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# Access to *Syn* $\alpha$ -Amino- $\beta$ -Hydroxyesters by N–H Insertion on *O*-Protected $\alpha$ -Diazo- $\beta$ -Hydroxyesters

Thomas Defuentes,<sup>[a]</sup> Jérôme Lhoste,<sup>[a]</sup> Catherine Gaulon-Nourry,<sup>[a]</sup> Anne-Sophie Castanet,<sup>[a]</sup> and Anne-Caroline Chany\*<sup>[a]</sup>

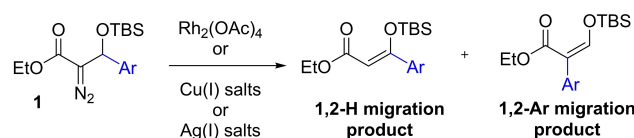
The N–H insertion reaction is a versatile method for creating C–N bonds under mild conditions, providing in particular an efficient access to both natural and non-natural  $\alpha$ -amino acid derivatives. In this field, the direct N–H insertion on  $\alpha$ -diazo- $\beta$ -hydroxyesters has not yet been investigated and constitutes a significant challenge, due to competitive migration processes. We report herein the first N–H insertions on *O*-protected  $\alpha$ -

diazo- $\beta$ -aryl- $\beta$ -hydroxyesters, enabling to synthesize a wide range of  $\alpha$ -amino- $\beta$ -hydroxyesters by tuning the nature of the amine and the aryl substituent. Overall, 28 N–H insertion products have been isolated, with moderate to good yields in most cases, and diastereoisomeric ratios up to 8.0:1 in favor of the *syn* diastereoisomer.

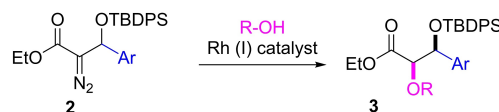
## Introduction

Exploring the reactivity of the diazo functionality has gained constant attention in organic synthesis, as a valuable method to set up functional diversity and elaborate complex scaffolds.<sup>[1]</sup> X–H insertions (X=O, NH or S),<sup>[2]</sup> for example, are known to allow the efficient and modular formation of C–O bonds,<sup>[3]</sup> C–N bonds<sup>[4]</sup> or C–S bonds.<sup>[5]</sup> The N–H insertion reaction, in particular, has demonstrated its efficiency in synthesizing both natural and non-natural amino acids with good functional group tolerance, under diverse reaction conditions,<sup>[2g]</sup> including transition metal or Lewis acid catalysis,<sup>[4]</sup> as well as photochemical,<sup>[6]</sup> mechanochemical<sup>[7]</sup> or electrochemical activation.<sup>[8]</sup> However, these reactions are usually restricted to  $\alpha$ -diazocarbonyl substrates with aryl, vinyl, alkyl, or electron-withdrawing substituents at the  $\beta$ -position. In contrast,  $\alpha$ -diazo- $\beta$ -hydroxyesters are quite challenging reactants as they easily undergo 1,2-H and 1,2-R migrations in the presence of Lewis acids or Rh(II), Cu(I) or Ag(I) catalysts (Scheme 1a).<sup>[9]</sup> We recently overcame this difficulty and achieved the previously elusive O–H insertion on *O*-protected  $\alpha$ -diazo- $\beta$ -hydroxyesters by using a rhodium(I) catalyst, which prevents the formation of migration products (Scheme 1b).<sup>[10]</sup> Besides, the N–H insertion reaction on  $\alpha$ -diazo- $\beta$ -hydroxyesters has not been reported although it would provide an easy access to  $\alpha$ -amino- $\beta$ -hydroxyesters, for

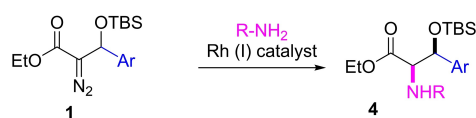
a) 1,2-H and 1,2-Ar migration reactions on *O*-silylated  $\alpha$ -diazo- $\beta$ -hydroxyesters<sup>[9b,i]</sup>



b) O–H insertion from *O*-silylated  $\alpha$ -diazo- $\beta$ -hydroxyesters<sup>[10]</sup>



c) This work: N–H insertion from *O*-silylated  $\alpha$ -diazo- $\beta$ -hydroxyesters



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

which efficient synthetic pathways are still being sought. We describe here how we tackled the challenge of achieving the unprecedented N–H insertion reactions on *O*-protected  $\alpha$ -diazo- $\beta$ -hydroxyesters (Scheme 1c).

## Results and Discussion

Based on our experience of O–H insertion on  $\alpha$ -diazo- $\beta$ -hydroxyesters, the feasibility of N–H insertion was investigated on *O*-*tert*-butyldiphenylsilyl  $\alpha$ -diazo- $\beta$ -hydroxy- $\beta$ -(*p*-nitro)-phenyl ester **2a**, prepared in two steps from ethyl diazoacetate and *p*-nitrobenzaldehyde.<sup>[10,11]</sup> The previously optimized reaction conditions for O–H insertion ([Rh(nbd)Cl]<sub>2</sub>, heptane, 5 equivalents of nucleophile, rt) were first applied to this substrate, using 5 equivalents of aniline as the nucleophile instead of an alcohol. Gratifyingly, the N–H insertion product **5aa** was isolated in 50%

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yield and a 3.4:1 dr (Table 1, entry 1), along with traces of 1,2-H and 1,2-Ar migration products. Attempts to increase the reaction temperature led to lower yields and significant degradation. In dichloroethane, **5aa** was isolated in a higher yield (65%), however with a lower dr (2.9:1) (Table 1, entry 2). Additionally, the product **10** was also isolated in 22% yield. The use of  $[\text{Rh}(\text{COD})\text{Cl}]_2$  instead of  $[\text{Rh}(\text{nbd})\text{Cl}]_2$  was briefly examined, however no conversion was observed in heptane and a limited 44% conversion was obtained in dichloroethane (Table 1, entries 3 and 4).

The influence of the silylated protecting group was then studied. Pleasingly, under the previous reaction conditions ( $[\text{Rh}(\text{nbd})\text{Cl}]_2$  1 mol%, heptane, 5 equivalents of aniline at rt), the TBS group proved superior to the TBDPS group, providing the N–H insertion product **4aa** in 80% yield in only 3 h (dr 2.4:1, Table 1, entry 5).<sup>[12]</sup> Comparable yield and dr were obtained in dichloroethane, however a longer reaction time was required (Table 1, entry 6). In heptane, increasing the temperature to 40 °C afforded **4aa** in 84% yield and a 2.3:1 dr in only 15 min (Table 1, entry 7). The use of microwave activation slightly improved the diastereoselectivity (2.6:1 dr) while retaining similar yield (Table 1, entry 8). Raising the

temperature to 50 °C further shortened the reaction time up to 5 minutes (Table 1, entry 9). In this case, the N–H insertion product **4aa** was isolated in 93% yield, however the dr was slightly lower (2.1:1). Microwave activation for 15 min at 40 °C was therefore selected as a good compromise between yield and diastereoselectivity. In order to draw a comparison between Rh(I), Rh(II), Cu(I) and Cu(II) catalysts, additional assays were carried out.  $\text{Rh}_2(\text{OAc})_4$  resulted in a low 28% conversion (Table 1, entry 10).  $\text{Cu}(\text{OTf})_2$  in heptane led to **4aa** in 65% isolated yield, and a 2.3:1 dr (Table 1, entry 11) while the yield dropped significantly when the reaction was performed in dichloroethane (31% yield, Table 1, entry 12).

Finally, the use of  $\text{Cu}(\text{OTf})$ -toluene provided **4aa** in limited yields around 50% in heptane or dichloroethane (Table 1, entries 13 and 14). According to the previous study, the Rh(I) catalyst  $[\text{Rh}(\text{nbd})\text{Cl}]_2$  proved the most efficient and was therefore selected to investigate further the N–H insertion on O-protected  $\alpha$ -diazo- $\beta$ -aryl- $\beta$ -hydroxyesters **1**. When the silyl ether was replaced by an acetate (**6a**) or a benzoate (**8a**), no insertion product was formed (Table 1, entries 15 and 16). Enamine **10** was the only isolated product and no ester migration products were detected, unlike previous observations in the frame of

**Table 1.** Optimization of the N–H insertion reaction with aniline.<sup>[a]</sup>

Entry	Catalyst	Substrate (P =)	Solvent	Time	T °C	Product	Yield (%) <sup>[b,c]</sup>	dr <sup>[d]</sup>
1	$[\text{Rh}(\text{nbd})\text{Cl}]_2$	<b>2a</b> (TBDPS)	heptane	overnight	rt	<b>5aa</b>	50	3.4:1
2	$[\text{Rh}(\text{nbd})\text{Cl}]_2$	<b>2a</b> (TBDPS)	dichloroethane	7 h	rt	<b>5aa</b>	65	2.9:1
3	$[\text{Rh}(\text{COD})\text{Cl}]_2$	<b>2a</b> (TBDPS)	heptane	overnight	rt	<b>5aa</b>	–	–
4	$[\text{Rh}(\text{COD})\text{Cl}]_2$	<b>2a</b> (TBDPS)	dichloroethane	overnight	rt	<b>5aa</b>	44 <sup>[e]</sup>	3.4:1
5	$[\text{Rh}(\text{nbd})\text{Cl}]_2$	<b>1a</b> (TBS)	heptane	3 h	rt	<b>4aa</b>	80	2.4:1
6	$[\text{Rh}(\text{nbd})\text{Cl}]_2$	<b>1a</b> (TBS)	dichloroethane	overnight	rt	<b>4aa</b>	82	2.6:1
7	$[\text{Rh}(\text{nbd})\text{Cl}]_2$	<b>1a</b> (TBS)	heptane	15 min	40	<b>4aa</b>	84	2.3:1
8	$[\text{Rh}(\text{nbd})\text{Cl}]_2$	<b>1a</b> (TBS)	heptane	15 min	40 (mw)	<b>4aa</b>	84	2.6:1
9	$[\text{Rh}(\text{nbd})\text{Cl}]_2$	<b>1a</b> (TBS)	heptane	5 min	50 (mw)	<b>4aa</b>	93	2.1:1
10	$\text{Rh}_2(\text{OAc})_4$	<b>1a</b> (TBS)	heptane	15 min	40 (mw)	<b>4aa</b>	28 <sup>[e,f]</sup>	1.4:1
11	$\text{Cu}(\text{OTf})_2$	<b>1a</b> (TBS)	heptane	15 min	40 (mw)	<b>4aa</b>	65	2.3:1
12	$\text{Cu}(\text{OTf})_2$	<b>1a</b> (TBS)	dichloroethane	15 min	40 (mw)	<b>4aa</b>	31	1.5:1
13	$\text{Cu}(\text{OTf})$ -toluene	<b>1a</b> (TBS)	heptane	15 min	40 (mw)	<b>4aa</b>	41	1.4:1
14	$\text{Cu}(\text{OTf})$ -toluene	<b>1a</b> (TBS)	dichloroethane	15 min	40 (mw)	<b>4aa</b>	53	2.1:1
15	$[\text{Rh}(\text{nbd})\text{Cl}]_2$	<b>6a</b> (Ac)	heptane	15 min	40 (mw)	<b>10</b>	44 <sup>[g]</sup>	–
16	$[\text{Rh}(\text{nbd})\text{Cl}]_2$	<b>8a</b> (Bz)	heptane	15 min	40 (mw)	<b>10</b>	92	–

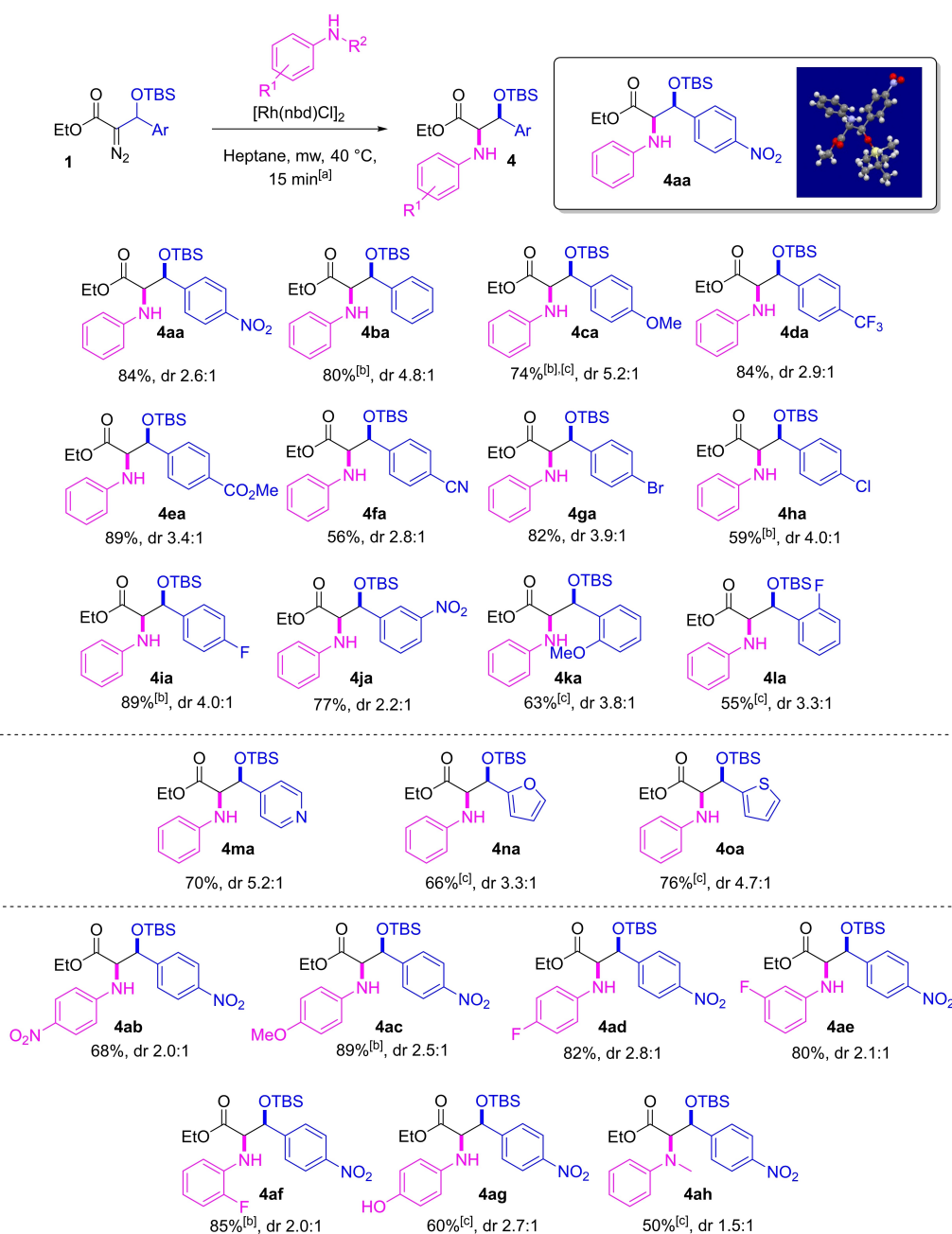
[a] Unless otherwise noted, all reactions were carried out at 0.26 mmol scale as follows: to a solution of the indicated substrate in the specified solvent (0.1 M) were added aniline (5 equiv) and the indicated catalyst (1 mol%). The reaction mixture was stirred at the indicated temperature for the indicated time. The reactions under microwave activation were conducted at 150 W for the time and the temperature indicated. [b] Isolated yield unless otherwise noted. [c] Complete conversion of the starting material unless otherwise noted. [d] Diastereoisomeric ratio estimated by <sup>1</sup>H NMR analysis of the crude product. [e] Conversion. [f] **4aa**/migration products ratio = 1:0.5. [g] Only 50% conversion observed.

O–H insertion.<sup>[10]</sup> In the end, *tert*-butyldimethylsilylether proved the most appropriate protecting group for the insertion of aniline and efficient reaction conditions were established as follows: [Rh(nbd)Cl]<sub>2</sub> (1 mol%), aniline (5 equiv), heptane, 40 °C, 15 min under microwave activation.

The influence of the alkyl ester residue was also briefly evaluated. The use of a *tert*-butyl ester instead of an ethyl ester under the optimized reaction conditions led to the corresponding N–H insertion product with a comparable yield (81%), albeit with a lower dr (1.4:1).<sup>[13]</sup>

The substrate scope of the N–H insertion with aniline was next explored, focusing first on the nature and the position of the aromatic substituent (Scheme 2). *O*-TBS-protected  $\alpha$ -diazo- $\beta$ -hydroxyesters **1 a–11** were synthesized by the classical aldol-type addition/protection two-step sequence.<sup>[9a,11]</sup>

The previously optimized reaction conditions were applied to these substrates, leading to the insertion products (**4 aa–4 la**) in moderate to excellent yields (55% to 89%). In sharp contrast to the O–H insertion reaction, the yields were not significantly affected by the nature of the substituent in *para* position.<sup>[10]</sup>



**Scheme 2.** Scope of the N–H insertion with anilines [a] Unless otherwise noted, all reactions were carried out at 0.26 mmol scale as follows: to a solution of the indicated substrate in heptane (0.1 M) in a microwave vial were added aniline (5 equiv) and [Rh(nbd)Cl]<sub>2</sub> (1 mol%). The reaction mixture was heated for 15 min at 40 °C under microwave irradiation at 150 W. Diastereoisomeric ratios estimated by <sup>1</sup>H NMR analysis of the crude product. [b] Reaction performed with 2 mol% of [Rh(nbd)Cl]<sub>2</sub>. [c] Yield estimated by <sup>1</sup>H NMR spectroscopy, after silica gel chromatography, from fractions containing pure N–H insertion product and fractions containing the N–H insertion product along with traces of migration products.

Indeed, comparable yields were observed for an electron-withdrawing substituent (NO<sub>2</sub>, CF<sub>3</sub>, CO<sub>2</sub>Me, CN and halogens), an electron-donating group (OMe) or an hydrogen. However, for substrates **4ba**, **4ca**, **4ha** and **4ia**, the use of 2 mol% of the catalyst was necessary to reach a full conversion. Furthermore, while a nitro group at the *para* or *meta* position afforded the insertion product in the same range of yield, an *o*-nitro substituent inhibited the N–H insertion. With methoxy and fluorine substituents at the *ortho* position, the corresponding N–H insertion products (**4ka** and **4la**) were isolated in acceptable yields, albeit lower than those obtained with *para*-substituted substrates, probably due to steric hindrance. Diastereomeric ratios were estimated between 2.2:1 (for **4ja**) and 5.2:1 (for **4ca**).

A higher diastereoselectivity was obtained with substrates displaying an electron-donating mesomeric effect such as a methoxy group or to a lesser extent halogens, or devoid of any substituents. The structure of the major diastereoisomer of the insertion product **4aa** was elucidated by X-ray diffraction.<sup>[14]</sup> Considering the strong analogy between the NMR spectra of the major and minor stereoisomers of all the insertion products **4**, a *syn* relationship was confidently assigned to each major diastereoisomer. A gram-scale reaction was also achieved from **1a** and aniline, delivering **4aa** in 93% isolated yield (dr 2.4:1), highlighting that the scale-up of the process was feasible. Additionally, three new substrates **1m**, **1n** and **1o** were synthesized in two steps from 4-pyridinecarboxaldehyde, furfural and thiophene-2-carboxaldehyde respectively, in order to investigate the feasibility of the N–H insertion on substrates bearing a heteroaromatic ring at the β-position (Scheme 2). Gratifyingly, products **4ma**, **4na** and **4oa** were isolated in good yields (66 to 76%) and moderate to good diastereoisomeric ratios (3.3:1 to 5.2:1).

The scope of the reaction was then evaluated on *p*-nitro substrate **1a**, using substituted anilines as the nucleophiles. *p*-nitro, *p*-methoxy and *p*-fluoro substituents were tolerated, leading to insertion products **4ab**, **4ac** and **4ad** respectively (Scheme 2). In comparison with aniline, similar yields were obtained for **4ac** (82%) and **4ad** (89%), while a slight decrease was observed for **4ab** (68%) resulting from *p*-nitroaniline. It is worth noting that *p*-methoxyaniline could be introduced as a protected NH<sub>2</sub> group.<sup>[15]</sup> Additionally, the position of the fluorine substituent on the aromatic ring did not affect the reaction efficiency. The N–H insertion using *p*-aminophenol furnished the N–H insertion product **4ag** in a 60% NMR estimated yield along with migration products. The corresponding O–H insertion product was not observed. This chemoselective carbene insertion into the N–H bond over the O–H bond is consistent with the higher nucleophilicity of the amine.<sup>[16,17]</sup> Noteworthy, the substituents on aniline did not significantly impact the diastereoselectivity of the reaction. Finally, the N–H insertion reaction was extended to *N*-methylaniline, affording **4ah** with a moderate 50% yield and a modest diastereoisomeric ratio (1.5:1).

The carbene insertion into the N–H bond of aliphatic amines was then investigated (Table 2). The previously optimized conditions were first applied to substrate **1a** in the

presence of five equivalents of benzylamine. However, the reaction did not take place at 40 °C under microwave activation (Table 2, entry 1). Increasing the temperature to 120 °C allowed the insertion product **4ai** to be isolated in 41% yield along with migration products (Table 2, entry 2). Conventional heating was also evaluated. Refluxing heptane led to the formation of product **4ai** in a 53% estimated NMR yield, accompanied with migration products, which proved difficult to separate (Table 2, entry 3). It is noteworthy that less degradation was observed using conventional heating rather than microwave activation. The use of THF under reflux overnight afforded **4ai** in 41% NMR yield with a good 4.7:1 dr (Table 2, entry 4). A similar yield was obtained in the presence of 2 mol% catalyst. Finally, conducting the reaction in refluxing dichloroethane for 5 h afforded the N–H insertion product in a 62% estimated NMR yield, with a 3.6:1 dr (Table 2, entry 5).<sup>[18]</sup>

We assessed then the feasibility of the N–H insertion with *n*-butylamine. No conversion was observed using the reaction conditions previously optimized for aniline (15 min, 40 °C under microwave activation; Table 2, entry 6). Increasing the temperature to 100 °C for 30 min furnished **4aj** in 24% NMR yield (Table 2, entry 7). Further attempts using microwave activation at higher temperature, for a longer reaction time and in the presence of 2 mol% of catalyst did not improve the yield. Although the reaction with butylamine produced a higher proportion of migration products compared to benzylamine, the N–H insertion product **4aj** was successfully isolated in 51% yield and a 4.3:1 dr, when the reaction was conducted in refluxing heptane (Table 2, entry 8). Finally, performing the reaction in refluxing dichloroethane resulted in a lower yield (36%) (Table 2, entry 9).

The moderate yields resulting from the carbene insertion into the N–H bond of benzylamine and butylamine could be explained by their higher nucleophilicity compared with aniline, enhancing their ability to coordinate to the catalyst and thus decreasing their efficiency. Indeed, N–H insertions involving aliphatic amines are less commonly reported in the literature compared to anilines.<sup>[4e,f,1]</sup>

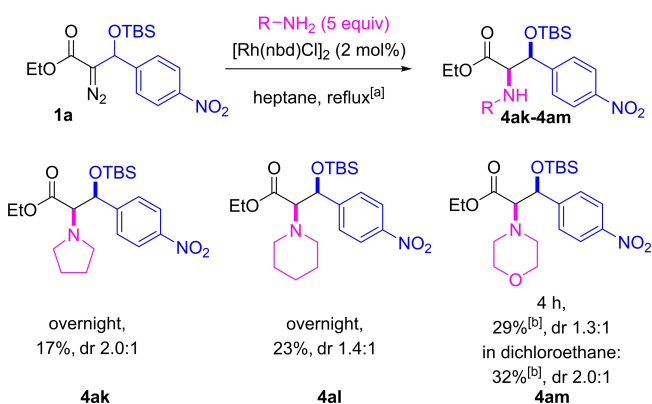
The reactivity of secondary aliphatic amines such as pyrrolidine, piperidine and morpholine was also evaluated. Disappointedly, the N–H insertion products **4ak**, **4al**, and **4am** were obtained with low isolated yields (17–29%) and dr (1.3:1–2.0:1) using the previously optimized conditions (heptane, reflux, overnight) in the presence of 1 or 2 mol% of catalyst (Scheme 3). Increasing the amount of the amine met with failure. Using dichloroethane instead of heptane led only to the formation of the migration products with piperidine and pyrrolidine, while **4am** was obtained in 32% isolated yield and a slightly better dr (2.0:1) with morpholine.

We focused then on the challenging metal carbene insertion into the N–H bond of ammonia, hampered by the strongly coordinating nature of ammonia to the metal catalyst. Rare examples have been reported,<sup>[19]</sup> using ammonia as solvated gas,<sup>[19a–c]</sup> ammonium salt<sup>[19a]</sup> or aqueous ammonia.<sup>[19d]</sup> No conversion was observed with substrate **1a**, even in the presence of 2 mol% of [Rh(nbd)Cl]<sub>2</sub> when ammonia was used as solvated gas in heptane, MTBE or dichloroethane (Table 3,

**Table 2.** Optimization of the insertion reaction conditions with benzylamine and butylamine.<sup>[a]</sup>

Entry	R-NH <sub>2</sub>	Solvent	Time	T °C	Ratio 4 a/migration	Yield (%) <sup>[b,c]</sup>	dr
1	Benzylamine	heptane	15 min	40 (mw)	–	0 <sup>[d]</sup>	–
2	Benzylamine	heptane	30 min	120 (mw)	1:0.4	41 <sup>[e]</sup>	3.0:1
3	Benzylamine	heptane	1 h	reflux	1:0.1	53	3.0:1
4	Benzylamine	THF	overnight	reflux	1:0.1	41 <sup>[f]</sup>	4.7:1
5	Benzylamine	dichloroethane	5 h	reflux	1:0.2	62 <sup>[g]</sup>	3.6:1
6	Butylamine	heptane	15 min	40 (mw)	–	0 <sup>[d]</sup>	–
7	Butylamine	heptane	30 min	100 (mw)	1:1	24 <sup>[f]</sup>	3.7:1
8	Butylamine	heptane	4 h	reflux	1:0.4	51 <sup>[e,f]</sup>	4.3:1
9	Butylamine	dichloroethane	2 h	reflux	1:0.6	36	3.3:1

[a] Unless otherwise noted, all reactions were carried out at 0.26 mmol scale as follows: to a solution of the indicated substrate **1a** in the indicated solvent (0.1 M) were added the aliphatic amine (5 equiv) and [Rh(nbd)Cl]<sub>2</sub> (1 mol%). The reaction mixture was stirred at the indicated temperature for the indicated time. The reactions under microwave activation were conducted at 150 W for the time and the temperature indicated. Diastereoisomeric ratios estimated by <sup>1</sup>H NMR analysis of the crude product. [b] Yields were estimated by <sup>1</sup>H NMR spectroscopy, after silica gel chromatography, from fractions containing pure N–H insertion product and fractions containing a mixture of migration products and N–H insertion product. [c] Unless otherwise noted, the reaction was complete. [d] No conversion was observed. [e] Isolated yield. [f] A similar result was obtained with 2 mol% of [Rh(nbd)Cl]<sub>2</sub>. [g] 50% isolated for one pure fraction.



**Scheme 3.** N–H insertion of secondary aliphatic amines [a] Unless otherwise noted, all reactions were carried out on 0.26 mmol scale as follows: to a solution of the substrate **1a** in heptane (0.1 M) were added the indicated amine (5 equiv) and [Rh(nbd)Cl]<sub>2</sub> (2 mol%). The reaction mixture was heated under reflux for the indicated time. Diastereoisomeric ratios estimated by <sup>1</sup>H NMR analysis of the crude product. [b] In the presence of 1 mol% of [Rh(nbd)Cl]<sub>2</sub>.

entries 1, 2 and 3). In addition, the absence of migration products strongly suggests catalyst deactivation by ammonia. The use of ammonium acetate (Table 3, entry 4) led to **4an** in only 5% isolated yield, along with the acetate insertion product **11** (74% isolated yield). We then turned our attention to aqueous ammonia. This reagent is safer and easier to handle than solvated ammonia, but might lead to potential competi-

tion between O–H and N–H insertion. In heptane, at room temperature no conversion was observed (Table 3, entry 5). At 60 °C, no chemoselectivity was observed between the N–H and the O–H insertion processes (**4an** vs **12**, Table 3, entry 6). To the contrary, in dichloroethane at 60 °C, in the presence of 1 mol% of [Rh(nbd)Cl]<sub>2</sub>, the N–H insertion product **4an** was isolated in 34% yield with an excellent dr (8.0:1) (Table 3, entry 7). However, unlike the results of Bi's team in the same solvent,<sup>[19d]</sup> the O–H insertion product **12** was also isolated in 13% yield. The influence of several parameters was then briefly studied. Increasing the amount of catalyst to 2 mol%, the temperature to reflux, or the amount of ammonia in water, favored the formation of O–H insertion and migration products over the expected N–H insertion product. Eventually, in the presence of ammonia in dioxane, the N–H insertion product **4an** was obtained in 14% yield along with 25% of O–H insertion product **12**. Beside, the use of BocNH<sub>2</sub>, which could provide **4an** after removal of the Boc protecting group,<sup>[20]</sup> didn't lead to the corresponding insertion product, neither in heptane nor in dichloroethane under reflux. In this case, only a mixture of migration products was isolated.

## Conclusions

In summary, we have successfully addressed the challenge of synthesizing  $\alpha$ -amino- $\beta$ -hydroxyesters by Rh(I)-catalyzed inser-

**Table 3.** Optimization of the N–H insertion with ammonia.<sup>[a]</sup>

Entry	Nitrogen source	Solvent	T °C	Time	Ratio 4 an : 12 : migration	Yield (%) (4 an : 12)	dr <sup>[b]</sup> (4 an)
1	NH <sub>3</sub> (gas)	heptane	rt	3 h	–	0 <sup>[c,d]</sup>	–
2	NH <sub>3</sub> (gas)	MTBE	rt	overnight	–	0 <sup>[c]</sup>	–
3	NH <sub>3</sub> (gas)	DCE	rt	overnight	–	0 <sup>[c]</sup>	–
4	NH <sub>4</sub> OAc	THF	reflux	1 h 30	–	5 <sup>[e]</sup>	–
5	NH <sub>3</sub> ·H <sub>2</sub> O	heptane	rt	overnight	–	0 <sup>[c]</sup>	–
6	NH <sub>3</sub> ·H <sub>2</sub> O	heptane	60	overnight	1:1: 0.3	29:28 <sup>[f]</sup>	5.6:1
7	NH <sub>3</sub> ·H <sub>2</sub> O	dichloroethane	60	3 h	1:0.4:0.6	34:13	8.0:1
8	NH <sub>3</sub> in dioxane (0.4 M)	– <sup>[g]</sup>	60	5 h 30	1:2.3:6.1	14:25 <sup>[h]</sup>	4.0:1

[a] All reactions were carried out on 0.26 mmol scale following protocols detailed in the SI. [b] Diastereoisomeric ratio estimated by <sup>1</sup>H NMR analysis of the crude product. [c] No conversion. [d] No conversion even in the presence of 2 mol % of catalyst. [e] Acetate insertion product **11** isolated in 74% yield. [f] Only 75% of conversion. [g] No additional solvent used. [h] 2 mol % catalyst.

tion of the carbene deriving from  $\alpha$ -diazo- $\beta$ -hydroxyesters into the N–H bond of various amines. Optimal conditions have been set up for the insertion reaction with both aromatic and aliphatic amines. For aromatic amines, the use of [Rh(nbd)Cl]<sub>2</sub> (1 or 2 mol %) along with 5 equivalents of the amine in heptane, under microwave activation, selectively induced the N–H insertion over the competing 1,2-H and 1,2-Ar migration. For aliphatic amines, thermal activation proved best suited in order to limit degradation, providing the N–H insertion product with moderate yields. Worthy of note is the formation of the N–H insertion product from aqueous ammonia with a high diastereoselectivity, albeit with a modest yield. Overall, 28 racemic N–H insertion products were synthesized in moderate to good yields for most of them and diastereoisomeric ratios up to 8.0:1, in favour of the *syn* diastereoisomer. This methodology offers a simple and efficient route to a variety of  $\alpha$ -amino- $\beta$ -hydroxyesters through the modulation of the aromatic substituent on the substrate and the nature of the amine. The synthetic interest of the method is enhanced by the fact that a wide range of enantioenriched  $\alpha$ -diazo- $\beta$ -hydroxyesters substrates could be conveniently prepared by enantioselective aldol-type addition.<sup>[21]</sup> The corresponding enantioenriched  $\alpha$ -amino- $\beta$ -hydroxyesters are thus expected to be easily generated through the N–H insertion described here, as previously reported in the frame of O–H insertion.

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## Conflict of Interests

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** diazocarbonyl compounds · N–H insertion · rhodium(I) catalyst ·  $\alpha$ -amino- $\beta$ -hydroxyesters · synthetic methods

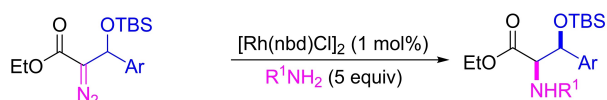
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## RESEARCH ARTICLE



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dr up to 8.0:1

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**Access to *Syn*  $\alpha$ -Amino- $\beta$ -Hydroxyesters by N–H Insertion on *O*-Protected  $\alpha$ -Diazo- $\beta$ -Hydroxyesters**



First N–H insertions were achieved on the challenging *O*-protected  $\alpha$ -diazo- $\beta$ -aryl- $\beta$ -hydroxyester scaffold, offering a simple and efficient access to a variety of  $\alpha$ -amino- $\beta$ -hydroxyesters through the modulation of the

aromatic substituent and the nature of the amine. Overall, 28 N–H insertion products were synthesized in moderate to good yields and diastereoisomeric ratios up to 8.0:1, in favour of the *syn* diastereoisomer.