Nucleophilic additions of lactam-derived enol triflates to aldehydes mediated by nickel(II) and chromium(II) salts[1]

Leah P. Easton and Gregory R. Dake

Abstract: Enol trifluoromethanesulfonates (triflates) derived from *N*-protected lactams undergo nickel(II)-chloride- and chromium(II)-chloride-promoted carbonyl additions to aldehydes. The yields of this process range from 42%–84%.

Key words: nickel(II) chloride, chromium(II) chloride, carbonyl addition, lactam-derived enol triflate.

Résumé : Sous l'influence du chlorure de nickel(II) ou du chlorure de chrome(II), les trifluorométhanesulfonates (triflates) d'énol obtenus à partir de lactames *N*-protégés donnent lieu à des réactions d'addition de carbonyles avec formation d'aldéhydes avec des rendements qui vont de 42% à 84%.

Mots clés : chlorure de nickel(II), chlorure de chrome(II), addition de carbonyle, triflate d'énol dérivé de lactames.

[Traduit par la Rédaction]

Introduction

To investigate the use of semipinacol reactions for the construction of alkaloid natural products (1), our group became interested in the preparation of compounds such as **A** (Scheme 1). Functionalized lactams appeared to be reasonable starting materials for the preparation of compounds like **A**. Currently we use a synthetic protocol that involves the following: (*a*) conversion of the *N*-protected lactam to its enol trifluoromethanesulfonate (triflate); (*b*) formation of a vinylstannane from the enol triflate using a palladium(0)-catalyzed coupling reaction; and (*c*) transmetalation of the stannane to a more nucleophilic lithium or magnesium species, which is reacted with a carbonyl compound. Although this procedure works well and can be scaled up, it does have drawbacks. Specifically, the requirement of hexamethyldistannane in the sequence is a liability because of its expense and toxicity (2).[3] Because of the known facility of mixtures of nickel(II) and chromium(II) salts in promoting additions of vinyl halides or triflates to carbonyl compounds (3), we were intrigued by the possibility of using such a process on a triflate derived from a lactam, thus possibly removing the need for hexamethyldistannane. A precedent for this proposed transformation is the use of a lactone-derived enol triflate in a nickel(II)–chromium(II) salt promoted aldehyde addition reaction, reported by Nicolaou and co-workers (4). Despite the growing use of lactam-derived enol triflates as substrates for metal-promoted (or catalyzed) reactions (5), we were unsure of the plausibility of our hypothesis. We are aware, to the best of our knowledge, of no examples of nickel(II)–chromium(II)-promoted carbonyl addition reactions using lactam-derived enol triflates. Our successful investigations on the feasibility of this process are disclosed in this report.

Results and discussion

The known enol triflate **1**[4] was selected to probe the viability of the nickel(II)–chromium(II)-promoted carbonyl addition. Enol triflate **1** was easily formed by deprotonating *N*-*tert*-butoxycarbonyl-2-piperidone with lithium hexamethyldisilazide followed by enolate quenching with *N*-(5-chloro-2-pyridyl)-triflimide. Unlike enol triflates derived from 5- and 7-membered ring lactams, which can be difficult to store and handle,[5] **1** can be purified by column chromatography on silica gel and can be stored for weeks in the freezer. The reaction between **1** and benzaldehyde, using a variety of different conditions, was initially explored (Scheme 2 and Table 1).

A typical set of reaction conditions suitable for the nickel(II)–chromium(II) carbonyl addition process were

Received 23 June 2003. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on 9 January 2004.

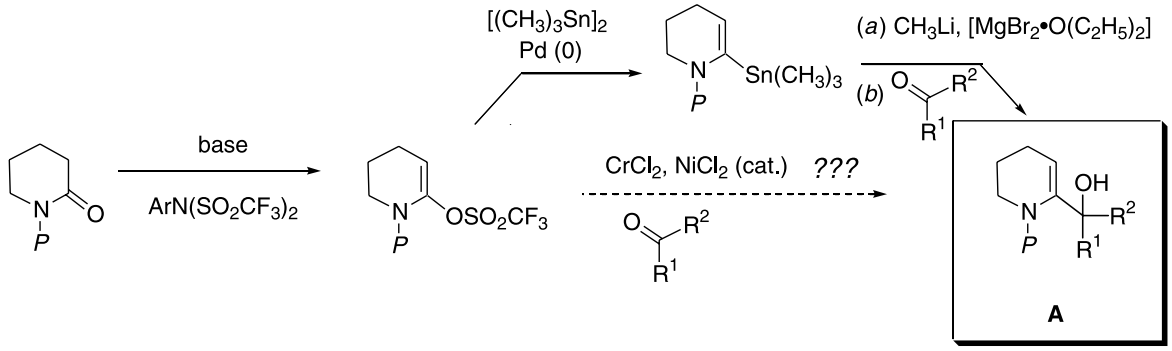
This article is dedicated to my teacher, mentor, and colleague, Professor Edward Piers.

L.P. Easton and G.R. Dake.[2] Department of Chemistry, 2036 Main Mall, University of British Columbia, Vancouver, BC V6T 1Z1, Canada.

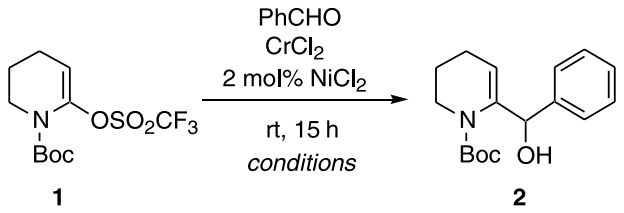
[1]This article is part of a Special Issue dedicated to Professor Ed Piers.
[2]Corresponding author (e-mail: gdake@chem.ubc.ca).
[3]The current cost for 5 g of hexamethyldistannane is Can$141.80 (Aldrich). The cost is even higher when one considers that only one "trimethyltin" group is transferred, and the other is discarded.
[4]References 5(*m*) and 5(*n*).
[5]See, for example, ref. 5(*f*).

 doi: 10.1139/V03-164

Scheme 1.



Scheme 2.



Scheme 3.

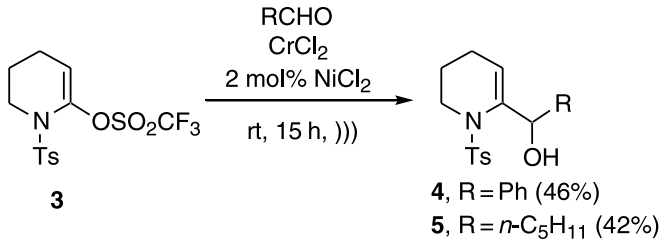


Table 1. Optimization of addition of enol triflate **1** to benzaldehyde.

Entry	equiv. PhCHO	equiv. $CrCl_2$	Solvent	Reaction parameter	Yield **2** (%)[a]
1	6	6	DMF–THF	Sonication	60
2	6	6	DMSO–THF	Sonication	10
3	6	6	DMSO	Sonication	26
4	6	6	DMF	Sonication	66
5	6	6	DMF	Stirring	50
6	6	4	DMF	Sonication	27
7	2	6	DMF	Sonication	63

[a]After isolation and purification.

used. Treatment of **1** with excess benzaldehyde (6 equiv), in the presence of 6 equiv of chromium(II) chloride and nickel(II) chloride (2 mol%), in a 1:1 mixture of degassed DMF–THF mixture at room temperature for 15 h produced the desired adduct **2** in 60% isolated yield (entry 1). The structure of **2** was established by spectroscopic methods. The IR spectrum of **2** contained absorptions typical of both alcohol (3404 cm^{-1}) and carbonyl (1682 cm^{-1}) functional groups. Key signals in the ^1H NMR spectrum of **2** at δ 5.35 ppm (d, J = 9.2 Hz, 1H) and δ 1.29 ppm (s, 9H) could be attributed to the allylic methine proton and the protons on the *tert*-butyl group. It is noteworthy that the alkoxide that is presumably generated after the carbonyl addition does not cyclize into the *tert*-butyl carbamate protecting group to form an oxazolidinone (6).

The choice of solvent had a substantial effect on the course of this reaction. For example, no reaction was observed to take place when using THF as the sole solvent, and using a 1:1 mixture of degassed THF and DMSO produced **2** in only 10% yield (entry 2). Omitting the ether solvent and running the reaction in DMSO alone improved the process somewhat (26% yield of **2**, entry 3). An amide solvent was clearly superior, as running the reaction in DMF alone restored the yield to acceptable levels, 66% (entry 4). Sonication probably better disperses the chromium(II) chloride during the reaction, compared with simple stirring (4). Using stirring to agitate the reaction mixture in DMF resulted in a lowered yield of **2** of 50% (entry 5). Unfortunately, the use of a smaller amount of chromium(II) chloride (4 equiv) drastically reduced the amount of adduct **2** that was isolated after reaction (27%, entry 6). In contrast, the use of a substantial excess of benzaldehyde is not necessary. Adduct **2** was isolated in 63% yield when 2 equiv of benzaldehyde was used with DMF as solvent (entry 7). These conditions (using either 6 or 2 equiv of electrophile) were adapted as our "standard protocol" for this process.

The effect of the different protecting groups on the nitrogen of the enol triflate nucleophile was then examined (Scheme 3). Although the *N*-toluenesulfonyl derivative **3** did react as a nucleophile using these reaction conditions, the efficiency of the reaction was much lower in comparison with the reactions of **1**. For example, the reaction of **3** with benzaldehyde produced allylic alcohol **4** in 46% yield. Hexanal could also be employed as an electrophile. Allylic alcohol **5** was isolated from the reaction of **3** and hexanal in 42% yield. Attempts to use other common protecting groups for

Scheme 4.

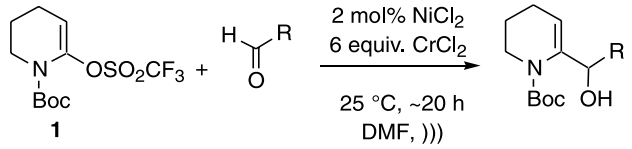
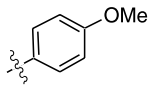
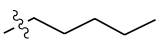
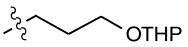
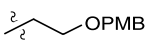
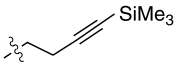


Table 2. Addition of Boc-protected enol triflate **1** to various aldehydes.

Entry	R	equiv. RCHO	Product	Yield (%)[a]
1		6	6	42
2		6	7	49
3		6	8	84
4		6	9	76
5		2	10	62
6		2	11	71
7		6	12	51

[a]After isolation and purification.

nitrogen, such as benzyloxycarbonyl (Cbz), trifluoromethansulfonyl (Tf), or benzoyl, were complicated by either the instability of the enol triflates or the formation of several byproducts during the chromium(II)–nickel(II)-promoted carbonyl addition process.

Using the standard conditions, a variety of aldehydes were then reacted with **1** to probe the scope and limitations of the electrophilic partner (Scheme 4 and Table 2). Electron-rich aromatic aldehydes such as *p*-anisaldehyde (entry 1) or furfural (entry 2) could be used in this reaction, although the yields of the products **6** and **7** were modest: 42% and 49%, respectively. Interestingly, aliphatic aldehydes react more effectively, and the carbonyl addition products could be isolated in much higher yields. As examples, the reactions of **1** with hexanal and isopropanal, using the standard conditions, resulted in the formation of allylic alcohols **8** and **9** in 84% and 76% isolated yields, respectively (entries 3 and 4). Considering the previous use of the chromium(II)–nickel(II)-promoted addition reaction in complex total synthesis (7), it was not surprising that common organic functional groups are compatible with these conditions. Functionalities such as acetals (entry 5, **10**, 62% yield), ethers (entry 6, **11**, 71% yield), and alkynes (entry 7, **12**, 51% yield) were well tolerated in the reaction of **1** under these conditions. Interestingly, attempts to react **1** with cinnamaldehyde were unsuccessful because of problems with decomposition.

Although the desired transformation does occur, this process has its own drawbacks. The first is the large amount of chromium(II) chloride that is required for reaction. Reducing the number of equivalents of chromium(II) salts would substantially improve this process. The lack of reactivity in ethereal solvents is a second handicap that we have uncovered. Although nitrogen-based ligand scaffolds have been used to generate catalytic versions of this carbonyl-addition reaction, those processes typically use THF as a solvent or co-solvent (8). Our preliminary investigations have found that no reaction occurs in THF, despite the presence of external ligands. Finally, the sonication of reaction mixtures is much more easily performed on a small scale. An alternative method for agitation would be required for large-scale reactions. The convenient resolution of all of these issues would generate a generally useful synthetic protocol.

Conclusion

Lactam-derived enol triflates have been demonstrated to undergo nickel(II)–chromium(II) salt mediated carbonyl addition reactions with aldehydes to produce functionalized allylic alcohols. Interestingly, reactions involving aliphatic aldehydes are typically higher yielding compared with aromatic aldehydes. With the feasibility of this protocol established, efforts to render this process *catalytic* in nickel and chromium (9) and to apply this reaction in the construction of nitrogen-containing natural products are underway in our laboratories.

Experimental

General information

All reactions were carried out under a nitrogen atmosphere in flame-dried glassware. Tetrahydrofuran was distilled from sodium, using benzophenone as an indicator. Dimethyl sulfoxide was distilled from calcium hydride under reduced pressure. Dimethyl formamide was dried over molecular sieves (4 Å) and degassed by sparging with nitrogen gas. Commercially available aldehydes (Aldrich) were distilled over sodium sulfate under reduced pressure prior to use. Nickel chloride (98%) was purchased from Aldrich and chromium chloride (99.9%) was purchased from Strem.

Thin-layer chromatography (TLC) was performed on DC-Fertigplatten SIL G-25 UV_{254} pre-coated TLC plates. Sonication was carried out using a Branson 3200 sonicator. Melting points were performed using a Mel-Temp II apparatus (lab devices U.S.A.) and are uncorrected. Infrared (IR) spectra were obtained using a PerkinElmer 1710 FT-IR spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded in deuterated chloroform, using a Bruker WH-400 spectrometer. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded in deuterated chloroform, using a Bruker AV-300 spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to deuterated chloroform (δ 7.24 ppm ^{1}H NMR; δ 77.0 ppm ^{13}C NMR). Low-resolution mass spectra (LR-MS) were recorded using either a Kratos-AEI model MS 50 or an Aligent 6890 series GC with a 5973 MS. Microanalyses were performed on either a Carlo Erba Elemental Analyzer Model 1106 or a CHN-O Elemental Analyzer Model 1108.

tert-Butyl 6-{[(trifluoromethyl)sulfonyl]oxy}-3,4-dihydropyridine-1(2*H*)-carboxylate (1)

To a solution of 367 mg of 1,1,1,3,3,3-hexamethyldisilazane (2.27 mmol) in 3 mL of THF at –78 °C was added 1.57 mL of *n*-butyllithium in hexane (2.26 mmol, 1.44 mol L^{-1}). After stirring for 20 min, the mixture was transferred via cannula to a solution of 300 mg of 1-(*tert*-butoxycarbonyl)piperidin-2-one (1.50 mmol) in 5 mL of THF at –78 °C. After stirring for 2 h, 1.18 g of *N*-(5-chloro-2-pyridyl)triflimide (3.00 mmol) in 5 mL of THF was added. The cold bath was removed, and the mixture was allowed to warm to 25 °C. After 1 h the reaction was quenched with 8 mL of a 10% aqueous solution of sodium hydroxide. The aqueous phase was extracted with three 5 mL portions of diethyl ether. The combined ethereal extracts were dried over sodium sulfate, filtered, and concentrated using rotary evaporation. Purification via flash chromatography (1:19 ethyl acetate – hexanes, containing 1% triethylamine) on silica gel gave 415 mg (84%) of a clear colourless oil. IR (film) (cm^{-1}): 1726, 1684, 1422, 1211, 1141. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.26 (t, *J* = 3.97 Hz, 1H), 3.60–3.56 (m, 2H), 2.24 (td, *J* = 6.71, 3.97 Hz, 2H), 1.77–1.70 (m, 2H), 1.47 (s, H).

Representative procedure for the coupling of lactam-derived enol triflates with aldehydes: _tert_-butyl 6-[hydroxy(phenyl)methyl]-3,4-dihydropyridine-1(2*H*)-carboxylate (2)

A round-bottom flask was charged with 111 mg of chromium(II) chloride (0.91 mmol) and 0.4 mg of nickel(II) chloride (0.003 mmol) and a stirbar. After capping the flask with a septum, DMF (1 mL) was added, and the thick green suspension was stirred for 10 min. Benzaldehyde (96 mg, 0.91 mmol) and a solution of **1** (50 mg, 0.15 mmol) in 1 mL of DMF were added sequentially. The flask containing the reaction mixture was placed in a sonication bath and sonicated for 15 h. Diethyl ether (5 mL) and water (2 mL, containing 1% of triethylamine) was added. The aqueous phase was extracted with three 3 mL portions of diethyl ether. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated in vacuo. Purification via flash chromatography (1:19 ethyl acetate – hexanes, containing 1% triethylamine) on silica gel gave 29 mg (66%) of clear colourless oil. IR (film) (cm^{-1}): 3404, 1682, 1394, 1368, 1256, 1160. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34–7.15 (m, 5H), 5.85 (bs, 1H), 5.45 (t, *J* = 3.66 Hz, 1H), 5.35 (d, *J* = 9.16 Hz, 1H), 3.73 (dt, *J* = 12.51, 4.27 Hz, 1H), 3.03 (t, *J* = 10.99 Hz, 1H), 2.19–2.13 (m, 2H), 1.83–1.68 (m, 2H), 1.29 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.6, 143.7, 142.9, 129.1, 127.9, 127.2, 119.7, 82.6, 67.2, 46.9, 29.4, 24.5, 24.4. LR-MS (EI) *m*/*z* (relative intensity): 289 ([M^+ + 1], 3), 233 (17), 215 (17), 189 (60), 187 (12), 172 (12), 171 (38), 170 (84), 156 (16), 143 (18), 130 (21), 115 (12), 105 (15), 82 (13), 77 (24), 59 (19), 57 (100), 55 (18).

1-[(4-Methylphenyl)sulfonyl]-1,4,5,6-tetrahydropyridin-2-yl trifluoromethanesulfonate (3)

To 1-(*p*-toluenesulfonyl)-piperidin-2-one (200 mg, 0.79 mmol) in THF (6 mL) at –78 °C was added a solution of potassium bis(trimethylsilyl)amide (189 mg, 0.947 mmol) in 2 mL of THF. After stirring for 45 min at –78 °C, a solution of 338 mg of *N*-phenyltriflimide (0.37 mmol) in 3 mL of THF was added. The mixture was allowed to warm to 25 °C. After 1 h the reaction was quenched with 5 mL of a saturated aqueous ammonium chloride solution. The aqueous phase was extracted with three 4 mL portions of dichloromethane. The combined extracts were dried over sodium sulfate, filtered, and concentrated via rotary evaporation. Purification via flash chromatography (1:3 ethyl acetate – hexanes, containing 1% triethylamine) on silica gel gave 195 mg (64%) of white crystals, mp 47 to 48 °C. IR (KBr) (cm^{-1}): 3436, 1674, 1425, 1362, 1213, 1173. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75 (d, *J* = 8.24 Hz, 2H), 7.32 (d, *J* = 8.24 Hz, 2H), 5.43 (t, *J* = 3.97 Hz, 1H), 3.60–3.64 (m, 2H), 2.42 (s, 3H), 2.09–2.14 (m, 2H), 1.53–1.45 (m, 2H).

{1-[(4-Methylphenyl)sulfonyl]-1,4,5,6-tetrahydropyridin-2-yl}(phenyl)methanol (4)

Cloudy colourless oil (yield: 46%). IR (film) (cm^{-1}): 3516, 1715, 1455, 1341, 1163. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (d, *J* = 8.55 Hz, 2H), 7.40–7.10 (m, 7H), 5.84 (d, *J* = 1.22 Hz, 1H), 5.46 (t, *J* = 3.66 Hz, 1H), 3.48–3.42 (m, 1H), 3.41–3.35 (m, 1H), 2.40 (s, 3 H), 1.88 (dt, *J* = 10.68, 1.22 Hz, 2H), 1.39–1.29 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.2, 143.4, 142.8, 138.1, 131.1, 129.6, 128.9, 128.8, 128.1, 121.5, 75.9, 48.6, 23.5, 22.9, 21.4. LR-MS (EI) *m*/*z* (relative intensity): 343 ([M^+ + 1], 8), 205 (11), 189 (19), 188 (100), 170 (22), 108 (23), 107 (25), 105 (18), 91 (36), 86 (37), 82 (27), 79 (38), 77 (35), 65 (13), 58 (15), 55 (29), 51 (12).

1-{1-[(4-Methylphenyl)sulfonyl]-1,4,5,6-tetrahydropyridin-2-yl}hexan-1-ol (5)

Clear colourless oil (yield: 42%). IR (film) (cm^{-1}): 3525, 1457, 1343, 1161. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 (d, *J* = 8.24 Hz, 2H), 7.26 (d, *J* = 7.94 Hz, 2H), 5.60 (t, *J* = 3.66 Hz, 1H), 4.47 (q, *J* = 6.10, 1H), 3.48–3.43 (m, 2 H), 3.19 (d, *J* = 6.10 Hz, 1H), 2.40 (s, 3H), 1.90–1.83 (m, 2H), 1.80–1.60 (m, 2H), 1.42–1.17 (m, 8H), 0.86 (t, *J* = 6.87 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.2, 142.9, 138.2, 131.1, 128.8, 119.8, 74.9, 48.7, 36.9, 33.1, 27.1, 24.0, 23.3, 23.0, 21.2, 15.4. LR-MS (EI) *m*/*z* (relative intensity): 337 ([M^+ + 1], 6), 182 (37), 126 (12), 112 (100), 111 (12), 91 (20), 82 (11), 55 (25).

tert-Butyl 6-[hydroxy(4-methoxyphenyl)methyl]-3,4-dihydropyridine-1(2*H*)-carboxylate (6)

Clear colourless oil (yield: 42%). IR (film) (cm^{-1}): 3384, 1695, 1683, 1512, 1395, 1368, 1248, 1160. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24–7.20 (m, H), 6.83–6.79 (m, 2H), 5.73 (bs, 1H), 5.43 (t, *J* = 3.66 Hz, 1H), 5.33 (d, *J* = 8.24 Hz, 1H), 3.77 (s, 3H), 3.70 (dt, *J* = 12.21, 3.97 Hz, 1H), 3.05 (t, *J* = 11.60 Hz, 1H), 2.17–2.12 (m, 2H), 1.80–1.69 (m, 2H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.8, 155.6, 143.3, 136.0, 128.4, 119.2, 114.6, 82.6, 76.9, 56.7, 47.0, 29.5, 24.5, 24.4. LR-MS (EI) *m*/*z* (relative intensity): 319 ([M^+ + 1], 4), 246 (11), 245 (53), 219 (19), 202 (19), 201 (86), 200 (69), 187 (15), 186 (100), 171 (11), 170 (55), 160 (22), 158 (13), 146 (13), 137 (18), 135 (30), 128 (10), 121 (10), 115 (12), 91 (13), 77 (32), 65 (11), 63 (11), 59 (90), 57 (85), 56 (12), 55 (21), 51 (16).

***tert*-Butyl 6-[2-furyl(hydroxy)methyl]-3,4-dihydropyridine-1(2*H*)-carboxylate (7)**

Clear colourless oil (yield: 49%). IR (film) (cm^{-1}): 3420, 1681, 1393, 1368, 1161. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.30 (s, 1H), 6.28 (dd, *J* = 3.36, 1.83 Hz, 2H), 5.43 (t, *J* = 3.66 Hz, 1H), 5.35 (s, 1H), 3.72–3.64 (m, 1H), 3.28–3.19 (m, 1H), 2.15 (td, *J* = 7.02, 3.66 Hz, 2H), 1.81–1.71 (m, 2H), 1.40 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.7, 155.8, 142.8, 141.2, 119.3, 111.5, 107.6, 82.8, 72.4, 46.7, 29.6, 24.5, 24.3. LR-MS (EI) *m/z* (relative intensity): 279 ([M^+ + 1], 3), 223 (16), 179 (20), 161 (24), 160 (12), 144 (13), 132 (13), 111 (31), 107 (16), 86 (14), 84 (22), 82 (12), 59 (10), 57 (100), 55 (30).

***tert*-Butyl 6-(1-hydroxyhexyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (8)**

Clear colourless oil (yield: 84%). IR (film) (cm^{-1}): 3424, 1742, 1683, 1393, 1368, 1256, 1163. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.38 (t, *J* = 3.66 Hz, 1H), 5.10 (bs, 1H), 4.05 (dd, *J* = 15.26, 7.32 Hz, 1H), 3.75 (dt, *J* = 11.90, 4.27 Hz, 1H), 3.14 (t, *J* = 8.85 Hz, 1H), 2.13–2.07 (m, 2H), 1.77–1.69 (m, 2H), 1.46 (s, 9H), 1.35–1.20 (m, 6H), 0.90–0.82 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.1, 143.4, 118.0, 82.6, 75.9, 47.0, 36.1, 33.2, 29.7, 27.3, 24.7, 24.3, 24.0, 15.4. LR-MS (GC) *m/z* (relative intensity): 283 ([M^+ + 1], 2), 209 (11), 152 (51), 139 (29), 138 (10), 126 (29), 113 (100), 112 (17), 111 (10), 110 (11), 84 (37), 82 (15), 57 (55), 56 (13), 55 (20), 54 (13).

***tert*-Butyl 6-(1-hydroxy-2-methylpropyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (9)**

White crystals (yield: 76%), mp 58–60 °C. IR (KBr) (cm^{-1}): 3378, 1670, 1656, 1396, 1367, 1166, 1032. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.38 (t, *J* = 3.66 Hz, 1H), 5.14 (bs, 1H), 3.83 (d, *J* = 8.85 Hz, 1H), 3.58 (t, *J* = 9.16 Hz, 1H), 3.04 (t, *J* = 9.77 Hz, 1H), 2.13–2.07 (m, 2H), 1.80–1.66 (m, 2H), 1.45 (s, 9H), 0.98 (d, *J* = 6.71 Hz, 3H), 0.73 (d, *J* = 6.71 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.2, 142.7, 119.2, 82.7, 82.6, 47.0, 33.0, 29.7, 24.7, 24.3, 21.2, 20.8. LR-MS (GC) *m/z* (relative intensity): 255 ([M^+ + 1], 3), 156 (12), 139 (13), 138 (18), 113 (100), 112 (34), 84 (11), 82 (10), 57 (51), 55 (11). Anal. calcd. for $C_{14}H_{25}NO_3$: C 65.85, H 9.87, N 5.47; found: C 66.25, H 9.98, N 5.28.

***tert*-Butyl 6-[1-hydroxy-4-(tetrahydro-2*H*-pyran-2-yloxy)butyl]-3,4-dihydropyridine-1(2*H*)-carboxylate (10)**

Clear colourless oil (yield: 62%). IR (film) (cm^{-1}): 3441, 2932, 1682, 1393, 1368, 1161. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.39 (t, *J* = 3.66 Hz, 1H), 5.14 (bs, 1H), 4.56–4.51 (m, 1H), 4.10 (q, *J* = 6.71 Hz, 1H), 3.87–3.79 (m, 1H), 3.75–3.65 (m, 2H), 3.50–3.43 (m, 1H), 3.41–3.32 (m, 1H), 3.18 (t, *J* = 10.38 Hz, 1H), 2.10 (td, *J* = 7.02, 3.66 Hz, 2H), 1.84–1.45 (m, 12H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.1, 143.2, 118.0, 100.2, 82.6, 75.7, 75.6, 69.0, 68.9, 63.8, 63.7, 47.0, 33.0, 32.2, 32.1, 29.7, 28.0, 26.9, 24.7, 24.3, 21.1, 21.0. LR-MS (EI) *m/z* (relative intensity): 355 ([M^+ + 1], 2), 198 (14), 197 (18), 196 (38), 171 (40), 170 (45), 167 (11), 155 (11), 154 (37), 152 (20), 149 (22), 126 (24), 113 (67), 112 (11), 110 (24), 97 (23), 85 (62), 82 (10), 67 (14), 57 (100), 55 (21).

***tert*-Butyl 6-{1-hydroxy-3-[(4-methoxybenzyl)oxy]propyl}-3,4-dihydropyridine-1(2*H*)-carboxylate (11)**

Clear colourless oil (yield: 71%). IR (film) (cm^{-1}): 3420, 2932, 2860, 1681, 1515, 1393, 1368, 1249, 1161. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.22 (d, *J* = 8.55 Hz, 2H), 6.84 (d, *J* = 8.55 Hz, 2H), 5.41 (t, *J* = 3.66 Hz, 1H), 5.05 (bs, 1H), 4.41 (dd, *J* = 18.01, 11.29 Hz, 2H), 4.37–3.31 (m, 1H), 3.77 (s, 3H), 3.59 (s, 1H), 3.56–3.44 (m, 2H), 3.19 (s, 1H), 2.10–2.05 (m, 2H), 1.92–1.77 (m, 2H), 1.75–1.65 (m, 2H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.6, 155.9, 143.1, 132.0, 130.7, 117.6, 115.2, 82.6, 74.1, 72.8, 68.9, 56.7, 46.9, 36.2, 29.7, 24.6, 24.2. Anal. calcd. for $C_{21}H_{31}NO_5$: C 66.82, H 8.28, N 3.71; found: C 66.53, H 8.47, N 4.11.

***tert*-Butyl 6-(1-hydroxy-5-trimethylsilanyl-pent-4-ynyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (12)**

Clear colourless oil (yield: 51%). IR (film) (cm^{-1}): 3417, 2961, 2175, 1681, 1392, 1368, 1250, 1162. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.40 (t, *J* = 3.66 Hz, 1H), 5.19 (bs, 1H), 4.19 (dd, *J* = 14.65, 8.24 Hz, 1H), 3.76 (dt, *J* = 11.90, 3.97 Hz, 1H), 3.15 (t, *J* = 10.68 Hz, 1H), 2.24 (t, *J* = 7.63 Hz, 2H), 2.10 (m, 2H) 1.86–1.64 (m, 4H), 1.46 (s, 9H), 0.11 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.1, 142.6, 118.5, 108.5, 86.0, 82.8, 74.7, 47.0, 35.0, 29.7, 24.6, 24.3, 18.3, 1.6. Anal. calcd. for $C_{18}H_{31}NO_3Si$: C 64.05, H 9.26, N 4.15; found: C 64.45, H 9.40, N 4.45.

Acknowledgement

We thank the University of British Columbia and the Natural Sciences and Engineering Research Council of Canada (NSERC) for the financial support of our research program. We also thank the Canadian Foundation for Innovation for enabling specific infrastructure acquisitions.

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