Remarkably Stable Tetrahedral Intermediates: Carbinols from Nucleophilic Additions to *N*-Acylpyrroles**

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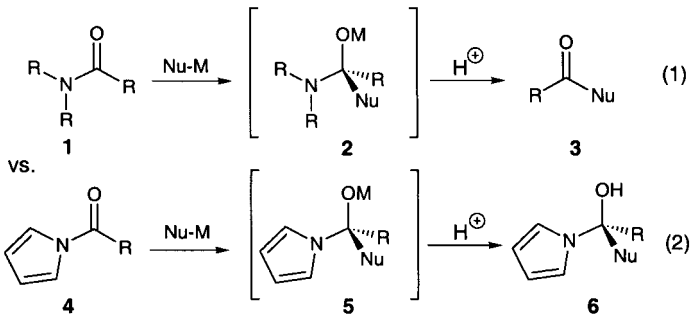
Tetrahedral intermediates resulting from the addition of nucleophiles to carboxylic acid derivatives are important, short-lived species in acyl-transfer reactions.[1] As a result of their transient nature, the utility of these compounds in organic chemistry remains limited. The isolation of tetrahedral intermediates could provide insight into the acyl-transfer process as well as useful compounds for organic synthesis. While the adducts formed by the addition of organometallic reagents to *N*-methoxy-*N*-methylamides[2] and tertiary amides[3] are relatively stable as their corresponding metal alkoxides (**2**),[4] their protonated counterparts rapidly decompose to the derived carbonyl derivative **3** [Eq. (1)].[5] Herein, we report a study of the stability and synthetic utility of the exceptionally stable tetrahedral intermediates **5** and **6** resulting from the addition of nucleophiles to *N*-acylpyrroles **4** [Eq. (2)].

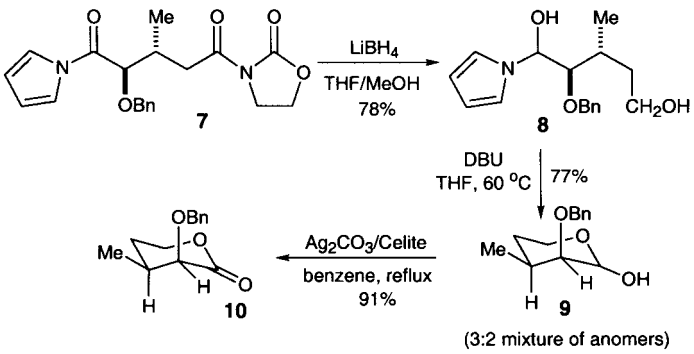


(1)

(2)

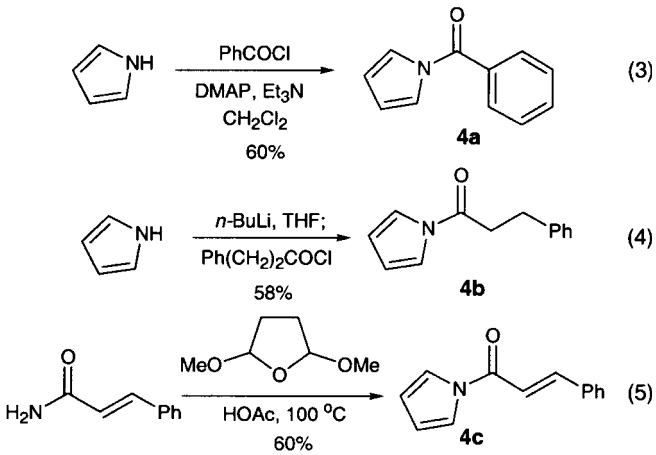
A few examples documenting the isolation of tetrahedral intermediates from nucleophilic additions to *N*-acylpyrroles have been reported.[6] In an early report, Brandange and co-workers demonstrated that the adducts derived from lithium enolate additions to *N*-acylpyrroles could be protonated to afford isolable "pyrrolyl carbinols".[6d,e] In a later study, Fukuyama and co-workers reported the isolation of several tetrahedral intermediates from the reduction of indolylamides with DIBAL-H.[7,10]

Our own interest in the chemistry of *N*-acylpyrroles began with the initial observation that the $LiBH_4$ reduction of compound **7**,[8] prepared from our previously reported Cu^{II}-catalyzed Mukaiyama–Michael reaction,[9] afforded the carbinol **8** in 78% yield (Scheme 1). When **8** was heated in the presence of DBU the lactol **9** was obtained and characterized as the lactone **10**. We felt that the high stability of these tetrahedral intermediates, as well as their potential synthetic utility as masked aldehyde or ketone equivalents, warranted further investigation.



Scheme 1. Isolation of pyrrolyl carbinol **8** (see reference [10] for abbreviations), and subsequent reaction to give **10**.

Several methods were used to prepare *N*-acylpyrroles for this study. Aryl and alkyl *N*-acylpyrroles were synthesized by the acylation of pyrrole with acid chlorides (Scheme 2, Eqs. (3)and (4)).[11,12] *N*-Cinnamoylpyrrole (**4c**) was prepared by the condensation of cinnamamide with 2,5-dimethoxytetrahydrofuran in acetic acid [Eq. (5)].[13]



Scheme 2. Synthesis of *N*-acylpyrroles.

We began our study by investigating the scope of organometallic additions to *N*-acylpyrroles (Table 1, Eq. (6)). Carbinol stability was found to be quite general, as aromatic (**4a**), alkyl (**4b**), and α,β-unsaturated (**4c**) *N*-acylpyrroles all afforded stable adducts **6a–g** after aqueous workup. Moreover, all the pyrrolyl carbinols could be purified by flash column chromatography. Grignard reagents were found to be competent nucleophiles. For example, the addition of MeMgCl and PhMgBr to **4a** and **4b** at −48 °C afforded the tertiary carbinols **6b,c** and **6e,f**, respectively, in good yields (76 to 86%). The reduction of *N*-acylpyrroles **4a** and **4b** with $LiBH_4$ afforded the secondary carbinols **6a** and **6d**, respectively, in high yields (94–95%). The facile reduction with $LiBH_4$ highlights the enhanced electrophilicity of these carbonyl derivatives, as $LiBH_4$ normally does not react with

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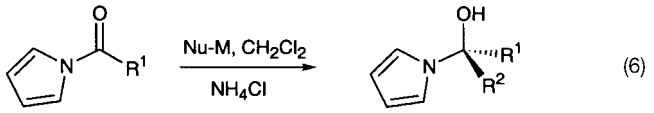
Table 1. 1,2-Additions to *N*-acylpyrroles **4** [Eq. (6)].



(6)

4 **6**

Entry	**4**	R^1	Nu-M	R^2	*T* [°C]	*t* [h]	Product	Yield [%]
1	**4a**	Ph	$LiBH_4$[a]	H	0	1	**6a**	95
2	**4a**	Ph	MeMgCl	Me	−48	10	**6b**	81
3	**4a**	Ph	PhMgBr	Ph	−48	6	**6c**	80
4	**4b**	CH_2CH_2Ph	$LiBH_4$[a]	H	0	3	**6d**	94
5	**4b**	CH_2CH_2Ph	MeMgCl	Me	−48	8	**6e**	76
6	**4b**	CH_2CH_2Ph	PhMgBr	Ph	−48	4	**6f**	86
7	**4c**	(*E*)-CH=CHPh	DIBAL-H	H	−78	2	**6g**	86

[a] Et_2O as solvent.

tertiary aliphatic amides.[14] Although the $LiBH_4$ reduction of *N*-cinnamoylpyrrole (**4c**) afforded a mixture of products, reduction with DIBAL-H afforded carbinol **6g** in 86% yield (Table 1, entry 7).[15]

These results illustrate the reactivity conferred by the pyrrole ring, which provides activation for nucleophilic addition yet is deactivated as a leaving group. The ketone-like reactivity of *N*-acylpyrroles may be attributed to nitrogen lone pair delocalization in the aromatic system reducing donation into the carbonyl moiety.[16] The stability of the protonated adducts may also be attributed to pyrrole aromaticity, as the lack of an accessible lone pair prevents nitrogen protonation and ensuing decomposition to the carbonyl derivative.

The structure of **6b** was confirmed by X-ray crystallography (Figure 1).[17,18] Interestingly, the C6–N1 bond length of 1.478 Å is longer than previously reported C_{sp^3}–$N_{pyrrole}$ bond lengths, which range from 1.412 to 1.458 Å.[19] Conversely, the C6–O1 bond length of 1.411 Å is shorter than the average C_{sp^3}–OH bond length of 1.432 Å.[20] The C6–C5 bond length is 1.522 Å, shorter than the average C_{sp^3}–C_{sp^3} bond length of 1.530 Å. The C6–C7 bond length is 1.527 Å, longer than the average C_{sp^3}–C_{aryl} bond length of 1.513 Å.[20] The elongated C6–N1 bond and the shortened C6–O1 bond are consistent with an anomeric effect resulting from the interaction of the oxygen lone pairs with the C–N σ^* orbital.[21]

The stability of pyrrolyl carbinols **6** encouraged us to investigate additions to 1,1′-carbonyldipyrrole (**11**) [Eq. (7)].[22] Although the bis(pyrrolyl) carbinols **12** resulting from the addition of PhMgBr and MeMgCl to **11** could be isolated and characterized, they were found to be considerably less stable than the corresponding pyrrolyl carbinols **6**. In addition, the quality of the Grignard reagent significantly affected the outcome of the addition. New or freshly prepared Grignard reagent afforded intermediate **12** as the major product, while older Grignard reagent provided mainly the *N*-acylpyrrole **4** resulting from decomposition of **12**.

The instability of carbinols **12** prompted us to examine the preparation of *N*-acylpyrroles directly from **11**. The addition of organometallic reagents to **11** followed by brief treatment of the unpurified material with 5 mol% DBU afforded *N*-acylpyrroles **4a** and **4e**–**h** in moderate to good yields (55 to

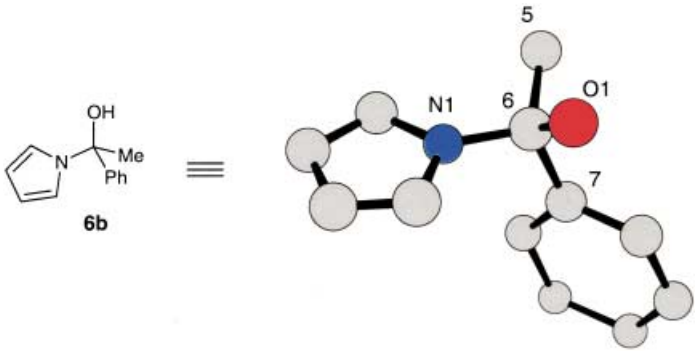
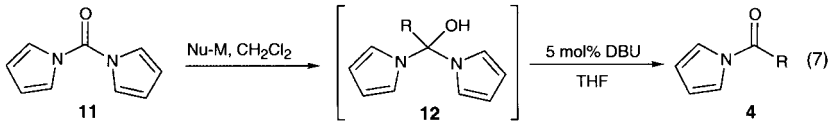


Figure 1. Structure of **6b**. Selected bond lengths [Å] and angles [°]: C6-N1 1.478, C6-O1 1.411, C6-C5 1.522, C6-C7 1.527; N1-C6-O1 108.2, N1-C6-C5 109.2, N1-C6-C7 110.4, C5-C6-C7 110.7.

87%; Table 2, Eq. (7)). Notably, this procedure provided access to *trans*-*N*-crotonylpyrrole (**4f**), which could not be prepared by using the previously described methods (see above).

Selected experiments were performed to probe the stability of **6**. Carbinol **6c** was found to be stable for extended periods (> 10 h) under mildly acidic (PPTS, 2:1 THF/H_2O) and mildly basic conditions (pyridine, Et_3N) at ambient temperatures, but quickly decomposed to pyrrole and benzophenone when treated with a catalytic amount of DBU in THF. The conversion of **6a**–**c** to their derived carbonyl compounds was monitored by in situ IR spectroscopy. Following addition

Table 2. Synthesis of *N*-acylpyrroles from 1,1′-carbonyldipyrrole (**11**) [Eq. (7)].



(7)

11 **12** **4**

Entry	Nu-M	*T* [°C]	*t* [h]	Carbinol	Yield [%]	*N*-Acylpyrrole	Yield [%]
1	PhMgBr	−48	7	**12a**	77[b]	4a	83
2	MeMgCl	−30	24	**12b**	92	**4d**	–
3	*n*-BuMgCl	−48	7	**12c**	–	**4e**	69
4	vinylMgBr	−78	21	**12d**	–	**4f**	58[c]
5	*trans*-1-propenylLi[a]	−78	1.5	**12e**	–	**4g**	87[c]
6		−78	0.5	**12f**	–	**4h**	55

[a] THF as solvent. [b] Yield for addition at −30 °C. [c] The *N*-acylpyrrole was obtained directly without treatment with DBU.

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of DBU (0.05 equiv) to a solution of the carbinol in THF, an absorption appeared corresponding to the newly formed C=O stretching frequency of carbonyl derivatives **13a–c** [Eq. (8)]. The time-dependent increase in the carbonyl absorption was used to determine the decomposition of the carbinol as a function of time (Figure 2).[23] The data document that steric

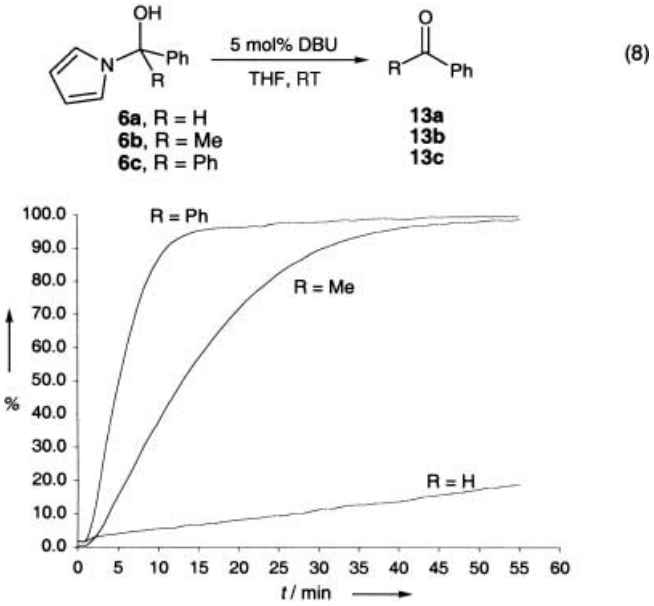

Figure 2. Conversion [%] of the carbinols **6a**, **6b**, and **6c** as a function of time.

congestion in the substrate accelerates the rate of conversion to **13**. Whereas **6a** (R = H) decomposes slowly over a 13-hour period, **6b** (R = Me) and **6c** (R = Ph) decompose completely in 40 and 15 minutes, respectively.

The effect of temperature and counterion on the stability of the deprotonated carbinols was also investigated. Three different bases (EtMgBr, *n*BuLi, NaHMDS) were used to deprotonate **6c** (R = Ph). The rate of conversion of the resulting metal alkoxide **5c** into benzophenone was monitored at −78, −30, and 0 °C using in situ IR spectroscopy (Figure 3, Eq. (9)). In a representative experiment, EtMgCl (1.2 equiv) was added to a solution of **6c** in THF at −78 °C. The carbinol O–H stretch at 3300 cm^{-1} immediately disappeared, which indicated complete deprotonation. No new IR absorptions were detected at −78 °C or upon warming to −30 °C.[24] However, upon continued warming to 0 °C, a new absorption at 1664 cm^{-1} corresponding to the benzophenone carbonyl stretching frequency was observed, which signaled slow decomposition of the magnesium alkoxide (**5c**, M = Mg^{II}) at 0 °C. In similar experiments, the lithium alkoxide decomposed at −30 °C, and the sodium alkoxide at −78 °C. Thus, the thermal stability of the alkoxide correlates well with the electronegativity of the counterion, with the stability decreasing in the order $Mg^{II} > Li^{I} > Na^{I}$.

The potential synthetic utility of pyrrolyl carbinols lies in their ability to function as masked carbonyl equivalents whose carbonyl functionality is revealed under suitably basic conditions. For example, treatment of **6f** with MeLi at 0 °C resulted in deprotonation and elimination of pyrrole to afford the ketone intermediate **14**, which was then intercepted by another equivalent of MeLi to afford the tertiary alcohol **15** in 98 % yield (Scheme 3, Eq. (10)). Alternatively, pyrrolyl carbinols may be protected from base by silyl ether formation. The secondary carbinol **6d** was silylated with TBSCl to afford the TBS ether **16** in 84 % yield [Eq. (11)]. The tertiary carbinol **6f** was silylated with TMSOTf to afford the TMS ether **17** in 86 % yield [Eq. (12)]. The silylated carbinols **16** and **17** were stable in the presence of *n*BuLi, MeMgCl, DIBAL-H, and DBU.[25] Deprotection of silyl ether **17** with nBu_4NF at −78 °C afforded **14** in 83 % yield.

In summary, the addition of organometallic reagents to *N*-acylpyrroles to afford stable, isolable tetrahedral intermediates is a general process. *N*-Acylpyrroles undergo additions with hydride and Grignard reagents to provide pyrrolyl

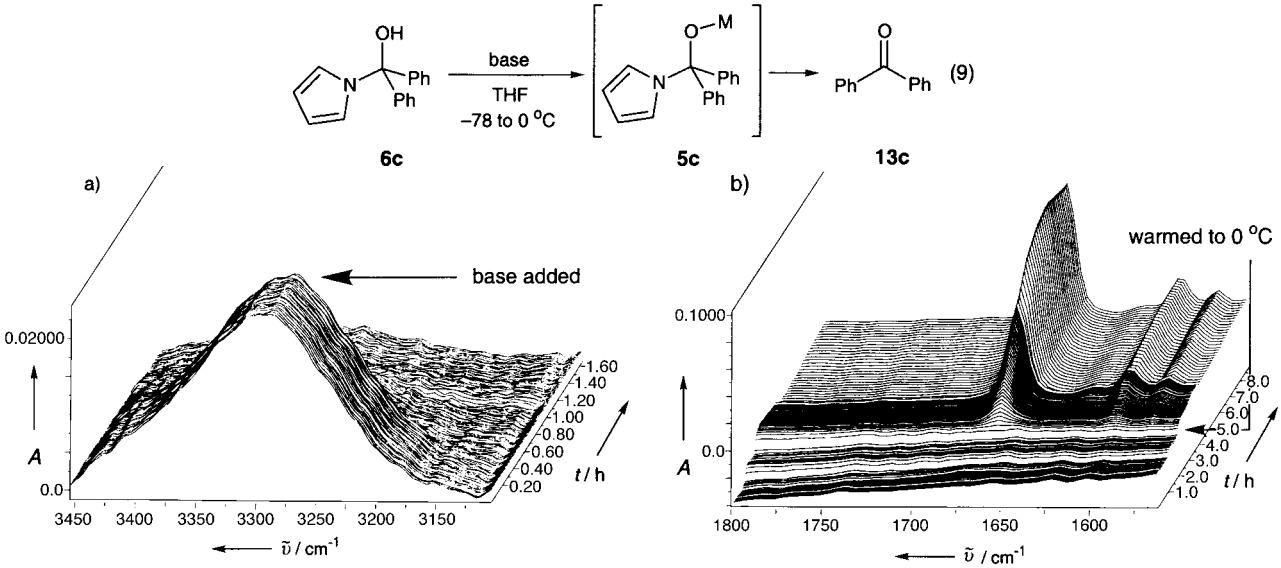

Figure 3. Monitoring the conversion of **6c** to benzophenone by in situ IR spectroscopy: a) Disappearance of the O-H stretch upon addition of EtMgCl. b) A benzophenone carbonyl absorption appears upon warming to 0 °C.

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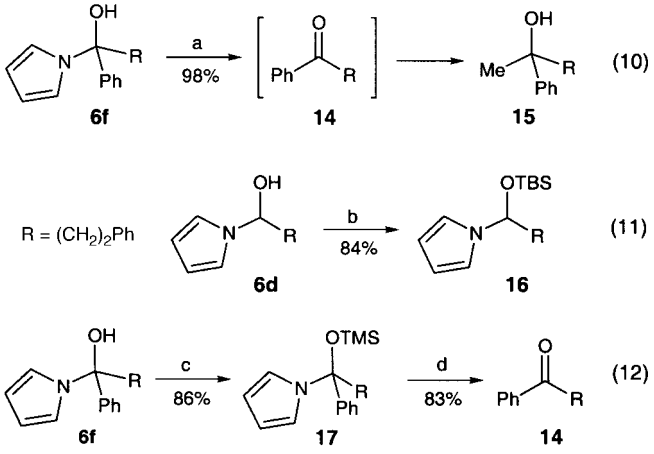

Scheme 3. Transformations of carbinols **6**. a) MeLi, THF, 0 °C; b) TBSCl, imidazole, CH_2Cl_2; c) TMSOTf, 2,6-lutidine, DMF; d) nBu$_4$NF, THF, −78 °C.

carbinols in good to high yields. The stability of the alkoxides generated by deprotonation of the carbinols depends on the electronegativity of the counterion in the order $Mg^{II} > Li^{I} > Na^{I}$. Conversion of the carbinols into the corresponding carbonyl compounds can be achieved with catalytic DBU. In addition, we have demonstrated that pyrrolyl carbinols are useful synthetic intermediates that are stable enough to undergo further synthetic transformations.

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[1] For discussions of the mechanism of acyl transfer reactions, see: a) T. C. Bruice, S. J. Benkovic, *Bioorganic Mechanisms*, Benjamin, New York, **1966**; b) S. L. Johnson, *Adv. Phys. Org. Chem.* **1967**, *5*, 237; c) M. L. Bender, *Mechanisms of Homogeneous Catalysis from Protons to Proteins*, Wiley-Interscience, New York, **1971**; d) A. J. Kirby, *Compr. Chem. Kinet.* **1972**, *10*, 57; e) W. P. Jencks, *Catalysis in Chemistry and Enzymology*, Dover, New York, **1987**; f) A. Fersht, *Structure and Mechanism in Protein Science*, W. H. Freeman, New York, **1999**.

[2] a) S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815; b) B. T. O'Neill in *Comprehensive Organic Synthesis, Vol. 1* (Eds.: B. M. Trost, I. Fleming, S. L. Schreiber), Pergamon Press, Oxford, **1991**, p. 399.

[3] F. Wingler, *Methoden Org. Chem.(Houben-Weyl) 4th ed. 1952–, Vol. 7/2a*, **1973**, p. 581.

[4] For two notable examples in which an amide tetrahedral intermediate has been isolated as the anion, see: a) M. Adler, M. Marsch, N. S. Nudelman, G. Boche, *Angew. Chem.* **1999**, *111*, 1345; *Angew. Chem. Int. Ed.* **1999**, *38*, 1261; b) C. Cox, H. Wack, T. Lectka, *J. Am. Chem. Soc.* **1999**, *121*, 7963.

[5] A remarkable exception is the synthesis of a hydrated adamantylamide tetrahedral intermediate by Kirby et al.: A. J. Kirby, I. V. Komarov, P. D. Wothers, N. Feeder, *Angew. Chem.* **1998**, *110*, 830; *Angew. Chem. Int. Ed.* **1998**, *37*, 785.

[6] a) M. S. Taggart, G. H. Richter, *J. Am. Chem. Soc.* **1934**, *56*, 1385; b) M. E. K. Cartoon, G. W. H. Cheeseman, *J. Organomet. Chem.* **1982**, *234*, 123; c) S. D. Lee, M. A. Brook, T. H. Chan, *Tetrahedron Lett.* **1983**, *24*, 1569; d) S. Brandange, B. Rodriguez, *Acta Chem. Scand. Ser. B* **1987**, *41*, 740; e) S. Brandange, E. Holmgren, H. Leijonmarck, B. Rodriguez, *Acta Chem. Scand.* **1995**, *49*, 922.

[7] E. Arai, H. Tokuyama, M. S. Linsell, T. Fukuyama, *Tetrahedron Lett.* **1998**, *39*, 71.

[8] T. D. Penning, S. W. Djuric, R. A. Haack, V. J. Kalish, J. M. Miyashiro, B. W. Rowell, S. S. Yu, *Synth. Commun.* **1990**, *20*, 307–312.

[9] D. A. Evans, K. A. Scheidt, J. N. Johnston, M. C. Willis, *J. Am. Chem. Soc.* **2001**, *123*, 4480.

[10] Abbreviations: Ac = acetyl; Bn = benzyl; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DIBAL-H = diisobutylaluminum hydride; DMF = *N*,*N*-dimethylformamide; DMAP = 4-dimethylaminopyridine; PPTS = pyridinium *p*-toluenesulfonate; TBS = dimethyl-*tert*-butylsilyl; THF = tetrahydrofuran; TMS = trimethylsilyl.

[11] C. D'Silva, R. Iqbal, *Synthesis* **1996**, 457.

[12] D. A. Evans, D. S. Johnson, *Org. Lett.* **1999**, *1*, 595.

[13] For the synthesis of *N*-benzoylpyrrole under similar conditions, see: F. M. Menger, J. A. Donohue, *J. Am. Chem. Soc.* **1973**, *95*, 432.

[14] H. C. Brown, S. Krishnamurty, *Tetrahedron* **1979**, *35*, 567.

[15] A quick purification is desirable for **6g**, as this compound is unstable to prolonged exposure to silica gel.

[16] The barrier to rotation about the amide bond for *N*-acetylpyrrole is about 7 kcal mol^{-1} less than for *N*,*N*-dimethylacetamide: K. Dahlqvist, S. Forsén, *J. Phys. Chem.* **1969**, *73*, 4124.

[17] We thank Mr. C. Wade Downey for solving the X-ray structure of **6b**.

[18] CCDC-185908 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[19] a) 1.412 Å: E. Sugahara, M. M. S. Paula, I. Vencato, C. V. Franco, *J. Coord. Chem.* **1996**, *39*, 59; b) 1.445 Å: S. Gomez, C. Vinas, M. Lamrani, F. Teixidor, R. Kivekas, R. Sillanpaa, *Inorg. Chem.* **1997**, *36*, 3565; c) 1.452 Å: A. Bach, L. Beyer, T. Gelbrich, K. H. Hallmeier, C. Hennig, M. Mobius, R. Richter, R. Szargan, V. Fernandez, J. Losada, *Z. Naturforsch. B* **1996**, *51*, 757; d) 1.458 Å: see ref. [19c].

[20] F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, R. Taylor, *J. Chem. Soc. Perkin Trans. 2* **1987**, S1.

[21] An elongated C–N bond and a shortened C–O bond were also observed in the X-ray crystal structure of the *anionic* complex $[(Ph)_2(NMe_2)C(OLi)\cdot THF]_2$ formed by the addition of PhLi to *N*,*N*-dimethylbenzamide.[4a]

[22] Prepared in 62% yield by the condensation of *N*,*N*′-carbonyldiimidazole with two equivalents of pyrrole at 125 °C: J. Bergman, R. Carlsson, B. Sjöberg, *J. Heterocycl. Chem.* **1977**, *14*, 1123.

[23] The carbinol was completely converted into the ketone or aldehyde in all three reactions.

[24] The reaction was warmed rapidly to minimize baseline drift.

[25] Solutions of **16** or **17** in THF were treated with *n*BuLi in hexanes (2 equiv), MeMgCl in THF (3 equiv), DIBAL-H in hexanes (3 equiv), and DBU in THF (3 equiv) and monitored by thin layer chromatography at −78 °C, −48 °C, and 0 °C for about 45 min at each temperature. Except for partial desilylation of **16** with *n*BuLi at 0 °C, no significant decomposition was observed under these reaction conditions.

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