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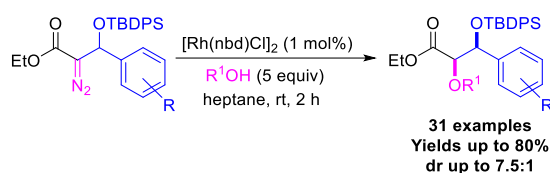
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Rhodium(I)-catalyzed O-H insertions on *O*-protected α -diazo- β -hydroxyesters

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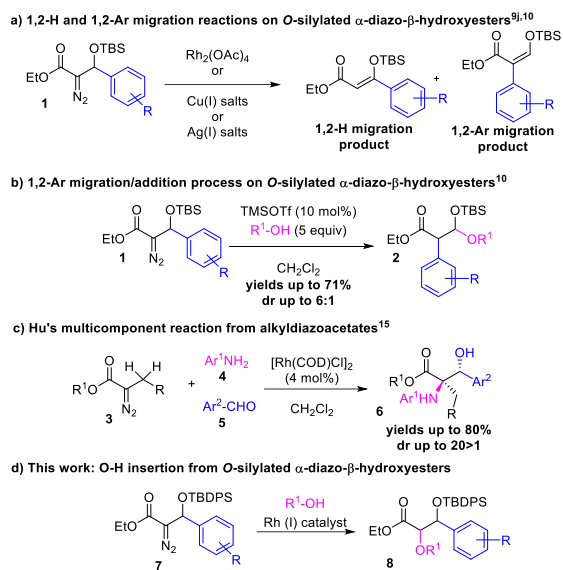
ABSTRACT: The X-H insertion reaction constitutes a powerful tool to create diversity through diazo decomposition of diazocarbonyl compounds. However, until now, the X-H insertion on α -diazo- β -aryl- β -hydroxyester scaffolds, readily prepared by aldol-type addition, remained a challenge for the organic chemist. We report herein the first O-H insertions on *O*-protected α -diazo- β -aryl- β -hydroxyesters, providing a straightforward access to a wide range of α,β -dioxxygenated esters through modulation of the alcohol and of the aryl substituent. The key feature to achieve this transformation is the use of Rh(I) catalysts, which proved crucial to favor the targeted O-H insertion product over the competing 1,2-H and 1,2-Ar migration products. Overall, 31 O-H insertion products have been prepared, in moderate to good yields, with diastereoisomeric ratio up to 7.5:1 in favor of the *syn* diastereoisomer.

INTRODUCTION

In the frame of the Diverted Total Synthesis (DTS) of structurally complex natural products derivatives, introducing structural diversity on small building blocks from a common precursor is a valuable approach.¹ Our ongoing research in this field has prompted us to investigate the reactivity profile of the diazo functionality of α -diazo- β -hydroxyesters. Diazocarbonyl compounds have been used for decades in a wide range of transformations (C-H insertion, X-H insertion, migration, cyclopropanation,...) in order to generate functional diversity.² For example, several transition metal-catalyzed X-H insertions (X = O, NH, S) and related asymmetric transformations, or photochemical X-H insertions have been reported on α -diazo- β -aryl-esters, α -diazo-propionates, α -diazo- β -vinyl-esters, α -diazo- β -keto-esters or α -diazo-malonates.^{2,3,4,5,6,7,8} On the contrary, while the synthesis of the α -diazo- β -hydroxyester scaffold is well described in the literature,^{2,9} the transformation of its diazo moiety has been scarcely conducted, despite the synthetic potential of the resulting products.¹⁰

We recently reported a first study exploring the reactivity of *O*-silylated α -diazo- β -hydroxyesters **1** in the presence of various catalysts. While the use of Rh₂(OAc)₄, copper (I) salts and silver (I) salts led to the formation of the 1,2-H and 1,2-Ar migration products (Scheme 1, a)), the use of Lewis acids such as TMSOTf provided original mixed monosilyl acetals **2** in moderate to good yields (Scheme 1, b)). The

ratio between these original acetals and the migration products fluctuates, depending on the catalyst used, the nature of the alcohol and the substituents on the aromatic ring.¹¹



Scheme 1. State of the art and objectives of the present work.

It should be noticed that, although of high synthetic interest, no O-H insertion product was detected during this study. More generally, no X-H insertion has been reported so far on *O*-protected α -diazo- β -hydroxyesters. Overcoming this synthetic challenge would be of high value, as a versatile method to access functionalized α,β -diheterofunctional esters.

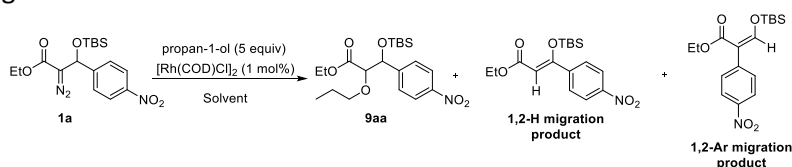
While Rh(II) complexes constitute the most popular catalysts in the field of X-H insertions, Rh(I) complexes have been recently known as effective catalysts in S-H,¹² C-H,¹³ Si-H¹⁴ and B-H insertions.¹⁵ Beside, Hu's team reported in 2017 the synthesis of α -amino- β -hydroxyesters **6** by a multicomponent reaction between alkyldiazoacetates **3**, amines **4** and aldehydes **5**, catalyzed by a Rh(I) specie (Scheme 1, c)).¹⁶ DFT calculations were used to investigate the reactivity of Rh(I) versus Rh(II)-carbene intermediates. This theoretical study concluded that the energy barrier for the 1,2-H migration was higher for Rh(I) carbene than for Rh(II) carbene. Supporting these computational results, the Rh(I) carbene was transformed into ammonium ylide by trapping with an amine before the 1,2-H shift occurred while the 1,2-H migration was found to be a very fast process from Rh(II) carbene. Inspired by these results, we questioned whether Rh(I) catalysts would favor the formation of an oxonium ylide, from *O*-protected α -diazo- β -hydroxyesters and an alcohol, over the competing 1,2-H migration products. The present work is thus tackling the challenge of performing O-H insertion reactions on *O*-protected α -diazo- β -hydroxyesters scaffolds, focusing on the evaluation of Rh(I) catalysts (Scheme 1, d)).

RESULTS

The initial study was performed on *O*-*tert*-butyldimethylsilyl α -diazo- β -hydroxy- β -(*p*-nitro)-phenyl ester **1a**.¹¹ This diazo substrate was easily prepared by nucleophilic addition of ethyl lithiodiazoacetate on *p*-nitrobenzaldehyde,^{9,10} followed by the protection of the resulting alcohol as a TBS silyl ether,¹⁷ well suited for the prospect of natural product synthesis. Gratifyingly, in the presence of [Rh(COD)Cl]₂ (1

mol%), at room temperature, **1a** reacted readily with propan-1-ol, used as the solvent, to yield the O-H insertion product **9aa** in 61% isolated yield along with the 1,2-H migration product (11% isolated yield) (Table 1, entry 1). It is important to note that an experiment conducted in the presence of $\text{Rh}_2(\text{OAc})_4$ instead of $[\text{Rh}(\text{COD})\text{Cl}]_2$ led exclusively to the formation of the migration products, in accordance with our previous results.¹¹ Building on this encouraging result, the amount of propan-1-ol was decreased to five equivalents and the reaction was conducted in various solvents (Table 1), in order to extend the methodology to a wide range of alcohols. Dichloromethane and deuterated chloroform clearly favored the migration reactions over the insertion process (Table 1, entries 2-4). Besides, toluene and *p*-xylene provided nearly equal amounts of insertion and migration products (Table 1, entries 5-7). Decreasing the temperature from room temperature to 0 °C had a detrimental effect, leading to a higher proportion of migrations products and lower yields (Table 1, entries 3 and 6). Gratifyingly, when the reaction was conducted in deuterated benzene or in alkanes like hexane, cyclohexane and heptane, the expected O-H insertion product **9aa** became the major product with a **9aa**/migration products ratio from 1:0.5 to 1:0.3 and yields ranging from 37% to 60% (Table 1, entries 8-11). Among the different solvents tested as an alternative to propan-1-ol, heptane proved the optimal one, providing both the best yield of the insertion product **9aa** (60% yield; **9aa**/migration products = 1:0.35) and the highest diastereoisomeric ratio (9:1).

Table 1. Screening of solvents^a

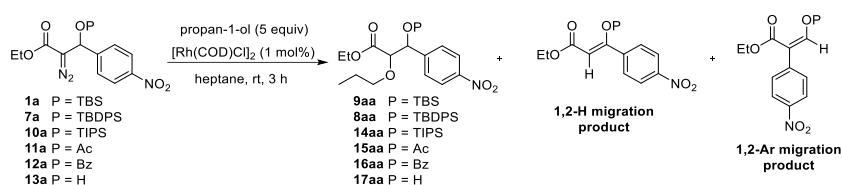


Entry	Solvent	T°C	Time (h)	Products ratio ^b			dr ^c	Yield (%) ^d
				9aa	1,2-H migration product	1,2-Ar migration product		
1	Propan-1-ol	rt ^e	22	1	0.2	0	4.8:1	65 ^f /11
2	CH ₂ Cl ₂	rt	24	1	2.1	0.2	4.3:1	22/53
3	CH ₂ Cl ₂	0	24	1	2.4	0.2	3.3:1	13/48
4	CDCl ₃	rt	24	1	4.2	0.3	3.7:1	11 ^g /51
5	Toluene	rt	48	1	0.9	0.1	6.8:1	33/34
6	Toluene	0	24	1	1.2	0.1	7.3:1	22/37
7	<i>p</i> -xylene	rt	4	1	0.7	0	6.8:1	35/38
8	C ₆ D ₆	rt	24	1	0.5	0	5.9:1	37/6
9	hexane	rt	4	1	0.4	0.1	7.9:1	45/24
10	cyclohexane	rt	4	1	0.3	0	7.8:1	53/23
11	heptane	rt	4	1	0.3	0.05	9:1	60/21

^a Unless otherwise noted, all reactions were carried out at 0.3 mmol scale as follows: a solution of the substrate **1a** in the indicated solvent (1.5 mL) was added to a solution of the $[\text{Rh}(\text{COD})\text{Cl}]_2$ catalyst (1 mol%) and propan-1-ol (5 equiv) in the indicated solvent (1.5 mL) at 0 °C and the reaction mixture was stirred at the indicated temperature for the specified time. ^b Ratio determined by ¹H NMR analysis of the crude product. ^c Estimated by ¹H NMR analysis of the crude product. ^d Unless otherwise stated, yields were estimated by ¹H NMR spectroscopy, after silica gel chromatography, from fractions containing either pure O-H insertion product **9aa** or a mixture of migration products and O-H insertion product **9aa**. ^e No conversion was observed at 0 °C. ^f 61% isolated yield. ^g Conversion estimated by ¹H NMR analysis of the crude product.

The influence of the alcohol protecting group was then investigated (Table 2). For this purpose, four additional substrates were prepared by nucleophilic addition of ethyl lithiodiazoacetate on *p*-nitrobenzaldehyde, followed by the protection of the resulting diazoaldol as silyl ethers (**7a**, **10a**), as acetate^{10h} (**11a**) or benzoate (**12a**) under classical conditions. Concerning the silyl protecting groups, TBDPS proved superior, providing the corresponding O-H insertion product **8aa** with a higher selectivity than observed from the TBS-protected substrate **1a** (**8aa**/migration products = 1:0.25 vs **9aa**/migration products = 1:0.35) along with a 10% yield increase (Table 2, entry 2). On the contrary, the reaction with the highly hindered TIPS protecting group was incomplete, resulting in a lower selectivity between O-H insertion and migration products, which were obtained in similar modest yields after purification (Table 2, entry 3). In the presence of an acetate or a benzoate ester protecting group, no O-H insertion product was detected (Table 2, entries 4 and 5). Instead, the 1,2-H migration product was observed in both cases, along with the ester migration products, as previously described.^{10h,i,18} Finally, when the reaction was carried out on the unprotected alcohol **13a**, only the 1,2-H and 1,2-Ar migration products were isolated (Table 2, entry 6), as it could be expected following the previous work of Wang.^{10j}

Table 2. Screening of protecting groups and catalysts.^a



Entry	Catalyst	Substrate (P =)	Products ratio ^b			dr ^b	Yield (%) ^c
			O-H insertion	1,2-H migration product	1,2-Ar migration		
1	[Rh(COD)Cl] ₂	1a (TBS)	1	0.3	0.05	9:1	60/21
2	[Rh(COD)Cl] ₂	7a (TBDPS)	1	0.2	0.05	9:1	70/13
3	[Rh(COD)Cl] ₂	10a (TIPS)	1 ^d	0.5	0.05	6.9:1	29/26
4	[Rh(COD)Cl] ₂	11a (Ac)	–	–	–	–	0/20 ^e
5	[Rh(COD)Cl] ₂	12a (Bz)	–	–	–	–	0/19 ^f
6	[Rh(COD)Cl] ₂	13a (H)	0	1	0.3	–	0/70
7	Rh(COD) ₂ OTf	1a (TBS)	1	2.3	0.8	9:1	21/68
8	Rh(COD) ₂ BF ₄	1a (TBS)	1	5.1	0.9	–	5/68
9	[Rh(C ₂ H ₄) ₂ Cl] ₂	1a (TBS)	0	1	0.2	–	0/40 ^g
10	[Rh(nbd)Cl] ₂	1a (TBS)	1	0.07	0.02	7.5:1	70 (67 ^h)/8
11	[Rh(nbd)Cl] ₂	7a (TBDPS)	1	0.06	0.2	7.3:1	74 (67 ^h)/13

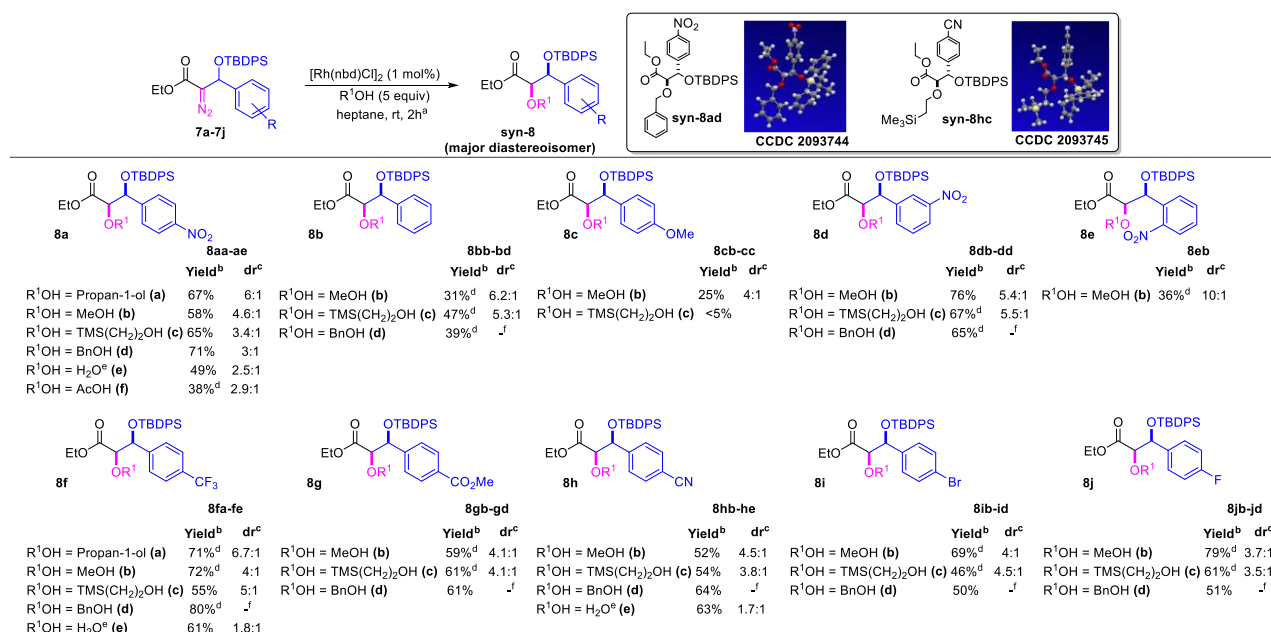
^a Reactions were performed at 0.3 mmol scale: a solution of diazo substrate in heptane (1.5 mL) was added to a solution of the Rh (I) catalyst (1 mol%) and propan-1-ol (5 equiv) in heptane (1.5 mL) at 0 °C and the reaction mixture was stirred at room temperature for 3 h. ^b Ratio determined by ¹H NMR analysis of the crude product. ^c Unless otherwise stated, yields were estimated by ¹H NMR spectroscopy, after silica gel chromatography, from fractions containing either pure O-H insertion product or a mixture of migration products and O-H insertion product. ^d Incomplete reaction. ^e Acetate migration product was also estimated in 58% yield. ^f Benzoate migration product was also estimated in 49% yield. ^g Incomplete reaction. In addition to **1a**, only migration products were observed on ¹H NMR of the crude product. ^h Isolated yield.

In parallel with the previous study, the influence of the catalyst ligands was assessed on substrate **1a**, through the use of four additional rhodium (I) species (Table 2, entries 7-10). The outcome of the reaction was highly dependent on the nature of the Rh(I) catalyst used. Disappointing results were obtained with Rh(COD)₂OTf, Rh(COD)₂BF₄ and [Rh(C₂H₄)₂Cl]₂ which strongly favored the migration reactions over O-H insertion (Table 2, entries 7-9). In contrast, [Rh(nbd)Cl]₂ proved slightly superior to [Rh(COD)Cl]₂ on both TBS- and TBDPS ether-protected substrates, affording insertion products **9aa** and **8aa** with an improved selectivity in 67% isolated yield (Table 2, entries 10 and 11). Additional assays aiming at lowering the amount of propan-1-ol unfortunately led to unreproducible results. From the preceding studies, appropriate reaction conditions for promoting the O-H insertion of propan-1-ol over migrations processes on diazo substrate **1a** were established as follows: propan-1-ol (5 equiv), [Rh(nbd)Cl]₂ (1 mol%), heptane (0.1 M), rt. These optimized reaction conditions were selected to study the scope of the O-H insertion reaction on *O*-TBDPS protected α -diazo- β -hydroxyesters (Scheme 2).

In order to investigate the influence of the nature of the alcohol, the followings were selected for their interest in multistep synthesis: MeOH (**b**), TMS-ethanol (**c**) and benzyl alcohol (**d**). The reaction proceeded well on the *p*-nitrophenyl substrate **7a** with all of them, providing the O-H insertion products **8ab-8ad** in good isolated yields (58-71%).¹⁹ The diastereoisomeric ratio of the products was ranging from 3:1 to 4.6:1. Gratifyingly, O-H insertion of water (**e**) could also be achieved in 49% yield (**8ae**, dr = 2.5:1) using 20 equivalents of water. Finally, the use of acetic acid provided the O-H insertion product **8af** in a low 38% yield.

The substrate scope of the O-H insertion reaction was next explored, focusing on the nature and the position of the aromatic ring substituent (Scheme 2). *O*-TBDPS-protected α -diazo- β -hydroxyesters **7b-7j** were synthesized by the usual aldol-addition/protection^{9,10f,17} two step sequence and subjected to several alcohols or water under the previously optimized reaction conditions.

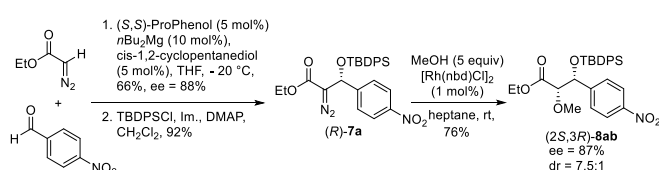
Yields ranging from 46% to 80% were obtained when the aromatic ring was substituted at the *para* or the *meta* position with an electron-withdrawing substituent (NO₂, CF₃, CN, CO₂Me, halogens). Diastereoisomeric ratios were estimated between 1.7:1 (observed for the insertion of water) and 7.3:1 (observed with propan-1-ol). On the contrary, the nitro substituent at the *ortho* position resulted in low yield of the insertion product with MeOH (**8eb**, 36%), albeit with an excellent 10:1 dr. Besides, low yield or only traces of the expected products were formed when the aromatic ring was substituted with the methoxy electron-donating group at the *para* position (**8cb**, **8cc**). Finally, the phenyl substrate **7b** devoid of any substituent led to moderate yields (31-47%) of insertion products **8bb-8bd** (dr >5.3:1). For these substrates, the migration products were mainly formed. As described by Wang's team, the nature of the aryl substituent has an influence on its migratory aptitude, with enhanced migration ability for electron-donating substituents.²⁰



Scheme 2. Reaction scope. ^a The reaction was performed as follows: to a solution of the substrate **7** in heptane (0.1 M) were added R¹OH (5 equiv) and [Rh(nbd)Cl]₂ (1 mol%) at room temperature. ^b Isolated yield unless otherwise noted. ^c Ratio determined by ¹H NMR analysis of the crude product. ^d Yield estimated by ¹H NMR spectroscopy, after silica gel chromatography, from fractions containing either pure O-H insertion product or a mixture of migration products and O-H insertion product. ^e Reaction performed with 20 equiv of H₂O. ^f Undetermined.

The structure of the major *syn* diastereoisomer of insertion products **8ad** and **8hc** was elucidated by X-ray diffraction.²¹ Considering the strong analogy between the NMR spectra of the major and minor stereoisomers of all the insertion products **8** obtained, a *syn* relationship was confidently assigned to each major diastereoisomer. Additionally, a gram-scale reaction was performed from **7a** and methanol affording **8ab** in 80% isolated yield, highlighting that the scale-up of the process was feasible.

An interesting feature of the methodology implemented here lies in the convenient access to the enantioenriched OH-insertion products. Indeed, Trost reported an efficient enantioselective aldol-type addition²² allowing the synthesis of a wide range of enantioenriched α -diazo- β -hydroxyesters substrates. As an example, enantioenriched *O*-TBDPS α -diazo- β -hydroxy- β -(*p*-nitro)-phenyl ester (*R*)-**7a** was prepared in two steps by the enantioselective Trost's aldol-addition between *p*-nitrobenzaldehyde and ethyl diazoacetate (66% yield, ee = 88%), followed by the protection of the alcohol as a TBDPS ether (92% yield) (Scheme 3). Enantioenriched substrate (*R*)-**7a** was subjected to the O-H insertion reaction with MeOH, leading to enantioenriched product (*2S,2R*)-**8ab** in 76% yield (ee = 87% ; dr = 7.5:1).²³



Scheme 3. Synthesis of (2*S*,3*R*)-8ab.

CONCLUSION

In summary, we have overcome here the synthetic challenge of performing O-H insertions on *O*-silyl protected α -diazo- β -aryl- β -hydroxyesters, by using Rh(I) catalysts. Conducting the reaction in heptane at room temperature, with 1 mol% of [Rh(nbd)Cl]₂ and 5 equivalents of the alcohol reagent, proved in our hands the optimal conditions to favor the *syn*-selective formation of the targeted O-H insertion product over the competing 1,2-H and 1,2-Ar migration products. Overall, 31 O-H insertion products have been prepared in this study, in moderate to good yields, with dr up to 7.5:1 in favour of the *syn*-diastereoisomer. This methodologic tool provides a straightforward access to a wide range of α,β -dioxxygenated esters scaffolds through modulation of the alcohol and of the aryl substituent on the diazoaldol substrate. As the enantioenriched substrates can be efficiently prepared by enantioselective aldol-type addition, the corresponding enantioenriched O-H insertion products could be easily generated, which constitutes a useful feature of this methodology. The main prospect of this work is its extension to other X-H insertions, in order to provide α,β -diheterofunctional esters, as valuable building-blocks in the frame of Diverted Total Synthesis.

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 noted, all reagents were commercially supplied and used without further purification. Tetrahydrofuran (THF) and dichloromethane were dried over activated alumina on a dry station purchased from Innovative Technologies. Heptane was dried over calcium hydride and distilled. All the reactions were carried out under argon atmosphere. 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 or 500 MHz) and ¹³C{¹H} (100.6 MHz or 125 MHz) NMR in CDCl₃ were recorded on a Bruker Avance 400 or on a Bruker Avance Neo 500. 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 the signals 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 as thin films on an Agilent Cary 630 FTIR Spectrometer. The wavenumbers of representative absorption peaks are given in cm⁻¹.

General procedure for the protection of the hydroxyl group as a *tert*-butyldiphenylsilyl ether^[1] (GP1)

To a solution of the corresponding α -diazo- β -hydroxyester (1 equiv) in CH_2Cl_2 (0.2 M) at 0 °C were added imidazole (2.0 equiv), DMAP (0.2 equiv) and TBDPSCI (1.1 equiv). The mixture was stirred at 0 °C for 30 min, then overnight at room temperature. The reaction mixture was quenched with water. The aqueous phase was extracted with CH_2Cl_2 (x3). 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 using the indicated solvent system to afford the desired product.

Ethyl 3-((*tert*-butyldiphenylsilyl)oxy)-2-diazo-3-(4-nitrophenyl)propanoate (7a)

The compound **7a** was prepared according to the **GP 1** using ethyl 2-diazo-3-hydroxy-3-(4-nitrophenyl)propanoate (700 mg, 2.64 mmol). Flash chromatography (cyclohexane : ethyl acetate 100 : 0 to 98 : 2) afforded **7a** isolated as a yellow oil (1.18 g, 2.34 mmol, 88%); R_f 0.5 (cyclohexane : ethyl acetate 9 : 1). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.19-8.17 (m, 2H), 7.68-7.66 (m, 2H), 7.53-7.51 (m, 4H), 7.45-7.36 (m, 4H), 7.32-7.29 (m, 2H), 5.80 (s, 1H), 4.04-3.95 (m, 2H), 1.11 (m, 12H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3) δ 164.5, 148.9, 147.6, 135.7 (4C), 132.5, 132.1, 130.3 (2C), 128.0 (2C), 127.9 (2C), 126.3 (2C), 124.0 (2C), 68.5, 61.1, 27.0 (3C), 19.6, 14.4. The signal for the diazo carbon was not observed due to extensive relaxation time. HRMS-ESI calculated for $\text{C}_{27}\text{H}_{29}\text{N}_3\text{NaO}_5\text{Si}$: m/z 526.1769 ($[\text{M}+\text{Na}]^+$), found : 526.1752. IR ν (cm^{-1}): 2962, 2933, 2862, 2095, 1693, 1529, 1350, 1253, 1112, 1063, 825, 732.

General procedure for the processes mentioned in Table 1 (GP2)

To a solution of $[\text{Rh}(\text{COD})\text{Cl}]_2$ (1 mol%) and propanol (5 equiv) in the indicated solvent (5mL/mmol) was added dropwise a solution of the *O*-TBS-protected- α -diazo- β -hydroxyester **1a** (1 equiv) in the same solvent (5 mL/mmol) at 0 °C. The reaction mixture was then stirred at the indicated temperature for the time indicated in Table 1. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography to afford compound **9aa**.

General procedure for the processes mentioned in Table 2 (GP3)

To a solution of the indicated catalyst (1 mol%) and propanol (5 equiv) in heptane (5 mL/mmol) was added dropwise a solution of the corresponding *O*-protected- α -diazo- β -hydroxyester (1 equiv) in heptane (5 mL/mmol) at 0°C. The reaction mixture was then stirred at rt for 3h. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography to afford the O-H insertion product.

General procedure for the formation of the O-H insertion products in scheme 2 (GP4)

To a solution of *O*-protected α -diazo- β -hydroxyester **7** (0.2 mmol) and R^1OH (5 equiv, 1mmol) in heptane (2 mL, 0.1 M) was added $[\text{Rh}(\text{nbd})\text{Cl}]_2$ (1 mol%). The reaction mixture was stirred at room temperature for the indicated time. The solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography using the indicated solvent system to afford the desired product.

Ethyl 3-((*tert*-butyldiphenylsilyl)oxy)-3-(4-nitrophenyl)-2-propoxypropanoate (8aa)

The compound **8aa** was prepared according to the **GP 4** using **7a** (110 mg, 0.219 mmol) and propanol (82 μL , 5 equiv). The reaction was complete in 3 h at rt. The $^1\text{H NMR}$ of the crude product indicates a mixture of **8aa** : **1,2-H migration** : **1,2-Ar migration** in a ratio 1:0.1:0.1. Flash chromatography

(cyclohexane : diethylether 100 : 0 to 98 : 2) afforded **8aa** isolated as a colourless oil (79 mg, 0.147 mmol, 67%, crude dr 6:1); R_f 0.25 (cyclohexane : ethyl acetate 9 : 1).

Major diastereomer $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.02 (d, $J = 8.7$ Hz, 2H), 7.72-7.70 (m, 2H), 7.45-7.41 (m, 3H), 7.37-7.31 (m, 5H), 7.23-7.19 (m, 2H), 5.03 (d, $J = 5.5$ Hz, 1H), 3.96 (qd, $J = 10.8, 7.1$ Hz, 1H), 3.92 (d, $J = 5.5$ Hz, 1H), 3.88 (qd, $J = 10.8, 7.1$ Hz, 1H), 3.37 (td, $J = 8.9, 6.6$ Hz, 1H), 3.17 (td, $J = 8.9, 6.6$ Hz, 1H), 1.52-1.43 (m, 2H), 1.08 (s, 9H), 1.04 (t, $J = 7.1$ Hz, 3H), 0.82 (t, $J = 7.4$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3) δ 169.9, 147.5, 147.3, 136.1 (2C), 135.9 (2C), 133.1, 132.8, 130.0, 129.9, 128.3 (2C), 127.7 (2C), 127.6 (2C), 122.9 (2C), 83.9, 75.8, 72.9, 60.8, 27.0 (3C), 22.8, 19.5, 14.1, 10.5.

Minor diastereomer $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.99 (d, $J = 8.7$ Hz, 2H), 7.61-7.59 (m, 2H), 7.45-7.41 (m, 3H), 7.37-7.31 (m, 5H), 7.23-7.19 (m, 2H), 5.09 (d, $J = 6.0$ Hz, 1H), 4.10 (q, $J = 7.1$ Hz, 2H), 3.45 (td, $J = 8.9, 6.5$ Hz, 1H), 3.17 (td, $J = 8.9, 6.5$ Hz, 1H), 1.52-1.43 (m, 2H), 1.08 (s, 9H), 1.04 (t, $J = 7.1$ Hz, 3H), 0.74 (t, $J = 7.4$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3) δ 170.6, 147.8, 147.4, 136.1 (2C), 135.9 (2C), 133.1, 132.8, 130.0, 129.9, 128.3 (2C), 127.8 (2C), 127.6 (2C), 122.9 (2C), 83.9, 75.8, 72.9, 61.2, 26.7 (3C), 22.8, 19.5, 14.1, 10.5.

HRMS-ESI calculated for $\text{C}_{30}\text{H}_{37}\text{NNaO}_6\text{Si}$: m/z 558.2282 ($[\text{M}+\text{Na}]^+$), found : 558.2282.

IR ν (cm^{-1}) : 2962, 2933, 2858, 1745, 1525, 1350, 1112, 858, 825.

Ethyl 3-((*tert*-butyldiphenylsilyl)oxy)-2-methoxy-3-(4-nitrophenyl)propanoate (8ab)

The compound **8ab** was prepared according to the **GP4** using **7a** (107 mg, 0.212 mmol) and methanol (45 μL , 5 equiv). The reaction was stirred overnight at rt. The $^1\text{H NMR}$ of the crude product indicates a mixture of **8ab** : **1,2-H migration** : **1,2-Ar migration** in a ratio 1:0.1:0.1. Flash chromatography (cyclohexane : diethyl ether 100 : 0 to 98 : 2) afforded **8ab** isolated as a colourless oil (63 mg, 0.124 mmol, 58%, crude dr 4.6:1); R_f 0.18 (cyclohexane : ethyl acetate 9 : 1).

Major diastereomer $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.05-8.03 (m, 2H), 7.70-7.68 (m, 2H), 7.46-7.41 (m, 3H), 7.38-7.34 (m, 5H), 7.25-7.21 (m, 2H), 5.02 (d, $J = 5.3$ Hz, 1H), 4.01 (qd, $J = 10.8, 7.1$ Hz, 1H), 3.91 (qd, $J = 10.8, 7.1$ Hz, 1H), 3.82 (d, $J = 5.3$ Hz, 1H), 3.22 (s, 3H), 1.08 (s, 9H), 1.07 (t, $J = 7.1$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3) δ 169.6, 147.6, 147.1, 136.1 (2C), 135.9 (2C), 133.0, 132.7, 130.1, 130.0, 128.3 (2C), 127.8 (2C), 127.7 (2C), 123.0 (2C), 85.3, 75.6, 61.0, 58.8, 27.0 (3C), 19.5, 14.1.

Minor diastereomer $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.00-7.98 (m, 2H), 7.63-7.60 (m, 2H), 7.46-7.41 (m, 3H), 7.38-7.34 (m, 5H), 7.25-7.21 (m, 2H), 5.09 (d, $J = 5.5$ Hz, 1H), 4.11 (q, $J = 7.1$ Hz, 1H), 3.82 (d, $J = 5.3$ Hz, 1H), 3.29 (s, 3H), 1.08 (s, 9H), 1.07 (t, $J = 7.1$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3) δ 170.1, 147.5, 147.3, 136.1 (2C), 135.9 (2C), 132.8, 132.7, 130.1, 129.7, 128.4 (2C), 127.8 (2C), 127.7 (2C), 123.0 (2C), 85.4, 75.8, 61.3, 59.1, 26.7 (3C), 19.4, 14.2.

HRMS-ESI calculated for $\text{C}_{28}\text{H}_{33}\text{NNaO}_6\text{Si}$: m/z 530.1969 ($[\text{M}+\text{Na}]^+$), found : 530.1970.

IR ν (cm^{-1}) : 2977, 2933, 2862, 1748, 1525, 1350, 1112, 825.

Synthesis of 8ab on a 1 g scale

The compound **8ab** was prepared according to the **GP4** using **7a** (1.06 g, 2.10 mmol) and methanol (450 μL , 5 equiv). Flash chromatography (cyclohexane : ethylacetate 100 : 0 to 98 : 2) afforded **8ab** isolated as a colourless oil (860 mg, 1.69 mmol, 80%, crude dr 5.9:1).

Ethyl 2-(benzyloxy)-3-((*tert*-butyldiphenylsilyl)oxy)-3-(4-nitrophenyl)propanoate (8ad)

The compound **8ad** was prepared according to the **GP4** using **7a** (110 mg, 0.219 mmol) and benzylic alcohol (114 μL , 5 equiv). The reaction was stirred overnight at rt. The $^1\text{H NMR}$ of the crude product

indicates a mixture of **8ad** : **1,2-H migration** in a ratio 1:0.05. Flash chromatography (cyclohexane : diethylether 100 : 0 to 98 : 2) afforded **8ad** isolated as a white solid (91 mg, 0.156 mmol, 71%, crude dr 3:1); R_f 0.41 (cyclohexane : ethyl acetate 9 : 1).

Major diastereomer: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.00-7.98 (m, 2H), 7.68-7.65 (m, 2H), 7.42-7.39 (m, 3H), 7.34-7.29 (m, 5H), 7.28-7.25 (m, 3H), 7.20-7.18 (m, 2H), 7.17-7.13 (m, 2H), 5.07 (d, $J = 5.3$ Hz, 1H), 4.56 (d, $J = 11.6$ Hz, 1H), 4.29 (d, $J = 11.6$ Hz, 1H), 4.04 (d, $J = 5.3$ Hz, 1H), 3.96 (qd, $J = 10.8, 7.1$ Hz, 1H), 3.86 (qd, $J = 10.8, 7.1$ Hz, 1H), 1.06 (s, 9H), 1.04 (t, $J = 7.1$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3) δ 169.6, 147.5, 147.2, 137.0, 136.1 (2C), 135.9 (2C), 132.9, 132.7, 130.0 (2C), 128.4 (2C), 128.3 (2C), 128.2 (2C), 128.0, 127.7 (2C), 127.6 (2C), 122.9 (2C), 82.8, 75.9, 72.9, 61.0, 27.0 (3C), 19.5, 14.1.

Minor diastereomer: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.95-7.93 (m, 2H), 7.68-7.65 (m, 2H), 7.42-7.39 (m, 3H), 7.34-7.29 (m, 5H), 7.28-7.25 (m, 3H), 7.20-7.18 (m, 2H), 7.17-7.13 (m, 2H), 5.11 (d, $J = 5.9$ Hz, 1H), 4.58 (d, $J = 11.9$ Hz, 1H), 4.31 (d, $J = 11.9$ Hz, 1H), 4.07 (d, $J = 5.9$ Hz, 1H), 3.96 (qd, $J = 10.8, 7.1$ Hz, 1H), 3.86 (qd, $J = 10.8, 7.1$ Hz, 1H), 1.05 (s, 9H), 1.04 (t, $J = 7.1$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3) δ 170.3, 147.5, 147.2, 137.0, 136.1 (2C), 135.9 (2C), 132.9, 132.7, 130.0 (2C), 128.4 (2C), 128.3 (2C), 128.2 (2C), 128.0, 127.7 (2C), 127.6 (2C), 122.9 (2C), 82.6, 75.8, 73.0, 61.3, 27.0 (3C), 19.4, 14.2.

HRMS-ESI calculated for $\text{C}_{34}\text{H}_{37}\text{NNaO}_6\text{Si}$: m/z 606.2282 ($[\text{M}+\text{Na}]^+$), found : 606.2283.

IR ν (cm^{-1}): 2962, 2933, 2858, 1745, 1525, 1350, 1112, 825, 743.

Ethyl 3-((*tert*-butyldiphenylsilyloxy)-3-(4-cyanophenyl)-2-(2-(trimethylsilyl)ethoxy)propanoate (8hc)

The compound **8hc** was prepared according to the **GP4** using **7h** (112 mg, 0.231 mmol). The reaction was stirred overnight at rt. The $^1\text{H NMR}$ of the crude product indicates a mixture of **8hc**:**1,2-H migration** : **1,2-Ar migration** in a ratio 1:0.05:0.1. Flash chromatography (Petroleum ether : ethyl acetate 100 : 0 to 90 : 10) afforded **8hc** isolated as a colourless oil (71 mg, 0.125 mmol, 54%, crude dr 3.8:1) in one pure fraction and migration products in a second fraction (8 mg, 0.017 mmol, 7%). R_f 0.41 (cyclohexane : ethyl acetate 9 : 1).

Major diastereomer: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.77-7.73 (m, 2H), 7.51-7.46 (4H), 7.43 (m, 1H), 7.42-7.33 (m, 3H), 7.35-7.33 (m, 2H), 7.28-7.24 (m, 2H), 4.99 (d, $J = 5.5$ Hz, 1H), 3.99 (qd, $J = 10.8, 7.1$ Hz, 1H), 3.93 (d, $J = 5.5$ Hz, 1H), 3.88 (qd, $J = 10.8, 7.1$ Hz, 1H), 3.83 (ddd, $J = 10.8, 9.2, 6.3$, 1H), 3.32 (ddd, $J = 11.0, 9.2, 5.3$ Hz, 1H), 1.11 (s, 9H), 1.07 (t, $J = 7.1$ Hz, 3H), 0.89 (ddd, $J = 13.8, 11.0, 6.3$ Hz, 1H), 0.79 (ddd, $J = 13.8, 10.7, 5.3$ Hz, 1H), 0.00 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3) δ 170.1, 145.3, 136.1 (2C), 136.0 (2C), 133.2, 132.8, 131.5 (2C), 130.0, 129.9, 128.2 (2C), 127.7 (2C), 127.6 (2C), 119.0, 111.5, 83.5, 76.1, 68.8, 60.8, 27.0 (3C), 19.4, 18.1, 14.1, -1.33 (3C).

Minor diastereomer: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.77-7.73 (m, 2H), 7.51-7.46 (4H), 7.43 (m, 1H), 7.42-7.33 (m, 3H), 7.35-7.33 (m, 2H), 7.28-7.24 (m, 2H), 5.07 (d, $J = 6.0$ Hz, 1H), 4.19-4.09 (m, 2H), 3.59 (m, 1H), 3.35 (m, 1H), 1.23 (t, $J = 7.1$ Hz, 3H), 1.07 (s, 9H), 0.93-0.75 (m, 2H), -0.06 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3) δ 170.7, 145.6, 136.1 (2C), 136.0 (2C), 133.2, 132.8, 131.5 (2C), 130.0, 129.9, 128.2 (2C), 127.7 (2C), 127.6 (2C), 119.0, 111.5, 83.5, 76.0, 69.0, 61.1, 27.0 (3C), 19.4, 18.1, 14.1, -1.4 (3C).

HRMS-ESI calculated for $\text{C}_{33}\text{H}_{43}\text{NNaO}_4\text{Si}_2$: m/z 596.2623 ($[\text{M}+\text{Na}]^+$), found : 596.2613.

IR ν (cm^{-1}): 2955, 2933, 2858, 2230, 1745, 1432, 1253, 1112, 840.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

~~The data underlying this study are available in the published article and its 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 **8ad** and **8hc** are available in the Supporting Information file. This material is available free of charge at <https://pubs.acs.org>.

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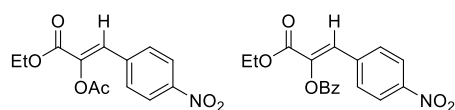
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