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Trifluoroacetylation-Induced Houben−Hoesch-Type Cyclization of Cyanoacetanilides: Increased Nucleophilicity of CN Groups

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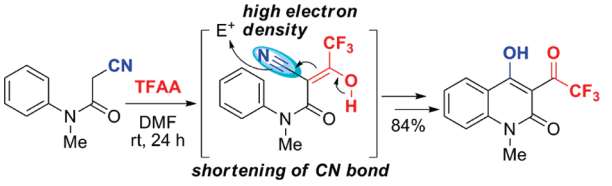
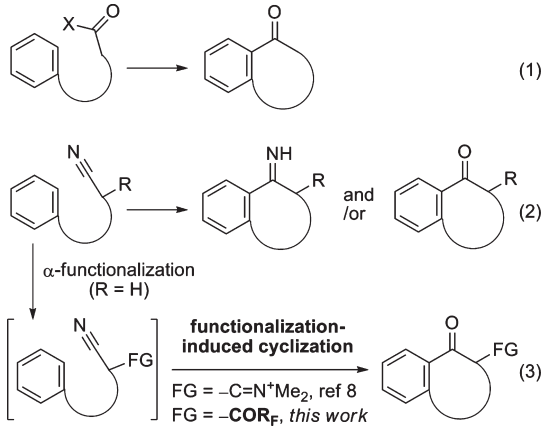


Trifluoroacetic anhydride-mediated tandem trifluoroacetylation/cyclization of cyanoacetanilides proceeded efficiently under mild conditions to give 4-hydroxy-3-trifluoroacetylquinolin-2(1*H*)-ones in good yields. Isolation and direct observation of the reaction intermediates revealed that α-trifluoroacetylation resulted in the shortening of C≡N bonds and that the electron density of CN groups was high. A plausible reaction mechanism based on the results is also described.

Benzene-fused cyclic ketones, such as 1-tetralone, chromone, and 4-quinolinone, are key structural features of numerous pharmaceuticals and biologically active natural products.[1,2] One of the general and convenient methods for the synthesis of such ketones is the intramolecular Friedel−Crafts reaction (eq 1),[3] in which acid chlorides and carboxylic acid derivatives[4,5] serve as cyclization precursors. Compared with Friedel−Crafts reactions, the electrophilic substitution of aromatic C−H bonds with intramolecular nitriles[6,7] (eq 2) has attracted less attention because of the lower reactivity of nitriles. However, nitriles are generally considered to be superior to acid chlorides and carboxylic acids in terms of handling, preparation, and functionalization. Therefore, the development of mild and efficient methods for achieving electrophilic aromatic substitution with intramolecular CN groups is highly desirable. We envisioned that functionalization of the cyclization precursor at the α-position of the CN group would be useful not only to increase the reactivity of CN groups but also to synthesize functionalized cyclic ketones from simple precursors (eq 3). In fact, during the course of our efforts to synthesize quinoline alkaloids, we recently reported the tandem α-formylation/intramolecular electrophilic aromatic substitution with CN electrophiles.[8] In these reactions, we proposed that the electrophilic aromatic substitution with nitriles was facilitated through an iminium cation intermediate (eq 3, FG = $-C{=}N^{+}Me_2$).



We herein report the trifluoroacetylation-induced cyclization of cyanoacetanilide[9] to give 4-hydroxy-3-trifluoroacetylquinolin-2(1*H*)-ones under mild conditions (eq 3, FG = $-COCF_3$). Introducing the CF_3 group into organic molecules would be expected to impart unique new physical properties, chemical reactivity, and biological activity to the molecules.[10] Crystallographic analysis and IR spectra measurement of the isolated reaction intermediates revealed that α-trifluoroacetylation shortened the CN bond length and increased the electron density. These properties resulted in accelerating both the reaction of the CN group with a

(1) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.
(2) (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166–187. (b) Barr, S. A.; Boyd, D. R.; Sharma, N. D.; Loke, P. L. *Heterocycles* **2009**, *79*, 831–850.
(3) For reviews of Friedel−Crafts and related reactions, see: (a) Olah, G. A. *Friedel−Crafts Chemistry*; Wiley-Interscience: New York, 1973. (b) Heaney, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 733−752 and 753−768.
(4) For a review, see: Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999; pp 1422−1433.
(5) For intramolecular Friedel−Crafts acylation of Meldrum's acid derivatives, see: (a) Fillion, E.; Fishlock, D. *Tetrahedron* **2009**, *65*, 6682–6695. (b) Fillion, E.; Dumas, A. M. *J. Org. Chem.* **2008**, *73*, 2920–2923. (c) Fillion, E.; Fishlock, D. *J. Am. Chem. Soc.* **2005**, *127*, 13144–13145. (d) Fillion, E.; Fishlock, D. *Org. Lett.* **2003**, *5*, 4653–4656.
(6) For Houben−Hoesch reactions, see: (a) Spoerri, P. E.; DuBois, A. S. *Org. React.* **1949**, *5*, 387–412. (b) Sato, Y.; Yato, M.; Ohwada, T.; Saito, S.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 3037–3043. (c) Nakamura, S.; Sugimoto, H.; Ohwada, T. *J. Org. Chem.* **2008**, *73*, 4219−4224 and references cited therein.
(7) For the Pd-catalyzed addition of aromatic C−H bonds to nitriles, see: (a) Zhou, C.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 2302–2303. (b) Zhou, C.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3551–3558.
(8) Kobayashi, Y.; Harayama, T. *Tetrahedron Lett.* **2009**, *50*, 6665–6667.
(9) Cyanoacetanilides **1a**−**f** were easily prepared, purified, and obtained as solids, see: Kobayashi, Y.; Harayama, T. *Org. Lett.* **2009**, *11*, 1603–1606.
(10) (a) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991. (b) Hiyama, T. *Organofluorine Compounds. Chemistry and Application*; Springer: Berlin, 2000. (c) Kirsch, P. *Modern Fluoroorganic Chemistry, Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, 2004. (d) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell: Oxford, 2004.

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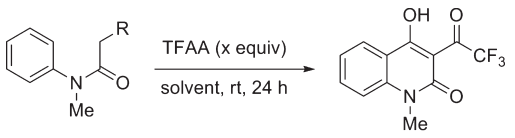
TABLE 1. Survey and Optimization of Reaction Conditions[a,b]



1a, **2** **3a**

entry	substrate (R)	*x* (equiv)	solvent[c]	yield of **3a**[d] (%)
1	**1a** (CN)	1.0	DMF	14
2	**1a**	2.0	DMF	38
3	**1a**	3.0	DMF	84
4[e]	**1a**	3.0	DMF	89
5	**1a**	3.0		0[f]
6	**1a**	3.0	DMA	0[f]
7[g]	**2** (CO_2Et)	3.0	DMF	0[f]

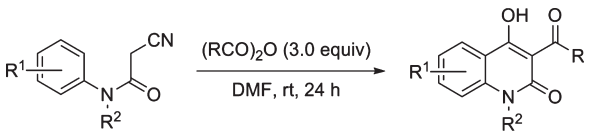
[a]Unless otherwise stated, all reactions were carried out with 3.0 mmol of each substrate. [b]TFAA = trifluoroacetic anhydride. [c]DMF = *N*,*N*-dimethylformamide, DMA = *N*,*N*-dimethylacetamide. [d]Isolated yields. [e]15 mmol of **1a** was employed. [f]No reaction occurred. [g]1.0 mmol of **2** was employed.

Vilsmeier-type reagent and the subsequent electrophilic aromatic substitution.

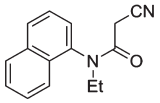
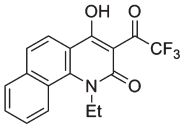
We first examined the reaction of cyanoacetanilide **1a** with trifluoroacetic anhydride (TFAA) in *N*,*N*-dimethylformamide (DMF) (Table 1, entries 1−4). We found that 3 equiv of TFAA was required to obtain the desired quinolinone (**3a**) in good yield (entry 3 versus entries 1 and 2). Quinolinone **3a** was isolated as a precipitate through a simple aqueous workup, and therefore, the reaction could be easily performed on a gram-scale (entry 4). The reaction was completely suppressed when no solvent was used (entry 5) or when the solvent was changed to *N*,*N*-dimethylacetamide (DMA, entry 6),[11] suggesting the crucial role of DMF in this tandem reaction. Furthermore, the presence of CN functionality in the substrate was found to be essential for the formation of **3a** (entry 3 versus entry 7).

Having identified the optimum conditions for the reaction of **1a** with TFAA, we examined the substrate scope for the reaction between cyanoacetanilides **1a**−**f** and various acid anhydrides (Table 2). When secondary cyanoacetanilide **1b** was employed, annulation to afford **3b** did not occur (entry 1), most likely due to conformational constraints.[12] The tandem reaction of **1c** in which the *para* position was substituted with a methyl group proceeded smoothly to afford quinolinone **3c** in 82% yield (entry 2). The tandem reaction was successfully carried out with an arene bearing an electron-withdrawing substituent (entry 3), in contrast to the Houben−Hoesch reaction, which requires electron-rich arene substrates to afford good yields of ketones.[6] The halogenated product **3d** could, in principle, be further functionalized through transition-metal-catalyzed coupling reactions. The tandem reaction was sensitive to steric hindrance, and the reaction of the *ortho*-substituted cyanoacetanilide **1e** required a higher temperature to proceed smoothly (entry 4). Applying the same methodology to cyanoacetanilide **1f** produced tricyclic compound **3f** in 60% yield (entry 5). Next, we examined several acid anhydrides in place of TFAA (entries 6−10).

TABLE 2. Substrate Scope and Limitations[a]



1 **3–8**

entry	**1** (R^1, R^2)	anhydride (R)	product, yield[b] (%)
1	**1b** (H, H)	CF_3	**3b**, 0[c]
2	**1c** (*p*-Me, Me)	CF_3	**3c**, 82
3	**1d** (*p*-Br, Me)	CF_3	**3d**, 60
4[d]	**1e** (*o*-Me, Me)	CF_3	**3e**, 55
5	**1f** 	CF_3	**3f**, 60 
6	**1a** (H, Me)	CH_3	**4a**, 0[e]
7	**1a**	C_6H_5	**5a**, 0[e]
8	**1a**	CF_2Cl	**6a**, 85
9	**1a**	CF_3CF_2	**7a**, 86
10	**1a**	$CF_3CF_2CF_2$	**8a**, 84

[a]All reactions were carried out with 3.0 mmol of each substrate. [b]Isolated yields. [c]The reaction resulted in a complex mixture. [d]The reaction was carried out at 50 °C. [e]No reaction occurred.

Notably, cyanoacetanilides **1a** did not react with either acetic anhydride or benzoic anhydride (entries 6 and 7). In contrast, fluorine-containing acid anhydrides, such as $(CF_2ClCO)_2O$, $(CF_3CF_2CO)_2O$, and $(CF_3CF_2CF_2CO)_2O$, efficiently promoted the tandem reaction to furnish the corresponding quinolinones **6a**−**8a** in 84−86% yields (entries 8−10). It is important to note that the isolation of all products **3**−**8** could be easily accomplished by precipitation and filtration.

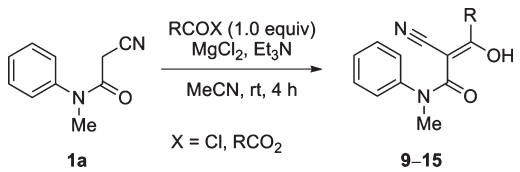
In order to gain mechanistic insight into the tandem reaction, we synthesized several plausible reaction intermediates (Table 3). Using 1.0 equiv of acid anhydride (or acid chloride), 1.0 equiv of $MgCl_2$, and 2.0 equiv of Et_3N in MeCN, the active methylene group of **1a** was acylated to the corresponding intermediates **9**−**15** in 11−85% yields (Table 3). Interestingly, a comparison among the chemical shifts (ppm) in the ^{13}C NMR spectra of these intermediates revealed that the CN carbon atoms of **12**−**15**, having stronger electron-withdrawing groups, were shielded (entries 4−7) relative to those of **9**−**11** (entries 1−3).[6c] In addition, the wavenumbers in the IR spectra of **12**−**15** were approximately 10 cm^{-1} higher than those of **9**−**11**. These results suggest that CN groups in **12**−**15** have higher electron density and stronger C≡N bonds.[13] In fact, X-ray crystallographic analysis of **9** and **15** (Figure 1) demonstrated that

(11) MeCN, DMSO, and THF were also ineffective solvents.

(12) (a) Pederson, B. F.; Pederson, B. *Tetrahedron Lett*. **1965**, *6*, 2995–3001. (b) Nanjan, M. J.; Kannappan, V.; Ganesan, R. *Indian J. Chem*. **1979**, *18B*, 461–463. (c) Itai, A.; Toriumi, Y.; Tomioka, N.; Kagechika, H.; Azumaya, I.; Shudo, K. *Tetrahedron Lett*. **1989**, *30*, 6177–6180.

(13) Presumably, the inductive effect of adjacent perfluoro-substituents is responsible for the shortening of the CN bonds. A similar tendency was observed for the CN groups of *para*-substituted benzonitriles (*p*-RC_6H_4CN); e.g., R = CF_3: ^{13}C NMR 117.5 ppm, IR 2237 cm^{-1}; R = H: ^{13}C NMR 118.8 ppm, IR 2230 cm^{-1}; R = OMe: ^{13}C NMR 119.2 ppm, IR 2217 cm^{-1}. See: Hatsuda, M.; Seki, M. *Tetrahedron* **2005**, *61*, 9908–9917.

TABLE 3. Comparison among ^{13}C NMR and IR Spectra of CN Groups



entry	product (R)	yield[a] (%)	^{13}C NMR[b] (ppm)	IR[c] (cm^{-1})
1	**9** (CH_3)	75	115.2	2211
2	**10** (C_6H_5)	53	116.1	2212
3	**11** (4-$NO_2C_6H_4$)	85	115.1	2213
4	**12** (CF_3)	58	**110.8**	**2223**
5	**13** (CF_2Cl)	20	**111.2**	**2222**
6	**14** (CF_3CF_2)	40	**110.6**	**2224**
7	**15** ($CF_3CF_2CF_2$)	11	**110.6**	**2224**

[a]Isolated yields. [b]Chemical shifts of CN groups observed in $CDCl_3$. [c]Wavenumbers of C≡N absorption bands.

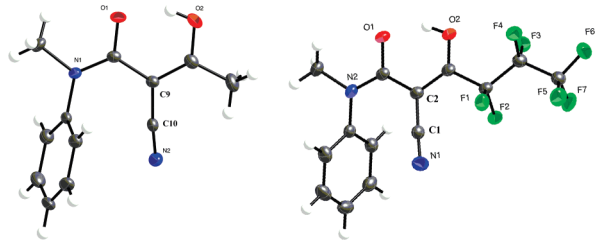
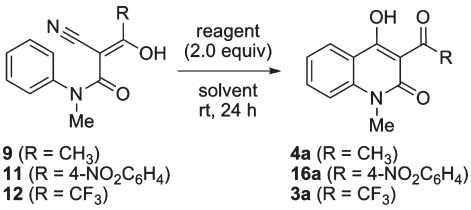


FIGURE 1. ORTEP diagrams of **9** (left) and **15** (right). Selected bond length and angles (deg) of **9** (Å): C(10)−N(2) 1.157(4); C(9)−C(10)−N(2) 175.0(3). Selected bond length (Å) and angles (deg) of **15**: C(1)−N(1) 1.136(2); C(2)−C(1)−N(1) 176.70(18).

the CN bond length of **15** (1.136(2) Å) was significantly shorter than that of **9** (1.157(4) Å).[14]

We then compared the reactivity of the CN groups in intermediates **9**, **11**, and **12** (Table 4). The TFAA-mediated intramolecular electrophilic aromatic substitution of **9** and **11** did not occur (entries 1 and 2). However, treatment of **12** with TFAA in DMF cleanly afforded **3a** in 89% yield (entry 3). These experimental results verified the reactivity of the CN group of **12** and the lack of reactivity of those of **9** and **11**. These results also indicate that the tandem reaction of **1a** proceeded via a *C*-trifluoroacetylation−cyclization sequence (**1a** → **12** → **3a**, vide infra). We found that 1.0 equiv of TFAA was sufficient to mediate the cyclization of **12** in high yield (entry 4). In the tandem reaction of **1a**, it seems that the extra equivalent of TFAA was required for the efficient conversion of **1a** to **12** (Table 1, entry 2 versus 3). Although **12** did not react with TFAA in the absence of solvent (entry 5), we did observe the cyclization of **12** in DMA albeit in moderate yield (entry 6). These findings suggest that DMF plays a crucial role in the *C*-acylation step (**1a** → **12**) (Table 1, entry 3 versus 6) and that it plays a significant role for cyclization (**12** → **3a**). Subsequent experiments also indicated that TFAA played an important role in the cyclization step. When **12** was treated with trifluoroacetic acid (TFA) instead of TFAA, no reaction occurred, and unreacted **12** was recovered (entry 7),

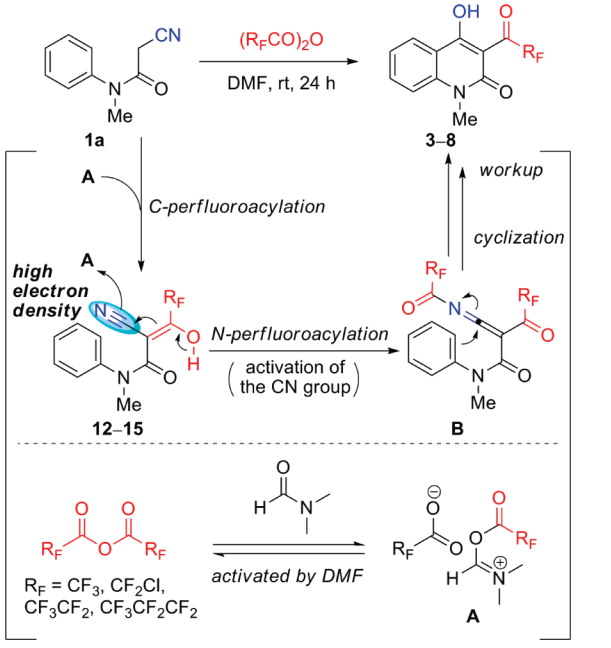
TABLE 4. Control Experiments[a]



entry	substrate (R)	reagent	solvent	product, yield[b] (%)
1	**9** (CH_3)	TFAA	DMF	**4a**, 0[c]
2	**11** (4-$NO_2C_6H_4$)	TFAA	DMF	**16a**, 0[c]
3[d]	**12** (CF_3)	TFAA	DMF	**3a**, 89
4[d,e]	**12**	TFAA	DMF	**3a**, 80
5	**12**	TFAA		**3a**, 0[c]
6	**12**	TFAA	DMA	**3a**, 50
7	**12**	TFA	DMF	**3a**, 0[c]
8	**12**	Ac_2O	DMF	**3a**, 0[c]

[a]Unless otherwise specified, all reactions were carried out with 0.3 mmol of each substrate. [b]Isolated yields. [c]No reaction occurred. [d]1.0 mmol of **12** was employed. [e]1.0 equiv of TFAA was used.

SCHEME 1. Plausible Mechanism for Perfluoroacylationinduced Cyclization of Cyanoacetanilides



indicating that a Brønsted-acid-mediated Houben−Hoesch reaction did not occur in the tandem reaction. Acetic anhydride (Ac_2O) also failed to mediate the cyclization of **12** (entry 8).

A plausible mechanism for the tandem *C*-acylation/cyclization that is consistent with these results is shown in Scheme 1. Reaction of the active methylene group of **1a** with the Vilsmeier-type intermediate **A**[15] derived from DMF and TFAA ($R_F = CF_3$)[16] is a probable initial step. The electronic density and nucleophilicity of the CN group were increased by introduction of a trifluoroacetyl substituent into the

(14) CCDC 763341 (**9**) and CCDC 763342 (**15**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(15) (a) Lamarre, C.; Stella, L. *Synlett* **1999**, 725–726. (b) Mekhalfia, A.; Mutter, R.; Heal, W.; Chen, B. *Tetrahedron* **2006**, *62*, 5617–5625.

(16) It was also reported that DMF remained unchanged when it reacted with Ac_2O; see ref 15b.

geminal position (*C*-perfluoroacylation). This reactive CN group would be subject to electrophilic attack[17] by **A** or TFAA (*N*-perfluoroacylation), thus promoting the subsequent cyclization of the activated intermediate **B** to give quinolinones **3**−**8**.

In conclusion, we have developed a practical perfluoroacylation-induced cyclization of cyanoacetanilides. We found that (i) fluorine-containing anhydrides were activated by DMF to form reactive acylation reagents and (ii) introduction of the perfluoroacyl substituent in the geminal position of the CN group greatly influenced the physical properties and chemical reactivity of the CN group. Further synthetic applications based on the results of this study are currently under investigation and will be reported in due course.

Experimental Section

General Procedure for the Synthesis of 3. To a solution of cyanoacetanilide **1a** (523 mg, 3.0 mmol) in DMF (3.0 mL) was added TFAA (1.25 mL, 9.0 mmol) at room temperature. The mixture was stirred at rt for 24 h, when TLC indicated the reaction was complete. The reaction mixture was then poured into ice-cold water (100 mL). The precipitate was collected by filtration and washed with water (three times). Recrystallization from $CHCl_3$/*n*-hexane gave pure **3a** (683 mg, 84%). *The mother and washing liquors are acidic. They were treated with solid $NaHCO_3$ before disposal.*

4-Hydroxy-1-methyl-3-(2,2,2-trifluoroacetyl)quinolin-2(1*H*)-one (3a): yellow solid; mp 172−173 °C ($CHCl_3$/*n*-hexane); ^{1}H NMR ($CDCl_3$, 50 °C) δ 14.31 (br, 1H), 8.19 (dd, 1H, J = 8.0, 1.6 Hz), 7.74 (ddd, 1H, J = 8.0, 8.0, 1.6 Hz), 7.31−7.25 (m, 2H), 3.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 185.6 (q, J = 37.0 Hz), 175.4, 158.9, 142.9, 136.4, 126.5, 122.5, 116.7 (q, J = 284 Hz), 114.5, 114.3 (q, J = 3.0 Hz), 103.8, 29.2; HRMS (ESI-TOF) calcd for $C_{12}H_7F_3NNa_2O_3$ ($[M - H + 2Na]^+$) 316.0168, found 316.0170.

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Supporting Information Available: Detailed experimental procedures, characterization data for all new compounds, and CIF files of **9** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) Some papers reported that electronic factors significantly influenced the reactivity of CN groups toward electrophiles or metal complexes (EWG-C_6H_4*CN* ≫ EDG-C_6H_4*CN*); see: (a) Reference 7. (b) Nakao, Y.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 13904–13905. (c) Moorthy, J. N.; Singhal, N. *J. Org. Chem.* **2005**, *70*, 1926–1929. (d) Tobisu, M.; Kita, Y.; Ano, Y.; Chatani, N. *J. Am. Chem. Soc.* **2008**, *130*, 15982–15989. (e) Haddenham, D.; Pasumansky, L.; DeSoto, J.; Eagon, S.; Singaram, B. *J. Org. Chem.* **2009**, *74*, 1964–1970. (f) Bonnamour, J.; Bolm, C. *Chem.*−*Eur. J.* **2009**, *15*, 4543–4545.