JOC Article

Efficient Synthesis of Novel NK_1 Receptor Antagonists: Selective 1,4-Addition of Grignard Reagents to 6-Chloronicotinic Acid Derivatives

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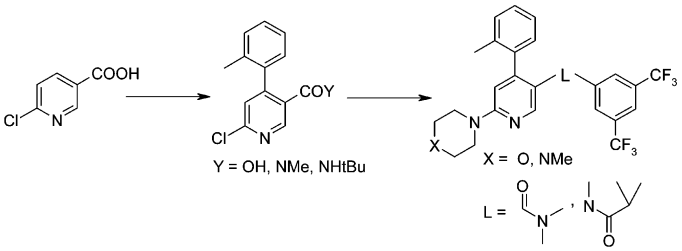

A new efficient synthesis of two novel classes of NK_1 receptor antagonists, among them befetupitant and netupitant, starting from 6-chloronicotinic acid is described. The introduction of the *o*-tolyl substituent at C(4) of the pyridine ring was achieved by a one-pot selective 1,4-Grignard addition/oxidation sequence to 6-chloronicotinic acid or a derivative of it. The scope of this addition/oxidation sequence was examined. It was also shown that the carboxylic function can be converted to a methyl amino group by a Hofmann rearrangement followed by reduction. Furthermore, a new high-yielding synthesis of 2-(3,5-bistrifluoromethylphenyl)-2-methyl propionic acid based on the carbonylation of the tertiary alcohol obtained by Grignard addition of 3,5-bis(trifluoromethyl)bromobenzene to acetone was established.

Introduction

Neurokinin (NK) receptors belong to the family of G-protein coupled receptors and are divided into three subtypes: NK_1, NK_2, and NK_3. The endogenous ligand for the NK_1 receptors is the 11 amino acid neuropeptide substance P.[1] Following the discovery of the first non-peptide NK_1 receptor antagonist CP-96,345,[2] a remarkable number of structurally diverse small molecule NK_1 receptor antagonists have been identified by many pharmaceutical companies in the past decade.[3] Recent clinical trials have demonstrated important therapeutic applications for NK_1 receptor antagonists in the treatment of depression and anxiety and in the control of chemotherapy-induced nausea and vomiting.[4] Two compound classes such as the nicotinamide **1** and the "inverse nicotinamides" befetupitant (**2**) and netupitant (**3**) have been identified at Roche as potent in vitro and in vivo NK_1 receptor antagonists.[5]

The strategy applied by Discovery Chemistry to synthesize compounds **1**−**3** and a large number of their congeners relied on an ortho-metalation−iodination sequence of 2,5-disubstituted pyridines **5**, **9**, and **10** followed by a Suzuki coupling to allow for rapid parallel lead optimization (Schemes 1 and 2). The iodination step required a large excess of ^{n}BuLi (3−4 equiv), low temperature (−78 °C), and afforded only moderate yields. In addition, *o*-tolylboronic acid used to introduce the aryl moiety

† Safety & Technical Sciences, Synthesis & Process Research.
‡ Discovery Chemistry, Lead Generation.

(1) Almeida, T. A.; Rojo, J.; Nieto, P. M.; Pinto, F. M.; Hernandez, M.; Martin, J. D.; Candenas, M. L. *Curr. Med. Chem.* **2004**, *11*, 2045−2081 and references therein.

(2) (a) Snider, R. M.; Constantine, J. W.; Lowe, J. A., III; Longo, K. P.; Lebel, W. S.; Woody, H. A.; Drozda, S. E.; Desai, M. C.; Vinick, F. J.; Spencer, R. W.; Hess, H.-J. *Science* **1991**, *251*, 435−437. (b) Lowe, J. A., III; Drozda, S. E.; Snider, R. M.; Longo, K. P.; Zorn, S. H.; Morrone, J.; Jackson, E. R.; McLean, S.; Bryce, D. K.; Bordner, J.; Nagahisa, A.; Kanai, Y.; Suga, O.; Tsuchiya, M. *J. Med. Chem.* **1992**, *35*, 2591−2600.

(3) Albert, J. S. *Expert Opin. Ther. Pat.* **2004**, *14*, 1421−1433 and references therein.

(4) Duffy, R. A. *Expert Opin. Emerging Drugs* **2004**, *9*, 9−21 and references therein.

(5) (a) Bös, M.; Branca, Q.; Galley, G.; Godel, T.; Hoffmann, T.; Hunkeler, W.; Schnider, P.; Stadler, H. EP1035115, 2000. (b) Hoffmann, T.; Bös, M.; Stadler, H.; Schnider, P.; Hunkeler, W.; Godel, T.; Galley, G.; Ballard, T. M.; Higgins, G. A.; Poli, S. M.; Sleight, A. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1362−1365.

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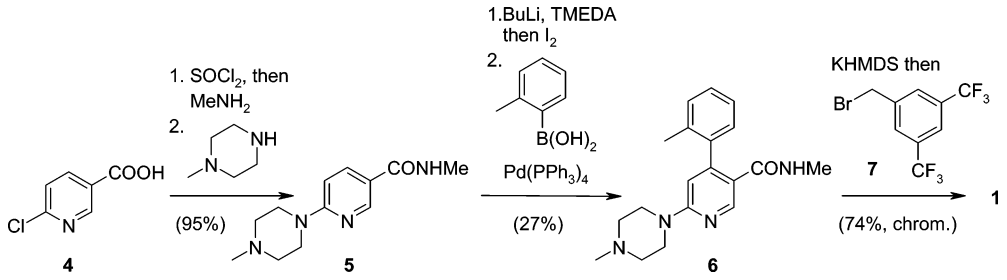
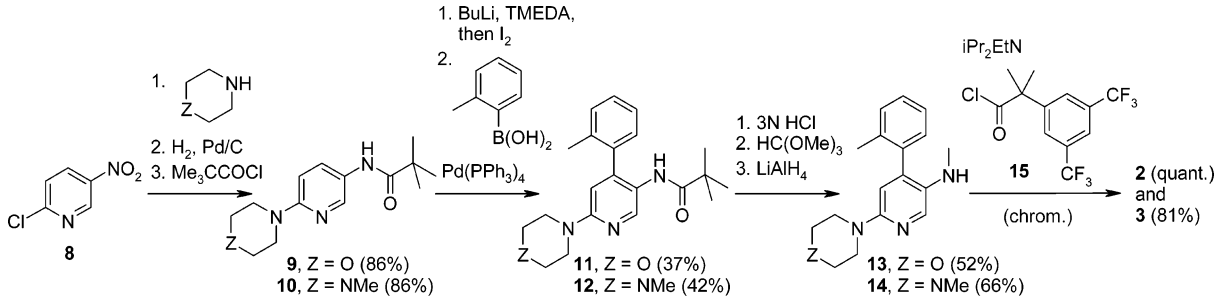
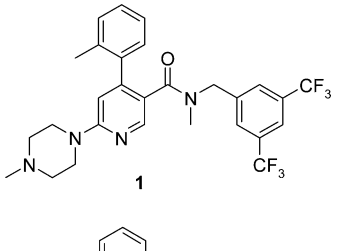
SCHEME 1

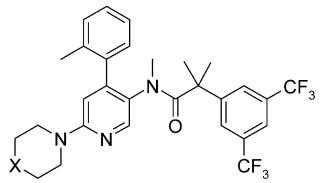


SCHEME 2



at C(4) of the pyridine ring was rather expensive. By this approach, **1** was prepared in five linear steps with an overall yield of 19% and **2** and **3** were prepared in nine steps with an overall yield of 21% and 15%, respectively. To supply larger amounts of these compounds for clinical evaluation, a cheaper, higher yielding, and technically feasible synthesis was therefore required. Herein, we report a practical and efficient approach for both compound classes.[6]

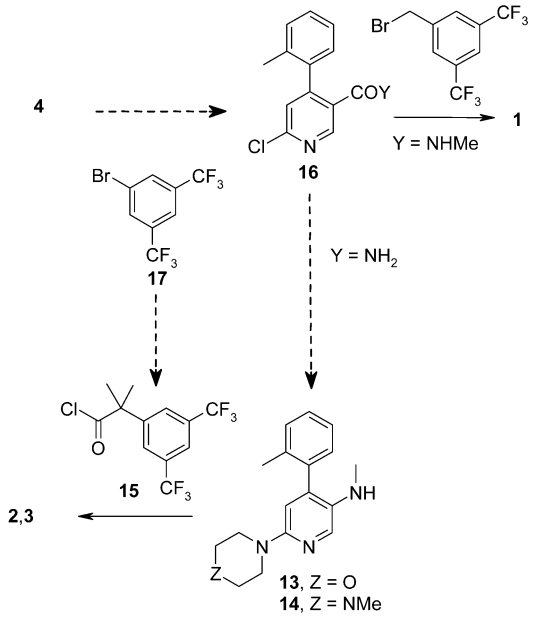




Results and Discussion

We considered introducing the C(4) substituent of compounds **1**−**3** by treating a 6-chloronicotinic acid derivative with *o*-tolylmagnesium chloride to obtain an *o*-tolylpyridine of structure **16** (Scheme 3). The subsequent steps toward **1** would then be straightforward. For **2** and **3**, the carboxyl function of **16** should be rearranged to known methylamines **13** and **14**. A new route to the acid chloride **15** starting with cheap bromobenzene **17** was also envisaged (vide infra). The well-reported

SCHEME 3



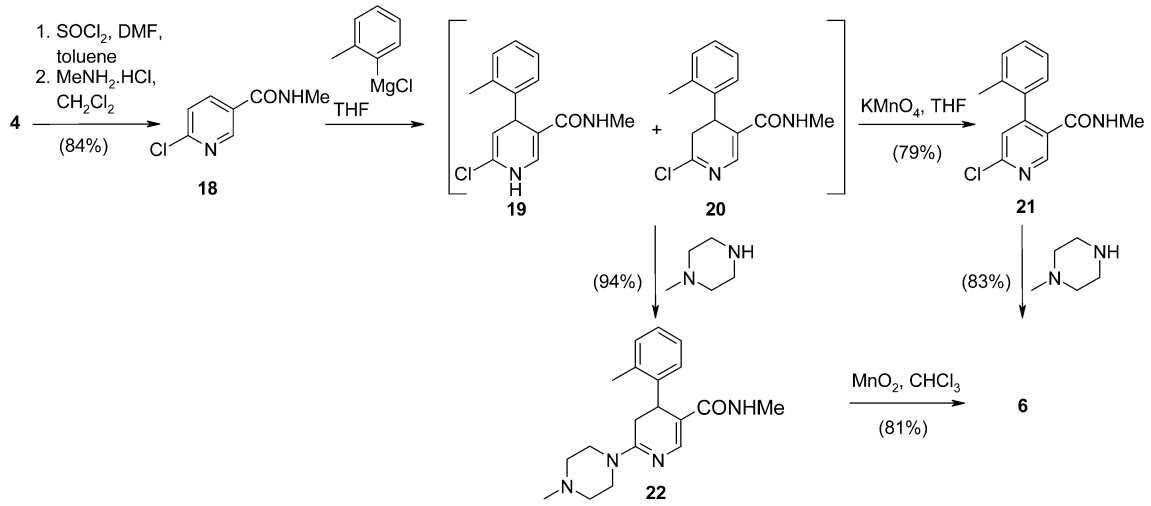
pyridine chemistry shows that nucleophilic addition of organolithium or magnesium compounds to 3-substituted pyridines often requires quaternization of the heterocyclic nitrogen, and the regioselectivity depends on the structure of the nucleophile and of the substituent.[7] 1,4-Regioselectivity was enhanced in alkyl nicotinates by quaternization of the heterocyclic nitrogen and by the use of organocopper reagents.[8] However, the oxazoline of nicotinic acid led to 1,4-dihydropyridine after

(6) These syntheses have been described in patents: Hilpert, H.; Hoffmann-Emery, F.; Rimmler, G.; Rogers-Evans, M.; Stahr, H. EP1103546, 2001.

(7) For reviews on the chemistry of dihydropyridines, see: (a) Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1−16. (b) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223−243. For reviews on regioselective substitution, see: (c) Comins, D. L.; O'Connor, S. *Adv. Heterocycl. Chem.* **1988**, *44*, 199−267.

(8) (a) Comins, D. L.; Stroud, E. D.; Herrick, J. J. *Heterocycles* **1984**, *22*, 151−157. (b) Shiao, M.-J.; Chia, W.-L.; Shing, T.-L.; Chow, T. J. *J. Chem. Res. (S)* **1992**, 247. (c) Bennasar, M.-L.; Juan, C.; Bosch, J. *Tetrahedron Lett.* **1998**, *39*, 9275−9278.

SCHEME 4

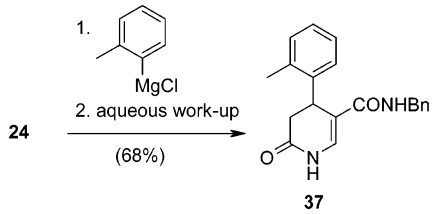


treatment with organometallic reagents without activation.[9] Ethyl and arylmagnesium bromide were added to the center C(4) of *N*-methyl or *N*-*tert*-butyl nicotinamide carrying an electron-withdrawing group at the center C(5) or C(6).[10] A good yield of 4-alkyl or 4-aryl nicotinamide was obtained after oxidation with NCS. *N*-(Phenyl)pyridine-3-carboxamide[11] and *N*-(*tert*-butyl)pyridine-3-carboxamide[12] were reported to undergo 1,4-addition of organolithium and organomagnesium reagents, respectively, whereas the corresponding 2- and 4-regioisomers were deprotonated.

Synthesis of 1. These literature precedents led us to treat methyl nicotinamide **18** (easily prepared from 6-chloronicotinic acid (**4**) via the acid chloride) with *o*-tolylmagnesium chloride without further activation. The reaction was clean and gave presumably a mixture of the dihydropyridines **19** and **20** (Scheme 4), which were unstable upon solvent removal. Thus, the extraction solution was oxidized with $KMnO_4$ producing **21** in 79% yield after chromatography and **21** was further treated with *N*-methylpiperazine affording **6** quantitatively as a crude product. Alternatively, the solution containing **19** and **20** was first treated with *N*-methylpiperazine to form the crude substitution product **22** in 94% yield, which was oxidized with MnO_2 leading to **6** in 81% yield after chromatography. As already described by Discovery Chemistry, alkylation of **6** with benzylbromide **7** in the presence of KHMDS gave **1** in 74% yield.[5a] Thus, the new route delivered **1** in only four steps with an overall yield of 47%.

Synthesis of 2 and 3. To access the inverse nicotinamides **2** and **3**, the same strategy as that for **1** was used to introduce the aryl substituent at C(4), followed by a Hofmann rearrangement to convert the carboxylic function at C(3) into an amine. Performing the Grignard addition/oxidation sequence on primary amide **30** or on acid **4** offered the shortest route to **2** and **3**. However, the addition of *o*-tolylmagnesium chloride to **4** followed by a one-pot oxidation with $Mn(OAc)_3$[13] afforded 4-*o*-tolylpyridine **31** in only a moderate yield of 51% and the same addition to **30** resulted in a complex mixture (Scheme 5). Because the methylamide **18**, a secondary amide, provided good results, *tert*-butylamide **23** and benzylamide **24** were prepared via the acid chloride of **4**. Compounds **23** and **24** both underwent regioselective addition of *o*-tolylmagnesium chloride giving *o*-tolylpyridine **25** following a one-pot oxidation with DDQ[14] in 98% yield after chromatography and *o*-tolylpyridine **26** after oxidation with $Mn(OAc)_3$ in 88% yield after chromatography, respectively. Yields obtained with other oxidants are summarized in Table 1.

Attempts to isolate the addition product after aqueous workup led to the corresponding pyridone as exemplified for the benzylamide **24** in eq 1.



(1)

The *o*-tolylpyridines **25** and **26** were heated in neat morpholine to yield the crude substitution products **27** and **28** in quantitative yield. Crude **25** obtained after removal of THF and precipitation of the salts by trituration in *tert*-butylmethyl ether was also treated with morpholine. After an aqueous basic workup, crude **27** was obtained in 89% yield based on **23**. Cleavage of the *tert*-butyl group of **27** was best performed in neat methanesulfonic acid at 100 °C for 5 h giving 95% crude primary amide **33**. The cleavage of the benzyl group of **28** turned out to be more tedious. Hydrogenolysis resulted in a complex mixture, whereas heating **28** in methanesulfonic acid and sulfuric acid (5:1) at 100 °C for 6 h afforded **33** in only 39% yield.

Compound **2** carries a methylamino group at C(3) of the pyridine ring. Because monoalkylation of amines via direct alkylation is known to be difficult leading partially to dialkylated products, monomethylation was reported to be achieved by converting the amine to the corresponding formimine,[15] forma-

(9) (a) Meyers, A. I.; Gabel, R. A. *Heterocycles* **1978**, *11*, 133−138. (b) Meyers, A. I.; Gabel, R. A. *J. Org. Chem.* **1982**, *47*, 2633−2637.

(10) Schlecker, W.; Huth, A.; Ottow, E.; Mulzer, J. *Tetrahedron* **1995**, *51*, 9531−9542.

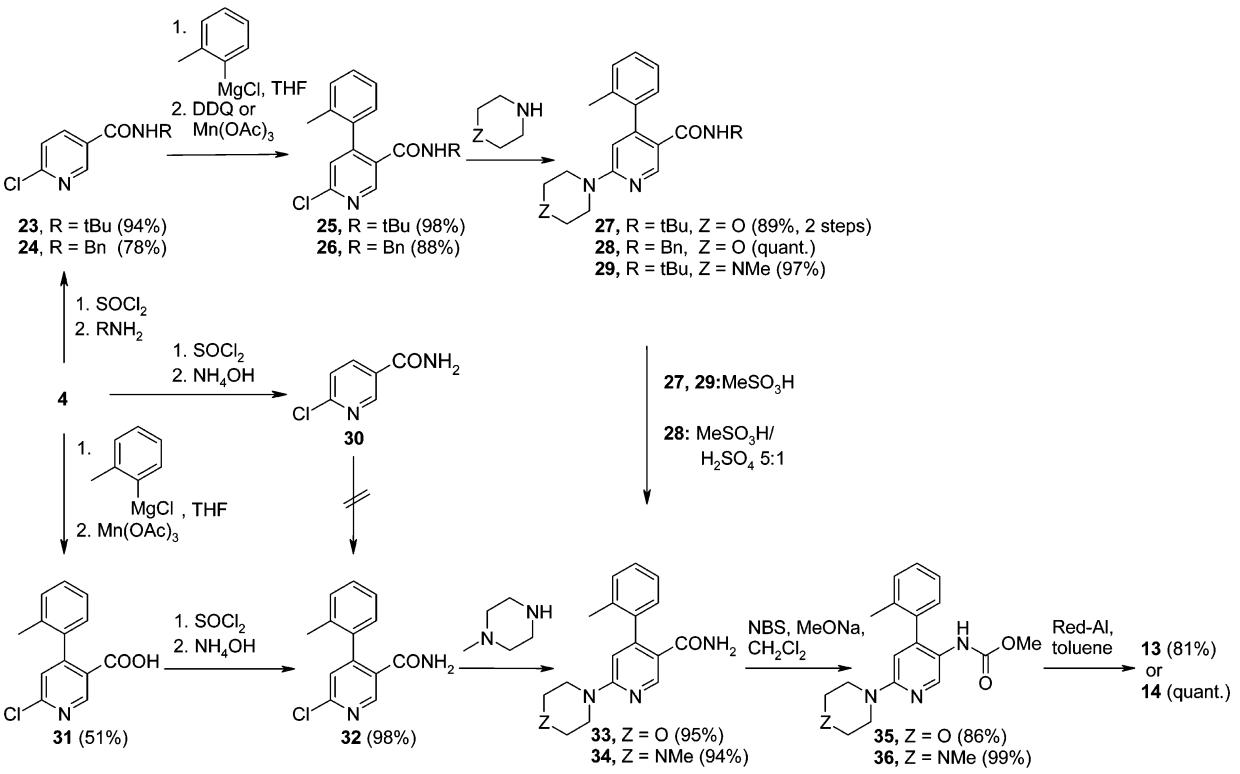
(11) Epsztajn, J.; Bieniek, A.; Brzezinski, J. Z.; Jozwiak, A. *Tetrahedron Lett.* **1983**, *24*, 4735−4738.

(12) Bonnet, V.; Mongin, F.; Trécourt, F.; Quéguiner, G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4245−4249.

(13) Varma, R. S.; Kumar, D. *Tetrahedron Lett*. **1999**, *40*, 21−24.

(14) Vanden Eynde, J. J.; Delfosse, F.; Mayence, A.; Van Haverbeke, Y. *Tetrahedron* **1995**, *51*, 6511−6516.

SCHEME 5

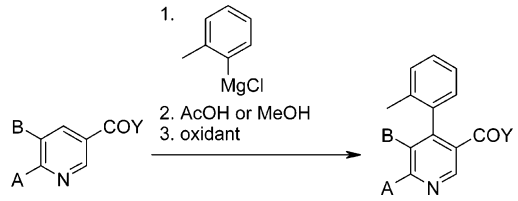


mide,[16] alkyl imidate,[17] or into a carbamate[18] followed by a reduction. Thus, amide **33** was rearranged to the corresponding methyl carbamate **35**, which was reduced to the desired methylamine **13**. The conditions of the Hofmann rearrangement best run between −5 °C and 0 °C were inspired by the work of Senanayake.[19] The optimal ratio of base to *N*-bromosuccinimide has been reported to be 2.5:1. In our case, 1.4 equiv of NBS and 3.5 equiv of sodium methoxide had to be used to reach complete conversion. Dichloromethane replaced advantageously methanol as the solvent, simplifying the workup because no solvent had to be removed before the extraction and keeping the yield unchanged at 86% of **35** after crystallization. The reduction of the methyl carbamate **35** was successfully achieved using Red-Al[20] in toluene at 50 °C for 2 h yielding 81% of methylamine **13** after crystallization. A portion of 4.7 equiv of Red-Al was required to achieve complete conversion. Alternatively, 10 equiv of a commercial $LiAlH_4$ solution in THF and heating at 50 °C for 24 h brought the reduction also to completion in nearly quantitative crude yield. However, with solid $LiAlH_4$ in dioxane, the reaction did not take place even at 100 °C.

Coupling of methylamine **13** with the acid chloride **15** in the presence of Hünig's base in dichloromethane gave **2** in 86% yield after crystallization. Thus, **2** was synthesized from **4** in seven steps and 50% overall yield.

Following an analogous route to that for **2**, compound **3** was prepared from *o*-tolylpyridine **25** via **29**. Alternatively, the

TABLE 1. Addition of *o*-Tolylmagnesium Chloride to Nicotinic Acid Derivatives[a]



entry	compd	A	B	Y	oxidant	yield[b] (%)
1	**4**	Cl	H	OH	$KMnO_4$	**31** (33)
					$Mn(OAc)_3$	**31** (51)
2	**23**	Cl	H	NH^{t}Bu	$KMnO_4$	**25** (26)
					$Mn(OAc)_3$	**25** (46)
					DDQ	**25** (98)
					o-chloranil	**25** (82)
3	**24**	Cl	H	NHBn	$KMnO_4$	**26** (45)
					$Mn(OAc)_3$	**26** (88)
					DDQ	**26** (66)
4	**38**	Cl	H	NEt_2	DDQ	**39** (86)
5	**40**	Me	H	NH^{t}Bu	DDQ	**41** (84)
6	**42**	morpholinyl	H	NH^{t}Bu	DDQ	**27** (44)
7	**43**	Cl	Cl	NH^{t}Bu	DDQ	**44** (55)[c]
8	**45**	Cl	H	OMe		complex mixture[21]
9	**46**	Cl	H	O^{t}Bu		complex mixture

[a] The addition was run in THF using 3.0−5.0 equiv. of *o*-tolylmagnesium chloride. The mixture was neutralized using AcOH or MeOH, and the oxidant was added. [b] Yield of product isolated after chromatography. [c] Isolated after digestion; not optimized.

(15) (a) Kessler, P.; Chatrenet, B.; Goeldner, M.; Hirth, C. *Synthesis* **1990**, 1065−1068. (b) Barluenga, J.; Bayón, A. M.; Asensio, G. *J. Chem. Soc., Chem. Commun*. **1984**, 1334−1335.

(16) Krishnamurthy, S. *Tetrahedron Lett.* **1982**, *23*, 3315−3318.

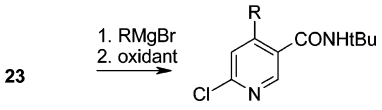
(17) Crochet, R. A., Jr.; DeWitt, B. C., Jr. *Synthesis* **1974**, 55−56.

(18) (a) Ganesan, A.; Heathcock, C. H. *Tetrahedron Lett.* **1993**, *34*, 439−440. (b) Carbamate prepared by a Hofmann rearrangement: Granados, R.; Alvarez, M.; Lopez-Calahorra, F.; Salas, M. *Synthesis* **1983**, 329−330.

(19) Senanayake, C. H.; Fredenburgh, L. E.; Reamer, R. A.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Am. Chem. Soc*. **1994**, *116*, 7947−7948.

(20) de Keravenant, B. French Patent No. 2.151.568, 1973.

TABLE 2. Addition of Grignard Reagents to 23[a]



49- 51

entry	R	oxidant	yield (%)
1	4-F-2-$CH_3C_6H_3$	I_2	**49** (81)[b]
2	4-F−C_6H_4	DDQ	**50** (48)[c]
3	$(CH_3)_2CH$[d]	DDQ	**51** (56)[c]
4	2-ClC_6H_4	DDQ	no reaction

[a] Reactions were run with 3.0 equiv of Grignard. [b] Yield isolated after chromatography and crystallization. [c] Yield isolated after digestion; method not optimized. [d] *i*-PrMgCl was used.

intermediate primary amide **34** was obtained by conversion of acid **31** to amide **32** via the corresponding acid chloride and heating **32** in neat *N*-methylpiperazine. Hofmann rearrangement of **34** in the presence of NBS and sodium methoxide gave the methyl carbamate **36** which was reduced with excess Red-Al to the methylamine **14**. Coupling of **14** with the acid chloride **15** gave **3**. Thus, compound **3** was prepared from **4** via **23** in seven steps and 63% overall yield and via **31** in six steps and 34% overall yield.

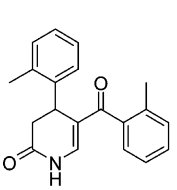
Scope of the 1,4-Grignard Addition. To extend the scope of the 1,4-Grignard addition/oxidation sequence, this reaction was performed with various derivatives of 6-chloronicotinic acid, as summarized in Table 1. Tertiary amide **38** also underwent the addition regioselectively (entry 4). Varying the substituent at C(6) (entries 5 and 6) led to lower yields with increasing electron-donating character. An additional chlorine substituent at C(5) was well tolerated (entry 7). Esters (entries 8 and 9) led to complex mixtures. Other Grignard reagents also added to *tert*-butylamide **23**, as shown in Table 2. *p*-Fluoro-*o*-tolylmagnesium bromide,[22] *p*-fluorophenylmagnesium bromide, and isopropylmagnesium chloride afforded good to moderate yields of **49**−**51**, respectively, whereas *o*-chlorophenylmagnesium bromide[23] unexpectedly did not react at all.

Synthesis of Propionic Acid 54. The acid chloride **15** used in the syntheses of **2** and **3** was obtained by treatment of the corresponding propionic acid **54** with oxalyl chloride[5] (Scheme 6).

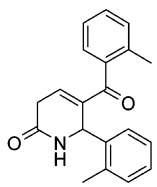
The Discovery Chemistry synthesis of **54** employed two sequential α-methylations of the expensive acetic acid **52** performed by deprotonation with ^{n}BuLi and trapping of the dianion with 1 equiv of iodomethane. On a small scale, **54** was obtained in an acceptable quality after crystallization. On a larger scale, however, the amount of impurities **55** and **56** in the crude product increased and crystallization was not sufficiently efficient to get pure **54**. Thus, a new route to **54** was designed starting from the less-expensive bromide **17**.[24] The Grignard reagent of **17** was generated in Et_2O by gentle heating in the presence of magnesium turnings,[25] and acetone was added to form the crude tertiary alcohol **53** in 98% yield. The carbonylation of **53** was first attempted under Koch−Haaf conditions,[26] i.e. by generating carbon monoxide in situ by acid-catalyzed decomposition of formic acid. To prevent rapid loss of carbon monoxide, the reaction is generally carried out by slow addition of the substrate (usually an alcohol or an olefin) dissolved in formic acid to a strong acid (usually sulfuric acid) with slow or even without stirring. However, because the reaction is diffusion controlled, reproducibility is usually low. Treatment of **53** with formic acid in sulfuric acid[27] resulted in dimer **57**. In neat trifluoromethanesulfonic acid, which is known to dissolve a 7-fold amount of carbon monoxide compared to sulfuric acid,[28] **54** was obtained at 0 °C in a yield varying between 11% and 56%. Dimers **57** and **58** were the major side products. Running the reaction under 1 bar CO did not improve the results. In methanesulfonic acid, **57** was formed exclusively. In $ClSO_3H$, $ClSO_3H$/AcOH 1:2, CF_3SO_3H/CH_2Cl_2 1:1, or H_3PO_4, decomposition or complex mixtures were observed. Because the concentration of carbon monoxide in the reaction mixture is a critical factor and the alcohol **53** has a limited stability in the presence of strong acids, the carbonylation was investigated under higher CO pressures. Thus, crude **53** was successfully carbonylated under 30 bar carbon monoxide in dichloromethane in the presence of trifluoromethanesulfonic acid and 0.5 equiv of water. Fluorosulfonic acid also promoted the carbonylation but rendered the isolation of the product more difficult. Other acids (sulfuric acid, methanesulfonic acid, hydrobromic acid, hydrochloric acid, and chlorosulfonic acid) induced only dehydration or decomposition. The use of 0.5 equiv of water improved the selectivity slightly. Finally, a simple extraction afforded **54** in 96% yield based on bromide **17** and in >99% purity. On a larger scale, the carbonylation was conveniently carried out by adding a solution of **53** in dichloromethane continuously by a pump to an autoclave containing the trifluoromethanesulfonic acid under CO pressure.

In summary, short and high-yielding syntheses of 2,4-disubstituted nicotinamide **1** and 2,4-disubstituted inverse nicotinamides **2** and **3** starting from 6-chloronicotinic acid have been described. The *o*-tolyl group at C(4) was introduced on secondary nicotinamides **18** and **23** by a regioselective 1,4-Grignard addition/oxidation sequence to afford the *o*-tolylpyridines **21** and **25**, respectively. **21** was converted in two further steps into **1**, which was thus obtained in four steps from **4** with

(21) The following compounds were isolated by column chromatography:



47 (26%)



48 (16%)

(22) With this Grignard reagent, oxidation with I_2 gave a better yield than that with DDQ. See also ref 6.

(23) Lindholm, A.; Klasson-Wehler, E.; Wehler, T.; Bergman, A. *J. Labelled Compd. Radiopharm.* **1987**, *24*, 1011−1019.

(24) This synthesis has been described in a patent: Hoffmann-Emery, F.; Scalone, M.; Spurr, P. WO2002079134, 2002.

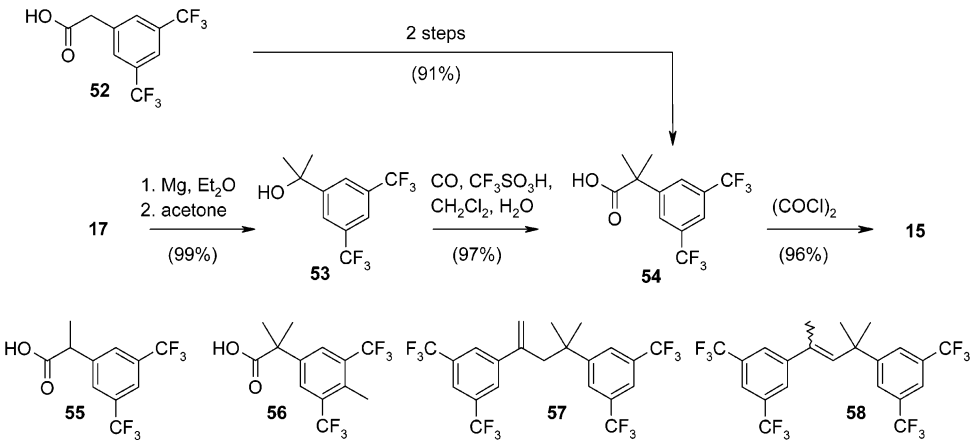
(25) During the preparation of this manuscript, formation of this Grignard reagent via Knochel's procedure (using ^{i}PrMgCl at low temperature) has been described. The authors also reported that the formation of this Grignard failed in THF using magnesium turnings but was successful with granules or dust: Leazer, J. L., Jr.; Cvetovich, R.; Tsay, F.-R.; Dolling, U.; Vickery, T.; Bachert, D. *J. Org. Chem.* **2003**, *68*, 3695−3698.

(26) (a) Haaf, W. *Chem. Ber.* **1966**, *99*, 1149−1152; *Org. Synth. Coll., Vol. V* **1973**, 739−742. (b) Olah, G. A. *Friedel−Crafts and Related Reactions*; Interscience: London, 1964; Vol. III, Part 2, pp 1284−ff. (c) Falbe, J. *Carbon Monoxide in Organic Synthesis*; Springer-Verlag: Berlin, 1970; Chapter III. Falbe, J. *Carbon Monoxide in Organic Synthesis*, 2nd ed.; Springer-Verlag: Berlin, 1980; Chapter 5.

(27) (a) Takahashi, Y.; Yoneda, N.; Nagai, H. *Chem. Lett.* **1985**, 1733−1734. (b) Takahashi, Y.; Yoneda, N. *Synth. Commun.* **1989**, *19*, 1945−1954.

(28) Booth, B. L.; El-Fekky, T. A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2441−2446.

SCHEME 6



an overall yield of 47%. Compound **25** was converted in four steps into methylamines **13** and **14** applying a Hofmann rearrangement/reduction sequence to "invert" the amide. Acylation of **13** and **14** with acid chloride **15** afforded **2** and **3**. Thus, **2** and **3** were prepared from **4** in seven steps with an overall yield of 50% and 63%, respectively. A selective, high-yielding, two-step synthesis of the propionic acid **54**, the precursor of **15**, was also established.

Experimental Section

6-Chloro-*N*-methyl-4-*o*-tolyl-nicotinamide (21). *o*-Tolylmagnesium chloride (1 M solution in THF, 22.0 mL, 22.0 mmol) was added over 30 min to a solution of **18** (1.5 g, 8.8 mmol) in THF (18.0 mL) cooled to 0 °C. The resulting brown solution was stirred for 2 h at room temperature and cooled to 0 °C, and cold (4 °C) 5% aqueous NH_4Cl (30.0 mL, 28.0 mmol) was added over 15 min. After separation of the phases, the aqueous phase was extracted with THF (2 × 30 mL). The combined organic extracts were washed with 5% aqueous NH_4Cl (2 × 30 mL), dried (Na_2SO_4), and treated at room temperature in four portions with $KMnO_4$ (0.9 g, 5.7 mmol). The suspension was stirred for 5.5 h, filtered, and concentrated on a rotary evaporator at 35 °C. The residue was dissolved in CH_2Cl_2 (4 mL) and purified by chromatography on silica gel (46 g) using CH_2Cl_2/MeOH 99:1 as eluent, yielding 1.8 g (79%) of **21** as a light yellow crystalline foam. A sample was crystallized from EtOH/water yielding **21** as a white powder: mp 102.5−104.5 °C; IR (Nujol) ν 3289, 3062, 2933, 2244, 1643, 1573, 1535, 1493, 1458, 1337, 1315, 1273, 1152, 1096, 909, 854, 758, 723 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (s, 1H), 8.30 (d br, 1H), 7.45 (s, 1H), 7.31−7.12 (m, 3H), 7.09 (d, J = 7.6 Hz, 1H), 2.56 (d, J = 4.8 Hz, 3H), 2.09 (s, 3H); ISP-MS (*m*/*z*) 263 (M + H$^+$, 27), 262 (13), 261 (M + H$^+$, 100). Anal. Calcd for $C_{14}H_{13}ClN_2O$: C, 64.50; H, 5.03; N, 10.74; Cl, 13.60. Found: C, 63.77; H, 5.32; N, 10.27; Cl, 14.19 (compound is hygroscopic).

6-(4-Methylpiperazin-1-yl)-4-*o*-tolyl-4,5-dihydropyridine-3-carboxylic Acid Methylamide (22). *o*-Tolylmagnesium chloride (1 M solution in THF, 43.8 mL, 43.8 mmol) was added over 30 min to a solution of **18** (3.0 g, 17.6 mmol) in THF (42 mL) cooled to 0 °C. The resulting brown solution was stirred for 1 h at room temperature and cooled to 0 °C, and cold (4 °C) 5% aqueous NH_4Cl (50.0 mL, 46.7 mmol) was added over 15 min. After phase separation, the aqueous phase was extracted with THF (2 × 50 mL). The combined organic extracts were washed with 5% aqueous NH_4Cl (2 × 50 mL), dried (Na_2SO_4), and treated at room temperature with *N*-methylpiperazine (9.8 mL, 87.4 mmol). The suspension was stirred for 2.5 h, and cold 5% aqueous NH_4Cl (40.0 mL, 37.4 mmol) was added. The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), concentrated under reduced pressure at 40 °C, and dried under high vacuum at room temperature for 18 h yielding **22** (5.4 g, 94%). A sample was further purified by chromatography on silica gel using dichloromethane/MeOH 19:1 as eluent yielding **22** as a white powder: mp 136.4−137.1 °C; IR (Nujol) ν 3305, 2925, 2854, 2786, 1619, 1585, 1527, 1460, 1361, 1312, 1288, 1266, 1208, 1149, 997 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.15 (d, J = 6.8 Hz, 1H), 7.11−7.04 (m, 2H), 6.98 (d, J = 7.2 Hz, 1H), 5.37 (s br, 1H), 4.24 (m, 1H), 3.48 and 2.23 (2t br, 2 × 4H), 2.76 (d, J = 4.8 Hz, 3H), 2.69−2.65 (m, 2H), 2.46 (s, 3H), 2.19 (s, 3H); ISP-MS (*m*/*z*) 327 (M + H$^+$, 100), 270 (12). Anal. Calcd for $C_{19}H_{26}N_4O$: C, 69.91; H, 8.03; N, 17.16. Found: C, 69.39; H, 8.03; N, 17.29 (compound is hygroscopic).

***N*-Methyl-6-(4-methylpiperazin-1-yl)-4-*o*-tolyl-nicotinamide (6). 21** (3.2 g, 12.2 mmol) was stirred in *N*-methylpiperazine (6.7 mL, 60.3 mmol) at 100 °C for 2.5 h. After cooling to room temperature, the reaction mixture was partitioned between deionized water (30 mL) and EtOAc (30 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with deionized water (20 mL) and brine (20 mL), dried (Na_2SO_4), concentrated under reduced pressure at 40 °C, and dried under high vacuum at room temperature for 18 h. The residue was purified by column chromatography on silica gel (160 g) yielding **6** (3.3 g, 83%) as a beige solid.

Alternatively, **22** (1.5 g, 4.6 mmol) dissolved in dichloromethane (15 mL) was treated at room temperature with MnO_2 (5.4 g, 55.1 mmol). The suspension was stirred for 18 h at 65 °C, cooled to room temperature, filtered, and concentrated under reduced pressure at 40 °C. The residue was purified by column chromatography on silica gel (26 g) yielding **6** (1.2 g, 81%) as a beige solid: mp 132.0−133.0 °C; IR (Nujol) ν 3269, 2927, 2855, 2789, 1625, 1596, 1555, 1491, 1459, 1408, 1377, 1321, 1295, 1229, 1143, 1003, 780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.35−7.27 (m, 3H), 7.20−7.18 (m, 1H), 6.32 (s, 1H), 5.10 (s, 1H), 3.67 and 2.51 (2t, J = 5.2 Hz, 2 × 4H), 2.61 (d, J = 4.8 Hz, 3H), 2.35 (s, 3H), 2.12 (s, 3H); ISP-MS (*m*/*z*) 325 (M + H$^+$, 100), 268 (32). Anal. Calcd for $C_{19}H_{24}N_4O$: C, 70.34; H, 7.46; N, 17.27. Found: C, 69.75; H, 7.39; N, 17.00 (compound is hygroscopic).

***N*-*tert*-Butyl-6-chloro-4-*o*-tolyl-nicotinamide (25). Representative Procedure for the Grignard Addition/Oxidation Sequence.** *o*-Tolylmagnesium chloride (1 M solution in THF, 28.2 mL, 28.2 mmol) was added slowly to a stirred solution of **23** (2.0 g, 9.4 mmol) in THF (10 mL) cooled to 0 °C. The resulting brown suspension was stirred for 3 h at room temperature and for 18 h at 30 °C and cooled to 0 °C. AcOH (2.69 mL, 47.0 mmol) was added over 15 min followed by DDQ (3.2 g, 14.1 mmol) in one portion, and after 1 h of stirring at room temperature, the suspension was poured into half-saturated aqueous Na_2CO_3 (100 mL) and EtOAc

(100 mL). The precipitate was filtered off and washed with EtOAc (2 × 20 mL). The phases of the filtrate were separated, and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with deionized water (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated on a rotary evaporator. The residue was dissolved in CH_2Cl_2 (10 mL) and filtered on silica gel (15 g) using EtOAc/*n*-heptane 1:1 as eluent yielding 2.8 g (98%) of **25** as a light yellow crystalline foam. A sample was further purified by column chromatography using EtOAc/*n*-hexane 1:9 as eluent yielding **25** as a white powder: mp 117.1−118.1 °C; IR (Nujol) ν 3305, 3066, 3040, 2924, 2854, 1635, 1585, 1547, 1454, 1390, 1319, 1222, 1087 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.41 (m, 1H), 7.33 (m, 2H), 7.18 (m, 2H), 5.06 (s br, 1H), 2.13 (s, 3H), 1.05 (s, 9H); ^1H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.56 (s, 1H), 7.44 (s, 1H), 7.35−7.18 (m, 4H), 2.10 (s, 3H), 1.06 (s, 9H); ISP-MS (*m*/*z*) 305 (29), 304 (15), 303 (M + H^+, 100). Anal. Calcd for $C_{17}H_{19}ClN_2O$: C, 67.43; H, 6.32; N, 9.25. Found: C, 67.18; H, 6.35; N, 9.08.

***N*-*tert*-Butyl-6-morpholin-4-yl-4-*o*-tolyl-nicotinamide (27).** *o*-Tolylmagnesium chloride (1 M solution in THF, 746 mL, 746 mmol) was added over 20 min to a solution of **23** (40.0 g, 187 mmol) in THF (200 mL) with cooling so that the temperature never exceeded 20 °C. The resulting dark green fluid suspension was stirred for 18 h at 30 °C and cooled to 0 °C. Methanol (45.4 mL, 1.1 mol) was added over 30 min, followed, after 10 min, by DDQ (50.8 g, 224 mmol). After 1 h of stirring at room temperature, the reaction mixture was concentrated to ca. 450 g under reduced pressure at 30 °C. The black oil obtained was heated to 50 °C, and *t*-BuOMe (800 mL) was added under vigorous stirring. The yellow-green suspension was refluxed for 30 min, cooled to room temperature, and stirred for 1 h at room temperature. The precipitate was filtered off and washed with *t*-BuOMe (4 × 200 mL), and the filtrate was concentrated under reduced pressure and dried under high vacuum at room temperature for 18 h yielding crude **25** (68.5 g). This material (68.0 g) was stirred in morpholine (217.4 mL) at 100 °C for 5 h. After cooling to room temperature, the reaction mixture was partitioned between deionized water (500 mL) and EtOAc (500 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (2 × 500 mL). The combined organic extracts were washed with deionized water (2 × 500 mL) and brine (250 mL), dried (Na_2SO_4), concentrated under reduced pressure, and dried under high vacuum at room temperature for 18 h yielding **27** (58.7 g, 89% based on **23**) as a brown foam: IR (Nujol) ν 3420, 2963, 2922, 2847, 1649, 1582, 1483, 1234, 1211, 1115 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.37−7.35 (m, 1H), 7.33−7.29 (m, 2H), 7.21−7.18 (m, 1H), 6.30 (s, 1H), 5.00 (s br, 1H), 3.81 and 3.60 (2t, J = 5.0 Hz, 2 × 4H), 2.13 (s, 3H), 1.03 (s, 9H); EI-MS (*m*/*z*) 353 (M^+, 81), 322 (75), 296 (54), 281 (100), 167 (32). Anal. Calcd for $C_{21}H_{27}N_3O_2$: C, 71.36; H, 7.70; N, 11.89. Found: C, 71.14; H, 7.67; N, 11.79.

Alternatively, *o*-tolylmagnesium chloride (1 M solution in THF, 76.0 mL, 76.0 mmol) was added over 15 min to a solution of **42** (5.0 g, 19.0 mmol) in THF (35.0 mL) cooled to 0 °C. The resulting brown suspension was stirred for 18 h at room temperature and for 4 h at reflux and cooled to 0 °C. MeOH (4.6 mL) was added over 25 min, followed by DDQ (12.8 g, 22.8 mmol). After 1 h at room temperature, the suspension was concentrated under reduced pressure to a fluid oil (ca. 55 g) and heated to 50 °C, and under vigorous stirring, *t*-BuOMe (100 mL) was added. The resulting suspension was stirred for 16 h at room temperature, and the precipitate was filtered off and washed with *t*-BuOMe (4 × 25 mL). The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography using EtOAc/*n*-heptane 1:1 as eluent yielding **27** (2.5 g, 44%) as a brown crystalline foam.

6-Morpholin-4-yl-4-*o*-tolyl-nicotinamide (33). 27 (58.2 g, 162.5 mmol) was stirred in methanesulfonic acid (115.9 mL, 1.79 mol) at 100 °C for 5 h. The reaction mixture was poured onto ice-cold deionized water (580 mL), and *t*-BuOMe (200 mL) was added. After vigorous stirring, the phases were separated and the aqueous phase was extracted with *t*-BuOMe (2 × 200 mL). The combined organic extracts were washed with deionized water (2 × 100 mL). The combined aqueous phases were brought to pH = 14 by addition of 28% aqueous NaOH (300 mL) and extracted with *t*-BuOMe (400 mL and 2 × 200 mL). These second organic extracts were combined, washed with deionized water (2 × 200 mL) and brine (100 mL), dried (Na_2SO_4), concentrated under reduced pressure, and dried under high vacuum at 40 °C for 8 h yielding **33** (46.4 g, 95%) as a light beige powder: mp 53.1−56.7 °C; IR (Nujol) ν 3465, 3326, 3178, 2924, 2854, 1662, 1588, 1528, 1489, 1452, 1378, 1234, 1117 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 1H), 7.38−7.30 (m, 3H), 7.21−7.19 (m, 1H), 6.30 (s, 1H), 5.40 and 5.09 (2s br, 2 × 1H), 3.81 and 3.63 (2t, J = 5.0 Hz, 2 × 4H), 2.15 (s, 3H); ISP-MS (*m*/*z*) 320 (M + Na^+, 6), 298 (M + H^+, 100).

Alternatively, **28** (0.5 g, 1.3 mmol) was stirred in methanesulfonic acid (2.5 mL) and concentrated H_2SO_4 (0.25 mL) at 100 °C for 1 h. After addition of concentrated H_2SO_4 (0.25 mL), stirring was pursued for 22 h at 100 °C. The reaction mixture was cooled to room temperature and slowly poured onto aqueous saturated Na_2CO_3 (75 mL) cooled with ice. EtOAc (50 mL) was added, and after vigorous stirring, the phases were separated. The aqueous phase was saturated with NaCl and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with aqueous saturated Na_2CO_3 (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated on a rotary evaporator. The residue was purified by flash chromatography using CH_2Cl_2/MeOH 95:5 as eluent yielding **33** (0.15 g, 39%) as a yellow resin.

(6-Morpholin-4-yl-4-*o*-tolylpyridin-3-yl)-carbamic Acid Methyl Ester (35). *N*-Bromosuccinimide (pract. 97%, 39.7 g, 216.3 mmol) was suspended in CH_2Cl_2 (230 mL) and cooled to −5 °C, and sodium methoxide (5.4 M solution in methanol, 100.1 mL, 540.5 mmol) was added over 30 min. The milky fluid suspension obtained was stirred at −5 °C for 15 h, and then a solution of **33** (45.9 g, 154.4 mmol) in CH_2Cl_2 (230 mL) was added over 20 min. The dropping funnel was rinsed with methanol (25 mL). The reaction mixture was further stirred for 7 h at −5 °C, acidified by the addition of 1 N aqueous HCl (332 mL), and diluted with CH_2Cl_2 (200 mL). After vigorous stirring, the phases were separated and the organic phase was washed with deionized water (2 × 400 mL). The aqueous phases were extracted with CH_2Cl_2 (2 × 200 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and dried under high vacuum at room temperature for 16 h. The residue (53.6 g of orange foam) was dissolved in CH_2Cl_2 (53.6 mL) at room temperature under stirring, and $^iPr_2O$ (268 mL) was added. After 30 min, *n*-heptane (536 mL) was added over 30 min and CH_2Cl_2 was distilled off at 40 °C under 300 mbar. The suspension was further stirred for 16 h at room temperature and for 2 h at −10 °C and filtered off. The precipitate was washed with *n*-heptane cooled to −10 °C (2 × 50 mL) and dried under high vacuum at 40 °C for 16 h yielding **35** (43.2 g, 86%) as a beige powder. Crude **35** (5.2 g of orange foam) prepared similarly starting from 4.5 g of **33** (14.3 mmol) was dissolved in EtOAc (26 mL) and *n*-hexane (26 mL). Alox 1 basic (5.2 g) was added and after 30 min filtered off. The filter cake was washed with EtOAc/*n*-hexane 1:1 (2 × 25 mL). The filtrate was concentrated in a rotary evaporator at 40 °C and dried under high vacuum. The residue (4.9 g of orange foam) was dissolved at room temperature in CH_2Cl_2 (5 mL), and $^iPr_2O$ (25 mL) was added in one portion. After 30 min of stirring at room temperature, *n*-heptane (50 mL) was added over 30 min, CH_2Cl_2 was distilled off, and the suspension was stirred for 2 h at 0 °C. The precipitate was filtered off, washed with *n*-heptane (20 mL), and dried under 10 mbar at 40 °C for 16 h yielding **35** (3.4 g, 69%) as a yellow powder: mp 125.4−130.5 °C; IR (Nujol) ν 3243, 2922, 2852, 1704, 1606, 1594, 1518, 1466, 1404, 1377, 1251, 1223, 1112, 1075, 954, 778, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.82 (s br, 1H), 7.36−7.27 (m, 3H), 7.12 (d, J = 7.6 Hz, 1H), 6.43 (s, 1H), 5.89 (s br, 1H), 3.84−3.81 (m, 4H), 3.67 (s, 3H), 3.49−3.46 (m, 4H), 2.12 (s, 3H); ISP-MS (*m*/*z*) 350 (M + Na^+, 3), 328 (M + H^+, 100), 296 (13).

Anal. Calcd for $C_{18}H_{21}N_3O_3$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.64; H, 6.43; N, 12.80.

Methyl-(6-morpholin-4-yl-4-*o*-tolylpyridin-3-yl)-amine (13). A solution of Red-Al (70% solution in toluene, 80.7 mL, 285 mmol) and toluene (100 mL) was added over 10 min to a solution of **35** (20.0 g, 61.1 mmol) in toluene (120 mL) with cooling such that the temperature did not exceed 50 °C. The resulting orange solution was stirred for 1 h at 50 °C and cooled to 0 °C, and 1 N aqueous NaOH (160 mL) was added over 15 min (*Caution*: *strongly exothermic*). The phases were separated, and the aqueous phase (cloudy) was extracted with toluene (2 × 100 mL). The combined organic extracts were washed with deionized water (2 × 100 mL) and brine (50 mL), dried (Na_2SO_4), concentrated under reduced pressure, and dried under high vacuum at room temperature. The residue was dissolved in CH_2Cl_2 (50 mL) at room temperature, and *n*-heptane (220 mL) was added. Impurities precipitated as an orange-brown resin, and the solution was decanted and concentrated under reduced pressure. The residue was dissolved in *n*-heptane (48 mL) at 40 °C, and after about 30 min, a light yellow suspension formed which was allowed to cool to room temperature and then further chilled to −10 °C. After 1 h at −10 °C, the precipitate was filtered off, washed with *n*-heptane (2 × 20 mL), and dried under high vacuum at 40 °C for 8 h yielding **13** (14.1 g, 81%) as a light yellow powder: mp 68.3−76.0 °C; IR (Nujol) ν 3345, 2923, 2854, 1611, 1503, 1451, 1396, 1376, 1239, 1119, 951 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.34−7.24 (m, 3H), 7.14 (d, J = 7.2 Hz, 1H), 6.45 (s, 1H), 3.85−3.83 (m, 4H), 3.40−3.31 (m, 4H), 2.97 (s br, 1H), 2.78 (s, 3H), 2.14 (s, 3H); ISP-MS (*m*/*z*) 284 (M + H$^+$, 100). Anal. Calcd for $C_{17}H_{21}N_3O$: C, 72.06; H, 7.47; N, 14.83. Found: C, 72.04; H, 7.65; N, 14.58.

2-(3,5-Bistrifluoromethylphenyl)-*N*-methyl-*N*-(morpholin-4-yl-4-*o*-tolylpyridin-3-yl)-isobutyramide (2). A solution of **15** (11.8 g, 36.9 mmol) in CH_2Cl_2 (5.0 mL) was added over 15 min to a solution of **13** (10.0 g, 35.3 mmol) and ^{i}Pr$_2$EtN (8.3 mL, 48.3 mmol) in CH_2Cl_2 (70 mL) cooled to 0 °C. After 3 h of stirring at 0 °C, the reaction mixture was poured onto deionized water (80 mL), and after 30 min of stirring at room temperature, the phases were separated. The organic phase was washed with deionized water (80 mL), 2% aqueous NaOH (80 mL), deionized water (80 mL), and 5% aqueous $NaHCO_3$ (80 mL). The aqueous phases were separately extracted with the same portion of CH_2Cl_2 (40 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to a volume of 50 mL, filtered on paper, and completely evaporated. The residue was dissolved in EtOH (100 mL) at 50 °C and concentrated in a rotary evaporator. The beige foam obtained was dissolved in EtOH (55 mL) at 50 °C and seeded with some crystals of **2**. The resulting beige suspension was stirred for 2 h at room temperature, for 1 h at 0 °C, and for 1 h at −20 °C and then filtered (glass filter P3). The precipitate was washed with EtOH (2 × 10 mL), cooled to −20 °C, and dried under 25−40 mbar at 50 °C for 2 h, followed by 16 h at 50 °C under high vacuum yielding **2** (16.3 g, 81%) as a white powder: mp 128.8−129.9 °C; IR (Nujol) ν 2923, 2855, 1638, 1605, 1594, 1485, 1453, 1375, 1364, 1287, 1266, 1236, 1190, 1170, 1124 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.76 (s, 1H), 7.65 (s, 2H), 7.26 (s br, 4H), 6.50 (s, 1H), 3.82 (m, 4H), 3.52 (m, 4H), 2.56, 2.33, 2.14 (3s br, 6H), 1.50 and 1.33 (2s br, 6H); ISP-MS (*m*/*z*) 588 (M + Na$^+$, 10), 566 (M + H$^+$, 100), 452 (16). Anal. Calcd for $C_{29}H_{29}F_6N_3O_2$: C, 61.59; H, 5.17; F, 20.16; N, 7.43. Found: C, 61.65; H, 5.22; F, 20.37; N, 7.50.

The mother liquors were evaporated under reduced pressure to an orange oil, which was crystallized from EtOH/H_2O 2:1 at 0 °C to give a beige powder (2.8 g). This solid was recrystallized from EtOH at −20 °C yielding **2** (1.0 g, 5%) as an off-white powder of mp 126.3−127.3 °C.

***N*-*tert*-Butyl-6-(4-methylpiperazin-1-yl)-4-*o*-tolyl-nicotinamide (29). 25** (14.6 g, 45.2 mmol) was stirred in *N*-methylpiperazine (43.8 mL, 394 mmol) at 100 °C for 4 h. After cooling to room temperature, the reaction mixture was partitioned between deionized water (146 mL) and EtOAc (146 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (2 × 73 mL). The combined organic extracts were washed with deionized water (73 mL) and brine (73 mL), dried (Na_2SO_4), concentrated under reduced pressure at 40 °C, and dried under high vacuum at room temperature for 18 h yielding **29** (17.1 g, 97%) as a brown, thick oil. A sample was purified by column chromatography to give **29** as a beige solid: mp 116.1−117.6 °C; IR (Nujol) ν 3421, 2964, 2937, 2844, 2793, 1655, 1590, 1521, 1490, 1452, 1297, 1239, 1219, 1141, 1006 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.38−7.29 (m, 3H), 7.21−7.19 (m, 1H), 6.32 (s, 1H), 4.99 (s, 1H), 3.66 and 2.51 (2t, J = 5.2 Hz, 2 × 4H), 2.35 (s, 3H), 2.13 (s, 3H), 1.02 (s, 9H); ISP-MS (*m*/*z*) 337 (M + H$^+$, 100), 310 (10). Anal. Calcd for $C_{22}H_{30}N_4O$: C, 72.10; H, 8.25; N, 15.29. Found: C, 71.85; H, 8.01; N, 15.27.

6-(4-Methylpiperazin-1-yl)-4-*o*-tolyl-nicotinamide (34). 34 was obtained from **29** (16.7 g, 45.6 mmol) following the procedure described to prepare **33** from **27**. Using EtOAc as solvent for the extraction yielded crude **34** (13.3 g, 94%) as a light beige powder.

Alternatively, **32** (1.0 g, 4.1 mmol) was stirred in *N*-methylpiperazine (9.0 mL, 80.1 mmol) at 100 °C for 2 h. The reaction mixture was concentrated at room temperature under high vacuum, and the residue was purified by filtration on silica gel (20 g) using CH_2Cl_2 as eluent yielding **34** (1.2 g, 95%) as a light yellow foam. A sample was further purified by column chromatography using CH_2Cl_2/MeOH 98:2 to 95:5 as eluent yielding **34** as a colorless foam: mp 163.6−164.5 °C; IR (Nujol) ν 3464, 3166, 2926, 2854, 2796, 1662, 1589, 1490, 1456, 1378, 1327, 1237, 1141 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s br, 1H), 7.38−7.29 (m, 3H), 7.22−7.20 (m, 1H), 6.31 (s, 1H), 5.30 and 5.08 (2s br, 2 × 1H), 3.68 and 2.51 (2t, J = 5.2 Hz, 2 × 4H), 2.33 (s, 3H), 2.15 (s, 3H); ISP-MS (*m*/*z*) 311 (M + H$^+$, 100), 254 (62). Anal. Calcd for $C_{18}H_{22}N_4O$ (0.4H_2O): C, 68.07; H, 7.24; N, 17.64. Found: C, 68.06; H, 7.09; N, 17.31.

[6-(4-Methylpiperazin-1-yl)-4-*o*-tolylpyridin-3-yl]-carbamic Acid Methyl Ester (36). 36 was obtained from **34** (1.0 g, 3.2 mmol) following the procedure described to prepare **35** from **33**, except that **34** was dissolved in MeOH. At the end of the workup, the combined aqueous phases were brought to pH = 8 by addition of 1 N aqueous NaOH and further extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and dried under high vacuum at room temperature for 16 h yielding **36** (1.08 g, 99%) as a beige foam: IR (Nujol) ν 3216, 2923, 2853, 1714, 1609, 1598, 1503, 1457, 1224, 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s br, 1H), 7.37−7.26 (m, 3H), 7.11 (d, J = 7.6 Hz, 1H), 6.47 (s, 1H), 5.92 (s br, 1H), 3.78 (s br, 4H), 3.68 (s, 3H), 2.89 (s br, 4H), 2.59 (s, 3H), 2.11 (s, 3H); ISP-MS (*m*/*z*) 341 (M + H$^+$, 100), 284 (36), 252 (13).

Methyl-[6-(4-methylpiperazin-1-yl)-4-*o*-tolylpyridin-3-yl]-amine (14). A solution of Red-Al (70% solution in toluene, 44.82 mL, 158.3 mmol) and toluene (50.0 mL) was added over 10 min to a solution of **36** (11.0 g, 32.3 mmol) in CH_2Cl_2 (60.0 mL) cooled so that the temperature did not exceed 50 °C. The resulting orange solution was stirred for 1 h at 50 °C and cooled to 0 °C, and 1 N aqueous NaOH (88.0 mL) was added over 15 min (*Caution: strongly exothermic*). The reaction mixture was diluted with EtOAc (100 mL), and after vigorous stirring, the phases were separated. The aqueous phase (cloudy) was extracted with EtOAc (2 × 50 mL). The organic extracts were washed with deionized water (2 × 50 mL) and brine (50 mL), dried (Na_2SO_4), concentrated in a rotary evaporator at 40 °C, and dried under high vacuum at room temperature for 3 h giving an orange resin (10.6 g). This resin was twice dissolved in 50 mL of CH_2Cl_2, concentrated in a rotary evaporator at 40 °C, and then dried under high vacuum at 40 °C for 4 h yielding 9.8 g of crude **14** (9.8 g, quantitative) as an orange resin: IR (Nujol) ν 3411, 3022, 2935, 2881, 2795, 2745, 1611, 1501, 1447, 1397, 1246, 1228, 1138, 1010, 953 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.33−7.24 (m, 3H), 7.18−7.13 (m, 1H), 6.47 (s, 1H), 3.46−3.38 (m, 4H), 2.94 (s br, 1H), 2.78 (s,

3H), 2.57−2.55 (m, 4H), 2.35 (s, 3H), 2.14 (s, 3H); ISP-MS (*m*/*z*) 297 ($M + H^+$, 100), 240 (14).

2-(3,5-Bistrifluoromethylphenyl)-*N*-methyl-*N*-(6-(4-methylpiperazin-1-yl)-4-*o*-tolylpyridin-3-yl)-isobutyramide (3). **3** was obtained from **14** (9.60 g, 32.4 mmol) and **15** (10.90 g, 34.2 mmol) following the procedure described to prepare **2** from **13** and **15** affording crude **3** (19.6 g). A reference sample of **3** was prepared by dissolving 2.0 g of crude **3** in $^iPr_2O$ (20 mL) at room temperature. After 1 h of stirring at room temperature, the precipitate was filtered off, washed with $^iPr_2O$ (2.0 mL), and dried at 40 °C under 25 mbar for 16 h yielding **3** (1.0 g, 5.3%) with mp = 159.1−159.8 °C. The rest (17.6 g) of the crude product was suspended in $^iPr_2O$ (56 mL) and stirred at reflux temperature for 30 min. The suspension was cooled slowly to 0 °C and stirred for 1 h at 0 °C. The precipitate was filtered off, washed with cold (−20 °C) $^iPr_2O$ (20 mL), and dried at 50 °C under 25 mbar for 16 h yielding **3** (12.5 g, 67%) as white crystals: mp 156.2−160.0 °C; IR (Nujol) ν 2925, 2853, 2795, 1647, 1610, 1598, 1500, 1460, 1367, 1277, 1187, 1172, 1149 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.75 (s, 1H), 7.66 (s, 2H), 7.27 (s br, 4H), 6.51 (s, 1H), 3.58 (s br, 4H), 2.52 (s br) and 2.35−2.13 (m br, 13H), 1.49 and 1.33 (2s br, 6H); ISP-MS (*m*/*z*) 579 ($M + H^+$, 100). Anal. Calcd for $C_{30}H_{32}F_6N_4O$: C, 62.28; H, 5.57; F, 19.70; N, 9.68. Found: C, 62.22; H, 5.61; F, 19.60; N, 9.61.

2-(3,5-Bistrifluoromethylphenyl)-propan-2-ol (53). For the formation of the Grignard reagent, an aliquot (10 mL) of a solution of **17** (150 g, 507 mmol) in Et_2O (400 mL) was added to a suspension of magnesium turnings (16.1 g, 65.9 mmol). After the reaction had been started by gently heating, the rest of the ethereal solution was added dropwise over 1 h, during which time the temperature was kept at ca. 30 °C. Treatment of a sample of the reaction mixture with water revealed the disappearance of **17**. A solution of acetone (56.0 mL, 762 mmol) in Et_2O (100 mL) was added to the resulting fine suspension over 45 min, and the temperature was kept between 16 and 22 °C. Addition of 25% aqueous NH_4Cl (110 mL) at ca. 20 °C led to the formation of a suspension of magnesium salts which were filtered off and washed with Et_2O (3 × 200 mL). After drying (Na_2SO_4), the filtrate was rotary evaporated to dryness and finally dried under high vacuum affording **53** (137 g, 99%) as a yellow crystalline solid: mp 59−60 °C [lit.[29] 60.5−61.5 °C] (99.2% pure by GC). This material was used in the successive carbonylation step without further purification. An analytically pure sample of **53** was obtained by crystallization from pentane as a white solid: mp 62.5−63.5 °C; IR (Nujol) ν 3323, 2921, 2853, 1624, 1467, 1376, 1278, 1117, 962, 900, 799, 716, 683 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.95 (s, 2H), 7.77 (s, 1H), 1.84 (s, 1H), 1.63 (s, 6H); EI-MS (*m*/*z*): 257 ($M^+ - CH_3$), 253 ($M^+ - F$). Anal. Calcd for $C_{11}H_{10}F_6O$: C, 48.54; H, 3.70; F, 41.88. Found: C, 48.46; H, 3.73; F, 41.63.

2-(3,5-Bistrifluoromethylphenyl)-2-methyl Propionic Acid (54). A 185-mL Hastelloy C4 autoclave was charged under an argon flow with CH_2Cl_2 (25 mL), triflic acid (22.3 mL, 250 mmol), and water (0.45 mL, added dropwise). The autoclave was closed and pressurized with 30 bar of CO, and stirring was started. With the aid of a membrane pump, a solution of **53** (14.1 g, 51.8 mmol) in CH_2Cl_2 (35 mL) was added to the solution in the autoclave under vigorous stirring at 20 °C and at a flow of 1 mL/min. After stirring for a further 2 h at 20 °C, the autoclave was vented and the CO atmosphere was replaced by argon (three cycles of 8 bar argon venting under vigorous stirring). The reaction mixture was treated dropwise at 2 °C under stirring with a solution of NaOH (13.2 g, 330 mmol) in water (130 mL). After stirring for 30 min, the organic phase was separated and extracted with water (10 mL), and the combined aqueous phases were extracted with CH_2Cl_2 (3 × 150 mL) and filtered through a sintered glass filter. Addition at 8−12 °C of HCl (11 mL of a 36.5% aqueous solution, 350 mmol) afforded a suspension which was extracted with CH_2Cl_2 (2 × 100 mL). The organic phase was washed with water (100 mL), dried (Na_2SO_4), rotary evaporated to dryness, and finally dried under high vacuum for 5 h providing **54** (15.0 g, 97%) as a pale brown crystalline solid: mp 105.5−107 °C; IR (Nujol) ν 2923, 1707, 1623, 1464, 1376, 1279, 1239, 1176, 1136, 900, 845, 684 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 12−10 (broad, 1H), 7.84 (s, 2H), 7.80 (s, 1H), 1.68 (s, 6H); EI-MS (*m*/*z*): 300 (M^+), 281 ($M^+ - F$), 255 ($M^+ - COOH$), 227 ($M^+ - COOH - C_2H_4$). Anal. Calcd for $C_{12}H_{10}F_6O_2$: C, 48.01; H, 3.36; F, 37.97. Found: C, 47.99; H, 3.32; F, 37.90.

2-(3,5-Bistrifluoromethylphenyl)-2-methyl Propionyl Chloride (15). Oxalyl chloride (8.76 mL, 100.0 mmol) was added slowly to a stirred suspension of **54** (15.0 g, 50.0 mmol) in CH_2Cl_2 (127.5 mL) and DMF (0.60 mL) cooled to 0 °C. The reaction mixture was stirred for 1 h at 0 °C and for 16 h at room temperature and concentrated in a rotary evaporator at 40 °C. The residue was dissolved in toluene (60 mL), concentrated under reduced pressure twice, and dried under high vacuum at room temperature for 2 h yielding **15** (15.2 g, 96%) as a yellow oil, which was used without further purification: IR (Nujol) ν 2991, 2944, 1806, 1772, 1632, 1472, 1394, 1372, 1278, 1243, 1188, 1136, 961, 900, 683 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.86 (s, 1H), 7.77 (2, 2H), 1.77 (s, 6H); EI-MS (*m*/*z*) 299 (2, $M^+ - F$), 271 (6), 255 (100, $M^+ - COCl$), 227 (61).

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Supporting Information Available: Experimental procedures and analytical data of compounds **18**, **23**, **24**, **26**, **28**, **31**, **32**, **37**−**44**, **46**−**51**, and **57**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) Takeuchi, K.; Kurosaki, T.; Okamoto, K. *Tetrahedron* **1980**, *36*, 1557−1563.