Palladium Catalysis

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Palladium-Catalyzed Carbonylative α-Arylation for Accessing 1,3-Diketones**

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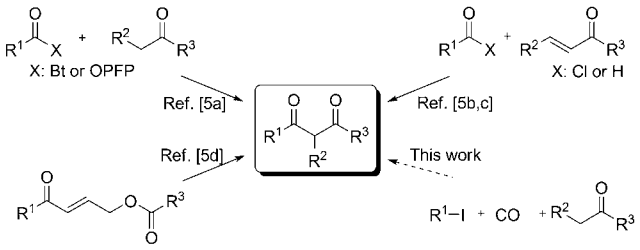
The palladium-catalyzed coupling between aryl halides and enolizable reagents has become a convenient method for the construction of $C(sp^2)$–$C(sp^3)$ bonds to generate allylic and benzylic carbonyl derivatives, which are found in a vast number of pharmaceuticals and bioactive compounds.[1] Owing to the significant contributions from the groups of Hartwig, Buchwald, and others, efficient protocols for the direct α-arylation of ketones, esters, amides, aldehydes, nitriles, malonates, etc. have been developed.[2] Furthermore, the mechanistic understanding of the enolate binding modes and the C–C bond-forming reductive elimination step has been clarified, enabling chemists to design specific variants of the α-arylation.[3]

The addition of carbon monoxide into the catalytic cycle of the α-arylation would provide a straightforward entry to β-keto carbonyl compounds from simple aryl halides and carbonyl derivatives having one or two protons in the α position. In particular, the synthesis of 1,3-diketones is of high importance, as such compounds exhibit biological activity, serve as versatile building blocks, and act as attractive platforms for accessing various heterocyclic compounds.[4] Numerous strategies for the synthesis of 1,3-diketones have been reported; these compounds are typically obtained by the aldol condensation of an enolate and a carbonyl compound followed by oxidation of the resulting 3-hydroxy ketone. However, only a few approaches have been oriented towards their direct synthesis (Scheme 1).[5] Previously, Tanaka and Kobayashi reported on the intermolecular carbonylative α-arylation of malonate derivatives under high pressures of carbon monoxide (20 atm).[6,7] However, attempts to include ketones were unsuccessful and instead resulted in the alkoxycarbonylation of the enolate derivative to an acylated enol.

Herein, we report on the identification of a catalytic system based on palladium for an effective carbonylative α-arylation strategy for the direct synthesis of 1,3-diketones from aryl iodides and simple ketones. Notably, the method relies on the use of only stoichiometric amounts of carbon monoxide, which makes this approach highly adaptable for the ^{13}C labeling of one of the carbonyl groups of the 1,3-diketone product.[8]



Scheme 1. Direct approaches to 1,3-diketones. Bt = benzotriazole, PFP = pentafluorophenyl.

To identify an effective catalytic system for the carbonylative α-arylation of ketones, we examined the coupling of 4-iodoanisole (**2**) and propiophenone (**3**).[9] A catalytic system consisting of $[Pd(dba)_2]$ and *rac*-binap, traditionally used in the α-arylation of ketones, was chosen as the starting point.[10,2e] The reactions were run using a two-chamber system with the ex situ generation of CO from 9-methyl-9*H*-fluorene-9-carbonyl chloride (**1**), as earlier described.[8] The addition of **1** to the CO-producing chamber in 1.5 equivalents with respect to **2** combined with 5 mol% of catalyst, which was composed of $[Pd(dba)_2]$ and $HBF_4P(t\mathrm{Bu})_3$, and stoichiometric base resulted in good CO incorporation and a promising 67% yield of **4** was obtained (Table 1, entry 1). To avoid the competing aminocarbonylation and/or amination with NaHMDS, propiophenone, and NaHMDS were premixed for 1 hour at ambient temperature before they were added to the reaction mixture, as reported by Hartwig and coworkers.[11,12] Changing the solvent to toluene resulted in exclusive formation of the direct α-arylated product **5**; this result can be explained by the enhanced basicity of the sodium enolate in nonpolar solvents (Table 1, entry 2). A decrease in the temperature lowered the yield of the reaction (Table 1, entry 3). Different bases such as NaH, KHMDS, and LiHMDS were inferior to NaHMDS (Table 1, entries 4–6). On the other hand, ligands possessing a rigid ferrocene backbone gave cleaner reactions and excellent yields of **4** were secured when dppf and D*i*PrPF were employed (Table 1, entries 7 and 10). A comparable yield was obtained when the reaction was run with the ketone in a slight excess with respect to the base (Table 1, entry 11).[13,14] An increase in the steric bulk on the phosphines resulted in the formation of the benzylic ketone **5** as the sole product, thus demonstrating the delicate balance often observed in the design of palladium catalysts (Table 1, entry 9). Finally, it is interesting to note that attempts to run these reactions under an atmosphere of

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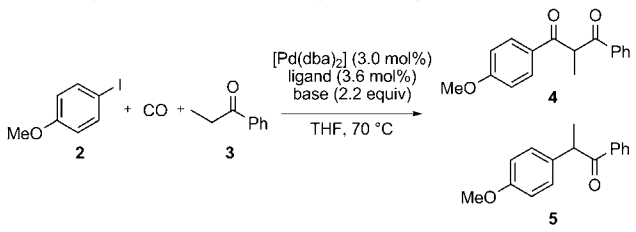
Table 1: Optimization of the carbonylative α-arylation.[a]

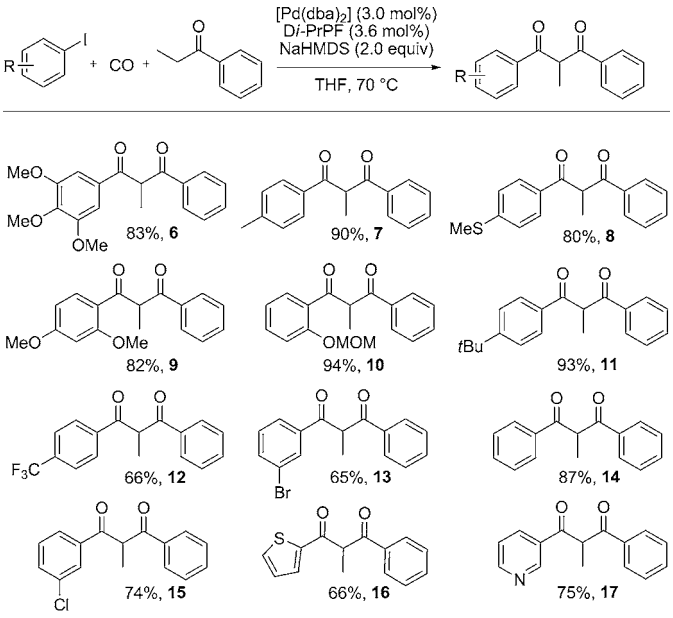


Entry	Ligand	Base	Ratio[b] 4/5	Yield[c]
1	(±)-binap	NaHMDS	10:1	67
2[d]	(±)-binap	NaHMDS	>1:19	–
3[e]	(±)-binap	NaHMDS	>19:1	52
4	(±)-binap	NaH	>19:1	60
5	(±)-binap	KHMDS	1:1	–
6	(±)-binap	LiHMDS	8:1	–
7	dppf	NaHMDS	>19:1	80
8	PPF*t*Bu	NaHMDS	>19:1	61
9	D*t*BuPF	NaHMDS	>1:19	–
10	D*i*PrPF	NaHMDS	>19:1	85
11[f]	D*i*PrPF	NaHMDS	>19:1	85

[a] Chamber A: **1** (0.45 mmol), $[Pd(dba)_2]$ (5.0 mol%), $HBF_4P(tBu)_3$ (5.0 mol%), DIPEA (0.68 mmol) in THF (2 mL). Chamber B: **3** (0.66 mmol) and base (0.66 mmol) were premixed for 1 h in THF (2 mL) at RT before being added to a mixture of **2** (0.3 mmol), ligand (3.6 mol%), $[Pd(dba)_2]$ (3.0 mol%). The reaction mixture was stirred for 17 h at 70°C. [b] Determined by ^1H NMR analysis. [c] Yields of the isolated product. [d] Toluene as solvent in Chamber B. [e] Reaction conducted at 40°C. [f] Base (0.60 mmol). binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, DIPEA = diisopropylethylamine, dppf = 1,1′-bis(diphenylphosphino)ferrocene, PPF*t*Bu = (2*R*)-1-{(1*R*)-1-[bis(1,1-dimethylethyl)phosphino]ethyl}-2-(diphenylphosphino)ferrocene, D*i*PrPF = 1,1′-bis(diisopropylphosphino)ferrocene, D*t*BuPF = 1,1′-bis(di-*tert*-butylphosphino)ferrocene, THF = tetrahydrofuran.

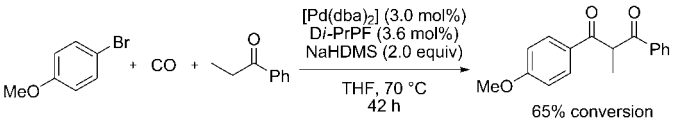
CO (balloon) provided lower coupling yields and surprisingly a 1:1 mixture of **4** and **5**.

With these optimized reaction conditions in hand, we set out to test the generality of this reaction. Gratifyingly, a variety of aryl iodides coupled successfully to propiophenone (Scheme 2). Electron-rich aryl iodides proved especially effective, thus providing the 1,3-diketones in almost quantitative yields. Despite the catalyst poisoning often observed by sulfur-containing motifs, the coupling of 4-iodothioanisole gave the desired product **8** in a good 80% yield. The MOM-protected 2-iodophenol performed particularly well to give the 3-methyl flavone precursor **10** in an excellent 94% yield. The electron-poor aryl iodides displayed a slightly inferior performance, thus indicating that the CO incorporation is dependent on the electronic properties of the arylpalladium(II) intermediate formed after the oxidative addition.[14] Nevertheless, good chemoselectivity was obtained in the reactions of 3-bromo- and 3-chloroiodobenzene, **13** and **15**, respectively, which allow for the further functionalization of the resulting 1,3-diketones. In addition, heterocyclic compounds, such as thiophenes and pyridines, were equally adaptable to the applied reaction conditions and formed the carbonylated α-arylation products **16** and **17** in good yields. On the other hand, the corresponding aryl bromides proved less effective under the applied reaction conditions and



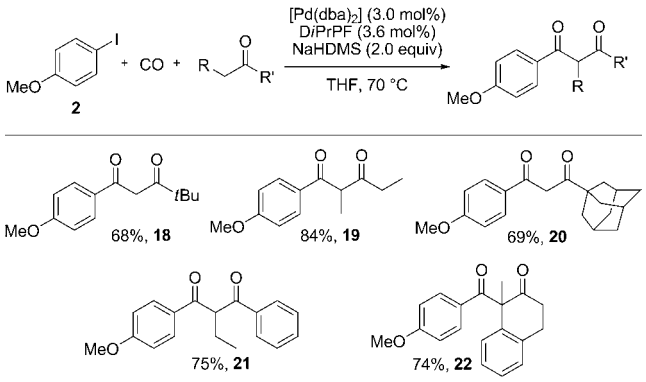
Scheme 2. Carbonylative α-arylation with a variety of aryl iodides. Reaction conditions: Chamber A: **1** (0.75 mmol), $[Pd(dba)_2]$ (5.0 mol%), $HBF_4P(tBu)_3$ (5.0 mol%), DIPEA (1.13 mmol) in THF (3 mL). Chamber B: **3** (1.10 mmol) and NaHMDS (1.00 mmol) were premixed for 1 h in THF (3 mL) at RT before being added to a mixture of aryl iodide (0.50 mmol), D*i*PrPF (3.6 mol%), and $[Pd(dba)_2]$ (3.0 mol%). The reaction mixture was stirred for 17 h at 70°C. HMDS = hexamethyldisilazane.

showed diminished levels of reactivity. For example, 4-bromoanisole resulted in 65% conversion into the desired 1,3-diketone exclusively after a reaction time of 42 hours (Scheme 3).



Scheme 3. 4-Bromoanisole in the carbonylative α-arylation.

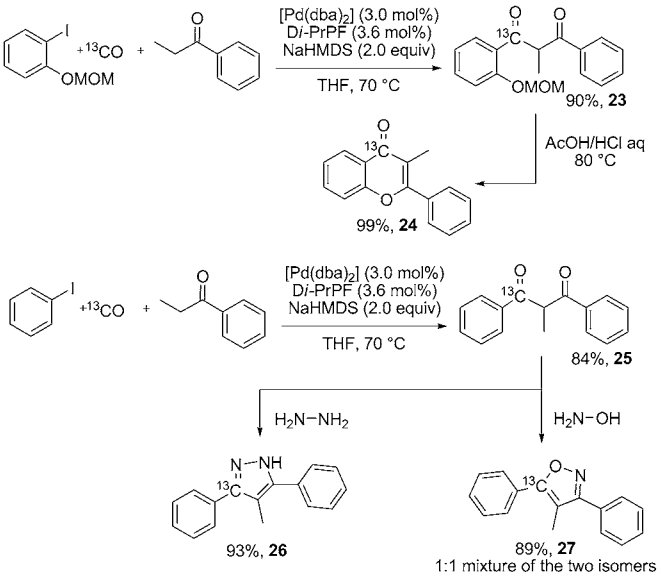
Different ketones were then evaluated with the test substrate 4-iodoanisole (**2**; Scheme 4). To our delight, these ketones coupled smoothly when subjected to the optimized carbonylative α-arylation conditions, thus further expanding the scope of this reaction. Comparable results were produced with dialkyl ketones after they were premixed with NaHMDS for 1 hour (**18**–**20**). Furthermore, an increase in the steric bulk on the α carbon to the carbonyl group did not affect the outcome of the reaction, as with **21**. In contrast, the reactions of acetophenone and cyclohexanone led to complex reaction mixtures, most likely as a result of a competing aldol reaction during the coupling (results not shown). Finally, a satisfactory 74% yield of **22** was obtained in the coupling of 2-tetralone with **2** after treatment of the resulting coupling product with methyl iodide owing to an otherwise a problematic purification.[15]



Scheme 4. Carbonylative α-arylation with different ketones. Reaction conditions: Chamber A: **1** (0.75 mmol), $[Pd(dba)_2]$ (5.0 mol%), $HBF_4P(tBu)_3$ (5.0 mol%), DIPEA (1.13 mmol) in THF (3 mL). Chamber B: ketone (1.10 mmol) and NaHMDS (1.00 mmol) were premixed for 1 h in THF (3 mL) at RT before being added to a mixture of **2** (0.50 mmol), D*i*PrPF (3.6 mol%), and $[Pd(dba)_2]$ (3.0 mol%). The reaction mixture was stirred for 17 h at 70°C. The yields refer to the isolated products.

The fact that only a small excess of carbon monoxide was used in the reaction prompted us to investigate the possibility of exploiting this method for the ^{13}C-labeling of 1,3-diketones. As such compounds are viable precursors to a wide range of heterocyclic compounds including pyrazoles, isoxazoles, and flavones, this approach would represent a new strategy for the synthesis of carbon-isotope-labeled heterocycles.[16]

The ^{13}C-labeled variant of the carboxylic acid chloride **1** prepared from 9-fluorenone was utilized as the carbon monoxide precursor in 1.5 equivalents (Scheme 5).[8a] Starting from MOM-protected 2-iodophenol, the ^{13}C-labeled 1,3-diketone **23** was obtained in a 90% yield. Subsequent hydrolysis of the methoxymethyl ether protecting group and dehydrative cyclization formed the 3-methyl flavone **24**



Scheme 5. Cyclizations of ^{13}C-labeled 1,3-diketones. MOM = methoxymethyl.

quantitatively. Finally, carbon isotope labeling of the heterocyclic core structure in [^{13}C]-3,5-diphenylpyrazole **26** and [^{13}C]-3,5-diphenylisoxazole **27** was successfully achieved in two steps starting from iodobenzene and ^{13}C-labeled carbon monoxide, which was generated ex situ in the two-chamber system.[17]

In summary, the Pd-catalyzed carbonylative α-arylation of ketones with aryl iodides provides a new route to 1,3-diketones, which serve as direct precursors to important building blocks and heterocyclic compounds. Furthermore, this technique proves effective for carbon isotope labeling of biologically relevant structures such as flavones, pyrazoles, and isoxazoles. Protocols that allow for the expansion of this approach to the use of esters and amides, as well as other aryl halides are currently in progress and will be reported in due course.

Experimental Section

1-(2-(Methoxymethoxy)phenyl)-2-methyl-3-phenylpropane-1,3-dione (**10**, Scheme 2): A two-chamber reactor was employed as earlier described.[8a] In a glovebox, 9-methyl-9*H*-fluorene-9-carbonyl chloride **1** (0.75 mmol), $[Pd(dba)_2]$ (5 mol%) and $HBF_4P(tBu)_3$ (5 mol%) were dissolved in THF (3 mL) in Chamber A. DIPEA (diisopropylethylamine) (1.13 mmol) was then added and the chamber was fitted with a Teflon® sealed screwcap.

A solution of the ketone (1.10 mmol) dissolved in THF (1 mL) was added dropwise to a solution of NaHMDS (1.0 mmol) in 1 mL THF. The reactor was fitted with a screwcap and the reaction mixture was stirred at RT for approximately 1 h. In a glovebox, 1-iodo-2-(methoxymethoxy)benzene (0.5 mmol), D*i*PrPF (3.6 mol%) and $[Pd(dba)_2]$ (3.0 mol%) were dissolved in THF (1 mL) in Chamber B. The generated enolate mixture was then added and this chamber was also fitted with a Teflon sealed screwcap.

The loaded two-chamber system was then removed from the glovebox and heated at 70°C for 17 h. The crude reaction mixture from Chamber B was quenched with 1M HCl (0.7 mL) and water was added. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography using 10% ethyl acetate in pentane as eluent to give 140 mg (94% yield) of the title product as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.03$ (d, 2H, $J = 7.8$ Hz), 7.91 (dd, 1H, $J = 1.7$, 7.8 Hz), 7.60–7.56 (m, 1H), 7.49 (t, 2H, $J = 7.8$ Hz), 7.43–7.39 (m, 1H), 7.13 (d, 2H, $J = 8.4$ Hz), 7.05 (t, 1H, $J = 8.4$ Hz), 5.38 (q, 1H, $J = 7.2$ Hz), 4.82 (q, 2H, $J = 7.1$ Hz), 3.11 (s, 3H), 1.52 ppm (d, 3H, $J = 7.2$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 197.8$, 197.2, 156.4, 135.9, 134.2, 133.3, 131.4, 128.9, 128.7, 126.8, 122.1, 114.7, 94.2, 56.2, 54.7, 14.2 ppm. HRMS $C_{18}H_{18}O_4$ [M+Na^+]; calculated 321.1103, found 321.1105.

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[1] For reviews on palladium catalyzed α-arylation, see: a) D. A. Culkin, J. F. Hartwig, *Acc. Chem. Res.* **2003**, *36*, 234; b) G. C. Lloyd-Jones, *Angew. Chem.* **2002**, *114*, 995; *Angew. Chem. Int. Ed.* **2002**, *41*, 953; c) C. C. C. Johansson, T. J. Colacot, *Angew. Chem.* **2010**, *122*, 686; *Angew. Chem. Int. Ed.* **2010**, *49*, 676.

[2] For a representative selection see: a) B. C. Hamann, J. F. Hartwig, *J. Am. Chem. Soc.* **1997**, *119*, 12382; b) M. Palucki, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 11108; c) T. Satoh, J. Inoh, Y. Kawamura, Y. Kawamura, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239; d) X. Liu, J. F. Hartwig, *J. Am. Chem. Soc.* **2004**, *126*, 5182; e) K. H. Shaughnessy, B. C. Hamann, J. F. Hartwig, *J. Org. Chem.* **1998**, *63*, 6546; f) K. D. Hesp, R. J. Lundgren, M. Stradiotto, *J. Am. Chem. Soc.* **2011**, *133*, 5194; g) W. A. Moradi, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7996; h) J. Cossy, A. de Filippis, D. G. Pardo, *Org. Lett.* **2003**, *5*, 3037; i) G. D. Vo, J. F. Hartwig, *Angew. Chem.* **2008**, *120*, 2157; *Angew. Chem. Int. Ed.* **2008**, *47*, 2127; j) M. R. Biscoe, S. L. Buchwald, *Org. Lett.* **2009**, *11*, 1773.

[3] a) D. A. Culkin, J. F. Hartwig, *Organometallics* **2004**, *23*, 3398; b) D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 5816; c) A. C. Albéniz, M. Catalina, P. Espinet, R. Redón, *Organometallics* **1999**, *18*, 5571.

[4] a) A. V. Kel'in, *Curr. Org. Chem.* **2003**, *7*, 1691; b) A. V. Kel'in, A. Maioli, *Curr. Org. Chem.* **2003**, *7*, 1855.

[5] a) D. Lim, F. Fang, G. Zhou, D. M. Coltart, *Org. Lett.* **2007**, *9*, 4139; b) T. Fukuyama, T. Doi, S. Minamino, S. Omura, I. Ryu, *Angew. Chem.* **2007**, *119*, 5655; *Angew. Chem. Int. Ed.* **2007**, *46*, 5559; c) K. Sato, S. Yamazoe, R. Yamamoto, S. Ohata, A. Tarui, M. Omote, I. Kumadaki, A. Ando, *Org. Lett.* **2008**, *10*, 2405; d) M. Sada, S. Matsubara, *J. Am. Chem. Soc.* **2010**, *132*, 432.

[6] T. Kobayashi, M. Tanaka, *Tetrahedron Lett.* **1986**, *27*, 4745.

[7] For *intramolecular* carbonylative α-arylations, see: a) E. Negishi, C. Copéret, T. Sugihara, I. Shimoyama, Y. Zhang, G. Wu, J. M. Tour, *Tetrahedron* **1994**, *50*, 425; b) E. Negishi, H. Makabe, I. Shimoyama, G. Wu, Y. Zhang, *Tetrahedron* **1998**, *54*, 1095; c) Z. Zheng, H. Alper, *Org. Lett.* **2009**, *11*, 3278.

[8] a) P. Hermange, A. T. Lindhardt, R. H. Taaning, K. Bjerglund, D. Lupp, T. Skrydstrup, *J. Am. Chem. Soc.* **2011**, *133*, 6061; b) P. Hermange, T. M. Gøgsig, A. T. Lindhardt, R. H. Taaning, T. Skrydstrup, *Org. Lett.* **2011**, *13*, 2444; c) D. U. Nielsen, R. H. Taaning, A. T. Lindhardt, T. M. Gøgsig, T. Skrydstrup, *Org. Lett.* **2011**, *13*, 4454.

[9] Electron-rich arylpalladium(II) intermediates are known to promote the carbon monoxide incorporation to a higher extent than the corresponding electron-poor intermediates, see: a) P. E. Garrou, R. F. Heck, *J. Am. Chem. Soc.* **1976**, *98*, 4115; b) T. Ishiyama, H. Kizaki, T. Hayashi, A. Suzuki, N. Miyaura, *J. Org. Chem.* **1998**, *63*, 4726; c) Y. Wan, M. Alterman, M. Larhed, A. Hallberg, *J. Org. Chem.* **2002**, *67*, 6232.

[10] J. M. Fox, X. Huang, A. Chieffi, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 1360.

[11] T. Hama, J. F. Hartwig, *Org. Lett.* **2008**, *10*, 1549.

[12] Palladium-catalyzed C–N couplings using LiHMDS as an ammonia surrogate have been described in the literature, see: S. Lee, M. Jørgensen, J. F. Hartwig, *Org. Lett.* **2001**, *3*, 2729.

[13] It has been demonstrated that the aldol product from the condensation of aldehydes is reversible, releasing the reactive enolate intermediate by a retro-aldol process, see: R. Martín, S. L. Buchwald, *Angew. Chem.* **2007**, *119*, 7374; *Angew. Chem. Int. Ed.* **2007**, *46*, 7236.

[14] Similar trends have been reported by the group of Beller, see: a) X.-F. Wu, H. Neumann, A. Spannenberg, T. Schulz, H. Jiao, M. Beller, *J. Am. Chem. Soc.* **2010**, *132*, 14596; b) X.-F. Wu, P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem.* **2010**, *122*, 7474; *Angew. Chem. Int. Ed.* **2010**, *49*, 7316; c) X.-F. Wu, H. Neumann, M. Beller, *Chem. Eur. J.* **2010**, *16*, 9750.

[15] N. A. Beare, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 541.

[16] a) S. T. Heller, S. R. Natarajan, *Org. Lett.* **2006**, *8*, 2675; b) M. Rowley, H. B. Broughton, I. Collins, R. Baker, F. Emms, R. Marwood, S. Patel, S. Patel, C. I. Ragan, S. B. Freedman, P. D. Leeson, *J. Med. Chem.* **1996**, *39*, 1943; c) X. Liu, C.-B. Chan, S.-W. Jang, S. Pradoldej, J. Huang, K. He, L. H. Phun, S. France, G. Xiao, Y. Jia, H. Luo, K. Ye, *J. Med. Chem.* **2010**, *53*, 8274.

[17] Patent application currently proceeding: T. Gøgsig, R. H. Taaning, A. T. Lindhardt, T. Skrydstrup, (Aarhus University, Denmark) Process for the synthesis of 1,3-dicarbonyl compounds using carbon monoxide. PA 2011 70515, Sept. 20th, **2011**.

