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Regioselective addition of organomagnesium reagents to *N*-silyl activated nicotinic acid esters—a convenient method for the synthesis of 4,4-disubstituted 1,4-dihydronicotinates

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ABSTRACT

The addition of RMgX or R_2Mg to nicotinic acid esters, activated with triisopropylsilyl triflate, was investigated. The regioselectivity of this reaction, where 4-unsubstituted and 4-substituted pyridine derivatives were employed as starting materials, was examined. Depending on the structure of the organomagnesium reagent varying ratios of 1,2-, 1,4-, and 1,6-regioisomers were obtained but in any case the 1,4-addition products were clearly predominating. Desilylation of the isomeric pure addition products with LiOH provided stable 4,4-disubstituted dihydropyridines, which could be easily *N*-alkylated with alkylhalides in high yield. Furthermore, it was shown that the silyl protecting group of the obtained dihydropyridines can be easily replaced by an acyl group.

1. Introduction

In the last few decades a large number of different synthetic concepts for the formation of 1,4-dihydropyridines have been developed. Besides the Hantzsch[1] type synthesis, the different methods are mostly based on addition reactions to activated pyridine derivatives, i.e., pyridinium salts.[2] Depending on the nature of the nucleophile, these intermediates are attacked at the 2-, 4- or 6-position. Based on the HSAB-principle relatively hard nucleophiles like Grignard reagents are shown to form predominantly 1,2-dihydropyridines whereas lithium-dialkylcuprates[3] or organozinc reagents[5] preferentially add to the 4-position of the pyridine ring. In addition, the formation of 1,4-dihydropyridines is strongly influenced by substituents in the γ-position of the pyridine derivative. In this context Almqvist et al.[4] reported that the addition of organozinc derivatives in the presence of catalytic amounts of CuCN·2LiBr to 2- or 3-substituted *N*-acylpyridinium salts led selectively to 4-substituted 1,4-dihydropyridines. However, when 4-picoline was used as a substrate only the corresponding 1,2-dihydropyridine was formed. Merely a few methods are reported for the preparation of 4,4-disubstitued dihydropyridines. For example, acid catalyzed condensation of 3,3-disubstituted glutaraldehydes with either secondary amines or primary amides leads to 1,4-dihydropyridines exhibiting two substituents in 4-position.[5] A serious drawback of this method is the laborious and often complex synthesis of the required glutaraldehydes. Another method was described by Goldmann,[6] who synthesized a spirocyclic dihydropyridine derivative with a sulfoxy moiety, which he subjected to a reductive desulfination reaction to give upon a ring opening reaction a 4,4-disubstituted 1,4-dihydropyridine. Clayden et al. reported the formation of spirocyclic dihydropyridines with the spirocyclic center in 4-position by intramolecular cyclization involving anionic nucleophiles.[7] He further published the spirocyclization reaction of *N*-arylisonicotinamides induced by the generation of electrophilic pyridinium cation intermediates.[8] Another concrete example is the addition of benzyltin reagents to γ-substituted *N*-acylpyridinium salts. According to Yamaguchi and coworkers,[9] the alkylation of activated pyridines, which are substituted with an electron withdrawing group in 4-position, leads selectively to 4,4-disubstituted 1,4-dihydropyridines. In a recent study, we reported the regioselective formation of 4,4-disubstituted 1,4-dihydropyridines, by trapping reactions of *N*-silylpyridinium ions with nucleophiles.[10] It had been found that quarternisation of γ-substituted pyridine derivatives with triisopropylsilyl triflate followed by the addition of an organomagnesium reagent at ambient temperature led to the formation of 4,4-disubstituted dihydropyridines with high regiocontrol. Herein we report on an extension of the application of *N*-silylpyridinium ion chemistry, the direct synthesis of 4,4-disubstituted 1,4-dihydronicotinic acid derivatives.

2. Results and discussion

The first series of experiments was performed with ethyl nicotinate (**1**). Though our study primarily aimed at the synthesis of

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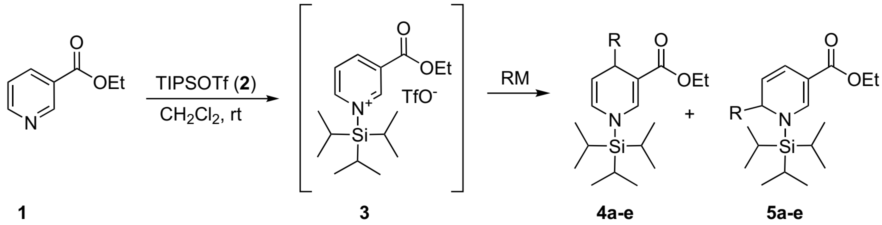
4,4-disubstituted 1,4-dihydropyridines, compound **1** seemed interesting as a starting point, as trapping reactions of this pyridine derivative **1**, activated with triisopropylsilyl triflate (**2**), would provide insight in the reactivity and regioselectivity of the parent system. Grignard reagents like dialkyl- and diarylmagnesium derivatives had been successfully employed in our earlier study,[10] mentioned above. Accordingly, these reagents were employed here as well. All trapping reactions were carried out in the same way. In brief, 1 equiv of **1** was treated with an equimolar amount of silyl triflate **2** at room temperature (for 15 min in CH_2Cl_2) followed by 2 equiv of the respective organomagnesium reagent at −75 °C. The reaction mixture was allowed to react for 3 h before it was quenched by addition of phosphate buffer and extracted with CH_2Cl_2 to give a crude product, which was characterized by ^{1}H NMR spectroscopy prior to its purification by column chromatography. According to ^{1}H NMR analysis in all cases the 1,4-dihydropyridine derivatives **4a**–**e** resulting from a 1,4-addition reaction had formed alone or in combination with the 1,6-addition products **5a**–**e**, but with the amount of the latter, when present, always being distinctly lower than those of the former compound. But in no case the regioisomeric 1,2-addition products were found in the crude product (Table 1).

In case of the trapping reaction of **3** with MeMgBr according to ^{1}H NMR analysis only 21% of the regioisomeric addition products **4a** and **5a** was present in the crude product but 79% of the starting material **1** (Table 1, entry 1). Also the regioselectivity of the reaction reflected by the ratio of the regioisomers **4a** and **5a** amounting to 80/20 was not fully pleasing. Column chromatography yielded finally only 7% of the major isomer, the 1,4-addition product **4a**. In contrast, when Me_2Mg was employed, both the product/educt ratio ((**4a**+**5a**)/**1**=52/48) and the regioselectivity were significantly improved (**4a**/**5a**=92/8; Table 1, entry 2). After column chromatography **4a** was isolated in a 41% yield. Trapping the intermediate **3** with *iso*-propylmagnesium chloride resulted in the exclusive formation of **4b** (**4b**/**5b**=100/0), which was isolated in 45% yield (Table 1, entry 3). When *i*-Pr_2Mg was used instead, the product/educt ratio ((**4b**+**5b**)/**1**) rose from 71/29 to 96/4 (Table 1, compare entry 3 to entry 4). But this time also 5% of the corresponding 1,6-dihydropyridine **5b** was present in the crude product. As observed for related compounds the 1,6-dihydropyridine derivative **5b** was completely oxidized during workup and the subsequent column chromatography. Accordingly, it did not interfere with the isolation of the major isomer **4b**, which was finally obtained in a yield of 60% (Table 1, entry 4).

Further trapping reactions with *t*-BuMgCl and *t*-Bu_2Mg as nucleophiles proceeded both with high regioselectivity (**4c**/**5c**=98/2; Table 1, entries 5 and 6). Again the product/educt ratio and the yield of the 1,4-addition product **4c** were higher when the diorganomagnesium derivative, i.e., *t*-Bu_2Mg ((**4c**+**5c**)/**1**=95/5) instead of *t*-BuMgCl ((**4c**+**5c**)/**1**=68/32) was used. When benzyl- or phenylmagnesium reagents were employed the nucleophilic attack occurred exclusively at the 4-position of the *N*-silylpyridinium salt **3** (**4d**/**5d**=100/0, **4e**/**5e**=100/0; Table 1, entries 7–10). Bn_2Mg and Ph_2Mg both affected a higher product/educt ratio ((**4d**+**5d**)/**1**=92/8, (**4e**+**5e**)/**1**=85/15; Table 1, entries 8 and 10) as compared to the reaction with BnMgCl ((**4d**+**5d**)/**1**=60/40; Table 1, entry 7) and PhMgBr ((**4e**+**5e**)/**1**=65/35; Table 1, entry 9), respectively. Also the yields significantly increased when the respective diorganomagnesium derivatives instead of the Grignard reagents were used. Thus, whereas the addition of BnMgCl provided 52% of the desired 1,4-dihydropyridine derivative **4d**, 79% of this product was isolated when Bn_2Mg was employed (Table 1, entries 7 and 8). Using Ph_2Mg instead of PhMgCl as a trapping reagent increased the yield of **4e** from 55% to 70% (Table 1, entries 9 and 10).

Further experiments were conducted with 4-phenylsubstituted nicotinic acid derivative **6**. Compound **6** was picked for two reasons. First of all, we wanted to gain insight how addition reactions to nicotinic acid ester **1** are altered in the presence of a 4-substituent. In addition, the 4-phenylsubstituted nicotinic acid **6** differs from a starting compound used in an earlier study for analogous reactions only by the additional ester function.[10] Accordingly, results from experiments with **6**, when compared with those from the aforementioned study, should also allow to uncover the influence of an ester group in 3-position on the outcome of the addition reactions. Finally, we were interested to establish a synthetic access to 4,4-disubstituted dihydropyridines provided with an ester function.

Table 1
Addition[a] of organomagnesium reagents to *N*-silylpyridinium ion **3**



Entry	Nucleophile (RM)	Product/educt ratio[b]		1,4-Dihydropyridine	
		4/**5**	(**4**+**5**)/**1**	Product no.	Yield[c] (%)
1	MeMgBr	80/20	21/79	**4a**	7
2	Me_2Mg	92/8	52/48	**4a**	41
3	*i*-PrMgCl	100/0	71/29	**4b**	45
4	*i*-Pr_2Mg	95/5	96/4	**4b**	60
5	*t*-BuMgCl	98/2	68/32	**4c**	30
6	*t*-Bu_2Mg	98/2	95/5	**4c**	52
7	BnMgCl	100/0	60/40	**4d**	52
8	Bn_2Mg	100/0	92/8	**4d**	79
9	PhMgBr	100/0	65/35	**4e**	55
10	Ph_2Mg	100/0	85/15	**4e**	70

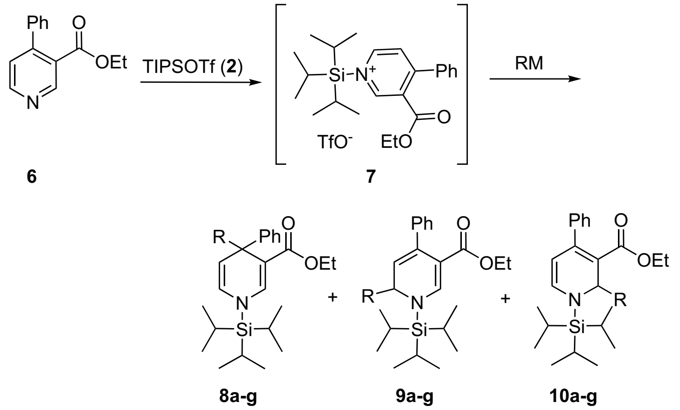
[a] Compound **1** was dissolved in CH_2Cl_2 and treated with 1 equiv of silyl triflate **2** at room temperature. After 15 min the solution was cooled to −75 °C and 2.0 equiv of the corresponding organomagnesium reagent was added. After 3 h work up was performed by addition of phosphate buffer (pH 7, c=1.0 M) and extraction of the aqueous layer with CH_2Cl_2.

[b] According to ^{1}H NMR of the crude product.

[c] Isolated yield.

Treatment of *N*-silylpyridinium salt **7** with methylmagnesium compounds led to complex reaction mixtures so that neither a product could be identified nor isolated (Table 2, entries 1 and 2). Satisfying results were achieved when ethylmagnesium reagents were employed (Table 2, entries 3 and 4). As observed for **3,** the use of the diethylmagnesium compound led to an almost complete consumption of the starting material ((**8b**+**9b**+**10b**)/**6**=98/2; Table 1, entry 4), whereas in case of the reaction with the Grignard reagent significant amounts of the starting material **6** remained left ((**8b**+**9b**+**10b**)/**6**=58/42; Table 1, entry 3). Thereby the reagents had added preferentially to the C-4-position of **7**, but to a significant extent also the 1,2- and 1,6-addition products **9b** and **10b** had been formed the ratio of the regioisomers amounting to 61/35/4 (**8b**/**9b**/**10b**) for EtMgCl and to 64/22/14 (**8b**/**9b**/**10b**) for Et$_2$Mg. For the 4,4-disubstituted regioisomer **8b** the yields amounted to 20% and 55%, respectively (Table 2, entries 3 and 4). In contrast the 1,2- and 1,6-adducts **9b** and **10b**, that had formed only in minor amounts, could not be isolated. According to ^{1}H NMR analysis, the regioselectivity of the alkylation of activated **6** with *i*-PrMgCl or *i*-Pr$_2$Mg was highly satisfying amounting to 99/1/0 and 100/0/0, respectively (**8c**/**9c**/**10c**; Table 2, entries 8 and 9). In line with the product/educt ratio that was most pleasing for the diorganomagnesium compound ((**8c**+**9c**+**10c**)/**6**=97/3) the 4,4-disubstituted dihydropyridine **8c** was isolated in 63% and 91% yields, respectively (Table 2, entries 8 and 9). When sterical demanding *t*-BuMgCl was employed the regioselectivity was also quite satisfactory (**8d**/**9d**/**10d**=94/6/0; Table 2, entry 10). According to ^{1}H NMR analysis a 1,6-addition occurred only in 6%. Column chromatography provided the 1,4-addition **8d** in a 47% yield. Changing the nucleophile from *t*-BuMgCl to *t*-Bu$_2$Mg led to a somewhat lower C-4-selectivity of 86% (**8d**/**9d**/**10d**=86/14/0; Table

Table 2
Addition[a] of various organomagnesium reagents to *N*-triisopropylsilylpyridinium ions **7**



Entry	Nucleophile (RM)	Cu(I)-salt (15 mol %)	Product/educt ratio[b]		1,4-Dihydropyridine	
			8/**9**/**10**	(**8**+**9**+**10**)/**6**	Product no.	Yield[c] (%)
1	MeMgBr	—	—[d]	—	**8a**	[e]
2	Me$_2$Mg	—	—[d]	—	**8a**	[e]
3	EtMgCl	—	61/35/4	58/42	**8b**	20
4	Et$_2$Mg	—	64/22/14	98/2	**8b**	55
5	EtMgCl	CuBr·Me$_2$S	97/3/0	33/67	**8b**	15
6	EtMgCl	CuCN	99/1/0	70/30	**8b**	25
7	Et$_2$Mg	CuBr·Me$_2$S	76/14/1	45/55	**8b**	23
8	*i*PrMgCl	—	99/1/0	70/30	**8c**	63
9	*i*Pr$_2$Mg	—	100/0/0	97/3	**8c**	91
10	*t*BuMgCl	—	94/6/0	40/60	**8d**	47
11	*t*Bu$_2$Mg	—	86/14/0	89/11	**8d**/**9d**	56/5[f]
12	AllMgCl	—	—[d]	—	**8e**	[e]
13	All$_2$Mg	—	—[d]	—	**8e**	[e]
14	BnMgCl	—	72/28/0	69/31	**8f**/**9f**	38/7
15	Bn$_2$Mg	—	50/49/1	98/2	**8f**/**9f**	45/24
16	BnMgCl	CuBr·Me$_2$S	95/5/0	95/5	**8f**	41
17	BnMgCl	Me$_2$S[g]	85/15/0	46/54	**8f**	40
18	Bn$_2$Mg	CuBr·Me$_2$S	62/38/0	66/34	**8f**	28
19	BnMgCl	CuCN	99/1/0	95/5	**8f**	38
20	BnMgCl	CuCN[h]	59/41/0	95/5	**8f**/**9f**	31/25
21	BnMgCl	Bu$_4$N$^+$I$^-$	90/10/0	60/40	**8f**	38
22	BnMgCl	Bu$_4$N$^+$Br$^-$	92/8/0	46/54	**8f**	39
23	BnMgCl	Bu$_4$N$^+$Cl$^-$	85/15/0	43/57	**8f**	44
24	PhMgCl	—	90/10/0	13/87	**8g**	7
25	Ph$_2$Mg	—	98/2/0	63/37	**8g**	46

[a] Compound **6** was dissolved in CH$_2$Cl$_2$ and treated with 1 equiv of silyl triflate **2** at room temperature. After 15 min the solution was cooled to −75 °C and 2.0 equiv of the corresponding organomagnesium reagent was added. Work up was performed by addition of phosphate buffer (pH 7, c=1.0 M) and extraction of the aqueous layer with CH$_2$Cl$_2$.

[b] According to ^{1}H NMR of the crude product.

[c] Isolated yield.

[d] Not determinable.

[e] Not isolated.

[f] Contaminated with 9% **8d**.

[g] Addition of 20 mol %.

[h] 1.0 equiv.

2, entry 11) but again to a higher product/educt ratio ((**8d**+**9d**+**10d**)/**6**=89/11 and a higher yield of **8d** (56%). The corresponding 1,6-addition product **9d** was isolated in 5% yield, but according to ^{1}H NMR analysis, it was still contaminated with 9% of regioisomer **8d**. Treatment of *N*-silylpyridinium salt **7** with allylmagnesium nucleophiles led similar to the reactions with methylmagnesium reagents to complex product mixtures (Table 2, entries 12 and 13). According to ^{1}H NMR analysis, the addition of BnMgCl to **7** yielded a product with a product ratio of **8f**/**9f**/**10f**=72/28/0 in favor of the 1,4-addition product **8f**. From this mixture **8f** could be isolated in a 38% yield and, in addition, the corresponding 1,6-dihydropyridine **9f**, in 7% yield (Table 2, entry 14). Based on the results obtained with ethyl- and isopropylmagnesium reagents (Table 2, entries 3, 4 and 8, 9), it was expected that the application of Bn$_2$Mg as a nucleophile (Table 2, entry 15) would improve both, the regioselectivity and the yield for this reaction. However, the ratio of the 1,4- and 1,6-addition products was extremely low and amounted approximately to 1:1 (**8f**/**9f**/**10f**=50/49/1; Table 2, entry 15). According to ^{1}H NMR analysis, this time also the corresponding 1,2-addition product **10f** was present in the reaction mixture, though in very low amount (1%). Column chromatography provided the addition products **8f** and **9f** in 45% and 24% yields, respectively. When PhMgCl was used as a nucleophile the 1,4-adduct **8g** prevailed in a 90:10 ratio over the 1,6-dihydropyridine **9g** (**8g**/**9g**/**10g**=90/10/0; Table 2, entry 24). As obvious from the product/educt ratio ((**8g**+**9g**+**10g**)/**6**=13/87), only low amounts of the addition products had formed. Accordingly, only 7% of the major regioisomer **8g** could be isolated. More satisfying results were obtained when the corresponding diphenylmagnesium organyl was employed. In line with the distinctly improved product/educt ratio ((**8g**+**9g**+**10g**)/**6**=63/37), the yield of **8g** rose to 46%. Besides also the regioselectivity had improved slightly (**8g**/**9g**/**10g**=98/2/0, Table 2, entry 25).

For the trapping reactions of triisopropylsilyl activated 4-phenylpyridine Braeckow and Wanner[10] had found that the yields for the 1,4-addition products are significantly higher when diorganomagnesium derivatives instead of the Grignard reagents are used. This phenomenon was observed here as well. But the regioselectivities reported by Braeckow et al. for alkylation reactions of triisopropylsilyl activated 4-phenylpyridine were in some cases significantly different from those obtained for the corresponding reactions with triisopropylsilyl activated nicotinate **7** in this study. Whereas *i*-Pr$_2$Mg and *t*-Bu$_2$Mg (Table 2, entries 9 and 11) as trapping reagents showed, independent of the pyridine derivative, a very high C-4-selectivity, the reactions carried out with the other diorganomagnesium compounds led to a different outcome. Et$_2$Mg and Bn$_2$Mg added predominantly at the C-4 position when activated 4-phenyl pyridine served as a substrate.

In contrast, trapping of activated **6** with Et$_2$Mg or Bn$_2$Mg (Table 2, entries 4 and 15) resulted in a mixture of regioisomers in which the proportion of the C-4 adducts **8b** and **8f** amounted only to 64% (**8b**/**9b**/**10b**=64/22/14) and 50% (**8f**/**9f**/**10f**=50/49/1), respectively. Furthermore, for reactions of the parent system, the triisopropylsilyl activated 4-phenylpyridine with Me$_2$Mg, Allyl$_2$Mg and Ph$_2$Mg as nucleophiles a predominant attack at the C-2 position has been reported. In contrast, when **7** was reacted with Me$_2$Mg and Allyl$_2$Mg (Table 2, entries 2 and 13), respectively, only complex mixtures of products were obtained and Ph$_2$Mg added almost exclusively to the 4-position of **7** providing the 4,4-disubstituted dihydropyridine **8g** (Table 2, entry 25).

Prompted by the disappointing results obtained with benzyl- and ethylmagnesium reagents as nucleophiles (Table 2, entries 3, 4 and 14, 15), we performed some additional experiments with the aim to optimize the 1,4-regioselectivity of these reactions. In case of 4-unsubstituted pyridine derivatives it is well documented that when catalytic amounts of Cu(I)-salts are present the addition of organomagnesium compounds to *N*-acylpyridinium salts proceeds almost exclusively to the 4-position.[11] Thus, it seemed worthwhile to study the influence of different Cu(I)-salts on the reaction of organomagnesium reagents with 4-substituted *N*-silylpyridinium salts. The respective alkylation reactions were thereby conducted under the same conditions as those described above, but with the corresponding Cu(I)-salt being present (Table 2, entries 5–7 and 16–20).

The first experiment performed with ethylmagnesium chloride in the presence of 15 mol % CuBr$\cdot$Me$_2$S proceeded with a significantly improved regioselectivity. As compared to the uncatalyzed version, the proportion of the C-4 adduct **8b** rose from 61% (**8b**/**9b**/**10b**=61/35/4) to 97% (**8b**/**9b**/**10b**=97/3/0). Unfortunately, the product/educt ratio was distinctly lower ((**8b**/**9b**/**10b**)/**6**=33/67, instead of 58/42; Table 2, compare entry 5 with entry 3) and 4,4-disubstituted addition product **8b** was only isolated in a 15% yield. When EtMgCl was replaced by Et$_2$Mg, keeping everything else the same, the regioselectivity became lower (**8b**/**9b**/**10b**=76/14/1; Table 2, entry 7). But when EtMgCl was combined with 15 mol % CuCN instead of 15 mol % CuBr$\cdot$Me$_2$S the nucleophile added almost exclusively to the 4-position of **7** the ratio of the regioisomers amounting to **8b**/**9b**/**10b**=99/1/0 (Table 2, entry 6). Unfortunately, in this case neither the product/educt ratio nor the isolated yield of **8b** was satisfying ((**8b**+**9b**+**10b**)/**6**=70/30, yield 25%, Table 2, entry 6).

Further experiments were performed with organomagnesium derivatives with a benzyl residue (Table 2, entries 16–20). The alkylation reaction with benzylmagnesium chloride in the presence of 15 mol % CuBr$\cdot$Me$_2$S showed, according to ^{1}H NMR analysis, a significant improvement of the C-4-selectivity compared to the reaction without any additive (Table 2, compare entries 14 and 16). While the reaction without any additive had given rise to a mediocre 72% proportion of the desired 1,4-dihydropyridine **8f** (**8f**/**9f**/**10f**=72/28/0, Table 2, entry 14), the presence of catalytic amounts of CuBr$\cdot$Me$_2$S led to a satisfying 95% yield (**8f**/**9f**/**10f**=95/5/0, Table 2, entry 16). Thereby, the yield of **8f** remained quite unaffected (41%, Table 2, compare entries 14 and 16). When Bn$_2$Mg instead of the benzyl Grignard reagent was used, the regioselectivity only slightly rose (**8f**/**9f**/**10f**=62/38/0, Table 2, entry 18), and the yield sank (28%, Table 2, entry 18) as compared to the uncatalyzed reaction, similar to what had been observed for the corresponding reactions with ethyl magnesium derivatives (Table 2, compare entries 15 and 18 and entries 4 and 7).

To determine whether Me$_2$S introduced with the copper catalyst might have affected the regiochemistry, an additional experiment was performed with 20 mol % Me$_2$S (Table 2, entry 17). It is conceivable that Me$_2$S coordinates to the organometallic compound and thus modifies its electronic properties or that it affects the position of the equilibrium between the free pyridine **6** and the *N*-silylpyridinium salt **7**. In fact, the proportion of the 4-addition product **8f** rose significantly when 20 mol % Me$_2$S was employed (**8f**/**9f**/**10f**=85/15/0; Table 2, entry 17, compare with entry 14). After column chromatography 1,4-dihydropyridine **8f** was isolated in 40% yield. Thus, already the addition of Me$_2$S itself improves the regioselectivity of the Grignard addition reaction (Table 2, entry 17) but obviously less than it is the case with CuBr$\cdot$Me$_2$S (Table 2, entry 16). When another Cu(I)-salt, i.e., 15 mol % CuCN was employed (Table 2, entry 19) the C-4-selectivity, which had already been very high with CuBr$\cdot$Me$_2$S (Table 2, entry 16), was further improved. According to ^{1}H NMR analysis the ratio between the 1,4- and the 1,6-adduct now amounted to 99:1 (**8f**/**9f**) with no 1,2-isomer **10f** being present (**8f**/**9f**/**10f**=99/1/0; Table 2, entry 19). Also the product/educt ratio was quite pleasing ((**8f**+**9f**+**10f**)/**6**=95/5; Table 2, entry 19), and compound **8f** was isolated in a 38% yield (Table 2, entry 19).

As a consequent extension of the experiment employing catalytic amounts of CuCN an addition reaction with 2 equiv of a preformed ‘higher order cyanocuprate’ was performed. Though the product/educt ratio remained unchanged ((**8f**+**9f**+**10f**)/**6**=95/5; Table 2, entry 20), the regioselectivity declined dramatically, to 59/

41/0 (**8f**/**9f**/**10f**; Table 2, entry 20). After column chromatography 31% of the 1,4-dihydropyridine **8f**, and 25% of the corresponding 1,6-regioisomer **9f** was obtained.

It is well known that the reactivity of RMgX or R_2Mg is modified by addition of different salts like RO^-M^+ or $Alk_4N^+X^-$.[12] According to Pajerski et al. Grignard reagents **11** when combined with tetraalkylammonium salts **12** may form organomagnesiate salts **13**.[12c]

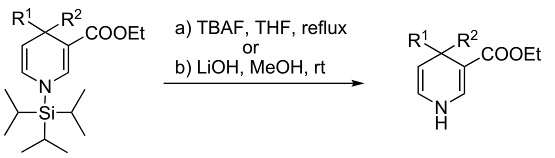
$$\underset{\mathbf{11}}{\mathrm{RMgX}} + \underset{\mathbf{12}}{\mathrm{Bu_4N^+\,X^-}} \longrightarrow \underset{\mathbf{13}}{\mathrm{RMgX_2^-\,Bu_4N^+}} \qquad (1)$$

Therefore, further addition reactions of benzylmagnesium chloride to *N*-silylpyridinium **7** were undertaken, but this time in the presence of various tetrabutylammonium halides. However, only catalytic amounts of these salts were employed, as additional halide ions, due to their higher nucleophilicity compared to triflate ions, run the risk of shifting the equilibrium between the *N*-silylpyridinium salt **7** and the free pyridine **6** toward the latter.[10]

When 10 mol % tetrabutylammonium iodide or bromide was added, the regioselectivity rose significantly in favor of the C-4 addition product **8f**. Whereas in the absence of any additive the ratio of regioisomers had been 72/28/0 (**8f**/**9f**/**10f**, Table 2, entry 14), it amounted to 90/10/0 and 92/8/0 (**8f**/**9f**/**10f**) when tetrabutylammonium iodide and bromide, respectively, were present (Table 2, entries 21 and 22). But the yields for the 1,4-dihydropyridine **8f** did not change significantly (38–39%, Table 2, compare entries 14, 21 and 22). In case of tetrabutylammonium chloride as additive the increase in regioselectivity was far less pronounced (**8f**/**9f**/**10f**=85/15/0; Table 2, entry 23). According to the above data the addition of tetrabutylammonium halides leads to an improved regioselectivity in the addition of Grignard reagents to *N*-silylpyridinium salt **7**, which points toward the formation of organomagnesium salts **13** as reactive intermediates.

Addition reactions of organomagnesium derivatives to *N*-silylpyridinium ions not only provide an efficient access to *N*-sily-4,4-dihydropyridines but also to the corresponding saturated piperidine derivatives, easily accessible by reduction with $NaBH_4$ as demonstrated earlier.[10] To further explore the versatility of the *N*-silyl-1,4-dihydropyridines as synthetic building blocks the removal of the *N*-silyl group to provide the parent compounds was studied. As a representative example dihydropyridine **8c** was used. At first fluoride based reagents were tested as they are most common to effect desilylation reactions. But despite extensive experimentation employing tetrabutylammonium fluoride on silica gel as a fluoride source in THF at various temperatures (up to 50 °C and for 20 h) no more than 27% of the desilylated product **15** was obtained.

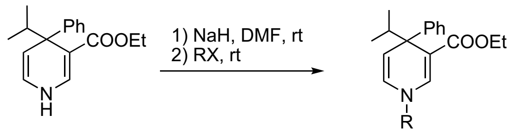
Finally, LiOH in MeOH was found to efficiently effect the desired desilylation reaction of **8c**. Applying 1.6 equiv of LiOH in MeOH at room temperature for 20 h, conditions found optimal for this reaction, afforded **15** in 91% yield. To expand the desilylation reaction on another substrate a 4,4-diethylsubstituted dihydropyridine **14** was synthesized from ethyl 4-ethylpyridine-3-carboxylate following the general procedure for the trapping reactions of **7**. Like **8c** also the 4,4-disubstituted dihydropyridine **14** could be deprotected with LiOH in MeOH providing **16** in 86% yield (Scheme 1).



8c R^1 = Ph, R^2 = *i*Pr
14 R^1 = R^2 = Et

15 (a: 27%, b: 91%)
16 (b: 86%)

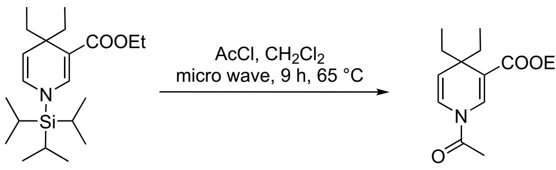
Scheme 1. Deprotection of the nitrogen moiety.



15

17 R = Me (90%)
18 R = Bn (85%)
19 R = Allyl (83%)

Scheme 2. N-Alkylation of **19**.



14

20 (74%)

Scheme 3. Reaction of **14** with acetyl chloride.

The deprotected dihydropyridine derivatives provide easy access to their *N*-alkyl substituted counterparts as exemplified by the conversion of **15** (Scheme 2). Deprotonation with NaH in DMF to generate the anion of **15** and subsequent treatment with alkyl halides, methyl iodide, allyl and benzyl bromide, provided the corresponding alkylated products **17**–**19** in good yields (83–90%).

Further experiments revealed that the *N*-silyl-1,4-dihydropyridine derivatives can be easily transformed to the corresponding *N*-acyl substituted compounds by reacting them with acid chlorides. When **14**, selected as an example, was heated together with acetyl chloride under microwave conditions the *N*-acyldihydropyridine **20** was formed, which was isolated in 74% yield (Scheme 3).

3. Conclusion

To sum up, it has been shown, that the addition of various organomagnesium reagents to γ-unsubstituted *N*-silyl activated ethyl nicotinates leads almost selectively to 4,4-disubstituted 1,4-dihydropyridines. When 4-substituted nicotinic acid derivatives were employed as starting materials, the regiochemistry is strongly influenced by the organomagnesium reagent. While sterically demanding magnesium nucleophiles preferentially add at the 4-position of the 4-substituted pyridine moiety, benzyl- and ethylmagnesium compounds showed a comparatively high C-6-selectivity. Employing catalytic amounts of different additives, e.g., Cu(I)-salts or tetrabutylammonium halides led to an improved 1,4-regioselectivity. The 4,4-disubstituted dihydropyridines obtained were easily deprotected in high yields when treated with lithium hydroxide at ambient temperature. N-Alkylation of these products led to *N*-alkyl-1,4-dihydropyridines. Finally, the silyl group of the dihydropyridines can be easily replaced by an acyl group upon treatment with an acid chloride.

4. Experimental

4.1. General experimental

All reactions were performed using flame-dried glassware under argon atmosphere. All solvents were freshly dried using standard procedures.[1] ^1H and ^{13}C NMR spectra were recorded on a JNMR-GX 400 (Joel, 400 MHz) or a JNMR-GX 500 (Joel, 500 MHz) spectrometer, respectively. Infrared spectra were obtained on a Perkin Elmer Model 1600 FT-IR spectrometer. Microanalytical data for carbon, hydrogen, and nitrogen were determined on a Heraeus Rapid Analyser and on an Elementar Vario EL Analyser. Flash chromatography was performed with 40–63 mesh silica gel or 50–150 mesh aluminum oxide (neutral Brockmann activity III). Preparative HPLC was performed with a Hibar® LiChrosorb® Si 60 column (5 μm, 25×250 nm). Ethyl-4-phenylpyridin-3-carboxylat **6** was synthesized according a literature procedure.[1]

4.2. General procedure for the preparation of dialkylmagnesium reagents[1] (GP1)

Commercial available alkylmagnesium halide solution in Et_2O was diluted with Et_2O to yield 1.0 M stock solutions. 1,4-Dioxane (1.1 equiv) was added slowly to the mechanically stirred Grignard solution at room temperature. The heterogeneous solution was stirred over night to complete precipitation. The resulting suspension was centrifuged to yield clear R_2Mg solutions, which were stored under nitrogen at 4 °C.

4.3. General procedure for the addition of organomagnesium reagents to *N*-silylpyridinium salts (GP2)

The corresponding nicotinic acid derivate was dissolved in CH_2Cl_2 and treated with 1.0 equiv of triisopropylsilyl triflate **2** at room temperature. After 15 min the clear solution was cooled to −75 °C, followed by dropwise addition of the magnesium reagent. The resulting yellow to red colored mixtures were stirred at −75 °C for 3 h. Work up was performed by addition of phosphate buffer (pH 7, *c*=1.0 M) and extraction of the aqueous layer with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography on silica gel yielded the final products, which were stored under argon atmosphere at −20 °C.

4.4. General procedure for desilylation (GP3)

The corresponding *N*-silylprotected dihydropyridine in methanol was stirred together with LiOH for the time given. Subsequent removal of the solvent in vacuo and purification of the raw material by flash chromatography on silica gel yielded the desired dihydropyridine.

4.5. General procedure for N-alkylation of 15 (GP4)

To a suspension of NaH (2.0 equiv) in DMF was added a solution of **15** at room temperature followed by stirring for 15 min. To this obtained turbid solution a 1.5 fold excess of the corresponding alkyl halide was added. After the time given, the reaction was quenched with water. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The raw material was purified by flash chromatography on silica gel to yield the desired product.

4.6. Ethyl 4-methyl-1-triisopropylsilyl-1,4-dihydropyridine-3-carboxylate 4a

Procedure *A*: According to GP2 from **1** (50 mg, 0.33 mmol), **2** (101 mg, 0.331 mmol, 91.0 μL) in CH_2Cl_2 (4 mL) and MeMgCl (2.0 M in Et_2O, 49.6 mg, 0.662 mmol, 331 μL). Work up was performed with phosphate buffer (4 mL) and triple extraction with CH_2Cl_2 (20 mL each). Purification by flash chromatograpy on Al_2O_3 (*n*-pentane/EtOAc=90/10).

Yield 7.5 mg (7%), yellow oil. TLC R_f=0.55 (*n*-heptane/Et_2O=50/50, SiO_2). ^{1}H NMR ($CDCl_3$) δ=1.08–1.10 (m, 3H, CH_3), 1.10 (d, *J*=7.2 Hz, 9H, CH(C*H*$_3$)$_2$), 1.11 (d, *J*=7.2 Hz, 9H, CH(C*H*$_3$)$_2$), 1.26 (t, *J*=7.2 Hz, 3H, CH_2C*H*$_3$), 1.22–1.36 (m, 3H, C*H*(CH_3)$_2$), 3.30–3.36 (m, 1H, CH=CHC*H*), 4.09–4.23 (m, 2H, C*H*$_2$$CH_3$), 4.83 (dd, *J*=8.0/4.7 Hz, 1H, NCH=C*H*), 5.89 (dd, *J*=8.0/1.3 Hz, 1H, NC*H*=CH), 7.25 (d, *J*=1.3 Hz, 1H, NC*H*=C) ppm. ^{13}C NMR ($CDCl_3$) δ=11.3 (q, 3C, *C*H(CH_3)$_2$), 14.4 (q, 1C, CH_2*C*H$_3$), 17.7 (q, 3C, CH(*C*H$_3$)$_2$), 17.9 (d, 3C, CH(*C*H$_3$)$_2$), 25.1 (q, 1C, CH_3), 26.5 (d, 1C, CH=CH*C*H), 106.1 (s, 1C, NCH=*C*), 110.7 (d, 1C, NCH=*C*H), 126.2 (d, 1C, N*C*H=CH), 140.8 (d, 1C, N*C*H=C), 168.7 (s, 1C, CO) ppm. MS (CI, CH_5^+): *m*/*z* (%)=324 (100) $[M+H]^+$, 308 (29), 278 (17). IR (film): 3057 cm^{-1}, 2949, 2894, 2868, 1696, 1660, 1590, 1463, 1306, 1257, 1240, 1183. HRMS (EI, 70 eV): M^+ calcd for $C_{18}H_{33}NO_2Si$ (323.2281): found 323.2297.

Procedure *B*: According to procedure *A* with Me_2Mg (0.45 M in Et_2O, 35.9 mg, 0.662 mmol, 1.47 mL) instead of MeMgCl. Purification by flash chromatography on Al_2O_3 yielded 44 mg (41%) of **4a** as a yellow oil.

4.7. Ethyl 4-isopropyl-1-triisopropylsilyl-1,4-dihydropyridine-3-carboxylate 4b

Procedure *A*: According to GP2 from **1** (100 mg, 0.662 mmol), **2** (203 mg, 0.662 mmol, 182 μL) in CH_2Cl_2 (8 mL) and *i*-PrMgCl (2 M in Et_2O, 136 mg, 1.32 mmol, 662 μL). Work up was performed with phosphate buffer (8 mL) and triple extraction with CH_2Cl_2 (25 mL each). Purification by flash chromatograpy on SiO_2 (*n*-pentane/EtOAc=80/20).

Yield 105 mg (45%), colorless oil. TLC R_f=0.36 (*n*-heptane/Et_2O=50/50, SiO_2). ^{1}H NMR ($CDCl_3$) δ=0.81 (d, *J*=7.0 Hz, 3H, CH(C*H*$_3$)$_2$), 0.86 (d, *J*=7.0 Hz, 3H, CH(C*H*$_3$)$_2$), 1.08 (d, *J*=7.5 Hz, 9H, CH(C*H*$_3$)$_2$), 1.09 (d, *J*=7.5 Hz, 9H, CH(C*H*$_3$)$_2$), 1.26 (t, *J*=7.1 Hz, 3H, CH_2C*H*$_3$), 1.23–1.37 (m, 3H, C*H*(CH_3)$_2$), 1.75–1.88 (m, 1H, C*H*(CH_3)$_2$), 3.32 (dd, *J*=5.1/3.5 Hz, 1H, CH=CHC*H*), 4.06–4.23 (m, 2H, C*H*$_2$$CH_3$), 4.77 (dd, 7.9/5.1 Hz, 1H, NCH=C*H*), 6.05 (dd, *J*=7.9/1.2 Hz, 1H, NC*H*=CH), 7.36 (d, *J*=1.2 Hz, 1H, NCH=C) ppm. ^{13}C NMR ($CDCl_3$) δ=11.3 (d, 3C, *C*H(CH_3)$_2$), 14.4 (q, 1C, CH_2*C*H$_3$), 17.2 (q, 1C, CH(*C*H$_3$)$_2$), 17.7 (q, 6C, CH(*C*H$_3$)$_2$), 18.7 (q, 1C, CH(*C*H$_3$)$_2$), 33.0 (d, 1C, *C*H(CH_3)$_2$), 37.7 (d, 1C, CH=CH*C*H), 59.2 (t, 1C, *C*H$_2$$CH_3$), 104.0 (s, 1C, NCH=*C*), 104.8 (d, 1C, NCH=*C*H), 128.4 (d, 1C, N*C*H=CH), 141.8 (d, 1C, N*C*H=C), 168.9 (s, 1C, CO) ppm. MS (CI, CH_5^+): *m*/*z* (%)=352 (100) $[M+H]^+$, 308 (85). IR (film): ν=3053 cm^{-1}, 2958, 2867, 2305, 1718, 1684. Anal. Calcd for $C_{20}H_{37}NO_2Si$ (351.61): C 68.32, H 10.61, N 3.98. Found: C 68.35, H 11.03, N 4.01.

Procedure *B*: According to procedure *A* with *i*-Pr_2Mg (0.4 M in Et_2O, 151 mg, 1.32 mmol, 3.30 mL) instead of *i*-PrMgCl. Purification by flash chromatography on SiO_2 yielded 139 mg (60%) of **4b** as a colorless solid.

4.8. Ethyl 4-*tert*-butyl-1-triisopropylsilyl-1,4-dihydropyridine-3-carboxylate 4c

Procedure *A*: According to GP2 from **1** (50 mg, 0.33 mmol), **2** (101 mg, 0.331 mmol, 91.0 μL) in CH_2Cl_2 (4 mL) and *t*-BuMgCl (1.7 M in Et_2O, 77.1 mg, 0.660 mmol, 389 μL). Work up was performed with phosphate buffer (4 mL) and triple extraction with CH_2Cl_2 (20 mL each). Purification by flash chromatography on SiO_2 (*n*-heptane/EtOAc=97/3).

Yield 37 mg (30%), colorless oil. TLC R_f=0.57 (SiO_2, *n*-heptane/Et_2O=50/50). ^{1}H NMR ($CDCl_3$): δ=0.80 (s, 9H, $C(CH_3)_3$), 1.06 (d, *J*=7.6 Hz, 9H, CH(C*H*$_3$)$_2$), 1.07 (d, *J*=7.6 Hz, 9H, CH(C*H*$_3$)$_2$), 1.24 (t, *J*=7.1 Hz, 3H, CH_2C*H*$_3$), 1.30 (sept., J=7.6 Hz, 3H, C*H*(CH_3)$_2$), 3.15 (d, *J*=6.0 Hz, 1H, CH=CHC*H*), 4.04–4.20 (m, 2H, C*H*$_2$$CH_3$), 4.88 (dd, *J*=7.6/6.0 Hz, 1H, NCH=C*H*), 6.10 (dd, *J*=7.6/1.1 Hz, 1H, NC*H*=CH), 7.42 (d, *J*=1.1 Hz, 1H, NC*H*=C) ppm. ^{13}C NMR ($CDCl_3$): δ=11.4 (q, 3C, *C*H(CH_3)$_2$), 14.4 (q, 1C, CH_2*C*H$_3$), 17.8 (q, 6C, CH(*C*H$_3$)$_2$), 26.1 (q, 3C, C(*C*H$_3$)$_3$), 38.4 (s, 1C, *C*(CH_3)$_3$), 41.1 (d, 1C, CH=CH*C*H), 59.3 (t, 1C, *C*H$_2$$CH_3$), 103.1 (s, 1C, NCH=*C*), 106.1 (d, 1C, NCH=*C*H), 128.2 (d, 1C, N*C*H=CH), 142.0 (d, 1C, N*C*H=C), 170.3 (s, 1C, CO) ppm. MS (CI, CH_5^+): *m*/*z* (%)=366 (97, $[M+H]^+$), 320 (28), 308 (100). IR (film): ν=3059 cm^{-1}, 2949, 2896, 2869, 1697, 1653, 1585, 1463, 1251. Anal. Calcd for $C_{21}H_{39}NO_2Si$ (365.64): C 68.98, H 10.75, N 3.83. Found: C 68.91, H 10.75, N 3.86.

Procedure B: According to procedure *A* with *t*-Bu_2Mg (0.4 M in Et_2O, 91.4 mg, 0.660 mmol, 1.66 mL) instead of *t*-BuMgCl. Purification by flash chromatography on SiO_2 yielded 62 mg (52%) of **4c** as a colorless oil.

4.9. Ethyl 4-benzyl-1-triisopropylsilyl-1,4-dihydropyridine-3-carboxylate 4d

Procedure A: According to GP2 from **1** (50 mg, 0.33 mmol), **2** (101 mg, 0.331 mmol, 91.0 μL) in CH_2Cl_2 (4 mL) and BnMgCl (1.0 M in Et_2O, 59.8 mg, 0.397 mmol, 397 μL). Work up was performed with phosphate buffer (5 mL) and triple extraction with CH_2Cl_2 (20 mL each). Purification by flash chromatography on Al_2O_3 (*n*-pentane/Et_2O=70/30).

Yield 68.0 mg (52%), colorless oil. TLC R_f=0.66 (*n*-pentane/Et_2O=50/50, SiO_2). ^1H NMR ($CDCl_3$) δ=1.00 (d, *J*=7.4 Hz, 9H, $CH(CH_3)_2$), 1.02 (d, *J*=7.4 Hz, 9H, $CH(CH_3)_2$), 1.17–1.27 (m, 3H, $CH(CH_3)_2$), 1.28 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 2.69 (dd, *J*=12.9/7.8 Hz, 1H, CH_2Ph), 2.78 (dd, *J*=12.9/3.7 Hz, 1H, CH_2Ph), 3.62–3.67 (m, 1H, CHCHC), 4.11–4.23 (m, 2H, CH_2CH_3), 4.70 (dd, *J*=7.8/4.8 Hz, 1H, NCH=CH), 5.86 (dd, *J*=7.8/1.1 Hz, 1H, NCH=CH), 7.09–7.15 (m, 3H, $H_{arom.}$), 7.18–7.24 (m, 3H, $2H_{arom.}$, NCH=C) ppm. ^{13}C NMR ($CDCl_3$) δ=11.2 (q, 6C, $CH(CH_3)_3$), 17.6 (q, 3C, $CH(CH_3)_3$), 14.5 (q, 1C, CH_2CH_3), 34.0 (d, 1C, CHCHC), 44.4 (t, 1C, CH_2CH_3), 59.4 (t, 1C, CH_2Ph), 103.9 (s, 1C, NCH=C), 108.0 (d, 1C, NCH=CH), 125.6 (d, 1C, C_{para}), 127.3 (d, 1C, NCH=CH), 127.8 (d, 2C, $C_{arom.}$), 129.9 (d, 2C, $C_{arom.}$), 139.5 (s, 1C, $C_{arom.}$), 141.9 (d, 1C, NCH=C), 168.7 (s, 1C, CO) ppm. MS (CI, CH_5^+): *m*/*z* (%)=400 (58) $[M+H]^+$, 354 (12), 308 (100). IR (film): ν=3062 cm^{-1}, 3028, 2944, 2867, 1722, 1683, 1589, 1277. HRMS (ESI^+): $[M+H]^+$ calcd for $C_{24}H_{38}NO_2Si$ (400.2672), found 400.2670.

Procedure B: According to procedure *A* with Bn_2Mg (0.4 M in Et_2O, 138 mg, 0.397 mmol, 933 μL) instead of BnMgCl. Purification by flash chromatography on Al_2O_3 yielded 103 mg (79%) of **4d** as a colorless oil.

4.10. Ethyl 4-phenyl-1-triisopropylsilyl-1,4-dihydropyridine-3-carboxylate 4e

Procedure A: According to GP2 from **1** (50 mg, 0.33 mmol), **2** (101 mg, 0.331 mmol, 91.0 μL) in CH_2Cl_2 (4 mL) and PhMgBr (2.97 M in Et_2O, 54.2 mg, 0.397 mmol, 223 μL). Work up was performed with phosphate buffer (5 mL) and triple extraction with CH_2Cl_2 (15 mL each). Purification by flash chromatography on Al_2O_3 (*n*-pentane/Et_2O=70/30).

Yield 70 mg (55%), colorless crystals, mp 63–65 °C. TLC R_f=0.74 (*n*-pentane/Et_2O=50/50, SiO_2). ^1H NMR ($CDCl_3$) δ=1.12 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 1.14 (d, *J*=7.5 Hz, 9H, $CH(CH_3)_2$), 1.15 (d, *J*=7.5 Hz, 9H, $CH(CH_3)_2$), 1.36 (sept., *J*=7.5 Hz, 3H, $CH(CH_3)_2$), 3.93–4.09 (m, 2H, CH_2CH_3), 4.49 (d, *J*=4.7 Hz, 1H, CHCHC), 4.93 (dd, *J*=7.8/4.7 Hz, 1H, NCH=CH), 6.02 (dt, *J*=7.8/1.2 Hz, 1H, NCH=CH), 7.13–7.18 (m, 1H, H_{para}), 7.25–7.31 (m, 4H, $H_{arom.}$), 7.42 (d, *J*=1.2 Hz, 1H, NCH=C) ppm. MS (CI, CH_5^+): *m*/*z* (%)=386 (100) $[M+H]^+$, 340 (24), 308 (82). IR (film): ν=3060 cm^{-1}, 3026, 2947, 2893, 2868, 1698, 1658, 1590, 1463, 1298, 1252. Anal. Calcd for $C_{23}H_{35}NO_2Si$ (385.61): C 71.64, H 9.15, N 3.63. Found: C 71.41, H 9.35, N 3.57.

Procedure B: According to procedure *A* with Ph_2Mg (0.4 M in Et_2O, 179.7 mg, 0.397 mmol, 993 μL) instead of PhMgBr. Purification by flash chromatography on Al_2O_3 yielded 89 mg (70%) of **4e** as a colorless solid.

4.11. Ethyl 4-ethyl-4-phenyl-1-triisopropylsilyl-1,4-dihydropyridine-3-carboxylate 8b

Procedure A: According to GP2 from **6** (50.0 mg, 0.220 mmol), **2** (64.7 mg, 60.5 μL, 0.220 mmol) in CH_2Cl_2 (4 mL) and EtMgCl (2.8 M in Et_2O, 39.1 mg, 0.440 mmol, 156 μL). Work up was performed with phosphate puffer (5 mL) and triple extraction with CH_2Cl_2 (20 mL each). Purification by flash chromatography on SiO_2 (*n*-pentane/CH_2Cl_2=94/6) provided **8b** as colorless crystals.

Yield 18.2 mg (20%), colorless crystals, mp 63–65 °C. TLC R_f=0.60 (*n*-heptane/Et_2O=50/50, SiO_2). ^1H NMR ($CDCl_3$) δ=0.98 (t, *J*=7.2 Hz, 6H, $COOCH_2CH_3$, CH_2CH_3), 1.14 (d, *J*=7.5 Hz, 9H, $CH(CH_3)_2$), 1.15 (d, *J*=7.5 Hz, 9H, $CH(CH_3)_2$), 1.36 (sept., *J*=7.5 Hz, 3H, $CH(CH_3)_2$), 1.50–1.61 (m, 1H, CH_2CH_3), 2.54–2.64 (m, 1H, CH_2CH_3), 3.82–3.97 (m, 2H, $COOCH_2CH_3$), 4.34 (d, *J*=7.9 Hz, 1H, NCH=CH), 6.03 (dd, *J*=7.9/1.2 Hz, 1H, NCH=CH), 7.12 (tt, *J*=7.3/1.3 Hz, 1H, H_{para}), 7.26–7.31 (m, 2H, H_{meta}), 7.42–7.46 (m, 2H, H_{ortho}), 7.56 (d, *J*=1.2 Hz, 1H, NCH=C) ppm. ^{13}C NMR ($CDCl_3$) δ=10.7 (q, 1C, CH_2CH_3), 11.2 (d, 3C, $CH(CH_3)_2$), 14.0 (q, 1C, $COOCH_2CH_3$), 17.7 (q, 3C, $CH(CH_3)_2$), 17.8 (q, 3C, $CH(CH_3)_2$), 30.3 (t, 1C, CH_2CH_3), 43.9 (s, 1C, CH=CHC), 58.9 (t, 1C, $COOCH_2CH_3$), 105.2 (s, 1C, NCH=C), 113.7 (d, 1C, NCH=CH), 134.8 (d, 1C, NCH=CH), 125.1 (d, 1C, C_{para}), 127.3 (d, 2C, $C_{arom.}$), 127.5 (d, 2C, $C_{arom.}$), 141.7 (d, 1C, NCH=C), 152.4 (s, 1C, $C_{arom.}$), 168.3 (s, 1C, CO) ppm. MS (EI, 70 eV): *m*/*z* (%)=384 (100) $[M^+-C_2H_5]$. IR (film): ν=3085 cm^{-1}, 3056, 3023, 2949, 2894, 2869, 1698, 1660, 1576, 1463, 1307. Anal. Calcd for $C_{25}H_{39}NO_2Si$ (413.68): C 72.59, H 9.50, N 3.39. Found: C 72.43, H 9.45, N 3.36.

Procedure B: According to procedure *A* with Et_2Mg (0.45 M in Et_2O, 36.3 mg, 0.440 mmol, 975 μL) instead of EtMgCl. Flash chromatography on SiO_2 provided 50 mg (55%) of **8b** as colorless crystals.

Procedure C: According to GP2 from **6** (25.0 mg, 0.110 mmol), **2** (33.7 mg, 30.3 μL, 0.11 mmol) in CH_2Cl_2 (3 mL) and EtMgCl (2.8 M in Et_2O, 19.5 mg, 0.220 mmol, 79.0 μL), but with the addition of $CuBr\cdot Me_2S$ (3.40 mg, 0.017 mmol) before **2** was introduced. Work up was performed with phosphate buffer (3 mL) and triple extraction with CH_2Cl_2 (15 mL each). Purification by flash chromatography on SiO_2 yielded 7 mg (15%) of **8b**.

Procedure D: According to *C* with Et_2Mg (0.4 M in Et_2O, 18.1 mg, 0.220 mmol, 550 μL) instead of EtMgCl. Flash chromatography on SiO_2 provided 10.6 mg (23%) of **8b** as colorless crystals.

Procedure E: According to *C* with CuCN (1.60 mg, 0.017 mmol) instead of $CuBr\cdot Me_2S$. Flash chromatography on SiO_2 provided 11.4 mg (25%) of **8b** as colorless crystals.

4.12. Ethyl 4-isopropyl-4-phenyl-1-triisopropylsilyl-1,4-dihydropyridine-3-carboxylate 8c

Procedure A: According to GP2 from **6** (200 mg, 0.880 mmol), **2** (270 mg, 242 μL, 0.880 mmol) in CH_2Cl_2 (10 mL) and *i*-PrMgCl (2.0 M in Et_2O, 181 mg, 1.76 mmol, 880 μL). Work up was performed with phosphate buffer (10 mL) and triple extraction with CH_2Cl_2 (30 mL each). Purification by flash chromatography on SiO_2 (*n*-pentane/EtOAc=94/6).

Yield 239 mg (63%), colorless oil. TLC R_f=0.34 (*n*-heptane/Et_2O=50/50, SiO_2). ^1H NMR ($CDCl_3$) δ=0.84 (d, *J*=6.8 Hz, 3H, $CH(CH_3)_2$), 1.00 (d, *J*=6.8 Hz, 3H, $CH(CH_3)_2$), 1.04–1.11 (m, 3H, CH_2CH_3), 1.14 (d, *J*=7.5 Hz, 9H, $CH(CH_3)_2$), 1.15 (d, *J*=7.5 Hz, 9H, $CH(CH_3)_2$), 1.15 (sept., *J*=7.5 Hz, 3H, $CH(CH_3)_2$), 3.30 (sept., *J*=6.8 Hz, 1H, $CH(CH_3)_2$), 3.84–4.00 (m, 2H, CH_2CH_3), 4.59 (d, *J*=8.1 Hz, 1H, NCH=CH), 6.24 (dd, *J*=8.1/1.4 Hz, 1H, NCH=CH), 7.10 (tt, *J*=7.5/1.1 Hz, $1H_{para}$), 7.27 (t, *J*=7.5 Hz, 2H, H_{meta}), 7.34 (d, *J*=1.4 Hz, 1H, NCH=C), 7.53 (dd, *J*=7.5/1.1 Hz, 2H, H_{ortho}) ppm. ^{13}C NMR ($CDCl_3$) δ=11.3 (d, 3C, $CH(CH_3)_3$), 14.1 (q, 1C, CH_2CH_3), 16.0 (q, 1C, $CH(CH_3)_3$), 17.8 (q, 6C, $CH(CH_3)_3$), 20.4 (q, 1C, $CH(CH_3)_3$), 30.2 (d, 1C, $CH(CH_3)_3$), 47.1 (s, 1C, CH=CHCH), 58.9 (t, 1C, CH_2CH_3), 107.6 (d, 1C, NCH=CH), 107.8 (s, 1C, NCH=C), 125.0 (d, 1C, C_{para}), 126.6 (d, 1C, NCH=CH), 126.9 (d, 2C, C_{meta}), 129.8 (d, 2C, C_{ortho}), 139.8 (d, 1C, NCH=C), 149.1 (s, 1C, $C_{arom.}$), 168.0 (s, 1C, CO) ppm. MS (CI, CH_5^+): *m*/*z* (%)=428 (100) $[M+H]^+$, 384 (94), 350 (12). IR (film): ν=3086 cm^{-1}, 3057, 3019, 2948, 2868, 1698, 1622, 1575, 1463, 1269, 1251. Anal. Calcd for $C_{26}H_{41}NO_2Si$ (427.71): C 73.01, H 9.66, N 3.27. Found: C 72.81, H 10.06, N 3.25.

Procedure *B*: According to procedure *A* with *i*-Pr$_2$Mg (0.4 M in Et$_2$O, 195 mg, 1.76 mmol, 880 μL) instead of *i*-PrMgCl. Purification by flash chromatography on SiO$_2$ yielded 345 mg (91%) of **8c** as a colorless oil.

4.13. Ethyl 4-*tert*-butyl-4-phenyl-1-triisopropylsilyl-1,4-dihydropyridine-3-carboxylate 8d and ethyl 2-*tert*-butyl-4-phenyl-1-triisopropylsilyl-1,6-dihydropyridine-3-carboxylate 9d

Procedure *A*: According to GP2 from **6** (50.0 mg, 0.220 mmol), **2** (74.2 mg, 66.6 μL, 0.240 mmol) in CH$_2$Cl$_2$ (5 mL) and *t*-Bu$_2$Mg (0.4 M in Et$_2$O, 61.0 mg, 0.440 mmol, 1.1 mL). Work up was performed with phosphate buffer (10 mL) and triple extraction with CH$_2$Cl$_2$ (25 mL each). Purification by flash chromatography on SiO$_2$ (*n*-pentane/EtOAc=95/5) followed by preparative HPLC (Si 60, 5 μm, heptane/EtOAc=98/2, 20 mL/min, **8d**: t_R=26.59 min, **9d**: t_R=32.83 min).

Yield (**8d**) 54.6 mg (56%), colorless crystals, mp 95–96 °C. TLC R_f=0.67 (*n*-heptane/EtOAc=50/50, SiO$_2$). HPLC (Si 60, heptane/EtOAc=95/5, 0.75 mL/min, t_R=6.42 min). ^{1}H NMR (CDCl$_3$) δ=0.88 (t, *J*=7.2 Hz, 3H, CH$_2$C*H*$_3$), 1.13 (d, *J*=7.5 Hz, 18H, CH(C*H*$_3$)$_2$), 1.19 (s, 9H, C(CH$_3$)$_3$), 1.36 (sept., *J*=7.5 Hz, 3H, C*H*(CH$_3$)$_2$), 3.74–3.87 (m, 2H, C*H*$_2$CH$_3$), 4.68 (d, *J*=7.8 Hz, 1H, NCH=C*H*), 6.02 (dd, *J*=7.8/1.2 Hz, 1H, NC*H*=CH), 7.05 (t, *J*=7.4 Hz, 1H, H$_{para}$), 7.21 (t, *J*=7.4 Hz, 2H, H$_{meta}$), 7.55 (d, *J*=1.2 Hz, 1H, NCH=C), 7.60 (d, *J*=8.5 Hz, 2H, H$_{ortho}$) ppm. ^{13}C NMR (CDCl$_3$) δ=11.3 (d, 3C, *C*H(CH$_3$)$_2$), 13.8 (q, 1C, CH$_2$*C*H$_3$), 17.8 (q, 6C, CH(*C*H$_3$)$_2$), 27.4 (q, 3C, C(*C*H$_3$)$_3$), 40.6 (s, 1C, *C*(CH$_3$)$_3$), 50.0 (s, 1C, CH=CH*C*), 58.8 (t, 1C, *C*H$_2$CH$_3$), 106.6 (s, 1C, NCH=*C*), 112.9 (d, 1C, NCH=*C*H), 123.6 (d, 1C, N*C*H=CH), 124.2 (d, 1C, C$_{para}$), 126.6 (d, 2C, C$_{meta}$), 130.1 (d, 2C, C$_{ortho}$), 141.4 (d, 1C, N*C*H=C), 150.7 (s, 1C, C$_{arom.}$), 169.5 (s, 1C, CO) ppm. MS (CI, CH$_5^+$): *m*/*z* (%)=442 (100) [M+H]$^+$, 396 (11), 384 (81), 364 (12). IR (KBr): ν=3056 cm^{-1}, 3006, 2967, 2950, 2865, 1689, 1654, 1568. Anal. Calcd for C$_{27}$H$_{43}$NO$_2$Si (441.74): C 73.42, H 9.81, N 3.17. Found: C 73.44, H 9.67, N 3.15.

Yield (**9d**) 5 mg (5%, contaminated with 9% **8d**), colorless oil. TLC R_f=0.67 (*n*-heptan/EtOAc=50/50, SiO$_2$). HPLC t_R=6.98 min (Si 60, heptane/EtOAc=95/5, 0.75 mL/min). ^{1}H NMR (CDCl$_3$) δ=0.89 (t, *J*=7.0 Hz, 3H, CH$_2$C*H*$_3$), 0.92 (s, 9H, C(CH$_3$)$_3$), 1.13 (d, *J*=7.6 Hz, 9H, CH(C*H*$_3$)$_2$), 1.15 (d, *J*=7.6 Hz, 9H, CH(C*H*$_3$)$_2$), 1.34 (sept., *J*=7.6 Hz, 3H, C*H*(CH$_3$)$_2$), 3.66 (dd, *J*=6.9/1.0 Hz, 1H, NC*H*CH), 3.82–4.00 (m, 2H, C*H*$_2$CH$_3$), 5.07 (d, *J*=6.9 Hz, 1H, NCHC*H*), 7.15–7.27 (m, 5H, H$_{arom.}$), 7.73 (d, *J*=1.0 Hz, 1H, NCH=C) ppm. MS (CI, CH$_5^+$): *m*/*z* (%)=442 (100) [M+H]$^+$, 396 (27), 384 (96). HRMS (ESI$^+$): M$^+$+H calcd for C$_{27}$H$_{44}$NO$_2$Si (442.3141), found 442.3128.

Procedure *B*: According to procedure *A* with *t*-BuMgCl (1.7 M in Et$_2$O, 51.4 mg, 0.440 mmol, 259 μL) instead of *t*-Bu$_2$Mg. Flash chromatography on SiO$_2$ provided 45.4 mg (47%) of **8d** as colorless crystals.

4.14. Ethyl 4-benzyl-4-phenyl-1-triisopropylsilyl-1,4-dihydropyridine-3-carboxylate 8f and ethyl 6-benzyl-4-phenyl-1-triisopropylsilyl-1,6-dihydropyridine-3-carboxylate 9f

Procedure *A*: According to GP2 from **6** (50.0 mg, 0.220 mmol), **2** (67.4 mg, 60.5 μL, 0.220 mmol) in CH$_2$Cl$_2$ (4 mL) and BnMgCl (1.0 M in Et$_2$O, 66.4 mg, 0.440 mmol, 440 μL). Work up was performed with phosphate buffer (5 mL) and triple extraction with CH$_2$Cl$_2$ (20 mL each). Purification by flash chromatography on SiO$_2$ (*n*-pentane/EtOAc=94/6) whereas regioisomer **8f** eluated first.

Yield (**8f**) 40 mg (38%), colorless crystals, mp 129–130 °C. TLC R_f=0.25 (*n*-heptane/Et$_2$O=50/50, SiO$_2$). ^{1}H NMR (CDCl$_3$) δ=0.91 (d, *J*=7.4 Hz, 9H, CH(C*H*$_3$)$_2$), 0.94 (d, *J*=7.4 Hz, 9H, CH(C*H*$_3$)$_2$), 1.05 (t, *J*=7.1 Hz, 3H, CH$_2$C*H*$_3$), 1.08–1.20 (m, 3H, C*H*(CH$_3$)$_2$), 2.90 (d, *J*=13.0 Hz, 1H, CH$_2$), 3.97 (d, *J*=13.0 Hz, 1H, CH$_2$), 3.90–4.08 (m, 2H, C*H*$_2$CH$_3$), 4.50 (d, *J*=7.9 Hz, 1H, NCH=C*H*), 5.79 (dd, *J*=7.9/1.3 Hz, 1H, NC*H*=CH), 7.08–7.21 (m, 6H, H$_{arom.}$), 7.23 (d, *J*=1.3 Hz, 1H, NCH=C), 7.34 (t, *J*=7.7 Hz, 2H, H$_{arom.}$), 7.51–7.56 (m, 2H, H$_{arom.}$) ppm. ^{13}C NMR (CDCl$_3$): δ=11.0 (d, 3C, *C*H(CH$_3$)$_2$), 14.2 (q, 1C, CH$_2$*C*H$_3$), 17.4 (q, 3C, CH(*C*H$_3$)$_2$), 17.5 (q, 3C, CH(*C*H$_3$)$_2$), 44.1 (t, 1C, CH$_2$), 45.3 (s, 1C, CH=CH*C*), 59.0 (t, 1C, *C*H$_2$CH$_3$), 105.9 (s, 1C, NCH=*C*), 113.4 (d, 1C, NCH=*C*H), 124.5 (d, 1C, N*C*H=CH), 125.3 (d, 1C, C$_{arom.}$), 125.6 (d, 1C, C$_{arom.}$), 127.4 (d, 2C, C$_{arom.}$), 127.5 (d, 2C, C$_{arom.}$), 127.6 (d, 2C, C$_{arom.}$), 131.0 (d, 2C, C$_{arom.}$), 140.1 (s, 1C, C$_{arom.}$), 141.9 (d, 1C, N*C*H=C), 152.3 (s, 1C, C$_{arom.}$), 168.3 (s, 1C, CO) ppm. MS (CI, CH$_5^+$): *m*/*z* (%)=476 (85) [M+2H]$^+$, 430 (16), 384 (100). IR (film): ν=3085 cm^{-1}, 3059, 3027, 2947, 2893, 2867, 1696, 1661, 1575, 1463, 1279, 1235. Anal. Calcd for C$_{30}$H$_{41}$NO$_2$Si (474.75): C 75.74, H 8.69, N 2.94. Found: C 75.47, H 8.74, N 2.84.

Yield (**9f**): 7 mg (7%), colorless oil. TLC R_f=0.19 (*n*-heptane/Et$_2$O=50/50, SiO$_2$). ^{1}H NMR (CDCl$_3$) δ=0.96 (t, *J*=7.1 Hz, 3H, CH$_2$C*H*$_3$), 1.16 (d, *J*=7.5 Hz, 9H, CH(C*H*$_3$)$_2$), 1.17 (d, *J*=7.5 Hz, 9H, CH(C*H*$_3$)$_2$), 1.39 (sept., *J*=7.5 Hz, 3H, C*H*(CH$_3$)$_2$), 2.55 (dd, *J*=12.2/3.9 Hz, 1H, CH$_2$), 3.16 (dd, *J*=12.2/11.0 Hz, 1H, CH$_2$), 3.88–4.11 (m, 3H, C*H*$_2$CH$_3$, NCH), 4.86 (d, *J*=6.5 Hz, 1H, NCHC*H*), 7.13–7.18 (m, 2H, H$_{arom.}$), 7.20–7.28 (m, 6H, H$_{arom.}$), 7.31–7.37 (m, 2H, H$_{arom.}$), 7.75 (d, *J*=1.2 Hz, 1H, NCH=C) ppm. ^{13}C NMR (CDCl$_3$) δ=11.6 (d, 3C, *C*H(CH$_3$)$_2$), 14.0 (q, 1C, CH$_2$*C*H$_3$), 18.1 (q, 3C, CH(*C*H$_3$)$_2$), 18.2 (q, 3C, CH(*C*H$_3$)$_2$), 39.8 (t, 1C, CH$_2$), 54.8 (d, 1C, NCH), 59.0 (t, 1C, *C*H$_2$CH$_3$), 107.3 (s, 1C, NCH=*C*), 112.4 (d, 1C, NCH*C*H), 126.4 (d, 1C, C$_{arom.}$), 126.5 (d, 1C, C$_{arom.}$), 127.4 (d, 2C, C$_{arom.}$), 127.7 (d, 2C, C$_{arom.}$), 128.2 (d, 2C, C$_{arom.}$), 130.0 (d, 2C, C$_{arom.}$), 136.4 (s, 1C, C$_{arom.}$), 137.7 (s, 1C, C$_{arom.}$), 141.7 (s, 1C, C$_{arom.}$), 148.0 (d, 1C, N*C*H=C), 166.8 (s, 1C, CO) ppm. MS (CI, CH$_5^+$): *m*/*z* (%)=476 (84) [M+2H]$^+$, 430 (20), 384 (100). IR (film): ν=3081 cm^{-1}, 3059, 3027, 2948, 2894, 2868, 1693, 1614, 1600, 1539. HRMS (EI, 70 eV): M$^+$ calcd for C$_{23}$H$_{34}$NO$_2$Si (384.2359), found 384.2369.

Procedure *B*: According to procedure *A* with Bn$_2$Mg (0.4 M in Et$_2$O, 90.9 mg, 0.440 mmol, 1.10 mL) instead of BnMgCl. Flash chromatography on SiO$_2$ provided 47 mg (45%) of **8f** as colorless crystals and 35 mg (24%) of **9f** as a colorless oil.

Procedure *C*: According to GP2 from **6** (25.0 mg, 0.110 mmol), **2** (33.7 mg, 30.3 μL, 0.110 mmol) in CH$_2$Cl$_2$ (3 mL) and BnMgCl (1.0 M in Et$_2$O, 33.2 mg, 0.220 mmol, 220 μL), but in the presence of CuBr·Me$_2$S (3.40 mg, 0.017 mmol) before **2** was introduced. Work up was provided with phosphate buffer (3 mL) and triple extraction with CH$_2$Cl$_2$ (15 mL each). Flash chromatography on SiO$_2$ provided 21 mg (41%) of **8f** as colorless crystals.

Procedure *D*: According to procedure *C* with Bn$_2$Mg (0.4 M in Et$_2$O, 45.4 mg, 0.220 mmol, 550 μL) instead of BnMgCl. Flash chromatography on SiO$_2$ provided 14.5 mg (28%) of **8f** as colorless crystals.

Procedure *E*: According to procedure *C* with Me$_2$S (1.6 μL, 0.022 mmol) instead of CuBr·Me$_2$S. Flash chromatography on SiO$_2$ provided 20.7 mg (40%) of **8f** as colorless crystals.

Procedure *F*: According to procedure *C* with CuCN (1.6 mg, 0.022 mmol) instead of CuBr·Me$_2$S. Flash chromatography on SiO$_2$ provided 38 mg (38%) of **8f** as colorless crystals.

Procedure *G*: According to procedure *C* with TBAI (8.1 mg, 0.022 mmol) instead of CuBr·Me$_2$S. Flash chromatography on SiO$_2$ provided 40.2 mg (38%) of **8f** as colorless crystals.

Procedure *H*: According to procedure *C* with TBABr (7.1 mg, 0.022 mmol) instead of CuBr·Me$_2$S. Flash chromatography on SiO$_2$ provided 41 mg (39%) of **8f** as colorless crystals.

Procedure *I*: According to procedure *C* with TBACl (0.5 M in CH$_2$Cl$_2$, 6.1 mg, 0.022 mmol, 44.0 μL) instead of CuBr·Me$_2$S. Flash chromatography on SiO$_2$ provided 45.9 mg (44%) of **8f** as colorless crystals.

Procedure *J*: BnMgCl (1.0 M in Et$_2$O, 66.4 mg, 0.440 mmol, 440 μL) was added dropwise to a suspension of CuCN (19.7 mg, 0.220 mmol) in THF (1.5 mL) at −78 °C. After stirring for 30 min at −78 °C and 10 min at rt the cyanocuprate solution was used according to GP2 with **6** (40.0 mg, 0.176 mmol) and **2** (53.9 mg, 48.4 μL, 0.176 mmol) in CH_2Cl_2 (2.5 mL). Flash chromatography on SiO_2 provided 26.0 mg (31%) of **8f** as colorless crystals and 21.1 mg (25%) of **9f** as a colorless oil.

4.15. Ethyl 4,4-diphenyl-1-triisopropylsilyl-1,4-dihydropyridine-3-carboxylate 8g

Procedure *A*: According to GP2 from **6** (30.0 mg, 0.132 mmol), **2** (40.1 mg, 35.9 μL, 0.132 mmol) in CH_2Cl_2 (4 mL) and PhMgBr (2.97 M in Et_2O, 54.2 mg, 0.397 mmol, 223 μL). Work up was performed with phosphate buffer (5 mL) and triple extraction with CH_2Cl_2 (20 mL each). Purification by flash chromatography on SiO_2 (*n*-pentane/EtOAc=95/5).

Yield 4.3 mg (7%), colorless crystals, mp 124–126 °C. TLC R_f=0.38 (*n*-heptane/Et_2O=50/50, SiO_2). ^1H NMR ($CDCl_3$) δ=0.91 (t, *J*=7.2 Hz, 3H, CH_2CH_3), 1.03 (d, *J*=7.7 Hz, 9H, $CH(CH_3)_2$), 1.15 (d, *J*=7.7 Hz, 9H, $CH(CH_3)_2$), 1.33–1.44 (m, 3H, $CH(CH_3)_2$), 3.90–4.04 (m, 2H, CH_2CH_3), 5.26 (d, *J*=6.6 Hz, 1H, NCH=C*H*), 5.83 (d, *J*=1.1 Hz, 1H, NCH=C), 6.84 (dd, *J*=6.6/1.1 Hz, 1H, NC*H*=CH), 7.10–7.14 (m, 2H, $H_{arom.}$), 7.18–7.30 (m, 6H, $H_{arom.}$), 7.48–7.52 (m, 2H, $H_{arom.}$) ppm. ^{13}C NMR ($CDCl_3$) δ=11.7 (d, 3C, $CH(CH_3)_2$), 13.8 (q, 1C, CH_2CH_3), 17.9 (q, 3C, $CH(CH_3)_2$), 18.0 (q, 3C, $CH(CH_3)_2$), 54.8 (d, 1C, NCH=CH*C*), 59.6 (t, 1C, CH_2CH_3), 106.1 (s, 1C, NCH=*C*), 107.5 (d, 1C, NCH=*C*H), 126.2 (d, $C_{arom.}$), 126.7 (d, $C_{arom.}$), 127.0 (d, $C_{arom.}$), 127.4 (d, $C_{arom.}$), 127.7 (d, $C_{arom.}$), 127.8 (d, $C_{arom.}$), 141.7 (d, 1C, NCH=C), 143.9 (s, 1C, $C_{arom.}$), 147.4 (s, 1C, $C_{arom.}$), 167.3 (s, 1C, CO) ppm. MS (CI, CH_5^+): *m*/*z* (%)=462 (100) $[M+H]^+$. IR (film): ν=3053 cm^{-1}, 3025, 2947, 2890, 2868, 1706, 16.73, 1510, 1257, 1226. Anal. Calcd for $C_{29}H_{39}NO_2Si$ (461.73): C 75.44, H 8.51, N 3.03. Found: C 75.11, H 8.50, N 3.00.

Procedure *B*: According to procedure *A* with Ph_2Mg (0.31 M in Et_2O, 47.1 mg, 0.264 mmol, 850 μL) instead of PhMgBr. Flash chromatography provided 28 mg (46%) of **8g** as colorless crystals.

4.16. Ethyl 4,4-diethyl-1-triisopropylsilyl-1,4-dihydropyridine-3-carboxylate 14

According to GP2 from ethyl 4-ethylpyridin-3-carboxylate[12] (100 mg, 0.558 mmol), **2** (172.7 mg, 154 μL, 0.558 mmol) in CH_2Cl_2 (8 mL) and Et_2Mg (0.4 M in Et_2O, 92.3 mg, 1.12 mmol, 2.79 mL). Work up was performed with phosphate buffer (15 mL) and triple extraction with CH_2Cl_2 (40 mL each). Purification by flash chromatography on SiO_2 (isohexane/EtOAc=95/5) provided **14**, which was contaminated with 3% of the C-6 substituted regioisomer.

Yield 149 mg (73%), yellow oil. TLC R_f=0.53 (*n*-heptane/EtOAc=50/50, SiO_2). ^1H NMR ($CDCl_3$) δ=0.79–0.85 (m, 6H, CH_2CH_3), 1.07 (d, *J*=7.5 Hz, 18H, $CH(CH_3)_2$), 1.20–1.33 (m, 6H, $CH(CH_3)_2$, $COOCH_2CH_3$), 2.01–2.12 (m, 4H, CH_2CH_3), 4.06 (d, *J*=8.0 Hz, 1H, NCH=C*H*), 4.08 (q, *J*=7.1 Hz, 2H, $COOCH_2CH_3$), 6.02 (dd, *J*=8.0/1.3 Hz, 1H, NC*H*=CH), 7.43 (d, *J*=1.3 Hz, 1H, NCH=C) ppm. ^{13}C NMR ($CDCl_3$) δ=10.6 (q, 2C, CH_2CH_3), 11.3 (d, 3C, $CH(CH_3)_2$), 14.3 (q, 1C, $COOCH_2CH_3$), 17.7 (q, 6C, $CH(CH_3)_2$), 34.2 (t, 2C, CH_2CH_3), 41.6 (s, 1C, CH=CH*C*), 58.9 (t, 1C, $COOCH_2CH_3$), 102.9 (s, 1C, NCH=*C*), 113.3 (d, 1C, NCH=*C*H), 127.3 (d, 1C, N*C*H=CH), 143.5 (d, 1C, N*C*H=C), 168.7 (s, 1C, CO) ppm. MS (CI, CH_5^+): *m*/*z* (%)=366 (100) $[M+H]^+$, 336 (30), 320 (20). IR (KBr): ν=2959 cm^{-1}, 2869, 1696, 1664, 1586, 1462, 1264. HRMS (EI, 70 eV): M^+ calcd for $C_{19}H_{34}NO_2Si$ (348.2723), found 348.2734.

4.17. Ethyl 4-isopropyl-4-phenyl-1,4-dihydropyridine-3-carboxylate 15

According to GP 3 from **8c** (700 mg, 1.64 mmol) and LiOH (71.0 mg, 2.96 mmol) in MeOH (18 mL) for 28 h. After removal of the solvent the raw product was purified by flash chromatography on SiO_2 (isohexane/EtOAc=80/20).

Yield 405 mg (91%), colorless crystals, mp 96–101 °C. TLC R_f=0.18 (*n*-heptane/Et_2O=50/50, Al_2O_3). ^1H NMR ($CDCl_3$) δ=0.84 (d, *J*=6.7 Hz, 3H, $CH(CH_3)_2$), 1.03 (d, *J*=6.7 Hz, 3H, $CH(CH_3)_2$), 1.10 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 3.35 (sept., *J*=6.7 Hz, 1H, $CH(CH_3)_2$), 3.84–4.02 (m, 2H, CH_2CH_3), 4.53 (dd, *J*=8.1/1.3 Hz, 1H, NCH=C*H*), 5.64 (s, 1H, NH), 6.26 (ddd, *J*=8.1/4.4/1.3 Hz, 1H, NC*H*=CH), 7.09–7.14 (m, 1H, H_{para}), 7.25–7.31 (m, 3H, 2H_{meta}, NCH=C), 7.54–7.59 (m, 2H, H_{ortho}) ppm. ^{13}C NMR ($CDCl_3$) δ=14.2 (q, 1C, $CH(CH_3)_2$), 16.0 (q, 1C, $CH(CH_3)_2$), 20.5 (q, 1C, CH_2CH_3), 30.2 (d, 1C, $CH(CH_3)_2$), 47.9 (s, 1C, CH=CH*C*), 59.1 (t, 1C, CH_2CH_3), 105.8 (s, 1C, NCH=*C*), 105.9 (d, 1C, NCH=*C*H), 122.9 (d, 1C, N*C*H=CH), 125.1 (d, 1C, C_{para}), 127.0 (d, 2C, C_{meta}), 129.7 (d, 2C, C_{ortho}), 135.5 (d, 1C, N*C*H=C), 149.1 (s, 1C, $C_{arom.}$), 167.7 (s, 1C, CO) ppm. MS (ESI^+): *m*/*z* (%)=270 (26) (M^+), 228 (83), 200 (100). IR (film): ν=3415 cm^{-1}, 3388, 3058, 2969, 2872, 1672, 1662, 1597, 1477, 1366, 1280, 1223, 1147. Anal. Calcd for $C_{17}H_{21}NO_2$ (271.36): C 75.25, H 7.80, N 5.16. Found: C 75.31, H 7.86, N 5.23.

4.18. Ethyl 4,4-diethyl-1,4-dihydropyridine-3-carboxylate 16

According to GP 3 from **14** (150 mg, 0.410 mmol) and LiOH (19.6 mg, 0.820 mmol) in MeOH (3 mL) for 36 h. After removal of the solvent the raw product was purified by flash chromatography on SiO_2 (isohexane/EtOAc=85/15).

Yield 74 mg (86%), colorless crystals, mp 125–127 °C. TLC R_f=0.48 (EtOAc, SiO_2). ^1H NMR ($CDCl_3$) δ=0.81–0.96 (m, 6H, CH_2CH_3), 1.22 (t, *J*=7.2 Hz, 3H, OCH_2CH_3), 2.04–2.13 (m, 4H, CH_2CH_3), 4.00 (dd, *J*=8.1/1.5 Hz, 1H, NCH=C*H*), 4.08 (q, *J*=7.2 Hz, 2H, OCH_2CH_3), 5.31 (s, 1H, NH), 6.05 (ddd; *J*=8.1/4.2/1.3 Hz, 1H, NC*H*=CH), 7.36 (dd, *J*=5.7/1.3 Hz, 1H, NCH=C) ppm. ^{13}C NMR ($CDCl_3$) δ=10.6 (q, 2C, CH_2CH_3), 14.4 (q, 1C, $COOCH_2CH_3$), 34.4 (t, 2C, CH_2CH_3), 42.4 (s, 1C, CH=CH*C*), 59.0 (t, 1C, $COOCH_2CH_3$), 101.1 (s, 1C, NCH=*C*), 111.7 (d, 1C, NCH=*C*H), 123.6 (d, 1C, N*C*H=CH), 138.9 (d, 1C, N*C*H=C), 168.3 (s, 1C, CO) ppm. MS (CI, CH_5^+): *m*/*z* (%)=272 (51), 242 (50), 226 (48), 210 (100) $[M+H]^+$, 196 (45), 180 (48), 108 (57). IR (KBr): ν=3340 cm^{-1}, 3103, 2994, 2962, 2930, 2870, 1676, 1649, 1597, 1506, 1291. Anal. Calcd for $C_{12}H_{19}NO_2$ (209.28): C 68.87, H 9.15, N 6.69. Found: C 68.87, H 9.05, N 6.58.

4.19. Ethyl 4-isopropyl-1-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate 17

According to GP4 from **15** (100 mg, 0.369 mmol) in DMF (3 mL), NaH (17.7 mg, 0.737 mmol) in DMF (3 mL) and MeI (78.5 mg, 0.553 mmol, 34.6 μL). Work up was performed after 2.5 h by addition of water (15 mL) and extraction with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with a saturated NaCl solution (20 mL) and dried over $MgSO_4$. The raw product was purified by flash chromatography on SiO_2 (isohexane/EtOAc=80/20).

Yield 95 mg (90%), colorless crystals, mp 103–106 °C. TLC R_f=0.52 (*n*-heptane/Et_2O=50/50, Al_2O_3). ^1H NMR ($CDCl_3$) δ=0.82 (d, *J*=6.8 Hz, 3H, $CH(CH_3)_2$), 1.00 (d, *J*=6.8 Hz, 3H, $CH(CH_3)_2$), 1.10 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 3.07 (s, 3H, NCH_3), 3.34 (sept., *J*=6.8 Hz, 1H, $CH(CH_3)_2$), 3.86–4.00 (m, 2H, CH_2CH_3), 4.55 (d, *J*=8.1 Hz, 1H, NCH=C*H*), 6.05 (dd, *J*=8.1/1.8 Hz, 1H, NC*H*=CH), 7.08–7.13 (m, 1H, H_{para}), 7.12 (d, *J*=1.8 Hz, 1H, NCH=C), 7.25–7.30 (m, 2H, H_{meta}), 7.55 (dd, *J*=8.5/1.1 Hz, 2H, H_{ortho}) ppm. ^{13}C NMR ($CDCl_3$) δ=14.2 (q, 1C, CH_2CH_3), 16.0 (q, 1C, $CH(CH_3)_2$), 20.6 (q, 1C, $CH(CH_3)_2$), 29.9 (d, 1C, $CH(CH_3)_2$), 40.8 (q, 1C, NCH_3), 47.4 (s, 1C, CH=CH*C*), 59.0 (t, 1C, CH_2CH_3), 104.7 (s, 1C, NCH=*C*), 107.0 (d, 1C, NCH=*C*H), 125.0 (d, 1C, C_{para}), 126.9 (d, 2C, C_{meta}), 127.9 (d, 1C, N*C*H=CH), 129.6 (d, 2C, C_{ortho}), 140.1 (d, 1C, N*C*H=C), 149.0 (s, 1C, $C_{arom.}$), 167.7 (s, 1C, CO) ppm. MS (CI, CH_5^+): *m*/*z* (%)=286 (92) $[M+H]^+$, 242 (100), 240 (28), 208 (40). IR (film): ν=3078 cm^{-1}, 3054, 2964, 2930, 2865, 1686, 1584, 1397, 1291, 1193. Anal. Calcd for $C_{18}H_{23}NO_2$ (285.39): C 75.76, H 8.12, N 4.91. Found: C 75.80, H 8.29, N 4.78.

4.20. Ethyl 1-benzyl-4-isopropyl-4-phenyl-1,4-dihydropyridine-3-carboxylate 18

According to GP4 from **15** (100 mg, 0.369 mmol) in DMF (2 mL), NaH (17.7 mg, 0.737 mmol) in DMF (3 mL) and benzyl bromide (65.8 μL, 94.6 mg, 0.553 mmol). Work up was performed after 3.5 h by addition of water (10 mL) and extraction with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with a saturated NaCl solution (20 mL) and dried over $MgSO_4$. The raw product was purified by flash chromatography on SiO_2 (isohexane/EtOAc=90/10).

Yield 113 mg (85%), yellow crystals, mp 64–67 °C. TLC R_f=0.34 (*n*-heptan/Et_2O=50/50, SiO_2). ^{1}H NMR ($CDCl_3$) δ=0.82 (d, J=6.6 Hz, 3H, $CH(CH_3)_2$), 1.03 (d, J=6.6 Hz, 3H, $CH(CH_3)_2$), 1.09 (t, J=7.2 Hz, 3H, CH_2CH_3), 3.36 (sept., J=6.6 Hz, 1H, $CH(CH_3)_2$), 3.86–4.00 (m, 2H, CH_2CH_3), 4.44 (s, 2H, CH_2), 4.58 (d, J=8.2 Hz, 1H, NCH=C*H*), 6.09 (dd, J=8.2/1.6 Hz, 1H, NC*H*=CH), 7.11 (t, J=7.4 Hz, 1H, H_{para}), 7.24–7.41 (m, 8H, NCH=C, $H_{arom.}$), 7.53–7.57 (m, 2H, $H_{arom.}$) ppm. ^{13}C NMR ($CDCl_3$) δ=14.2 (q, 1C, CH_2CH_3), 16.0 (q, 1C, $CH(CH_3)_2$), 20.6 (q, 1C, $CH(CH_3)_2$), 30.0 (d, 1C, $CH(CH_3)_2$), 47.7 (s, 1C, CH=CH*C*), 57.5 (t, 1C, CH_2), 59.1 (t, 1C, CH_2CH_3), 105.3 (s, 1C, NCH=*C*), 107.5 (d, 1C, NCH=*C*H), 125.1 (d, 1C, $C_{arom.}$), 126.9 (d, 2C, $C_{arom.}$), 127.0 (d, 2C, $C_{arom.}$), 127.1 (d, 1C, N*C*H=CH), 127.8 (d, 1C, $C_{arom.}$), 128.8 (d, 2C, $C_{arom.}$), 129.7 (d, 2C, $C_{arom.}$), 137.3 (s, 1C, $C_{arom.}$), 139.8 (d, 1C, N*C*H=C), 148.8 (s, 1C, $C_{arom.}$), 167.6 (s, 1C, CO) ppm. MS (CI, CH_5^+): m/z (%)=362 (100) $[M+H]^+$, 318 (39), 284 (8). IR (film): ν=3086 cm^{-1}, 3062, 3029, 2968, 2935, 2871, 1693, 1582, 1574, 1454, 1445, 1415, 1365, 1287. Anal. Calcd for $C_{24}H_{27}NO_2$ (361.49): C 79.74, H 7.53, N 3.87. Found: C 79.62, H 7.55, N 3.81.

4.21. Ethyl 1-allyl-4-isopropyl-4-phenyl-1,4-dihydropyridine-3-carboxylate 19

According to GP4 from **15** (50.0 mg, 0.184 mmol) in DMF (1 mL), NaH (8.80 mg, 0.369 mmol) in DMF (1 mL) and allyl bromide (24.0 μL, 33.4 mg, 0.276 mmol). Work up was performed after 2.5 h by addition of water (15 mL) and extraction with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with a saturated NaCl solution (20 mL) and dried over $MgSO_4$. The raw product was purified by flash chromatography on SiO_2 (isohexane/EtOAc=90/10).

Yield 48 mg (83%), colorless crystals, mp 76–77 °C. TLC R_f=0.43 (*n*-heptane/Et_2O=50/50, SiO_2). ^{1}H NMR ($CDCl_3$) δ=0.83 (d, J=6.6 Hz, 3H, $CH(CH_3)_2$), 1.01 (d, J=6.6 Hz, 3H, $CH(CH_3)_2$), 1.09 (t, J=7.1 Hz, 3H, $COOCH_2CH_3$), 3.35 (sept., J=6.6 Hz, 1H, $CH(CH_3)_2$), 3.85 (dt, J=5.1/1.6 Hz, 2H, NCH_2), 3.87–4.01 (m, 2H, CH_2CH_3), 4.58 (d, J=8.2 Hz, 1H, NCH=C*H*), 5.23–5.32 (m, 2H, $NCH_2CH=CH_2$), 5.80–5.91 (m, 1H, $NCH_2CH=CH_2$), 6.08 (dd, J=8.2/1.8 Hz, 1H, NC*H*=CH), 7.11 (tt, J=7.4/1.2 Hz, 1H, H_{para}), 7.15 (d, J=1.8 Hz, 1H, NCH=C), 7.25–7.31 (m, 2H, H_{meta}), 7.53–7.57 (m, 2H, H_{ortho}) ppm. ^{13}C NMR ($CDCl_3$) δ=14.2 (q, 1C, CH_2CH_3), 16.0 (q, 1C, $CH(CH_3)_2$), 20.6 (q, 1C, $CH(CH_3)_2$), 30.1 (d, 1C, $CH(CH_3)_2$), 47.7 (s, 1C, CH=CH*C*), 56.2 (t, 1C, NCH_2), 59.0 (t, 1C, CH_2CH_3), 105.1 (s, 1C, NCH=*C*), 107.1 (d, 1C, NCH=*C*H), 117.7 (t, 1C, $NCH_2CH=CH_2$), 125.1 (d, 1C, C_{para}), 127.0 (d, 2C, C_{meta}), 127.1 (d, 1C, N*C*H=CH), 129.7 (d, 2C, C_{ortho}), 133.6 (d, 1C, $NCH_2CH=CH_2$), 139.5 (d, 1C, N*C*H=C), 149.0 (s, 1C, $C_{arom.}$), 167.7 (s, 1C, CO) ppm. MS (CI, CH_5^+): m/z (%)=312 (62) $[M+H]^+$, 268 (100), 234 (21). IR (film): ν=3081 cm^{-1}, 3060, 2967, 2936, 2900, 2865, 1685, 1585, 1574, 1418, 1297, 1283. Anal. Calcd for $C_{20}H_{25}NO_2$ (311.43): C 77.14, H 8.09, N 4.50. Found: C 77.05, H 8.07, N 4.44.

4.22. Ethyl 1-acetyl-4,4-diethyl-1,4-dihydropyridine-3-carboxylate 20

A solution of **14** (100 mg, 0.273 mmol) and AcCl (58.3 μL, 64.4 mg, 0.820 mmol) in CH_2Cl_2 (4 mL) was heated to 65 °C under microwave conditions. After 9 h, the colorless solution was quenched by addition of phosphate puffer (15 mL). The aqueous layer was extracted three times with EtOAc (25 mL each). The combined organic layers were washed with a saturated NaCl solution (25 mL), dried ($MgSO_4$), and concentrated in vacuo. Compound **20** was purified by flash chromatography on SiO_2 (isohexane/EtOAc=90/10).

Yield 51.0 mg (74%), colorless oil. TLC R_f=0.31 (*n*-heptan/EtOAc=50/50, SiO_2). ^{1}H NMR (tetrachlorethane, 100 °C) δ=0.82 (t, J=7.4 Hz, 6H, CH_2CH_3), 1.16–1.28 (m, 2H, CH_2CH_3), 1.32 (t, J=6.9 Hz, 3H, $COOCH_2CH_3$), 2.07–2.17 (m, 2H, CH_2CH_3), 2.29 (s, 3H, $COCH_3$), 4.23 (q, J=6.9 Hz, 3H, $COOCH_2CH_3$), 4.58 (d, J=8.3 Hz, 1H, NCH=C*H*), 6.99 (br s, 1H, NC*H*=CH), 8.06 (br s, 1H, NCH=C) ppm. ^{13}C NMR (tetrachlorethane, 100 °C) δ=9.6 (q, 2C, CH_2CH_3), 14.1 (q, 1C, $COOCH_2CH_3$), 20.9 (q, 1C, $COCH_3$), 33.1 (t, 2C, CH_2CH_3), 42.8 (s, 1C, CH*C*), 59.9 (t, 1C, $COOCH_2CH_3$), 112.7 (s, 1C, NCH=*C*), 117.5 (d, 1C, NCH=*C*H), 121.3 (d, 1C, N*C*H=CH), 133.4 (d, 1C, N*C*H=C), 166.2 (s, 1C, CO), 166.3 (s, 1C, CO) ppm. MS (CI, CH_5^+): m/z (%)=252 (100) $[M+H]^+$, 222 (36), 180 (33). IR (KBr): ν=3115 cm^{-1}, 2964, 2932, 2874, 1698, 1673, 1609, 1459, 1374, 1320, 1228. Anal. Calcd for $C_{14}H_{21}NO_3$ (251.33.28): C 66.91, H 8.42, N 5.57. Found: C 66.72, H 8.66, N 5.62.

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