Available online at www.sciencedirect.com
ScienceDirect
Catalysis Today 121 (2007) 22–26
CATALYSIS TODAY
www.elsevier.com/locate/cattod

Cerium-catalyzed oxidative C–C bond forming reactions

Jens Christoffers [a,b,*], Thomas Werner [a,c], Michael Rössle [a,b]

[a] Institut für Organische Chemie, Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany
[b] Institut für Reine und Angewandte Chemie, Carl von Ossietzky-Universität Oldenburg, D-26111 Oldenburg, Germany
[c] Degussa AG, Paul Baumann-Str. 1, D-45764 Marl, Germany

Available online 18 December 2006

Abstract

With respect to economical and ecological considerations, molecular oxygen is the oxidant of choice for functionalization of organic substrates. On the basis of our cerium-catalyzed α-hydroxylation of β-dicarbonyl compounds, we have developed an oxidative process for C–C bond formation in the presence of simple olefins like styrene. Products of these reactions, which are isolated as endoperoxidic 1,2-dioxane derivatives with potential anti-malaria activity, are hydroperoxides. These peroxides are disproportionated to 1,4-dicarbonyl compounds in a Kornblum–DeLaMare fragmentation. Actually, β-dicarbonyl compounds can be directly converted in a two-step one-pot procedure to give the 1,4-diketones in high yield. Compounds with 1,4-dicarbonyl structural motif are important intermediates for the synthesis of heterocyclic compounds and commonly only accessible by an Umpolung strategy.

Keywords: Cerium; Catalysis; Dicarbonyl compounds; Oxidation; Dioxygen; Peroxides; 1,4-Diketones

1. Introduction

In 1951, Kornblum and DeLaMare reported on base-induced fragmentations of dialkyl peroxides into ketones and alcohols [1]. Since then, this process has received much attention from synthetic organic chemists. Of particular interest is the selective conversion of endoperoxides to hydroxyketones [2]. According to this fragmentation, 1,4-dicarbonyl compounds **2** are obtained after activation of the OH-group by acetylation [3] of 3-hydroxy-1,2-dioxane derivatives **1**. The latter can be regarded as the cyclotautomers of γ-hydroperoxyketones **3**. Therefore, a simple access to these peroxides could be the basis for a valuable synthetic route to 1,4-diketones, [4] an important structural motif for the preparation of heterocyclic compounds [5] (Scheme 1).

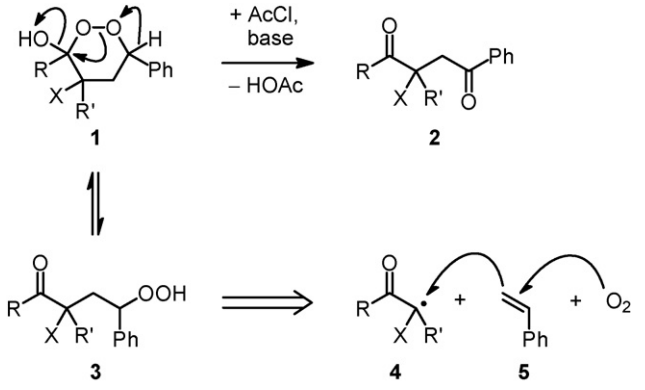
In contrast to 1,3- and 1,5-dicarbonyl compounds being accessible by Claisen or Michael reactions, [6] the synthesis of 1,4-dicarbonyl functionalized carbon skeletons requires an Umpolung strategy, carried out by either the classic utilization of α-halogen ketones [7] or more modern strategies involving 1,3-dithian derivatives [8]. Both methodologies are multistep sequences and require stoichiometric amounts of reagents, such as halogen sources or bases. For this reason, they are not very attractive with regard to economical and ecological considerations. An atom-economic Umpolung strategy, however, is the use of the Stetter reagent or other organocatalytic systems [9].

2. Results and discussion

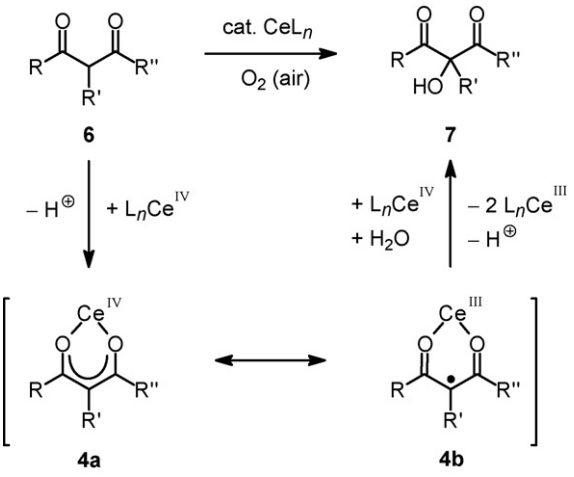
In order to contribute to the field of 1,4-dicarbonyl compounds **2**, we have developed a process leading to γ-hydroperoxyketones **3** by attack of an α-radical **4** to styrene **5** and trapping of the intermediate radical by molecular oxygen [10]. This development is clearly a result of our earlier observation that β-dicarbonyl compounds **6** are cleanly α-hydroxylated in the presence of molecular oxygen and catalytic amounts of cerium-salts (Scheme 2) [11]. Key feature of this reaction is the utilization of dioxygen as the oxidant, which can be regarded as optimal in terms of economical and ecological considerations. Moreover, the solvent isopropanol and the catalyst $CeCl_3 \cdot 7H_2O$ are inexpensive and non-toxic. Cyclic β-oxo esters oxidize most rapidly under these conditions. Respective products **7a** and **7b** are obtained in almost quantitative yields with 1 mol% of the

* Corresponding author at: Institut für Reine und Angewandte Chemie, Carl von Ossietzky-Universität Oldenburg, D-26111 Oldenburg, Germany. Tel.: +49 441 798 4744; fax: +49 441 798 3873.
E-mail address: jens.christoffers@uni-oldenburg.de (J. Christoffers).

0920-5861/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.cattod.2006.11.008



Scheme 1. Transformation of 3-hydroxy-1,2-dioxane derivatives **1** into 1,4-dicarbonyl compounds **2** by Kornblum–DeLaMare fragmentation; R, R′: alkyl, cycloalkyl; X: ester, ketone.



Scheme 3. Proposed mechanism for the cerium-catalyzed α-hydroxylation of β-dicarbonyl compounds **6**. Coligands L_n at Ce(III) or Ce(IV) in structures **4a** and **4b** are omitted for clarity and simplicity.

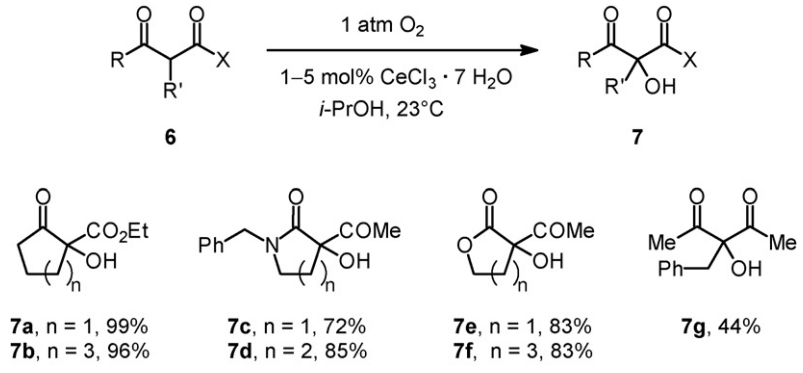
catalyst. Since no byproducts are formed in these cases, the workup and purification is a simple filtration through some SiO_2 or distillation. Lactams **7c** and **7d** and lactones **7e** and **7f** require 5 mol% of the catalyst. As small amounts of α-chlorinated byproducts are formed and some decomposition under reaction conditions occurs, purification is accomplished by chromatography and yields are in the range of 70–90%. The use of acyclic starting materials is to date somewhat problematic. A representative example is product **7g** which can be isolated with 44% yield.

The exact stoichiometry of this hydroxylation could be established from oxygen uptake measurements being half an equivalent of O_2 per equivalent of formed products **7**. In some cases, the formation of α-chlorinated byproducts is observed, presumably resulting from a nucleophilic attack of the chloride counterion of the catalyst to an electrophilic reaction intermediate. Regarding the mechanism of the catalysis, we have made the following proposal: the role of dioxygen might only be to oxidize Ce(III)-species to Ce(IV) under reaction conditions according to the following equation:

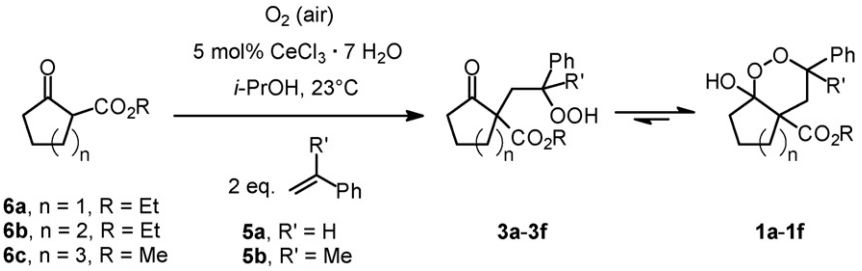
$$2H^+ + 2Ce(III) + \tfrac{1}{2}O_2 \rightarrow H_2O + 2Ce(IV)$$

This oxidation is of course not commonly observed. In our case, the redox potential of Ce(III)/Ce(IV) is shifted by coordination to the β-dicarbonyl compound under the formation of a diketonate complex **4a**. The hydroxy group in product **7** could result from a nucleophilic attack of water to an electrophilic reaction intermediate. Ce(IV)-ions, e.g. as hydrate or chloro complexes in solution, readily form Ce(IV)-diketonate species **4a** (Scheme 3) under reaction conditions. As known of the stoichiometric use of Ce(IV) reagents, e.g. CAN, for the formation of α-radicals, [12] we propose ligand-to-metal electron transfer generating species **4b**. In this complex, the center metal formally has the oxidation state +III and a neutral β-diketone ligand with an unpaired electron localized in the α-position. This radical species might then be the electrophilic reaction intermediate [13] which forms the hydroxylation products **7** or the chlorinated byproducts upon reaction with water or chloride as nucleophiles.

In order to utilize the cerium-catalyzed α-radical formation for C–C coupling reactions, we carried out the conversion in the presence of olefins (Scheme 4). Actually, the partial pressure of oxygen must be reduced from 1 atm (pure O_2) to 0.2 atm (air) in order to prevent α-hydroxylation as the dominating process. Moreover, an excess of the alkene needs to be applied because some olefin polymerization occurs. The hydroperoxide products **3** are isolated as cyclotautomeric 1,2-dioxane derivatives **1**. These compounds have three stereogenic centers, which are for this reason obtained as mixtures of at least two



Scheme 2. Cerium-catalyzed α-hydroxylation of β-dicarbonyl compounds **6**.



Scheme 4. Insertion of styrene (**5a**) or α-methylstyrene (**5b**).

Table 1
Substituents, yields, and diastereomeric ratios in the olefin insertion reaction

Product	R	*n*	R′	Yield (%)	dr
1a	Et	1	H	68	60:40
1b	Et	2	H	50	50:50
1c	Me	1	Me	55	40:30:30
1d	Et	1	Me	87	65:35
1e	Et	2	Me	72	60:40
1f	Me	3	Me	53	80:20

diastereoisomers without any significant stereoselectivity. Yields and drs of some representative examples are presented in Table 1.

After separation by column chromatography, the relative configuration of some isomers was assigned by single crystal X-ray crystallography. In Fig. 1, one of the isomers of compound **1a** is depicted as an ORTEP-representation. Actually, the 1,2-dioxane ring is in an ideal chair-conformation with the equatorial phenyl group as a conformational anchor at C11. The two six-membered rings are in a *cis*-decalin-like conformation. Additional stabilization of the overall structure is gained by H-bonding between the hemiacetal–hydroxy-function O3 and the ester carbonyl group O4. The compound has a melting point of 118 °C without decomposition.

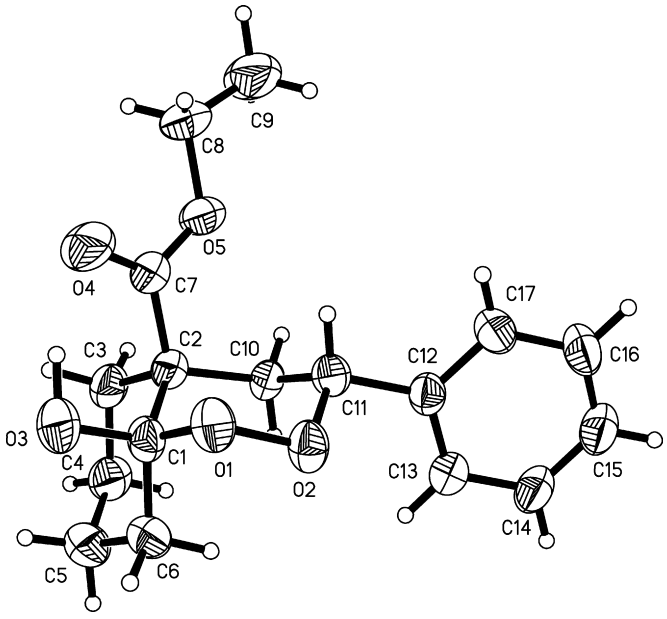
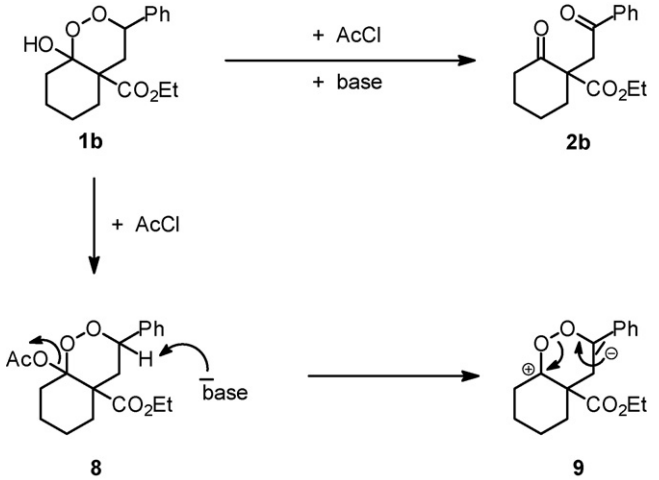


Fig. 1. ORTEP-representation of one isomer of 1,2-dioxane derivative **1b**.

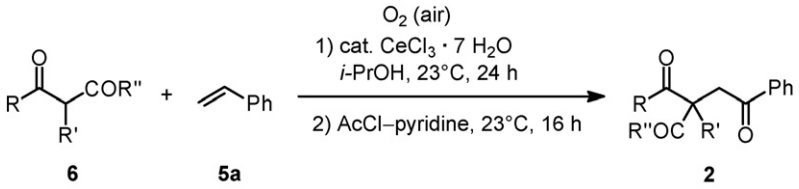
Although the endoperoxides **1** are stable and well-behaved compounds, their synthetic application is of course limited due to the fact that they are obtained as mixtures of diastereoisomers. We aimed to convert these mixtures to unique materials and experimented with a number of transition metal-mediated transformations of the peroxide moiety. However, most successful turned out to be the treatment of the 3-hydroxy-1,2-dioxanes **1** with a mixture of acetyl chloride and pyridine, which initiated a fragmentation giving the 1,4-dicarbonyl structural motif already mentioned in Section 1 of this article (Scheme 5).

From a mechanistic point of view, this fragmentation is initiated by activation of the hydroxy group by acetylation (structure **8**). Deprotonation in α-position to the phenyl group leads to elimination of an acetate ion under breaking of the O–O bond generating two carbonyl groups. This step can formally be rationalized from a zwitterionic structure **9**.

In order to avoid the rather tedious isolation and purification of the endoperoxides **1**, we were looking to develop a one-pot procedure for the preparation of 1,4-diketones **2** from 1,3-dicarbonyl compounds **6**. An optimized protocol is summarized in Scheme 6. In the first step, the starting materials are converted with catalytic amounts of $CeCl_3{\cdot}7H_2O$ at ambient temperature for a couple of hours in isopropanol. The solvent and all other volatile materials are removed in vacuum



Scheme 5. Kornblum–DeLaMare fragmentation of 3-hydroxy-1,2-dioxane derivatives 1 leading to 1,4-diketones **2**.



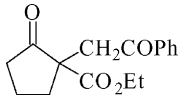
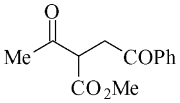
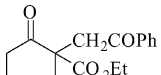
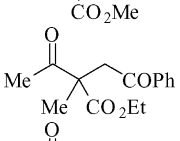
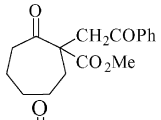
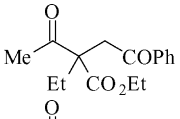
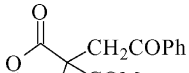
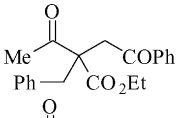
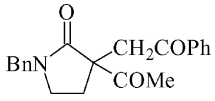
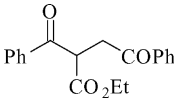
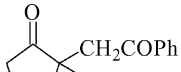
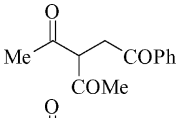
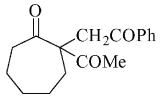
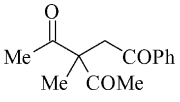
Scheme 6. Formation of 1,4-dicarbonyl compounds **2** by a two-step one-pot reaction consisting of cerium-catalyzed C–C coupling with styrene (**5a**) and subsequent Kornblum–DeLaMare fragmentation.

afterwards and the residue containing the peroxide, some polystyrene and the cerium species are treated with AcCl–pyridine. After stirring again at ambient temperature, the mixture is separated by column chromatography to give the tricarbonyl compounds **2**.

In Table 2, products **2** are listed together with their yields over two steps in the one-flask procedure. Acyclic (right column) and cyclic starting materials (left) have been investigated; yields for the latter are generally higher than for the acyclic compounds. For cyclic β-ketoesters **6a–6c** as well as for α-acetylbutyrolactone (**6d**), -lactam (**6e**), and -cyclopentanone (**6f**), the yield of the diketone **2** was generally good and independent of the ring size. Yields of 61–87% over two steps indicate a range of 78–93% for each step. For the seven-membered ring diketone **2g**, the yield drops dramatically to 14%.

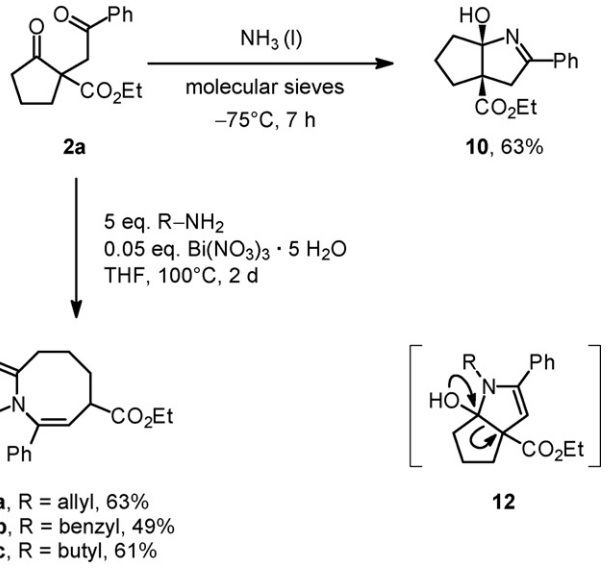
The best yield achieved for an acyclic product was 72% for β-ketoester **2h**. Yields for these classes of substrates seem to be dependent on the steric demand of the α-alkyl substituent. This is illustrated by the decrease in the order H (**2h**), Me (**2i**), Bn (**2k**), Et (**2j**) from 72% to 42% yield. Replacement of the acetyl group in **2h** by a benzoyl residue in **2l** lowered the yield from 72% to 56%. The α-isopropyl derivative did not give any product under these reaction conditions. The effect was even more extreme for the acetylacetone derivatives **2m** and **2n**. Introduction of the Me group resulted in a decrease from 28% to 10%. For the α-benzyl substituted β-diketone, no conversion was observed. In these cases, however, the low yields might also be due to the instability of the starting materials **6** under basic reaction conditions. It is well known that aliphatic 1,3-diketones tend to decompose according to a retro-Claisen reaction.

Table 2
List of products **2a–2n** and yields

	Product	Yield (%)[a]		Product	Yield (%)[a]
2a		69	**2h**		72
2b		61	**2i**		68
2c		71	**2j**		42
2d		87	**2k**		53
2e		72	**2l**		56
2f		61	**2m**		28
2g		14	**2n**		10

[a] Total yield over two steps.

The 1,4-dicarbonyl moiety in compounds **2** is the most important starting point for the preparation of pyrrole and thiophene derivatives (Paal–Knorr and Paal synthesis) [14]. In order to prove the utility of these products, we aimed to convert them into highly substituted dihydropyrrole derivatives bearing at least one quaternary carbon atom within the five-membered ring. An unusual result during these investigations was the formation of new eight-membered ring lactams **11** (Scheme 7) [15]. After experimentation with several acidic catalysts, we were able to identify an optimized protocol using catalytic amounts of $Bi(NO_3)_3{\cdot}5H_2O$ [16]. Benzyl-, allyl- and *n*-butylamine were used as nucleophilic components. A mechanistic rationale for the C–C bond cleavage might involve



Scheme 7. Unexpected formation of new 1,4,5,6,7,8-hexahydroazocin-8-one-4-carboxylates **11**.

a retro-Claisen reaction of an azabicyclo [3.3.0] intermediate **12**, which moreover makes a *Z*-configuration of the C–C double bond reasonable. This intermediate **12** is evidenced by the following result: if diketone **2a** is converted with NH_3 under again optimized conditions, the bicyclic compound **10** is obtained as the only isolable product. This compound is stable under reaction conditions and does not decompose further to give an eight-membered ring.

3. Conclusion

The most important basis for the synthesis of heterocyclic compounds such as pyrrole, furan and thiophene derivatives are 1,4-diketones like **2**. In contrast to 1,3- and 1,5-dicarbonyl compounds, which are accessible by Claisen or Michael reactions, the direct synthesis of 1,4-dicarbonyl compounds is still a challenging task and commonly requires α-halogenation of ketones or other Umpolung strategies. With regard to atom economy, however, both methods are not optimal.

We have introduced a cerium-catalyzed C–C coupling of 1,3-dicarbonyl compounds **6** with styrene derivatives **5** and oxygen yielding 4-hydroperoxyketones **3**, which exist as 3-hydroxy-1,2-dioxane derivatives **1**. Base-induced Kornblum–DeLaMare fragmentation of these intermediate products affords compounds **2** with a 1,4-dicarbonyl moiety. This cerium-catalyzed reaction sequence can be operated as a high yielding one-pot procedure. Starting from simple starting materials and utilizing atmospheric oxygen as oxidant, these results can – in terms of economical and ecological considerations – be regarded as a challenging starting point for further developments.

As an example of heterocyclic synthesis, we further converted these 1,4-diketones **2** with primary amines to eight-membered ring lactams **11**, being a new and promising molecular scaffold for medicinal chemistry. This rather unexpected Paal–Knorr like transformation proceeds with optimal results when catalyzed by bismuth salts.

Acknowledgements

This work was generously supported by the Deutsche Forschungsgemeinschaft (Normalverfahren and SFB 706) and by the Fonds der Chemischen Industrie (fellowship for M.R.). Thanks to Dr. W. Frey, Universität Stuttgart, for crystallography.

References

[1] N. Kornblum, H.E. DeLaMare, J. Am. Chem. Soc. 73 (1951) 880.
[2] (a) B.W. Greatrex, D.K. Taylor, E.R.T. Tiekink, J. Org. Chem. 69 (2004) 2580;
(b) B.W. Greatrex, N.F. Jenkins, D.K. Taylor, E.R.T. Tiekink, J. Org. Chem. 68 (2003) 5205;
(c) G. Özer, N. Saracoglu, M. Balci, J. Org. Chem. 68 (2003) 7009.
[3] D.R. Kelly, H. Bansal, J.J.G. Morgan, Tetrahedron Lett. 43 (2002) 9331.
[4] (a) M. Yuguchi, M. Tokuda, K. Orito, J. Org. Chem. 69 (2004) 908, Selection of other new 1,4-diketone syntheses;
(b) R. Ballini, L. Barboni, G. Giarlo, J. Org. Chem. 68 (2003) 9173;
(c) Y. Yamamoto, H. Maekawa, S. Goda, I. Nishiguchi, Org. Lett. 5 (2003) 2755;
(d) M. Yasuda, S. Tsuji, Y. Shigeyoshi, A. Baba, J. Am. Chem. Soc. 124 (2002) 7440.
[5] (a) B.K. Banik, S. Samajdar, I. Banik, J. Org. Chem. 69 (2004) 213;
(b) G. Minetto, L.F. Raveglia, M. Taddei, Org. Lett. 6 (2004) 389;
(c) R. Dhawan, B.A. Arndtsen, J. Am. Chem. Soc. 126 (2004) 468;
(d) H.S.P. Rao, S. Jothilingam, J. Org. Chem. 68 (2003) 5392;
(e) B.W. Greatrex, M.C. Kimber, D.K. Taylor, E.R.T. Tiekink, J. Org. Chem. 68 (2003) 4239;
(f) D.S. Mortensen, A.L. Rodriguez, K.E. Carlson, J. Sun, B.S. Katzenellenbogen, J.A. Katzenellenbogen, J. Med. Chem. 44 (2001) 3838;
(g) R.U. Braun, K. Zeitler, T.J.J. Müller, Org. Lett. 3 (2001) 3297.
[6] (a) J. Christoffers, in: I. Horvath (Ed.), Encyclopedia of Catalysis, vol. 5, Wiley, New York, 2003, p. 99;
(b) N. Krause, A. Hoffmann-Röder, Synthesis (2001) 171;
(c) B.E. Rossiter, N.M. Swingle, Chem. Rev. 92 (1992) 771.
[7] (a) M.A. Calter, C. Zhu, Org. Lett. 4 (2002) 205, Recent examples;
(b) M.A. Calter, C. Zhu, R.J. Lachicotte, Org. Lett. 4 (2002) 209;
(c) F. Stauffer, R. Neier, Org. Lett. 2 (2000) 3535.
[8] A.B. Smith III, C.M. Adams, Acc. Chem. Res. 37 (2004) 365, Review.
[9] D. Enders, T. Balensiefer, Acc. Chem. Res. 37 (2004) 534, Review.
[10] (a) M. Rössle, T. Werner, A. Baro, W. Frey, J. Christoffers, Angew. Chem. 116 (2004) 6709;
M. Rössle, T. Werner, A. Baro, W. Frey, J. Christoffers, Angew. Chem. Int. Ed. 43 (2004) 6547;
(b) J. Christoffers, T. Werner, W. Frey, A. Baro, Eur. J. Org. Chem. (2003) 4879;
(c) M. Rössle, T. Werner, W. Frey, J. Christoffers, Eur. J. Org. Chem. (2005) 5031.
[11] (a) J. Christoffers, T. Werner, Synlett (2002) 119;
(b) J. Christoffers, T. Werner, S. Unger, W. Frey, Eur. J. Org. Chem. (2003) 425;
(c) J. Christoffers, T. Werner, W. Frey, A. Baro, Chem. Eur. J. 10 (2004) 1042;
(d) M. Pohmakotr, A. Pinsa, T. Mophuang, P. Tuchinda, S. Prabpai, P. Kongsaeree, V. Reutrakul, J. Org. Chem. 71 (2006) 386;
(e) J. Christoffers, A. Baro, T. Werner, Adv. Synth. Catal. 346 (2004) 143, Review.
[12] (a) V. Gyollai, D. Schanzenbach, L. Somsak, T. Linker, Chem. Commun. (2002) 1294;
(b) T. Linker, U. Linker, Angew. Chem. 112 (2000) 934;
T. Linker, U. Linker, Angew. Chem. Int. Ed. 39 (2000) 902;
(c) V. Nair, L. Balagopal, R. Rajan, J. Mathew, Acc. Chem. Res. 37 (2004) 21, Reviews;
(d) T. Linker, in: P. Renaud, M.P. Sibi (Eds.), Radicals in Organic Synthesis, vol. 1, Wiley-VCH, Weinheim, 2001, p. 219;
(e) V. Nair, J. Mathew, J. Prabhakaran, Chem. Soc. Rev. 26 (1997) 127.
[13] (a) C. Limberg, Angew. Chem. 115 (2003) 6112, Reviews;
C. Limberg, Angew. Chem. Int. Ed. 42 (2003) 5932, Reviews;
(b) P. Hlavica, Eur. J. Biochem. 271 (2004) 4335.
[14] (a) K.A. Hansford, S.A.P. Guarin, W.G. Skene, W.D. Lubell, J. Org. Chem. 70 (2005) 7996;
(b) M. Yuguchi, M. Tokuda, K. Orito, J. Org. Chem. 69 (2004) 908;
(c) S. Demirayak, A.C. Karaburun, R. Beis, Eur. J. Med. Chem. 39 (2004) 1089;
(d) S. Raghavan, K. Anuradha, Synlett (2003) 711;
(e) P.E. Just, K.I. Chane-Ching, P.C. Lacaze, Tetrahedron 58 (2002) 3467;
(f) V.F. Ferreira, M.C.B.V. de Souza, A.C. Cunha, L.O.R. Pereira, M.L.G. Ferreira, Org. Prep. Proc. Int. 33 (2001) 413, Review.
[15] M. Rössle, J. Christoffers, Synlett (2006) 106.
[16] (a) B.K. Banik, I. Banik, M. Renteria, S.K. Dasgupta, Tetrahedron Lett. 46 (2005) 2643;
(b) J.S. Yadav, B.V.S. Reddy, B. Eeshwaraiah, M.K. Gupta, Tetrahedron Lett. 45 (2004) 5873.