15aa



Entry ^a	propan-1-ol (equiv)	cat. (mol%)	T °C	Solvent	Yield (%) ^b		
					2a+17a	15aa	16aa
1	65	10	rt	CH ₂ Cl ₂	17	50	16
2	5	10	rt	CH ₂ Cl ₂	17	38 ^c	27
3	1.1	10	rt	CH ₂ Cl ₂	33	-	50
4	5	5	rt	CH ₂ Cl ₂	15	39 ^c	28
5	5	1	rt	CH ₂ Cl ₂	16	40 ^c	25
6	5	10	rt	Cl(CH ₂) ₂ Cl	19	36 ^c	31
7	5	10	rt	Toluene	15	32 ^c	38
8	5	10	rt	THF	31	12	43
9	5	10	rt	Et ₂ O	26	17	50
10	5	10	rt	CH ₃ CN	10	0	68
11	5	10	0	CH ₂ Cl ₂	16	41	30
12	5	10	-10	CH ₂ Cl ₂	15	48	18
13	5	10	-20	CH ₂ Cl ₂	16	55 ^{c,d}	14

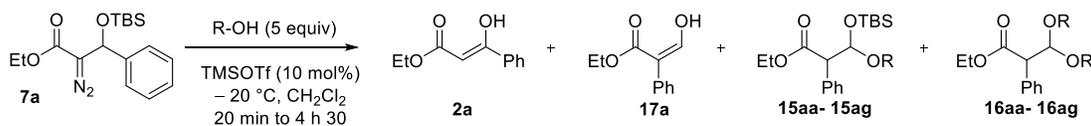
^a The reaction was performed by adding a solution of TMSOTf (0.1 M in CH₂Cl₂) dropwise to a solution of **7a** and propan-1-ol in CH₂Cl₂. ^b Unless otherwise stated, yields were estimated by ¹H NMR spectroscopy, after silica gel chromatography, from fractions containing a mixture of migration product (**2a** and **17a**), monosilyl acetal **15aa** and acetal **16aa**. ^c Isolated yields. ^d dr **15aa** = 1.5:1.

The catalyst loading was then studied. There was a negligible effect on the yield when it was reduced from 10 mol% to 1 mol% (**Table 2, entries 2, 4 and 5**). In order to introduce a reproducible amount of TMSOTf, especially on experiments done on small scales, we pursued the study with 10 mol%. We next examined how the solvent affected the products distribution. Dichloroethane gave similar results to those obtained with dichloromethane (**Table 2, entry 6**) while in toluene the formation of acetal **16aa** was slightly favored (**Table 2, entry 7**). More polar solvents such as THF and Et₂O promoted the formation of **16aa** over the mixed acetal **15aa** (**Table 2, entries 8 and 9**) and the use of acetonitrile provided exclusively acetal **16aa**, with no trace of mixed monosilyl acetal **15aa** (**Table 2, entry 10**). The following assays were thus conducted in CH₂Cl₂. The influence of the catalyst's addition rate was next briefly examined but did not affect the outcome of the reaction. Then, the effect of the temperature on the reaction selectivity was studied.

Decreasing the reaction temperature led to a significant increase of the ratio **15aa/16aa** as the isolated yield of the mixed acetal **15aa** reached 55% at – 20 °C (**Table 2, entries 11-13**). However, decreasing further the temperature to – 78 °C resulted in no conversion. In the end, the optimized conditions to promote the formation of the mixed monosilyl acetal **15aa** were as follows: TMSOTf (10 mol%), CH₂Cl₂ (0.1 M), at – 20 °C for 1 h. Besides, a rapid survey of other silylated protecting groups revealed that the TBS group was the most appropriate.²⁴ When no protecting group was introduced, acetal **16aa** was obtained in 36% yield.

In order to assess the scope of the reaction, six primary and secondary alcohols were evaluated towards diazo substrate **7a** under the previously optimized reaction conditions (**Table 3**). Gratifyingly, the expected mixed monosilyl acetals **15aa** to **15ag** were obtained in homogeneous yields between 47 and 59%. Increasing the steric hindrance of the alcohol induced a better diastereoselectivity (from 1.4:1 dr with MeOH to 2.2:1 dr with propan-2-ol).

Table 3. Influence of the alcohol on the formation of mixed monosilyl acetal 15a



Entry ^a	Alcohol	Products	Yield		
			15^b (dr)	16^d	2a+17a^d
1	Propan-1-ol	aa	55 (1.5:1)	14	16
2	MeOH	ab	59 (1.4:1)	-	-
3	TMS(CH ₂) ₂ OH	ac	59 ^c (1.5:1)	13 ^c	9 ^c
4	Allylic alcohol	ad	53 (1.7:1)	12	9
5	BnOH	ae	47 (2:1)	28	12
6	Propan-2-ol	af	48 (2.2:1)	12	35
7	Cyclohexanol	ag	49 (2:1)	10	10

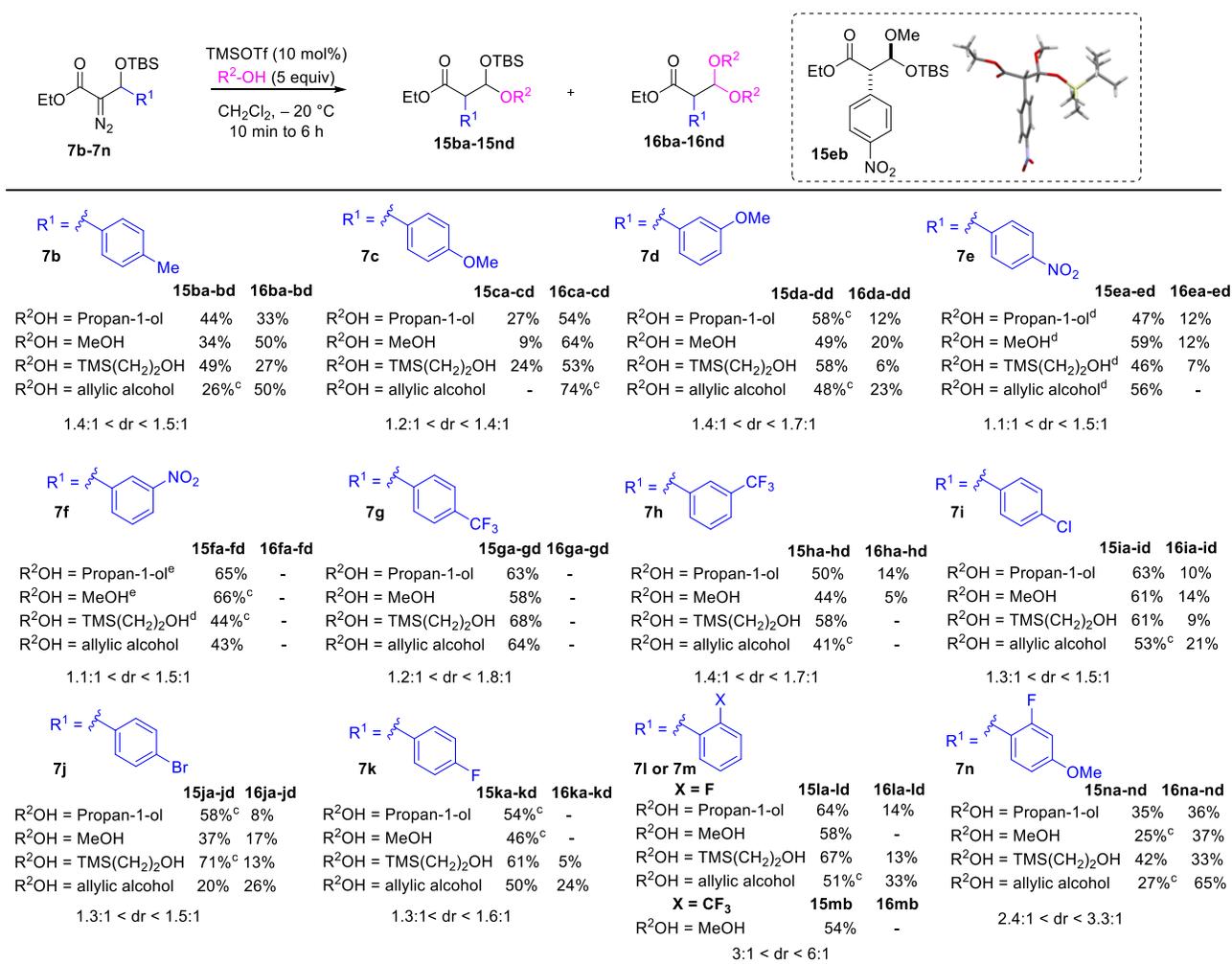
^a For conditions, see Supporting Information. ^b Isolated yields. ^c Yields estimated by ¹H NMR spectroscopy, after silica gel chromatography, from fractions containing a mixture of migration products (**2a+17a**), monosilyl acetal **15** and acetal **16**. ^d Yields estimated by ¹H NMR spectroscopy, after silica gel chromatography, from fractions containing a mixture of migration products (**2a+17a**) and acetal **16**.

The substrate scope of the reaction was next investigated, focusing on the influence of the aromatic ring substitution on the formation of the mixed monosilyl acetals. Several *O*-TBS protected α -diazo- β -hydroxy esters

were synthesized in two steps (See Supporting Information)^{5b,7a,21,22} and each one was subjected to four alcohols under the previously optimized reaction conditions. The results are summarized in **Scheme 3**.

Electron-donating substituents (Me, OMe) were first investigated. A strong impact of the substituent position on the products distribution was observed. When an electron-donating substituent was located at the *para* position (compounds **7b**, **7c** and **7n**), the formation of acetals **16** was clearly favored at the expense of mixed monosilyl acetals **15**. In contrast, a 3-methoxy-substituent was well tolerated, leading to mixed monosilyl acetals **15da-15dd** as the major products (48-58% yield). We then switched to electron-withdrawing substituents (NO₂, CF₃, halogens). The mixed monosilyl acetals were isolated in moderate to high yields (up to 71%), regardless of the substituent position on the aromatic ring. The most electron-withdrawing substituents (NO₂, CF₃, F) strongly disfavored the formation of the acetals **16** which were not detected in the crude reaction mixtures in many instances. The reaction performed on a 600 mg scale (1.6 mmol) on substrate **7e** with MeOH proceeded smoothly, delivering the pure mixed acetal **15eb** in 57% yield (350 mg), highlighting that the scale up of the process was feasible. The structure of the major diastereomer of **15eb** was confirmed by X-ray diffraction. Noteworthy, the presence of a substituent at the *ortho* position did not significantly alter the yields in mixed acetal **15** while it led to an increase of the diastereoselectivity (up to 6:1 dr for **15mb**).

Scheme 3. Substrate scope of the reaction^{a,b}



^a The reaction time for each experiment is specified in the supporting information. ^b Unless otherwise noted, yields were estimated by ¹H NMR spectroscopy, after silica gel chromatography, from fractions containing a mixture of migration product (**2** and **17**), monosilyl acetal **15** and acetal **16**. ^c Isolated yields. ^d Reaction conducted at rt. ^e Reaction carried out at 0 °C.

Mechanistic aspects

The products ratio (migration products **2,17**/monosilyl acetal **15**/acetal **16**) observed with the TMSOTf/alcohol system proved largely dependent on the experimental conditions and on the substrate substitution pattern. It is important to note that when monosilyl acetal **15** was subjected to the reaction conditions (catalytic TMSOTf/excess alcohol), no transacetalization into acetal **16** was observed.

In an effort to rationalize the results obtained in the case of TMSOTf, two competitive mechanisms have emerged (**Scheme 4**). Both of them involve *in situ* generated TfOH as the active catalyst, which could trigger one mechanism (**pathway 1, Scheme 4**) or another (**pathway 2, Scheme 4**) through initial competitive protonation on two distinct sites on substrate **7**.²⁵

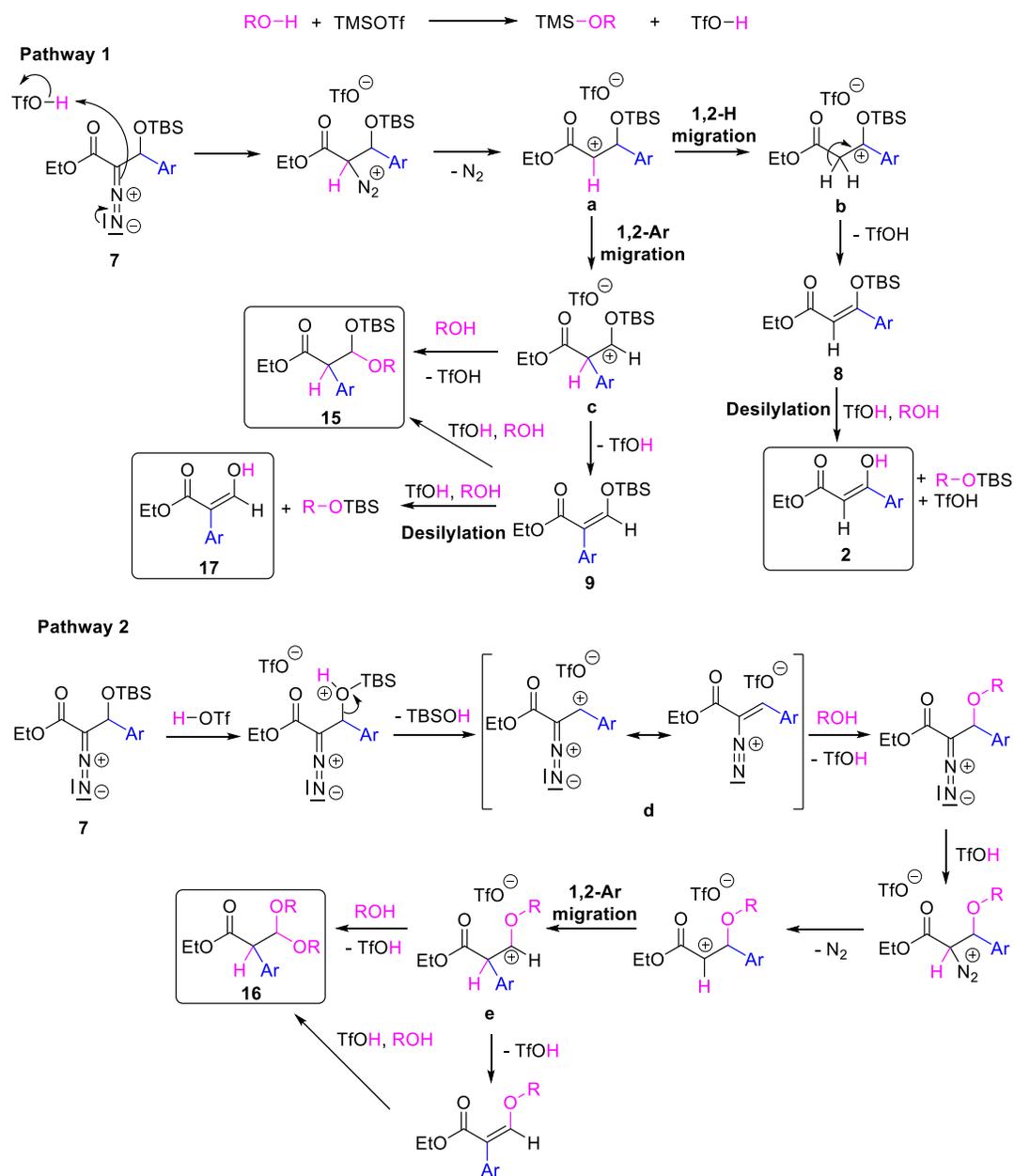
At first, we propose that the formation of monosilyl acetal **15** and the migration products **2** and **17** could result from the initial protonation of the nucleophilic diazotated carbon of *O*-protected α -diazo- β -hydroxy- β -aryl-ester **7** (**Scheme 4, pathway 1**), as already reported in such protic conditions.²⁶ Dediazotation would then trigger 1,2-H and 1,2-Ar migration processes, generating carbocations **b** and **c**. Proton loss on these intermediates would be followed by TfOH-induced desilylation of the resulting silyl ethers **8** and **9**, eventually providing the observed deprotected migration products **2** and **17**. Besides, mixed silyl acetal **15** would result either from the TfOH-catalyzed nucleophilic addition of the alcohol on the migration product **9** or from direct trapping of carbocation **c** by the alcohol.²⁷ Concerning the formation of acetal **16**, a second mechanism seems likely to be involved, initiated by the protonation of the TBS-ether oxygen (**Scheme 4, pathway 2**). Accordingly, elimination of TBS-OH would generate stabilized carbocation **d**, prone to undergo alcohol addition, in a similar way than the trapping of vinyldiazonium intermediates by various nucleophiles recently reported by Brewer's team.²⁸ The resulting β -alkoxy- α -diazoester could be easily protonated by TfOH on the diazotated carbon as in Pathway 1, and undergo 1,2-Ar migration triggered by dediazotation.²⁹ The resulting carbocation **e** could eventually lead to acetal **16** *via* proton loss followed by TfOH-catalyzed addition of the alcohol on the resulting conjugated system, or through direct trapping by the alcohol.

The above mechanistic hypotheses seem consistent with the evolution of the experimental results when the amount of alcohol is modulated. When excess alcohol is used, pathway 1 proceeds preferentially, leading to monosilyl acetal **15** as the major product (**Table 2, entry 1**). In accordance with Wang's results on substrate **7**,^{7a} 1,2-Ar migration is expected to prevail, favoring the formation of carbocation **c** over carbocation **b**. When a large excess of alcohol is used (65 equiv), rapid addition of the alcohol occurs either on intermediate **c** or on the resulting migration product **9** to yield monosilyl acetal **15**. This hypothesis is supported by the observation of only traces of the deprotected migration product **17** along with minor amounts of the deprotected migration product **2** (**Table 1, entry 13**). Concurrently, competitive pathway 2 proceeds as a minor extent, rationalizing the formation of minor acetal **16**. As the amount of alcohol is reduced (**Table 2, entries 2-3**), the ratio of monosilyl acetal **15** decreases in favor of the migration products and acetal **16**, until no monosilyl acetal was detected with 1.1 equiv of alcohol (**Table 2, entry 3**). Under these conditions, through pathway 1, the amount of alcohol is not sufficient for the monosilyl acetal to be formed competitively to the deprotected migration product **17**. In contrast, pathway 2 still proceeds to yield acetal **16**.³⁰

The influence of the aromatic ring substituent on the products ratio was then analyzed, regarding the proposed competing mechanisms. Our results pointed out that while electron-withdrawing groups on the phenyl ring favored the formation of mixed silyl acetal **15** over acetal **16**, the presence of electron-donating groups led to a significant increase of the amount of acetal **16** formed. This tendency could be rationalized by the relative

stabilities of carbocations **a** and **d** involved in pathways 1 and 2 respectively. Indeed, electron-donating groups enhance the stability of benzylic carbocation **d** generated in pathway 2, thus favoring, to some extent, this pathway, until becoming preponderant on *p*-methoxyphenyl and *p*-methylphenyl substrates using various alcohols. To the contrary, electron-withdrawing groups decrease the stability of carbocation **d**, thus favoring pathway 1 through the formation of carbocation **a**.³¹ This hypothesis is in accordance with the interesting total selectivity observed with highly electron-withdrawing nitro and trifluoromethyl substituents, yielding monosilyl acetal **15** as the major product *via* pathway 1.

Scheme 4. Proposed mechanism



CONCLUSION

In summary, we reported herein the synthesis of original stable α -aryl β -monosilyl acetal esters **15** from *O*-TBS α -diazo- β -hydroxy esters **7**, under the action of excess alcohol and a catalytic amount of TMSOTf. Depending on the reaction conditions and the electronic nature of the aryl substituent, monosilyl acetal **15** or the corresponding acetal **16** could be selectively obtained, while minimizing the unwilled migration products. Mechanistic rationale was proposed, involving initial TfOH-protonation of the substrate either on the diazotated carbon or on the TBS-ether, triggering two competitive pathways through dediazotation. This methodology allows access to a wide diversity of structures as: (i) the aryl substituent is easily modulated beforehand through aldol addition on diazoester, (ii) the method tolerates an interesting range of primary and secondary alcohols. Overall, 56 α -aryl β -monosilyl acetal esters **15** have been prepared in this study, in moderate to good yields with dr up to 6:1. These silylated building-blocks constitute useful synthetic equivalents of α -substituted β -oxoesters, with high potential for further transformations like Mukaiyama aldol or Hosomi-Sakurai reactions. In addition, replacement of the alcohol by a thiol or an amine could pave the way for accessing original mixed monosilyl O,S or O,N acetals.

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.

General informations

Unless otherwise stated, all reagents were from commercial source and used without further purification. Tetrahydrofuran (THF) was dried over activated alumina on a dry station purchased from Innovative Technologies. Dichloromethane, stabilized with amylene, was dried over calcium hydride and distilled. All reactions were carried out under an argon atmosphere in flame-dried glassware. Analytical thin-layer chromatography (TLC) was performed on TLC plates (silica gel 60 F254) and visualized by UV lamp (254 nm) and phosphomolybdic acid solution. Column chromatography was performed using The Reveleris® flash chromatography systems. ^1H (400 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded using a Bruker Avance 400. Chemical shifts (δ) are given in part per million (ppm) from TMS as the internal standard. Coupling constants are given in Hertz (Hz) and the multiplicity of signal is indicated as follows: s (singulet), d (doublet), t (triplet), dt (doublet of triplets), dq (doublet of quartets), ddt (doublet of doublet of triplets), ddd (doublet of doublet of doublets), br s (broad singulet), m (multiplet). High-resolution mass spectra (HRMS) were recorded with a Bruker microTOF QIII mass spectrometer using ESI techniques. IR spectra were recorded on a Perkin Elmer FT-IR Spectrum One spectrometer equipped with an ATR unit. The wavenumbers of representative absorption peaks are given in cm^{-1} .

General procedure 1 for the silylation of the α -diazo- β -hydroxy ester³²

To a solution of the α -diazo- β -hydroxy ester (10 mmol, 1 equiv) in CH_2Cl_2 (50 mL) at 0 °C were added imidazole (25 mmol, 2.5 equiv), DMAP (1 mmol, 0.1 equiv) and TBSCl (15 mmol, 1.5 equiv). The mixture was stirred at 0 °C for 30 min, then overnight at room temperature. The reaction was hydrolyzed with water and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with water, brine, dried over MgSO_4 and filtered. Solvent was removed under reduced pressure and the crude product was purified by flash chromatography.

Ethyl 3-((*tert*-butyldimethylsilyl)oxy)-2-diazo-3-phenylpropanoate (**7a**)⁷

Compound **7a** was prepared according to the general procedure 1 from ethyl 2-diazo-3-hydroxy-3-phenylpropanoate (3.94 g, 17.9 mmol). Flash chromatography (cyclohexane : ethyl acetate 100 : 0 to 98 : 2) gave **7a** as a yellow liquid (5.81 g, 17.36 mmol, 97%); R_f 0.62 (cyclohexane : ethyl acetate 9 : 1).

¹H NMR (400 MHz, CDCl₃) δ 7.40-7.31 (m, 4H), 7.30-7.26 (m, 1H), 5.81 (s, 1H), 4.32-4.19 (m, 2H), 1.28 (t, 3H, J = 7.1 Hz), 0.91 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H); ¹³C NMR (100.6 MHz, CDCl₃) δ 165.8, 141.7, 128.6 (2C), 127.9 (2C), 125.5, 68.8, 61.0, 25.9 (3C), 18.4, 14.7, -4.9, -5.1. The signal for the diazo carbon was not observed due to extensive relaxation time.

General procedures for Table 1

Procedure for the screening of the following catalysts: Rh₂(OAc)₄ (1mol%), Rh₂(Oct)₄ (1mol%), AgClO₄ (10 mol%), AgBF₄ (10 mol%), AgOTf (10 mol%), Cu(MeCN)₄BF₄ (10 mol%), Cu(MeCN)₄PF₆ (10 mol%), Cu(OTf)₂ (10 mol%), Yb(OTf)₃ (5 mol%), In(OTf)₃ (5 mol%), Sc(OTf)₃ (5 mol%), SnCl₄ (10 mol%). (**Table 1, entries 1-12**).

To a solution of the catalyst (1 to 10 mol%) in CH₂Cl₂ (3 mL) was added dropwise a solution of **7a** (200 mg, 0.600 mmol) in propan-1-ol (3 mL) at rt. The reaction mixture was stirred for the time indicated in table 1 while the gas evolved and the solution color diminished. After hydrolysis (2 mL of water), the aqueous phase was extracted with CH₂Cl₂ (5 mL) three times. The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. When stated in table 1 further purification of the crude material was performed by flash chromatography (cyclohexane/AcOEt 95:5).

Procedure for the use of TMSOTf (10 mol%)

To a solution of **7a** (150 mg, 0.450 mmol) in propan-1-ol (2.2 mL) was added a solution of TMSOTf (10 mol%) in CH₂Cl₂ (2.2 mL) at rt. The reaction mixture was stirred for 40 min at rt while the gas evolved and the solution color diminished. The reaction mixture was hydrolysed by the addition of a saturated aqueous solution of NaHCO₃ and the aqueous phase was extracted three times with CH₂Cl₂. The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (cyclohexane/AcOEt 95:5).

General procedure 2 for the synthesis of acetals **15** (Table 3 and scheme 3)

To a solution of *O*-protected α -diazo- β -hydroxy ester (0.5 mmol, 1 equiv) and the corresponding alcohol (2.5 mmol, 5 equiv) in CH₂Cl₂ (4.50 mL) was added dropwise a solution of TMSOTf (0.5 mL, 0.1 M solution in CH₂Cl₂, 0.05 mmol, 0.1 equiv) at the specified temperature. The mixture was stirred at this temperature until complete consumption of starting material was ascertained by TLC. It was then quenched by a saturated aqueous NaHCO₃ solution. The aqueous phase was extracted with CH₂Cl₂ three times and the combined organic layers were washed with brine, dried over MgSO₄ and filtered. Solvent was removed under reduced pressure and the crude product was purified by flash chromatography using the indicated solvent system to afford the desired product.

Ethyl 3-((*tert*-butyldimethylsilyl)oxy)-2-phenyl-3-propoxypropanoate (**15aa**) (Table 3, entry 1)

Compound **15aa** was prepared according to the general procedure 2 from **7a** (140 mg, 0.418 mmol) and propan-1-ol (159 μ L). The reaction was complete in 30 min at -20 °C. The ¹H NMR of the crude product indicates a mixture of **15aa/16aa/2a+17a** in a ratio 1/0.3/0.2. Flash chromatography (cyclohexane : ethyl acetate 99.5 : 0.5) afforded pure monosilyl acetal **15aa** as a colorless liquid (84 mg, 0.230 mmol, 55%, isolated yield, dr : 1.0 / 1.5). A colorless

liquid fraction containing a mixture of acetal **16aa** (14%, NMR yield) and migration products (16%, NMR yield) was also obtained.

15aa (minor diastereomer): $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.42-7.37 (m, 2H), 7.33-7.22 (m, 3H), 5.33 (d, 1H, $J = 8.2$ Hz), 4.13 (dq, 1H, $J = 10.8$ Hz, 7.1 Hz), 4.05 (dq, 1H, $J = 10.8$, 7.1 Hz), 3.84 (d, 1H, $J = 8.2$ Hz), 3.40 (dt, 1H, $J = 8.9$, 6.5 Hz), 3.10 (dt, 1H, $J = 8.9$, 6.5 Hz), 1.32-1.20 (m, 2H), 1.21 (t, 3H, $J = 7.1$ Hz), 0.89 (s, 9H), 0.60 (t, 3H, $J = 7.4$ Hz), 0.16 (s, 3H), 0.13 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3) δ 171.6, 135.3, 129.0 (2C), 128.4 (2C), 127.5, 99.2, 68.3, 60.8, 59.0, 25.8 (3C), 22.8, 18.1, 14.2, 10.4, -3.8, -4.9; HRMS (ESI/Q-TOF) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{20}\text{H}_{34}\text{NaO}_4\text{Si}$ 389.2119; found 389.2116.

15aa (major diastereomer): $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.42-7.37 (m, 2H), 7.33-7.22 (m, 3H), 5.24 (d, 1H, $J = 8.3$ Hz), 4.19 (dq, 1H, $J = 10.8$, 7.1 Hz), 4.07 (dq, 1H, $J = 10.8$, 7.1 Hz), 3.81 (d, 1H, $J = 8.3$ Hz), 3.69 (dt, 1H, $J = 8.8$, 6.4 Hz), 3.45 (dt, 1H, $J = 8.8$, 6.4 Hz), 1.66-1.54 (m, 2H), 1.23 (t, 3H, $J = 7.1$ Hz), 0.92 (t, 3H, $J = 7.4$ Hz), 0.68 (s, 9H), -0.01 (s, 3H), -0.46 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3) δ 171.6, 135.4, 129.4 (2C), 128.5 (2C), 127.7, 99.4, 68.8, 60.7, 59.3, 25.6 (3C), 23.1, 18.0, 14.2, 10.7, -4.2, -5.3; HRMS ((ESI/Q-TOF) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{20}\text{H}_{34}\text{NaO}_4\text{Si}$ 389.2119; found 389.2116.

16aa: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.42-7.37 (m, 2H), 7.33-7.25 (m, 3H), 5.04 (d, 1H, $J = 8.8$ Hz), 4.17 (dq, 1H, $J = 10.8$, 7.1 Hz), 4.08 (dq, 1H, $J = 10.8$, 7.1 Hz), 3.88 (d, 1H, $J = 8.8$ Hz), 3.70 (dt, 1H, $J = 9.1$, 6.4 Hz), 3.49 (dt, 1H, $J = 9.1$, 6.7 Hz), 3.40 (dt, 1H, $J = 9.1$, 6.4 Hz), 3.17 (dt, 1H, $J = 9.1$, 6.7 Hz), 1.65-1.55 (m, 2H), 1.36-1.26 (m, 2H), 1.23 (t, 3H, $J = 7.1$ Hz), 0.92 (t, 3H, $J = 7.4$ Hz), 0.64 (t, 3H, $J = 7.4$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3) δ 171.5, 135.1, 129.0 (2C), 128.5 (2C), 127.6, 104.1, 69.8, 68.7, 60.9, 56.5, 23.1, 22.9, 14.2, 10.7, 10.5; HRMS (ESI/Q-TOF) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{17}\text{H}_{26}\text{NaO}_4$ 317.1723; found 317.1712.

Ethyl 3-((*tert*-butyldimethylsilyloxy)-3-methoxy-2-(4-nitrophenyl)propanoate (**15eb**)

Compound **15eb** was prepared according to the general procedure 2 using **7e** (604 mg, 1.59 mmol) and methanol (320 μL). The solution of TMSOTf was added at 0 $^\circ\text{C}$ and the reaction was stirred for 1 h at rt. The $^1\text{H NMR}$ of the crude product indicates a mixture of **15eb/16eb/2a+17a** in a ratio 1/0.05/0.05. Flash chromatography (cyclohexane : ethyl acetate 99.5 : 0.5) afforded monosilyl acetal **15eb** as a colorless oil (350 mg, 0.91 mmol, 57%, isolated yield, crude dr : 1.1 / 1.0).

15eb (minor diastereomer): $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.21-8.15 (m, 2H), 7.61-7.55 (m, 2H), 5.34 (d, 1H, $J = 7.5$ Hz), 4.16 (dq, 1H, $J = 10.8$, 7.1 Hz), 4.10 (dq, 1H, $J = 10.8$, 7.1 Hz), 3.96 (d, 1H, $J = 7.5$ Hz), 3.17 (s, 3H), 1.23 (t, 3H, $J = 7.1$ Hz), 0.88 (s, 9H), 0.17 (s, 3H), 0.14 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3): δ 170.3, 147.5, 142.4, 130.2 (2C), 123.6 (2C), 99.1, 61.5, 58.3, 53.5, 25.7 (3C), 18.1, 14.2, -4.1, -4.9; HRMS (ESI/Q-TOF) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{18}\text{H}_{29}\text{NNaO}_6\text{Si}$ 406.1656; found 406.1653.

15eb (major diastereomer): $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.21-8.15 (m, 2H), 7.61-7.56 (m, 2H), 5.22 (d, 1H, $J = 7.6$ Hz), 4.21 (dq, 1H, $J = 10.8$, 7.1 Hz), 4.14 (dq, 1H, $J = 10.8$, 7.1 Hz), 3.95 (d, 1H, $J = 7.6$ Hz), 3.41 (s, 3H), 1.24 (t, 3H, $J = 7.1$ Hz), 0.70 (s, 9H), 0.03 (s, 3H), -0.33 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3): δ 170.3, 147.6, 142.4, 130.5 (2C), 123.6 (2C), 99.7, 61.4, 58.3, 54.1, 25.6 (3C), 18.0, 14.2, -4.2, -5.2; HRMS (ESI/Q-TOF) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{18}\text{H}_{29}\text{NNaO}_6\text{Si}$ 406.1656; found 406.1659.

ASSOCIATED CONTENT

Supporting Information

Full experimental details, including the preparation of protected α -diazo- β -hydroxy esters and spectroscopic data for all new compounds; X-ray crystallographic data of **15eb**. This material is available free of charge at <https://pubs.acs.org>.

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