

Asymmetric Organocatalytic Diels–Alder Reactions on Solid Support

Sami A. Selkälä, Jan Tois, Petri M. Pihko,* Ari M. P. Koskinen

Laboratory of Organic Chemistry, Department of Chemical Technology, Helsinki University of Technology, FIN-02015 HUT, Finland

Fax: (+358)-9-451-2538, e-mail: Petri.Pihko@hut.fi

Received: May 20, 2002; Accepted: July 1, 2002

Abstract: Asymmetric organocatalysis on solid support combines the environmental advantages of metal-free catalysts and the ease of operation of solid-supported reagents. Enantioselective organocatalytic Diels–Alder reactions have been demonstrated by two different solid-supported chiral organocatalysts. The catalysts are easy to recover and they can be reused. The reactivity of the catalyst can be tuned by changing the solid support.

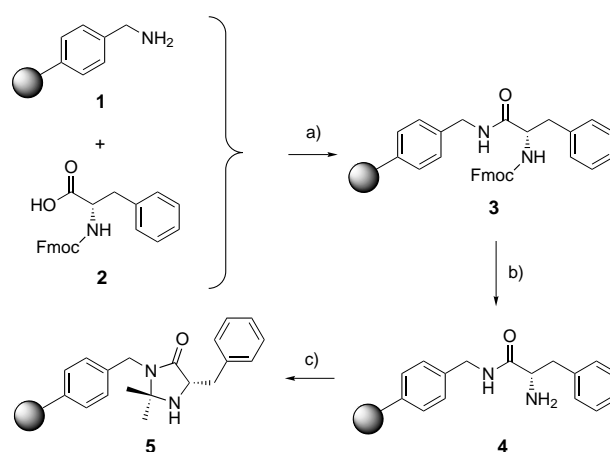
Keywords: asymmetric catalysis; cycloaddition; organocatalysis; solid-phase catalysis

Organocatalytic methods hold considerable promise among novel catalytic asymmetric processes owing to their potential advantages over metal-catalyzed processes: 1) no expensive metals are required to start with, 2) there is no risk of metal leakage into the environment (or the product) and 3) the active catalysts are often easier to study and modify. In addition, effective organocatalysts are very often easily accessible, simple, stable molecules (amino acids, sugar derivatives, peptides or peptidomimetics).^[1] Unlike typical metal-catalyzed asymmetric processes, organocatalytic reactions can often be performed in wet solvents and in an aerobic atmosphere. The first examples of asymmetric organocatalysis date back to the proline-catalyzed Hajos–Parrish reaction^[2a, b] from the 1970's and the cinchona-derived organocatalysts^[2c] from the 1980's. In recent years, proline catalysis has expanded rapidly to cover asymmetric aldol,^[3a] Mannich,^[3b] Michael^[3c], Diels–Alder^[3d] and α -amination^[3e, f] reactions. MacMillan and coworkers,^[4] in turn, have demonstrated the utility of chiral imidazolidinones in asymmetric catalytic reactions, such as the Diels–Alder reaction,^[4a, b] 1,3-dipolar cycloaddition,^[4c] Friedel–Crafts alkylation,^[4d] and indole alkylation.^[4e] We envisaged that the advantages of organocatalysis would be best exploited by immobilizing the catalysts on a solid support. In this paper, we present the synthesis of two easily recyclable immobilized organocatalysts and show that they are

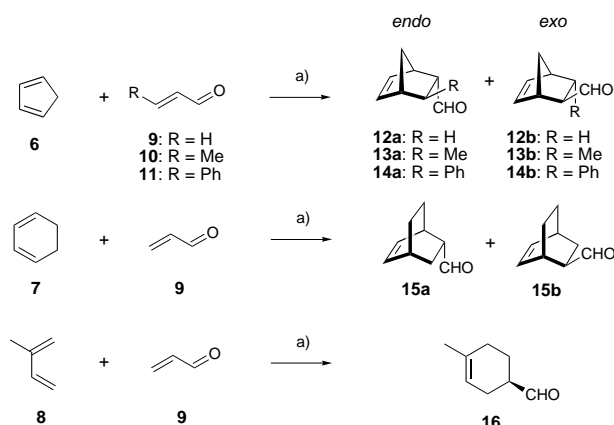
highly effective in catalytic asymmetric Diels–Alder reactions, affording cycloadducts in up to 99% ee.^[5,6]

We began with the synthesis of the polymer-supported catalyst **5** (Scheme 1). JandaJelTM-NH₂ (**1**)^[7] was chosen as the solid support due to its compatibility with a wide variety of solvents. Commercially available *N*-Fmoc-protected (*S*)-phenylalanine **2** was used for the amide **3** formation.^[8] The formed *N*-Fmoc-amide **3** was deprotected with 20 wt % piperidine in DMF.^[9] The final catalyst **5** was prepared from the resin bound α -amino amide **4** by cyclization with 50% acetone in DMF. The product resin **5** was analyzed by Kaiser and chloranil tests.^[8]

We then examined the capacity of our polymer-supported chiral amine catalyst **5** to effect enantioselective Diels–Alder cycloadditions between three different dienes **6**–**8** and three α,β -unsaturated aldehydes **9**–**11** (Scheme 2). Cyclopentadiene **6** as the diene component was found to give the best yields (60–73%) with the α,β -unsaturated aldehydes **9**–**11** tested (Table 1, Entries 1, 3, and 5). Excellent levels of enantioselectivity (83–99% ee) were observed in these



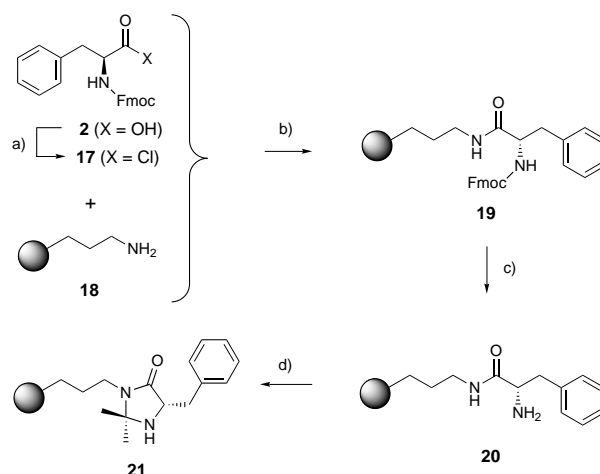
Scheme 1. Preparation of the JandaJelTM-supported organocatalyst **5**. Reagents and conditions: a) HOBt, CH₂Cl₂, DIC, 2.5 h, r.t.; b) 20% piperidine/DMF, 50 min, r.t.; c) 50% acetone/DMF, 20 h, 80 °C. (HOBt = 1-hydroxybenzotriazole hydrate, DIC = diisopropylcarbodiimide).



Scheme 2. Diels–Alder reactions catalyzed by solid-supported organocatalysts between dienes **6**–**8** and dienophiles **9**–**11**. Reagents and conditions: a) 3.3–20 mol % **5** or **21**, CH₃CN,^[14] (3.3–20 mol %) 0.1–0.4 M aqueous solution of HCl. Ratio of solvent/aq. HCl: 16–8:1.

reactions, equaling or even surpassing those obtained with the corresponding solution phase catalysts.^[4a]

As anticipated, catalyst **5** turned out to be easily recoverable. The recycled catalyst could readily be reused: after filtration of the reaction mixture to recover the catalyst, the catalyst was simply treated with a mixture of α,β -unsaturated aldehyde, diene and the solvent/water mixture to set up another reaction. Addition of acid was not necessary when the recycled catalyst was used. The *endo:exo* selectivities, enantioselectivities, yields and reaction rates generally remained at similar levels (entries 2, 4, 6 in Table 1 represent experiments with the recovered catalyst). We also found that 5–10 mol % of the catalyst **5** was enough to mediate the cycloaddition (entries 2–5, 6 and 8).



Scheme 3. Preparation of the silica-supported organocatalyst **21**. Reagents and conditions: a) SOCl₂, CH₂Cl₂, 2 h, r.t., (80%); b) 3 equiv. **17**, 3 equiv. DIPEA, 1 equiv. **18**, CH₂Cl₂, r.t.; c) 20% piperidine/DMF, 60 min, r.t.; d) 50% acetone/DMF, 20 h, 80 °C. (DIPEA = *N,N*-diisopropylethylamine).

Probing the scope of the reaction components revealed that with cyclohexa-1,3-diene **7** and isoprene **8**, only acrolein **9** was found to afford isolable yields of the cycloaddition products (entries 7 and 8). No reaction was observed with crotonaldehyde **10** and cinnamaldehyde **11** when combined with cyclohexa-1,3-diene **7** and isoprene **8** in the presence of the catalyst **5**. We reasoned that the highly polar transition state of the reaction and the iminium ion intermediates^[4a] would be better stabilized by a more polar solid support environment, such as silica gel.

Accordingly, as our second catalyst, we prepared the silica-supported^[11] chiral imidazolidinone catalyst **21**

Table 1. Enantioselective Diels–Alder cycloadditions catalyzed by JandaJel™-bound amine catalyst **5**.

Entry	Diene	Aldehyde	Catalyst [mol %] ^[a]	t [h]	<i>endo</i> ^[a] [% ee]	<i>exo</i> ^[b] [% ee]	Yield [%] ^[c]
1	6	9	20	24	5.1 (89)	1 (83)	73
2	6	9	10 ^[d]	24	4.9 (75)	1 (75)	68
3	6	10	10	24	1.2 (91)	1 (89)	60
4	6	10	10 ^[d]	24	1.2 (88)	1 (87)	58
5	6	11	20	24	1 (99)	1.2 (99)	70
6	6	11	10 ^[d]	24	1 (97)	1.2 (95)	65
7	7	9	20	25	13 (98)	1	30
8	8	9	5	32	(70)	–	24

^[a] Calculated based on the amine loading (mmol/g) of the supported catalyst. The loading is based on the original nitrogen loading of the support but a correction has been made for the mass gain of the catalyst during its preparation.

^[b] *endo:exo* ratios were determined by ¹H NMR from the aldehyde product mixture. For determination of the ee values, the aldehyde products were first reduced to alcohols with excess NaBH₄ in EtOH, and the resulting alcohols were analyzed by GLC using Supelco γ -DEX™ 120 column. Absolute and relative configurations were assigned by chemical correlation to compounds obtained by known solution phase methods^[4a,10] or by analogy.

^[c] Yields of isolated, purified aldehydes.

^[d] Reaction was performed with catalyst recovered from previous run.

(Scheme 3). Starting from *N*-Fmoc-protected (*S*)-phenylalanine **2**, coupling with *n*-propylamine-functionalized silica gel **18**^[12] was achieved *via* the acid chloride **17**.^[13] The resulting amide **19**^[8] was deprotected (20% piperidine/DMF) and the final catalyst **21** was prepared from the silica bound α -amino amide **20** by cyclization with 50% acetone in DMF. The product **21** was analyzed by Kaiser and chloranil tests.^[8]

The silica gel-supported chiral amine **21** turned out to be a highly active catalyst for enantioselective Diels–Alder cycloadditions. For comparison with the polymer-bound catalyst **5**, the same set of reactions between dienes **6** – **8** and α,β -unsaturated aldehydes **9** – **11** (Scheme 2) was employed. The catalyst was effective in amounts as low as 3.3 mol % (entries 1–3, Table 2). Significantly, the enantioselectivities remained generally on a high level (90–91% ee, entries 1, 3–5) with catalyst **21**. However, reaction of cyclopentadiene **6** with crotonaldehyde **10** gave only moderate ee (52% ee, *endo* isomer) (entry 2). The *endo:exo* selectivities with **21** were slightly higher those obtained with catalyst **5**. Catalyst **21** could also be readily recovered by filtration (see the Experimental Section).

The reactivity of the silica-bound catalyst **21**, however, differed considerably from the polymer-bound catalyst **5**. Most significantly, **21** was highly effective in the cycloaddition between cyclohexa-1,3-diene **7** or isoprene **8** and acrolein **9** (79–83% yield; Table 2, entries 4 and 5), contrasting favorably with catalyst **5**. With cyclopentadiene **6** as the diene component, acrolein **9** (entry 1) afforded a better yield (73%) of the cycloadduct than did crotonaldehyde **10** or cinnamaldehyde **11** (33–41% yield, entries 2 and 3).

The ease with which these solid-supported organocatalytic Diels–Alder reactions can be performed, and the fact that the reactivity of these organocatalysts appears to be quite sensitive to the nature of the solid support, makes these types of catalysts highly amenable to both high-throughput screening and large-scale process development. It should also be noted that all Diels–Alder cycloadditions performed in this study were conducted at room temperature with wet solvents.

In conclusion, we have synthesized polymer- and silica-supported chiral imidazolidinone catalysts **5** and

21, and demonstrated their effectiveness in catalytic enantioselective Diels–Alder reactions. Furthermore, the reactivity of the catalysts can readily be tailored by changing the support medium. The solid-supported organocatalysts are easily recovered by filtration and the catalyst can be directly reused. Further studies to define and expand the scope of support-tailored organocatalysts are in progress, and a full account of this study is forthcoming.

Experimental Section

Preparation of Catalyst 5

Fmoc-Phe-OH **2** (400 mg, 1.03 mmol, 500 mol %) and 1-hydroxybenzotriazole hydrate (141 mg, 1.03 mmol, 500 mol %) were dissolved in CH₂Cl₂ (4 mL) and DMF (1 mL). Diisopropylcarbodiimide (131 mg, 1.03 mmol, 500 mol %) was dissolved in DMF (1 mL) and added into the reaction mixture. The resulting mixture was stirred for 10 minutes, and then transferred to a flask containing JandaJel™-NH₂ **1** (1 mmol N/g; 206 mg, 0.21 mmol, 100 mol %) and CH₂Cl₂ (4 mL). The stirring was continued for 2.5 hours at room temperature and the product resin **3** was filtered, washed with CH₂Cl₂ (4 × 5 mL), DMF (4 × 4 mL), MeOH (2 × 4 mL) and THF (3 × 2 mL). The whitish product resin **3** was subjected to the Kaiser test^[8a] and the result was negative (yellowish beads).

The JandaJel bound amide **3** was treated with 20% piperidine in DMF (4 mL) and the stirring was continued at r.t. for 50 min. The resulting resin **4** was washed with DMF (4 × 4 mL), MeOH (2 × 4 mL) and THF (3 × 2 mL) and dried in vacuum to give 365 mg of yellowish resin. The product resin **4** was subjected to the Kaiser test^[8a] and the result was positive (blue beads).

The JandaJel bound α -amino amide **4** (365 mg) was treated with DMF (2.5 mL) and acetone (2.5 mL). The mixture was stirred under argon atmosphere at 85–90 °C (bath temperature) for 15.5 h. After this time, more acetone (1 mL) and DMF (1 mL) were added. The stirring was continued at 85–90 °C for 4.5 h. The reaction mixture was allowed to cool to r.t. and the resulting resin **5** was washed with DMF (4 × 4 mL), MeOH (2 × 4 mL) and THF (3 × 2 mL). The product resin **5** was dried in vacuum to give 273 mg of yellowish resin. Catalyst **5** was subjected to the Kaiser test^[8a] and the result was negative

Table 2. Enantioselective Diels–Alder cycloadditions catalyzed by silica-supported amine catalyst **21**.

Entry	Diene	Aldehyde	Catalyst [mol %] ^[a]	t [h]	<i>endo</i> ^[b] [% ee]	<i>exo</i> ^[b] [% ee]	Yield [%] ^[c]
1	6	9	3.3	24	6.6 (91)	1 (-)	73
2	6	10	3.3	25	2 (52)	1 (6)	41
3	6	11	3.3	64	1.1 (90)	1 (90)	33
4	7	9	20	24	14 (90)	1	83
5	8	9	20	24	(90)	–	79

^[a] Calculated as described in Table 1.

^[b] The *endo:exo* selectivities and the ee values were determined as described in Table 1.

^[c] Yields of isolated, purified aldehydes.

(brownish beads). The resin **5** was also subjected to the chloranil test^[8b] and the result was positive (blue beads).

Preparation of Catalyst **21**

A mixture of *n*-propylamino-functionalized silica gel **18** (0.53 mmol N/g; 400 mg, 0.21 mmol, 100 mol %) and Fmoc-Phe-Cl **17**^[13] (260 mg, 0.64 mmol, 305 mol %) was treated with CH₂Cl₂ (5 mL). *N,N*-Diisopropylethylamine (82 mg, 0.63 mmol, 298 mol %) was added to the stirred mixture and the stirring was continued at room temperature for 3 days. The resulting resin **19** was washed with CH₂Cl₂ (3 × 3 mL), DMF (3 × 3 mL) and MeOH (3 × 3 mL). The product **19** was dried in vacuum to give 468 mg of white resin. The resulting amide **19** was subjected to the chloranil test^[8b] and the result was positive (blue beads).

Silica bound amide **19** (448 mg) was treated with 20% piperidine in DMF (4 mL) and the stirring was continued at room temperature for 60 minutes. The resulting resin **20** was washed with DMF (3 × 4 mL), MeOH (3 × 4 mL) and THF (3 × 3 mL), affording a mass balance of 636 mg of whitish resin. The product resin **20** was subjected to the Kaiser test^[8a] and the result was positive (blue beads).

The silica bound α -amino amide **20** (605 mg) was treated with DMF (2 mL) and acetone (2 mL). The mixture was stirred under argon atmosphere at 80–85 °C for 18 hours. After this, a second portion of acetone (1 mL) and DMF (1 mL) was added. The stirring was continued at 80–85 °C for 2 h. The reaction mixture was allowed to cool to room temperature and the resulting resin **21** was washed with DMF (3 × 3 mL), MeOH (3 × 3 mL) and THF (3 × 3 mL). The product resin **21** was dried in a vacuum to give 397 mg of yellowish resin. Catalyst **21** was subjected to the Kaiser test^[8a] and the result was negative (brownish beads). Catalyst **21** was also subjected to the chloranil test^[8b] and the result was positive (blue beads).

Typical Procedure for the Diels–Alder Cycloaddition (Table 2, entry 5)

The silica-supported catalyst **21** (53 mg, 0.1 mmol, 20 mol %) was treated with CH₃CN (2 mL) and 0.4 M aqueous solution of HCl (0.25 mL). The mixture was stirred for 2 minutes and acrolein **9** (100 μ L, 1.5 mmol, 300 mol %) was added. The resulting mixture was stirred for 2 minutes and cyclohexa-1,3-diene **7** (50 μ L, 0.5 mmol, 100 mol %) was added. The resulting mixture was stirred 24 hours at room temperature in a sealed vial. The catalyst **21** was filtered off and the filtrate was concentrated to a volume of 0.5 mL. The crude product was purified by flash chromatography (silica gel, 5% ether/pentane) to give the product as colorless oil; yield: 56 mg (83%); 90% ee. Analytical data of the product matched those reported in the literature.^[10] The enantiomeric excess was determined as follows: A small portion of the aldehyde product mixture was diluted with EtOH (1 mL) and excess NaBH₄ was added. The resulting mixture was stirred for 1 h and 5 wt % aqueous citric acid (1 mL) was added to quench the reaction. The reaction mixture was extracted with Et₂O (3 × 3 mL) and the organics were washed with brine (3 mL). The combined organics were dried (MgSO₄), filtered through a 2 cm pad of silica and concentrated to give the pure alcohols. The ee was

determined by GLC [Supelco γ -DEXTM 120 column (30 m × 0.25 mm, 0.25 μ m film), He carrier gas, velocity 28 cm/sec, FID detection (300 °C)]; for the (*R*)-*endo*-cycloadduct *t*_r 10.3 min and for the (*S*)-*endo*-cycloadduct *t*_r 10.7 min.

Acknowledgements

Financial support has been provided by the Neste Foundation and the National Technology Agency (TEKES). We also thank Prof. Kyösti Kontturi (HUT) for GC time.

References and Notes

- [1] For recent reviews on organocatalytic reactions, see: a) P. I. Dalko, L. Moisan, *Angew. Chem., Int. Ed.* **2001**, *40*, 3726; *Angew. Chem.* **2001**, *113*, 3840; b) B. List, *Synlett* **2001**, 1675; for a review of peptides and peptidomimetics as organocatalysts, see: c) E. R. Jarvo, S. J. Miller, *Tetrahedron* **2002**, *58*, 2481.
- [2] a) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496; b) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615; c) H. Hiemstra, H. Wynberg, *J. Am. Chem. Soc.* **1981**, *103*, 417.
- [3] a) B. List, R. A. Lerner, C. F. Barbas, III, *J. Am. Chem. Soc.* **2000**, *122*, 2395; b) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas, III, *J. Am. Chem. Soc.* **2001**, *123*, 5260; c) J. M. Betancort, K. Sakthivel, R. Thayumanavan, C. F. Barbas, III, *Tetrahedron Lett.* **2001**, *42*, 4441; d) R. Thayumanavan, B. Dhevalapally, K. Sakthivel, F. Tanaka, C. F. Barbas, III, *Tetrahedron Lett.* **2002**, *43*, 3817; e) B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656; f) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jørgensen, *Angew. Chem., Int. Ed.* **2002**, *41*, 1790; *Angew. Chem.* **2002**, *114*, 1868.
- [4] a) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243; b) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 2458; c) W. S. Jen, J. J. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874; d) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370; e) J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172.
- [5] Independently from us, the Cozzi group recently disclosed a *homogeneous* polymer-supported imidazolidinone catalyst for the enantioselective Diels–Alder reaction: M. Benaglia, G. Celentano, M. Cinquini, A. Puglisi, F. Cozzi, *Adv. Synth. Catal.* **2002**, *344*, 149.
- [6] For recent reviews of enantioselective Diels–Alder reactions and their applications in total synthesis, see: a) E. J. Corey, *Angew. Chem., Int. Ed.* **2002**, *41*, 1650; *Angew. Chem.* **2002**, *114*, 1724; b) K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem., Int. Ed.* **2002**, *41*, 1668; *Angew. Chem.* **2002**, *114*, 1742; b) Y. Hayashi, in *Cycloaddition Reactions in Organic Synthesis*, (Eds.: S. Kobayashi, K. A. Jørgensen), Wiley-VCH, Weinheim, **2001**, pp. 5–56.

- [7] Available from Aldrich. See also: P. H. Toy, K. D. Janda, *Tetrahedron Lett.* **1999**, 40, 6329.
- [8] We used the Kaiser^[8a] and chloranil^[8b] tests to detect the presence of primary and secondary free amines, respectively, for the purposes of monitoring the reactions on solid support. See: a) E. Kaiser, R. L. Colescott, C. D. Bossinger, P. I. Cook, *Anal. Biochem.* **1970**, 34, 595 (Kaiser test); b) T. Vojkovsky, *Pept. Res.* **1995**, 8, 236 (chloranil test).
- [9] J. D. Fontenot, J. M. Ball, J. M. Miller, C. M. David, R. C. Montelaro, *Pept. Res.* **1991**, 4, 19.
- [10] K. Ishihara, K. Kurihara, M. Matsumoto, H. Yamamoto, *J. Am. Chem. Soc.* **1998**, 120, 6920.
- [11] For examples of a silica-supported organocatalyst, see: K.-i. Shimizu, H. Suzuki, E. Hayashi, T. Kodama, Y. Tsuchiya, H. Hagiwara, Y. Kitayama, *Chem. Commun.* **2002**, 1068 and references cited therein.
- [12] The *n*-propylamine loading was 0.53 mmol/g in the silica gel used.
- [13] L. A. Carpino, B. J. Cohen, K. E. Stephens, Jr, S. Y. Sadat-Aalae, J.-H. Tien, D. C. Langridge, *J. Org. Chem.* **1986**, 51, 3732; M. Beyermann, M. Bienert, H. Niedrich, *J. Org. Chem.* **1986**, 51, 721.
- [14] MeOH was also used successfully as the solvent with the catalyst **5**. In this case, however, the product aldehydes were converted into their corresponding dimethyl acetals.