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Recoverable PEG-Supported Copper Catalyst for Highly Stereocontrolled Nitroaldol Condensation

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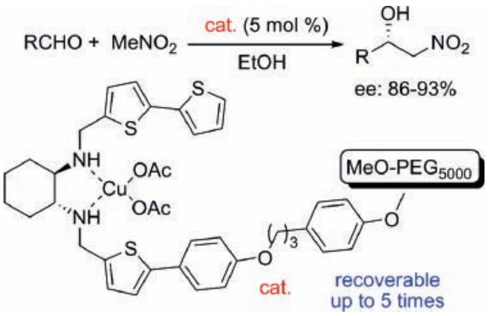
ABSTRACT



A new poly(ethylene glycol)-modified DAT2–Cu(OAc)$_2$ complex smoothly catalyzes a base-free nitroaldol condensation in a highly enantioselective manner (ee up to 93%) also in reagent-grade solvent and in the presence of air. Effective recovery and recycling (up to five runs) of supported catalysts are documented.

Nitroaldol condensations (commonly termed Henry reactions)[1] represent one of the most versatile and employed carbon−carbon forming transformations in natural product synthesis.[2] As a consequence, particular emphasis has been addressed to the discovery of catalytic enantioselective variants of this protocol, through the use of both bio- and chemocatalysis (organic as well as organometallic).[3]

Despite this flurry of activity, very little has been done toward the recovering and reutilization of the active species in asymmetric Henry condensations.[4] This aspect, in combination with the peculiar atom economy[5] of the reaction, would certainly expand the utility of enantioselective Henry protocols for large-scale production of fine chemicals. During our ongoing research focused on the stereoinductive properties of C_2-symmetric diaminobithiophenes (DAT2, **1**, Figure 1)[6] in metallo-catalyzed transformations,[7] we demonstrated that the combination of **1** with Cu(OAc)$_2$[8] (0.1−5 mol %) smoothly promoted the condensation of nitromethane with a variety of aldehydes in excellent enantiomeric excess.[9] The ready synthetic accessibility and facile manipulation of

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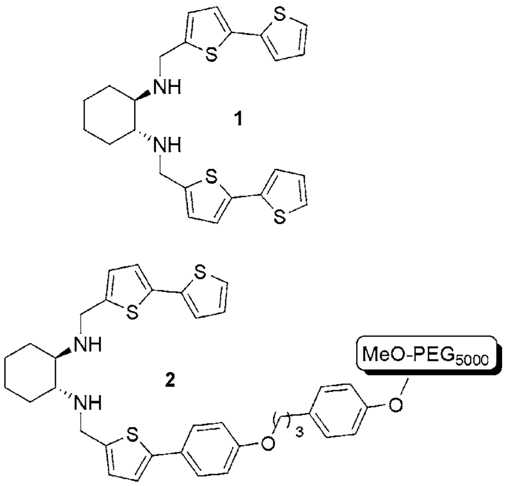
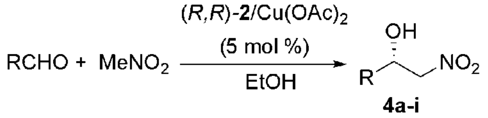


Figure 1. DAT2 ligand **1** and PEG-supported analogues **2**.

thiophene-based compounds allowed us to prepare in few steps a C_1-symmetric DAT2 analogue tethered to poly(ethylene glycol) (MeO-PEG$_{5000}$, **2**, Figure 1)[10] that was effectively employed in Pd-catalyzed asymmetric allylic alkylations. Here, the recovery of the supported ligand for several runs without any loss of activity was demonstrated. Prompted by these promising findings, we decided to explore the potential of **2** as the chiral ligand in copper-catalyzed base-free Henry reactions. Poly(ethylene glycol)-modified chiral catalysts have already found numerous applications in asymmetric organic and metallo-organic-based reactions.[11]

Table 1. Scope of Method[a]



3a: R = 4F-C$_6$H$_4$
3b: R = C$_6$H$_5$
3c: R = C$_7$H$_{15}$
3d: R = 2NO$_2$-C$_6$H$_4$
3e: R = 4Cl-C$_6$F$_4$
3f: R = *t*Bu
3g: R = C$_6$F$_5$
3h: R = C$_y$
3i: R = 3,5(MeO)$_2$-C$_6$F$_3$

entry	RCHO	4	yield (%)[b]	ee (%)[c]
1	**3a** R = 4F-C$_6$H$_4$	**4a**	traces[d]	
2	**3a**	**4a**	89	89 (*S*)
3	**3b** R = C$_6$H$_5$	**4b**	85	88 (*S*)
4	**3c** R = C$_7$H$_{15}$	**4c**	75	93 (*S*)
5	**3d** R = 2NO$_2$-C$_6$H$_4$	**4d**	71	90 (*S*)
6	**3e** R = 4Cl-C$_6$H$_4$	**4e**	75	90 (*S*)
7	**3f** R = *t*-Bu	**4f**	89	92 (*S*)
8	**3g** R = C$_6$F$_5$	**4g**	81	84 (*S*)
9	**3h** R = Cy	**4h**	90	89 (*S*)
10	**3i** R = 3,5(OMe)$_2$-C$_6$H$_3$	**4i**	65	83 (*S*)

[a] The reactions were carried out under a nitrogen atmosphere in dry EtOH for 40 h. Aldehyde/MeNO$_2$ 1:40 elsewhere otherwise reported. [b] Isolated yields after flash chromatography. [c] Determined by HPLC with a chiral column. Absolute configuration was assigned by comparison of the HPLC retention times with known samples (see ref 8). [d] Aldehyde/MeNO$_2$ 1:10.

However, a very few examples[12] of effective recovery of organometallic catalysts, through the use of PEG chemistry, have been reported.[13] An initial drawback to circumvent was the poor solubility of **2** in EtOH (optimal reaction media) that prevented *homogeneous* conditions from operating (Table 1, entry 1). However, we were delighted to find out that, by increasing the MeNO$_2$/4F-C$_6$H$_4$CHO (**3a**) ratio to 40:1,[14] **2** was successfully solubilized, furnishing (*S*)-**4a** in excellent conversion (>98%) and good enantiomeric excess (89%, entry 2). The adopted reagents' ratio is the best compromise to obtain higher chemical and optical outcomes. In fact, if lower amounts of MeNO$_2$ caused a poor solubilization of the catalyst (slow reaction rates), higher quantities of MeNO$_2$ led to a drop of stereoselection.[15] Then, a range of aromatic (electron-rich and electron-poor) and aliphatic (linear and branched) aldehydes (**3b**−**i**) was screened. Under optimal conditions (EtOH, 0 °C, 40 h) nitroalcohols **4b**−**i** were obtained in excellent conversions (85−98%) and high enantiomeric excesses (83−93%). The erosion in stereoinduction observed (Δee $\approx$ 1−7) with respect to the Henry condensation in the presence of **1**−Cu(OAc)$_2$ can be tentatively ascribed to the higher amount of nitromethane needed with PEG-modified DAT2.

Focusing on operational simplicity, we endeavored to run the present nitroaldol condensation (**3e**+MeNO$_2$) in an open-air vial with reagent-grade EtOH as the solvent. Remark-

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(14) In the case of **1**-based catalysis, the optimal MeNO$_2$/**3** ratio was 10:1.

(15) The model reaction (MeNO$_2$/4F-C$_6$H$_4$CHO) carried out in nitromethane as the solvent led to (*S*)-**4a** in 96% conversion and 50% ee.

ably, **4e** was obtained in >98% conversion (40 h, 0 °C) and 84% ee.

The high reaction conversions and the possibility of removing solvent and excess $MeNO_2$ easily from the reaction crude under vacuum called for a ready recovering of the whole metal−ligand system. To this aim, we initially isolated the precatalytic PEG−DAT2−$Cu(OAc)_2$ **5** species starting from **2**. Equimolar amounts of **2** and $Cu(OAc)_2$ were stirred overnight under nitrogen at room temperature in degassed CH_2Cl_2, furnishing the desired copper complex **5** as a pale green solid in 84% yield (Figure 2).

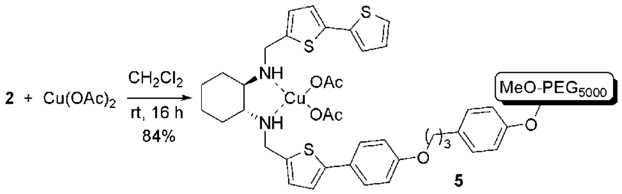

Figure 2. Synthesis of MeO-PEG_{5000}−DAT2−$Cu(OAc)_2$ **5**.

Then, preformed **5** (5 mol %) was employed in several consecutive runs of the nitroaldol reaction between $MeNO_2$ and PhCHO. After each iteration, elimination of the volatiles and repeated washings of the catalyst with Et_2O allowed **5** to be recovered and reused in the next run without the need for further additions of copper salt.

Gratifyingly, the stereochemical induction of **5** over five runs remained unaltered, furnishing constant values of enantiomeric excesses (84−87%), with a slight erosion in chemical conversions by the fourth iteration (Figure 3).

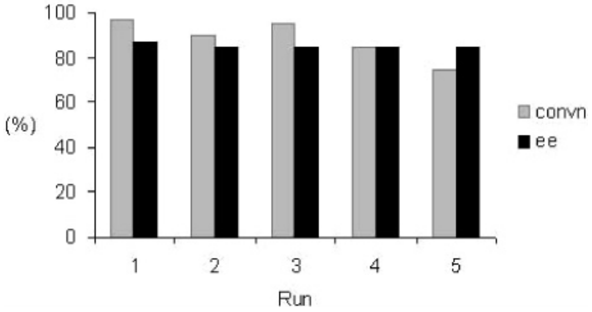

Figure 3. Proof of recoverability of **5** (up to five times) in the catalytic enantioselective condensation of $MeNO_2$ with PhCHO.

Noticeably, after five runs, 81% of the initial amount of catalyst was recovered.

To prove the integrity of the ligand after the experiments, the recovered PEG-supported catalyst was dissolved in CH_2Cl_2 (0.3 mL/0.1 g of polymer) and treated dropwise with a 0.3 M solution of KCN (5 mol/equiv) in water. The mixture was stirred at room temperature for 15 min, then diluted with CH_2Cl_2, dried, filtered, and concentrated under vacuum to give a solid residue that was analyzed by NMR as such. Further purification of this material was possible by the usual procedure to afford a ligand identical by NMR to a sample freshly prepared.

PEG−DAT2−$Cu(OAc)_2$ formed in situ was also subjected to the recovering/reusing experiment with different substrates. In particular, five aldehydes (**3a**−**e**) were consecutively condensed with $MeNO_2$ in the presence of the same batch of **2**−$Cu(OAc)_2$ (5 mol %, 0 °C, 40 h). Interestingly, the chemo/stereochemical outputs recorded (see Supporting Information) were consistent with those obtained with fresh catalyst. Such evidence underlines the effectiveness of our workup procedure (purification/recovering/recycling) and recommends the present copper catalyst for applications in combinatorial synthetic approaches such as "one-pot multisubstrate screening" methods.[16]

In conclusion, we have successfully demonstrated the suitability of PEG-modified DAT2 ligand **2** in promoting highly stereoselective copper-catalyzed Henry reactions. Excellent conversions and ees up to 93% were obtained under mild and operationally simple conditions. Finally, unique properties of preformed complex **5** allowed the reusability of the entire organometallic species for several iterations without any significant loss in activity. Studies addressing the use of this type of catalytic system in environmentally friendly stereocontrolled transformations are underway.

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Supporting Information Available: Experimental procedures, $^{1}H/^{13}C$ NMR spectra, chiral HPLC analyses of the known molecules, and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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