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Rh^{I}-Catalyzed Regio- and Stereospecific Carbonylation of 1-(1-Alkynyl)cyclopropyl Ketones: A Modular Entry to Highly Substituted 5,6-Dihydrocyclopenta[*c*]furan-4-ones

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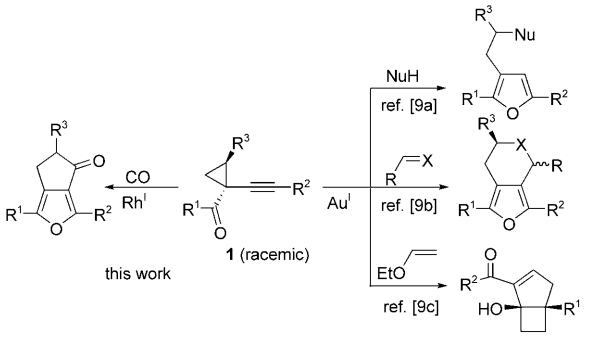
The rich appearance of highly substituted furans as key structural units in many bioactive natural products and important pharmaceuticals, and general application as versatile building blocks in organic synthesis have stimulated many efforts in exploration of novel methodology.[1,2] Most recently, much attention has been paid on the development of metal-catalyzed transformations, including the cyclization of allenyl ketones,[3] 3-alkyn-1-ones,[3,4] (*Z*)-2-en-4-yn-1-ols[5] and 2-(1-alkynyl)-2-alken-1-ones[6] or cycloisomerization of alkylidenecyclopropyl ketones[7]/cyclopropenyl ketones.[8] Very recently, 1-(1-alkynyl)-cyclopropyl ketones have been successfully developed by Schmalz[9a] and Zhang[9b–c] as readily available substrates for efficient construction of highly substituted furans and other cyclic compounds under the catalysis of gold(I) complexes (Scheme 1). Our continued effort to explore new reactions for synthesis of tetrasubstituted furans with high efficiency,[6e] has led us to target 3,4-fused bicyclic tetrasubstituted furans[10] as product for investigation. We envisaged that 1-(1-alkynyl)-cyclopropyl ketones might undergo some interesting transformation initiated by the rhodium(I)-catalyzed activation of the carbon–carbon σ bond of cyclopropane ring.[11] Herein we wish to report our recent result that rhodium(I)-catalyzed a highly regioselective and stereospecific carbonylation reaction of 1-(1-alkynyl)-cyclopropyl ketones to afford 1,3,5-tri- or 1,3,5,6-tetrasubstituted 5,6-dihydro-cyclopenta[*c*]furan-4-ones[12] initiated by the activation of the carbon–carbon σ bond.



Scheme 1. Previous work and our proposal.

Initially, we tested the carbonylation reaction of 1-(2-phenyl)-1-(2-phenylethynyl)cyclopropyl methyl ketone **1a** in the presence of 1 atm of CO (balloon) in the presence of various catalysts (see Supporting Information). After some attempts, we were pleased to find that the carbonylation reaction of **1a** proceeds very smoothly in 1,2-dichloroethane at 70 °C under the catalysis of 5 mol % of $[\{Rh(CO)_2Cl\}_2]$ (standard conditions) or $[\{Rh(cod)Cl\}_2]$ to give 1-methyl-3,5-diphenyl-5,6-dihydrocyclopenta[*c*]furan-4-one[12] (**2a**) in excellent yields with trace amount of (*E*)-2-methyl-5-phenyl-3-styrylfuran (**3a**). Addition of silver salts led to lower yields of **2a** and higher yields of byproduct **3a.** Interestingly byproduct **3a** can be afforded as the only major product in 74 % isolated yield when the reaction was run under the catalysis of 5 mol % of $[\{Rh(cod)Cl\}_2]/AgPF_6$ under N_2 atmosphere (without CO). The structure of **2a** was determined by single-crystal X-ray diffraction analysis.[13]

With standard reaction conditions in hand, we turned our attention to studying the reaction scope of this transformation. Various 2-substituted 1-(1-alkynyl)-cyclopropyl ketones were studied and the results are summarized in Table 1. Sev-

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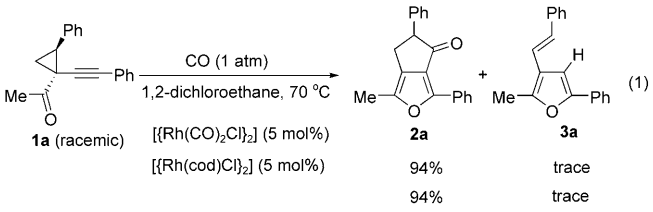
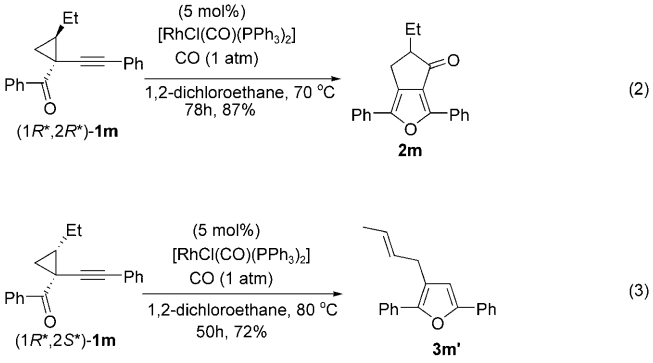


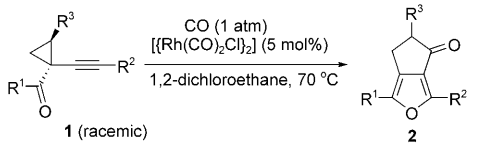
eral points are noteworthy: 1) under standard reaction conditions, various substituted 3,4-fused bicyclic furans could be prepared in good to excellent yields with high regioselectivity; 2) various substituents and functional groups could be introduced to R^1, R^2 position and the reactions proceeded smoothly; 3) the cyclopropyl group at the R^2 position of substrates **1d** and **1i** was kept untouched, demonstrating the inertness of the isolated unactived cyclopropane ring under the reaction conditions; 4) when R^3 is not an aryl group, it was found that $[RhCl(CO)(PPh_3)_2]$ (84%) is a much better catalyst than the corresponding $[\{Rh(CO)_2Cl\}_2]$ (50% yield).



Reactions of (1*R**,2*R**)-**1m** and its diastereoisomer (1*R**,2*S**)-**1m** were examined to determine whether the configuration of substituted cyclopropane ring affects the reaction pathway. To our surprise, the reactions of (1*R**,2*R**)-**1m** could indeed give the desired carbonylation product **2m** in 87% isolated yield under the catalysis of 5 mol% $[RhCl(CO)(PPh_3)_2]$ (this catalyst is crucial to this substrate, other catalysts such as $[\{Rh(CO)_2Cl\}_2]$ give only **3m′**), but (1*R**,2*S**)-**1m** did not afford the expected product under the similar conditions; instead, a trisubstituted furan **3m'** was obtained in 72% yield through a direct cycloisomerization reaction.

Furthermore, we are pleased to find that various *trans*-1,2,5,6-tetrasubstituted 5,6-dihydrocyclopenta[*c*]furan-4-ones could be synthesized from the corresponding 2,3-disubstituted 1-(1-alkynyl)-cyclopropyl ketones with high efficiency (Table 2). It is interesting to find that this Rh^I-catalyzed carbonylation is regiospecific (as a single regioisomer, no other carbonylation product were observed) and stereospecific with the retention of stereochemistry, which is determined by the X-ray structure of **4a** and **5a** (Figure 1).[13] Residue R^4 does not affect the reaction pathway via comparison the

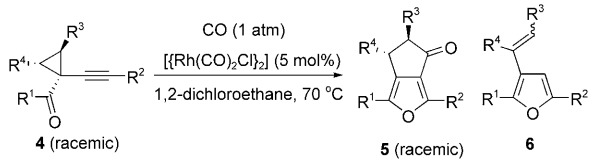
Table 1. Synthesis of 1,3,5-trisubstituted 5,6-dihydrocyclopenta[*c*]furan-4-ones.[a]



Entry	**1**: $R^1/R^2/R^3$	*t* [h]	Yield [%] **2**
1[b]	Me/1-naphthyl/Ph (**1b**)	42	**2b** (84)
2	Me/n-C_4H_9/Ph (**1c**)	22	**2c** (80)
3	Me/1-cyclohexenyl/Ph (**1d**)	17	**2d** (79)
4	Me/cyclopropyl/Ph (**1e**)	24	**2e** (69)
5	Me/Ph/4-MeOPh (**1f**)	22	**2f** (76)
6	Me/4-MeOPh/4-MeOPh (**1g**)	40	**2g** (86)
7	Ph/Ph/Ph (**1h**)	18	**2h** (94)
8	Ph/cyclopropyl/Ph (**1i**)	21	**2i** (86)
9	Ph/n-C_4H_9/Ph (**1j**)	49	**2j** (82)
10[c]	Me/$AcOC_2H_4$/Ph (**1k**)	52	**2k** (87)
11	Ph/Ph/H (**1l**)	18	**2l** (50, 84[d])

[a] All reactions were carried out using **1** (0. 5 mmol) under standard conditions and yield is isolated yield. [b] 5 mol% of $[\{Rh(cod)Cl\}_2]$ was used as catalyst. [c] Another 5 mol% of $[\{Rh(cod)Cl\}_2]$ was added after reacting 19 h. [d] 5 mol% of $[RhCl(CO)(PPh_3)_2]$ was used as catalyst.

Table 2. Synthesis of 1,3,5,6-tetrasubstituted 5,6-dihydrocyclopenta[*c*]furan-4-ones.



Entry	**4**: $R^1/R^2/R^3/R^4$	*t* [h]	Yield [%] **5**
1[a]	Me/Ph/Ph/PhCO (**4a**)	20	**5a** (50)
2	Ph/Ph/Ph/PhCO (**4b**)	17	**5b** (90)
3[a,b]	Ph/cyclopropyl/Ph/PhCO (**4c**)	40	**5c** (43)
4[a,b]	Ph/n-C_4H_9/Ph/PhCO (**4d**)	42	**5d** (38)
5	Ph/4-MeOPh/Ph/PhCO (**4e**)	10	**5e** (85)
6	Ph/4-NO_2Ph/Ph/PhCO (**4f**)	22	**5f** (95)
7	Ph/1-naphthyl/Ph/PhCO (**4g**)	37	**5g** (68)
8	Ph/Ph/Ph/EtOCO (**4h**)	28	**5h** (90)

[a] 20–40% of the corresponding trisubstituted furans **6** were isolated as a mixture of *E*/*Z* isomer. [b] The reaction was run at reflux.

results of **5a** and **5b**. Effects of other three groups R^1, R^2, and R^3 to the reaction are similar to the case of trisubstituted 5,6-dihydrocyclopenta[*c*]furan-4-ones.

A plausible mechanism is depicted in Scheme 2. Regioselective oxidative addition[11] of the C1−C2 bond of cyclopropane of (1*R**,2*R**)-**1m** generates rhodacyclobutane **7**, the configuration of which might favor to undergo a rapid cycloisomerization to fused furan-derived rhodacyclopentane **8**. Insertion of carbon monoxide generates fused furan derivative rhodacyclohexanone **9** and subsequent reductive elimination furnishes the carbonylation product. However, The intermediate rhodacyclobutane **10**, generated from the other diastereoisomer (1*R**,2*S**)-**1m** does not afford the expected bicyclic rhodacyclopentane **8** (the reason is not clear yet), instead, a 1,2-allenyl ketone **11** may be produced via a tandem process involving β-hydride elimination, reductive

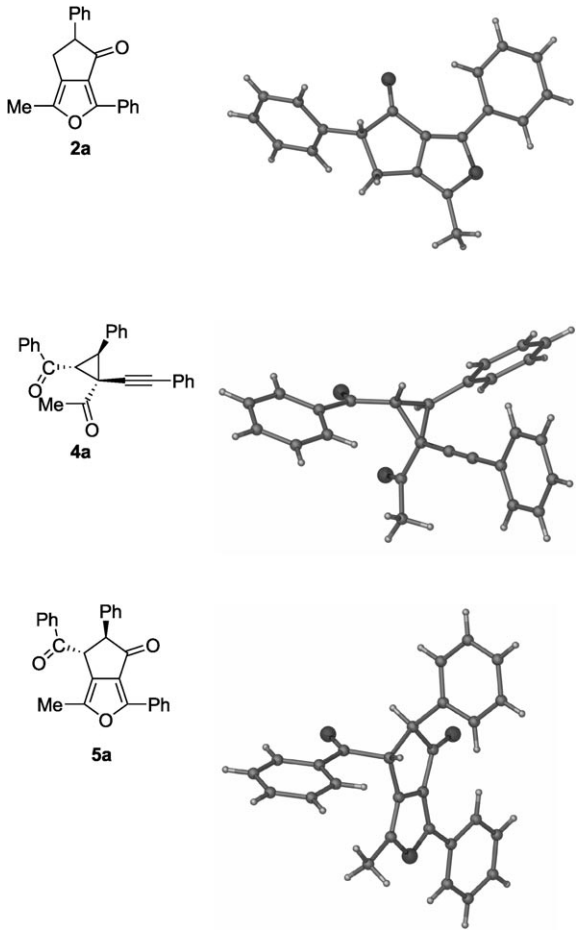
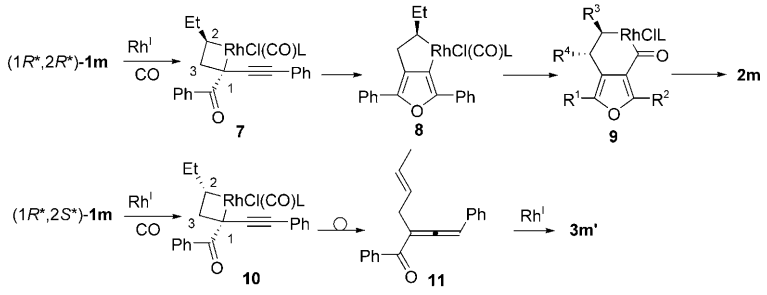


Figure 1. Ball-and-stick models for the crystal structures of compounds **2a**, **4a** and **5a.**

elimination and isomerization, which will yield trisubstituted furan **3m'** via a Rh^I-catalyzed direct cycloisomerization.[14]

In summary, we have demonstrated a Rh^I-catalyzed regio- and stereoselective carbonylation reaction of 2-substituted or 2,3-disubstituted 1-(1-alkynyl)-cyclopropyl ketones, which provides an efficient, highly atom-economic route to synthesize 1,3,5-tri- and 1,3,5,6-tetrasubstituted 5,6-dihydrocyclopenta[*c*]furan-4-ones under mild conditions. Further studies concerning mechanism, synthesis of optically pure substrates (e.g. **1** and **4**) and their transformation, and synthetic application are underway.



Scheme 2. Plausible mechanism of this carbonylation reaction.

Experimental Section

Typical procedure for the synthesis of 2a (Scheme 1): The solution of 1-(2-phenyl-1-(2-phenylethynyl)cyclopropyl)ethanone (**1a**; 65.0 mg, 0.25 mmol) and $[\{RhCl(CO)_2\}_2]$ (4.9 mg, 0.0125 mmol) in 1,2-dichloroetane (5 mL) was degassed and then recharged with CO. Then the reaction mixture was stirred at 70 °C and the TLC analysis showed the reaction was complete after 22 h. The reaction mixture was concentrated under reduced temperature and the residue was purified by column chromatography on silica gel to give **2a** (68.0 mg, 94 %). M.p.139–141 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.28–8.22 (m, 2H), 7.48–7.39 (m, 2H), 7.39–7.31 (m, 3H), 7.31–7.25 (m, 3H), 4.22 (dd, J=8.7, 4.8 Hz, 1H), 3.38 (dd, J=16.2, 8.7 Hz, 1H), 2.99 (dd, J=16.2, 4.8 Hz, 1H), 2.41 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.54, 149.80, 142.88, 140.27, 130.77, 129.36, 129.30, 128.81, 128.73, 127.85, 127.09, 125.48, 124.99, 61.02, 27.44, 12.30 ppm; MS (EI): m/z: 288 [M^+] (100); HRMS: m/z: calcd for $C_{20}H_{16}O_2$: 288.1150, found: 288.1149.

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Keywords: carbonylation · C–C activation · cyclization · regioselectivity · rhodium

[1] For reviews, see: a) X. L. Hou, H. Y. Cheung, T. Y. Hon, P. L. Kwan, T. H. Lo, S. Y. T. Tong, H. N. C. Wong, *Tetrahedron* **1998**, *54*, 1955; b) B. A. Keay, *Chem. Soc. Rev.* **1999**, *28*, 209; c) T. L. Gilchrist, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2849; d) X. L. Hou, Z. Yang, K-S. Y, H. N. C. Wong in *Progress in Heterocyclic Chemistry, Vol. 19* (Eds.: G. W. Gribble, J. A. Joule), Pergamon, Oxford, **2008**, p. 176.

[2] a) R. J. Sundberg in *Comprehensive Heterocyclic Chemisry, Vol. 5* (Eds.: A. R. Katrizky, C. W. Rees), Pergamon, New York, **1984**, p. 313; b) H. Heaney in *Natural Products Chemistry* (Ed.: K. Nakanishi), Kodansha, Toyko, **1974**, p. 297; c) B. H. Lipshutz, *Chem. Rev.* **1986**, *86*, 795; d) T. H. Brown, M. A. Armitage, R. C. Blakemore, P. Blurton, G. J. Durant, C. R. Ganellin, R. G. Ife, M. E. Parsons, D. A. Rawlings, B. P. Slingsby, *Eur. J. Med. Chem.* **1990**, *25*, 217; e) M. Shipman, *Contemp. Org. Synth.* **1995**, *2*, 1; f) L. A. Paquette, *Org. Lett.* **2000**, *2*, 4095.

[3] a) J. A. Marshall, E. D. Robinson, *J. Org. Chem.* **1990**, *55*, 3450; b) J. A. Marshall, G. S. Bartley, *J. Org. Chem.* **1994**, *59*, 7169; c) J. A. Marshall, E. M. Wallace, *J. Org. Chem.* **1995**, *60*, 796; d) A. S. K. Hashmi, *Angew. Chem.* **1995**, *107*, 1749; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1581; e) A. S. K. Hashmi, T. L. Ruppert, T. Knofel, J. W. Bats, *J. Org. Chem.* **1997**, *62*, 7295; f) A. S. K. Hashmi, L. Schwarz, J. H. Choi, T. M. Frost, *Angew. Chem.* **2000**, *112*, 2382; *Angew. Chem. Int. Ed.* **2000**, *39*, 2285; g) S. Ma, L. Li, *Org. Lett.* **2000**, *2*, 941; h) S. Ma, Z. Yu, *Angew. Chem.* **2002**, *114*, 1853; *Angew. Chem. Int. Ed.* **2002**, *41*, 1775; i) S. Ma, J. Zhang, L. Lu, *Chem. Eur. J.* **2003**, *9*, 2447; j) J. T. Kim, A. V. Kel'in, V. Gevorgyan, *Angew. Chem.* **2003**, *115*, 102; *Angew. Chem. Int. Ed.* **2003**, *42*, 98; k) A. W. Sromek, A. V. Kel'in, V. Gevorgyan, *Angew. Chem.* **2004**, *116*, 2330;

Angew. Chem. Int. Ed. **2004**, *43*, 2280; l) M. H. Suhre, M. Reif, S. F. Kirsch, *Org. Lett.* **2005**, *7*, 3925; m) A. W. Sromek, M. Rubina, V. Gevorgyan, *J. Am. Chem. Soc.* **2005**, *127*, 10500; n) A. Dudnik, V. Gevorgyan, *Angew. Chem.* **2007**, *119*, 5287; *Angew. Chem. Int. Ed.* **2007**, *46*, 5195; o) T. Schwier, A. W. Sromek, D. M. L. Yap, D. Chernyak, V. Gevorgyan, *J. Am. Chem. Soc.* **2007**, *129*, 9868.

[4] a) Y. Fukuda, H. Shiragami, K. Utimoto, H. Nozaki, *J. Org. Chem.* **1991**, *56*, 5816; b) A. V. Kel′in, V. Gevorgyan, *J. Org. Chem.* **2002**, *67*, 95; c) A. W. Sromek, A. V. Kel′in, V. Gevorgyan, *Angew. Chem.* **2004**, *116*, 2330; *Angew. Chem. Int. Ed.* **2004**, *43*, 2280.

[5] Y. H. Liu, F. Song, Z. Song, M. Liu, B. Yan, *Org. Lett.* **2005**, *7*, 5409.

[6] a) T. Yao, X. Zhang, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 11164; b) T. Yao, X. Zhang, R. C. Larock, *J. Org. Chem.* **2005**, *70*, 7679; c) Y. H. Liu, S. Zhou, *Org. Lett.* **2005**, *7*, 4609; d) N. T. Patil, H. Wu, Y. Yamamoto, *J. Org. Chem.* **2005**, *70*, 4531; e) Y. Xiao, J. Zhang, *Angew. Chem.* **2008**, *120*, 1929; *Angew. Chem. Int. Ed.* **2008**, *47*, 1903.

[7] a) S. Ma, J. Zhang, *Angew. Chem.* **2003**, *115*, 193; *Angew. Chem. Int. Ed.* **2003**, *42*, 183; b) S. Ma, L. Lu, J. Zhang, *J. Am. Chem. Soc.* **2004**, *126*, 9645.

[8] a) A. Padwa, J. M. Kassir, S. L. Xu, *J. Org. Chem.* **1991**, *56*, 697; b) S. Ma, J. Zhang, *J. Am. Chem. Soc.* **2003**, *125*, 12386.

[9] a) J. Zhang, H.-G. Schmalz, *Angew. Chem.* **2006**, *118*, 6856; *Angew. Chem. Int. Ed.* **2006**, *45*, 6704; b) G. Zhang, X. Huang, G. Li, L. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 1814; c) G. Li, X. Huang, L. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 6944.

[10] Only a very few examples of approach to 3–4 fused bicyclic furans have been reported, see: a) M. Suzuki, H. Ohtaka, Y. Kameya, N. Hamanaka, R. Noyori, *J. Org. Chem.* **1989**, *54*, 5292; b) M. E. Price, N. E. Schore, *J. Org. Chem.* **1989**, *54*, 2777; c) Y. Siqot, P. Frere, T. Nozdryn, J. Cousseau, M. Salle, M. Jubauct, J. Orduna, J. Carin, A. Corguesa, *Tetrahedron Lett.* **1997**, *38*, 1919; d) ref. [9b].

[11] For examples of rhodium catalyzed reaction of cyclopropanes via selective activation of carbon–carbon σ bond, see: a) H. Ogoshi, J. Setsune, Z. Yoshida, *J. Chem. Soc. Chem. Commun.* **1975**, 234; b) M. Hidai, M. Orisaku, y. Uchida, *Chem. Lett.* **1980**, 753; c) U. M. Dzhemilev, R. I. Khusnutdinov, N. A. Shchadneva, G. A. Tolstikov, *Izv. Akad. Nauk SSSR Ser. Khim.* **1990**, 1598; U. M. Dzhemilev, R. I. Khusnutdinov, N. A. Shchadneva, G. A. Tolstikov, *Bull. Acad. Sci. USSR DIV. Chem. Sci.* **1990**, *39*, 1447; d) Y. Koga, K. Narasaki, *Chem. Lett.* **1999**, 705; e) D. F. Taber, K. Kanai, Q. Jiang, G. Bui, *J. Am. Chem. Soc.* **2000**, *122*, 6807; f) Z.-X. Yu, P. A. Wender, K. N. Houk, *J. Am. Chem. Soc.* **2004**, *126*, 9154; g) T. Matsuda, T. Tsuboi, M. Murakami, *J. Am. Chem. Soc.* **2007**, *129*, 12596; h) M. A. A. Walczak, P. Wipf, *J. Am. Chem. Soc.* **2008**, *130*, 6924; i) L. Jiao, S. Ye, Z.-X. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 7178; j) S. Y. Kim, S. I. Lee, S. Y. Choi, Y. K. Chung, *Angew. Chem.* **2008**, *120*, 4992; *Angew. Chem. Int. Ed.* **2008**, *47*, 4914.

[12] For examples of approach to substituted 5,6-dihydrocyclopenta[*c*]-furan-4-ones, see: a) G. A. Kraus, Z. Wan, *Synlett* **1997**, 1259; b) N. D. Pearson, N. J. P. Broom, P. J. O'Hanlon, *Tetrahedron Lett.* **1994**, *35*, 3771; c) T. R. Hoye, C. J. Dinsmore, D. S. Johnson, P. F. Korkowski, *J. Org. Chem.* **1990**, *55*, 4518; d) W. Münzenmaier, H. Straub, *Justus Liebigs Ann. Chem.* **1977**, 313.

[13] CCDC 708767 (**2a**), 708768 (**4a**) and 708769 (**5a**) 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.

[14] J. A. Marshall, E. D. Robinson, *J. Org. Chem.* **1990**, *55*, 3450.

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