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Charge-Transfer Interactions: An Efficient Tool for Recycling Bis(oxazoline)-Copper Complexes in Asymmetric Henry Reactions

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Abstract: An anthracenyl-modified chiral bis(oxazoline) copper complex has been demonstrated to efficiently promote nitroaldol reactions between structurally varying aldehydes and nitromethane or nitroethane. The catalyst was recovered through formation of a charge transfer complex between the chiral ligand and trinitrofluorenone and its subsequent precipitation with pentane. The efficiency of this procedure was proved through several consecutive catalytic cycles that allowed the sturdy formation of the expected product with a high enantioselectivity. The catalyst's stability was also put to the test in an original multi-substrate procedure. Following the same recovery concept, a new heterogeneous procedure was tested for which trinitrofluorenone was covalently linked to a silica support. Asymmetric heterogeneous catalysis was performed under these conditions as one of the few examples demonstrating the potential catalyst recycling in nitroaldol reactions through reversible, non-covalent interactions.

Keywords: asymmetric catalysis; bis(oxazolines); catalyst recycling; charge transfer complex; nitroaldol reaction

Introduction

The Henry (nitroaldol) reaction is a well known access to a wide range of interesting intermediates starting from easily available aldehydes and nitroalkane derivatives.[1] The asymmetric version of the reaction produces enantiomerically enriched β-nitroalkanols that can be reduced into β-amino alcohols, or transformed by the Nef reaction to give β-hydroxy carbonyl compounds, for instance. Biologically active compounds such as levamisole or propanolol can then be obtained after few transformations.[2]

Shibasaki and co-workers reported about twenty years ago the first example of a catalytic asymmetric nitroaldol reaction promoted by lanthanum alkoxide precursors in the presence of *(S)*-(−)-binaphthol as ligand.[3] Starting from this promising result, other asymmetric metal-based catalysts have been reported[4] involving, for instance, zinc complexes in the presence of various ligands derived from semi-aza-crown backbones,[5] ferrocenyl-substituted aziridinylmethanol compounds[6] or C_2-symmetrical bis(oxazolidine) ligands.[7] Cobalt[8] or chromium[9] salts linked to chiral salen ligands also recently showed their ability to promote the asymmetric nitroaldolization with high yields and enantioselectivities. Many copper-based asymmetric catalytic systems have been described with chiral diamine-based ligands,[10] salen or Schiff base derivatives[11] and sulfonyldiamines[12] or sulfonimidamides.[13] Chiral bis(oxazolines) as ligand in combination with copper species were first described by Jørgensen et al. to promote the asymmetric Henry reaction of α-keto esters with nitromethane.[14,15] The use of copper acetate bis(oxazoline) to catalyze the addition of nitromethane to aldehydes was reported by Evans and co-workers.[16] They optimized the reaction conditions with different ligands and solvents, and noted the efficiency of $Cu(OAc)_2{\cdot}H_2O$ for both Lewis acid properties and Brønsted base ability. Good activities and enantioselectivities were obtained under these conditions in the presence of ligand **1a** (Figure 1) in ethanol at room temperature. Reactions with a 5 mol% amount of chiral catalyst were tested by Singh et al.[17] by using different metallic salts such as $Cu(OTf)_2$, $Zn(OAc)_2{\cdot}H_2O$ or $Mg(OAc)_2{\cdot}H_2O$ but $Cu(OAc)_2{\cdot}H_2O$

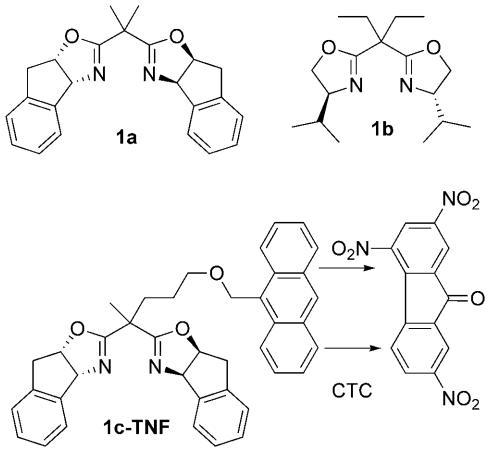


Figure 1. Bis(oxazoline) ligands.

led to the best result for the preparation of 2-nitro-1-phenyl-ethanol with ligand **1b** (81% *ee*).

Some efforts have also been devoted towards the recovery and reuse of those efficient asymmetric catalytic systems to follow at best the principles of green chemistry.[18] Immobilized (*S*)-(−)- binaphthol onto nanocrystalline magnesium oxide,[19] or lanthanum-lithium-binaphthol complexes bonded to silica and MCM-41,[20] were able to efficiently carry out the asymmetric nitroaldol reaction in several successive catalytic runs. Chromium salen derivatives have been electropolymerized giving rise to an efficient insoluble catalyst reusable in an original multisubstrate procedure.[9a] A chiral copper acetate complex tethered to poly(ethylene glycol) was also used in a recycling procedure demonstrating a high activity and stability.[21] Very recent examples describe the heterogeneization of chiral copper complexes on silica supports.[22] Park et al. demonstrated recently the easy recyclability of chiral copper amino complexes when the nitroaldol reaction was performed in ionic liquids.[23] Bellemin-Laponnaz and Gade covalently attached chiral oxazoline ligands to carbosilane dendrimers and used the corresponding copper complexes as immobilized, and thus recoverable, catalysts in a membrane bag.[24] All these procedures led interestingly to the formation of the expected products with high enantioselectivity values that remained almost stable along with the successive catalytic runs. The recycling procedures were tested for about a maximum of five runs but were, however, always accompanied by a non-negligible loss of activity leading to diminished isolated yields.

We have previously reported a new efficient immobilization strategy for the recovery and reuse of asymmetrical bis(oxazoline)-type catalysts based on the formation of the corresponding charge-transfer complex (CTC) arising from an electronic transfer between the anthracene functionality of the new bis(oxazoline)-type ligand and 2,4,7-trinitrofluorenone (TNF). At the end of the catalytic transformation, pentane is poured into the reaction mixture, which results in the precipitation of the catalyst. Products were then removed for analysis before additional solvent and substrates were added for the reuse of the catalyst. Complex **1c-TNF** depicted in Figure 1 was thus successfully used 12 times in a Diels–Alder reaction leading to the formation of the expected products with high yields and enantioselectivities, exactly matching the results obtained by the corresponding homogeneous system.[25]

The aim of the present work deals with the use of ligand **1c** (Figure 1) under optimized conditions to obtain various nitroalcohol derivatives in high yields and enantioselectivities and the fine-tuning of the procedure allowing its efficient recovery and reuse by formation of CTC.

Results and Discussion

Electron-donor bis(oxazoline) ligand **1c** has been previously synthesized by our team, starting from diethyl malonimidate (route A, Figure 2).[25] This synthesis implied the direct introduction of the chiral moiety (1*R*,2*S*-aminoindanol) at the first step to obtain bis(oxazoline) **2**, followed by the addition of the anthracene moiety (40% yield). The methyl substituent on the bridging group was then introduced at the last step leading to an overall yield of about 7%. Aiming at improving the access to this ligand, a new way was considered (route B), starting with a fragment already containing the methyl group. Diethyl 2-methylmalonimidate **4** was obtained by bubbling HCl in ethanol in the presence of 2-methylmalononitrile, prepared according to a reported procedure.[26] The same methodology used for route **A** was pursued to synthesize chiral bis(oxazoline) **3**, by addition of (1*R*,2*S*)-aminoindanol onto **4**. This intermediate bis(oxazoline) **3** could be recrystallized for analysis in 46% yield, but it was pure enough as a crude mixture to be further used without purification. Ligand **1c** was thus prepared in 51% yield, in two steps from 2-methylmalonimidate **4**, by a nucleophilic substitution on a mesylate derivative of anthracene. Thanks to this new route, the overall yield was consequently improved to 25%.

Some catalytic tests between benzaldehyde **5a** and nitromethane **6a** were then performed in the presence of ligand **1c**, to find optimal conditions using $Cu(OAc)_2 \cdot H_2O$ as precatalyst for the nitroaldol reaction (Scheme 1). The procedure described by Evans et al. was reproduced (10 mol% precatalyst, reaction performed in ethanol at room temperature in the absence of additional base)[16] and led to the best results. In a typical transformation, the copper bis(oxazoline) complex was formed by mixing ligand **1c** with copper

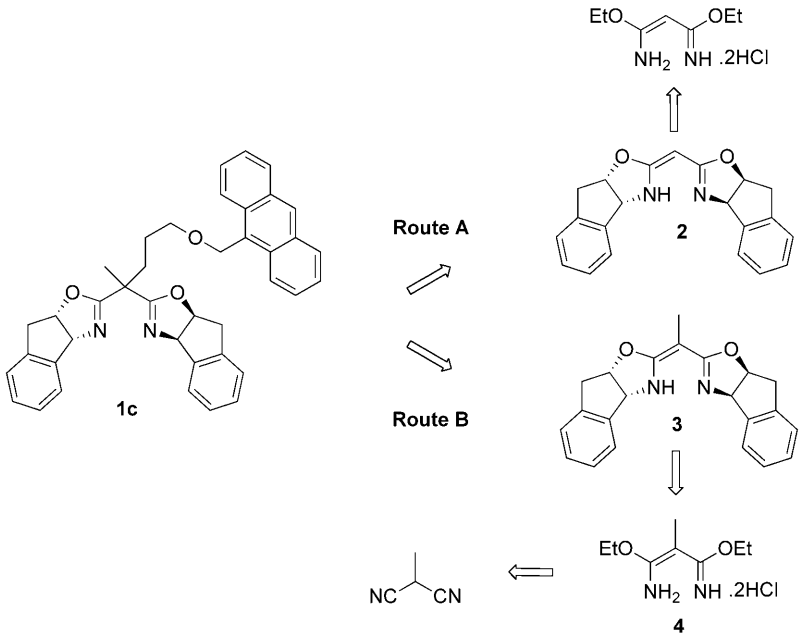
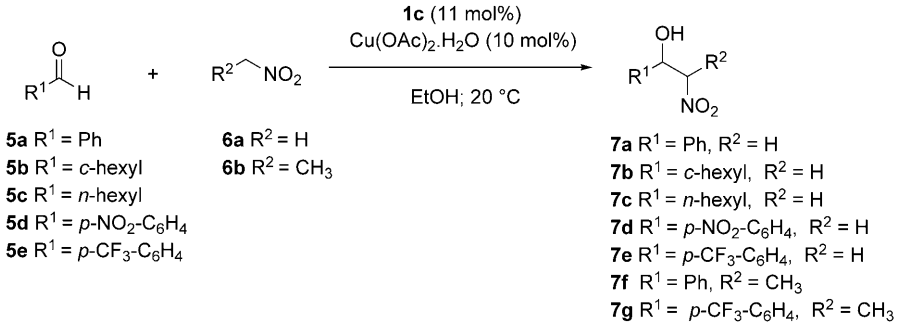


Figure 2. Different routes towards bis(oxazoline) **1c**.



Scheme 1. Nitroaldol reactions catalyzed by ligand **1c**-$Cu(OAc)_2$.

acetate in a 1/1 ratio in ethanol and the resulting solution was stirred for 1 h. Nitromethane and the aldehyde were then successively introduced and the reaction mixture was stirred for 24 h. The targeted compound **7a** was therefore isolated in high yield (89%) and excellent enantioselectivity (90% *ee*, Table 1, run 1), indicating that the presence of the additional anthracene moiety on **1c** was not detrimental to the enantiofacial discrimination, by comparison to the results obtained with ligand **1a**.

These reaction conditions were then applied to perform the recycling procedure. At the end of the first run, trinitrofluorenone (10 mol%) was added and the mixture was stirred one additional hour to form the CTC in solution, as indicated by the immediate coloration to deep red. Pentane was then poured for the CTC precipitation which was recovered by filtration, through removal of the products solution. New substrates were then added to the resulting catalyst to perform thus successive catalytic runs. The results are summarized in Table 1.

Table 1. Recycling procedure of **1c**-$Cu(OAc)_2{\cdot}H_2O$/TNF in EtOH for the formation of **7a**.

Run	*t* [h]	Conv. [%][a]	Yield **7a** [%][b]	*ee* **7a** [%][c]
1	24	>95	89	90 (*R*)
2	36	93	84	90 (*R*)
3	48	90	83	90 (*R*)
4	72	92	80	88 (*R*)
5	72	80	72	87 (*R*)
6	96	75	63	84 (*R*)
7	120	66	59	82 (*R*)

[a] Determined by NMR spectroscopy.
[b] Isolated yield.
[c] Determined by chiral IB HPLC, for the configuration assignment, see Supporting Information.

The recovered catalyst was then engaged in the second run with additional substrates and product **7a** could be further isolated but the reaction time had to be increased to maintain an important isolated yield (Table 1, entry 2). Satisfyingly, however, a similar high enantioselectivity (90%) was obtained for this second transformation conducted in the presence of TNF, showing almost no influence of the formed charge transfer complex on the selectivity of the catalysis. Catalyst **1c-TNF** was further recovered by precipitation and subsequent filtration for five additional consecutive catalytic runs showing only a slight decrease in the enantioselectivity values along with the reuses but the reaction time had to be substantially lengthened in the last cycles. Partial leaching of the catalyst was indeed proved by adding fresh substrate **5a** and nitromethane to the recovered product solution arising from the first run. After 24 h stirring, the mixture was analyzed indicating that additional 25% conversion occurred to form the expected product with the same enantioselectivity. Although the isolated yield of the targeted product **7a** regularly decreased with the recycling showing an incomplete recovery of the catalyst by precipitation, this procedure is one of the very few examples for the use of copper bis(oxazoline) complexes durably enantioselective, at least for five cycles, in the nitroaldol reaction.[22b,24]

The domain of relevance of the complex **1c**-$Cu(OAc)_2 \cdot H_2O$ was further demonstrated by the transformation of various aldehydes with either nitromethane or nitroethane (Scheme 1). As depicted in Table 2, the anthracene-modified bis(oxazoline) **1c** proved to be efficient for the formation of nitroalcohols arising from aliphatic aldehydes or from substituted aromatic ones. The values that were obtained matched those reported for the analogous *gem*-dimethylindanol-derived bis(oxazoline) **1a**. Evans indeed described this procedure for the enantioselective synthesis of compounds **7a**, **7b** and **7d**, isolated in 94, 93 and 81% *ee*, respectively.[16] A non-negligible decrease of the enantioselectivity was only observed for the formation of **7d** by using ligand **1c**, probably as a result of the competitive non-catalyzed reaction, occurring rapidly with nitromethane in the case of substrate **5d**. In our hands, substrates **5c** and **5e** were engaged in the Henry reaction with complex **1a**-$Cu(OAc)_2 \cdot H_2O$, leading to the expected products **7c** and **7e** with, respectively, 89 and 87% *ee*s. These values are also close to those reported in Table 2, on using ligand **1c**.

Table 2. Nitroaldol reaction between various aldehydes and nitromethane or nitroethane catalyzed by complex **1c**-$Cu(OAc)_2 \cdot H_2O$ in EtOH.[a]

Product	Conv. [%][b]	Yield [%][c]	*anti*/*syn*[b]	*ee* (%)[d] (*anti*/*syn*)
7a	>95	89	–	90 (*R*)
7b	>95	79	–	90 (*R*)
7c	>95	87	–	91 (*R*)
7d	96	71	–	74 (*R*)
7e	91	83	–	82 (*R*)
7f	71	65	66/34	73/73
7g	76	68	65/35	67/63

[a] Reactions were performed for 24 h at 20 °C.
[b] Determined by NMR spectroscopy.
[c] Isolated yield.
[d] Determined by chiral HPLC, for the configuration assignment, see Supporting Information.

The use of the anthracene-modified bis(oxazoline) ligand **1c** is thus not detrimental, both in terms of activity and enantioselectivity, for the formation of those nitroalcohol adducts. The reaction with nitroethane was also studied in the presence of two aromatic aldehydes **5a** and **5e** and smoothly led to the preparation of diastereomeric mixtures of compounds **7f** and **7g** with in both cases, the formation of the *anti* isomer as major product. This selectivity is in total contrast with the one observed through a Brønsted base catalysis, since the use of Et_3N afforded mainly the *syn* isomer.[27]

Due to the lower reactivity of nitroethane compared to nitromethane, a complete conversion of the aldehydes could not be reached in one day, but both targeted products were nevertheless isolated in about 65% yield. The enantioselectivity of the transformation was measured for all compounds and both isomers of 2-nitro-1-phenylpropan-1-ol **7f** were prepared in 73% *ee*, by using bis(oxazoline) **1c**. This catalytic system was, however, slightly less selective for the formation of 2-nitro-1-(4-trifluoromethylphenyl)-propan-1-ol **7g**, for which the highest enantioselectivity was obtained for the formation of the *anti* (major) isomer (67% *ee*, Table 2).[28]

We have therefore employed complex **1c**-$Cu(OAc)_2 \cdot H_2O$ in a multi-substrate recycling procedure (Table 3). This approach consists in introducing new structurally different substrates at each recycling of the precipitated CTC-catalyst. Such a procedure was rarely described in the literature, but may be used as a proof for the sturdiness of the reused catalytic batch.[29] As the efficiency of the catalyst was evaluated with different substrates in homogeneous conditions, the recycling procedure was thus realized in the presence of those various aldehydes starting with the use of nitromethane. The first run of the transformation involved the selective formation of 2-nitro-1-phenylethanol **7a**. At the end of the transformation, TNF was added to the reaction mixture followed by dilution with pentane which resulted in the precipitation of the corresponding charge transfer complex. The product solution was removed through filtration and **7a** could be easily isolated in the expected yield and enantioselectivity (Table 3, entry 1). At-

Table 3. Multi-substrates recycling procedure of **1c**-$Cu(OAc)_2 \cdot H_2O$/TNF in EtOH for the formation of various nitroalcohols at room temperature.

Run	Product	*t* [h]	Conv. [%][b]	Yield [%][c]	*anti*/*syn*[b]	*ee* [%][d] (*anti*/*syn*)
1	**7a**	24	>95	90	–	91 (*R*)
2	**7f**	24	<5	–	–	–
3	**7b**	36	80	69	–	83 (*R*)
4	**7c**	48	53	46	–	87 (*R*)
5	**7d**	72	88	79	–	49 (*R*)
6	**7e**	96	89	82	–	70 (*R*)
7[a]	**7f**	60	94	86	40/60	25/43
8[a]	**7g**	60	>95	82	41/59	4/13
9	**7a**	144	72	61	–	80 (*R*)

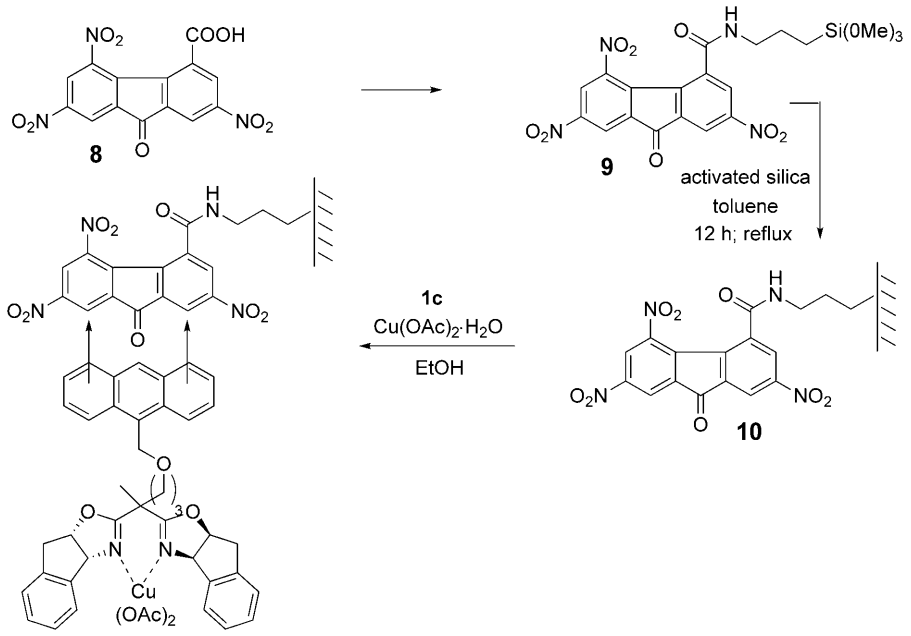
[a] 10 mol% Et_3N was added.
[b] Determined by NMR spectroscopy.
[c] Isolated yield.
[d] Determined by chiral HPLC.

tempts to realize a second run in the presence of benzaldehyde and nitroethane under similar conditions in terms of reaction time and temperature failed, however (entry 2).[30] Gratifyingly, nevertheless, in a third cycle, the recovered complex **1c-TNF** could catalyze the formation of 1-cyclohexyl-2-nitroethanol **7b** with a high enantioselectivity of 83%. Some catalyst leaching probably occurred since a slight increase in the reaction time was necessary to obtain the desired product in a valuable yield. This was accompanied with a diminution in the selectivity of the transformation, in comparison to the values obtain with a new catalyst batch (compare Table 3, entry 3 with Table 2, entry 2). The subsequent run was associated to the preparation of compound **7c** which could be isolated with 87% *ee*, a value similar to the one obtained in analogous conditions with a fresh catalyst. The fifth use of the catalyst led to the formation of 2-nitro-1-(4-nitrophenyl)-ethanol **7d**, for which 3 days reaction time were necessary to achieve reasonable conversion (Table 3, entry 5). Some catalyst leaching along the recycling is here evidenced by the low enantioselectivity value; that is, 49% instead of 74%, as a proof of the presence of the competitive racemic non-catalyzed reaction, that can occur in a high rate for this substrate. The catalyst batch was engaged in a next cycle to prepare another structurally different nitroalcohol compound and this 6th run led to the preparation of enantioenriched 2-nitro-1-(4-trifluoromethylphenyl)-ethanol **7e**, with up to 70% *ee*. Attempts to perform the Henry reaction in the presence of nitroethane were then renewed, but the transformation was this time conducted in the presence of a catalytic amount of triethylamine to enhance the reaction rate by activating nitroethane. Contrary to the previous test (Table 3, entry 2), the expected mixture of isomers for **7f** was isolated in high yield (Table 3, entry 7) albeit with a reversed diastereomeric ratio, since the *syn* compound was preferentially prepared, as already described for analogous copper catalysts in the presence of a base.[31] Accordingly, the enantioselectivities were drastically diminished (see Table 2 for comparison). The same trend occurred for the 8th use of the catalyst concerning the preparation of an isomeric mixture of nitroalcohol **7g**. We assume that, in these last two cases, the triethylamine-catalyzed transformation was probably in strong competition with the reaction driven by the recovered chiral copper complex **1c**, leading to poor selectivities. Interestingly, however, the preparation of **7a** was attempted in the last 9th cycle, and after prolonged reaction time this compound was isolated with 80% *ee*, a high value considering both the number of cycles performed with the same catalyst batch, and the different conditions that were successively used for this recycling strategy.

In order to improve the recycling procedure, the interaction between ligand **1c** and TNF grafted on an insoluble support was then considered. We indeed aimed to avoid the precipitation step by facilitating the filtration procedure and performing the catalytic transformation directly under heterogeneous conditions.

Activated silica modified by covalently grafted trinitrofluorenone was synthesized as a new material able to form supported CTC with ligand **1c** (Scheme 2). 2,5,7-Trinitro-9-oxo-9*H*-fluorene-4-carboxylic acid **8** was synthesized in two steps from diphenic acid.[32] By coupling with a trimethoxysilane functionalized propylamine in the presence of DCC, the trimethoxysilyl derivative **9** was obtained[33] and directly grafted on activated silica as a suspension in refluxing toluene[34] to yield the modified silica support **10** with a 0.191 mmol g^{-1} loading, as determined by elemental analysis.

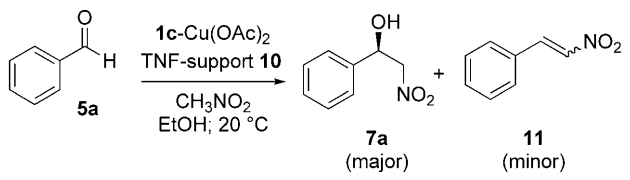
The heterogeneous catalyst was then formed by reacting **1c** and $Cu(OAc)_2 \cdot H_2O$ followed by addition of the resulting complex as an ethanol solution to support **10**, in an equimolar amount according to grafted



Scheme 2. Synthesis of the TNF-spport **10**.

TNF, to match at best the conditions that were used in the preceding procedure. Tests on the influence of the activated silica on the reaction course were firstly realised using catalyst **1a**-$Cu(OAc)_2{\cdot}H_2O$ (10 mol%) in the presence of a similar amount of non-modified support (i.e., simple activated silica) in ethanol. The transformation afforded 2-nitro-1-phenyl-ethanol **7a** in 58% isolated yield after 24 h reaction in a satisfying *ee* of 90%. Its formation was, however, accompanied by the synthesis in a non-negligible amount of compound **11** (2-nitrovinyl)-benzene, about 10%, arising from a dehydration step from **7a** probably favoured by the intrinsic acidity of support **10**. The heterogeneous asymmetric catalysis was then started in a recycling procedure by successive additions of nitromethane and benzaldehyde on **1c**-$Cu(OAc)_2{\cdot}H_2O$/**10** (Scheme 3). At the end of each run, pentane was firstly added to the reaction mixture and the silica-supported catalyst was removed from the products in solution by filtration. Results are presented in Table 4.

Compared to the homogeneous procedure in ethanol, the reaction time was raised up to 36 h in the first run (Table 4) to afford good conversions and



Scheme 3. Nitroaldol reaction in the presence of silica-supported TNF **10**/**1c**-$Cu(OAc)_2$.

Table 4. Heterogeneous recycling procedure of **1c**-$Cu(OAc)_2{\cdot}H_2O$/**10** with or without addition of pentane for the formation of **7a**.

Run	*t* [h]	Conv. [%][a]	Ratio[a] **7a**/**11**	Yield **7a** [%][b]	*ee* **7a** [%][c]
with addition of pentane					
1	36	93	88/12	74	89 (*R*)
2	72	95	89/11	72	89 (*R*)
…					
5	72	64	91/9	54	84 (*R*)
…					
7	120	64	89/11	51	83 (*R*)
without addition of pentane					
1′	36	>95	91/9	84	89 (*R*)
2′	72	95	86/14	72	88 (*R*)
3′	72	75	90/10	60	84 (*R*)
4′	72	66	88/12	55	82 (*R*)
5′	72	56	88/12	44	76 (*R*)

[a] Determined by NMR spectroscopy.
[b] Isolated yield.
[c] Determined by chiral IB HPLC.

product **7a** was satisfyingly isolated in 74% yield and 89% *ee*. In this case also, a non-negligible amount of unsaturated product **11** was detected.

After the first run, pentane was added in order to compare the results with the catalytic runs realized with **1c**-$Cu(OAc)_2.H_2O$/TNF. The second cycle was performed with an increased reaction time that allowed isolating compound **7a** with the same yield and enantioselectivity. The **7a**/**11** ratio remained quite stable as did the enantioselectivity along the succes-

sive catalytic cycles. As noticed for the preceding recycling procedure, however, the recovery of the catalyst was accompanied with a continuous decrease in activity, but the targeted product was nevertheless interestingly isolated with a quite stable enantioselectivity for seven runs.

This recycling protocol was further simplified and implied finally the direct recovery of the catalytic support by filtration after each run without addition of pentane (Table 4). In this case, however, the amount of supported TNF **10** used was two-fold according to the initially introduced chiral complex to favour, at best, the charge transfer interaction. Consequently, the reaction mixture was twice diluted. After the catalytic reaction, silica was washed once with ethanol to recover the most part of the product and reused in a subsequent cycle.

As expected, the first run afforded exactly the same results as before, indicating that the dilution was not detrimental to the efficiency of the transformation (Table 4, run 1′). The second run gave also good results in terms of activity and enantioselectivity (88% *ee*), proving the good stability of the catalyst between the two first runs under similar reaction conditions as those described previously, and avoiding the use of the apolar solvent favourable for the formation of the CTC. At the third run, the activity decreased, however, and compound **7a** was isolated in only 60% yield, albeit with a good enantioselectivity of 84%. Along the following runs, a regular loss of activity and enantioselectivity was nevertheless observed and at the last run (Table 4, run 5′) product **7a** was obtained in only 44% yield with 76% *ee*. These results nevertheless prove that chiral bis(oxazoline) copper complexes can be maintained at the surface of a solid silica support through non-covalent reversible CTC interactions, allowing the production of scalemic nitroalcohols with high enantioselectivity for at least four consecutive catalytic runs. To attest for the integrity of the chiral ligand **1c**, the copper complex was recovered from the silica support **10** after these five successive catalytic runs. The solid was indeed thoroughly washed with toluene, as a competitor solvent to disfavour the CTC interactions between anchored-TNF and the anthracene moiety of the ligand. Copper was then removed from the resulting mixture by washing with EDTA and **1c** was thus isolated in 58% yield. The ligand was identical by NMR to a fresh sample. It was furthermore submitted again to complexation with $Cu(OAc)_2 \cdot H_2O$ and involved in a Henry reaction between benzaldehyde and nitromethane to yield compound **7a** with the same expected high enantioselectivity (90%).

Conclusions

Various Henry reactions have thus been performed by using the catalytic system bis(oxazoline) **1c**-$Cu(OAc)_2$ affording the expected nitroalcohols with high yields and enantioselectivities. We have demonstrated that the chiral complex was recoverable through formation of charge transfer interactions with trinitrofluorenone and it was involved in consecutive catalytic cycles.

A precipitation procedure by addition of pentane proved to be efficient for up to seven reuses of the catalyst in a mono-substrate procedure for the formation of 2-nitro-1-phenylethanol. This methodology was also employed in an original multi-substrate procedure, for which the structure of the substrate was changed at each reuse of the same catalyst batch, and the corresponding product was isolated in its pure form, free of any product traces from the preceding run. A decrease in the product yield was unfortunately unavoidable along the recycling which is, however, frequently reported concerning the Henry reaction, whereas the selectivity of the transformation proved to be more stable. Direct asymmetric heterogeneous catalysis could also be performed *via* covalent linking of modified TNF on a silica support, leading to promising results in terms of activity and enantioselectivity that were furthermore not decreased compared to those obtained under homogeneous similar conditions. This procedure is one of the few[23] for which asymmetric catalysts efficient to promote the enantioselective Henry reaction are recovered through non-covalent, reversible interactions. Work is still in progress to further stabilize the reversible charge transfer interaction and minimize, at best, the catalyst leaching in an effort to develop continuous asymmetric flow procedures.

Experimental Section

(3a*R*,3a′*R*,8a*S*,8a′*S*)-2,2′-[5-(Anthracen-9-ylmethoxy)-pentane-2,2-diyl]bis(8,8a-dihydro-3a*H*-indeno[1,2-*d*]-oxazole) (1c)

In a dried Schlenk tube, TMEDA (174 μL, 1.17 mmol) and diisopropylamine (253 μL, 1.80 mmol) were mixed in 5 mL THF and the solution was cooled to −20 °C. The lithium diisopropylamide solution was then obtained by a slow addition of *n*-BuLi (2.26 mL, 1.6 M in hexane, 3.61 mmol) during 30 min at −20 °C. The uncoloured solution was then allowed to stir at room temperature. After 1 h, the solution of LDA was transferred in a second Schlenk containing **3** (565 mg, 1.64 mmol) in 15 mL THF and the mixture was stirred at room temperature during 2 h. 3-(Anthracen-9-ylmethoxy)-propyl methanesulfonate (1.08 g, 3.28 mmol) in 10 mL THF was then added to the solution and the mixture was heated at 60 °C and stirred during 24 h. Water was added to the so-

lution and the aqueous layer was extracted with diethyl ether (3×30 mL). The organic layer was dried over $MgSO_4$ and then concentrated. The crude product was purified on silica gel (cyclohexane/ethyl acetate = 1:1) to afford the pure product as a yellow solid; yield: 479 mg (51%); mp 61 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.38 (s, 3H), 1.41–1.45 (m, 2H), 1.88–2.01 (m, 2H), 2.9 (d, 2H, J = 18.6 Hz), 3.18–3.33 (m, 2H), 3.52 (t, 2H, J = 6.3 Hz), 5.14–5.25 (m, 2H), 5.29 (s, 2H), 5.50 (dd, 2H, J = 8.3 Hz, J = 3.9 Hz), 7.13–7.25 (m, 6H), 7.46–7.51 (m, 6H), 7.99 (d, 2H, J = 9.3 Hz), 8.29 (d, 2H, J = 9.3 Hz), 8.44 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 20.7, 24.3, 32.7, 39.6, 64.6, 70.5, 76.4, 83.1, 124.5, 124.9, 125.0, 125.5, 125.6, 126.0, 127.3, 128.3, 128.9, 130.9, 131.4, 139.5, 139.6, 141.8, 168.4; HR-MS (EI): m/z = 592.2721, calcd. for $C_{40}H_{36}O_3N_2^+$: 592.2720; $[\alpha]_D$: +199 (c 1, $CHCl_3$); IR (KBr): ν = 2935.5, 1646.3, 1090.6, 997.0 cm^{-1}.

Homogeneous Catalysis and Recovery of the Catalyst by CTC Formation and Precipitation

Ligand **1c** (33 mg, 0.055 mmol) dissolved in EtOH (1 mL) was added to $Cu(OAc)_2 \cdot H_2O$ (10 mg, 0.05 mmol) and the blue-green solution was stirred for 1 h at room temperature. Then, nitroalkane (5.0 mmol) was added drop wise to the solution and the homogeneous mixture was then stirred for 10 additional minutes. The aldehyde (0.5 mmol) was then introduced and the solution was stirred at room temperature during 24 h. Then, trinitrofluorenone (TNF) (16 mg, 0.05 mmol) was added to the green mixture to form the CTC in solution. After 30 min stirring, the catalyst was precipitated as an insoluble CTC by addition of pentane (8 mL). The catalyst, recovered by filtration and drying, was reused in a renewed catalytic run after solubilisation in EtOH (1 mL). The product-containing solution was then evaporated under vacuum, the residue was purified by preparative thin layer chromatography (pentane:diethyl ether = 4:1) and analyzed by HPLC for the determination of the *ee* (see below).

(*R*)-(−)-2-Nitro-1-phenylethanol (7a): ^{1}H NMR: ($CDCl_3$, 250 MHz): δ = 2.99 (br. s, 1H), 4.53 (dd, 1H, J_1 = 13.3 Hz and J_2 = 3.5 Hz), 4.64 (dd, 1H, J_1 = 13.3 Hz and J_2 = 9.3 Hz), 7.38–7.45 (m, 5H); ^{13}C NMR: ($CDCl_3$, 250 MHz): δ = 71.1, 81.3, 126.1 , 129.0, 129.1, 138.3. HPLC: (IB, hexane/*i*-PrOH = 9:1, 1.0 mL.min^{-1}, 210 nm): t_R (major) = 10.13 min, t_S = 11.73 min; $[\alpha]_D^{20}$: −48.3 (c 1.00, $CHCl_3$) for 90% *ee*; Lit[9a] $[\alpha]_D^{20}$: −30.8 (c 1.00, $CHCl_3$), [62% *ee*, (*R*)-isomer].

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