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Asymmetric conjugate addition of α-keto esters to nitroolefins catalyzed by chiral Cu^{II} hydroxo complexes

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Dedicated to Professor H. Kagan on the occasion of his 80th birthday

ABSTRACT

As a part of our research project on hard anion-late transition metal complexes as mild acid–base catalysts, we describe herein that Cu^{II} hydroxo complexes having chiral N-substituted-diaminocyclohexanes are mild and selective catalysts, which are applicable to the catalytic asymmetric conjugate addition of α-keto esters to nitroolefins. The reaction proceeded diastereoselectively without the detectable formation of self-aldol products, affording the corresponding coupling products with *anti*-stereochemistry in an enantioselective manner.

1. Introduction

The development of environmentally friendly atom-economical organic transformations is an important goal in the field of current synthetic organic chemistry. Direct in situ activation of acidic compounds and its application to asymmetric catalysis have witnessed great progress in the last decade,[1] and various C–C bond-forming reactions without pre-activation of substrates have been developed using novel chiral Lewis acid catalysts, basic metal catalysts, enamine catalysis, and Brønsted acid catalysts.[2–4] However, we believe that further studies to create mild and selective catalysts are necessary in order to expand the scope of available substrates as well as to develop novel catalytic reactions.

We have been working on asymmetric catalysis under proton-transfer conditions and unique C–C bond-forming reactions, halogenation reactions, and aza-Michael reactions have been developed.[5] During these studies, we found that charged anionic-ligands such as a hydroxide ion on late transition metals can act as a mild endogenous base. Since monomeric Pd hydroxo complexes dissociated from Pd μ-hydroxo complexes **1** can function as both a Lewis acid and a Brønsted base, the reactions with 1,3-dicarbonyl compounds such as β-keto esters and malonates give chiral bidentate Pd enolates cleanly. As a part of our research project on hard anion-late transition metal complexes as mild acid–base catalysts, we herein describe that Cu^{II} hydroxo complexes having chiral diamines are effective acid–base catalysts, being applicable to a novel catalytic asymmetric reaction of α-keto esters.

Because α-keto esters are versatile building blocks, asymmetric addition reactions of dialkylzinc reagents, arylboronic acids, enol silanes, and nitromethane to the keto group have been well investigated.[6] In contrast, they have rarely been used as a pronucleophile,[7] although pyruvic acid, a representative 1,2-dicarbonyl compound, is an important donor unit in biosynthesis. This is probably because the high reactivity as an electrophile may limit their use as a pronucleophile, and because they are considered to be less acidic than 1,3-dicarbonyl compounds. However, strongly basic catalysts would induce undesired side reactions such as self-aldol condensation reactions. Therefore, the development of selective catalysts with mild reactivity is desirable. To this end, we thought that our acid–base catalysis using basic charged anion-coordinating transition metal complexes would be effective to achieve selective transformations of α-keto esters.

2. Results and discussion

To test our hypothesis, we selected the catalytic asymmetric conjugate addition of α-keto esters to nitroolefins as a model reaction, which should be useful for the synthesis of highly functionalized compounds.[8,9] It is noteworthy that a catalytic version of this type of reactions had not been reported before our recent work.[10] Only one example using a nearly stoichiometric amount of strongly basic *t*-BuOK (0.9 equiv) has been reported,[11] but the chemical yield of the desired product was less than 50%. Based on our previous studies,[5] we first tested the Pd μ-hydroxo complexes **1**. However, all reactions examined were sluggish, and the desired product was obtained in less than 15% yield (48 h, rt). This may be due to that the Pd hydroxo complex is not sufficiently basic to abstract the α-proton of the substrate (see Scheme 1).

To overcome this problem, we planned to investigate a Cu hydroxo complex. We expected that it should show stronger basicity than the palladium complex **1**, judging from their electronegativity

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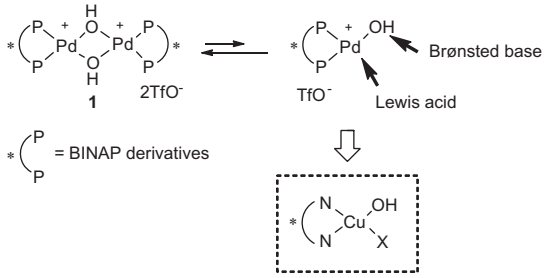
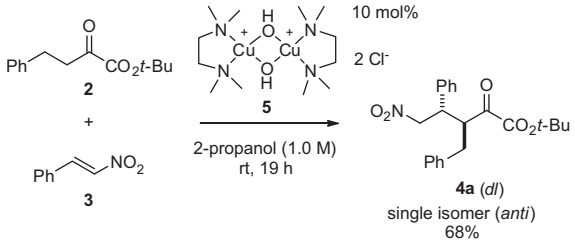


Scheme 1. Transition metal hydroxo complexes as acid–base catalysts.

(Pd: 2.2, Cu: 1.9).[12] The following facts discussed in the literature also support our idea: (1) In Glaser–Hay dimerization reactions of terminal alkynes, Cu acetylides are formed as a result of deprotonation by the Cu hydroxo complex.[13] (2) In oxidative coupling reactions of naphthols, an acid–base reaction of the Cu hydroxo complex gives a Cu naphthoxide as a key intermediate.[14] To our delight, the reaction of α-keto ester **2** with nitroolefin **3** was efficiently promoted by 10 mol % of known $[(TMEDA)Cu(\mu\text{-}OH)]_2Cl_2$ **5** [TMEDA = tetramethylethylenediamine].[15] While the reactions in normal organic solvents such as THF, toluene, CH_2Cl_2, and CH_3CN resulted in only modest yield (<25% yield), the reaction in 2-propanol proceeded smoothly to give the desired product **4a** at a synthetically useful level (68% yield after 19 h) (Scheme 2).

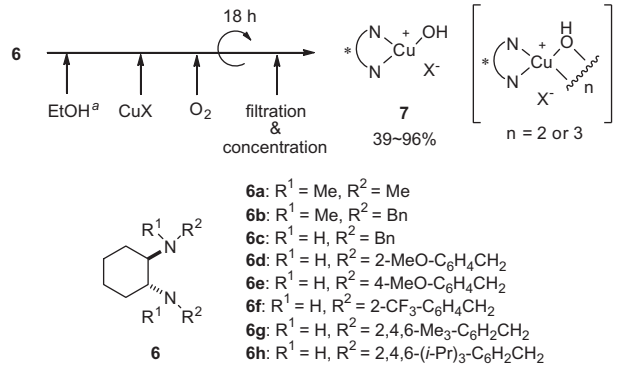


Scheme 2. Conjugate addition of **2a**–**3a** catalyzed by $[(TMEDA)Cu(\mu\text{-}OH)]_2Cl_2$.

This result prompted us to investigate an asymmetric version of this reaction. Chiral Cu hydroxo complexes having optically active N-substituted diaminocyclohexane derivatives were prepared according to the reported procedure[14–16] (Scheme 3). It was reported that the resulting Cu complex exists as its dimer or trimer in a solid phase, depending on the amount of substitution at the nitrogen atom. However, it is generally considered that they are in equilibrium with the monomer in the solution, which participates in the reaction as the active species.[14] Therefore, we describe the Cu complex **7** as a monomer and calculated it on the basis of the formula of [(diamine)Cu(OH)Cl], although the exact structure is unclear at present.

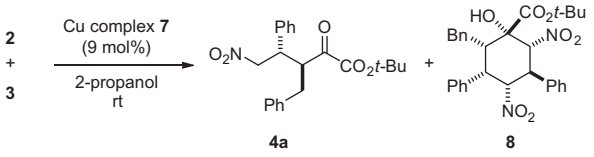
Results of the catalyst screening are summarized in Table 1. Although Cu complexes having *N,N,N′,N′*-tetraalkyl-substituted diaminocyclohexanes **6a** and **6b** as a chiral ligand could promote the model reaction, negligible asymmetric induction was observed. Moreover undesired cyclic compound **8** which arose from over-reaction with a second nitroolefin was also formed in an appreciable amount (entries 1 and 2). In contrast, modest to good enantioselectivities (37–56%) were observed using secondary amine ligands (entries 3–6). However, in these reactions, the chemical yield of **4a** was less than 20%, accompanied with the compound **8** in 31–36% yield.

We speculated that a Cu nitronate intermediate generated in the first conjugate addition reacted directly with the remaining nitroolefin to give **8**. If this was the case, it was expected that the over-reaction would be minimized by employing bulkier diamine ligands to prevent the nitroolefin from approaching the Cu nitronate.



Scheme 3. Preparation of Cu hydroxo complexes. [a]THF was used in the case of $Cu(CH_3CN)_4(PF_6)$.

Table 1
Catalyst screening

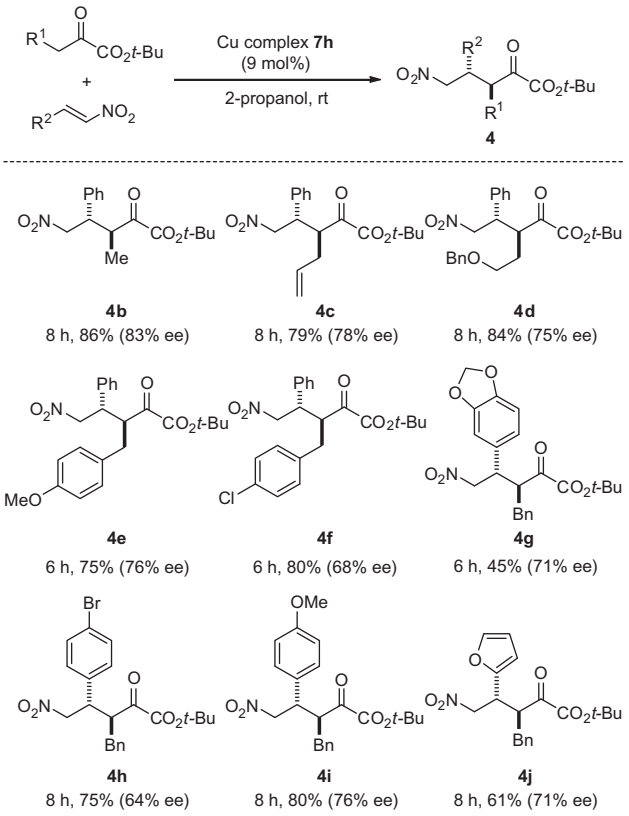


Entry	Catalyst **7** [diamine, X]	Time (h)	**4aa** Yield % (% ee)	**8** Yield[a] % (% ee)
1[b]	**6a**, X = Cl	10	59 (0)	10
2[b]	**6b**, X = Cl	47	12 (0)	27
3[b]	**6c**, X = Cl	10	6 (37)	35 (39)
4	**6d**, X = Cl	2	14 (40)	30
5	**6e**, X = Cl	10	17 (41)	36
6	**6f**, X = Cl	27	31 (56)	31
7	**6g**, X = Cl	6	73 (76)	10 (66)
8[c]	**6g**, X = Cl	72	42 (84)	14
9	**6g**, X = Br	24	45 (75)	21
10	**6g**, X = I	6	24 (41)	36
11	**6g**, X = OTf	52	44 (77)	13
12	**6g**, X = PF_6	178	38 (80)	14
13	**6h**, X = Cl	6	79 (80)	6 (11)

[a] Yield based on **2**.
[b] 0.4 M.
[c] 0 °C.

Additionally, such bulky ligands might improve the chiral environment of the putative Cu enolate of **2a**, allowing for better enantioselectivity. As we hoped, the chemical yield and the ee of the product were greatly improved, when bulkier **6g** was used as a ligand. Although the best enantioselectivity of 84% was achieved at 0 °C, the reaction became slow (entry 8). Further studies on the influence of counter anions revealed that chloride ion gave the best results (entries 9–12). In entry 13, the catalyst having a much bulkier **6h** gave a slightly better ee. The reaction was complete within 6 h to afford **4a** in 79% yield and with 80% ee. Interestingly, the ee of **8** was decreased dramatically compared to that of the parent compound **4a** in this reaction (vide infra).

As in the case of the Cu complex **5**, 2-propanol was the best solvent for this asymmetric reaction, and other usual organic solvents gave low chemical yields. The reaction was always *anti*-selective, and only a trace amount of *syn*-epimer was detected. The relative and absolute stereochemistries of **4a** and **8** were determined by comparing the reported analytical data.[10] Interestingly, the Cu catalyst **7** gave the opposite enantiomer of the product obtained from $Ni(OAc)_2$–**6c** complex that has been recently developed by us,[10] even though both diamine ligands were synthesized from the same chiral source. It should be noted that the diastereoselectivity of this



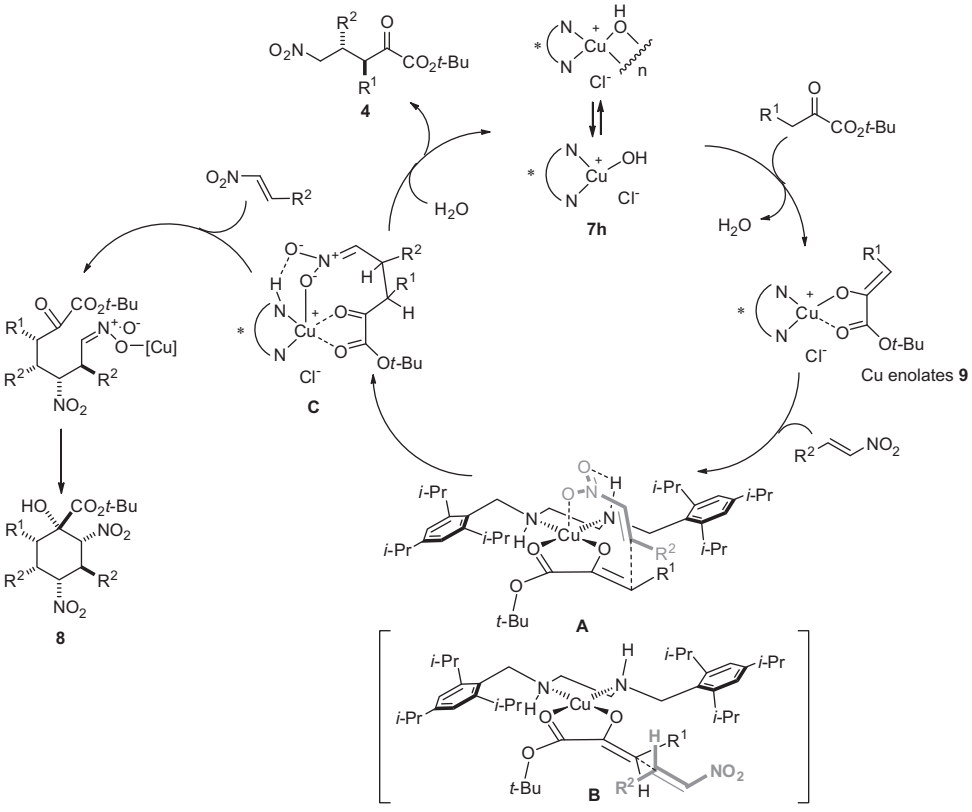
Scheme 4. Catalytic asymmetric conjugate addition of various α-keto esters to nitroolefins.

reaction is complementary to the *syn*-selectivity generally observed in organocatalytic reactions of aldehydes and ketones.[8]

Under the optimized conditions, the scope of the reaction was investigated (Scheme 4). Thus, the reactions were carried out in 2-propanol (1 M) at room temperature in the presence of 9 mol % of **7h** (X = Cl). As shown in Scheme 4, this reaction was applicable to various substrates in respect to both α-keto esters and nitroolefins. Regardless of the size and electronic properties of the substrates, all reactions examined reached completion within 8 h, affording the corresponding products in good yield with good to high enantioselectivity (63–83% ee). Since the reaction conditions are mild, various functional groups including ethers, halogens, and the acid-sensitive furan ring were tolerant. Like **4a**, these reactions proceeded in a highly diastereoselective manner. Notably, the starting materials and the solvent could be used without purification, and no precaution to remove moisture was necessary.

3. Mechanistic considerations

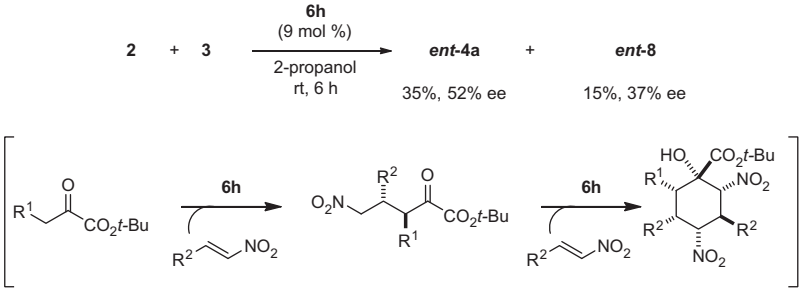
A proposed catalytic cycle of the present reaction is outlined in Scheme 5. The Cu hydroxo complex **7h** would react with α-keto esters to give the corresponding chiral Cu enolates. Since Cu^{II} usually takes a square planar geometry,[17] we assume that a bidentate enolate **9** is formed. The C–C bond-forming event would occur through the coordination of the nitoolefins to the Cu ion. Although an acyclic transition state model **B** cannot be ruled out, the excellent diastereoselectivity observed in this reaction can be explained by assuming a cyclic transition state model **A**. Based on molecular modeling studies and the reported X-ray structure of similar Cu–diamine complexes,[18] it is most likely that the aryl groups of the diamine ligands are located at the pseudo-equatorial position, creating a C_2 symmetric chiral environment. Therefore, the ester



Scheme 5. Assumed catalytic cycle.

group of the substrate points away to avoid steric repulsion with the aryl group. Since the *re* face of the enolate is blocked by the *t*-butyl ester and the aryl group of the ligand, the reaction occurs at the *si* face of the enolate preferentially. The absolute and relative stereochemistry of the product can be predicted using this model. Based on the fact that the N–H bond within the ligand plays an important role for asymmetric induction (see Table 1, entries 1–3), we assume that hydrogen bonding between the nitro group and the N–H group is also operative in controlling the geometry of the nitroolefins. Finally, protonation of the resulting Cu nitronate **C** followed by dissociation of the desired product completes the catalytic cycle. The bulky ligands seem to be the factor in suppressing the undesired over-reaction of the intermediate **C**. In the meantime, when the Cu catalyst is sterically less hindered, the remaining nitroolefin can react with the Cu nitronate, affording the cyclic compound **8** as a major product.

Unlike **7c**, the ee of **8** obtained from the bulky **7h** was much lower than that of the parent compound **4a** as shown in entry 13 of Table 1. We assume that the bulky diamine **6h** is relatively easy to dissociate from the Cu catalyst because of the steric repulsion, which might promote less enantioselective conjugate addition of **2** as well as the second conjugate addition of **4a**. A control experiment indicated that the diamine ligand alone could catalyze the reaction, affording the opposite enantiomers *ent*-**4a** and *ent*-**8** with moderate enantioselectivity (Eq. 1). The difference in the ees between **4a** and **8** might arise from the kinetic resolution in the second conjugate addition.



(1)

As for the desired compound **4**, high enantioselectivity was achieved (Table 1, entry 13). This may be attributed to the Cu-catalyzed conjugate addition reaction being faster than that by the diamine. In contrast, the Cu- and the diamine-involved pathways to **8** might be retarded due to the steric interaction. Consequently, both routes are likely to contribute to the formation of **8** comparably, resulting in the drastic loss of the ee. On the contrary, the similar ees were observed in the case of **7c** (entry 3). This is probably because the Cu-involved pathway to give **8** prevailed, and because the dissociation of the ligand was minimized.[25] In addition, the reactivity of **4** and *ent*-**4** in the Cu- or diamine-catalyzed second conjugate addition as well as the reactivity of two diastereomeric isomers of the intermediate **C** in the reaction with the nitroolefins may be different. It is also necessary to consider such kinetic resolution for a further understanding of the reaction mechanism.

4. Conclusion

In conclusion, we have demonstrated that the Cu hydroxo complexes having N-substituted diaminocyclohexane derivatives can be used as mild acid–base catalysts for catalytic asymmetric conjugate addition of α-keto esters to nitroolefins. The reactions proceeded smoothly in a product-selective manner, and the desired products with *anti*-stereochemistry were obtained in good yield with up to 84% ee. In addition, a unique ligand effect in controlling the product selectivity was observed. Further studies to improve the reaction efficiency are under way in our laboratory.

5. Experimental section

5.1. General

NMR spectra were recorded on a JEOL JNM-LA400 spectrometer operating at 400 MHz for ^{1}H NMR and 100.4 MHz for ^{13}C NMR. Chemical shifts were reported downfield from TMS (=0) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported using the solvent signal as an internal reference. FAB-LRMS and HRMS were taken on JEOL Mstation JMS-700 using *m*-nitrobenzyl alcohol (*m*NBA) as matrix. ESI-LRMS and HRMS were taken on JMS T100LP using H_2O/acetonitrile (contained with 0.05% of formic acid) as mobile phase. Optical rotations were measured on a JASCO DIP-370 polarimeter. IR was measured on Thermo Nicolet AVATAR 370 FT-IR equipped with DuraScope™ or PerkinElmer Spectrum 100. Melting points were measured using Yamaco MP-J3. Precoated TLC plates (Silica Gel 60 F_{254}, 0.25 mm) were used for the TLC analysis. Flash column chromatography was performed with silica gel N 60 (40–100 μm) or NH silica gel (100–200 mesh). In some cases, purification was carried out using Yamazen medium-pressure liquid chromatography (MPLC) systems [pump, 580-D; UV-detector, prepUV-10VW; column, Yamazen HI-FLASH™]. The enantiomeric excesses (ees) were determined by chiral HPLC analysis, which was performed on JASCO Borwin Ver.1.5 systems consisting of the following: pump, PU-2080 Plus; detector, CD-2095 Plus measured at 254 nm or 280 nm; column, DAICEL CHIRALPAK AD-H, IC, and DAICEL CHIRALCEL OD-H; mobile phase, *n*-hexane/2-propanol (IPA), *n*-hexane/IPA/ethyl acetate, or *n*-hexane/ethanol. Solvents used in this paper were purchased and used directly. Other reagents were purified by usual methods. (*R*,*R*)-1,2-Diaminocyclohexane was purchased from commercial source and was used as received. Known chiral ligands, α-keto esters, and nitroolefins were prepared according to the literature procedures.

5.2. Ligand

Diamines **6a**,[19] **6b**,[19] **6c**,[20] **6d**,[21,22] **6e**,[22,23] **6f**,[22] and **6g**[24] are known compounds. The compound **6h** was synthesized as described below.

5.2.1. (1*R*,2*R*)-*N*,*N*′-Bis[(2,4,6-triisopropylphenyl)methyl]-1,2-diaminocyclohexane 6h

To a suspension of K_2CO_3 (2.21 g, 16.0 mmol) and (*R*,*R*)-1,2-diaminocyclohexane (456 mg, 4.00 mmol) in DMF (10 mL) was added 2,4,6-triisopropylbenzyl chloride (2.02 g, 8.00 mmol) in DMF (20 mL). After stirring at room temperature for 2 h, at 50 °C for 1 h, and at 100 °C for 3 h, the reaction mixture was quenched

with water (40 mL). The resultant mixture was extracted with Et_2O (20 mL × 3), and the combined organic layers were washed with water (40 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (NH silica gel, *n*-hexane/Et_2O = 15:1) to give **6h** in 45% yield as a colorless solid (981 mg).

Mp 59–61 °C; IR (neat) ν 3307, 2958, 2924, 2865, 1608, 1458, 1261, 1114, 876 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.88 (s, 4H), 3.93 (d, J = 11.5 Hz, 2H), 3.41 (d, J = 11.5 Hz, 2H), 3.21–3.06 (m, 4H), 2.91–2.75 (m, 2H), 2.35–2.19 (m, 4H), 1.78 (d, J = 8.1 Hz, 2H), 1.43–1.04 (m, 28H), 0.98 (d, J = 6.8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 147.1, 132.0, 120.6, 63.0, 43.7, 34.3, 31.8, 29.1, 25.1, 24.8, 24.3, 24.2, 24.1; LRMS (ESI) *m/z* 547 $[M+H]^+$; HRMS (ESI) calcd for $C_{38}H_{63}N_2$ 547.49912 $[M+H]^+$, found 547.49915; $[\alpha]_D^{27} = -56.5$ (*c* 1.01, $CHCl_3$).

5.3. Complex 7a–7h (X = Cl)

Complexes **7a**–**7h** were prepared according to the literature procedure.[15]

A mixture of the ligand of interest and CuCl (1 equiv) in ethanol (95%) was stirred at room temperature for 18 h under O_2 atmosphere. The resulting solution was filtered through filter paper and concentrated under reduced pressure. The obtained green solid was used without further purification.

5.4. General procedure for the catalytic asymmetric conjugate addition of α-keto esters to nitroolefin

The Cu μ-hydroxo complex **7h** (9 mol %) and an α-keto ester (0.1 mmol) were combined under N_2 atmosphere in 2-propanol (0.1 mL) at room temperature. A *trans*-β-nitroolefin (0.1 mmol) was added to the resulting solution and the mixture was stirred for 6–8 h. After dilution with ethyl acetate, the solution was passed through a pad of SiO_2 and concentrated under reduced pressure. Further purification by MPLC (*n*-hexane/ethyl acetate = 9:1) was carried out to give the pure product. The ee of the product was determined by chiral HPLC analysis. The absolute stereochemistry of the products was assigned by analogy to that of the compound **4a**.[10]

5.4.1. (3*S*,4*S*)-*tert*-Butyl 3-benzyl-5-nitro-2-oxo-4-phenylpentanoate 4a[10]

CHIRALCEL OD-H, *n*-hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm, τ_{major} 22.8 min, τ_{minor} 59.6 min; $[\alpha]_D^{28} = -28.0$ (*c* 1.03, $CHCl_3$) (80% ee).

5.4.2. (3*S*,4*S*)-*tert*-Butyl 3-methyl-5-nitro-2-oxo-4-phenylpentanoate 4b[10]

CHIRALPAK IC, *n*-hexane/ethanol = 98:2, flow rate 1.0 mL/min, λ = 280 nm, τ_{major} 12.8 min, τ_{minor} 22.3 min; $[\alpha]_D^{27} = -8.5$ (*c* 1.01, acetone) (83% ee).

5.4.3. (3*S*,4*S*)-*tert*-Butyl 3-(2′-nitro-1′-phenylethyl)-2-oxohex-5-enoate 4c[10]

CHIRALPAK IC, *n*-hexane/2-propanol = 98:2, flow rate 1.0 mL/min, λ = 254 nm, τ_{major} 13.1 min, τ_{minor} 23.6 min; $[\alpha]_D^{28} = -1.8$ (*c* 1.00, $CHCl_3$) (78% ee).

5.4.4. (3*S*,4*S*)-*tert*-Butyl 3-[2′-(benzyloxy)ethyl]-5-nitro-2-oxo-4-phenylpentanoate 4d[10]

CHIRALPAK AD-H, *n*-hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm, τ_{major} 14.0 min, τ_{minor} 15.1 min; $[\alpha]_D^{29} = +6.4$ (*c* 1.15, $CHCl_3$) (75% ee).

5.4.5. (3*S*,4*S*)-*tert*-Butyl 3-(4′-methoxybenzyl)-5-nitro-2-oxo-4-phenylpentanoate 4e[10]

CHIRALCEL OD-H, *n*-hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm, τ_{major} 29.9 min, τ_{minor} 35.5 min; $[\alpha]_D^{29} = -19.7$ (*c* 1.06, $CHCl_3$) (76% ee).

5.4.6. (3*S*,4*S*)-*tert*-Butyl 3-(4′-chlorobenzyl)-5-nitro-2-oxo-4-phenylpentanoate 4f[10]

CHIRALCEL OD-H, *n*-hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm, τ_{major} 26.0 min, τ_{minor} 29.9 min; $[\alpha]_D^{29} = -15.2$ (*c* 1.07, $CHCl_3$) (68% ee).

5.4.7. (3*S*,4*S*)-*tert*-Butyl 4-(3′,4′-methylenedioxyphen)-3-benzyl-5-nitro-2-oxopentanoate 4g

Mp 92–94 °C; IR (neat) ν 2981, 1722, 1552, 1487, 1247, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.23 (m, 2H), 7.23–7.16 (m, 1H), 7.15–7.09 (m, 2H), 6.70 (d, J = 1.7 Hz, 1H), 6.70 (d, J = 8.1 Hz, 1H), 6.65 (dd, J = 8.7, 1.7 Hz, 1H), 5.92 (d, J = 1.5 Hz, 1H), 5.91 (d, J = 1.5 Hz, 1H), 4.76 (dd, J = 12.7, 5.1 Hz, 1H), 4.67 (dd, J = 12.7, 9.5 Hz, 1H), 4.20–4.11 (m, 1H), 3.83 (apparent td, J = 9.5, 5.1 Hz, 1H), 2.98 (apparent d, J = 8.3 Hz, 2H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 159.0, 148.0, 147.3, 136.9, 130.1, 128.9, 128.7, 126.9, 121.6, 108.6, 108.4, 101.2, 84.2, 78.1, 50.8, 45.6, 36.1, 27.5; LRMS (FAB) *m/z* 450 $[M+Na]^+$; HRMS (FAB) calcd for $C_{23}H_{25}NaNO_7$ 450.1529 $[M+Na]^+$, found 450.1531; CHIRALPAK IC, *n*-hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm, τ_{major} 14.5 min, τ_{minor} 20.2 min; $[\alpha]_D^{29} = -16.1$ (*c* 0.63, $CHCl_3$) (71% ee).

5.4.8. (3*S*,4*S*)-*tert*-Butyl 3-benzyl-4-(4′-bromophenyl)-5-nitro-2-oxopentanoate 4h[10]

CHIRALCEL OD-H, *n*-hexane/2-propanol/ethyl acetate = 90:7:3, flow rate 1.0 mL/min, λ = 280 nm, τ_{major} 22.1 min, τ_{minor} 72.7 min; $[\alpha]_D^{29} = -12.7$ (*c* 1.30, $CHCl_3$) (64% ee).

5.4.9. (3*S*,4*S*)-*tert*-Butyl 3-benzyl-4-(4′-methoxyphenyl)-5-nitro-2-oxopentanoate 4i[10]

CHIRALCEL OD-H, *n*-hexane/2-propanol/ethyl acetate = 90:7:3, flow rate 1.0 mL/min, λ = 254 nm, τ_{major} 26.3 min, τ_{minor} 65.7 min; $[\alpha]_D^{29} = -21.2$ (*c* 1.05, $CHCl_3$) (76% ee).

5.4.10. (3*S*,4*S*)-*tert*-Butyl 3-benzyl-4-(furan-2′-yl)-5-nitro-2-oxopentanoate 4j[10]

CHIRALCEL OD-H, *n*-hexane/2-propanol/ethyl acetate = 90:7:3, flow rate 1.0 mL/min, λ = 254 nm, τ_{major} 14.2 min, τ_{minor} 30.1 min; $[\alpha]_D^{27} = +3.8$ (*c* 0.73, THF) (71% ee).

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