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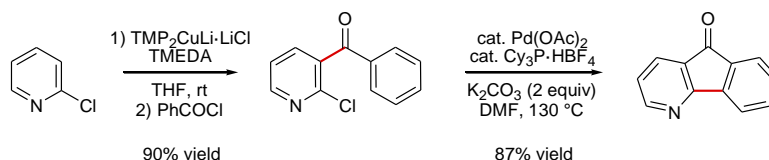
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Efficient two-step access to azafluorenones and related compounds

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Abstract:

Crystals of a lithiocuprate prepared from copper(I) chloride and lithium 2,2,6,6-tetramethylpiperidide (2 equiv) were isolated and analysed by X-ray diffraction as (TMP)₂Cu(Cl)Li₂·THF. The observation of this species is consistent with its having a role in deprotocupration-arylation for a higher-order bis(amido)cuprate. Phenyl pyridyl ketones, phenyl quinolyl ketones and phenyl thienyl ketones were prepared in tetrahydrofuran by this sequence using the lithiocuprate and aroyl chlorides as electrophiles. Diaryl ketones bearing a chloro group at the 2 position (of a pyridyl or phenyl group) thus synthesized were next converted through palladium-catalysed ring closure to polycycles of the 5*H*-indeno[1,2-*b*]pyridin-5-one, 11*H*-indeno[1,2-*b*]quinolin-11-one, 9*H*-indeno[2,1-*c*]pyridin-9-one and 8*H*-indeno[2,1-*b*]thiophen-8-one families.

Introduction

Azafluorenones represent the heterocyclic cores of many molecules of biological interest; derivatives have, for example, been described for their antifungal,¹ antibacterial,² and antimalarial³ properties.

In the course of the development of lithium-metal amido-based heterometallic bases, synergic reagents with which to functionalize aromatic compounds unsuitable for reaction with traditional organolithium bases have been identified and developed.⁴ Amongst these, the cuprate base prepared *in situ* from CuCl and 2 equiv of LiTMP (TMP = 2,2,6,6-tetramethylpiperido), in addition to achieving regioselective deprotonation, gave metallated derivatives capable of reacting *in situ* with aroyl chlorides to afford the corresponding ketones.⁵ We realized that this approach, applied to the synthesis of 2-chloro diaryl ketones, could be combined with transition metal-catalysed cyclization to afford a straightforward method by which to synthesize azafluorenones and related compounds. In addition, whereas coupling involving C-H bond activation has been the subject of numerous investigations,⁶ to our knowledge only one study has been devoted to azafluorenone synthesis, this using 2-bromo diaryl ketone reagents,⁷ which are more expensive than the corresponding chloro analogues.

Results and discussion

Recently, in order to gain more information about the lithiocuprate base, we attempted its crystallization. In the present case, the treatment of LiTMP with CuCl in toluene/THF followed by concentration and recrystallization from toluene at -20 °C afforded colourless crystals which X-ray diffraction showed to be (TMP)₂Cu(Cl)Li₂·THF **1** (Figure 1).⁸ A dimer is revealed in the solid state based on a (LiCl)₂ core with the halide ions remote from copper. The structure is closely related to the dimers of (TMP)₂Cu(CN)Li₂·THF⁹ and (TMP)₂Cu(I)Li₂·THF,¹⁰ with Cu maintaining a near linear geometry (N(1)-Cu(1)-N(2) 174.45(11)°) and the amides acting as inter-metal bridges (Cu(1)-N(1)-Li(1) 92.1(2), Cu(1)-N(2)-Li(2) 84.77(19)°). However, in contrast to the cyanide- and iodide-based dimers, in which the THF-solvated Li⁺ ions reside within ±0.14 and ±0.15 Å, respectively, of planes defined by the (LiX)₂ (X = N, I) metallocyclic cores of the structures, in **1** they are significantly displaced (by ±0.49 Å) from the analogous (LiCl)₂ core plane. Lastly, we can empirically view formation of the higher-order dimer as resulting from the formal insertion of two units of *in situ*-generated LiCl·THF¹¹ into a lower-order dimer based on a (NCuNLi)₂ ring.¹⁰

Whereas early synthetic work with these systems presumed the use of higher-order cuprates such as (TMP)₂Cu(CN)Li₂ as deprotocuprating agents,⁹ this cuprate structure-type has been established to be in competition¹⁰

¹¹ with lower-order (TMP)₂CuLi and both higher- and lower-order lithiocuprates have proved capable of being isolated from similar media.¹⁰ Moreover, the conditions employed here – 2:1 combination of lithium amide with CuCl in THF/TMEDA – favour retention in solution of *in situ*-formed LiCl.¹² Combined with recent synthetic results concerning the metallation of halopyridines^{5c} and the theoretical modelling of cuprate bases,¹⁰ these data suggest that efficient deprotonation-arylation requires only the presence of components consistent with the formulation of a higher-order bis(amido)cuprate. Indeed, spectroscopic studies on **1** show the presence in both benzene and THF solutions of the higher-order cuprate alongside a small but detectable amount of another species.⁸ Based on recent studies that reported the characterization of TMP₂CuLi it is possible to attribute the minor signals to the *in situ* formation of this lower-order cuprate.¹⁰

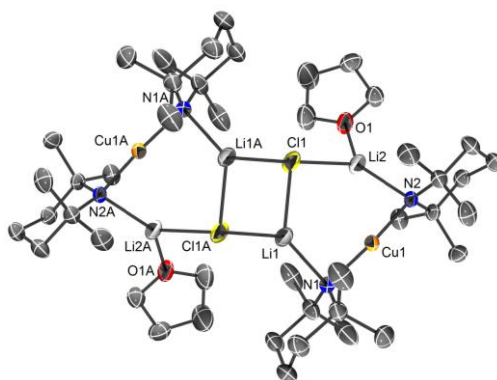


Figure 1. ORTEP diagram (50% probability) of the dimer of lithiocuprate **1** with H-atoms omitted.¹³

Table 1. Synthesis of **2**, **3a-c**, **4**, **5** and **6** by deprotonation followed by arylation (TMEDA = *N,N,N',N'*-tetramethylethylene-diamine).

$$\text{Ar-H} \xrightarrow[\text{THF, rt, 2 h}]{\begin{array}{l} 1) (\text{TMP})_2\text{CuLi}\cdot\text{LiCl} (1 \text{ equiv}) \\ \text{TMEDA} (1 \text{ equiv}) \\ 2) \text{ClC(O)Ar}' \end{array}} \text{Ar-C(=O)Ar}'$$

Entry	Ar-H	ClC(O)Ar'	Product	Yield (%)
1			2	44 ^{a,5}
2			3a	90 ^{a,5}
3			3b	80 ^a
4			3c	59 ^a
5			4	56 ^a
6			5	57 ^b (35) ^a
7			6	85 ^b

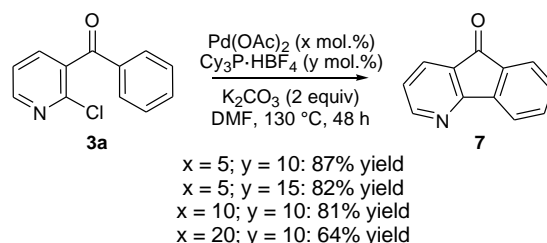
^aTrapping step performed at rt.

^bTrapping step performed at 60 °C.

Our deprotonation-arylation method was next applied to the synthesis of 3-benzoyl-2-chloroquinoline and -2-chloropyridine **2** and **3a** (44 and 90% yield, respectively),⁵ compounds for which subsequent cyclization could lead to heterocyclic tricycles (Table 1, entries 1,2). We also chose the diaryl ketones **3b-c**,¹⁴ **4**,¹⁵ **5**¹⁶ and **6**¹⁷ as other potential candidates to evaluate the combination of deprotonation-arylation with transition metal-catalysed cyclization, and prepared them by extending the method (Table 1, entries 3-7). In particular, we discovered that the trapping step usually performed at room temperature can be improved in the thiophene series by raising the temperature to 60 °C (Table 1, entries 6,7).

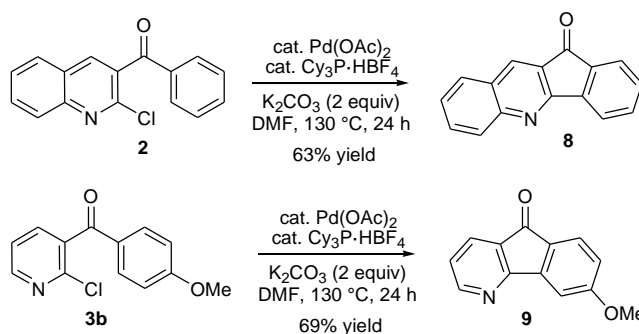
We next turned to the synthesis of azafluorenones and related compounds. Owing to their presence in natural products and compounds of medicinal interest, the synthesis of fluorenones has received significant attention.¹⁸ With the aim of developing a short access method to such compounds, here we have targeted a route involving cyclization of the ketones **2-6**.

4-Azafluorenone (**7**) was previously synthesized by several groups,¹⁹ and sometimes under harsh conditions. For example, Stauffer and co-workers prepared the tricycle by heating 2-phenylnicotinic acid at 190 °C in polyphosphoric acid, 2-phenylnicotinic acid being prepared in two steps from 2-chloro-3-cyanopyridine.²⁰ The cyclization of 2-chloro-3-benzoylpyridine (**3a**) to 4-aza-fluorenone (**7**)²¹ was first optimized. Inspired by a previously described cyclization of 2-chloro diaryl aniline to carbazole,²² the reactions were attempted in the presence of catalytic amounts of Pd(OAc)₂ and electron-rich bulky trialkyl phosphine, and used K₂CO₃ as a base. Using Cy₃P in DMF at 130 °C, different transition metal-ligand ratios were tested. The best result was observed using 5 mol% of Pd(OAc)₂ and 10 mol% of phosphine; using 20 mol% of Pd(OAc)₂ and 10 mol% of phosphine, a lower yield was observed due to recovered starting material (Scheme 1).



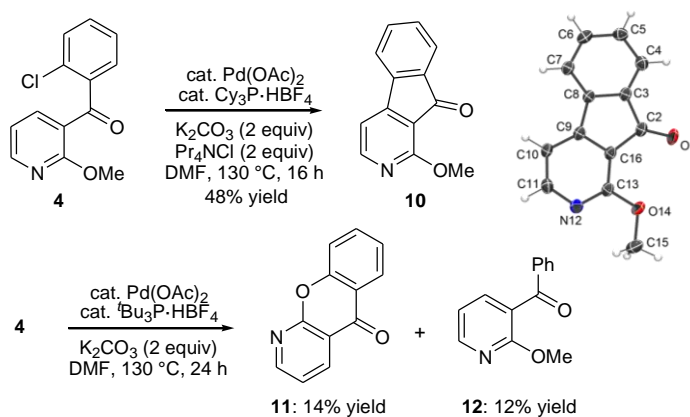
Scheme 1. Optimization of the Pd(OAc)₂-Cy₃P ratio for the cyclization affording 5*H*-indeno[1,2-*b*]pyridin-5-one (or 4-azafluorenone, **7**).

Under the best reaction conditions identified in Scheme 1,²³ 11*H*-indeno[1,2-*b*]quinolin-11-one (**8**)²⁴ and 8-methoxy-5*H*-indeno[1,2-*b*]pyridin-5-one (**9**)²⁵ were formed from the ketones **2** and **3b** respectively, and isolated in 63-69% yield (Scheme 2). The ketone **3c**, expected to allow further coupling thanks to an additional chloro group, did not afford the expected chloro cyclized product; bare 5*H*-indeno[1,2-*b*]pyridin-5-one (**7**) was the sole product identified using Cy₃P or ^tBu₃P.

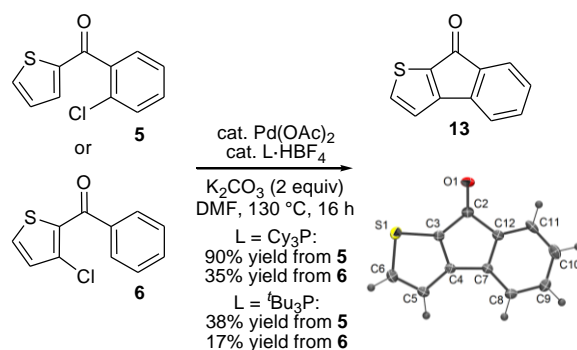


Scheme 2. Cyclization of **2** and **3b** giving 11*H*-indeno[1,2-*b*]quinolin-11-one (**8**) and 8-methoxy-5*H*-indeno[1,2-*b*]pyridin-5-one (**9**).

Starting from the diaryl ketone **4**, in which the 2-chloro group is connected to the phenyl component, the cyclization proved more difficult. Recourse to a tetraalkylammonium chloride, as recommended by Kraus and Kempema for the cyclization of bromo diaryl ketones,⁷ led to the expected methoxy-substituted 9*H*-indeno[2,1-*c*]pyridin-9-one **10**²⁶ in 48% yield. Using ^tBu₃P in this case did not give the same result and led to the cyclized demethylated aza-xanثone **11**²⁷ and the non-cyclized dechlorinated product **12**,^{5b} both of which were isolated in low yields (Scheme 3).



Scheme 3. Synthesis and ORTEP diagram (50% probability) of 1-methoxy-9*H*-indeno[2,1-*c*]pyridin-9-one (**10**)



Scheme 4. Synthesis and ORTEP diagram (50% probability) of 8*H*-indeno[2,1-*b*]thiophen-8-one (**13**).

8*H*-Indeno[2,1-*b*]thiophen-8-one (**13**) was efficiently synthesized by Campo and Larock from 3-(2-bromophenyl)-thiophene using palladium-catalysed cyclocarbonylation.²⁸ Starting from **5**, which bears the chloro group on the phenyl ring, both Cy_3P and ${}^t\text{Bu}_3\text{P}$ were tested as ligand in DMF at 130 °C, affording **13**²⁹ in 90 and 38% yield, respectively. Lower 35 and 17% yields were respectively obtained from **6**, for which the chloro group is present on the thiophene ring (Scheme 4).

Conclusion

In summary, different heterocyclic diaryl ketones were synthesized by deprotocupration-arylation using a lithiocuprate which crystallised as $(\text{TMP})_2\text{Cu}(\text{Cl})\text{Li}_2 \cdot \text{THF}$. The diaryl ketones bearing a halogen at the 2 position of one of the aryl groups, their cyclization under palladium catalysis was considered. Cy_3P was identified as a more suitable ligand than ${}^t\text{Bu}_3\text{P}$ for performing the reactions. Except when a second halogen was present on the 2-chloro diaryl ketone, azafluorenones and related compounds (including quinolyl or thienyl moieties instead of pyridyl) were isolated in medium to high yields.

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- 8 Compound **1**: mp 173–175 °C; elemental analysis calcd (%) for $\text{C}_{44}\text{H}_{88}\text{Cu}_2\text{Li}_4\text{N}_4\text{O}_2\text{Cl}_2$: C 56.77, H 9.53, N 6.02, Cl 7.62; found: C 56.34, H 9.69, N 6.03, Cl 7.92; ${}^1\text{H}$ NMR (500 MHz, 298K, C_6D_6): δ 3.71 (br, m, 4H; THF), 2.09 (br, m, 2H; TMP-3,5), 1.84 (s, 6H; TMP-Me), 1.71–1.68 (m, 18H; TMP-Me), 1.50 (br, m, 6H; TMP-3,5), 1.43 (br, m, 4H; THF), 1.18 ppm (m, 4H; TMP-4); ${}^{13}\text{C}$ NMR (125 MHz, 298K, C_6D_6 , G = lower-order or Gilman-type cuprate TMP_2CuLi , L = higher-order or Lipschutz-type cuprate **1**): δ 68.7 (THF), 54.6 (TMP-2, G), 54.0 (TMP-2, L), 52.1 (TMP-2, L), 42.6 (TMP-3,5 G), 42.4 (TMP-3,5 L), 41.1 (TMP-3,5 L), 40.6 (TMP-Me, G), 39.0 (TMP-Me L), 38.6 (TMP-Me, L), 35.0 (TMP-Me, G), 34.6 (TMP-Me, L), 32.0 (TMP-Me, L), 25.3 (THF), 20.6 (TMP-4, L), 19.8 (TMP-4, L), 19.7 ppm (TMP-4, G); ${}^7\text{Li}$ NMR spectroscopy (194 MHz, 298K, C_6D_6 , G = TMP_2CuLi , L = **1**): δ 1.9 (s, 6Li, L), 1.3 ppm (s, Li, G); ${}^1\text{H}$ NMR (500 MHz, 298K, d_8 -THF): 3.65 (br, m, 4H; THF), 1.81 (br, m, 4H; THF), 1.68 (br, m, 4H; TMP-4), 1.38, 1.09 (s, 24H, TMP-Me), 1.33 ppm (br, m, 8H, TMP-3,5); ${}^1\text{H}$ NMR (500 MHz, 273K, d_8 -THF): δ 3.65 (br, m, 4H; THF), 1.81 (br, m, 4H; THF), 1.67 (br, m, 4H; THF), 1.34, 1.08 (s, 24H, TMP-Me), 1.31 ppm (br, m, 8H, TMP-3,5); ${}^{13}\text{C}$ NMR (125 MHz, 298K, d_8 -THF, G = TMP_2CuLi , L = **1**): δ 68.2 (THF), 54.2 (TMP-2 L), 50.0 (TMP-2 G), 41.9 (TMP-3,5 L), 38.6 (TMP-3,5 G), 37.3 (br, m, TMP-Me, L), 32.2, 32.1 (TMP-Me G), 26.4 (THF), 20.5 (TMP-4 L), 19.3 ppm (TMP-4, G); ${}^{13}\text{C}$ NMR (125 MHz, 273K, d_8 -THF, G = TMP_2CuLi , L = **1**): δ 65.1 (THF), 51.3 (TMP-2 L), 47.1 (TMP-2 G), 39.1 (TMP-3,5 L), 35.7 (TMP-3,5 G), 34.8 (br, m, TMP-Me, L), 29.4, 29.3 (TMP-Me G), 23.0 (THF), 18.0 (TMP-4 L), 17.5 ppm (TMP-4, G); ${}^7\text{Li}$ NMR spectroscopy (194 MHz, 298K, d_8 -THF): δ 0.7 ppm (s); ${}^7\text{Li}$ NMR spectroscopy (194 MHz, 273K, d_8 -THF): δ 0.2 ppm (s).

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- 13 Selected bond lengths (Å) and angles (°): Li1–Cl1 2.344(6), Li1–Cl1A 2.328(6), Li1–N1 1.966(6), Li2–Cl1 2.371(6), Li2–N2 2.016(6), Cu1–N1 1.908(2), Cu1–N2 1.918(2), Cl1A–Li1–Cl1 98.7(2), Li1–Cl1–Li1A 81.3(2), Cl1–Li1–N1 128.5(3), Cl1–Li2–N2 128.2(3), N1–Cu1–N2 174.45(11).
- 14 (a) The ¹H and ¹³C NMR data of **3b** are analogous to those described: Kobayashi, K.; Suzuki, T.; Horiuchi, M.; Shiroyama, Y.; Konishi, H. *Synthesis* **2011**, 2897–2906; (b) Compound **3c**: orange oil; ¹H NMR (300 MHz, CDCl₃) δ 7.43 (m, 4H), 7.57 (dd, 1H, *J* = 7.6 and 1.7 Hz), 7.88 (dd, 1H, *J* = 7.6 and 2.0 Hz), 8.52 ppm (dd, 1H, *J* = 4.8 and 2.0 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 122.7 (CH), 127.3 (CH), 130.9 (CH), 131.2 (CH), 132.8 (C), 133.3 (CH), 134.9 (C), 137.1 (C), 139.5 (CH), 148.6 (C), 151.8 (CH), 193.1 ppm (C=O); HRMS (ESI): *m/z* calcd for C₁₂H₇³⁵Cl₂NNaO [(M+Na)⁺] 273.9802, found 273.9805.
- 15 Compound **4**: yellow powder; mp 65 °C; ¹H NMR (300 MHz, CDCl₃) δ 3.81 (s, 3H), 7.01 (dd, 1H, *J* = 7.5 and 4.9 Hz), 7.37 (m, 3H), 7.46 (m, 1H), 7.99 (dd, 1H, *J* = 7.5 and 2.0 Hz), 8.34 ppm (dd, 1H, *J* = 4.9 and 2.0 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 53.9 (CH₃), 117.1 (CH), 121.8 (C), 126.9 (CH), 129.7 (CH), 129.9 (CH), 131.5 (CH), 131.6 (C), 139.7 (C), 140.6 (CH), 151.3 (CH), 162.2 (C), 193.7 ppm (C=O); HRMS (ESI): *m/z* calcd for C₁₃H₁₁³⁵ClNO₂ [(M+H)⁺] and C₁₃H₁₀³⁵ClNNaO₂ [(M+Na)⁺] 248.0478 and 270.0298, found 248.0483 and 270.0298, respectively.
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- 22 Nethererton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295–4298.
- 23 General procedure: A degassed mixture of K₂CO₃ (0.28 g, 2.0 mmol), Pd(OAc)₂ (11 mg, 50 μmol), Cy₃P·HBF₄ (37 mg, 0.1 mmol), the required ketone (1.0 mmol), and in some cases Pr₄NCl (0.44 g, 2 mmol), in DMF (4 mL) was heated at 130 °C for 16 to 48 h. After filtration over a celite pad, washing using CH₂Cl₂ (3 x 10 mL), and removal of the solvent under reduced pressure, the product was isolated after purification by flash chromatography on silica gel.
- 24 The ¹H NMR data of **8** are analogous to those described: Prostavkov, N. S.; Pleshakov, V. G.; Zain-ul-Abidin, M.; Kordova, I. R.; Zakharov, V. F.; Zvolinskii, V. P. *Zh. Org. Khim.* **1982**, *18*, 640–652.
- 25 Compound **9**: yellow powder; mp 113 °C; ¹H NMR (300 MHz, CDCl₃) δ 3.96 (s, 3H), 6.92 (dd, 1H, *J* = 8.3 and 2.3 Hz), 7.24 (dd, 1H, *J* = 7.4 and 5.1 Hz), 7.41 (d, 1H, *J* = 2.3 Hz), 7.7 (d, 1H, *J* = 8.3 Hz), 7.89 (dd, 1H, *J* = 7.4 and 1.6 Hz), 8.62 ppm (dd, 1H, *J* = 5.1 and 1.6 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 56.1 (CH₃), 106.4 (CH), 116.7 (CH), 123.7 (CH), 126.4 (CH), 127.8 (C), 129.8 (C), 131.2 (CH), 146.5 (C), 153.4 (CH), 164.2 (C), 166.1 (C), 190.3 ppm (C=O); HRMS (ESI): *m/z* calcd for C₁₃H₉NNaO₂ [(M+Na)⁺] 234.0531, found 234.0534.
- 26 Compound **10**: yellow powder; mp 160 °C; ¹H NMR (300 MHz, CDCl₃) δ 4.13 (s, 3H), 7.15 (d, 1H, *J* = 5.0 Hz), 7.44 (td, 1H, *J* = 7.2 and 1.6 Hz), 7.49–7.60 (m, 2H), 7.71 (ddd, 1H, *J* = 7.2, 1.1 and 0.8 Hz), 8.37 (d, 1H, *J* = 5.0 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 54.4 (CH₃), 109.8 (CH), 113.4 (C), 121.5 (CH), 124.3 (CH), 131.5 (CH), 134.1 (C), 134.2 (CH), 141.1 (C), 155.0 (CH), 156.4 (C), 161.0 (C), 191.5 (C=O); HRMS (ESI): *m/z* calcd for C₁₃H₉NNaO₂ [(M+Na)⁺] 234.0531, found 234.0532.
- 27 The ¹H and ¹³C NMR data of **11** are analogous to those described: Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 3117–3119.
- 28 Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 5616–5620.
- 29 Mp 106 °C (Arcus, C. L.; Barrett, G. C. *J. Chem. Soc.* **1960**, 2098–2102; mp 107–109 °C).

Supplementary Material

Supplementary data associated with this article and containing X-ray diffraction analysis and CIF files of **1** (CCDC 884940), **10** (CCDC 885440), and **13** (CCDC 885439), and NMR spectra of **3c**, **4**, **6**, **9**, **10** and **13** can be found in the online version, at <http://dx.doi.org/10.1016/j.tetlet.xxxxxx>.