J|A|C|S
COMMUNICATIONS

Published on Web 04/15/2004

Organocatalytic Enantioselective Conjugate Addition to Alkynones

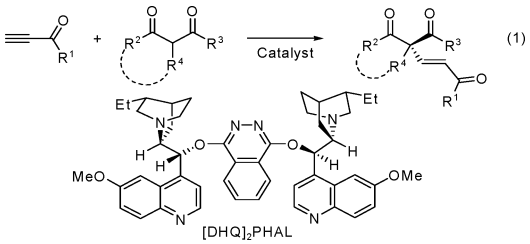
Marco Bella and Karl Anker Jørgensen*

Danish National Research Foundation: Center for Catalysis, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark

Received February 5, 2004; E-mail: kaj@chem.au.dk

Conjugate addition to α,β-unsaturated compounds is an established and useful synthetic strategy which has been used widely in organic synthesis, such as for the generation of quaternary carbon centers in a stereoselective manner.[1] A variety of different alkenones have been found useful as substrates for these conjugate addition reactions. In contrast, there are only isolated reports dealing with the analogous conjugate addition reaction to the corresponding alkynones,[2] and to the best of our knowledge no successful catalytic enantioselective additions to alkynones, leading to e.g. optically active quaternary carbon centers, have been reported.[3] An advantage of the conjugate additions to alkenones is that the products obtained from the reaction with alkynones contain a C═C double bond which is an ideal "anchor" functionality for further transformations.

This communication presents the first organocatalytic enantioselective conjugate addition of β-dicarbonyl compounds to alkynones (eq 1).

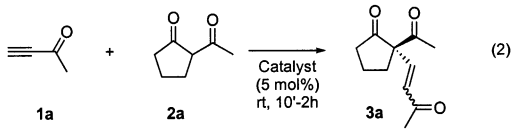


To verify the feasibility of such a type of transformation, we chose to test the addition of acetyl cyclopentanone **2a** to commercially available butyn-2-one **1a** in the presence of organocatalysts based on the cinchona alkaloids and some derivatives (eq 2) (see Supporting Information for a list and structures of the cinchona alkaloids and derivatives tested).

Complete conversion is observed at room temperature from a few minutes (Et_3N) to 2 h (cinchona alkaloids and derivatives), and analytically pure products are isolated in quantitative yield after addition of Et_2O, filtration, and evaporation of the solvent. Anhydrous conditions or inert atmosphere are not required. The solution may be directly analyzed by CSP-GC allowing a fast and high throughput screening of reaction conditions and catalysts. Several solvents have been investigated, and toluene was selected as the best solvent, although some halogenated solvents also afforded good enantioselectivities. Of the cinchona alkaloids and some derivatives tested, $[DHQ]_2PHAL$ (eq 1) proved to be the most promising catalyst for the reaction of acetyl cyclopentanone **2a** with butyn-2-one **1a**, giving the addition product **3a** as a 2:1 mixture of *E*/*Z*-isomers with 70% ee and 40% ee for the (*E*)- and (*Z*)-enone, respectively (Table 1, entry 7). The reaction also proceeds efficiently with just 1 mol % of catalyst (entry 8). The proline derivative (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine (entry 12) effectively catalyses the reaction, but the products are obtained as racemates.

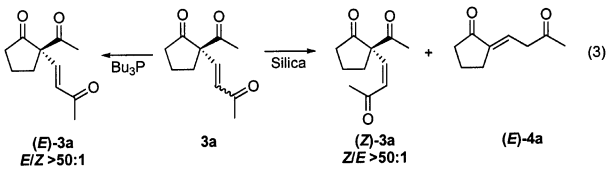
The *E*/*Z*-enones obtained are configurationally stable and may be separated by column chromatography. However, addition of a catalytic amount of Bu_3P (10 mol %) (I_2 can also be used) selectively isomerizes the *E*/*Z* mixture of **3a** to the more stable (*E*)-**3a** (eq 3). On the other hand a 1:1 mixture of the *E*/*Z*-enone of **3a** in the presence of silica gel leads to (*Z*)-**3a** in 34% isolated yield (68% based on only the (*Z*) isomer, 40% ee) while the (*E*)-enone furnishes compound (*E*)-**4a** (eq 3). As expected the configuration of the newly formed quaternary center is identical in both geometric isomers, and is not affected by the isomerization reaction.

Table 1. Screening of Catalysts for the Organocatalytic Conjugate Addition of Acetyl Cyclopentanone **2a** to Butyn-2-one **1a** in the Presence of Cinchona Alkaloids and Some Derivative[a] (5 mol %)[4]



entry	catalyst	*E*/*Z*[b]	ee (*E*) (%)[c]	ee (Z) (%)[c]
1	Et_3N	2.0:1	-	−
2	quinine	1.4:1	33	−10
3	cinchonine	1.9:1	−16	0
4	*O*-Ac-quinine	2.0:1	50	0
5	$[DHQ]_2AQN$	1.7:1	24	0
6	$[DHQ]_2PYR$	1.7:1	70	−10
7	$[DHQ]_2PHAL$	2.0:1	70	40
8	$[DHQ]_2PHAL$[d]	1.4:1	68	39
9	$[DHQ]_2PHAL$[e]	2.0:1	65	33
10	$[DHQ]_2PHAL$[f]	2.0:1	71	48
11	$[DHQD]_2PHAL$	1.1:1	−56	−20
12	*g*	1.5:1	0	0

[a] Reaction performed with 0.10 mmol of **2a** and 0.12 mmol of **1a** in 2 mL of toluene; 99% conversion in all cases after 2 h. [b] Determined by ^1H NMR. [c] Enantiomeric excess determined by GC or HPLC; the sign refers to the sign of optical rotation. [d] Catalyst loading 1 mol %. [e] Reaction temperature 45 °C. [f] 20 mL of toluene and 10 mol % catalyst. [g] Catalyst (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine.

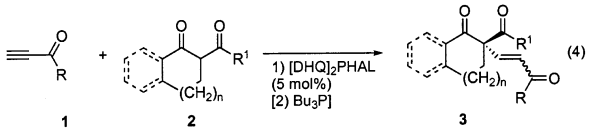


To the best of our knowledge, no report exists of any successful conjugate addition of β-diketones catalyzed by cinchona alkaloids and derivatives,[5] although the conjugate addition of β-ketoesters to activated olefins is a well-known methodology.[6] Alkynones are more active electrophiles under the present conditions compared to the alkenones; when performing the reaction in the presence of $[DHQ]_2PHAL$ or Et_3N as the catalyst with e.g. buten-2-one, no significant amounts of product were formed after 4 d, even if a stoichiometric amount of the base is added.

An increase in enantioselectivity is found when aromatic alkynones are employed. The conjugate addition of different

10.1021/ja0493594 CCC: $27.50 © 2004 American Chemical Society

Table 2. Enantioselective Conjugated Addition of Alkynones **1b**−**h** to β-Diketones **2a**−**e** Catalyzed by $[DHQ]_2PHAL$ (5 mol %)



1 2 3

ent	R		*n*,R^1	Y %[a]	*E*/*Z*[b]	ee *E*/*Z* %[b]	Y %[a]	ee (*E*) %[c]
1	Ph	**1b**	0,Me **2a**	**3b** 99	1.0:1	88/89	92	88
2	*p*-F-Ph	**1c**	0,Me **2a**	**3c** 99	1.1:1	95/88	85	91
3	*p*-Cl-Ph	**1d**	0,Me **2a**	**3d** 99	1.0:1	95/90	82	92
4	*p*-NO_2-Ph	**1e**	0,Me **2a**	**3e** 99	1:1.4	77/88	−	−
5	*p*-CF_3-Ph	**1f**	0,Me **2a**	**3f** 99	1.4:1	95/88	88	92
6	*p*-OCH_3-Ph	**1g**	0,Me **2a**	**3g** 99	1.5:1	90/70	−	−
7	*p*-F-Ph	**1c**	1,Me **2b**	**3h** 95	1.6:1	95/95	−	−
8	*p*-Cl-Ph	**1d**	1,Me **2b**	**3i** 95	1.2:1	95/95	70	95
9[d]	*p*-Cl-Ph	**1d**	Ph,0,Me **2c**	**3j** 95	1.2:1	80/82	−	−
10[d]	*p*-Cl-Ph	**1d**	Ph,0,Et **2d**	**3k** 95	1.3:1	80/85	−	−
11[d]	Ph	**1b**	Ph,1,Me **2e**	**3l** 99	1.5:1	94/88	−	−
12[d]	*p*-Cl-Ph	**1d**	Ph,1,Me **2e**	**3m** 99	1.3:1	94/88	75	92
13[d]	*p*-Cl-Ph	**1d**	Ph,1,Me **2e**	**3m** 97[e]	1.3:1	95/92	−	−
14[d]	Me	**1a**	Ph,1,Me **2e**	**3n** 97	1.8:1	84/62	−	−
15[d]	$(CH_2)_2$Ph	**1h**	Ph,1,Me **2e**	**3o** 95	1.4:1	77/44	−	−

[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] Enantiomeric excess determined by HPLC. [d] Isolated yield of (*E*)-isomer. [d] Aromatic ring present in **2**. [e] Reaction temperature −55 °C and reaction time 9 d.

β-diketones to aromatic alkynones catalyzed by $[DHQ]_2PHAL$ proceeds in high yields and enantioselectivities (eq 4). Furthermore, the isomerization of the mixture of *E*/*Z*-enones to the (*E*)-isomer can be performed in a one-pot procedure without affecting the yield or the enantioselectivity. Table 2 shows the results for the catalytic enantioselective conjugate addition of β-diketones to aromatic and aliphatic alkynones, including the results for both the first direct addition step as well as examples for the two-step, one-pot procedure providing exclusively the (*E*)-isomer.

Acetyl cyclopentanone **2a** reacts smoothly with the aromatic alkynones **1b**−**g** in the presence of $[DHQ]_2PHAL$ (5 mol %), and excellent yields of the enones **3b**−**g** are obtained (Table 2, entries 1−6). The enones are obtained as mixtures of the *E*/*Z*-isomers, and the (*E*)-enones are in most cases obtained with slightly higher ee than the (*Z*)-enones. The *p*-chloro-, *p*-fluoro-, and *p*-trifluoromethyl substituted aromatic alkynones **1c**, **1d**, and **1f**, respectively, give 95% ee for the (*E*)-enones, **3c**, **3d**, and **3f**, respectively (entries 2, 3, 5). The ee for the corresponding (*Z*)-enones is only slightly lower (entries 2, 3, 5). Other cyclic diketones such as acetyl cyclohexanone **2b**, also react with **1c**,**d** to give the corresponding enones **3h**,**i** as an *E*/*Z*-mixture in excellent yields and ee's of 95% for both isomers (entries 7, 8). Further examples of the addition of β-diketones to aromatic alkynones are given in entries 9−13. These reactions also proceed in excellent yields and with up to 94% ee of the (*Z*)-enone adduct.

The two different alkyl-substituted alkynones **1a**,**h** reacted also smoothly with β-diketones and a β-ketoester. Table 2 entries 14, 15 present the results for the reactions with the β-diketone **2e** which proceeds in high yields and up to 84% ee. The Supporting Information gives the results for various other substrates to demonstrate further the generality of this new catalytic enantioselective conjugate addition reaction.

Entries 1−3, 5, 8, and 12 of Table 2 show some examples for the one-pot procedure (eq 4) using the $[DHQ]_2PHAL$ catalyst (5 mol %) for the enantioselective addition of the β-diketones to the aromatic alkynones in the first step, followed by the use of a catalytic amount of Bu_3P (10 mol %) for the (*Z*)- to (*E*)-isomerization. The (*E*)-isomer of the addition adducts is isolated in high yields and maintains the enantiomeric excess as an average between the values obtained for the (*Z*)- and (*E*)-isomers.

The absolute configuration of the chiral quaternary carbon center formed has been assigned to be (*R*) on the basis of reduction of one of the enones to the saturated system and by comparison of the HPLC-retention times and optical rotations with a known compound (see Supporting Information).[1k]

In summary, we have developed the first catalytic enantioselective conjugate addition to alkynones. For both aromatic and aliphatic alkynones, the addition of β-diketones proceeds in high yields and good to high enantioselectivity, giving a mixture of (*E*)- and (*Z*)-enones. A one-pot procedure has been developed, furnishing exclusively the (*E*)-isomer in high yields and maintaining the enantiomeric excesses of the products. Further work is in progress to understand these additions to develop other catalytic enantioselective reactions of alkynones and to use the optically active products in future syntheses.

Acknowledgment. This work was made possible by a grant from The Danish National Research Foundation.

Supporting Information Available: Complete experimental procedures, characterization, and further results presented in a table (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) See e.g.: (a) Christoffers, J. *Chem. Eur. J.* **2003**, 9, 4862. (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (c) Sibi, M.; Manyem, P. S. *Tetrahedron* **2000**, *56*, 8033. (d) Leonard, J.; Díez-Barra, E.; Merino, S. *Eur. J. Org. Chem.* **1998**, *2051*, 1. (e) Yamamoto, Y.; Pyne, S. G.; Schinzer, D.; Feringa, B. L.; Jansen, J. F. G. A. *Methoden Org. Chem. (Houben-Weyl)* **1995**, *E21b*, 2011. (f) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771. (g) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187. (h) Christoffers, J.; Mann, A. *Angew. Chem.* **2001**, *113*, 4725, *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (i) Corey, E. J.; Guzman-Perez, A. *Angew. Chem.* **1998**, *110*, 402, *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (j) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. Most recent examples of sterocontrolled quaternary centers formation via conjugate addition: (k) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240. (l) Harada, S.; Kumagai, N.; Kinoshita, T.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2582. (m) Christoffers, J.; Baro, A. *Angew. Chem.* **2003**, *115*, 1726, *Angew. Chem., Int. Ed.* **2003**, *42*, 1688.

(2) For stoichiometric sparteine-mediated addition to alkynones see: Papillon, J. P. N.; Taylor, R. J. K. *Org. Lett.* **2002**, *4*, 119; diastereoselective addition: Guillena, G.; Najera, C. *J. Org. Chem.* **2000**, *65*, 7310.

(3) For racemic conjugate Michael additions of carbon nucleophiles to alkynones see, e.g.: (a) Hattori, K.; Grossman, R. B. *J. Org. Chem.* **2003**, *68*, 1409. (b) Michaud, D.; Hamelin, J.; Texier-Boullet, F. *Tetrahedron* **2003**, *59*, 3323. (c) Chavan, S. P.; Sharma, A. K.; Ethiraj, K. S. *Synlett* **2001**, 857. (d) Kwon, D. W.; Cho, M. S.; Kim, Y. H. *Synlett* **2001**, 627. (e) Kalita, D.; Khan, A. T.; Barua, N. C.; Bez, G. *Tetrahedron* **1999**, *55*, 5177. (f) Grossman, R. B.; Pendharkar, D. S.; Patrick, B. O. *J. Org. Chem.* **1999**, *64*, 7178. (g) Lopez, A.; Moreno-Manas, M.; Pleixats, R.; Roglans, A.; Ezquerra, J.; Pedregal, C. *Tetrahedron* **1996**, *52*, 8365. (h) Murahashi, S.-I.; Naota, T.; Taki, H.; Mizuno, M.; Takaya, H.; Komiya, S.; Mizhuho Oyasato, N.; Hiraoka, M. Hirano, M.; Fukuoka, A. *J. Am. Chem. Soc.* **1995**, *117*, 12436. For attempted catalytic asymmetric reaction see: (i) Grossman, R. B.; Comesse, S.; Rasne, R. M.; Hattori, K.; Delong, M. N. *J. Org. Chem.* **2003**, *68*, 871.

(4) Cinchona alkaloids bearing an unprotected hydroxyl functionality gave in the reaction conditions *O*-addition to alkynones. In entries 2 and 3, the active catalysts are a 2:1 *E*/*Z* mixture of 4-(*O*-cinchonin)-buten-2-one and 4-(*O*-quinin)-buten-2-one, respectively. Alkynones are known to react smoothly with hydroxy functionalities.

(5) Tae et al. recently reported a stoichiometric racemic addition of β-diketones to ethyl propyolate in 45% yield: Tae, J.; Kim, K.-O. *Tetrahedron Lett.* **2003**, *44*, 2125. For Michael conjugate addition of cyclic β-diketones see, e.g.: (a) Challenger, S.; Derrick, A.; Silk, T. V. *Synth. Commun.* **2002**, 2911. (b) Christoffers, J. *Chem. Commun.* **1997**, 943. Christoffers, J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3141. (c) Eaton, P. E.; Jobe, P. G. *Synthesis* **1983**, 796. (d) Dave, V.; Whitehurst, J. S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 393. (e) There are very limited examples in the literature of asymmetric Michael additions of β-diketones: see e.g.: Chen, Z.; Zhu, G.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Org. Chem.* **2003**, *68*, 871 and ref 1k.

(6) Kacprzak, K.; Gawronski, J. *Synthesis* **2001**, 961.

JA0493594