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Efficient, Enantioselective Iminium Catalysis with an Immobilized, Recyclable Diarylprolinol Silyl Ether Catalyst

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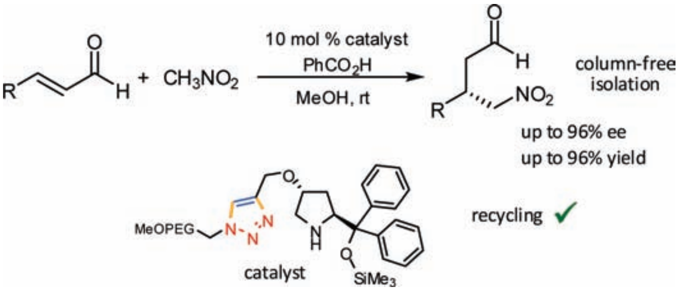
ABSTRACT



A highly efficient approach for the synthesis, application, and recycling of immobilized diarylprolinol silyl ethers was developed. The MeOPEG-supported Jørgensen−Hayashi catalyst provides unchanged reactivity and selectivity as compared to the homogeneous catalyst, as demonstrated for the Michael addition of nitromethane to α,*β*-unsaturated aldehydes via iminium activation. In addition, the immobilization allows for a simple, column-free isolation of pure, sensitive aldehyde products and therefore may be useful for application in more complicated syntheses.

Starting from a few unusual transformations showing non-traditional reactivities, organocatalysis has emerged as an inspiring area of general concepts during the past decade and is now appreciated as the third branch of enantioselective catalysis that complements the fields of enzyme and (organo)metal catalysis.[1] In particular, catalysis of transformations with secondary amines (aminocatalysis) can be considered as one of the most applicable methods in terms of reaction diversity and due to the versatility of the different activation modes (enamine, iminium, dienamine, SOMO catalysis as well as their combinations in multiple domino processes).[2] Among the multitude of known amine-based catalysts, α,α-diarylprolinol derivatives inter alia have proven to be privileged catalysts.[3] High catalyst loadings, however, as well as complicated purification processes due to the similarity of catalyst and (often sensitive) products are major drawbacks.

Catalyst immobilization[4,5] may offer a solution to these problems in facilitating both product separation as well as catalyst recovery and reuse, and hence can contribute to more efficient chemical syntheses. Despite these options and the increasing number of applications[6] due to the versatility of the Jørgensen−Hayashi catalyst **1**, only a few approaches

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(1) (a) Special issue on organocatalysis : *Chem. Rev.* **2007**, *107* (12), 5413−5883. (b) *Asymmetric Organocatalysis*; List, B., Ed.;Top. Curr. Chem. 291; Springer: Berlin, 2010. (c) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, 2005. (d) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638.

(2) For recent reviews, see: (a) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (b) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (c) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037.

(3) (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4284. For a comprehensive review, see: (c) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3*, 922.

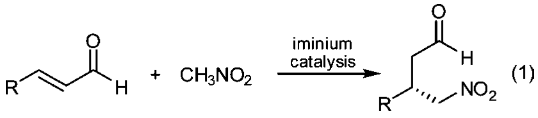
10.1021/ol100166z

for its immobilization have been described,[7] while most recycling attempts implied complications that are often attributed to desilylation processes.

1 $R^1 = SiMe_3$
2 $R^1 = H$
3 $R^2 = SiMe_3$
4 $R^2 = CH_3$

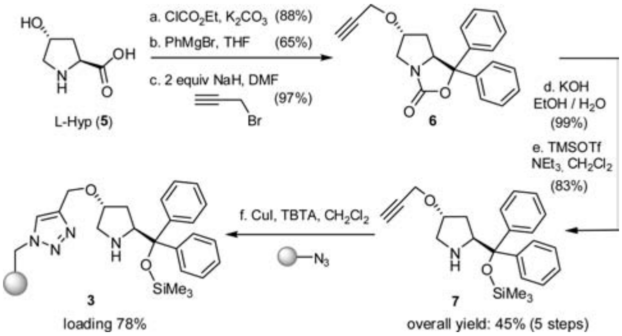
Herein, we report the design of a soluble-polymer supported diarylprolinol silyl ether catalyst and its successful application and recycling for the iminium-catalyzed enantioselective synthesis of γ-nitroaldehydes (Scheme 1).

Scheme 1. Iminium-Catalyzed Enantioselective Synthesis of γ-Nitroaldehydes



With respect to the crucial prerequisite of retaining activity and selectivity upon immobilization and the hereby often inherently associated limitations of insoluble polymer catalysts, soluble supports provide a useful blend between the advantages of both heterogeneous and homogeneous catalysis.[8] They allow for highly simplified workup procedures, e.g., via polarity-triggered precipitation and filtration, but also provide improved transferability of established homogeneous reaction conditions minimizing additional optimization studies. Based on our experience in the preparation of MeOPEG-supported carbene-catalysts via regioselective, Cu-catalyzed [3 + 2]-cycloaddition to create a stable 1,2,3-triazole linkage,[9c] we extended our efforts toward the application of this well-established atom-economic immobilization approach[9] for the synthesis of a widely applicable Jørgensen–Hayashi-type amino catalyst.

Scheme 2. Synthesis of the MeOPEG-Immobilized Diphenylprolinol Trimethylsilyl Ether from L-Hyp



We started the synthesis from inexpensive, commercially available *trans*-L-hydroxy proline (L-Hyp) and could obtain the versatile enantiopure alkyne-precursor **7** over five steps in a very good overall yield of 45% (Scheme 2). It is noteworthy that an attempted route starting from L-Boc-Hyp-OMe led to significant deterioration of the catalyst's optical purity. Effective linkage of this TMS-prolinol **7** to the azido-functionalized MeOPEG support was achieved in the presence of TBTA as Cu ligand[10,11] to suppress the undesired complexation by the secondary amine.[9d] Catalyst loading was conveniently determined by ^{1}H NMR analysis using the singlet of the polymer's methoxy group as reference for integration.

To evaluate the performance of our polymer-supported catalyst, we selected the iminium-catalyzed synthesis of γ-nitro aldehydes via a Henry-type reaction of nitromethane with α,β-unsaturated aldehydes as published by Hayashi et al.[12a] While these valuable synthetic precursors can be quickly accessed by this route, their purification can prove difficult due to the sensitivity of the γ-nitro aldehydes.[12b] As a model reaction we performed the Michael addition of nitromethane and cinnamaldehyde with the MeOPEG-supported catalyst under Hayashi's best conditions (Table 1, entry 1) and gratifyingly found highly comparable results (entry 2) for our immobilized catalyst. A short survey of a

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(4) (a) Ding, K.; Uozumi, Y. *Handbook of Asymmetric Heterogeneous Catalysis*, Wiley-VCH: Weinheim, 2008. (b) Benaglia, M. *Recoverable and Recyclable Catalysts*; Wiley-VCH: Weinheim 2009.

(5) For reviews on the immobilization of organocatalysts, see: (a) Cozzi, F. *Adv. Synth. Catal.* **2006**, *348*, 1367. (b) Benaglia, M. *New J. Chem.* **2006**, *30*, 1525. (c) Gruttadauria, M.; Giacalone, F.; Noto, R. *Chem. Soc. Rev.* **2008**, *37*, 1666.

(6) For some selected recent applications, see: (a) Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 1304. (b) Franzén, J.; Fisher, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 787. (c) Jiang, H.; Elsner, P.; Jensen, K. L.; Falcicchio, A.; Marcos, V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 6844. (d) Hong, B.-C.; Kotame, P.; Tsai, C.-W.; Liao, J.-H. *Org. Lett.* **2010**, DOI: 10.1021/ol902840x.

(7) Enamine examples: (a) Zu, L.; Li, H.; Wang, J.; Yu, X.; Wang, W. *Tetrahedron Lett.* **2006**, *47*, 5131. (b) Li, Y.; Liu, X.-Y.; Zhao, G. *Tetrahedron: Asymmetry* **2006**, *17*, 2034. (c) During the finalization of this manuscript a paper describing enamine catalysis with a PS-supported catalyst related to **3** appeared: Alza, E.; Pericàs, M. A. *Adv. Synth. Catal.* **2009**, *351*, 3051. (d) Zheng, Z.; Perkins, B. L.; Ni, B. *J. Am. Chem. Soc.* **2010**, *132*, 50. Iminium examples: (e) Röben, C.; Stasiak, M.; Janza, B.; Greiner, A.; Wendorff, J. H.; Studer, A. *Synthesis* **2008**, 2163. (f) Maltsev, O. V.; Kucherenko, A. S.; Zlotin, S. G. *Eur. J. Org. Chem.* **2009**, 5134. Combined: (g) Varela, M. C.; Dixon, S. M.; Lam, K. S.; Schore, N. E. *Tetrahedron* **2008**, *64*, 10087.

(8) For recent reviews, see: (a) Bergbreiter, D. E.; Tian, J.; Hongfa, C. *Chem. Rev.* **2009**, *109*, 530. (b) Dickerson, T. J.; Reed, N. N.; Janda, K. D. *Chem. Rev.* **2002**, *102*, 3325.

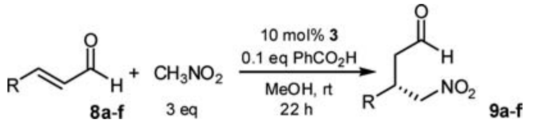
(9) For catalyst immobilization via [3 + 2]-cycloaddition, see: (a) Font, D.; Sayalero, S.; Bastero, A.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2008**, *10*, 337. (b) Schätz, A.; Hager, M.; Reiser, O. *Adv. Funct. Mater.* **2009**, *19*, 2109. (c) Zeitler, K.; Mager, I. *Adv. Synth. Cat.* **2007**, *349*, 1851. (d) Chouhan, G.; Wang, D.; Alper, H. *Chem. Commun.* **2007**, 4809. (e) Luo, J.; Pardin, C.; Lubell, W. D.; Zhu, X. X. *Chem. Commun.* **2007**, 3406. (f) Alza, E.; Rodríguez-Escrich, C.; Sayalero, S.; Bastero, A.; Pericàs, M. A. *Chem.—Eur. J.* **2009**, *15*, 10167, and references cited within these articles.

(10) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853.

(11) For a novel, highly efficient ligand promoting Cu-catalyzed 1,3-dipolar cycloadditions, see: Ozçubukçu, S.; Ozkal, E.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2009**, *11*, 4680.

(12) (a) Gotoh, H.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 5307. (b) Palomo, C.; Landa, A.; Mielgo, A.; Oiarbide, M.; Puente, A.; Vera, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 8431.

Table 1. Scope of the Asymmetric Michael Addition of CH_3NO_2 to α,β-Unsaturated Aldehydes with MeOPEG-Supported Catalyst **3**



entry	R		yield[a] (lit.)[b] (%)	ee[c] (lit.)[b] (%)
1[d]	Ph	**a**	90/52[e]	95/77[e]
2	Ph	**a**	94	94
3	*p*-MeO-Ph	**b**	80 (88)	94 (95)
4	*o*-MeO-Ph	**c**	90	93
5	*p*-NMe_2-Ph	**d**	48	92
6	*p*-NO_2−Ph	**e**	87 (76)	89 (95)
7	furyl	**f**	95 (82)	90 (93)

[a] Isolated yields. [b] Literature values according to Hayashi et al.[12a] using 10 mol % of **1** and 0.2 equiv of PhCOOH. [c] Determined by chiral-phase HPLC. [d] Literature values for catalyst **1**.[12a] [e] Literature values for catalyst **2**.

Table 2. Survey of Recycling Experiments[a] of Catalyst **3** in the Michael Addition of Nitromethane and Cinnamaldehyde **8a**

cycle	time (d)	yield[b] (%)	ee[c] [%]	time = 22 h	yield[b] (%)	ee[c] (%)
1	1	94	93		94	93
2	2	90	91		62	92
3	3	83	91		70	92
4	4	87	91		67	91
5					50	91
1[#d]					90	93
2[#d,e]					96[f]	93

[a] Left column: “full conversion” experiments. Right column: isochron experiments ($t = 22$ h). [b] Isolated yields. [c] See table 1. [d] **8c** was used as starting material. [e] Run after regeneration procedure (stirring with **8c** in MeOH). [f] Yield less the potential “preloaded” 0.1 equiv of extra aldehyde **8c**.

number of different solvents did not allow for any improvements. Interestingly, in water our fully soluble catalyst proved to be inefficient, thus suggesting a boundary occurring or “on water”[13] promoted catalysis for other water-compatible iminium catalysts, such as Palomo’s pyrrolidine catalysts bearing long hydrophobic aliphatic chains.[12b]

We therefore could directly adopt the published conditions without any further optimization. Importantly, a simple basic wash (satd $NaHCO_3$) of the reaction mixture after diethyl ether-induced precipitation and subsequent filtration of the catalyst was sufficient to get access to pure γ-nitro aldehydes in high yields and enantiomeric excess without the need of any further chromatographic purification.

Application of our catalyst showed a similar generality in the scope of the reaction as was demonstrated for the nonsupported counterpart. For both electron-rich (entries 3, 4, and 7) and electron-poor aromatic substituents (entry 6) of the unsaturated aldehyde the corresponding products could be obtained in high enantiomeric excess and often with higher yields as a result of the greatly facilitated workup procedure.

Next we turned our attention to recycling studies. While the mass recovery of the catalyst was greater than 95% and the catalyst showed excellent selectivities in five subsequent cycles, we, however, noticed increasing reaction times to reach full conversion (see Table 2). Despite this obvious sign of decreasing catalyst activity in various immobilization studies such elongated reaction times are frequently overlooked or are difficult to identify due to the diverse and differing data presentation.[14] The performance of time-constant (isochron, $t = 22$ h) recycling reactions revealed a deactivation of our catalyst (Table 2, cycle 1−5; right column). Despite the activity loss within these five isochron experiments the catalyst still achieves a valuable average yield of 68% for each of the five runs with an unchangingly high selectivity of 92% ee.

With respect to other immobilization studies of diarylprolinol silyl ethers[7] the loss of catalytic activity is well-known and commonly attributed to a desilylation event of the catalyst[7c,g] and the subsequent trapping of this free prolinol derivative in a cyclic unreactive hemiaminal species.[15] Having selected this model reaction with a reported high difference in both efficiency and selectivity for the catalysis with the TMS-diarylprolinol ether **1** or its non-silylated counterpart **2** (90%, 95% ee vs 52%, 77% ee) we could directly judge our recycling results by comparison of yield and ee. While no erosion in the high stereoselectivity was observed for our catalyst, we questioned whether the possible loss of the TMS group was decisive for the deactivation problem.

To test our hypothesis of other deactivation modes than a desilylation we decided to perform additional recycling studies with the immobilized methyl ether catalyst **4** which should not be prone to a detrimental ether cleavage under the standard reaction and recycling conditions. In fact, we found a similar loss in activity for the methoxy catalyst **4** (run 1: 95%, 78% ee; run 2: 80%,[16] 81% ee) together with an a priori decreased ee due to the reduced sterical demand of this methyl ether if compared to its TMS counterpart **3** (cf. **4** (78% ee) vs **3** (94% ee)).

Preliminary NMR experiments taking advantage of the solubility of the MeOPEG-supported methoxy catalyst **4** were undertaken to gain further insights in the catalysts deactivation mode. Making use of the catalyst’s methoxy group as a “probe” pointed to the presence of at least one additional catalyst-derived species besides the main unchanged recycled catalyst, which could presumably stem from catalyst with

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(13) For a detailed discussion on the role of water in organocatalytic reactions, see: (a) Gruttadauria, M.; Giacalone, F.; Noto, R. *Adv. Synth. Catal.* **2009**, *351*, 33. (b) Raj, M.; Singh, V. K. *Chem. Commun.* **2009**, 6687. (c) Hayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8103. (d) Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 8100.

(14) Gladysz, J. A. *Pure Appl. Chem.* **2001**, *73*, 1319.

(15) (a) Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1498. (b) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296.

(16) Reaction time of second cycle: 2 days (first cycle: 1 day).

nonreleased product indicating a deactivation via product inhibition. Based on these first hints, we could develop a waste-free catalyst regeneration without the need of extra reagents. We were pleased to find that simple stirring of the recovered and washed TMS catalyst **3** with a solution of the α,β-unsaturated aldehyde (being the starting material for the next cycle) could fully restore the catalyst's initial activity (Table 2, cycle $1^{\#}$ and $2^{\#}$). In fact, during this treatment the release of some additional product (stemming from the former cycle) could be observed while other byproducts could not be detected. Consequently, this displacement approach allows for complete recyclability of the immobilized catalyst providing almost quantitative yield after the standard reaction time *without any loss of enantioselectivity*.

In conclusion, we have developed a highly efficient approach for the synthesis, application, and recycling of immobilized diarylprolinol ether catalysts providing unchanged reactivity and selectivity as compared to the nonsupported catalyst. In addition, our immobilization allows for a simple, column-free isolation of pure, sensitive aldehyde products and therefore may be useful for application in more complicated syntheses.

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Supporting Information Available: Experimental details and spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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