[7] W. Vetter, E. Scholz, C. Gaus, J. F. Müller, D. Haynes, *Arch. Environ. Toxicol. Chem.* **2001**, *41*, 221 – 231.
[8] W. Vetter, J. Hiebl, N. J. Oldham, *Environ. Sci. Technol.* **2001**, *35*, 4157 – 4162.
[9] W. Vetter, *ACS Symp. Ser.* **2001**, *773*, 243 – 259.
[10] W. Vetter, L. Alder, R. Kallenborn, M. Schlabach, *Environ. Poll.* **2000**, *110*, 401 – 409.
[11] D. J. Faulkner, *The Handbook of Environmental Chemistry*, *Vol. 1*, Part A, Springer, Berlin, **1980**, pp. 229 – 254.
[12] G. W. Gribble, D. H. Blank, J. P. Jasinski, *Chem. Commun.* **1999**, 2195 – 2196.
[13] D. Brown, D. Griffiths, M. E. Rider, R. C. Smith, *J. Chem. Soc. Perkin Trans. 1*, **1986**, 455 – 464.
[14] P. H. Daniels, J. L. Wong, J. L. Atwood, L. G. Canada, R. D. Rogers, *J. Org. Chem.* **1980**, *45*, 435 – 440.
[15] M. D. Rosa, G. C. Nieto, F. F. Gago, *J. Org. Chem.* **1989**, *54*, 5347 – 5350.
[16] S. L. Buchwald, A. Gutierrez, S. Berk, K. Kreutzer, US Patent 5220020, **1993**.
[17] COLLECT, Data Collection Software, B. V. Nonius, Netherlands, **1998**.
[18] Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, *276*, 307 – 326.
[19] G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, *46*, 467 – 473.
[20] G. M. Sheldrick, SHELXL-97 (Release 97-2), Universität Göttingen, Germany, **1997**.
[21] CCDC-173675 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

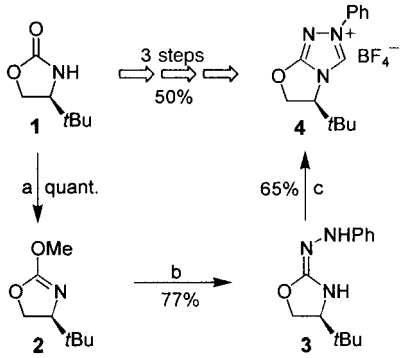
An Efficient Nucleophilic Carbene Catalyst for the Asymmetric Benzoin Condensation**

Dieter Enders* and Ulrike Kallfass

Since the early work of Ugai et al.[1] and Breslow et al.[2] it is known that thiazolium salts, such as 3-ethylthiazolium bromide or the naturally occurring thiamine (vitamin B_1), catalyze the condensation of benzaldehyde to benzoin under basic conditions. In 1966 Sheehan et al.[3–4] reported the first investigations into an asymmetric variant of the benzoin condensation by using (*S*)-4-methyl-3-(1-naphthyl)-ethylthiazolium bromide[4] as a precatalyst; the 52% *ee* obtained was remarkable for that time. In the following years, a great number of differently substituted chiral thiazolium salts were synthesized and tested in the asymmetric benzoin condensation.[5–10] However, the enantiomeric excesses hardly increased (1 – 57%).

A true breakthrough in which 1,2,4-triazolium salts[11–12] were employed was described in 1995 by our group in cooperation with Teles et al. (BASF)[13]. We reported the first efficient chiral system of this class of compounds, (4*S*,5*S*)-4-(2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-1-phenyl-4*H*-1,2,4-triazol-1-ium perchlorate, in 1996[11] (yield of benzoin 66%, 75% *ee*, 1.25 mol% cat.). These results allowed the enantioselective benzoin condensation to be extended for the first time to a variety of aromatic aldehydes (yields 22 – 72%, 20 – 86% *ee*). Later, comparable enantioselectivities were found with chiral bicyclic triazolium salts developed by Knight and Leeper (20 – 82.5% *ee*).[12]

We report herein the synthesis of a novel enantiopure bicyclic triazolium salt **4** and its application as an efficient chiral catalyst in the form of the corresponding Wanzlick carbene in the asymmetric variant of the benzoin condensation. We used a modification of the Knight and Leeper synthesis[12] for the three-step conversion of the oxazolidin-2-one **1**[14] into the triazolium salt **4**, which was isolated as a crystalline solid (Scheme 1). Methylation of **1** with Meerwein's reagent yielded iminoether **2**, which was transformed into phenylhydrazone **3**. Final cyclization with trimethylorthoformate gave **4** (50% yield over three steps). The structure of the salt **4** was confirmed by X-ray crystallographic analysis.



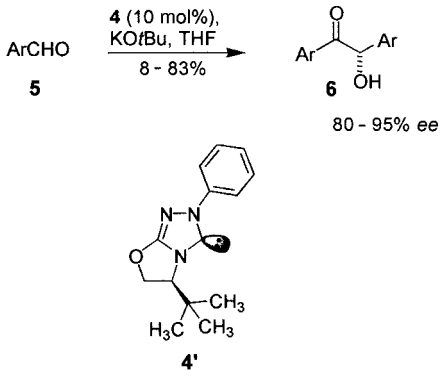
Scheme 1. Synthesis of triazolium salt **4**. a) Me_3OBF_4 (1.2 equiv), CH_2Cl_2, room temperature, 15 h; b) $PhNHNH_2$ (1 equiv), NEt_3 (1 equiv), THF, 80 °C, 7 d; c) HBF_4 (1 equiv) in diethyl ether, CH_2Cl_2, room temperature; $HC(OMe)_3$ (20 equiv), MeOH, 80 °C, 12 h.

Bicyclic chiral triazolium salt **4** (10 mol%) was used as a precatalyst in the asymmetric benzoin condensation; benzoin was obtained in very good yields (83%) and with the highest enantioselectivities ever reported (90% *ee*). The condensation of different substituted aromatic aldehydes **5** led to the corresponding α-hydroxyketones **6** in moderate to good yields and with excellent enantiomeric excesses of up to 95% (Scheme 2). The active catalyst is actually the corresponding nucleophilic Wanzlick carbene **4′**, which is formed in situ by deprotonation of **4** with KO*t*Bu in the presence of the aldehyde **5**. This nucleophilic carbene **4′** then enters the catalytic cycle of the thiazolium-catalyzed acyloin condensation, which was first proposed by Breslow more than 40 years ago.[2, 13]

After aqueous work-up and column chromatography, the acyloins **6a – j** were isolated in 6 – 100% yield and with enantiomeric excesses of 53 – 95% (Tables 1 and 2). As shown in Table 2, an increase in the amount of catalyst led to higher yields. The higher concentration of base or triazol-5-ylidene

[*] Prof. Dr. D. Enders, Dipl.-Chem. U. Kallfass
Institut für Organische Chemie, RWTH Aachen
Professor-Pirlet-Strasse 1, 52074 Aachen (Germany)
Fax: (+49) 241-8092-127
E-mail: enders@rwth-aachen.de

[**] This work was supported by the Fonds der Chemischen Industrie. We are grateful to Degussa AG, BASF AG, and Bayer AG for donations of chemicals.



Scheme 2. The asymmetric variant of the benzoin condensation, catalyzed by triazol-5-ylidene **4′**.

Table 1. Acyloins (*S*)-**6a–j**,[a] prepared by asymmetric benzoin condensation in the presence of precatalyst **4**.[b]

6	Ar	*T* [°C]	Yield [%]	*ee* [%][c]	$[\alpha]_D^{20}$[d]
a	Ph	18	83	90	+146.5
b	4-FC_6H_4	18	81	83	
b′	4-FC_6H_4	0	61	91	+117.5
c	4-ClC_6H_4	18	80	64	
c′	4-ClC_6H_4	0	44	89	+39.5
d	4-BrC_6H_4	18	82	53	
d′	4-BrC_6H_4	0	59	91	+9.6
e	3-ClC_6H_4	18	92	62	
e′	3-ClC_6H_4	0	85	86	+62.2
f	4-MeC_6H_4	18	16	93	+129.8
g	3-MeC_6H_4	18	70	86	
g′	3-MeC_6H_4	0	36	91	+138.1
h	4-$MeOC_6H_4$	18	8	95	+70.0
i	2-furyl[e]	0	100	64	
i′	2-furyl	−78	41	88	+57.4
j	2-naphthyl	18	69	80	−42.9

[a] Determined by polarimetry;[15] the absolute configurations of the products **6** were then assigned based on a uniform reaction mechanism. [b] General reaction conditions: aldehyde (10 mmol), **4** (10 mol%), KO*t*Bu (10 mol%), absolute THF (11 mL), 16 h. [c] Determined by HPLC with chiral stationary phases (Daicel AD2, Daicel OD3, (*S*,*S*)-Whelk-01). [d] $c = 1$ in MeOH. [e] Reaction time: 45 min.

Table 2. Influence of the reaction conditions on the yield and enantiomeric excess in the synthesis of benzoin (**6a**, Ar = Ph).[a]

4 [mol%]	KO*t*Bu [mol%]	Yield [%]	*ee* [%][b]
2.5	2.5	33	99
5.0	5.0	46	93
10.0	10.0	83	90

[a] General reaction conditions: aldehyde (10 mmol), absolute THF (11 mL), 18 °C, 16 h. [b] Determined by HPLC with chiral stationary phases (Daicel AD2, Daicel OD3, (*S*,*S*)-Whelk-01).

intermediate **4′**, which also has basic properties, led to a partial racemization (Table 2).

Generally, electron-rich aromatic aldehydes **6f–h** showed better asymmetric induction at room temperature than electron-deficient and therefore activated aromatic aldehydes **6b–e**. Nevertheless, the +I/+M substituents in the *para* position led to a distinct decrease in the TTN (total turnover number) of catalyst **4′** (see **6f**,**h**). To enhance the asymmetric induction for activated aldehydes, they were allowed to react at 0 °C (**6b′–e′**). When the highly reactive furane-2-carbaldehyde was employed, the reaction mixture was cooled to −78 °C; furoin (**6i′**) was isolated with a very good enantiomeric excess of 88%.

The enantiomeric excesses were determined by HPLC with chiral stationary phases. The absolute configuration of benzoin (**6a**) was found to be *S* by correlation of the optical rotation with that reported in the literature.[15] The absolute configurations of the acyloins **6** were then assigned as *S*, assuming a uniform reaction mechanism. The absolute configuration of the resulting acyloins can be explained by the relative topicity shown in Figure 1. The *tert*-butyl group

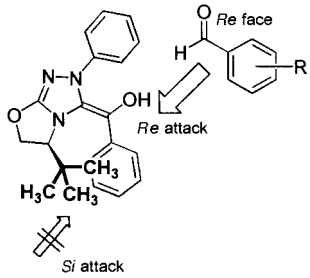


Figure 1. Postulated transition-state model (Breslow intermediate) to explain the facial selectivity in the asymmetric benzoin condensation in the presence of precatalyst **4**.

shields the *Si* face of the Breslow intermediate, which is formed during the catalytic cycle.[2] Therefore the attack of the incoming second aldehyde molecule occurs from the less-hindered *Re* face. Furthermore, the phenyl substituent on the N atom causes a preorientation of the attacking second aldehyde. It favorably approaches the Breslow intermediate with its *Re* face, thus leading to an *S* configuration at the newly formed stereogenic center.

The triazolium salt **4** is currently the most efficient precatalyst for the asymmetric variant of the benzoin condensation. The acyloins are obtained throughout in moderate to good yields and with very good enantiomeric excesses. The high asymmetric inductions are a result of the conformational rigidity of the bicyclic nucleophilic carbene catalyst **4′** and the shielding of the Breslow intermediate by the sterically demanding *tert*-butyl group.

Experimental Section

Synthesis of **2**: A dry, argon-flushed Schlenk tube was charged with a suspension of trimethyloxonium tetrafluoroborate (1.2 equiv) absolute dichloromethane (3 mL mmol^{-1}). A solution of **1** (1 equiv) in absolute dichloromethane (3 mL mmol^{-1}) was added, and the mixture was stirred for 15 h at room temperature. The mixture was then diluted with dichloromethane and washed with ice-cold saturated aqueous sodium hydrogen carbonate (3 × 3 mL per mmol^{-1} of oxazolidinone). The solution was dried over anhydrous magnesium sulfate and concentrated in vacuo to afford **2** as a colorless liquid in quantitative yield. The product was used in the next step without further purification.

Synthesis of **3**: A dry, argon-flushed Schlenk tube equipped with a reflux condenser was charged with iminoether **2** in absolute THF (1.5 mL mmol^{-1}) and with phenylhydrazine (1 equiv). Triethylamine (1 equiv) was then added, and the reaction mixture was heated at 80 °C for 7 d. The solution was cooled to room temperature and concentrated in vacuo. The crude product was purified by washing it several times with petroleum ether/diethyl ether (4:1, 5 mL mmol^{-1}). After drying under high vacuum, **3** was obtained as a pink solid in 77% yield.

  1433-7851/02/4110-1744 $ 20.00+.50/0 *Angew. Chem. Int. Ed.* **2002**, *41*, No. 10

Synthesis of **4**: A dry, argon-flushed Schlenk tube was charged with phenylhydrazone **3** (1.0 equiv) in absolute dichloromethane (10 mL mmol^{-1}) and with tetrafluoroboronic acid (1 equiv) in absolute diethyl ether (54 wt %). The solution was stirred for 30 minutes at room temperature, and then evaporated under reduced pressure. The highly hygroscopic salt was dissolved in orthoformate:methanol (2:1, 20 equiv) and transferred under argon into a pyrex tube; the sealed tube was then heated in a sand bath at 80 °C for 12 h. The mixture was cooled to room temperature and concentrated in vacuo. The crude product was dried under high vacuum for 2 h. The residue was recrystallized from methanol to give the triazolium salt **4** as an ochre crystalline solid in 65 % yield.

Synthesis of **6** (general procedure): The aromatic aldehyde (10 mmol) was added to a solution of **4** (331 mg, 1 mmol, 10 mol %) in absolute THF (0.7 mL mmol^{-1}) of at room temperature. The reaction mixture was tempered for 5 min, then KO*t*Bu (112 mg, 1 mmol, 10 mol %) in absolute THF (0.4 mL mmol^{-1}) was added dropwise. The reaction mixture was stirred for 16 h, poured into water, extracted twice with dichloromethane, and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (silica gel, diethyl ether:pentane 1:1) or by crystallization to give the aromatic acyloins as colorless crystalline solids or pale yellow oils.

Received: December 5, 2001 [Z18335]

[1] T. Ugai, S. Tanaka, S. Dokawa, *J. Pharm. Soc. Jpn.* **1943**, *63*, 269 – 300; [*Chem. Abstr.* **1951**, *45*, 5148e].
[2] a) R. Breslow, *J. Am. Chem. Soc.* **1958**, *80*, 3719 – 3726; b) R. Breslow, R. Kim, *Tetrahedron Lett.* **1994**, *35*, 699 – 702.
[3] J. Sheehan, D. H. Hunneman, *J. Am. Chem. Soc.* **1966**, *88*, 3666 – 3667.
[4] J. Sheehan, T. Hara, *J. Org. Chem.* **1974**, *39*, 1196 – 1199.
[5] W. Tagaki, Y. Tamura, Y. Yano, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 478 – 480.
[6] C. Zhao, S. Chen, P. Wu, Z. Wen, *Huaxue Xuebao* **1988**, *46*, 784 – 790.
[7] J. Marti, J. Castells, F. López-Calahorra, *Tetrahedron Lett.* **1993**, *34*, 521 – 524.
[8] R. L. Knight, F. J. Leeper, *Tetrahedron Lett.* **1997**, *38*, 3611 – 3614.
[9] A. U. Gerhard, F. J. Leeper, *Tetrahedron Lett.* **1997**, *38*, 3615 – 3618.
[10] C. A. Dvorak, V. H. Rawal, *Tetrahedron Lett.* **1998**, *39*, 2925 – 2928.
[11] a) D. Enders, K. Breuer, J. H. Teles, *Helv. Chim. Acta* **1996**, *79*, 1217 – 1221; b) D. Enders, K. Breuer, *Comprehensive Asymmetric Catalysis*, *Vol. 3*, Springer, Heidelberg, **1999**, pp. 1093 – 1102.
[12] R. L. Knight, F. J. Leeper, *J. Chem. Soc. Perkin. Trans. 1* **1998**, 1891 – 1893.
[13] a) D. Enders, K. Breuer, G. Raabe, J. Runsink, J. H. Teles, J.-P. Melder, K. Ebel, S. Brode, *Angew. Chem.* **1995**, *107*, 1119 – 1122; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1021 – 1024; b) J. H. Teles, J.-P. Melder, K. Ebel, R. Schneider, E. Gehrer, W. Harder, S. Brode, D. Enders, K. Breuer, G. Raabe, *Helv. Chim. Acta* **1996**, *79*, 61 – 83.
[14] For the synthesis from L-*tert*-leucine by reduction (a) and cyclization (b), see: a) D. A. Dickman, A. I. Meyers, G. A. Smith, R. E. Ganley, *Org. Synth.* **1990**, *Coll. Vol. 7*, 530 – 533; b) M. S. Newman, A. Kutner, *J. Am. Chem. Soc.* **1951**, *73*, 4199 – 4204.
[15] H. G. Rule, J. Crawford, *J. Chem. Soc.* **1937**, 138 – 145.

New Catalyst Systems for the Catalytic Conversion of Methane into Methanol**

Michael Muehlhofer, Thomas Strassner,* and Wolfgang A. Herrmann

The catalytic conversion of methane into methanol is one of the major challanges for chemists. Methane, as the major part of natural gas, is currently the cheapest source for hydrocarbons, and the need for methanol will increase in the near future. Catalytic homogeneous oxidation at low temperatures is economically interesting, but also very difficult to achieve as a result of the high stability of C–H bonds. Metal centers which allow a direct oxidative addition are probably needed for this approach to succeed.

Palladium and platinum compounds have been successfully used for the functionalization of alkanes and arenes.[1, 2] After the pioneering work of Shilov and Shteinman,[3] Periana et al.[2] and Fujiwara et al.,[1] in particular, reported interesting results. Some of the ligands which have been used in C–H activation are shown in Figure 1.

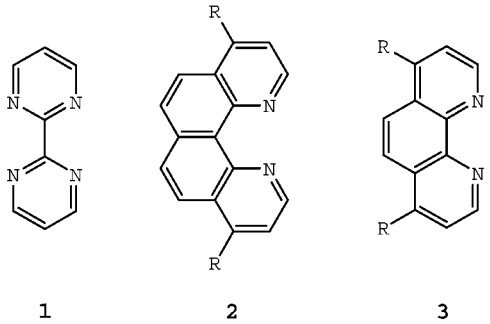


Figure 1. Ligands which have been successfully used in C–H activation reactions.

Up to now the catalytic system described by Periana and coworkers, a platinum complex with the bipyrimidine ligand **1**, has proven to be the most efficient and highly selective system providing methanol in yields of up to 72 %.[4] The major drawback of the system is the reaction medium: oleum leads to a large amount of diluted sulfuric acid when the formed ester is hydrolized. Very recently an even higher activity was reported for palladium and platinum complexes of ligand **3**.[5] This structural motif can also be found in other ligands, such as **2**, which are derived from 1,10-phenanthroline (Figure 1).[6] In general, however, only a small number of systems which are capable of functionalizing methane catalytically has been

[*] Dr. T. Strassner, M. Muehlhofer, Prof. Dr. W. A. Herrmann
Technische Universität München
Anorganisch-chemisches Institut
Lichtenbergstrasse 4, 85747 Garching (Germany)
Fax: (+49) 89-289-13473
E-mail: thomas.strassner@ch.tum.de

[**] C–H activation by N-heterocyclic carbenes, Part 1. This work was supported by Süd-Chemie AG.

Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

  1433-7851/02/4110-1745 $ 20.00+.50/0