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Regioselective and Transition-Metal-Free Addition of *tert*-Butyl Magnesium Reagents to Pyridine Derivatives: A Convenient Method for the Synthesis of 3-Substituted 4-*tert*-Butylpyridine Derivatives

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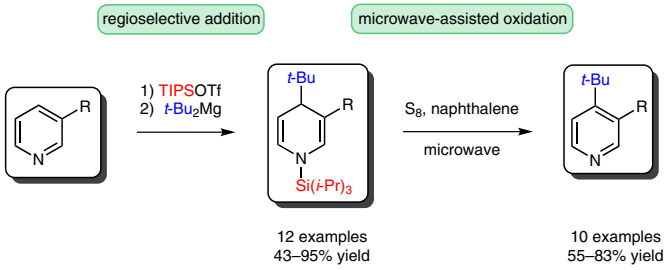

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Abstract A variety of 3,4-disubstituted pyridine derivatives with a *tert*-butyl group in the 4-position were synthesized in a transition-metal-free, two-step reaction sequence from 3-substituted pyridine precursors. Highly regioselective addition of *t*-Bu_2Mg to TIPS-activated pyridines and an efficient microwave-assisted aromatization with sulfur as oxidant afforded the desired 3,4-disubstituted pyridine derivatives in moderate to excellent yields. The method is compatible with many functional groups such as ester, amide, halide, nitrile or alkyne groups present in the 3-position.

Key words 3,4-disubstituted pyridines, N-activation, heterocycles, diorganomagnesium, nucleophilic addition, microwave

Pyridines represent important building blocks in organic synthesis and are widely used in medicinal chemistry.[1,2] As a substructure of a more complex molecule, they are very common in many natural products, biologically active compounds including drugs, and as key substrates for multicomponent reactions.[3] Pyridine derivatives exhibiting a *tert*-butyl group are not as widely distributed, but they are still found in pharmaceutical compounds such as anti-inflammatory agents,[4] cancer therapeutics,[5] and nervous system agents.[6] Notably, 3,4-disubstituted pyridine derivatives with a *tert*-butyl group in the 4-position can be found in many C17,20-lyase inhibitors developed for prostate cancer therapy.[7]

Well-known methods for the functionalization of pyridine derivatives such as cross-coupling reactions[8] or C–H activations[9] suffer from β-H elimination and homocoupling side reactions if tertiary alkyllithium or alkylmagnesium reagents are employed.[10] Thus, de novo synthesis or two-step reactions comprising the addition of nucleophiles to *N*-acylpyridinium ions and subsequent oxidation are often the methods of choice.[11] Although the latter strategy is of high value in synthetic organic chemistry, it is less suited for the synthesis of 4-*tert*-butyl substituted pyridine derivatives,[7] because the addition of *tert*-butyl nucleophiles to *N*-acylpyridinium ions as well as the subsequent rearomatization often proceed with low yields.[12] Recently, Knochel et al. reported a regioselective synthesis of 4-substituted pyridine derivatives including 4-(*tert*-butyl)nicotinonitrile, employing pyridine derivatives activated by $BF_3{\cdot}OEt_2$ and Grignard reagents in combination with LiCl or organozinc reagents as nucleophiles.[13] This method, however, requires pyridine derivatives with an electron-withdrawing group in the C-3 position. In addition, this approach suffers from the low stability of the formed dihydropyridine intermediates, precluding purification by chromatography, which can thus only be accomplished at the stage of the oxidized end product. This may be tedious if a starting material with similar physicochemical properties is still present. Alternatively, as described by Ready et al., lithium reagents may be added to 4-pyridineboronic esters to afford 4-substituted pyridines, such as 4-*tert*-butylpyridine.[14] Although highly attractive, this route suffers from the limited availability of boronic esters.

The regioselective trapping reactions of *N*-silylpyridinium ions with diorganomagnesium reagents represent an efficient approach to 4,4-disubstituted *N*-silyl-1,4-dihydropyridines[15] and dihydronicotinates,[16] as previously reported by us.

Based on these results, we envisaged that a related approach might allow a highly efficient and versatile access to 4-*tert*-butyl substituted pyridine derivatives with both

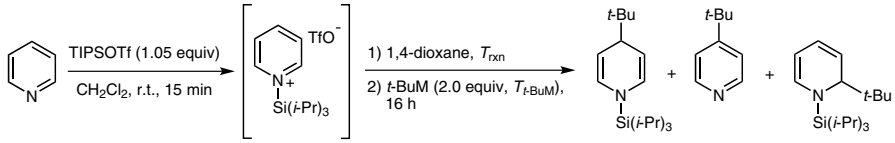
electron-withdrawing and electron-donating groups in the 3-position. Herein, we wish to report on the successful implementation of this plan.

To study the first step, the addition reaction for the introduction of a substituent in the 4-position, unsubstituted pyridine (**1**) was used as a model system because it is devoid of electron-donating or electron-withdrawing effects. For initial experiments, the reaction conditions published for the preparation of 4,4-dihydropyridines were used.[15,16] Thus, pyridine was first treated with 1.0 equivalents of TIPSOTf (15 min at r.t. in CH_2Cl_2) and subsequently with 2.0 equivalents of *t*-BuMgCl (Table 1, entry 2) or *t*-Bu_2Mg (Table 1, entry 1) at –78 °C. This afforded 1,4-dihydropyridine **3** and traces of its oxidation product 4-*tert*-butylpyridine (**4**) in a combined yield of 31% and 82%, respectively. As expected from previous results, the dialkylmagnesium reagent proved to provide far better yields than the Grignard reagent.[15,16] Interestingly, for the addition of *t*-BuMgCl, the yield increased from 31% to 41% when the reaction temperature was lowered from –78 to –85 °C and the Grignard reagent was cooled to –85 °C prior to the addition (Table 1, entry 3).

The high susceptibility of 1,4-dihydropyridine **3** to oxidation meant that the product obtained after aqueous workup was contaminated with 4-*tert*-butylpyridine (**4**), the amount of which varied with each reaction. Moreover, even in dihydropyridine **3** purified by LC, small amounts of the product **4** were constantly present. Accordingly, the yield of the purified product did not appropriately reflect the outcome of the reaction. Therefore, to determine regioselectivities and yields in every case, the amount of the products 1,2-dihydropyridine (**5**), 1,4-dihydropyridine (**3**) and 4-*tert*-butylpyridine (**4**) was quantified directly from the crude material obtained after aqueous workup by ^{1}H NMR spectroscopy employing 2,4,6-collidine as internal standard and by using the ^{13}C-^{1}H satellite peak integration technique developed by Claridge for the assessment of product ratios.[17] The high regioselectivity of the trapping reactions meant that the amount of 1,2-dihydropyridine **5** present in the crude reaction product did not suffice for a reliable NMR spectroscopic characterization of **5**. Therefore, the trapping reaction of TIPSOTf activated pyridine with *t*-BuMgCl was performed in THF at 0 °C, resulting in lower regioselectivity and thus giving isomer **5** in sufficient amounts (Table 1, entry 9).

To avoid the separate preparation of the diorganomagnesium reagent that had given far superior results compared with the readily available Grignard reagent, next the use of diorganomagnesium generated in situ was investigated. Thus, to a solution of the pyridinium ion **2** at –85 °C, first 4.4 equivalents 1,4-dioxane and subsequently 4.0 equivalents of precooled *t*-BuMgCl were added (Table 1, entry 4). In this case, the combined yield for **3** and **4** rose to 88%, thus being almost identical to the result obtained for

Table 1 Trapping Reaction of **2** with *tert*-Butyl Magnesium Reagents under Different Reaction Conditions



1 **2** **3** **4** **5**

Entry	T_{rxn} (°C)	$T_{t\text{-BuM}}$ (°C)	*t*-BuM (2.0 equiv)	1,4-Dioxane (equiv)	**3**/**4**/**5**[a]	Yield **3**/**4** (%)[a]
1	–78	r.t.	*t*-Bu_2Mg in THF/Et_2O (1:1)	–	–[c]	(82)[b]
2	–78	r.t.	*t*-BuMgCl in Et_2O	–	–[c]	(31)
3	–85	–85	*t*-BuMgCl in Et_2O	–	–[c]	(41)
4	–85	–85	*t*-BuMgCl in Et_2O[d]	4.4	–[c]	(88)
5	–85	–85	*t*-Bu_2Mg in THF/Et_2O (1:1)	–	96.4:2.9:0.7	(90)
6	–85	–85	*t*-Bu_2Mg in THF/Et_2O (1:1)	2.2	96.5:3.1:0.4	(97)
7	–85	–85	*t*-Bu_2Mg in THF	2.2	95.3:3.5:1.2	(90)
8	–85	–85	*t*-Bu_2Mg in Et_2O	2.2	98:2:0 9:1:0	(98) 94
9	0	r.t.	*t*-BuMgCl in Et_2O[f]	–	78:9:13	(20)[e]

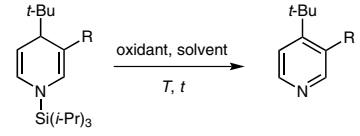
[a] Yield and product ratio of **3**, **4**, and **5** in the crude material were determined by ^{1}H NMR spectroscopy with 2,4,6-collidine as internal standard. Yield after aqueous workup is given in parentheses.
[b] Combined yield from two experiments because yields were strongly varying.
[c] Could not be determined.
[d] 4.0 equivalents were used.
[e] CH_2Cl_2 was replaced by THF after N-activation.
[f] 1.2 equivalents *t*-BuMgCl were used.

the conventional trapping reaction of **2** with *t*-Bu_2Mg at –85 °C, which had afforded the desired products **3** and **4**, in 90% yield (entry 5). A higher amount of dioxane, in turn, did not appear useful because it negatively influenced the homogeneity of the reaction mixture. Furthermore, 1,4-dioxane was also found to improve the combined yield for **3** and **4** for the trapping reaction of **2** with previously prepared dialkylmagnesium from 90% to 97% (compare entries 5 and 6). In this case, 2.2 equivalents dioxane proved to be sufficient.

Once additional 1,4-dioxane is present in the reaction mixture, it is likely that the Schlenk equilibrium between the Grignard and the diorganomagnesium species is continuously driven towards the latter, thus leading to an improved yield. Finally, the influence of the composition of the solvent containing *t*-Bu_2Mg was studied. Interestingly, when Et_2O/THF (1:1; Table 1, entries 1, 5 and 6) was replaced with pure THF, the yield decreased from 97% to 90% and the regioselectivity reduced from 99.6:0.4 to 98.8:1.2 (entry 7). In contrast, Et_2O turned out to be far more favorable for the dialkylmagnesium addition reaction, affording the desired 1,4-dihydropyridine **3** in almost quantitative yield of 98% according to NMR analysis with no 2-isomer **5** being detected (entry 8). After purification by flash chromatography, 1,4-dihydropyridine **3** and its oxidation product **4** could finally be isolated in an excellent combined yield of 94%. Clearly, the generation of the dialkylmagnesium reagent in situ with 1,4-dioxane is a very efficient and labor-saving approach, allowing the use of commercially available Grignard reagents. However, given that the combined application of previously formed dialkylmagnesium reagent and dioxane had led to better results with regard to yield and regioselectivity, it was used in all further addition reactions with the pyridinium salts.

In the next step, a mild and efficient method for the oxidation of 4-*tert*-butyl-*N*-silyl-1,4-dihydropyridines had to be established. For this purpose, both air-labile dihydropyridine **3** and air-stable dihydronicotinate **7**[16] were selected as model compounds and were subjected to oxidation reactions with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[18] MnO_2,[19] Pd/C, Pd/C with tetrabutylammonium fluoride (TBAF), *o*-chloranil,[20] SeO_2,[21] and S_8/naphthalene (Table 2).[21] Reaction of dihydropyridine **3** and dihydronicotinate **7** with DDQ afforded the corresponding 4-*tert*-butyl substituted oxidation products, pyridine derivative **4** and nicotinate **8**, in very low to moderate yields of only 13% (entry 1) and 41% (entry 7), respectively. With Pd/C and ambient air, 1,4-dihydropyridine **3** was easily oxidized under mild conditions, to give the aromatic compound **6** (81%; entry 2), whereas dihydronicotinate **7** turned out to be inert under these conditions (entry 4), which was also true when SeO_2 was applied to the latter (entry 10). In addition, only traces of pyridine derivative **8** were found if the oxidation of 1,4-dihydronicotinate **7** was attempted with MnO_2 at room

Table 2 Oxidation of 4-*tert*-Butyl-*N*-silyl-1,4-dihydropyridines **3** and **7**



R = H, **3**
R = COOEt, **7**

R = H, **4** (**6** hydrochloride)
R = COOEt, **8**

Entry	Dihydropyridine	Oxidant (equiv)	Solvent	*T* (°C)	*t* (min)	Prod.	Yield (%)
1	**3**	DDQ (1.1)	CH_2Cl_2	r.t.	30	**4**	13
2	**3**	Pd/C (0.05)	1,4-dioxane	r.t.	16 h	**6**	81
3	**3**	S_8 (1.1)	naphthalene	200[a]	10	**6**	90
4	**7**	Pd/C (0.05)	1,4-dioxane	r.t.	16 h	**8**	educt[b]
5	**7**	MnO_2 (5.0)	no solvent	r.t.	16 h	**8**	trace
6	**7**	MnO_2 (10)	CH_2Cl_2	60[c]	180	**8**	–[e]
7	**7**	DDQ (1.5)	CH_2Cl_2	r.t.	60	**8**	41
8	**7**	*o*-chloranil (2.0)	CH_2Cl_2	50	60	**8**	29[d]
9	**7**	Pd/C (0.05), TBAF (2.0)	1,4-dioxane	r.t.	16 h	**8**	–[e]
10	**7**	SeO_2 (1.4)	THF	r.t.	16 h	**8**	educt[b]
11	**7**	S_8 (1.1)	naphthalene	200[a]	10	**8**	96

[a] Microwave-assisted reaction, MW: 300 W.
[b] Starting material was completely recovered.
[c] Microwave assisted reaction, MW: 100 W.
[d] Contaminated with 16% ethyl nicotinate, because the *tert*-butyl group was lost during the oxidation.
[e] Full conversion into ethyl nicotinate.

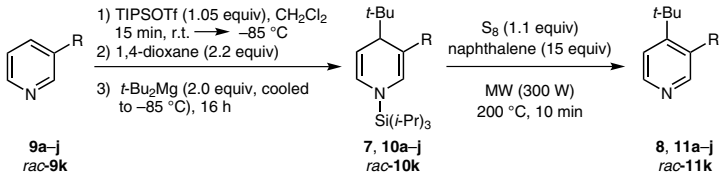
temperature (entry 5). Astonishingly, for the reaction of **7** with MnO_2 in CH_2Cl_2, if the temperature was raised to 60 °C by microwave irradiation[19] (entry 6) the *tert*-butyl group was lost, leading to ethyl nicotinate as the final product. To a lesser extent (16%), loss of the *tert*-butyl group was also observed if **7** was reacted with *o*-chloranil in CH_2Cl_2 at 60 °C (entry 8). Reaction with Pd/C and TBAF for desilylation (entry 9) gave again only ethyl nicotinate. Given the lability of the *tert*-butyl group observed for the oxidation reactions, we tested a sulfur-mediated aromatization as a promising alternative, although known procedures using sulfur in boiling xylene[22] or toluene[23] suffer from very long reaction times of up to 3 days.

To our delight, oxidation of **7** with sulfur in naphthalene under microwave heating to 200 °C led to complete conversion within 10 minutes, affording the desired 4-*tert*-butyl substituted nicotinate **8** in an excellent yield of 96% (Table 2, entry 11). In the same way, **3** could also be smoothly transformed into **4** and was isolated as hydrochloride **6** in 90% yield (entry 3).

In neither case was side product formation observed. Compared with the conventional sulfur mediated oxidations, the method reported herein using microwave for heating, represents a valuable alternative.

The optimized method described above for the addition of diorganomagnesium reagents to TIPSOTf activated pyridines and oxidation of the resulting *N*-silyl-1,4-dihydropyridines to the respective aromatic compounds was finally applied to the synthesis of a series of 3-substituted 4-*tert*-butylpyridine derivatives (Table 3). Thus, for the addition of a *tert*-butyl residue, pyridine derivatives **9a–j** and *rac*-**9k**[24] (entries 1–11) were activated by treatment with 1.05 equivalents TIPSOTf (2.0 equivalents in the case of **9i**)[25] and subsequently treated with 2.0 equivalents of *t*-Bu_2Mg in CH_2Cl_2 at –85 °C after prior addition of 2.2 equivalents 1,4-dioxane. The resulting 1,4-dihydropyridines **7**, **10b–j**, and *rac*-**10k** were finally oxidized to the corresponding 3-substituted 4-*tert*-butylpyridine derivatives **8**, **11b–l**, and *rac*-**11k** with sulfur in naphthalene under microwave heating or, in the case of ethynyl substituted pyridine **11j**, with Pd/C in ambient air.

Table 3 Substrate Scope of the Activation, Trapping, and Oxidation Method for the Synthesis of 4-*tert*-Butylpyridine Derivatives



9a–j *rac*-**9k** | **7**, **10a–j** *rac*-**10k** | **8**, **11a–j** *rac*-**11k**

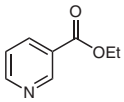
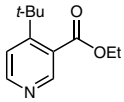
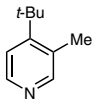
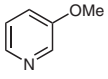
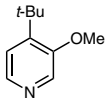
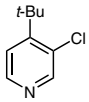
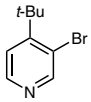
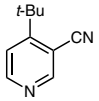
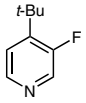
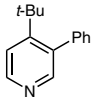
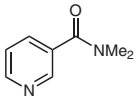
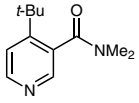
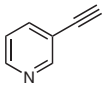
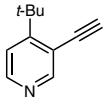
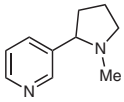
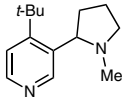
Entry	Educt	DHP (Yield (%)[a])	Product	Yield (%)[b]
1	**9a** 	**7** (86)[c]	**8** 	83
2	**9b** 	**10b** (89)	**11b** 	78
3	**9c** 	**10c** (93)	**11c** 	64
4	**9d** 	**10d** (78)	**11d** 	69
5	**9e** 	**10e** (95)	**11e** 	72

Table 3 (continued)

Entry	Educt	DHP (Yield (%)[a])	Product	Yield (%)[b]
6	**9f** 	**10f** (43)	**11f** 	30
7	**9g** 	**10g** (86)	**11g** 	47[d]
8	**9h** 	**10h** (88)	**11h** 	75
9	**9i** 	**10i** (74)	**11i** 	50[e]
10	**9j** 	**10j** (89)	**11j** 	31[f]
11	*rac*-**9k** 	*rac*-**10k** (81)	*rac*-**11k** 	62[g,h]

[a] Yield of 1,4-dihydropyridine (DHP) was determined by ^{1}H NMR spectroscopic analysis of the crude material after aqueous workup with 2,4,6-collidine as internal standard.
[b] Overall yield for both steps.
[c] Yield according to a reported procedure: 52%.[16]
[d] Isolated as the hydrochloride.
[e] N-activation with TIPSOTf (2.0 equiv).[25]
[f] Oxidation with Pd/C at room temperature.
[g] Trapping reaction with *t*-Bu_2Mg (1.1 equiv).
[h] Oxidation reaction at 120 °C.

The synthesis of the intermediate 1,4-dihydropyridines (**7**, **10b–j**, and *rac*-**10k**) was found to be highly regioselective and independent of the electron-withdrawing or electron-donating nature of the C-3 substituent. As a consequence, 1,4-addition products were strongly favored. Furthermore, *t*-Bu_2Mg clearly did not react with any of the functional groups present in the pyridine starting material, resulting mostly in good to excellent yields of the trapping product (74–95%). An exception was 3-cyanopyridine (**9f**; Table 3, entry 6) because the yield for the addition product **10f** amounted only to 43%. In addition, variation of the amount of TIPSOTf or *t*-Bu_2Mg from 1.0 to 2.0 equivalents applied in the reaction for both reagents did not lead to any improvement. Synthesis of known dihydropyridine **7** (entry 1) was achieved in 86% yield (lit.: 52%),[16] constituting a significant improvement on our previously reported trapping reaction.

High chemoselectivity was also observed for the transformation of *rac*-nicotine (*rac*-**9k**, Table 3, entry 11) into 1,4-dihydronicotinate *rac*-**10k** in 81% yield. Moreover, no silylation of the *N*-methylpyrrolidine ring followed by a ring opening was observed.[26] The next step, the sulfur mediated oxidation, proceeded smoothly within 10 minutes at 200 °C in a microwave reactor for the 3-substituted 1,4-dihydropyridines bearing an ester (**7**; entry 1), a methyl (**10b**; entry 2), a methoxy (**10c**; entry 3), a chloride (**10d**; entry 4), a bromide (**10e**; entry 5), a nitrile (**10f**; entry 6), a phenyl (**10h**; entry 8) or an amide group in the 3-position (**10i**; entry 9), providing the respective aromatic pyridine derivatives in 68–96% yield. In contrast, in the case of the oxidation of 3-fluoro substituted dihydropyridine **10g** (entry 7) the yield of the oxidation product **11g** amounted to only 55% because partial decomposition occurred. Notably, dihydronicotine *rac*-**10k** (entry 11) decomposed at 200 °C, but underwent complete oxidation within 10 minutes at a dis-

tinctly reduced temperature (i.e., 120 °C) with sulfur and naphthalene, yielding racemic 4-*tert*-butylnicotine *rac*-**11k** in good yield (77%).

Given that dihydropyridine **10j** (Table 3, entry 10) appeared to be labile in the presence of sulfur and naphthalene at 120 °C or 200 °C, clearly due to the ethynyl group in the 3-position, the oxidation was carried out under very mild conditions. Treatment of dihydropyridine **10j** with Pd/C at room temperature and ambient air (for method development see Table 2, entry 2) finally gave 4-(*tert*-butyl)-3-ethynylpyridine (**11j**) in 35% yield.

In conclusion, we developed a new transition-metal-free method for the synthesis of 3,4-disubstituted pyridine derivatives with a *tert*-butyl group in the 4-position and a series of substituents in the 3-position. To our knowledge, this is the first study focused on the introduction of a *tert*-butyl group into the 4-position of pyridine derivatives. Distinct advantages of our method are the high chemoselectivity and the excellent C-4 regioselectivity of the addition reaction. The method also benefits from the possibility to purify the *N*-silyl-1,4-dihydropyridine intermediates if necessary prior to oxidation to the aromatic compounds, which also proceeds very smoothly. Furthermore, many synthetically important functional groups such as an alkyl-aryl ether, ester, amide, halide, nitrile, alkyne, and tertiary amine are well tolerated by this methodology, which may be useful for further functionalization reactions. To explore the full potential of this method, further studies with regard to the applicability of a more diverse set of diorganomagnesium reagents such as diaryl-, secondary, and primary dialkylmagnesium compounds are under way.

Anhydrous reactions were carried out in vacuum-dried glassware under argon atmosphere. Microwave reactions were performed in sealed glass vials with a CEM Discover SP microwave synthesizer. THF, Et_2O, 1,4-dioxane, and CH_2Cl_2 were distilled prior to use under nitrogen atmosphere and dried according to standard procedures;[27] all other chemicals were used as purchased from commercial sources. TLC was carried out with plates purchased from Merck (silica gel 60 F_{254} on aluminum sheet). Flash chromatography (FC) was carried out with Merck silica gel 60 (40–63 μm mesh size) as stationary phase or activated basic alumina Brockmann I (150 μm mesh size) from Sigma–Aldrich, which was adjusted to the given activity grade.[28] Melting points were determined with a BÜCHI 510 melting point apparatus and are uncorrected. IR spectroscopy was performed with an FTIR Spectrometer 1600 and Paragon 1000 (PerkinElmer); oils were measured as film and solid samples as KBr pellets, all IR data are given in cm^{-1}. High-resolution (HR) mass spectrometry was performed with a Finnigan MAT 95 (EI) and Finnigan LTQ FT (ESI). ^1H and ^{13}C NMR spectra were recorded with a Bruker BioSpin Avance III HD (400 or 500 MHz) using TMS as internal standard and integrated with MestReNova (Version 10.0.2–15465), Mestrelab Research S.L. 2015.

Preparation of Di-*tert*-butylmagnesium Solution[29]

Commercially available *t*-BuMgCl (2 M in Et_2O) was diluted with THF or Et_2O at r.t. to afford a 1 M solution, which was carefully treated with 1,4-dioxane (1.2 equiv). The resulting suspension was stirred overnight at r.t., centrifuged, and the clear and colorless supernatant was transferred by using a cannula into a Schlenk flask. The concentration was determined by titration according to Chong's procedure.[30]

Synthesis of 4-*tert*-Butylpyridines; General Procedure

Trapping Reaction (GP-A)

TIPSOTf (1.05 equiv) was added to a solution of the corresponding pyridine derivative (1.0 equiv) in CH_2Cl_2 (6 mL/mmol) and the resulting mixture was stirred at r.t. for 15 min. The solution was cooled to –85 °C, treated with 1,4-dioxane (2.2 equiv) and, after 5 min, a –85 °C cold solution of *t*-Bu_2Mg (2.0 equiv) was added by using a transfer cannula. The reaction mixture was quenched after 16 h by the addition of water (6 mL/mmol) and saturated aqueous NaCl (10 mL/mmol). The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL/mmol), the combined organic layers were washed with saturated aqueous NaCl (15 mL/mmol), dried over Na_2SO_4, and the solvents were removed under reduced pressure. Quantitative analysis of the crude product by ^1H NMR spectroscopy using 2,4,6-collidine as internal standard revealed the amounts of the corresponding dihydropyridine and of its oxidation product. The crude material was then purified by flash chromatography (FC) to give the corresponding 4-*tert*-butyl-1,4-dihydropyridine as intermediate product.

Oxidation Reaction (GP-B)

Sulfur (1.1 equiv) and naphthalene (15 equiv) were added to the corresponding 4-*tert*-butyl-1,4-dihydropyridine and the resulting mixture was stirred at 200 °C under microwave conditions (300 W) for 10 min. The resulting residue was dissolved in Et_2O (15 mL/mmol) and the organic phase was washed with NaOH (2 × 15 mL/mmol). The combined aqueous layers were re-extracted with Et_2O (15 mL/mmol) and the combined organic layers were extracted with 2 M HCl (3 × 10 mL/mmol). The acidic aqueous layers were washed with Et_2O (15 mL/mmol) and the pH was adjusted to 9–10 by addition of K_2CO_3. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL/mmol) and the combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by FC.

4-(*tert*-Butyl)-1-(triisopropylsilyl)-1,4-dihydropyridine (3) and 4-(*tert*-Butyl)pyridine (4)

Prepared according to GP-A from **1** (79 mg, 1.0 mmol, 81 μL) in CH_2Cl_2 (6 mL) with TIPSOTf (0.32 g, 1.0 mmol, 0.28 mL), 1.4-dioxane (0.19 g, 2.2 mmol, 0.19 mL, 2.2 equiv) and *t*-Bu_2Mg (0.35 M in Et_2O, 2.0 mmol, 5.7 mL). Reaction time: 2 h. Quantitative analysis revealed 279 mg (95%) of **3** and 4 mg (3%) of **4**. Purification of the crude material by FC (Al_2O_3-basic, activity III, *n*-pentane) afforded **3** together with traces of its oxidation product **4**.

Yield: 263 mg (94%)*; colorless oil; R_f = 0.95 (SiO_2; *n*-pentane/Et_2O, 1:1).

IR (film): 3055, 2948, 2867, 1669, 1606, 1463, 1388, 1360, 1290, 1130, 1090, 1017, 988, 883, 854, 788, 713, 687 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83 (s, 9 H, C(CH_3)$_3$, **3**), 1.08 (d, *J* = 7.3 Hz, 18 H, CH(CH_3)$_2$, **3**), 1.19–1.27 (m, 3 H, C*H*(CH$_3$)$_2$, **3**), 1.32 (s, 0.1 × 9 H, CH_3, **4**), 2.66 (t, *J* = 4.2 Hz, 1 H, C*H*C(CH$_3$)$_3$, **3**), 4.50–4.53 (m, 2 H, NCHC*H*, **3**), 6.04–6.08 (m, 2 H, NCH, **3**), 7.27–7.28 (m, 0.1 × 2 H, NCHC*H*, **4**), 8.50–8.51 (m, 0.1 × 2 H, NCH, **4**).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.39 (*C*H(CH$_3$)$_2$, **3**), 17.84 (CH(*C*H$_3$)$_2$, **3**), 26.05 (C(*C*H$_3$)$_3$, **3**), 30.51 (C(*C*H$_3$)$_3$, **4**), 34.65 (*C*(CH$_3$)$_3$, **4**), 36.12 (*C*(CH$_3$)$_3$, **3**), 43.40 (*C*C(CH$_3$)$_3$, **3**), 101.18 (NCH*C*H, **3**), 120.71 (NCH*C*H, **4**), 130.07 (NCH, **3**), 149.67 (NCH, **4**), 159.91 (NCHCH*C*H, **4**).

* According to ^{1}H NMR spectroscopic analysis, isolated product after flash chromatography contained 250 mg (85%) of **3** and 13 mg (9%) of **4**.

4-(*tert*-Butyl)pyridin-1-ium Chloride (6)

Prepared according to GP-B from a mixture of **3** and **4** (282.6 mg; 0.28 g, 0.96 mmol of **3** and 2.6 mg, 19 µmol of **4**)* with sulfur (35 mg, 1.1 mmol) and naphthalene (1.9 g, 15 mmol). Purification by FC (SiO_2; *n*-pentane/Et_2O, 1:1) afforded **4** as a colorless liquid, which was treated with 2 M HCl in Et_2O (2.0 mL, 4.0 mmol) to give the corresponding hydrochloride **6**.

Yield: 0.15 g (90%); colorless hygroscopic solid.

IR (KBr): 2970, 1637, 1606, 1504, 1464, 1378, 1273, 1211, 1122, 1066, 1005, 929, 823, 741, 714 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.44–1.45 (m, 9 H, (CH$_3$)$_3$), 7.91 (d, *J* = 6.4 Hz, 2 H, NCHC*H*), 8.72–8.76 (m, 2 H, NCH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.16 ((CH$_3$)$_3$), 36.73 (*C*(CH$_3$)$_3$), 123.97 (NCH*C*H), 140.32 (NCH), 171.89 (NCHCH*C*).

HRMS (ESI): *m*/*z* [M – Cl$^-$]$^+$ calcd for $C_9H_{14}N$: 136.1121; found: 136.1121.

* Determined by ^{1}H NMR spectroscopic analysis with 2,4,6-collidine as internal standard prior to the synthesis.

4-(*tert*-Butyl)-3-methylpyridine (11b)

According to GP-A, a solution of **9b** (93 mg, 1.0 mmol, 97 µL) in CH_2Cl_2 (6 mL) was treated with TIPSOTf (0.32 g, 1.0 mmol, 0.28 mL), 1,4-dioxane (0.19 g, 2.2 mmol, 0.19 mL) and *t*-Bu_2Mg (0.43 M in Et_2O, 2.0 mmol, 4.7 mL). Quantitative analysis revealed 260 mg (85%) of dihydropyridine **10b** and 6 mg (4%) of the oxidation product **11b**. Purification by FC (Al_2O_3-basic, activity III, *n*-pentane). Oxidation of dihydropyridine **10b** was performed according to GP-B with sulfur (35 mg, 1.1 mmol) and naphthalene (1.9 g, 15 mmol). Purification by FC (SiO_2; *n*-pentane/Et_2O, 1:1) afforded **11b**.

Yield: 116 mg (78%); colorless oil; R_f = 0.46 (SiO_2; *n*-pentane/Et_2O, 1:1).

IR (film): 3102, 2966, 2874, 1590, 1539, 1485, 1461, 1403, 1380, 1365, 1308, 1260, 1240, 1201, 1174, 1102, 1084, 1037, 1022, 995, 929, 852, 829, 798, 755, 694 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 9 H, (CH$_3$)$_3$), 2.49–2.51 (m, 3 H, CH_3), 7.21 (d, *J* = 5.3 Hz, 1 H, NCHC*H*), 8.28–8.30 (m, 1 H, NC*H*C(CH$_3$)), 8.32–8.34 (m, 1 H, NC*H*CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.01 (*C*CH$_3$), 29.89 (C(*C*H$_3$)$_3$), 35.78 (*C*(CH$_3$)$_3$), 120.55 (NCH*C*H), 131.34 (NCH*C*CH$_3$), 147.75 (N*C*HCH), 152.94 (N*C*HC(CH$_3$)), 156.55 (*C*C(CH$_3$)$_3$).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{10}H_{15}N$: 149.1199; found: 149.1198.

4-(*tert*-Butyl)-3-methoxypyridine (11c)

According to GP-A, a solution of **9c** (108 mg, 963 µmol, 100 µL) in CH_2Cl_2 (6 mL) was treated with TIPSOTf (319 mg, 1.01 mmol, 280 µL), 1,4-dioxane (187 mg, 2.12 mmol, 180 µL) and *t*-Bu_2Mg (0.45 M in Et_2O, 1.93 mmol, 4.28 mL). Quantitative analysis revealed 227 mg (73%) of dihydropyridine **10c** and 32 mg (20%) of the oxidation product **11c**. Purification by FC (Al_2O_3-basic, activity III, *n*-pentane). Oxidation of dihydropyridine **10c** was performed according to GP-B with sulfur (34.0 mg, 1.06 mmol) and naphthalene (1.85 g, 14.4 mmol). Purification by FC (SiO_2; *n*-pentane/Et_2O, 1:1) afforded **11c**.

Yield: 102 mg (64%); colorless liquid; R_f = 0.22 (SiO_2; *n*-pentane/Et_2O, 1:1).

IR (film): 3105, 3056, 2999, 2959, 2914, 2869, 2840, 1590, 1546, 1488, 1463, 1416, 1393, 1362, 1305, 1262, 1239, 1214, 1190, 1171, 1103, 1087, 1025, 933, 892, 850, 828, 800, 695 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.36 (s, 9 H, (CH$_3$)$_3$), 3.94 (s, 3 H, OCH_3), 7.15 (d, *J* = 5.0 Hz, 1 H, NCHC*H*), 8.17 (d, *J* = 4.9 Hz, 1 H, NC*H*CH), 8.21 (s, 1 H, NC*H*COCH$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.90 (C(*C*H$_3$)$_3$), 34.79 (*C*(CH$_3$)$_3$), 55.68 (OCH_3), 121.04 (NCH*C*H), 133.96 (NCH*C*OCH$_3$), 142.73 (N*C*HCH), 146.64 (*C*C(CH$_3$)$_3$), 154.73 (NCH*C*OCH$_3$).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{10}H_{15}NO$: 165.1148; found: 165.1155.

4-(*tert*-Butyl)-3-chloropyridine (11d)

According to GP-A, a solution of **9d** (0.29 g, 2.5 mmol, 0.25 mL) in CH_2Cl_2 (15 mL) was treated with TIPSOTf (0.83 g, 2.6 mmol, 0.73 mL), 1,4-dioxane (0.49 g, 5.5 mmol, 0.47 mL) and *t*-Bu_2Mg (0.43 M in Et_2O, 5.0 mmol, 12 mL). Quantitative analysis revealed 641 mg (78%) of dihydropyridine **10d**. Purification by FC (Al_2O_3-basic, activity III, *n*-pentane). Oxidation of dihydropyridine **10d** was performed according to GP-B with sulfur (88 mg, 2.8 mmol) and naphthalene (4.8 g, 38 mmol). Purification by FC (SiO_2; *n*-pentane/Et_2O, 3:1) afforded **11d**.

Yield: 291 mg (69%); clear brownish liquid; R_f = 0.50 (SiO_2; *n*-pentane/Et_2O, 3:1).

IR (film): 3038, 3000, 2963, 2874, 1580, 1482, 1471, 1398, 1366, 1289, 1259, 1199, 1135, 1090, 1042, 932, 831, 748, 685 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, (CH$_3$)$_3$), 7.30 (d, *J* = 5.3 Hz, 1 H, NCHC*H*), 8.38 (d, *J* = 5.2 Hz, 1 H, NC*H*CH), 8.49 (s, 1 H, NCHCCl).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.68 (C(*C*H$_3$)$_3$), 36.09 (*C*(CH$_3$)$_3$), 122.19 (NCH*C*H), 131.52 (NCH*C*Cl), 147.89 (N*C*HCH), 151.28 (N*C*HCCl), 155.20 (*C*C(CH$_3$)$_3$).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_9H_{12}ClN$: 169.0653; found: 169.0651.

3-Bromo-4-(*tert*-butyl)pyridine (11e)

According to GP-A, a solution of **9e** (0.32 g, 2.0 mmol, 0.19 mL) in CH_2Cl_2 (12 mL) was treated with TIPSOTf (0.66 g, 2.1 mmol, 0.58 mL), 1,4-dioxane (0.39 g, 4.4 mmol, 0.38 mL) and *t*-Bu_2Mg (0.45 M in Et_2O, 4.0 mmol, 8.9 mL). Quantitative analysis revealed 708 mg (95%) of dihydropyridine **10e**. Purification by FC (Al_2O_3-basic, activity III, *n*-pentane). Oxidation of dihydropyridine **10e** was performed according to GP-B with sulfur (71 mg, 2.2 mmol) and naphthalene (3.8 g, 30 mmol). Purification by FC (SiO_2; *n*-pentane/Et_2O, 4:1) afforded **11e**.

Yield: 308 mg (72%); clear colorless liquid; R_f = 0.38 (SiO_2; *n*-pentane/Et_2O, 4:1).

IR (film): 3082, 3038, 2998, 2967, 2873, 1579, 1481, 1467, 1397, 1365, 1288, 1257, 1229, 1197, 1130, 1088, 1025, 1016, 931, 918, 831, 747, 732, 680 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.50 (s, 9 H, $(CH_3)_3$), 7.32 (d, *J* = 5.2 Hz, 1 H, NCHC*H*), 8.41 (d, *J* = 5.3 Hz, 1 H, NC*H*CH), 8.67 (s, 1 H, NCHCBr).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.74 ($C(CH_3)_3$), 36.65 ($C(CH_3)_3$), 121.10 (NCH*C*Br), 122.76 (NCH*C*H), 148.37 (N*C*HCH), 154.21 (N*C*HCBr), 156.57 (*C*C$(CH_3)_3$).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_9H_{12}BrN$: 213.0148; found: 213.0140.

4-(*tert*-Butyl)pyridine-3-carbonitrile (11f)

According to GP-A, a solution of **9f** (0.21 g, 2.0 mmol) in CH_2Cl_2 (12 mL) was treated with TIPSOTf (0.66 g, 2.1 mmol, 0.58 mL), 1,4-dioxane (0.39 g, 4.4 mmol, 0.38 mL) and *t*-Bu_2Mg (0.46 M in Et_2O, 4.0 mmol, 8.7 mL). Quantitative analysis revealed 276 mg (43%) of dihydropyridine **10f**. Purification by FC (Al_2O_3-basic, activity III; *n*-pentane/Et_2O, 9:1). Oxidation of dihydropyridine **10f** was performed according to GP-B with sulfur (71 mg, 2.2 mmol) and naphthalene (3.8 g, 30 mmol). Purification by FC (SiO_2; *n*-pentane/EtOAc, 1:1) afforded **11f**.

Yield: 96 mg (30%); yellow solid; mp 38–39 °C; R_f = 0.31 (SiO_2; *n*-pentane/EtOAc, 1:1).

IR (KBr): 3043, 2986, 2972, 2878, 2224, 1584, 1541, 1485, 1468, 1403, 1373, 1266, 1236, 1207, 1189, 1107, 1071, 981, 942, 930, 842, 788, 764, 695 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.52 (s, 9 H, $(CH_3)_3$), 7.40 (d, *J* = 5.4 Hz, 1 H, NCHC*H*), 8.68 (d, *J* = 5.4 Hz, 1 H, NC*H*CH), 8.82 (s, 1 H, NCHCCN).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.36 ($C(CH_3)_3$), 35.85 ($C(CH_3)_3$), 108.56 (NCH*C*CN), 118.10 (CN), 120.85 (NCH*C*H), 153.03 (N*C*HCH), 155.06 (NCHCCN), 162.37 (*C*C$(CH_3)_3$).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{10}H_{12}N_2$: 160.0995; found: 160.0997.

The analytical data were consistent with those previously reported.[13]

Ethyl 4-(*tert*-Butyl)pyridine-3-carboxylate (8)

According to GP-A, a solution of **9a** (305 mg, 2.00 mmol, 276 µL) in CH_2Cl_2 (12 mL) was treated with TIPSOTf (663 mg, 2.10 mmol, 582 µL), 1,4-dioxane (388 mg, 4.40 mmol, 376 µL) and *t*-Bu_2Mg (0.43 M in Et_2O, 4.00 mmol, 9.30 mL). Quantitative analysis revealed 628 mg (86%) of dihydropyridine **7**. Purification by FC (SiO_2; *n*-pentane/EtOAc, 9:1). Oxidation of dihydropyridine **7** was performed according to GP-B with sulfur (70.5 mg, 2.20 mmol) and naphthalene (3.85 g, 30.0 mmol). Purification by FC (SiO_2; hexanes/EtOAc, 4:1) afforded **8**.

Yield: 343 mg (83%); slightly yellowish oil; R_f = 0.42 (SiO_2; hexanes/EtOAc, 4:1).

IR (film): 2969, 2910, 2873, 1728, 1586, 1544, 1487, 1468, 1448, 1403, 1367, 1302, 1275, 1258, 1231, 1202, 1173, 1135, 1094, 1065, 1016, 959, 932, 873, 858, 837, 787, 754, 724, 687 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.39–1.42 (m, 12 H, $(CH_3)_3$, CH_2CH_3), 4.40 (q, *J* = 7.2 Hz, 2 H, CH_2), 7.35 (d, *J* = 5.5 Hz, 1 H, NCHC*H*), 8.51 (s, 1 H, NCHCCO), 8.55 (d, *J* = 5.5 Hz, 1 H, NC*H*CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.07 (CH_3CH_2), 30.49 (($CH_3)_3$), 36.01 ($C(CH_3)_3$), 61.85 (CH_2CH_3), 121.45 (NCHCH), 129.22 (NCH*C*CO), 149.36 (NCHCCO), 150.94 (N*C*HCH), 156.71 (NCHCH*C*), 169.87 (CCOOCH$_2$).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{12}H_{17}NO_2$: 207.1254; found: 207.1257.

4-(*tert*-Butyl)-3-fluoropyridin-1-ium Chloride (11g)

According to GP-A, a solution of **9g** (0.29 g, 3.0 mmol, 0.26 mL) in CH_2Cl_2 (18 mL) was treated with TIPSOTf (1.0 g, 3.2 mmol, 0.87 mL), 1,4-dioxane (0.58 g, 6.6 mmol, 0.57 mL) and *t*-Bu_2Mg (0.44 M in Et_2O, 6.0 mmol, 14 mL). Quantitative analysis revealed 805 mg (86%) of dihydropyridine **10g**. Purification by FC (Al_2O_3-basic, activity III, *n*-pentane). Oxidation of dihydropyridine **10g** was performed according to GP-B with sulfur (0.11 g, 3.3 mmol) and naphthalene (5.8 g, 45 mmol). Purification by FC (SiO_2; *n*-pentane/Et_2O, 2:1) afforded 4-(*tert*-butyl)-3-fluoropyridine as a colorless liquid, which was treated with 2 M HCl in Et_2O (4.5 mL, 9.0 mmol) to yield the corresponding hydrochloride **11g**.

Yield: 267 mg (47%); colorless solid; mp 125 °C; R_f (4-(*tert*-butyl)-3-fluoropyridine) = 0.39 (SiO_2; *n*-pentane/Et_2O, 2:1).

IR (film): 3040, 3070, 2994, 2963, 2875, 2699, 2517, 2076, 2052, 2025, 1900, 1643, 1595, 1526, 1513, 1485, 1460, 1400, 1368, 1349, 1256, 1236, 1226, 1205, 1150, 1106, 1078, 1028, 858, 827, 813 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.51 (d, *J* = 1.1 Hz, 9 H, $(CH_3)_3$), 7.88–7.93 (m, 1 H, NCHC*H*), 8.61 (d, *J* = 4.6 Hz, 1 H, NCHCF), 8.68 (d, *J* = 6.0 Hz, 1 H, NC*H*CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.73 (d, *J* = 3.1 Hz, $C(CH_3)_3$), 36.39 (d, *J* = 3.1 Hz, $C(CH_3)_3$), 125.60 (d, *J* = 5.4 Hz, NCH*C*H), 130.11 (d, *J* = 38.3 Hz, NCH*C*F), 137.51 (d, *J* = 4.4 Hz, NCHCH), 158.07 (d, *J* = 9.2 Hz, *C*C$(CH_3)_3$), 159.58 (d, *J* = 259.8 Hz, CF).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_9H_{13}FN$: 154.1027; found: 154.1026.

4-(*tert*-Butyl)-3-phenylpyridine (11h)

According to GP-A, a solution of **9h** (0.47 g, 3.0 mmol, 0.44 mL) in CH_2Cl_2 (18 mL) was treated with TIPSOTf (1.0 g, 3.2 mmol, 0.87 mL), 1,4-dioxane (0.58 g, 6.6 mmol, 0.57 mL) and *t*-Bu_2Mg (0.44 M in Et_2O, 6.0 mmol, 14 mL). Quantitative analysis revealed 976 mg (88%) of dihydropyridine **10h**. Purification by FC (Al_2O_3-basic, activity III, *n*-pentane). Oxidation of dihydropyridine **10h** was performed according to GP-B with sulfur (0.11 g, 3.3 mmol) and naphthalene (5.8 g, 45 mmol). Purification by FC (SiO_2; *n*-pentane/Et_2O, 1:2) afforded **11h**.

Yield: 477 mg (75%); colorless solid; mp 106–107 °C; R_f = 0.36 (SiO_2; *n*-pentane/Et_2O, 1:2).

IR (film): 3025, 3000, 2964, 2953, 1959, 1894, 1850, 1820, 1770, 1598, 1584, 1538, 1478, 1457, 1439, 1400, 1364, 1302, 1256, 1232, 1201, 1092, 1070, 1036, 1006, 992, 842, 774, 710, 696 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.18 (s, 9 H, $(CH_3)_3$), 7.25–7.29 (m, 2 H, CCHC*H*CH), 7.36–7.40 (m, 4 H, NCHC*H*, CC*H*CHCH, CCHCHC*H*), 8.16 (s, 1 H, NC*H*CCCHCHCH), 8.45 (d, *J* = 5.5 Hz, 1 H, NC*H*CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.83 ($C(CH_3)_3$), 36.85 ($C(CH_3)_3$), 121.54 (NCHCH), 127.63 (CCHCHCH), 127.87 (C*C*HCHCH), 130.75 (CCH*C*HCH), 137.83 (*C*CHCHCH), 141.76 (NCH*C*CCHCHCH), 149.07 (N*C*HCH), 152.63 (NCHCCCHCHCH), 156.57 (*C*C$(CH_3)_3$).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{15}H_{17}N$: 211.1361; found: 211.1355.

4-(*tert*-Butyl)-*N*,*N*-dimethylpyridine-3-carboxamide (11i)

According to GP-A, a solution of **9i** (0.45 g, 3.0 mmol) in CH_2Cl_2 (18 mL) was treated with TIPSOTf (1.9 g, 6.0 mmol, 1.7 mL), 1,4-dioxane (0.58 g, 6.6 mmol, 0.57 mL) and *t*-Bu_2Mg (0.39 M in Et_2O, 6.0 mmol, 15 mL). Quantitative analysis revealed 810 mg (74%) of dihydropyridine **10i**. Purification by FC (Al_2O_3-basic, activity III; *n*-pentane/EtOAc/CH_2Cl_2, 3:1:1). Oxidation of dihydropyridine **10i** was performed according to GP-B with sulfur (0.11 g, 3.3 mmol) and naphthalene (5.8 g, 45 mmol). Purification by FC (Al_2O_3-basic, activity III; EtOAc/CH_2Cl_2, 2:3) afforded **11i**.

Yield: 312 mg (50%); clear yellowish oil; R_f = 0.26 (Al_2O_3; EtOAc/CH_2Cl_2, 2:3).

IR (film): 2961, 2871, 1638, 1585, 1543, 1484, 1394, 1365, 1262, 1216, 1199, 1117, 1092, 1055, 933, 916, 843, 759, 696, 660 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (s, 9 H, $(CH_3)_3$), 2.85 (s, 3 H, NCH_3), 3.13 (s, 3 H, NCH_3), 7.36 (dd, *J* = 5.5/0.6 Hz, 1 H, NCHC*H*), 8.26–8.29 (m, 1 H, NCHCCO), 8.50 (d, *J* = 5.5 Hz, 1 H, NC*H*CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.41 ($C(CH_3)_3$), 34.85 (NCH_3), 36.23 ($C(CH_3)_3$), 39.36 (NCH_3), 122.14 (NCH*C*H), 131.24 (NCH*C*CO), 148.05 (NCHCCO), 149.84 (N*C*HCH), 155.95 (*C*C(CH$_3$)$_3$), 170.79 (CO).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{19}N_2O$: 207.1492; found: 207.1532.

4-(*tert*-Butyl)-3-ethynylpyridine (11j)

According to GP-A, a solution of **9j** (0.32 g, 3.0 mmol) in CH_2Cl_2 (18 mL) was treated with TIPSOTf (1.0 g, 3.2 mmol, 0.87 mL), 1,4-dioxane (0.58 g, 6.6 mmol, 0.57 mL) and *t*-Bu_2Mg (0.42 M in Et_2O, 6.0 mmol, 14 mL). Quantitative analysis revealed 848 mg (89%) of dihydropyridine **10j**. Purification by FC (Al_2O_3-basic, activity III; *n*-pentane). The colorless oil was dissolved in 1,4-dioxane (0.6 mL), treated with Pd/C (10% Pd, 0.16 g, 0.15 mmol) and the resulting suspension was stirred for 9 days at r.t. The mixture was filtered over Celite, washed with Et_2O (80 mL) and the organic layer was extracted with 2 M HCl (3 × 30 mL). The combined aqueous layers were washed with Et_2O (40 mL), neutralized with K_2CO_3, and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by FC (SiO_2; *n*-pentane/Et_2O, 1:1) to yield **11j**.

Yield: 146 mg (31%); colorless liquid; R_f = 0.47 (SiO_2; *n*-pentane/Et_2O, 1:1).

IR (film): 3298, 3205, 3035, 2992, 2963, 2909, 2871, 2098, 1583, 1537, 1483, 1463, 1448, 1398, 1365, 1291, 1263, 1203, 1193, 1102, 1075, 933, 850, 835, 789, 697 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49–1.50 (m, 9 H, $(CH_3)_3$), 3.52 (s, 1 H, CCH), 7.24–7.25 (m, 1 H, NCHC*H*), 8.44 (d, *J* = 5.4 Hz, 1 H, NC*H*CH), 8.65 (s, 1 H, NC*H*CCCH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.07 ($C(CH_3)_3$), 35.87 ($C(CH_3)_3$), 81.96 (*C*CH), 85.75 (C*C*H), 117.74 (NCHCCCH), 120.13 (NCH*C*H), 149.30 (NCHCH), 155.79 (N*C*HCCCH), 160.55 (*C*C(CH$_3$)$_3$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{13}N$: 159.1048; found: 159.1049.

***rac*-4-(*tert*-Butyl)-3-(1-methylpyrrolidin-2-yl)pyridine (*rac*-11k)**

According to GP-A, a solution of *rac*-**9k** (810 mg, 5.00 mmol, 798 µL) in CH_2Cl_2 (30 mL) was treated with TIPSOTf (1.66 g, 5.25 mmol, 1.45 mL), 1,4-dioxane (969 mg, 11.0 mmol, 941 µL) and *t*-Bu_2Mg (0.41 M in Et_2O, 5.50 mmol, 13.4 mL). Quantitative analysis revealed 1.53 g (81%) of dihydropyridine *rac*-**10k**. Purification by FC (Al_2O_3-basic, activity III; hexanes/EtOAc, 4:1). Oxidation of dihydropyridine *rac*-**10k** was performed according to GP-B with sulfur (176 mg, 5.50 mmol) and naphthalene (9.61 g, 75.0 mmol) at 120 °C. Purification by FC (SiO_2; Et_2O/Et_3N, 97:3) afforded *rac*-**11k**.

Yield: 671 mg (62%); colorless solid; mp 63 °C; R_f = 0.48 (SiO_2; Et_2O/Et_3N, 97:3).

IR (film): 3101, 3070, 3042, 2995, 2963, 2935, 2906, 2873, 2831, 2772, 2662, 1589, 1535, 1482, 1459, 1414, 1403, 1366, 1350, 1319, 1296, 1255, 1234, 1219, 1192, 1173, 1154, 1113, 1083, 1043, 974, 963, 922, 900, 841, 827, 709, 592, 573, 520 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 9 H, $(CH_3)_3$), 1.63–1.74 (m, 1 H, NCHC*H*H), 1.76–1.87 (m, 1 H, NCH_2CHH), 1.96–2.09 (m, 1 H, NCH_2CHH), 2.19 (s, 3 H, NCH_3), 2.22–2.37 (m, 2 H, NCHCH*H*, NC*H*-HCH_2), 3.24–3.31 (m, 1 H, NCH*H*CH_2), 3.82 (t, *J* = 8.2 Hz, 1 H, NC*H*CH_2), 7.16 (d, *J* = 5.4 Hz, 1 H, NCHC*H*), 8.35 (d, *J* = 5.4 Hz, 1 H, NC*H*CH), 8.96 (s, 1 H, NC*H*CCHNCH$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.90 (NCH_2CH_2), 31.39 ($C(CH_3)_3$), 35.53 ($C(CH_3)_3$), 36.41 ($NCHCH_2$), 40.29 (NCH_3), 56.82 (NCH_2CH_2), 65.61 ($NCHCH_2$), 119.71 (NCH*C*H), 138.32 (CH_3NCHC), 147.71 (N*C*HCH), 151.76 (NCHCCHNCH$_3$), 156.24 (*C*C(CH$_3$)$_3$) ppm.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{22}N_2$: 218.1783; found: 218.1774.

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Supporting Information

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