Tuning the Reactivity of *O-tert*-Butyldimethylsilylimidazolyl Aminals Towards Organolithium Reagents

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Abstract: *O-tert*-Butyldimethylsilylimidazolyl aminals are *N,O*-acetals that form readily from aldehydes, and although they function as aldehyde stabilizing and protecting groups under various conditions, we report here that they react with organolithium reagents similarly to the parent aldehydes. The mechanism involves the intermediate formation of a 2-imidazolyl anion as is exemplified by the isolation of 2-TBDMS-imidazole. Substitution of the imidazolyl moiety at the 2-position renders these aldehyde derivatives stable to organolithium reagents, thus allowing for the tuning of their reactivity.

Key words: aldehydes, *N,O*-acetals, protecting groups, organometallic reagents, Brook rearrangements

The silylation of aldehydes[1] and ketones[2,3] with *N*-(trimethylsilyl)-imidazole as well as other silylated azoles[2,3] has been known for more than thirty years to produce trimethylsilyl *N,O*-acetals and ketals. Nevertheless, these chromatographically labile carbonyl derivatives have not been used extensively as synthetic intermediates. Recently, a *tert*-butyldimethylsilyl aminal derivative of formaldehyde has been employed as a protecting group for the amino function of purines.[4] Similar *O-tert*-butyldimethylsilylimidazolyl aminals have been proposed as versatile aldehyde protecting groups.[5] The latter protecting group is rather useful in the case of labile chiral α-alkoxy aldehydes such as **1d**,**e**, which are prone to condensation and/or epimerization. Other previously prepared 5′-nucleosidyl aldehydes have been used without further purification in the next step, often a Wittig reaction.[6]

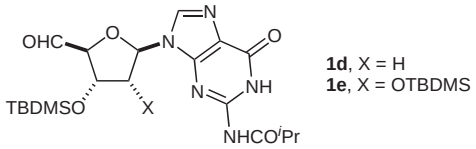

Figure 1

We were interested in purifying and storing such labile aldehydes as stable derivatives, which could successively react in situ with organolithium reagents. We wish to report here that *O-tert*-butyldimethylsilylimidazolyl aminals react with organolithium reagents similarly to the parent aldehydes. On the other hand, substitution at the 2-position of the imidazole moiety renders this protecting group stable in the presence of the above reagents.

In the initial exploratory work, we utilized stable aldehydes **1a**–**c** and transformed them to the corresponding *N,O*-acetals **2a**–**c** in high yields, under the previously reported conditions (Scheme 1).[5] In the case of aldehydes **1d**,**e**, application of the *N,O*-acetal formation conditions led to the isolation of **2d** and **2e**, respectively, as single diastereomers.[7] The high diastereoselectivity observed in the formation of **2d**,**e** could be attributed to the reversibility of the initial, *N,O*-hemiacetal-forming, reaction. The reaction is governed by thermodynamic control, and only one of the isomeric *N,O*-hemiacetals is subsequently trapped by TBDMSCl, thus leading to the most stable *N,O*-silylacetal.

Although we were unable to generate crystals of either **2d** or **2e** suitable for X-ray crystallography, molecular modeling and NOE results (Scheme 1) indicate that the *O*-TBDMS group lies away from the ribofuranose ring with the imidazolyl substituent being almost vertical to the ribofuranose plane. We thus propose an *S* configuration for the 5′-carbon.

The *N,O*-acetal function in **2d** was stable under the conditions used for cleaving the 2-amide protection (NH_4OH, MeOH, Scheme 1). It could readily be converted back to the aldehyde **1d** by short treatment (60 min) with NH_4F in methanol, at 60 ºC, under which conditions the secondary 3′-*O*-TBDMS group was stable.

As previously reported,[5] the *N,O*-acetals **2a**–**e** proved stable in the presence of MeMgCl with only traces of the corresponding aldehyde observed under prolonged reaction (results not shown). On the other hand, reaction of **2a**–**e** with LDA in THF at –78 °C followed by quenching at 0 °C with aq $NaHCO_3$, led to the isolation of the parent aldehyde in high yield (entries 1, 6, 9, 12, 15, Table 1).

The less reactive aromatic aldehydes could also be isolated in high yield after treatment of **2a**,**b** with 1 equivalent of *t*-BuLi, at –78 °C for 10 min followed by warming to 0 °C and quenching with aq $NaHCO_3$ (entries 1, 6). Appli-

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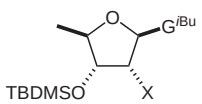
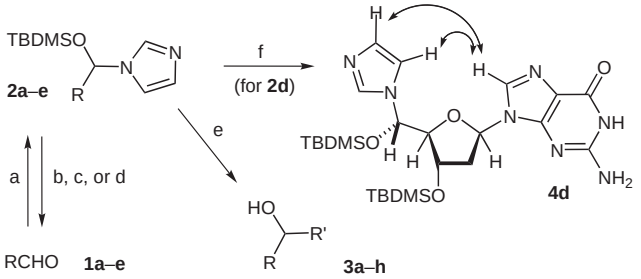
Table 1 Reactions of *N*,*O*-Acetals **2a**–**e**

Entry	SM	R	R′	Conditions[a]	Product	Yield%
1	**2a**	Ph	–	b or c	**1a**	90/89[b]
2	**2a**	Ph	Me	e	**3a**[8]	89
3	**2a**	Ph	*n*-Bu	e	**3b**[9]	90
4	**2a**	Ph	Ph	e	**3c**[10]	65
5	**2a**	Ph	*t*-Bu	e	**3d**[11]	84
6	**2b**	4-(MeO)C_6H_4	–	b or c	**1b**	88/85[b]
7	**2b**	4-(MeO)C_6H_4	Me	e	**3e**[8]	92
8	**2b**	4-(MeO)C_6H_4	*t*-Bu	e	**3f**[12]	80
9	**2c**	*t*-Bu	–	b	**1c**	85
10	**2c**	*t*-Bu	*t*-Bu	e	**3g**[13]	80
11	**2c**	*t*-Bu	Ph	e	**3d**	77
12	**2d**		–	b or d	**1d**	78/88[b]
13	**2d**		*t*-Bu	e	**3h**[c]	55
14	**2d**		–	f	**4d**	85
15	**2e**	X = OTBDMS	*t*-Bu	b or d	**1e**	82/90[b]

[a] Conditions are described in Scheme 1.
[b] Yields for the two possible routes, respectively.
[c] Isolated as a chromatographically separable mixture of diastereomers (ca. 1:1).

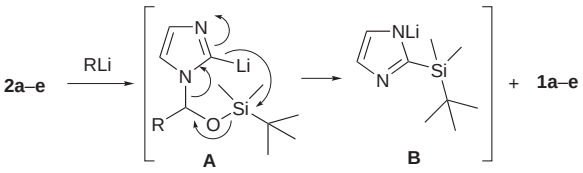
cation of 2 equivalents of an organolithium reagent, such as MeLi, *n*-BuLi, *t*-BuLi or PhLi to **2a**–**c** under the same conditions led to the corresponding alcohols **3a**–**g** which were isolated in high yields (Scheme 1, Table 1). Finally, **2d** reacted smoothly with 3 equivalents of *t*-BuLi at –78 °C providing a 1:1 diastereomeric mixture of the corresponding *t*-Bu adducts **3h** (entry 13).[14] The lack of diastereoselectivity in this step indicates that the chirality of the 5′-carbon of the *N*,*O*-acetal is most probably lost before the nucleophilic addition step, as suggested by the experimental evidence (*vide infra*).



Scheme 1 Synthesis and reactions of N,O-acetals **2a**–**e** and NOE contacts in **4d**. R and R′ groups are given in Table 1. Conditions: (a) TBDMSCl (1.5 equiv), imidazole (5 equiv), DMF, r.t. overnight (b) LDA, THF, –78 °C (c) R′Li (1.0 equiv), THF, –78 °C (d) NH_4F, MeOH, 60 °C, 1 h (e) R′Li (2.0 equiv), THF, –78 °C (f) NH_4OH in methanol.

Based on the results described above, we propose that the mechanism (Scheme 2) involves an initial proton abstraction of the 2-H proton of imidazole, as it is known that strong bases such as LDA or organolithium reagents can readily effect this proton abstraction.[15] This is indeed a standard functionalization route for substituted imidazoles. The resulting anion can induce an oxygen-to-carbon 1,4-silyl-migration reaction of the TBDMS group, thereby regenerating the aldehyde and a 2-TBDMS-imidazolyl anion.

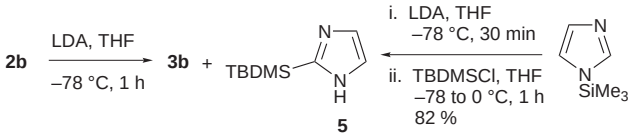
This is a novel type of a retro-[1,4]-Brook[16,17] (or West[18]) rearrangement, one of the less favored [1,*n*]-*O*- to *C*-silyl migrations related to the original [1,2]-*C* to *O*- Brook rearrangement.[19] It is reminiscent of the 1,4-*O*-to-*C* silyl migration reported by Keay and coworkers in furan systems.[17a–17c,17f] To our knowledge, this is the first instance of a retro-[1,4]-Brook rearrangement involving an imidazolyl system. More interestingly, it appears to be the first reported Brook-type rearrangement which involves



Scheme 2 Proposed reaction mechanism.

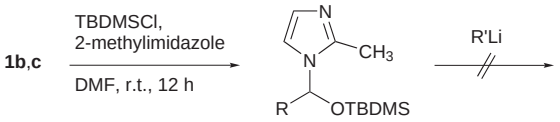
dissociation of the O-Si from the C-Si moieties through C-N bond cleavage. The increased stability of the resulting *N*-imidazolyl anion **B** relative to the initial 2-*C*-imidazolyl anion **A** (Scheme 2), as well as the liberation of the aldehyde through C-N bond cleavage, are most likely the driving forces for this reaction.

We were interested in providing further evidence in support of this intriguing reaction mechanism. The prediction put forth by the proposed mechanism was that it could be possible to isolate a 2-silyl-substituted imidazole from the reaction mixture as a side product. Such 2-silyl imidazoles have been reported to be unstable species,[20] although a 2-*tert*-butyldiphenyl-silylimidazole is known.[21] Short column chromatography of the crude reaction mixture from a scale-up reaction of **2b** (entry 8, Table 1) on deactivated silica did indeed lead to the isolation of a non-polar compound that was attributed to 2-*tert*-butylsilylimidazole based on its ^{1}H and ^{13}C NMR data.[22] In order to corroborate its structure we proceeded to an independent synthesis of **5** (Scheme 3) starting from *N*-trimethylsilylimidazole that yielded the same unstable compound in 82% yield as judged by its ^{1}H NMR and ^{13}C NMR spectra.[22]



Scheme 3 Independent synthesis of **5**.

Another prediction set forth by the proposed mechanism was that blocking of the proton abstraction from the 2-position of imidazole would stabilize these *N*,*O*-acetals and render them stable in the presence of basic organometallic reagents. Such a stabilization is of synthetic interest as it would provide the means for tuning the reactivity of *N*,*O*-acetals based on the need of either protection or reaction.



6b, R = 4-(MeO)C$_6$H$_4$, 92 %
6c, R = *t*Bu, 84 %

Scheme 4 Synthesis of 2-methyl analogs **6b**,**c**.

We therefore proceeded to the synthesis of the 2-methylimidazolyl analogs (**6b** and **6c**) of compounds **2b** and **2c**, respectively, which were obtained in high yield under the standard conditions (Scheme 4).[23] Application of 2 equivalents of any of the previously applied organolithium reagents at –78 °C to **6b** or **6c** caused no reaction after 1 h at –78 °C, whereas only traces of aldehyde were detected after warming up to 0 °C with the more reactive *t*-BuLi reagent. The results from this last experiment are a further indication of the validity of the proposed mechanism. Furthermore, they provide a synthetic tool that allows for the tuning of the reactivity of aldehyde *N*,*O*-acetals, depending on whether nucleophilic addition by organolithium reagents is desired or not.

In conclusion, we have shown that the reactivity of *O*-silyl imidazolyl aminals towards organolithium reagents can be tuned by the choice of the imidazole used. 2-Substituted imidazolyl aminals are stable, as is exemplified by the 2-methyl analogs (**6b**,**c**) whereas 2-unsubstituted imidazolyl aminals react readily with organolithium reagents with the same ease as the parent aldehydes. The experimental evidence supports the involvement of a novel type of a retro-[1,4]-Brook rearrangement. We believe that this duality of function will render these aldehyde derivatives useful to synthetic organic chemists.[24] Application of this new methodology to nucleoside and amino acid derivatives is currently in progress.

Acknowledgment

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References

(1) Ogawa, T.; Matsui, M. *Agr. Biol. Chem.* **1970**, *34*, 969.
(2) (a) Gasparini, J. P.; Grassend, R.; Maire, J. C.; Elguero, J. *J. Organomet. Chem.* **1980**, *188*, 141. (b) Gasparini, J. P.; Grassend, R.; Maire, J. C.; Elguero, J. *J. Organomet. Chem.* **1981**, *208*, 309.
(3) Andrews, P. A.; Bachur, N. R.; Musser, S. M.; Wright, J.; Callery, P. S. *J. Chromatogr.* **1987**, *419*, 271.
(4) Magnin, G. C.; Dauvergne, J.; Burger, A.; Biellmann, J.-F. *Tetrahedron Lett.* **1996**, *37*, 7833.
(5) Quan, L. G.; Cha, J. K. *Synlett* **2001**, 1925.
(6) (a) Saha, A. K.; Schairer, W.; Waychunas, C.; Prasad, C. V. C.; Sardaro, M.; Upso, D. A.; Kruse, L. I. *Tetrahedron Lett.* **1993**, *34*, 6017. (b) Kers, A.; Szabo, T.; Stawinski, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2585. (c) Brown, P.; Richardson, C. M.; Mensah, L. M.; Osborne, N. F.; Walker, G. *Biorg. Med. Chem.* **1999**, *7*, 2473. (d) Gunji, H.; Vasella, A. *Helv. Chim. Acta* **2000**, *83*, 1331.
(7) **2d**: Yield: 55%, white solid, mp (MeOH/H$_2$O): 264–265 °C. R_f (CH$_2$Cl$_2$/MeOH, 9:1): 0.34. ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.07, 0.08, 0.12, 0.16 (s, 3 H each), 0.82 (s, 18 H), 1.33, 1.36 (d, 3 H each), 1.72–1.80 (m, 1 H), 2.02–2.10 (m, 1 H), 2.95 (hpt, 1 H), 4.13 (d, 1 H, *J* = 1.4 Hz, H-4′), 4.53 (d, 1 H, *J* = 4.9 Hz, H-3′), 5.74 (d, 1 H, *J* = 1.5 Hz, H-5′), 5.85 (dd, 1 H, *J* = 11.0 Hz, 4.4 Hz, H-1′), 7.14 (s, 2 H), 7.60 (s, 1 H), 7.71 (s, 1 H), 11.78 (br s, 1 H), 12.15 ppm (br s, 1 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ –5.2, –4.8, –4.4, –4.1, 18.3, 18.6, 19.1, 19.6, 25.9, 36.7, 38.7, 70.6, 81.6, 85.6, 89.8, 115.9, 123.0, 128.8, 139.3, 139.5, 148.3, 148.7, 156.1, 180.1 ppm. IR (KBr): 2922, 1708, 1680, 1610, 1548, 840 cm^{-1}. MS (ESI): 632.4 [M + H]$^+$, 222.5 [B + H]$^+$. Anal. Calcd for $C_{29}H_{49}N_7O_5Si_2$: C, 55.12; H, 7.82; N, 15.52; Found: C, 55.30; H, 7.81; N, 15.55.
2e: Yield 50%, white solid, R_f (CH$_2$Cl$_2$/MeOH, 9:1): 0.38. ^{1}H NMR (300 MHz, CDCl$_3$) δ –0.38, –0.28, 0.07, 0.09, 0.16, 0.18 (s, 3 H each) 0.74, 0.89, 0.91 (s, 9 H each) 1.32 (s, 3 H)

1.36 (s, 3 H) 2.92–3.00 (hpt, 1 H) 4.18 (d, 1 H, H-4′) 4.32 (d, 1 H, H-3′) 4.73 (s,1 H, H-2′) 5.46 (d, 2 H, H-5′) 5.70 (s, 1 H, H-1′) 7.18 (d, 2 H) 7.58 (s, 1 H) 7.73 (s, 1 H) 11.48 (br s, 1 H) 12.25 ppm (br s, 1 H). MS (ESI): 762.6 $[M + H]^+$, 222.5 $[B + H]^+$. Anal. Calcd for $C_{35}H_{63}N_7O_6Si_3$: C, 55.15; H, 8.33; N, 12.86; Found: C, 55.00; H, 8.30; N, 12.90.

(8) Kamal, A.; Sandbhor, M.; Ramana, K. V. *Tetrahedron: Asymmetry* **2002**, *13*, 815.

(9) Arvidsson, P. I.; Davidsson, O.; Hilmersson, G. *Tetrahedron: Asymmetry* **1999**, *10*, 527.

(10) Chen, D.-W.; Ochiai, M. *J. Org. Chem.* **1999**, *64*, 6804.

(11) (a) Pini, D.; Rosini, C.; Bertucci, C.; Salvadori, P. *Gazz. Chim. Ital.* **1986**, *116*, 603. (b) Screttas, C. G.; Steele, B. R. *J. Org. Chem.* **1989**, *54*, 1013.

(12) Eichin, K. H.; Beckhaus, H. P.; Hellmann, S.; Fritz, H.; Peters, E. M. *Chem. Ber.* **1983**, *116*, 1787.

(13) (a) Olah, G. A.; Wu, A.; Faroog, O.; Prakash, G. K. *J. Org. Chem.* **1990**, *55*, 1792. (b) Roberts, D. D.; Hall, E. W. *J. Org. Chem.* **1988**, *53*, 2573.

(14) **3h′**: Yield 27%, white foam, R_f ($CHCl_3$/MeOH, 9:1): 0.53. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.11 (s, 6 H), 0.93 (s, 9 H), 1.26 (s, 9 H), 1.29 (s, 3 H), 1.31 (s, 3 H), 2.18 (dd, 1 H, *J* = 13.2 Hz, 5.5 Hz), 2.71 (hpt, 1 H), 2.72–2.78 (m, 1 H), 3.37 (s, 1 H, H-5′), 4.23 (s, 1 H, H-4′), 4.54 (d, 1 H, *J* = 5.9 Hz, H-3′), 5.33 (br s, 1 H, OH), 6.18 (dd, 1 H, *J* = 9.1 Hz, 5.5 Hz, H-1′), 7.73 (s, 1 H), 8.70 (br s, 1 H), 12.05 ppm (br s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ –4.2, –4.1, 18.4. 19.1, 19.4, 26.2, 27.0, 35.7, 36.8, 41.1, 77.0, 80.3, 88.0, 88.5, 123.4, 138.9, 147.2, 147.7, 155.5, 178.8 ppm. MS (ESI): 508.5 $[M + H]^+$, 222.5 $[B + H]^+$. Anal. Calcd for $C_{24}H_{41}N_5O_5Si$: C, 56.78; H, 8.14; N, 13.79; Found: C, 56.68; H, 8.18; N, 13.83.
3h″: Yield 28%, white foam, R_f ($CHCl_3$/MeOH, 9:1): 0.57. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.13 (s, 6 H), 0.93 (s, 9 H), 1.04 (s, 9 H), 1.26 (s, 3 H), 1.29 (s, 3 H), 2.25 (dd, 1 H, *J* = 13.2 Hz, 5.8 Hz), 2.70 (hpt, 1 H), 2.81–2.88 (m, 1 H), 3.57 (s, 1 H, H-5′), 4.29 (s, 1 H, H-4′), 4.76 (d, 1 H, *J* = 4.7 Hz, H-3′), 5.49 (br s, 1 H, OH), 6.18 (dd, H, *J* = 9.5 Hz, 5.9 Hz, H-1′), 7.77 (s, 1 H), 8.62 (br s, 1 H), 12.07 (br s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ –4.3, –3.6, 18.2, 19.0, 19.3, 26.1, 27.0, 34.2, 36.8, 42.1, 73.2, 80.7, 86.3, 91.4, 123.3, 139.2, 147.2, 147.7, 155.6, 178.7 ppm. MS (ESI): 508.5 $[M + H]^+$, 222.5 $[B + H]^+$.

(15) Iddon, B.; Ngochindo, R. I. *Heterocycles* **1994**, *38*, 2487.

(16) (a) Comanita, B. M.; Woo, S.; Fallis, A. G. *Tetrahedron Lett.* **1999**, *40*, 5283. (b) Lautens, M.; Delanghe, P. H. M.; Goh, J. B.; Zhang, C. H. *J. Org. Chem.* **1995**, *60*, 4213; and references therein.

(17) For earlier 1,4-*O*-to-C^{sp2} silyl migrations, see: (a) Bures, E. J.; Keay, B. A. *Tetrahedron Lett.* **1987**, *28*, 5965. (b) Bures, E. J.; Keay, B. A. *Tetrahedron Lett.* **1988**, *29*, 1247. (c) Spinazzé, P. G.; Keay, B. A. *Tetrahedron Lett.* **1989**, *30*, 1765. (d) Braun, M.; Mahler, H. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 896. (e) Kim, K. D.; Magriotis, P. A. *Tetrahedron Lett.* **1990**, *31*, 6137. (f) Beese, G.; Keay, B. A. *Synlett* **1991**, 33. (g) Wang, K. K.; Liu, C.; Gu, Y. G.; Burnett, F. N. *J. Org. Chem.* **1991**, *56*, 1914.

(18) West, R.; Lowe, R.; Stewart, H. F.; Wright, A. *J. Am. Chem. Soc.* **1971**, *93*, 282.

(19) Brook, A. G. *J. Am. Chem. Soc.* **1958**, *80*, 1886.

(20) (a) Pinkerton, F. H.; Thames, S. F. *J. Heterocycl. Chem.* **1972**, *9*, 67. (b) Jutzi, P.; Sakrib, W. *Chem. Ber.* **1973**, *106*, 2815.

(21) Mathews, D. P.; McCarthy, J. R.; Barbuch, R. J. *J. Heterocycl. Chem.* **1988**, *25*, 1845.

(22) **5**: Yield 82%, ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.07 (s, 6 H), 1.25 (s, 9 H), 5.0 (br s, NH), 6.98 ppm (s, 2 H). ^{13}C NMR (53.2 MHz, $CDCl_3$): δ 1.0 (CH_3), 25.9 (C), 30.3 (CH_3), 125.5 (CH), 135.7 ppm (C).

(23) **6b**: Yield 92%, oil. R_f ($CHCl_3$/MeOH, 98:2): 0.36. ^{1}H NMR (200 MHz, $CDCl_3$): δ –0.13, 0.05 [s, 3 H each, $Si(CH_3)_2$], 0.86 [s, 9 H, $SiC(CH_3)_3$], 2.24 (s, 3 H, CH_3), 3.72 (s, 3 H, OCH_3), 6.45 (s, 1 H, CHO), 6.79 (d, 1 H, *J* = 8.7 Hz, Ar-H), 6.81 (s, 1 H, Imid-H), 6.87 (s, 1 H, Imid-H), 7.09 ppm (d, 2 H, *J* = 8.7 Hz, Ar-H). ^{13}C NMR (53.2 MHz, $CDCl_3$): δ –5.0 ($2 \times CH_3$), 18.2 (C), 25.8 ($3 \times CH_3$), 36.6 (CH_3), 55.5 (CH_3), 80.6 (CH), 113.9 (C), 117.8 (C), 126.9 ($2 \times$ CH), 127.3 ($2 \times$ CH), 132.8 (C), 159.8 (C), 162.7 ppm (C). Anal. Calcd for $C_{18}H_{28}N_2O_2Si$: C, 65.02; H, 8.49; N, 8.42; Found: C, 65.22; H, 8.46; N, 8.45.
6c: Yield 84%, oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ –0.04, 0.03 [s, 3 H each, $Si(CH_3)_2$], 0.81 [s, 9 H, $SiC(CH_3)_3$], 0.86 [s, 9 H, $C(CH_3)_3$], 2.31 (s, 3 H, CH_3), 5.06 (s, 1 H, CHO), 6.80 (s, 1 H, Imid-H), 6.90 ppm (s, 1 H, Imid-H). ^{13}C NMR (53.2 MHz, $CDCl_3$): δ –3.4, –2.8 (each CH_3), 18.2 (C), 25.4 ($3 \times CH_3$), 25.7 ($3 \times CH_3$), 31.7 (C), 36.8 (CH_3), 86.4 (CH), 117.2 (CH), 121.2 (CH), 162.9 ppm (C).

(24) **Typical Procedure:** To a solution of the protected aldehyde **2a**–**e** (0.5 mmol) in dry THF (20 mL/mmol) was added the organolithium reagent (2 equiv, Table 1), drop-wise, at –78 °C. After stirring for 10 min at –78 °C the temperature was let to slowly increase to 0 °C. The reaction mixture was quenched with sat aq $NaHCO_3$ at 0 °C, diluted with ethyl acetate, the phases were separated and the organic phase was washed with water, dried over sodium sulfate, and concentrated under reduced pressure. The resulting crude **3a**–**h** was purified by silica gel chromatography. Yields are reported in Table 1.