


Combining Fluorous and Triazole Moieties for the Tagging of Chiral Azabis(oxazoline) Ligands

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Dedicated to Armin de Meijere on the occasion of his 70th birthday.

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Abstract: New fluorous-tagged azabis(oxazoline) ligands were prepared using the copper-catalyzed azide-alkyne cycloaddition as ligation method. The resulting ligands were tested in copper-catalyzed asymmetric benzoylations (up to 99% *ee*), nitroaldol (up to 90% *ee*), and Michael reactions (up to 82% *ee*). The combination of unpolar fluorinated alkyl chains and polar triazole moieties imposes properties that are beneficial for the catalysts with respect to recyclability and selectivity. The scope and limitation

of this strategy in comparison to analogous catalysts immobilized on methoxypolyethylene glycol (MeOPEG) or polystyrene is discussed. Moreover, this study shows that the choice of solvent for a given reaction is crucial to arrive at highly recyclable bis(oxazoline) catalysts.

Keywords: azabis(oxazolines); click reaction; fluorous tags; immobilization; kinetic resolution; nitroaldol reaction

Introduction

Azasemicorrins^[1] and bis(oxazolines)^[2] are recognized as privileged classes of chiral ligands, being able to form complexes with a broad variety of metals that are able to catalyze a great number of reactions with unparalleled enantioselectivity. Impressive progress has been made in the development of immobilized bis(oxazolines)^[3] since the first reports on covalent immobilization appeared in 2000.^[4] Azabis(oxazolines)^[4a,5] have proved to be especially suitable ligands for attachment onto supports owing to their comparatively strong binding to metals resulting in greatly reduced leaching when they are used in repeating cycles in catalyses.^[6]

Recent studies on catalyst immobilization by us^[6] and other groups^[7] revealed that the copper-catalyzed azide-alkyne cycloaddition (CuAAC) is a facile method for grafting catalysts onto polymers or nanoparticles. Using an azido-functionalized support and an alkyne-substituted ligand or metal-ligand complex, high loading of the immobilized derivative close to the maximum capacity of the support can be achieved.

As a drawback of this strategy it has been recognized that the ability of the triazole moiety to act as a coordination site for metals results in decreased enantioselectivities by non-specific coordination of the metal with that moiety rather than with the chiral ligand in the course of catalyst preparations.^[6a,d,7d] For example, in the asymmetric benzoylation of diol (\pm)-**1**, the MeOPEG-bound ligand **6** performed comparable to its non-immobilized counterpart **4b**, while with ligand **5** significantly lower enantioselectivities were achieved with respect to **4a** (Figure 1). We attributed the loss of selectivity with **5** to copper-complexation with the triazole unit, which might, in addition, be assisted through the coordination of adjacent ether units from the MeOPEG polymer.

Arguably, the most important application of attaching perfluoroalkyl moieties to organic compounds is to separate the so-tagged compound from a complex reaction mixture by fluorous biphasic separations, applying perfluorinated solvent, fluorous silica or perfluorinated tags.^[8] This property has provided an attractive method for catalyst recovery and recycling and, consequently, perfluorinated tags were attached to several metal-based catalysts^[9] including bis(oxazolines)^[10] and organocatalysts.^[11]

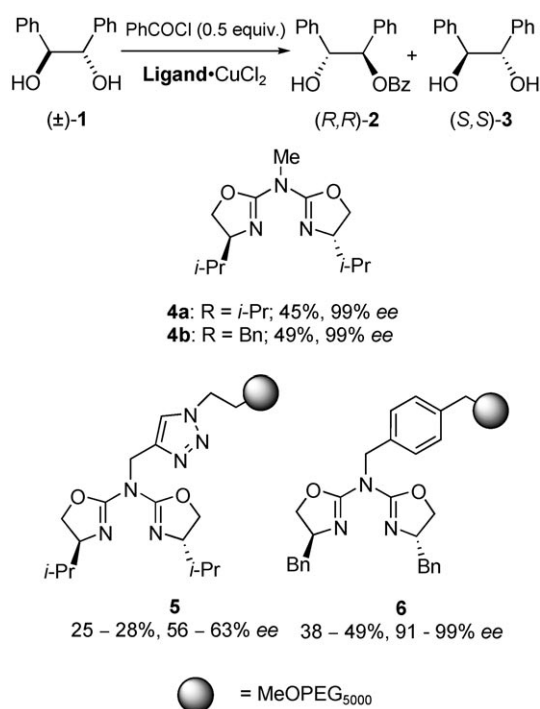


Figure 1. Application of azabis(oxazolines) in the asymmetric benzoylation of diol (\pm)-1.

Results and Discussion

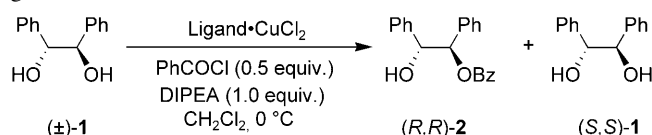
We report here that replacing the MeOPEG backbone in **5** with unpolar perfluoroalkyl tags can help to overcome the limitations outlined above. Besides greatly improved selectivities rivaling the non-tagged analogue **4a** the solubility profile imposed by a single perfluorotriazole tag is comparable to that observed by MeOPEG modification, that is, good solubility in solvents like dichloromethane, but low solubility in unpolar solvents like hexanes or diethyl ether, thus allowing for efficient recovery of ligands and catalysts. Upon attachment of multiple perfluorotriazole tags, the ligands and catalysts become insoluble in most organic solvents (hexanes, diethyl ether, THF, dichloromethane), thus allowing their recovery by simple filtration.

Initial attempts to synthesize a perfluoroalkyl tagged azabis(oxazoline) in analogy to **6** by direct alkylation of deprotonated **7** with **8** were unsuccessful. Nevertheless, propargylation of **7**^[6d] and chloride/azide exchange of **8**^[12] followed by the CuAAC of the resulting **9** and **10** proceeded with high yields to give rise to the monotagged azabis(oxazoline) ligand **11**. Likewise, ligation of **9** with azide **12**^[13] furnished the azabis(oxazoline) **13**, having three perfluoroalkyl chains and four triazoles incorporated (Scheme 1).

The fluororous-tagged ligands **11** and **13** were evaluated as ligands for metal catalysis. Starting with the copper(II)-catalyzed asymmetric monobenzoylation

of diols^[14] the soluble complex $\text{CuCl}_2\cdot\mathbf{11}$ showed excellent reactivity and enantioselectivity (Table 1, entries 3–8), being by far superior to the analogous MeOPEG-supported complex $\text{CuCl}_2\cdot\mathbf{5}$ (entries 1 and 2). Complete consumption of benzoyl chloride was

Table 1. Copper(II)-catalyzed asymmetric benzoylation of hydrobenzoin with fluororous tag bound azabis(oxazoline) ligands.^[a]



Entry	Mol%	Ligand	Run	Time [h]	Yield [%] ^[b]	<i>ee</i> of 2 [%] ^[c]
1 ^[d]	1.3	5	1	6	28	63
2 ^[d]	1.3	5	2	6	25	56
3	2	11	1	2	45	> 99
4	2	11	2	2	43	> 99
5	2	11	3	2	46	99
6	2	11	4	2	26	99
7	2	11	5	2	41	99
8	2	11	6	2	47	99
9	5	13	1	6	42	94
10	5	13	2	6	39	95
11	5	13	3	6	44	94
12	5	13	4	6	43	82

^[a] Ligand (2.2 mol%), CuCl_2 (2 mol%), PhCOCl (0.5 equiv.), DIPEA (1.0 equiv.), CH_2Cl_2 , 0 °C.

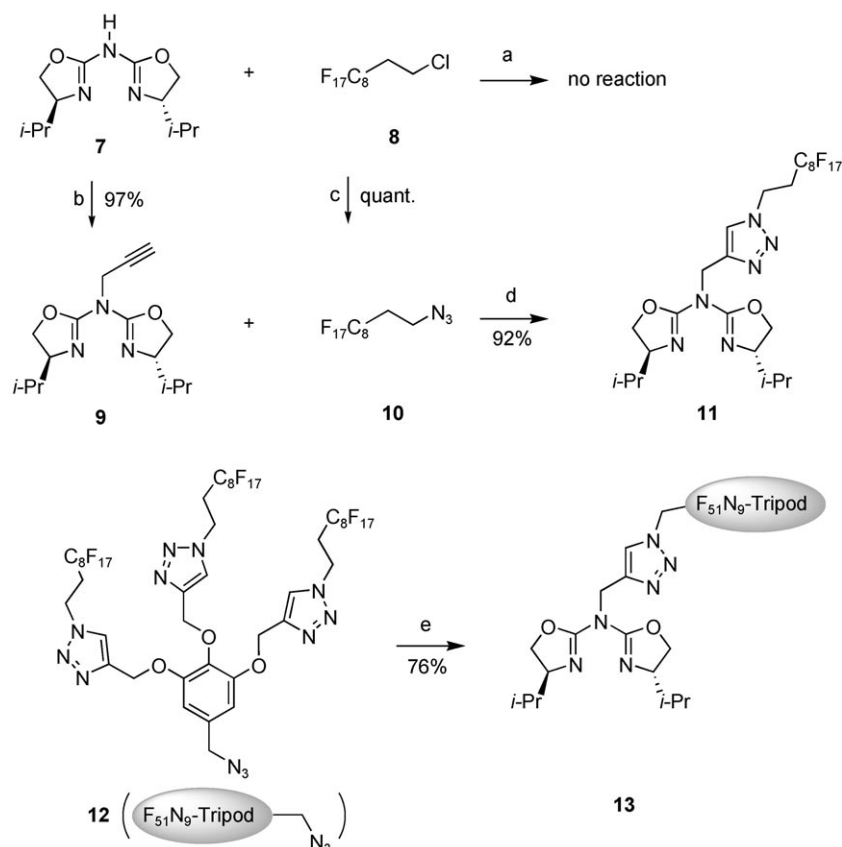
^[b] Isolated yield based on (\pm)-1 (maximum theoretical yield 50%).

^[c] Determined by chiral GC.

^[d] Taken from ref.^[6d]

observed within 2 h at 2 mol% of $\text{CuCl}_2\cdot\mathbf{11}$, giving rise to (*R,R*)-**2** in $\geq 99\%$ *ee*. $\text{CuCl}_2\cdot\mathbf{11}$ showed a comparable solubility profile like its MeOPEG-bound analogue $\text{CuCl}_2\cdot\mathbf{5}$ allowing, after removal of unreacted (\pm)-1 by filtration, its quantitative precipitation by the addition of diethyl ether to the reaction mixture. Thus, $\text{CuCl}_2\cdot\mathbf{11}$ was reused in six cycles without loss of its activity or selectivity (entries 3–8, Table 1), moreover, no metal leaching is observed. The heterogeneous three ponytailed complex $\text{CuCl}_2\cdot\mathbf{13}$ also catalyzed the benzoylation of (\pm)-1 effectively (entries 9–12), with greatly improved selectivity compared to the polystyrene bound analogue reported by us previously.^[6a] $\text{CuCl}_2\cdot\mathbf{13}$ could be recovered by simple filtration from the reaction mixture, however, in recycling experiments we noted a drop in selectivity after the third cycle.

Next we investigated the $\text{Cu}(\text{OAc})_2$ -catalyzed nitroaldol reaction for which Evans et al.^[15] reported excellent results with bis(oxazoline) ligands provided that the sterically bulky indabox ligand **14** (Figure 2,



Scheme 1. Synthesis of fluorous-tagged azabis(oxazolines): a) *n*-BuLi, THF, -78°C to room temperature; b) propargyl bromide (4 equiv.), *n*-BuLi (1.1 equiv.), THF, -78°C to room temperature, 24 h, 97%; c) NaN₃, acetone-H₂O (5:1); d) DIPEA (1.1 equiv.), CuI (6 mol%), THF, room temperature, 12 h, 92%; e) CuI (6 mol%), DIPEA (1.2 equiv.), THF, room temperature, 70 h, 76%.

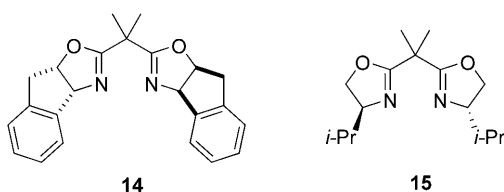


Figure 2.

Table 2, entry 1) is used. We were pleased to see that when aza(bisoxazoline) instead of bis(oxazoline) ligands are employed the simple valine-derived ligand **4a** also performs well, especially when THF is employed as solvent (Table 2, entries 2–5).

The single fluorous ponytailed complex **11**·Cu(OAc)₂ in a homogeneous reaction initially gave rise to the nitroaldol product **16** with comparable selectivities as observed with **4a** (Table 2, entry 6), with some erosion of enantioselectivity after three reaction cycles (entries 6–9). Similar results were obtained for the triple fluorous ponytailed complex **13**·Cu(OAc)₂ (entries 10–12).

Finally, we investigated the enantioselective Friedel–Crafts alkylation of indoles with benzyldenemal-

Table 2. Copper(II)-catalyzed asymmetric nitroaldol reaction.^[a]

Entry	Solvent	Ligand	Run	Yield [%] ^[b]	ee [%] ^[c]
1 ^[d]	EtOH	14	1	76	94 (<i>R</i>)
2	EtOH	15	1	73	63
3	THF	15	1	75	61
4	EtOH	4a	1	71	86
5	THF	4a	1	76	92
6	THF	11	1	68	90
7	THF	11	2	65	90
8	THF	11	3	63	86
9	THF	11	4	65	72
10	THF	13	1	59	86
11	THF	13	2	54	82
12	THF	13	3	57	70

^[a] Ligand (5.5 mol%), Cu(OAc)₂·H₂O (5 mol%), room temperature, 24 h.

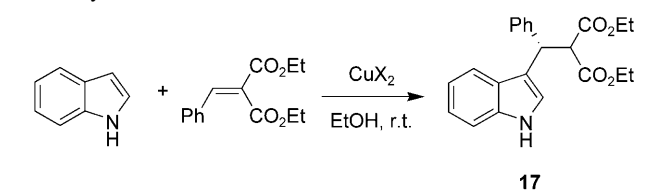
^[b] Isolated yield.

^[c] Determined by HPLC.

^[d] Taken from ref.^[15] **11** and **13** were recovered quantitatively by addition of hexane and were reused as such.

onates,^[17] which proceeds well with simple bis(oxazoline) and azabis(oxazoline) ligands, provided that the metal to ligand ratio is carefully adjusted.^[18] However, both ligands **11** and **13** in combination with various copper salts cannot rival the non-tagged ligand **4a** (Table 3, entries 1–2, 5–6) in the synthesis of **17**. Moreover, attempts to reuse the two complexes **11**·Cu(OTf)₂ or **13**·Cu(OTf)₂ were not successful, considerably lower enantioselectivities were observed in subsequent runs (entries 2–3, 6–7).

Table 3. Copper(II)-catalyzed enantioselective 1,4-addition to benzyldiene malonates.^[a]



Entry	Ligand	Run	CuX ₂	Yield [%] ^[b]	ee [%] ^[c]
1	4a	1	Cu(OTf) ₂	95	95
2	11	1	Cu(OTf) ₂	86	85
3	11	2	Cu(OTf) ₂	78	50
4	11	1	CuCl ₂	ND ^[d]	–
5	11	1	Cu(ClO ₄) ₂	93	72
6	13	1	Cu(OTf) ₂	84	68
7	13	2	Cu(OTf) ₂	76	46

^[a] Ligand (5.045 mol%), CuX₂ (5.0 mol%), EtOH, room temperature, 8 h.

^[b] Isolated yield.

^[c] Determined by HPLC.

^[d] NR = no reaction.

The difference in performance of the copper catalysts in combination with ligands **11** and **13** is clearly attributable to the choice of solvent in which the reactions have to be performed. While complexes with ligand **11** are soluble in dichloromethane, THF or alcohols, they can be effectively precipitated from hexanes or diethyl ether, allowing their quantitative recovery. No appreciable metal or ligand leaching (<0.1%) was observed when copper complexes of **11** were reisolated by precipitation from these solvents. Nevertheless, for reactions like the asymmetric 1,4-addition of indoles to malonates (Table 3) that require alcoholic solvents in order to achieve high selectivity,^[16] the recovered catalysts while showing the same activity were inferior in selectivity, indicating the presence of catalytically active copper centers outside the chiral environment of the ligand.

Copper complexes of **13** are insoluble in most organic solvents but showed appreciable solubility in ethanol or methanol (approx. 2 ± 1 mg mL⁻¹). Therefore, recovery of the catalysts by simple filtration was only effective for reactions that are carried out in di-

chloromethane or THF (Table 1 and 2) but not for reactions that called for the use of ethanol (Table 3). Nevertheless, experiments showed that also in THF, while no ligand leaching was observed, copper leaching was appreciable (approx. 3% in each run). Finally, we note that the counteranion in the copper complexes can have a large effect on the effectiveness to recycle the catalysts. While **13**·CuCl₂ is largely insoluble in THF (<0.5 mg mL⁻¹; approx. 3% copper leaching determined by total reflection X-ray fluorescence in each reaction cycle) **13**·Cu(OAc)₂ forms a gel in that solvent. After removal of THF and addition of dichloromethane/hexanes 1:5, recovery of the complex therefore by filtration proved to be difficult due to the morphology of the catalyst (mass recovery approx. 70% after each cycle).

Conclusions

Here we have demonstrated that tagging aza(bisoxazoline) ligands *via* the copper(I)-catalyzed alkyne-azide cycloaddition with perfluoroalkyl moieties opens the possibility to arrive at recyclable copper(II)-azabox complexes. Depending on the number of fluorine tags and triazole moieties, the resulting copper(II)-azabis(oxazoline) complexes are either soluble in solvents like dichloromethane, THF or ethanol but can be precipitated from diethyl ether or hexanes (MeOPEG-like properties) or are heterogeneous in dichloromethane or THF (polystyrene-like properties) and can be recovered by direct filtration from a reaction mixture.

The perfluoro tag apparently offsets the previously noted interference of the triazole moiety as an additional coordination site in metal catalyses. The success for efficient recyclability of the metal azabis(oxazoline) catalysts, however, is greatly dependent on the solvent that can be employed for a given reaction. When dichloromethane was used, the reisolated metal complexes could be reused without observable loss of reactivity and selectivity. THF only allowed the recycling of the catalysts approximately three times, while for reactions run in ethanol, recycling of the catalysts was not possible. The gel-like properties that some of the fluorine tagged catalysts described here adopt in polar solvents makes efficient recovery and reuse by filtration problematic.

Experimental Section

Ligand Synthesis

(S,S)-Bis(4-isopropyl-4,5-dihydrooxazol-2-yl)prop-2-ynylamine (9): To a stirred solution of **7** (239 mg, 1 mmol) in THF (10 mL) *n*-butyllithium (1.1 mmol, 690 µL of 1.6 N so-

lution in hexane) was added slowly at -78°C . After stirring for 10 min, propargyl bromide (4.0 mmol, 274 μL of an 80% solution in xylene) was added dropwise, and the solution was slowly warmed to room temperature overnight and stirred for another 10 h. Aqueous Na_2CO_3 was added and the mixture was concentrated. The residue was separated between CH_2Cl_2 and aqueous Na_2CO_3 . The aqueous phase was extracted twice with dichloromethane, and the combined organic phases were dried over MgSO_4 concentrated to give **9** as a light brown liquid; yield: 270 mg (97%). ^1H NMR (300 MHz, CDCl_3): δ =4.58 (d, 2H, J =2.3 Hz), 4.34 (dd, 2H, J =9.2, 8.3 Hz), 4.12 (dd, 2H, J =8.3, 6.7 Hz), 3.86 (ddd, 2H, J =9.2, 6.6, 6.1 Hz), 2.18 (t, 1H, J =2.4 Hz), 1.80–1.66 (m, 2H), 0.88 (d, 6H, J =6.8 Hz), 0.81 (d, 6H, J =6.8 Hz); ^{13}C NMR (75.5 MHz, CDCl_3): δ =156.4, 79.1, 71.7, 71.5, 69.7, 39.7, 32.7, 18.6, 17.6; IR: ν =3290, 3220, 2965, 2915, 2885, 1703, 1640, 1485, 1428, 1273, 1100, 985 cm^{-1} ; [α] $_{\text{D}}^{20}$: -58.7 (c 1.0, CH_3OH); MS (ES-MS): m/z =278.2 (MH^+); HR-MS: m/z =278.1875 [MH^+], calcd. for $\text{C}_{15}\text{H}_{23}\text{N}_3\text{O}_2$: 278.1869.

Single-ponytail perfluorinated azabox 11: To a stirred solution of **9** (830 mg, 2.99 mmol) in degassed dry THF (15 mL), 1-azido-perfluorodecane (1.46 g, 2.99 mmol), CuI (34 mg, 0.18 mmol) and DIPEA (606 μL , 3.29 mmol) were added and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with 0.1M EDTA solution, the product was extracted with CH_2Cl_2 (thrice). The combined organic layers were washed with brine and dried over Na_2SO_4 . After removal of the solvent, the crude product was recrystallized from hexane and ethylacetate to afford **11** as a colorless solid; yield: 2.1 g (92%); mp $124\text{--}125^{\circ}\text{C}$. ^1H NMR (300 MHz, CDCl_3): δ =7.69 (s, 1H), 5.13 (s, 2H), 4.63 (t, 2H, J =7.5 Hz), 4.39 (dd, 2H, J =9.1, 8.5 Hz), 4.13 (dd, 2H, J =8.3, 7.1 Hz), 3.87 (dt, 2H, J =9.1, 6.6 Hz), 2.69–2.86 (m, 2H), 1.77–1.66 (m, 2H), 0.91 (d, 6H, J =6.8 Hz), 0.82 (d, 6H, J =6.8 Hz); ^{13}C NMR (75.5 MHz, CDCl_3): δ =155.8, 143.9, 122.5, 70.6, 68.9, 44.1, 31.8, 17.6, 16.7; IR: ν =2963, 1750, 1635, 1553, 1485, 1416, 1373, 1333, 1196, 1146, 1095, 1048, 967, 935, 808, 704, 658, 609, 559, 529, 413 cm^{-1} ; MS (ES): m/z =767 (MH^+); HR-MS: m/z =766.1924 [MH^+], calcd. for $\text{C}_{25}\text{H}_{27}\text{F}_{17}\text{N}_6\text{O}_2$: 766.1917.

Triple-ponytails perfluorinated azabox 13: To a stirred solution of **9** (100 mg, 0.36 mmol) in degassed dry THF (10 mL), **12** (397 mg, 0.23 mmol), CuI (2.6 mg, 14 μmol) and DIPEA (45 μL , 0.27 mmol) were added and the reaction mixture was stirred at room temperature for 70 h. The reaction mixture was quenched with 0.1M EDTA solution, and the product was filtered and washed with water and ether and dried under reduced pressure to give **13** as a light brown solid; yield: 359 mg (76%); mp $153\text{--}155^{\circ}\text{C}$; IR: ν =3200, 2963, 2104, 1642, 1437, 1327, 1200, 1146, 1112, 972, 705, 657, 530 cm^{-1} ; MS (ES): m/z (%)=2042 (72), 2041 (MH^+ , 100), 1931 (38), 1930 (74), 1781 (31), 1764 (47).

General Procedure for the Preparation of Copper(II)-Aza(bisoxazoline) Complexes

11-CuCl₂ complex: A solution of ligand **11** (1.1 mmol) and CuCl_2 (1.0 mmol) in CH_2Cl_2 (25 mL) was stirred for 1 h, filtered, and the filtrate was concentrated under reduced pres-

sure. Recrystallization from CH_2Cl_2 gave the complex as green crystals.

13-CuCl₂ complex: Ligand **13** (1.1 mmol) and CuCl_2 (1.0 mmol) were stirred in CH_2Cl_2 (25 mL) for 2 h. The resulting green complex was filtered, washed once with THF and dried to afford the green complex.

General Procedure for the Catalytic Asymmetric Benzoylation

1,2-Diol (\pm)-**1** (1.0 mmol), diisopropylethylamine (DIPEA, 1.0 mmol) and 0.02 mmol of the fluorous tagged catalyst were charged in 4 mL of CH_2Cl_2 and cooled to 0°C . Benzoyl chloride (0.5 mmol) was added and the mixture was stirred at 0°C until the benzoyl chloride disappeared (TLC). After recovery of the catalyst (see below) the reaction mixture was poured into water and extracted three times with CH_2Cl_2 . The combined organic layers were dried over magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate).

Catalyst Recovery and Recycling

11-CuCl₂ complex (homogeneous): After completion of the reaction, the reaction mixture was filtered to remove unreacted (\pm)-**1**. Cold diethyl ether (5 mL) was added to the filtrate to precipitate the complex. The complex was recovered by filtration, dried and directly used for the next reaction.

13-CuCl₂ complex (heterogeneous): After completion of the reaction, the reaction mixture was filtered in order to recover the complex and washed with MeOH (2 mL), dried and reused directly.

General Procedure for the Copper Acetate-Catalyzed Direct Nitroaldol Reaction of Nitromethane with Aldehydes

To a Schlenk tube fluorous-tagged azabis(oxazoline) (0.055 mmol) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.05 mmol) were added under an air atmosphere. THF (2.5 mL) was added and the mixture was stirred for 1 h at room temperature ($20\text{--}25^{\circ}\text{C}$). To the resulting blue-green solution nitromethane (537 μL , 10 mmol) and benzaldehyde (102 μL , 1 mmol) were added. After stirring for the time indicated, the catalyst was recovered (see below) and the crude product was purified by column chromatography (hexanes/EtOAc, 85:15).

Catalyst Recovery and Recycling

11-Cu(OAc)₂ complex (homogeneous): After the completion of reaction, THF was removed; hexanes (5 mL) and dichloromethane (1 mL) were added to the reaction mixture in order to precipitate the complex. The recovered complex was dried and directly used for the next reaction.

13-Cu(OAc)₂ complex (gel): After the completion of reaction, THF was removed; hexanes (5 mL) and dichloromethane (1 mL) were added to the reaction mixture in order to precipitate the complex. The recovered complex was dried and directly used for the next reaction.

General Procedure for the Catalytic Asymmetric Michael Addition of Indole to Diethyl 2-Benzylidenemalonate

To a Schlenk tube fluorine-tagged azabis(oxazoline) (0.05 mmol) and $\text{Cu}(\text{OTf})_2$ (0.05 mmol) were added under an air atmosphere. THF (2 mL) was added and the mixture was stirred for 1 h at room temperature (20–25 °C). To the resulting blue-green solution diethyl 2-benzylidenemalonate (1 mmol, 1.0 equiv.) in EtOH (2 mL) was added and stirring was continued for 20 min before the indole (1.2 mmol, 1.2 equiv.) was added. After stirring for 8 h at room temperature, the catalyst was recovered (see below) and the crude product purified by column chromatography (performed with hexanes/DCM, 1:1, followed by DCM).

Catalyst Recovery and Recycling

11- $\text{Cu}(\text{OTf})_2$ complex (homogeneous): After the completion of reaction, the solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (0.5 mL) and diethyl ether was added (5 mL) to the filtrate to precipitate the complex. The recovered complex was dried and directly used for the next reaction.

13- $\text{Cu}(\text{OTf})_2$ complex (heterogeneous): After the completion of reaction, the reaction mixture was filtered in order to recover the complex and washed with EtOH, dried and reused directly.

Determination of Cu by Means of Total Reflection X-Ray Fluorescence

All work was performed in a laminar flow, clean work space. The solid samples were dissolved in 1 mL of high purity methanol (analytical grade for chromatography, Merck, Darmstadt) and an aliquote of 100 μL was mixed thoroughly with vanadium standard solutions (freshly prepared by dilution of $1000 \pm 2 \text{ mg L}^{-1}$ stock standard solution in 0.5% HNO_3 , Merck, Darmstadt). The mixed sample solutions and a blank sample were analyzed for Cu by means of total reflection X-ray fluorescence (TXRF, Atomika 8010, Oberschleißheim, Germany). Calibration was performed by internal vanadium standard addition and investigation of the blank sample approved contamination-free pre-treatment procedure. TXRF analysis offers simultaneous determination of multiple metals with an accuracy of ca. 2%. Beside copper only traces of Ta and Co were observed.

Leaching Experiments

13- CuCl_2 (15 mg, copper content = 430 μg) was suspended in 1.5 mL of THF. After filtration, the solvent was evaporated, and the residue was subjected to copper analysis as described above. Found: 13.9 μg copper (3% leaching). No appreciable amounts of ligand (<0.5 mg) were observed in the filtrate.

13- CuCl_2 (15 mg, copper content = 430 μg) was suspended in 1.5 mL of MeOH. After filtration, the solvent was evaporated, and the residue was subjected to copper analysis as described above. Found: 21.3 μg copper (5% leaching). Approx. $2 \pm 1 \text{ mg}$ of the ligand were observed in the filtrate.

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