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Synthesis and Application of a New Fluorous-Tagged Ammonia Equivalent

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Abstract: A novel fluorous-tagged ammonia equivalent has been developed. It is based on a nitrogen–oxygen bond, which can be cleaved in a traceless manner by a molybdenum complex or samarium diiodide. The application in the synthesis of ureas, amides, sulfonamides, and carbamates is described. The scope of the fluorous N–O linker is exemplified by the synthesis of itopride, a drug used for the treatment of functional dyspepsia. Itopride was synthesized with the aid of fluorous purification methods and the product was isolated in good overall yield, with high purity.

Keywords: ammonia equivalents · cleavage reactions · fluorous synthesis · itopride · molybdenum

Introduction

Amides, ureas, and sulfonamides are ubiquitous structural motifs within drug design and discovery. Thus, these classes of compounds are very often targeted and can be synthesized by using a solid-phase approach. In an attempt to address this process in a more efficient way we wanted to develop a fluorous-tagged ammonia equivalent. Fluorous linkers have several advantages over polymer linkers. Fluorous linkers have well-defined structures and molecular weights. In contrast, polymer linkers are functional materials with batch dependent loading. In addition, fluorous linkers have the following advantages over solid-phase linkers:[1] 1) Favorable homogeneous solution-phase reaction kinetics. 2) Amenable to quick adaptation of literature synthetic procedures. 3) Fluorous reactions can be monitored by conventional analytical methods such as TLC, NMR spectroscopy, HPLC, and IR spectroscopy. 4) Conventional methods such as chromatography, distillation, and recrystallization can be used for purification, in addition to the fluorous purification strategies.

Herein, we describe a novel fluorous-phase strategy for the synthesis of N-alkylated amides, ureas, and sulfonamides, which utilizes a nitrogen–oxygen bond as a linker.

Several masked forms of ammonia have been reported in the literature, for example, allylamine,[2] benzophenone imine,[3] and $Zn[N(SiMe_3)_2]$.[4] More recently, Trabanco et al.[5] reported the use of fluorous *tert*-butyl carbamate. In many cases, the ammonia surrogates are used in Buchwald–Hartwig palladium-catalyzed cross-coupling reactions to prepare aniline derivatives, however, other reaction types have also utilized ammonia equivalents. Benzhydrylamine has been used in a titanocene-catalyzed addition to alkynes to give primary alkylamines.[6] *tert*-Butyl carbamate has been used as an ammonia equivalent in Sharpless asymmetric aminohydroxylations.[7] *O*-Methylhydroxylamine has been used in the total synthesis of (±)-haouamine A.[8] Hydroxylamine has been used in palladium-catalyzed aminocarbonylations.[9] All of these examples indicate the need for alternatives to ammonia in organic synthesis.

Fluorous methods for synthesis and separation are poised to move from a relatively small, specialized field into the mainstream of organic synthesis.[1] The adaptation of fluorous methods into mainstream organic synthesis depends on the availability of a diverse assortment of proven reagents and tags, and we wanted to expand the toolbox in this respect.

We selected a protected hydroxylamine derivative **1**, shown in Scheme 1, as a possible ammonia surrogate for the use in alkylation, acylation, isocyanation, reductive amination, and sulfonation reactions, with the following rationale:

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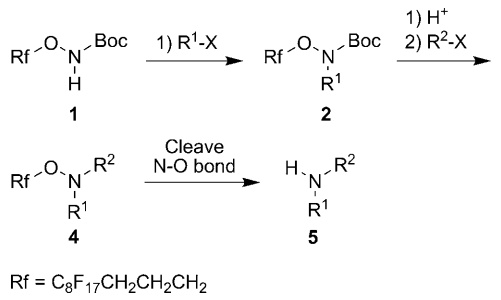


Scheme 1. Fluorous-tagged ammonia surrogate.

1) Hydroxylamines are more nucleophilic than amines due to the alpha effect.[10] This should make it easier to achieve full conversion of the fluorous-tagged reagent.
2) The N–O bond can be cleaved in several ways by using mild reagents that leave other classic nitrogen protecting groups like *tert*-butoxycarbonyl (Boc) and benzyloxycarbonyl (Cbz) intact.[11–14]
3) The N–O bond is inert to a range of aggressive reagents, which include Grignard and organolithium reagents,[15] and to reducing reagents such as $NaBH_3CN$ and $NaBH(OAc)_3$.[16,17]

The N–O bond and the C_8F_{17} tag in **1** are separated by three methylene groups to mitigate the electron-withdrawing effect from the fluorine atoms. We speculated that this *tert*-butyl-*N*-perfluoroalkoxycarbamate would serve as a convenient surrogate for ammonia in the synthesis of N-monoalkylated amides, ureas, and sulfonamides. The Boc group blocks one of the free positions, which alleviates problems of unwanted disubstitution on the alkoxyamine. Others have used *N*-Boc-protected, *O*-substituted hydroxylamines as nucleophiles following the same rationale. MacMillan and co-workers used *N*-Boc-*O*-TBS (*tert*-butyldimethylsilyl) hydroxylamine as a nucleophile in asymmetric iminium-ion-catalyzed conjugate addition to α,β-unsaturated aldehydes.[18] In a similar approach Vesley et al. used *N*-Boc-protected methoxyamine.[19] The organocatalytic asymmetric conjugate addition was further developed by Lu and Deng to involve α,β-unsaturated ketones by the use of a chiral primary amine catalyst, instead of a chiral secondary amine.[10] In the last case it is notable that *N*-Boc-protected benzyloxyamine was a superior nucleophile than *N*-Boc-protected benzylamine.

Results and Discussion

Methods in the literature for N-alkylation of *O*-alkyl-*N*-Boc-hydroxylamines include the use of Mitsunobu conditions[20] and Finkelstein conditions with NaH as a base.[21] Neither of these methods gave satisfactory results. Microwave heating at temperatures up to 120 °C did not push the reaction to completion with any of the previously reported methods. Instead we found that **1** was alkylated under relatively mild conditions by using Cs_2CO_3 in CH_3CN at 45 °C. Various alkyl halides were used including alkyl chlorides (Table 1, entries 7, 14, 19–21), alkyl bromides (Table 1, entries 1–6, 8–13, 15, 16, 18), and an alkyl iodide (Table 1, entry 17).

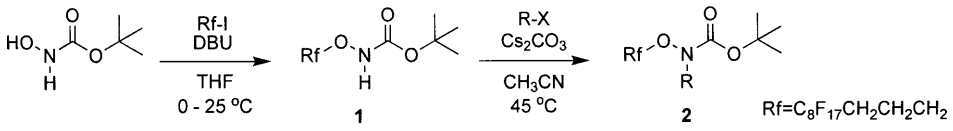
Addition of the alkyl halide to a preheated mixture of **1** and Cs_2CO_3 in CH_3CN gave the best results. In most cases, TLC indicated full conversion of **1** after two hours at 45 °C. The alkyl chlorides **2t** and **2u** required longer reaction times, up to five hours. The workup of the reactions was very simple. The reaction mixture was added directly on to a fluorous solid-phase extraction (F-SPE) cartridge together with water (2 mL). Excess of alkyl halide, Cs_2CO_3, and other non-fluorous materials were then eluted with MeOH/water (4:1) and the fluorous product was subsequently eluted with neat MeOH. The fluorous fraction was evaporated to give the product in high yield and with high purity. The UV purity for the aromatic products ranged from 79–100 %. In the case of silyl-alkynyl ether **2u**, the product was not pure after F-SPE, probably because the silyl ether had been partly hydrolyzed under the basic conditions. Subsequent flash chromatography gave pure **2u** in 45 % yield.

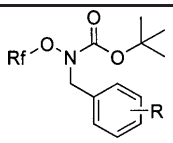
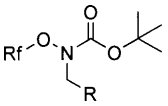
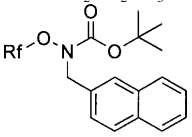
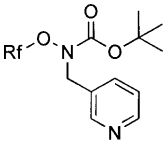
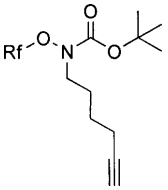
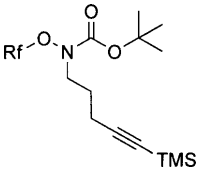
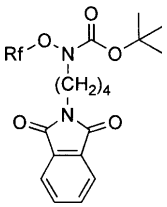
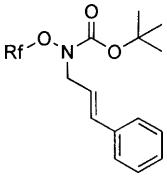
The Boc-group could be removed by using 10 equivalents of HCl in absolute ethanol with microwave heating at 80 °C for 15 min (Table 2). TLC of the reaction mixture showed full conversion and evaporation of the reaction mixture gave the pure hydrochloride salt. Deprotection with TFA in CH_2Cl_2 at room temperature also worked well.

The hydrochlorides of the perfluoroalkoxyamines were treated with different electrophiles, which included isocyanates, sulfonyl chlorides, and acid chlorides. DMF was used as the solvent for the isocyanate reaction, whereas THF was used in the cases of acid chlorides and sulfonyl chlorides. All of the reactions in Table 3 were performed at room temperature with triethylamine as a base. At the end of the reaction the mixture was transferred directly to a F-SPE cartridge and purified without aqueous workup or other purification steps. The non-fluorous materials were eluted with MeOH/water (4:1) and the fluorous product was eluted with neat MeOH. In two cases (**4d** and **4h**), the product had poor solubility in MeOH. In these cases a second purification with F-SPE were performed by using DMF as the fluorophilic eluent. All products in Table 3 were obtained in good to excellent yield (70–100 %), with purity in the range of 93–100 %.

We questioned whether the reductive N–O cleavage would allow the presence of various functional groups and considered several different methods. A range of different reagents have been used for reductive cleavage of N–O bonds, which included Li/4,4′-di-*tert*-butylbiphenyl (DTBB),[22,23] Na/Hg amalgam,[24,25] SmI_2,[14,26–30] $TiCl_3$,[31–34] indium,[8,11] $LiAlH_4$,[35,36] BH_3,[37] $[Mo(CO)_6]$,[13,24,38–49] $[Co_2(CO)_8]$,[50] $[Fe(CO)_5]$,[13,51] Zn/H^+,[43,52–55] NiB_2,[56] $Na_2S_2O_4$,[57] $[Ti(iPrO)_4]$/EtMgBr,[58] NiH_2,[59] trimethylsilyl chloride/KI,[60] and several types of catalytic hydrogenation, including Raney nickel.[61–83] Among the most popular and selective methods are $[Mo(CO)_6]/CH_3CN/H_2O$, SmI_2/THF,

Table 1. Synthesis of fluorous-tagged ammonia equivalent **1** and subsequent alkylation.

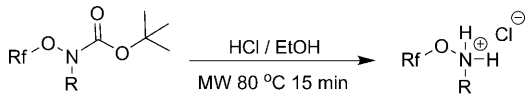


	Product **2**		X	Yield [%]		Product **2**		X	Yield [%]
									
1	**2a**	R = 4-Br	Br	99	15	**2o**	R = CH_2CH_2Ph	Br	94
2	**2b**	R = 4-NO_2	Br	99	16	**2p**	R = −CCH	Br	97
3	**2c**	R = 4-CN	Br	97	17	**2q**	R = $-CH_2CH_2CH_3$	I	100
4	**2d**	R = 4-Me	Br	100	18	**2r**		Br	96
5	**2e**	R = 4-CO_2Et	Br	99	19	**2s**		Cl	79
6	**2f**	R = 4-NHAc	Br	98	20[a]	**2t**		Cl	97
7	**2g**	R = 4-C=CH_2	Cl	94	21[a,b]	**2u**		Cl	45
8	**2h**	R = 3-OMe	Br	98					
9	**2i**	R = 3-F	Br	99					
10	**2j**	R = 3-Br	Br	100					
11	**2k**	R = 3-I	Br	98					
12	**2l**	R = 2-F	Br	97					
13	**2m**		Br	97					
14	**2n**		Cl	96					

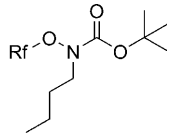
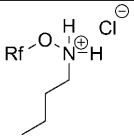
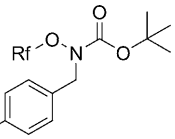
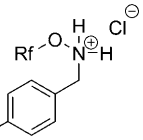
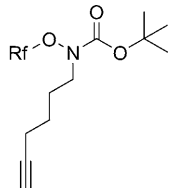
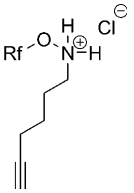
[a] Compounds **2t** and **2u** required 5 h of reaction time. [b] Compound **2u** was additionally purified by flash chromatography.

and In/EtOH/NH_4^+. We tested these three reagents on substrate **2o** in an initial study carried out to find the optimal cleavage conditions. Indium was clearly the least efficient. Addition of a large excess of the metal, different acids (NH_4^+ and AcOH), and sonication did not change the result. [$Mo(CO)_6$] and SmI_2 were both efficient, however, SmI_2 is less convenient to work with due to the high air sensitivity, so we proceeded with [$Mo(CO)_6$]. The latter reagent

Table 2. *N*-Boc deprotection of compounds **2d**, **2q**, and **2t**.

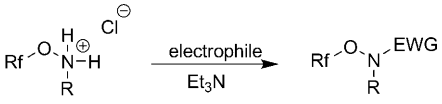


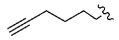
2 **3**

	Substrate **2**	Product **3**	Yield [%]
1	 **2q**	 **3a**	100
2	 **2d**	 **3b**	97
3	 **2t**	 **3c**	99

is traditionally used in CH_3CN/H_2O (15:1) at reflux for 2–3 h.[84] Under these conditions it is believed that $[Mo(CO)_6]$ is converted to the more reactive complex $[Mo(CH_3CN)_3(CO)_3]$.[13] $[Mo(CH_3CN)_3(CO)_3]$ is commercially available and we decided to compare this with $[Mo(CO)_6]$ in different solvents under microwave heating. The optimal conditions for reductive cleavage of the N–O bond in **2o** were heating the substrate by microwave irradiation at 130 °C for 15 min, with 1.5 equivalents of $[Mo(CH_3CN)_3(CO)_3]$ in MeOH. Before the sample was heated in the microwave, the Mo complex was dissolved with the aid of sonication of the reaction vessel for 10 min. The workup procedure was also changed from the traditional molybdenum procedure. Molybdenum is believed to form a stable complex with the amino alcohol once the N–O bond is cleaved and the stability of this complex is believed to cause a lower yield in some cases.[84] Decomplexation has previously been carried out by stirring the crude mixture with silica and triethylamine,[46] however, we did not find this procedure sufficient. Instead, we found that stirring the crude mixture overnight in air, in a two-phase system of aqueous sodium bicarbonate and ethyl acetate, was accompanied by a color change from brown to colorless and gave slightly higher yield and purity of **2o**. A plausible explanation is that molybdenum is oxidized by air and is thereby liberated from the product. This was supported by observing the change in color after only one hour when adding the mild oxidant potassium iodate. These optimized conditions for cleaving N–O bonds are highly chemoselective, compatible with numerous functional groups (Table 4), amongst them an internal allylic double bond (**5a**); terminal double bond (**5j**); acetanilide (**5l**), aryl iodide, bromide, and chloride (**5c**, **5d**, **5n**); nitrile (**5f**); ester (**5h**); and sulfonamide

Table 3. Reaction of **3** with different electrophiles.[a]



3a: R = *n*Bu
3b: R = 4-MePh-CH_2
3c: R = 

4

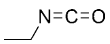
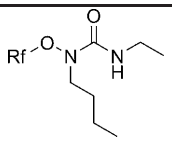
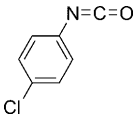
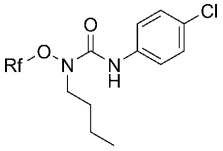
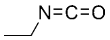
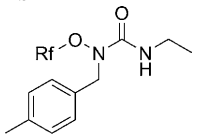
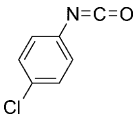
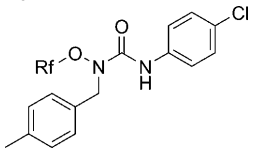
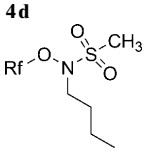
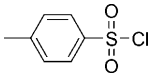
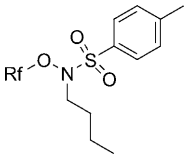
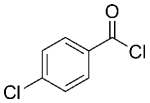
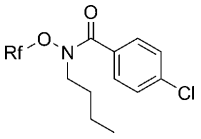
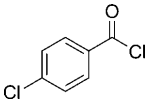
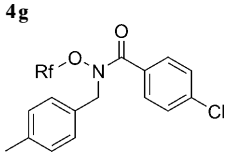
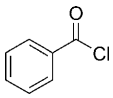
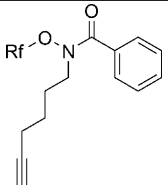
	Electrophile	Isolated product **4**	Yield [%]
1[b]		 **4a**	98
2[b]		 **4b**	100
3[b]		 **4c**	100
4[b]		 **4d**	85
5[c]		 **4e**	98
6[c]		 **4f**	96
7[c]		 **4g**	70
8[c]		 **4h**	79

Table 3. (Continued)

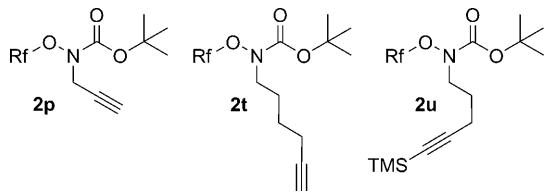
	Electrophile	Isolated product **4**	Yield [%]
9[c]		 **4i**	90

[a] EWG = electron-withdrawing group. [b] Reaction conditions: **3** (1 equiv, 0.3 mmol), triethylamine (1.1 equiv), DMF (2.5 mL), and isocyanate (1.5 equiv), 23 °C, 16 h. [c] Reaction conditions: **3** (1 equiv, 0.3 mmol), triethylamine (5 equiv), THF (2.5 mL), and acid chloride or sulfonyl chloride (3 equiv), 23 °C, 16 h.

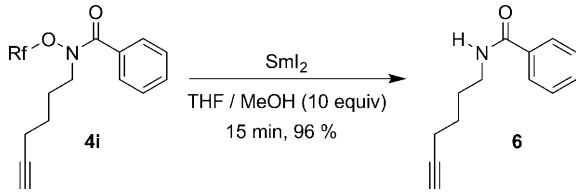
groups (**5w**). The products were obtained in moderate to excellent yield (20–100%) and with a UV purity ranging from 65–100%.

Low yield was observed in the cases with a fluoro-substituted benzyl group. In both **5l** and **5o**, unreacted starting material was found in the fluorous fraction. Increasing the reaction temperature to 150 °C did not improve the yield. N–O cleavage in substrate **2b** resulted in a complex mixture, probably due to competing reduction of the nitro group.

Attempts to cleave the N–O bond with [Mo(CH$_3$CN)$_3$(CO)$_3$] in substrates with a triple bond (Scheme 2) failed and gave complex mixtures. This can presumably be explained by the fact that molybdenum complexes, similar to the one used, are able to catalyze alkyne metathesis[85a] and other reactions involving carbon–carbon triple bonds.[85b] To circumvent the problem of removing the fluorous tag in substrates containing a triple bond, SmI_2 was used to cleave the N–O bond in substrate **4i**. The terminal triple bond in **4i** was unaffected after treatment with SmI_2 for 15 min in THF/MeOH at room temperature and the reaction yielded 96% of **6** with a UV purity of 100% (Scheme 3).

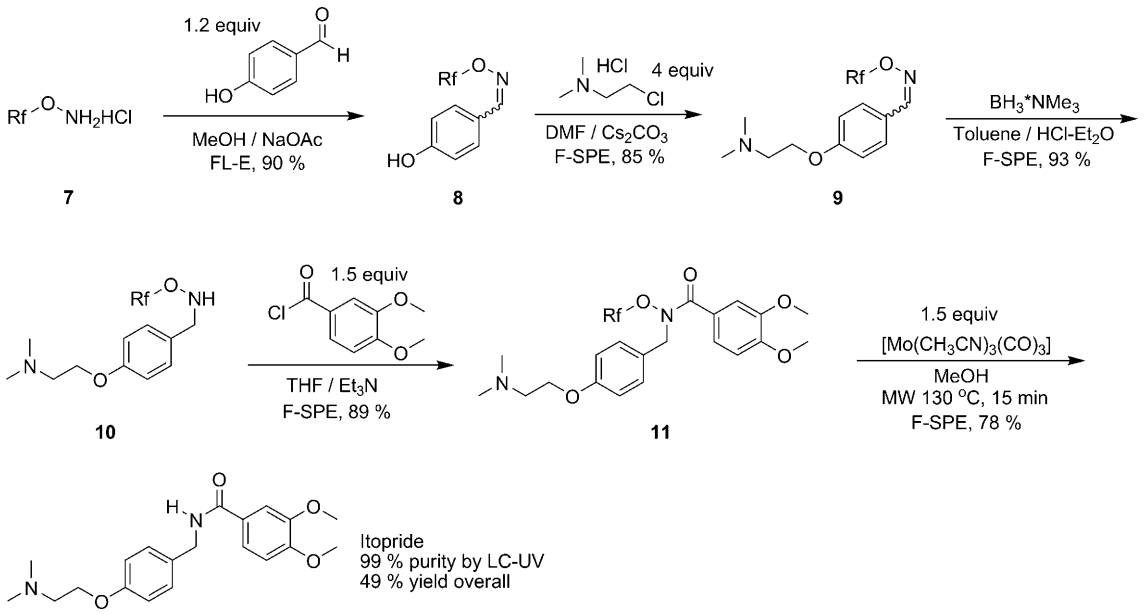


Scheme 2. Substrates in which the N–O bond could not be cleaved with Mo complexes.



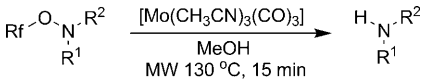
Scheme 3. SmI_2-mediated reduction of the N–O bond in substrate **4i**.

To demonstrate the scope of our fluorous-tagged ammonia equivalent we decided to employ this strategy for the synthesis of itopride, a drug used for the treatment of functional dyspepsia.[86] Itopride was synthesized as shown in Scheme 4. *N*-Boc deprotection of **1** in ethanol/HCl gave alkoxyamine **7** quantitatively. Treatment of **7** with 4-hydroxybenzaldehyde in methanol gave **8** in 90% yield after fluo-



Scheme 4. Fluorous synthesis of itopride.

Table 4. Removal of the fluorous tag through N–O cleavage with $[Mo(CH_3CN)_3(CO)_3]$.[a]



4 5

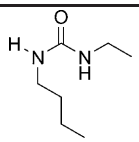
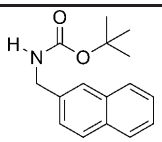
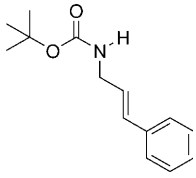
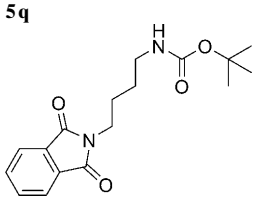
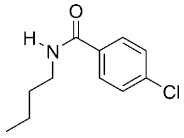
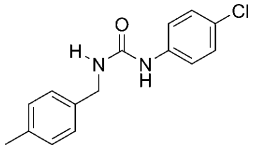
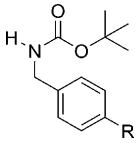
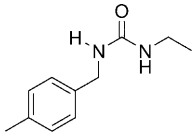
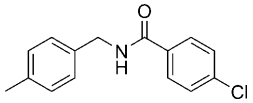
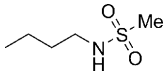
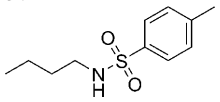
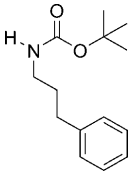
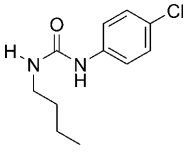
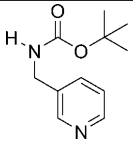
	Isolated product **5**	Yield [%]		Isolated product **5**	Yield [%]
1	 **5a**	92	17	 **5q**	87
2	 **5b**	95	18	 **5r**	99
3	 **5c**	100	19	 **5s**	93
4	 R = 4-Br (**5d**)	90	20	 **5t**	94
5	R = 4-NO_2 (**5e**)	0	21	 **5u**	88
6	R = 4-CN (**5f**)	87			
7	R = 4-CH_3 (**5g**)	81	22	 **5v**	97
8	R = 4-CO_2Et (**5h**)	94			
9	R = 4-NHAc (**5i**)	52	23	 **5w**	90
10	R = 4-CH=CH_2 (**5j**)	64			
11	R = 3-OMe (**5k**)	92	24	 **5x**	93
12	R = 3-F (**5l**)	20			
13	R = 3-Br (**5m**)	70	25	 **5y**	85
14	R = 3-I (**5n**)	100			
15	R = 2-F (**5o**)	10			

Table 4. (Continued)

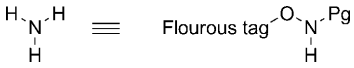
	Isolated product **5**	Yield [%]	Isolated product **5**	Yield [%]
16	 **5p**	60		

[a] Reaction conditions: **4** (1 equiv, 0.2 mmol), $[Mo(CH_3CN)_3(CO)_3]$ (1.5 equiv), MeOH (2.5 mL), ultrasound 15 min, microwave irradiation at 130 °C for 15 min. See the Experimental Section for a detailed workup procedure.

rous liquid extraction (FL-E). Phenol **8** was treated with 2-chloro-*N,N*-dimethylethanamine (4 equiv) in DMF/Cs_2CO_3. Aqueous workup and F-SPE yielded 85% of **9**. Oxime **9** was reduced to perfluoroalkoxyamine **10** by using borane trimethylamine complex and Et_2O/HCl in toluene. Aqueous workup and F-SPE yielded **10** in 93% yield. Other reducing agents such as $NaBH_3CN$ and $NaBH(OAc)_3$ did not give satisfactory results. The perfluoroalkoxyamine **10** was treated with 3,4-dimethoxybenzoyl chloride (1.5 equiv) in THF/Et_3N at room temperature. Subsequent aqueous workup and F-SPE yielded 89% of amide **11**. Finally the fluorous tag was removed by reductive N–O cleavage under the optimized conditions: $[Mo(CH_3CN)_3(CO)_3]$ in MeOH. Aqueous workup and F-SPE gave 78% of itopride with a UV purity of 99%. This fluorous approach is ideal for parallel synthesis of itopride analogues and the mild conditions should permit structural variations in most parts of the molecule.

Conclusion

The increased nucleophilicity of hydroxylamines compared to amines, combined with the orthogonal cleavage conditions, has led to the development of a very versatile fluorous-tagged ammonia equivalent.



This was demonstrated by the synthesis of a wide selection of N-monoalkylated amides, ureas, and sulfonamides. The release of the fluorous tag was achieved by using an improved and highly chemoselective reductive cleavage of the N–O bond; treatment with $[Mo(CH_3CN)_3(CO)_3]$ under microwave irradiation. Furthermore, the effectiveness of this new approach was illustrated by an efficient and flexible synthesis of itopride.

Experimental Section

General: Chemicals and solvents were obtained from commercial suppliers and used as received unless otherwise noted. THF and DMF were dried over 3 Å molecular sieves prior to use. Flash column chromatography was carried out using Scharlau 60 (230–400 mesh) silica gel (sorbil) and TLC was performed on Merck 60 F_{254} 0.25 μm silica gel plates. ^1H NMR and ^1H-decoupled ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, on a Bruker Avance DRX 500 instrument in deuterated chloroform (99.8%) unless otherwise noted. Chemical shifts for ^1H NMR spectra are reported in ppm with TMS as the internal reference. Chemical shifts for ^{13}C NMR spectra are reported in ppm relative to the chemical shift of $CHCl_3$. Coupling constants (*J* values) are in Hertz. The following abbreviations are used for the multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, ddt = double doublet of triplets, m = multiplet, and br = broad. Elemental analyses were performed at H. Lundbeck A/S, with a Flash EA1112 from Thermo Fischer Scientific. HRMS were performed on an Agilent/Bruker Daltonics LC-SPE-MS at H. Lundbeck A/S. The vacuum centrifuges applied were either HT-4 or EZ2 from Genevac. Fluorous solid-phase extraction (F-SPE) was carried out using cartridges from Fluorous Technologies and a FlashVac-10 from Biotage designed to accommodate 10 collection tubes with 25 mm diameter vessels. The solution of SmI_2 in THF (0.09 M) was prepared by a known procedure.[87]

General procedure for fluorous solid-phase extraction (F-SPE): Water (2 mL) was added to a 5 g F-SPE cartridge, followed by the reaction mixture. The non-fluorous fraction was eluted with methanol/water, 4:1 (60 mL). The fluorous fraction was eluted with MeOH (50 mL).

***Tert*-butyl-(3-perfluorooctyl)propoxycarbamate (1)**: A mixture of *tert*-butyl-*N*-hydroxycarbamate (17.0 g, 0.13 mol) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) (13 mL, 80 mmol) in dry THF (300 mL) was cooled to 0 °C . A solution of 3-(perfluorooctyl)propyl iodide (25.0 g, 42.5 mmol) in dry THF (100 mL) was added dropwise over 1.5 h. After 1 h the mixture became milky-white, the ice bath was removed, and the reaction mixture was stirred at room temperature overnight. The solvent was evaporated under vacuum, the residue was taken up in saturated aqueous sodium bicarbonate (300 mL), and extracted with ethyl acetate (3×200 mL). The combined organic phases were dried over anhydrous magnesium sulfate, evaporated, and purified by flash chromatography (heptane/ethyl acetate, 9:1) to yield **1** as a colorless oil (22.9 g, 91%). The oil was dissolved in dioxane (100 mL), cooled to −78 °C, and freeze dried in vacuo to give a white solid. M.p. 33–34 °C; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.49$ (s, 9H), 1.91–1.97 (m, 2H), 2.20–2.33 (m, 2H), 3.93 (t, $J = 6.0$ Hz, 2H), 7.10 ppm (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 19.3, 27.8 (t, $J = 22$ Hz), 28.1, 75.0, 82.0, 156.9 ppm; HRMS: *m/z* calcd for $C_{12}H_9F_{17}NO_3^+$: 538.0305 (dealkylated); found: 538.0302; elemental analysis calcd (%) for $C_{12}H_9F_{17}NO_3$: C 32.39, H 2.72, N 2.36; found: C 32.50, H 2.70, N 2.31.

General procedure A: Alkylation of 1: Compound **1** (200 mg, 0.34 mmol), cesium carbonate (274 mg, 0.84 mmol), and acetonitrile (2.5 mL) were added to a vial, which was then sealed with a septum. The mixture was heated to 45 °C and alkyl halide (2 equiv, 0.67 mmol) was added slowly through the septum by using a needle and syringe. In cases

when the alkyl halide was a solid, it was dissolved in DMF (500 μL) prior to addition. The reaction was stirred for 2 h at 45 °C and analyzed by TLC (heptane/ethyl acetate, 3:1). In most cases, starting material **1** was fully consumed after this time and the reaction mixture was purified directly by F-SPE. The fluorous fraction was concentrated in vacuo and dried in a vacuum centrifuge. The purity by LC-UV ranged from 79–100 %. (the products are shown in Table 1).

*Compound **2d***: This compound was obtained by following general procedure A, as a white solid (585 mg, 100 %, 100 % purity by LC-UV). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.50$ (s, 9H), 1.74–1.80 (m, 2H), 2.01–2.13 (m, 2H), 2.33 (s, 3H), 3.76 (t, $J = 5.8$ Hz, 2H), 4.55 (s, 2H), 7.14 (d, $J = 7.7$ Hz, 2H), 7.22 ppm (d, $J = 7.7$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 19.3$, 21.0, 27.9 (t, $J = 22$ Hz), 28.2, 53.5, 73.4, 81.7, 107–121 (8 fluorinated C), 128.6, 129.1, 133.6, 137.4, 156.7 ppm; HRMS: *m*/*z* calcd for $C_{20}H_{17}F_{17}NO_3^+$, 642.0931 (dealkylated); found: 642.0946.

General procedure B: Removal of the Boc group: Absolute ethanol (2.2 mL) and acetyl chloride (260 μL, 3.7 mmol) were added to a microwave vial. After stirring for 5 min under an argon atmosphere, Boc-protected amine (0.73 mmol) was added. The mixture was subjected to microwave irradiation for 15 min at 80 °C and then dried in a vacuum centrifuge at 40 °C to give the product as a hydrochloride salt. (The products are shown in Table 2).

*Compound **3b***: This compound was obtained by following general procedure B, as a white solid (437 mg, 97 %, >90 % purity by NMR spectroscopy). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.97$–2.03 (m, 2H), 2.21–2.33 (m, 2H), 2.37 (s, 3H), 4.20 (t, $J = 6.3$ Hz, 2H), 4.47 (s, 2H), 7.29 (d, $J = 7.8$ Hz, 2H), 7.40 ppm (d, $J = 7.8$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 20.3$, 21.2, 28.2 (t, $J = 22$ Hz), 54.4, 73.8, 126.7, 130.8, 131.8, 141.5 ppm; HRMS: *m*/*z* calcd for $C_{19}H_{17}F_{17}NO^+$: 598.1033 [M+H$^+$]; found: 598.1029.

General procedure C: Isocyanations: Isocyanate (1.5 equiv, 1 mmol) was added to a mixture of **3** (1 equiv, 0.32 mmol) and triethylamine (1.1 equiv, 0.35 mmol, 50 μL) in DMF (2.5 mL). The mixture was stirred overnight at room temperature and purified by F-SPE. The fluorous fraction was concentrated in vacuo and dried in a vacuum centrifuge to give the products **4a**, **4b**, **4c**, and **4d**. The purity by LC-UV ranged from 93–100 %. (The products are shown in Table 3).

*Compound **4c***: This compound was obtained by following general procedure C, as a yellow oil (218 mg, 100 %, 100 % purity by LC-UV). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.15$ (t, $J = 7.2$ Hz, 3H), 1.78–1.84 (m, 2H), 1.94–2.05 (m, 2H), 2.32 (s, 3H), 3.27–3.33 (m, 2H), 3.72 (t, $J = 6.2$ Hz, 2H), 4.59 (s, 2H), 5.73 (t, $J = 5.3$ Hz, 1H), 7.12 (d, $J = 7.8$ Hz, 2H), 7.22 ppm (d, $J = 7.8$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 15.2$, 19.5, 21.0, 27.7 (t, $J = 22$ Hz), 35.1, 53.6, 73.1, 129.0, 129.1, 133.5, 137.4, 160.2 ppm; HRMS: *m*/*z* calcd for $C_{22}H_{22}F_{17}N_2O_2^+$: 669.1404 [$M$+H$^+$]; found: 669.1420.

General procedure D: Acylations and sulfonylations: Acid chloride or sulfonyl chloride (3 equiv, 1 mmol) was added to a mixture of **3** (1 equiv, 0.34 mmol) and triethylamine (5 equiv, 1.7 mmol, 233 μL) in THF (2.5 mL). The mixture was stirred overnight at room temperature and purified by F-SPE. The fluorous fraction was concentrated in vacuo and dried in a vacuum centrifuge to give the products **4e**, **4f**, **4g**, **4h**, and **4i**. The purity by LC-UV ranged from 99–100 %. (The products are shown in Table 3).

*Compound **4h***: This compound was obtained by following general procedure D, as a white solid (197 mg, 79 %, 100 % purity by LC-UV). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.60$–1.84 (m, 4H), 2.35 (s, 3H), 3.65 (t, $J = 5.6$ Hz, 2H), 4.87 (m, 2H), 7.17 (d, $J = 7.8$ Hz, 2H), 7.26 (d, $J = 7.8$ Hz, 2H), 7.38 (d, $J = 8.3$ Hz, 2H), 7.61 ppm (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 19.1$, 21.1, 27.5 (t, $J = 22$ Hz), 50.8, 73.1, 128.4 (2 C), 129.4, 129.6, 132.5, 132.7, 136.9, 137.9, 169.0 ppm; HRMS: *m*/*z* calcd for $C_{26}H_{20}ClF_{17}NO_2^+$: 736.0906 [$M$+H$^+$]; found: 736.0923.

General procedure E: N–O cleavage with [Mo(CH$_3$CN)$_3$(CO)$_3$]: N–O substrate (1.0 equiv, 0.15 mmol), [Mo(CH$_3$CN)$_3$(CO)$_3$] (1.5 equiv, 67 mg, 0.22 mmol), and methanol (2.5 mL) were added to a microwave vial, which was then flushed with argon and sealed with a cap. The mixture was sonicated with ultrasound for 15 min and then heated in a microwave for 15 min at 130 °C. Saturated aqueous sodium bicarbonate (3 mL), water (3 mL), and ethyl acetate (6 mL) were added and the reaction mixture was stirred overnight with no cap (if the dark-brown color had not disappeared, the remaining molybdenum was oxidized with KIO_3 (2 equiv)). Water (20 mL) was added and the product was extracted with ethyl acetate (3×20 mL). The combined organic phases were evaporated and purified by F-SPE. The non-fluorous fraction was concentrated in vacuo and dried in a vacuum centrifuge. The purity by LC-UV ranged from 65–100 %. (The products are shown in Table 4).

*Compound **5t***: This compound was obtained by following general procedure E, as a white solid (23 mg, 94 %, 100 % purity by LC-UV). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.08$ (t, $J = 7.2$ Hz, 3H), 2.31 (s, 3H), 3.16 (q, $J = 7.2$ Hz, 2H), 4.59 (br s, 1H), 4.88 (br s, 1H), 7.11 (d, $J = 7.8$ Hz, 2H), 7.15 ppm (d, $J = 7.8$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 15.4$, 21.0, 35.3, 44.2, 127.4, 129.2, 136.2, 136.9, 158.2 ppm; HRMS: *m*/*z* calcd for $C_{11}H_{17}N_2O^+$: 193.1335 [M+H$^+$]; found: 193.1337.

N–O cleavage by samarium diiodide (6): A solution of SmI_2 in THF (3.1 mL 0.092 M) was slowly added to a solution of **4i** in dry THF (0.5 mL) under argon. The color of the SmI_2 changed from blue to green as it was added. The reaction mixture was stirred for 5 min and TLC showed full consumption of the starting material. The reaction mixture was quenched with aqueous $Na_2S_2O_3$, saturated aqueous sodium bicarbonate was added, and the aqueous layer was extracted with ethyl acetate (3×20 mL). Purification by F-SPE yielded **6** as a yellow solid (25 mg, 96 %, 100 % purity by LC-UV). An analytical sample was obtained by flash chromatography (heptane/ethyl acetate, 5:1). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.58$–1.65 (m, 2H), 1.71–1.79 (m, 2H), 1.96 (t, $J = 2.4$ Hz, 1H) 2.25 (dt, $J = 6.9$, 2.4 Hz) 3.45–3.50 (m, 2H), 6.29 (br s, 1H), 7.39–7.44 (m, 2H), 7.46–7.50 (m, 1H), 7.74–7.78 ppm (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 18.1$, 25.7, 28.7, 39.4, 68.7, 84.0, 126.8, 128.5, 131.3, 134.7, 167.5 ppm, HRMS: *m*/*z* calcd for $C_{13}H_{16}NO^+$: 202.1226 [M+H$^+$]; found: 202.1221.

Compound 7: Absolute ethanol (50 mL, 800 mmol) was added to a dry, argon-purged Schlenk flask. Acetyl chloride (4.8 mL, 67 mmol) was slowly added under argon backflow. The reaction mixture was stirred for 5 min, then **1** (7.60 g, 13 mmol) was added and the stirring was continued at 50 °C for 1 h. The reaction mixture was evaporated to give **7** as a white solid (6.76 g, 100 %, >95 % purity by GC–MS). ^{1}H NMR (500 MHz, [D$_4$]MeOH): $\delta = 1.98$–2.05 (m, 2H), 2.28–2.41 (m, 2H), 4.20 ppm (br t, 2H); ^{13}C NMR (125 MHz, [D$_4$]MeOH): $\delta = 20.3$, 28.3 (t, $J = 22$ Hz) 74.8, 107–122 ppm (8 fluorinated C): HRMS: *m*/*z* calcd for $C_{11}H_9F_{17}NO^+$: 494.0407 [M+H$^+$]; found: 494.0401.

Compound 8: A mixture of *O*-(3-perfluorooctyl)-propylhydroxylamine hydrochloride (2.09 g, 3.95 mmol), 4-hydroxybenzaldehyde (578 mg, 4.74 mmol), sodium acetate (650 mg, 7.90 mmol), and absolute ethanol (80 mL) was stirred overnight at room temperature. TLC showed the reaction had gone to completion. The product was purified by fluorous liquid extraction (FL-E) using HFE-7100 (80 mL) as the fluorous phase and methanol/water, 4:1 (3×100 mL) as the aqueous phase. Compound **8** was obtained as a white solid (2.11 g, 90 %, 99 % purity by LC-UV). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.99$–2.07 (m, 2H), 2.17–2.30 (m, 2H), 4.18–4.24 (m, 2H), 5.10 (br s, 1H), 6.83 (d, $J = 7.5$ Hz, 2H), 7.50 (d, $J = 7.5$ Hz, 2H), 8.03 ppm (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 20.3$, 27.8 (t, $J = 22$ Hz), 72.3, 115.7, 124.9, 128.8, 148.6, 157.1 ppm; HRMS: *m*/*z* calcd for $C_{18}H_{13}F_{17}NO_2^+$: 598.0669 [M+H$^+$]; found: 598.0668.

Compound 9: A mixture of **8** (1.06 g, 1.77 mmol), cesium carbonate (3.4 g, 10.6 mmol), and β-dimethylaminoethyl chloride hydrochloride (660 mg, 4.6 mmol) in DMF (10 mL) was stirred overnight at room temperature. The reaction mixture was purified by F-SPE to give **9** as white greasy crystals (1.004 g, 85 %, 90 % purity by LC-UV). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.99$–2.06 (m, 2H), 2.17–2.29 (m, 2H), 2.34 (s, 6H), 2.73 (t, $J = 5.7$ Hz, 2H), 4.08 (t, $J = 5.8$ Hz, 2H), 4.20 (t, $J = 6.0$ Hz, 2H), 6.91 (d, $J = 8.8$ Hz, 2H), 7.50 (d, $J = 8.8$ Hz, 2H), 8.03 ppm (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 20.3$, 27.8 (t, $J = 22$ Hz), 45.9, 58.2, 66.1, 72.3, 114.8, 124.70, 128.5, 148.6, 160.3 ppm; HRMS: *m*/*z* calcd for $C_{22}H_{22}F_{17}N_2O_2^+$: 669.1404 [$M$+H$^+$]; found: 669.1401.

Compound 10: Compound **9** (820 mg, 1.2 mmol), toluene (40 mL), borane trimethylamine complex (179 mg, 2.45 mmol), and 2 M HCl in di-

ethyl ether (5 mL) were added to a Schlenk flask, under argon. The reaction mixture was stirred overnight at room temperature and then quenched with 1 M aqueous sodium hydroxide. The product was extracted into ethyl acetate (3×50 mL) and then purified by F-SPE to give **10** as a brown solid (762 mg, 93%, 90% purity by LC-UV). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.78–1.85 (m, 2H), 2.00–2.12 (m, 2H), 2.33 (s, 6H), 2.72 (t, J = 5.7 Hz, 2H), 3.67 (t, J = 6.0 Hz, 2H), 3.96 (br d, J = 4.3 Hz, 2H), 4.05 (t, J = 5.7 Hz, 2H), 5.60 (br t, 1H), 6.88 (d, J = 8.5 Hz, 2H), 7.24 ppm (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.7, 27.1 (t, J = 22 Hz), 45.8, 56.0, 58.3, 66.0, 72.3, 114.5, 129.5, 130.2, 158.4 ppm; HRMS: m/z calcd for $C_{22}H_{22}F_{17}N_2O_2^+$: 671.1561 [$M$+H$^+$]; found: 671.1550.

Compound 11: A mixture of **10** (672 mg, 1.00 mmol), THF (40 mL), triethylamine (420 μL, 3.0 mmol), and 3,4 dimethoxybenzoyl chloride (302 mg, 1.50 mmol) was stirred for 2 h at room temperature. Aqueous sodium bicarbonate (100 mL) was added and the product was extracted into ethyl acetate (3×50 mL). Purification by F-SPE gave **11** as a light yellow oil (747 mg, 89%, 91% purity by LC-UV). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.65–1.72 (m, 2H), 1.83–1.95 (m, 2H), 2.33 (s, 6H), 2.73 (t, J = 5.8 Hz, 2H), 3.67 (t, J = 5.8 Hz, 2H), 3.88 (s, 3H), 3.90 (s, 3H), 4.06 (t, J = 5.8 Hz, 2H), 4.84 (s, 2H), 6.84 (d, J = 8.3 Hz, 1H), 6.91 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 1.8 Hz, 1H), 7.30 (d, J = 8.6 Hz, 2H), 7.34 ppm (dd, J = 8.3, 1.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.2, 27.6 (t, J = 22 Hz), 45.9, 51.4, 55.8, 55.9, 58.3, 66.0, 73.0, 110.0, 111.7, 114.7, 121.8,.126.2, 128.4, 129.7, 148.5, 151.2, 158.6, 169.5 ppm; HRMS: m/z calcd for $C_{20}H_{17}F_{17}NO_4^+$: 658.0881 (debenzylated); found: 658.0874.

Compound 12: A mixture of **11** (49 mg, 0.59 mmol), [Mo(CH$_3$CN)$_3$(CO)$_3$] (27 mg, 0.88 mmol), and methanol (2 mL) was sonicated with ultrasound for 15 min and then microwaved for 15 min at 130 °C. Saturated aqueous sodium bicarbonate (3 mL), water (3 mL), and ethyl acetate (6 mL) were added and the reaction mixture was stirred overnight with no cap on the vial. The product was extracted into ethyl acetate (3×20 mL) and the combined organic phases were evaporated and purified by F-SPE to give **12** (16.5 mg, 78%, 99% purity by LC-UV). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.33 (s, 6H), 2.72 (t, J = 5.7 Hz, 2H), 3.90 (s, 3H), 3.92 (s, 3H), 4.05 (t, J = 5.7 Hz, 2H), 4.56 (d, J = 5.5 Hz, 2H), 6.40 (br t, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.90 (d, J = 8.4 Hz, 2H), 7.25–7.29 (m, 3H), 7.45 ppm (d, J = 1.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 43.6, 45.9, 55.9, 56.0, 58.2, 66.0, 110.2, 110.6, 114.7, 119.2, 127.0, 129.2, 130.5, 148.9, 151.7, 158.3, 166.8 ppm; HRMS: m/z calcd for $C_{20}H_{27}N_2O_4^+$: 359.1965 [M+H$^+$]; found: 359.1967.

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[1] W. Zhang, *Chem. Rev.* **2009**, *109*, 749–795.
[2] S. Jaime-Figueroa, Y. Z. Liu, J. M. Muchowski, D. G. Putman, *Tetrahedron Lett.* **1998**, *39*, 1313–1316.
[3] G. Mann, J. F. Hartwig, M. S. Driver, C. Fernandez-Rivas, *J. Am. Chem. Soc.* **1998**, *120*, 827–828.
[4] D. Y. Lee, J. F. Hartwig, *Org. Lett.* **2005**, *7*, 1169–1172.
[5] A. A. Trabanco, J. A. Vega, M. A. Fernandez, *J. Org. Chem.* **2007**, *72*, 8146–8148.
[6] E. Haak, H. Siebeneicher, S. Doye, *Org. Lett.* **2000**, *2*, 1935–1937.
[7] J. A. Bodkin, G. B. Bacskay, M. D. Mcleod, *Org. Biomol. Chem.* **2008**, *6*, 2544–2553.
[8] P. S. Baran, N. Z. Burns, *J. Am. Chem. Soc.* **2006**, *128*, 3908–3909.
[9] X. Y. Wu, J. Wannberg, M. Larhed, *Tetrahedron* **2006**, *62*, 4665–4670.
[10] X. J. Lu, L. Deng, *Angew. Chem.* **2008**, *120*, 7824–7827; *Angew. Chem. Int. Ed.* **2008**, *47*, 7710–7713.
[11] S. Cicchi, M. Bonanni, F. Cardona, J. Revuelta, A. Goti, *Org. Lett.* **2003**, *5*, 1773–1776.
[12] A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, R. D. Shah, *J. Org. Chem.* **1996**, *61*, 3849–3862.
[13] M. Nitta, T. Kobayashi, *J. Chem. Soc. Perkin Trans. 1* **1985**, 1401–1406.
[14] J. Revuelta, S. Cicchi, A. Brandi, *Tetrahedron Lett.* **2004**, *45*, 8375–8377.
[15] N. Yamazaki, M. Atobe, C. Kibayashi, *Tetrahedron Lett.* **2001**, *42*, 5029–5032.
[16] P. Blaney, R. Grigg, Z. Rankovic, M. Thoroughgood, *Tetrahedron Lett.* **2000**, *41*, 6635–6638.
[17] P. Blaney, R. Grigg, Z. Rankovic, M. Thoroughgood, *Tetrahedron Lett.* **2000**, *41*, 6639–6642.
[18] Y. K. Chen, M. Yoshida, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 9328–9329.
[19] I. Ibrahem, R. Rios, J. Vesely, G. L. Zhao, A. Cordova, *Chem. Commun.* **2007**, 849–851.
[20] Y. K. Yang, S. Lee, J. Tae, *Bull. Korean Chem. Soc.* **2004**, *25*, 1307–1308.
[21] Y. K. Yang, J. Tae, *Synlett* **2003**, 2017–2020.
[22] M. Yus, G. Radivoy, F. Alonso, *Synthesis* **2001**, 0914–0918.
[23] F. Alonso, G. Radivoy, M. Yus, *Tetrahedron* **2000**, *56*, 8673–8678.
[24] A. R. Ritter, M. J. Miller, *J. Org. Chem.* **1994**, *59*, 4602–4611.
[25] G. E. Keck, S. Fleming, D. Nickell, P. Wieder, *Synth. Commun.* **1979**, *9*, 281–286.
[26] N. R. Natale, *Tetrahedron Lett.* **1982**, *23*, 5009–5012.
[27] G. E. Keck, T. T. Wager, S. F. McHardy, *Tetrahedron* **1999**, *55*, 11755–11772.
[28] S. H. Jung, J. E. Lee, H. Y. Koh, *Bull. Korean Chem. Soc.* **1998**, *19*, 33–35.
[29] G. E. Keck, S. F. McHardy, T. T. Wager, *Tetrahedron Lett.* **1995**, *36*, 7419-7422..
[30] S. G. Koenig, K. A. Leonard, R. S. Lowe, D. J. Austin, *Tetrahedron Lett.* **2000**, *41*, 9393–9396.
[31] B. L. Eriksen, P. Vedso, S. Morel, M. Begtrup, *J. Org. Chem.* **1998**, *63*, 12–16.
[32] S. I. Murahashi, Y. Kodera, *Tetrahedron Lett.* **1985**, *26*, 4633–4636.
[33] Y. Kodera, S. Watanabe, Y. Imada, S. Murahashi, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2542–2549.
[34] B. M. Trost, G. R. Dake, *J. Org. Chem.* **1997**, *62*, 5670–5671.
[35] G. R. Delpierre, M. Lamchen, *J. Chem. Soc.* **1963**, 4693–4701.
[36] N. K. A. Dalgard, K. E. Larsen, K. B. G. Torssell, *Acta Chem. Scand. Ser. B* **1984**, *38*, 423–432.
[37] S. Itsuno, M. Nakano, K. Miyazaki, H. Masuda, K. Ito, A. Hirao, S. Nakahama, *J. Chem. Soc. Perkin Trans. 1* **1985**, 2039–2044.
[38] A. Guarna, A. Guidi, A. Goti, A. Brandi, F. Desarlo, *Synthesis* **1989**, 175–178.
[39] R. Zimmer, M. Collas, M. Roth, H. U. Reissig, *Liebigs Ann. Chem.* **1992**, 709–714.
[40] M. J. Mulvihill, J. L. Gage, M. J. Miller, *J. Org. Chem.* **1998**, *63*, 3357–3363.
[41] G. Cardillo, S. Fabbroni, L. Gentilucci, R. Perciaccante, A. Tolomelli, *Tetrahedron: Asymmetry* **2004**, *15*, 593–601.
[42] N. Yamazaki, M. Atobe, C. Kibayashi, *Tetrahedron Lett.* **2001**, *42*, 5029–5032.
[43] M. Atobe, N. Yamazaki, C. Kibayashi, *J. Org. Chem.* **2004**, *69*, 5595–5607.
[44] T. Mineno, M. J. Miller, *J. Org. Chem.* **2003**, *68*, 6591–6596.
[45] S. Hanessian, R. Y. Yang, *Tetrahedron Lett.* **1996**, *37*, 8997–9000.
[46] R. Zimmer, H. U. Reissig, *J. Org. Chem.* **1992**, *57*, 339–347.
[47] P. G. Baraldi, A. Barco, S. Benetti, S. Manfredini, D. Simoni, *Synthesis* **1987**, 276–278.
[48] F. Z. Li, J. B. Brogan, J. L. Gage, D. Y. Zhang, M. J. Miller, *J. Org. Chem.* **2004**, *69*, 4538–4540.
[49] A. Goti, S. Cicchi, M. Cacciarini, F. Cardona, V. Fedi, A. Brandi, *Eur. J. Org. Chem.* **2000**, 3633–3645.
[50] C. Mukai, I. Nomura, O. Kataoka, M. Hanaoka, *Synthesis* **1999**, 1872–1874.

[51] M. Nitta, I. Sasaki, H. Miyano, T. Kobayashi, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3357–3358.
[52] M. Atobe, N. Yamazaki, C. Kibayashi, *Tetrahedron Lett.* **2005**, *46*, 2669–2673.
[53] S. Itó, S. Narita, K. Endo, *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3517–3519.
[54] R. Amoroso, G. Cardillo, P. Sabatino, C. Tomasini, A. Trere, *J. Org. Chem.* **1993**, *58*, 5615–5619.
[55] D. Enders, H. Kempen, *Synlett* **1994**, 969–971.
[56] A. Nose, T. Kudo, *Chem. Pharm. Bull.* **1981**, *29*, 1159–1161.
[57] P. M. Pojer, *Aust. J. Chem.* **1979**, *32*, 201–204.
[58] D. H. Churykau, V. G. Zinovich, O. G. Kulinkovich, *Synlett* **2004**, 1949–1952.
[59] J. J. Tufariello, H. Meckler, K. P. A. Senaratne, *Tetrahedron* **1985**, *41*, 3447–3453.
[60] J. S. Peng, D. H. Jiang, W. Q. Lin, Y. W. Chen, *Org. Biomol. Chem.* **2007**, *5*, 1391–1396.
[61] G. Augelmann, J. Streith, H. Fritz, *Helv. Chim. Acta* **1985**, *68*, 95–103.
[62] R. Huisgen, H. Hauck, R. Grashey, H. Seidl, *Chem. Ber./Recl.* **1968**, *101*, 2568–2584.
[63] S. T. Purrington, K. W. Sheu, *Tetrahedron Lett.* **1992**, *33*, 3289–3292.
[64] A. Alexakis, N. Lensen, P. Mangeney, *Tetrahedron Lett.* **1991**, *32*, 1171–1174.
[65] R. Huisgen, R. Grashey, H. Hauck, H. Seidl, *Chem. Ber./Recl.* **1968**, *101*, 2043–2055.
[66] V. A. Vaillancourt, S. D. Larsen, S. P. Tanis, J. E. Burr, M. A. Connell, M. M. Cudahy, B. R. Evans, P. V. Fisher, P. D. May, M. D. Meglasson, D. D. Robinson, F. C. Stevens, J. A. Tucker, T. J. Vidmar, J. H. Yu, *J. Med. Chem.* **2001**, *44*, 1231–1248.
[67] I. Ikeda, G. Takemoto, S. Komori, *Kog Kagaku Zasshi* **1971**, *74*, 419–424.
[68] D. P. Curran, J. F. Brill, D. M. Rakiewicz, *J. Org. Chem.* **1984**, *49*, 1654–1656.
[69] J. E. Baldwin, M. Otsuka, P. M. Wallace, *J. Chem. Soc. Chem. Commun.* **1985**, 1549–1550.
[70] Y. Aoyagi, N. Agata, N. Shibata, M. Horiguchi, R. M. Williams, *Tetrahedron Lett.* **2000**, *41*, 10159–10162.
[71] R. Huisgen, R. Grashey, H. Hauck, H. Seidl, *Chem. Ber./Recl.* **1968**, *101*, 2548–2558.
[72] R. Huisgen, R. Grashey, H. Seidl, H. Hauck, *Chem. Ber./Recl.* **1968**, *101*, 2559–2567.
[73] A. Lablache-Combier, M. L. Villaume, *Tetrahedron* **1968**, *24*, 6951–6957.
[74] A. Belly, R. Jacquier, J. Verducci, F. Petrus, *Bull. Soc. Chim. Fr.* **1972**, *1*, 330–336.
[75] V. N. Chistokletov, A. A. Petrov, *Zh. Obshch. Khim.* **1962**, *32*, 2385–2386.
[76] N. A. Lebel, T. A. Lajiness, *Tetrahedron Lett.* **1966**, *7*, 2173–2178.
[77] P. Burns, W. A. Waters, *J. Chem. Soc. C* **1969**, 27–29.
[78] E. C. Taylor, K. Mcdaniel, J. S. Skotnicki, *J. Org. Chem.* **1984**, *49*, 2500–2501.
[79] A. Alexakis, N. Lensen, P. Mangeney, *Synlett* **1991**, 625–626.
[80] R. Huisgen, H. Hauck, R. Grashey, H. Seidl, *Chem. Ber./Recl.* **1969**, *102*, 736–745.
[81] A. Vasella, R. Voeffray, *Helv. Chim. Acta* **1982**, *65*, 1134–1144.
[82] S. Cicchi, M. Marradi, P. Vogel, A. Goti, *J. Org. Chem.* **2006**, *71*, 1614–1619.
[83] S. Cicchi, J. Revuelta, A. Zanobini, M. Betti, A. Brandi, *Synlett* **2003**, 2305–2308.
[84] S. Cicchi, A. Goti, A. Brandi, A. Guarna, F. Desarlo, *Tetrahedron Lett.* **1990**, *31*, 3351–3354.
[85] a) M. Marradi, *Synlett* **2005**, 1195–1196; b) J. M. Khurana, S. Chauhan, A. Agrawal, *Org. Prep. Proced. Int.* **2004**, *36*, 201–276.
[86] G. Holtmann, N. J. Talley, T. Liebregts, B. Adam, C. Parow, *.N. Engl. J. Med.* **2006**, *354*, 832–840.
[87] J. M. Concellón, H. Rodriguez-Solla, E. Bardales, M. Huerta, *Eur. J. Org. Chem.* **2003**, 1775–1778.

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