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Sequential Au/Cu Catalysis: A Two Catalyst One-Pot Protocol for the Enantioselective Synthesis of Oxazole α-Hydroxy Esters *via* Intramolecular Cyclization/Intermolecular Alder-Ene Reaction

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Abstract:

A convenient protocol for the enantioselective synthesis of oxazole α-hydroxy ester derivatives **4** from readily available propargylamides **1** and alkylglyoxylates **3** was developed. The first step of the one-pot procedure is the selective intramolecular *in situ* formation of an alkylideneoxazoline **2**, which then in an intermolecular reaction is enantioselectively transformed to the oxazole α-hydroxy ester derivatives **4** in quantitative yield and good to excellent enantioselectivity via an asymmetric copper(II)-catalyzed Alder-ene reaction.

Keywords: propargylamides, gold catalysis, alkylglyoxylate, oxazole α-hydroxy ester, heterocycles

Introduction

Optically active α-hydroxy carbonyl moieties are a widespread motif in natural products and have been frequently used as convenient building blocks in organic synthesis.[1] The Alder-ene reaction is a powerful tool for the construction of carbon-carbon bonds and the development of enantioselective versions of that reaction has very important practical implications.[2] In this context, the groups of Mikami, Feng, Nakai, and Evans have reported catalytic enantioselective Alder-ene reactions with glyoxylate esters.[3] However, enantioselective metal-catalyzed Alder-ene reactions are relatively unexplored and the development of highly efficient catalysts still remains a great challenge.[4] To the best of our knowledge, so far no reports on a sequential enantioselective approach towards oxazole α-hydroxy esters **3** via an Alder-ene reaction have been reported.

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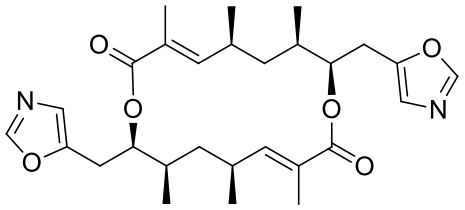
The unsubstituted oxazole moiety,[5] as well as the corresponding 5-methyloxazole,[6] and functionalized 5-methyloxazole derivatives[7] can be found in many naturally occurring products that are pharmaceutically active. Many biologically active oxazole-containing natural products were isolated from marine sources, nearly all of them containing the 2,4-disubstituted oxazole ring system.[8] However, a variety of *Streptomyces* strains have produced examples of 5-monosubstituted oxazoles with biological profiles ranging from herbicidal to antitumor activity, which includes *Conglobatin*[9] (**5**), a member of the oxazolomycin family.[10]



5

Figure 1. Structure of natural product *Conglobatin*

The 2-(oxazol-5-yl)ethyloxy nucleus is a key structural feature of the biologically active marine natural product *Conglobatin* **5.** The synthesis of oxazoles in complex molecular environments remains a challenge, in particular the construction of a stereogenic center in the β-position of the oxazole moiety. Therefore we envisioned the enantioselective synthesis of oxazole α-hydroxy esters **3** from easily available starting precursors.

In 2004, in the context of the early development[11] of gold catalysis,[12] our group reported the conversion of *N*-propargylcarboxamides into 5-methyloxazoles by using 2 mol% gold(III) chloride.[13] This method has since been applied in academic[14] and industrial research.[15] If less Lewis-acidic gold(I) precursors were used, we were able to isolate the intermediate alkylideneoxazolines, previously unknown compounds with a highly interesting reactivity profile.[16] This transformation has found broad application in the screening for new gold catalysts[17] as well as the development of new reaction methodologies like the reaction of alkylideneoxazolines with very reactive nitrogen electrophiles (azodicarboxylates) for Alder-ene reaction.[18] Herein, we report the sequential enantioselective syntheses of oxazole α-hydroxy esters using gold catalysis in combination with a copper-catalyzed Alder-ene reaction.

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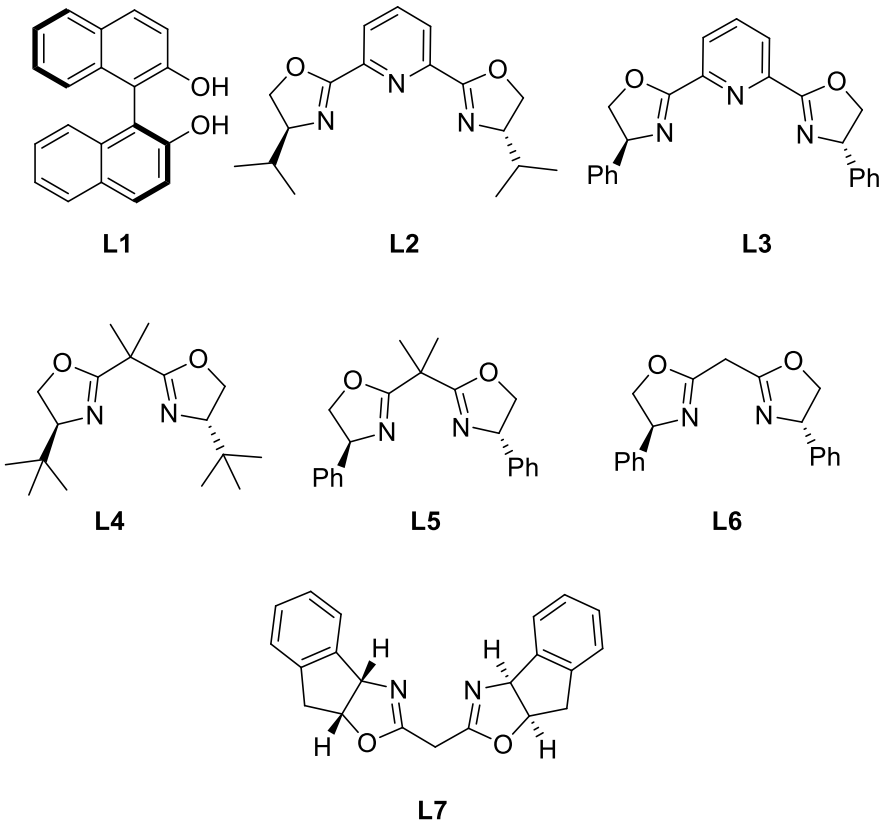
Results and discussion

We have recently reported on the gold-catalyzed cycloisomerization of *N*-propargylamides to the corresponding alkylideneoxazolines followed by aerobic oxidation to the corresponding hydroperoxymethyl oxazoles.[19] Due to this air-sensitivity, we started our study of an Alder-ene (carbonyl-ene) reaction with the direct treatment of the stable 3-nitro alkylideneoxazoline with its exocyclic double bond with ethyl glyoxalate in the presence of specific Lewis acidic catalysts in combination with different chiral ligands **L1**-**L7** (Scheme 1).



Scheme 1: Structures of chiral ligands [**L1** = (*S*)-(−)-1,1′-Bi(2-naphthol), **L2** = (*S*,*S*)-2,6-Bis(4-isopropyl-2-oxazolin-2-yl)pyridine, **L3** = (*S*,*S*)-2,6-Bis(4-phenyl-2-oxazolinyl)pyridine, **L4** = 2,2′-Isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline], **L5** = (*S*,*S*)-2,2'-Isopropylidene-bis(4-phenyl-2-oxazoline), **L6** = 2,2′-Methylenebis[(4*S*)-4-phenyl-2-oxazoline], **L7** = (3a*S*,3′a*S*,8a*R*,8′a*R*)-2,2′-Methylenebis[3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazole]].

As a model system, we examined the Alder-ene reaction of ethyl glyoxal **7** and alkylideneoxazoline **6** promoted by $(i\text{-PrO})_2TiCl_2$[2] in combination with chiral biaryl **L1** (Table 1, entry 1), which exhibited α-hydroxyl ester **8** in good yield but poor enantioselectivity (6% ee) . To improve the enantioselectivity of the reaction, $Cu(OTf)_2$ in combination with the often applied box ligands[3] was examined under different reaction conditions (Table 1, entries 2-13). Pybox ligands (**L2** and **L3**) gave no detectable enantioselectivity (0% ee) with **L2**, and only poor enantioselectivity (5% ee) with **L3**, in addition, the reaction times turned out to be much longer (entries 2-3). The initial attempt with 10 mol% of $Cu(OTf)_2$ and the same amount of chiral box ligand **L4** = 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] at room temperature showed a moderate enantioselectivity (26% ee) going along with very good yield (entry 4). Switching to phebox ligand **L5** = (*S,S*)-2,2'-isopropylidene-bis(4-phenyl-2-oxazoline) in combination with 10 mol% of $Cu(OTf)_2$ at room temperature produced a good enantioselectivity 70% ee in reasonable reaction time and high yield (89%; Table 1, entry 5). Attempts to reduce the catalyst loading were successful and still acceptable reaction times were observed with half the amount of the catalyst system without any change in enantioselectivity (Table 1, entry 6). Next, we performed the reaction at 0 °C which led to a doubling of the reaction time, but the selectivity was improved enantioselectivity (76% ee) in quantitative yield (Table 1, entry 7). Also the reaction at 0 °C with 5 mol% of $Cu(OTf)_2$ and 6 mol% **L5** in order to ensure a complete catalyst complex formation showed no improvement of the enantioselectivity (Table 1, entry 8). Two more box ligands, **L6** and **L7,** with the same catalyst ($Cu(OTf)_2$) gave 69% ee (**L6**, Table 1, entry 9) and 33% ee (**L7**, Table 1, entry 10). With the best ligand (**L5**) (Table 1, entry 11, 12, 13) we tried to further decrease the reaction temperature in order to obtain a higher enantioselectivity. In a series of reactions at -20 °C, -10 °C and -5 °C (Table 1, entry 11, 12, 13) a reaction temperature of -5 °C turned out to be ideal as the reaction time of 12 h is still acceptable and the ee rose to 81%. For even lower reaction temperatures no or only incomplete conversion was observed.

Table 1. Optimization of the Alder-Ene Reaction Conditions

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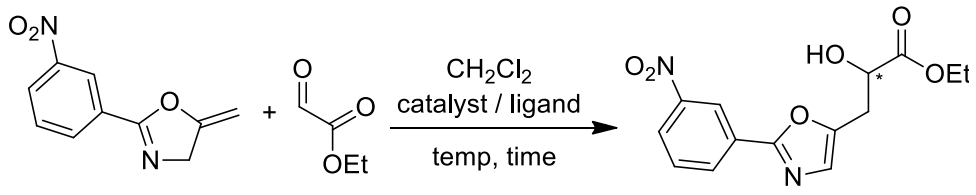

6 **7** **8**

Entry	Catalyst (mol%)	Ligand (mol%)	T, ºC	Time	Yield	ee[a]
1	(*i*-PrO)$_2$TiCl$_2$ (10)	L1 (10)	25	2.0 h	73%	6%
2	Cu(OTf)$_2$ (10)	L2 (10)	25	48 h	80%	0%
3	Cu(OTf)$_2$ (10)	L3 (10)	25	48 h	75%	5%
4	Cu(OTf)$_2$ (10)	L4 (10)	25	2.5 h	79%	26%
5	Cu(OTf)$_2$ (10)	L5 (10)	25	2.0 h	89%	70%
6	Cu(OTf)$_2$ (5)	L5 (5)	25	2.5 h	83%	71%
7	Cu(OTf)$_2$ (5)	L5 (5)	0	4.0 h	81%	76%
8	Cu(OTf)$_2$ (5)	L5 (6)	0	4.0 h	85%	64%
9	Cu(OTf)$_2$ (5)	L6 (5)	0	4.0 h	83%	69%
10	Cu(OTf)$_2$ (5)	L7 (5)	0	4.0 h	81%	33%
11	Cu(OTf)$_2$ (5)	L5 (5)	-20	24 h	-	NR
12	Cu(OTf)$_2$ (5)	L5 (5)	-10	24 h	-	Incomplete
13	Cu(OTf)$_2$ (5)	L5 (5)	-5	12.0 h	86%	81%

[a] Enantioselectivity determined by chiral HPLC.

Table 2. Solvent Influence of the Alder-Ene Reaction

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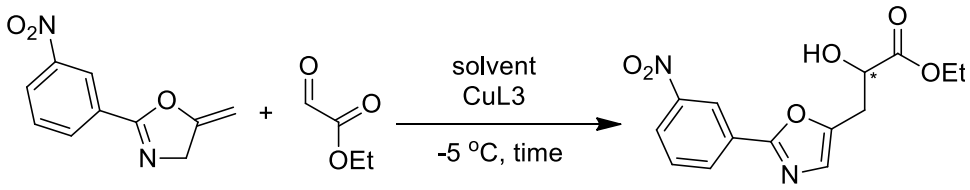

6 **7** **8**

Entry	Solvent	Time	Yield	ee[a]
1	CH_2Cl_2	12 h	87%	81%
2	$MeNO_2$	12 h	82%	58%
3	Toluene	12 h	76%	48%
4	THF	12 h	79%	46%
5	CH_3CN	24 h	66%	21%

[a] Enantioselectivity determined by chiral HPLC.

With the optimized catalyst system, we performed a screening of some solvents (Table 2). The Alder-ene reaction of **6** with **7** took place in all of the tested solvents (CH_2Cl_2, CH_3NO_2, Toluene, THF, and CH_3CN) but the best yield and the best ee value was obtained in CH_2Cl_2, thus we kept this as an optimal solvent for the subsequent reaction (Table 2, entry 1).

With the optimized conditions in hand for the Alder-ene reaction, we tried the sequential and enantioselective synthesis of the α–hydroxy ester **8** by a gold-catalyzed cycloisomerization of 3-nitro-*N*-(prop-2-yn-1-yl)benzamide to the corresponding alkylideneoxazoline **6** followed by the Alder-ene reaction using $Cu(OTf)_2$ and **L5.** To our delight, the sequential process turned out to be highly efficient and despite the presence of the gold catalyst the enantioselectivity still was good (82% ee) and an 84% yield over the two reactions was excellent (Table 3, entry 2). The challenge here is to avoid ligand exchange between the two metal centers.[20] The low affinity of gold(I) for nitrogen ligands[21] and the much more pronounced affinity of gold(I) for phosphane ligands,[22] in combination with the linear coordination at gold(I) not benefiting from a potential

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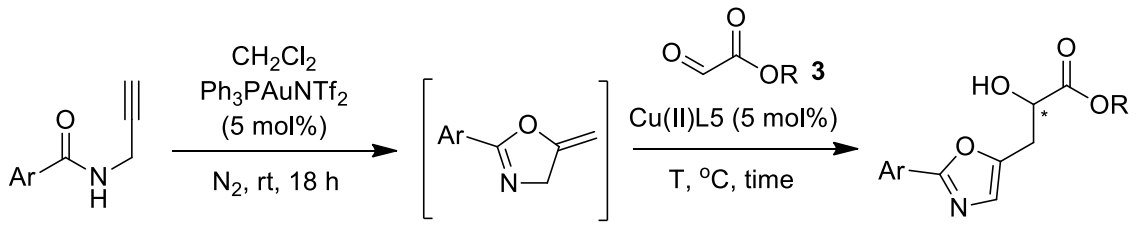
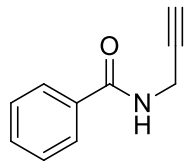
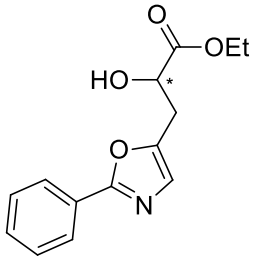
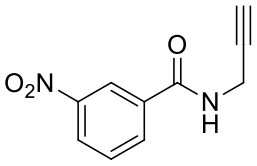
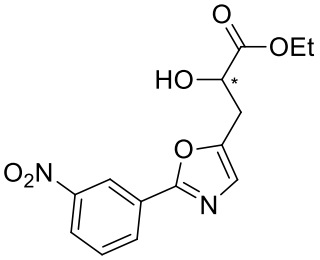
chelate effect, which the copper complex benefits from the *N*,*N*-chelation, helped to avoid such ligand exchange.

Table 3. One-pot Au/CuL5-catalysed sequential enantioselective synthesis of substituted oxazole α-hydroxy esters (**4**) *via* an Alder-ene reaction.



1 **2** **4**

Entry	Amides (1)	α-Hydroxy Esters (4)	T, °C	Time	Yield	ee [a]
1	 **1a**	 **4a**	-5	12 h	93%	48%
2	 **1b**	 **8**	-5	12 h	84%	82%

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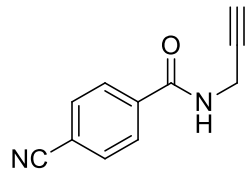
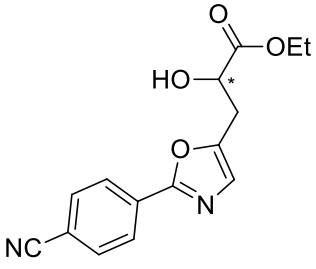
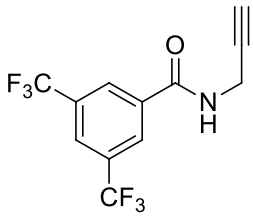
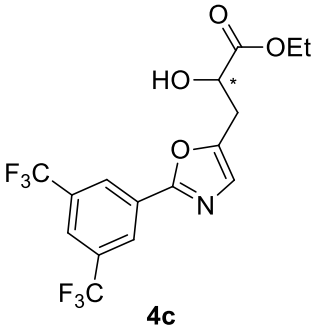
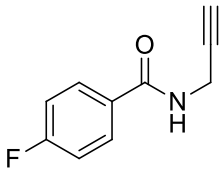
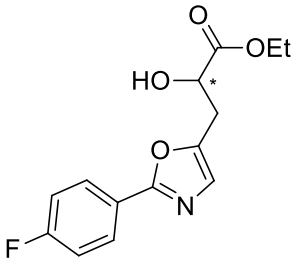
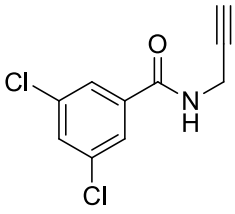
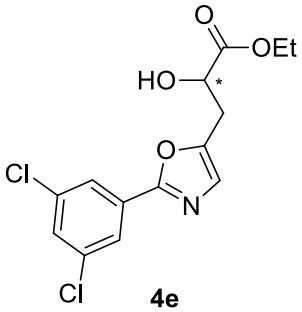
3	 **1c**	 **4b**	-5	16	90%	86%
4	 **1d**	 **4c**	-5	12 h	80%	84%
5	 **1e**	 **4d**	-5	16 h	81%	70%
6	 **1f**	 **4e**	-5	12 h	78%	71%

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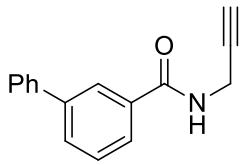
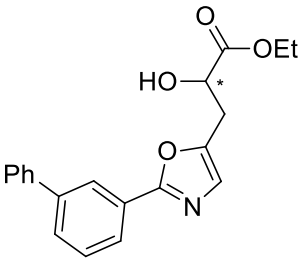
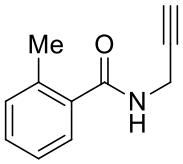
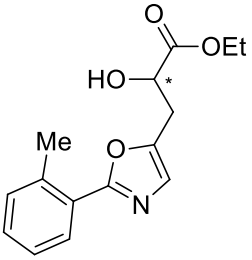
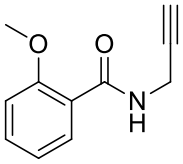
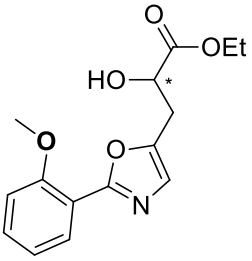
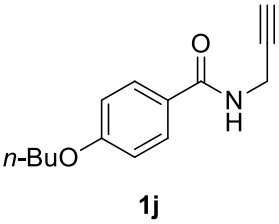
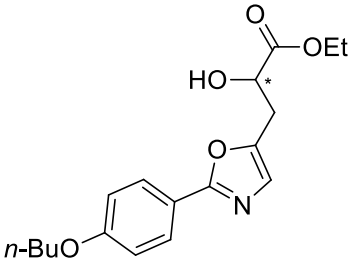
7	 **1g**	 **4f**	-5	12 h	85%	78%
8	 **1h**	 **4g**	-5	12 h	88%	72%
9	 **1i**	 **4h**	-5	16 h	83%	0%
10	 **1j**	 **4i**	-5	16 h	81%	56%

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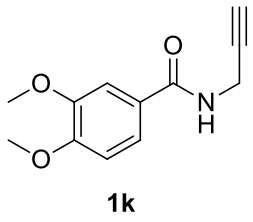
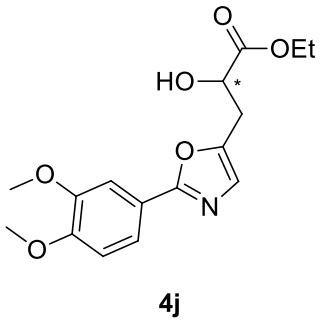
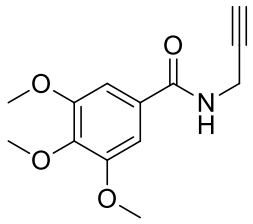
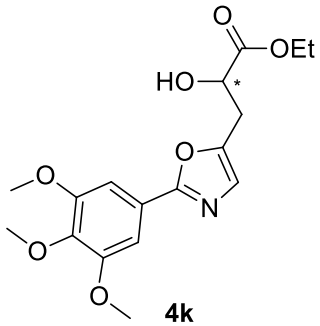
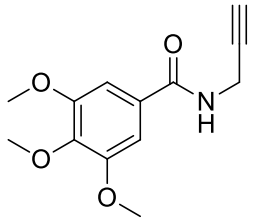
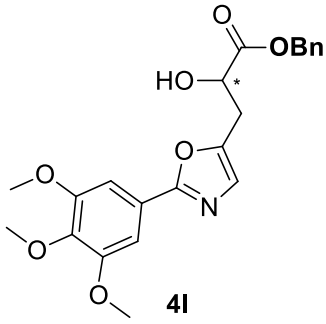
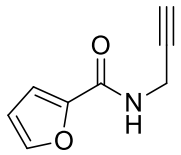
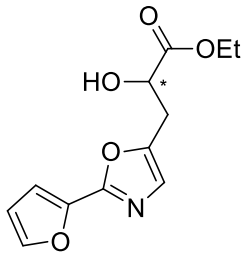
11	 **1k**	 **4j**	-5	16 h	92%	70%
12	 **1l**	 **4k**	-5	24 h	90%	69%
13	 **1l**	 **4l**	-5	24 h	81%	0%
14	 **1m**	 **4m**	**25**	48 h	84%	28%

[a] Enantioselectivity determined by chiral HPLC. [b] Reaction conditions: amide (1.0 mmol), and $Ph_3PAuNTf_2$ (0.05 mmol) in CH_2Cl_2 (4 mL) at rt under N_2 atmosphere for 18 h then cooled reaction mixture to -5 ^oC, was added ethyl or benzylglyoxylate (2.0 mmol) followed by addition of CuL5 (0.05 mmol) and stirred until completion of Alder-ene reaction.

The scope with respect to propargyl benzamides bearing diverse substituents on the arene ring was examined, too (Table 3). An unsubstituted arene provided the desired α–hydroxy ester in excellent yield 93% but only moderate enantioselectivity (48% ee; Table 3, entry 1). Electron-withdrawing groups, such as CN or CF_3 on either the para or meta position were also tolerated yielding the desired products in excellent enantioselectivity (86% ee, 84% ee) and excellent overall yields (Table 3, entries 3, 4). Halogen substituents (F or Cl either in *para* or *meta* position on benzamides) (Table 3: entries 5 and 6) were also well tolerated and produced the desired product in good enantioselectivity (70% ee, 71% ee) and excellent yields as well. A phenyl group as substituent in *meta* position afforded the desired product in very good enantioselectivity (78% ee) and excellent yield (Table 3, entry 7). An electron-donating methoxy group in the *ortho* position of the arene led to a complete loss of optical excess, which might be due to a coordination of the additional oxygen atom (Table 3, entry 9). Indeed the chiral induction could be restored by placing a methyl group instead of the methoxy (72% ee, 88% yield) (Table 3, entry 8). Electron-rich substituents such as *n*-BuO or 3,4-OMe, in both *para* and *meta* positions were well tolerated, leading to the formation of the desired products in good enantioselectivity (56% ee, 70% ee) and in excellent yield (Table 3, entries 10, 11). Electron-rich OMe groups in *meta* and *para* position were well tolerated delivering the product in excellent yield 90% and good enantioselectivity (69% ee) (Table 3, entry 12) when it was Alder-ene reaction with ethyl glyoxalate. It is noteworthy that the Alder-ene reaction with benzyl glyoxalate delivered only racemic product, which might be explained by the increased sterical demand of the benzyl group (Table 3, entry 13). Notably, this one-pot bimetallic sequential catalysis was suitable for furamide as well. For this starting material and the reaction had to be performed at room temperature of which might in part explain the moderate enantioselectivity (28% ee). In addition, the reaction time was much longer but the isolated yield of 84% was still very good (Table 3, entry 14).

In summary, we have developed an efficient one-pot sequential reaction protocol for the enantioselective synthesis of oxazole α-hydroxy esters **4**. Based on the compatibility of the two metals applied (gold and copper) no isolation of the intermediate oxazolines was necessary and the possibility to circumvent an additional purification step together with the versatility and the

fairly mild conditions of the transformation, underlay the high synthetic value for synthetic organic chemistry. One-pot sequential processes can avoid time-consuming and costly processes for purification of various precursors which makes them highly attractive for the pharmaceutical industry. The observation that phosphane ligands on gold(I) are compatible with an *N*,*N*-chelate ligand on a second metal like copper is important for the future development of heterobimetallic catalysis with gold.

Experimental Section

1. General methods:

All reactions were performed in oven-dried glassware under an atmosphere of nitrogen unless otherwise stated. Reactions were monitored by thin-layer chromatographic analysis.

Anhydrous CH_2Cl_2 was obtained from Solvent dispenser. "Evaporation" refers to the removal of solvent under reduced pressure using a rotory evaporator and then the removal of the last traces of solvent under high vacuum. "Dried" refers to the drying of organic extracts over $MgSO_4$. Commercial substances were used without further purification. NMR spectra were recorded on Bruker Avance 600, 500, 400 and 300 and Bruker ARX-250 spectrometers. Chemical shifts were referenced to residual solvent protons. Signal multiplicity as follows: s (singlet), d (doublet), t (triplet), q (quartet), qu (quintet), hept (heptate), m (multiplet). ^{13}C assignment was achieved *via* HSQC, HMBC and DEPT135 spectra. MS spectra were recorded on Finnigan MAT TSQ 700, Vakkum Generators ZAB-2F and JEOL JMS-700 spectrometer. IR spectra were recorded on a Bruker Vector 22. TLC analyses were performed using aluminum-backed silica gel TLC plates. Compounds were detected under a 254 nm ultraviolet lamp if applicable, or by staining with an acidified aqueous solution of ammonium molybdate, followed by development with a heat gun. Flash column chromatography was performed using Aldrich silica gel (70 – 230 mesh) packed by the slurry method. Melting points were obtained using a Gallenkamp MF-370 capillary tube melting point apparatus and are uncorrected. Low-resolution mass spectra were obtained on a Shimadzu GC mass spectrometer (EI). HRMS were obtained in lieu of elemental analysis. Enantiomer excesses were determined by chiral HPLC analysis on Daicel Chiralcel AS-H/IB-H in comparison with the authentic racemates. Optical rotations were reported as follows: $[\alpha]_D^T$ (c: g/100 mL, in $CHCl_3$). Ultra-Kryomat cooler was used for maintaining a low temperature.

2. General procedures for propargylic amides and Au-Cu catalyzed enantioselective synthesis of α–hydroxy esters:

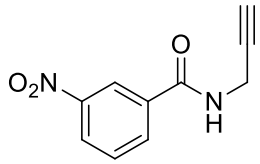
General procedure (GP 1) - Synthesis of propargylic amines:

To a solution of propargylamine (1.0 eq with respect to the acid chloride) in anhydrous CH_2Cl_2, Et_3N (1.0 eq) was added and DMAP (2.0 mol%). The reaction mixture cooled to 0 °C, and then acid chloride (1.0 eq) was added drop wise. After stirring for 15 min at 0°C continued stirring at room temperature for 3 h. After completion, the reaction mixture diluted with water and then extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and the solvent removed *in vacuo*. The crude product was purified by column chromatography or by recrystallization.

General procedure (GP 2) – Sequential synthesis of α-hydroxyl esters:

To a solution of propargylamine (50 mg, 1.0 eq) in dry CH_2Cl_2 (2.0 mL) was added $Ph_3PAuNTf_2$ (5.0 mol%) and the reaction mixture stirred at room temperature for 18 h in an inert atmosphere (N_2) to the dihydrooxazole formation reaction (monitored by TLC). Then the mixture was cooled to – 5 ^oC, at which time ethyl or benzyl glyoxylate (2.0 eq with respect to propargylicamide) and CuL5 (5.0 mol%) prepared green suspension (a dry flask was charged with $Cu(OTf)_2$ (5.0 mol%), phebox ligand **L5** (5.0 mol%), dry CH_2Cl_2 (2.0 mL) and stirred at room temperature for 4 h in an inert atmosphere (N_2) then the solution was turned to green suspension) was added via a syringe and continued stirring until Alder-Ene reaction being completed (monitored by TLC). After completion of the reaction, the crude product was directly purified by flash column chromatography.

3-Nitro-N-(prop-2-yn-1-yl)benzamide (1b)



1b

Prepared according to **GP1** using propargyl amine (0.29 g, 5.40 mmol), Et_3N (0.54 g, 5.40 mmol), DMAP (0.013 g, 0.10 mmol), dry CH_2Cl_2 (12.0 mL) and 3-Nitrobenzoyl chloride (1.0 g, 5.40 mmol). The residue triturated with petroleum ether and filtered to afford the title compound **1b** (1.05 g, 95%) as a pale yellow solid.

R_f = 0.46 (1 : 2, EtOAc/petrol); M.p = 146 – 148 ^oC; IR (neat, ν_{max}/cm^{-1}): 1529, 1579, 1649, 3299; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (s, 1H), 8.30 (dd, *J* = 0.9, 8.0 Hz, 1H), 8.12 (d, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 6.54 (bs, NH), 4.23 (dd, *J* = 2.4, 5.2 Hz, 2H), 2.25 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7 (s), 148.2 (s), 135.3 (s), 133.3 (s), 130.0 (s), 126.4 (s), 121.9 (s), 78.8 (s), 72.4 (s), 30.1 (s). MS (70 eV): *m/z* (%): 204 (61) [M^+]; HRMS (EI (+), 70 eV): $[C_{10}H_8N_2O_3]^+$: calcd 204.0535, found 204.0570.

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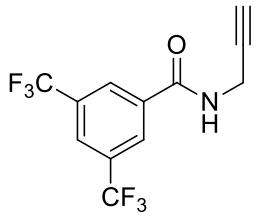
N-(prop-2-yn-1-yl)-3,5-bis(trifluoromethyl)benzamide (1d)

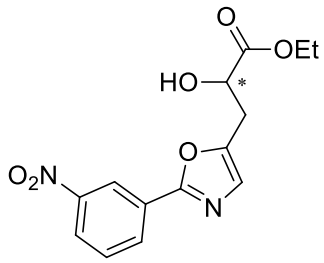


1d

Prepared according to **GP1** using propargylamine (0.20 g, 3.62 mmol), Et_3N (0.36 g, 3.62), DMAP (9.0 mg, 0.07 mmol), dry CH_2Cl_2 (12.0 mL) and 3,5-bis(trifluoromethyl)benzoyl chloride (1.0 g, 3.62 mmol). The residue triturated with petroleum ether and filtered to afford the title compound **1d** (0.92 g, 86%) as a pale yellow solid.

R_f = 0.61 (1 : 2, EtOAc/petrol); M.p = 88 – 90 ºC; IR (neat, ν_{max}/cm^{-1}): 1419, 1454, 1542, 1618, 1647, 3100, 3247; ^1H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 2H), 7.93 (s, 1H), 6.88 (bs, NH), 4.21 (dd, *J* = 2.4, 5.2 Hz, 2H), 2.22 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4 (s), 134.7 (s), 131.4 (q, *J* = 34.0 Hz, 2C), 126.5 (d, J = 3.0 Hz, 2C), 124.3 (qu, *J* = 4.0 Hz), 123.1 (q, *J* = 271.0 Hz, 2C), 77.6 (s), 71.3 (s), 29.0 (s); MS (70 eV): *m/z* (%): 295 (66) [M^+], 241 (100) [M^+-$C_3H_4N^{\cdot}$], 213 (68) [$C_8H_3F_6$]; HRMS (EI (+), 70 eV): $[C_{12}H_7NOF_6]^+$: calcd 295.0432, found 295.0409.

(+)-Ethyl 2-hydroxy-3-(2-(3-nitrophenyl)oxazol-5-yl)propanoate (8)

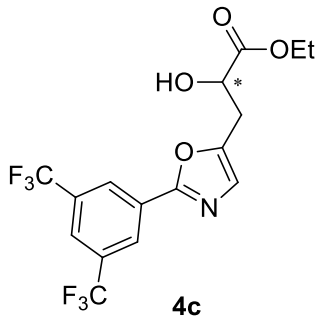


8

Prepared according to **GP2** from 3-nitro-N-(prop-2-yn-1-yl)benzamide **1b** (0.05 g. 0.245 mmol), ethyl glyoxylate (0.05 g, 0.49 mmol), dry CH_2Cl_2 (4.0 mL), $Ph_3PAuNTf_2$ (9.0 mg, 0.012 mmol), $Cu(OTf)_2$ (4.42 mg, 0.012 mmol) and (*S,S*)-2,2`-Isopropylidene-bis(4-phenyl-2-oxazoline) (4.10 mg, 0.012 mmol). Purification *via* flash column chromatography (1 : 2, EtOAc/petrol) afforded the title compound **8** (0.063 g, 84%) as a colourless solid.

$[\alpha]_D^{20}$ +4.9 (*c* 1.0, $CHCl_3$); >82% ee; HPLC DAICEL CHIRALCEL AS-H, *n*-hexane/2-propanol (85:15), flow rate = 1.0 mL/min, area: 550.861 (minor) and 5642.49 (major), retention time: 23.7 min (minor) and 26.9 min (major); R_f = 0.39 (1 : 1, EtOAc/petrol); M.p = 75 – 77 °C; IR (neat, ν_{max}/cm^{-1}): 3434, 3089, 1738, 1552, 1173, 715; ^1H NMR (400 MHz, CD_2Cl_2): δ 8.24 – 8.15 (m, 3H), 7.57 (t, *J* = 10.4 Hz, 1H), 6.95 (s, 1H), 4.43 (q, *J* = 7.3 Hz, 1H), 4.19 (q, *J* = 9.5 Hz, 2H), 3.14 (qd, *J* = 9.3, 20.8 Hz, 2H), 3.03 (s, 1H), 1.22 (t, *J* = 9.5 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 172.7 (s), 158.1 (s), 148.7 (s), 147.9 (s), 130.8 (s), 129.2 (s), 128.4 (s), 125.8 (s), 123.6 (s), 119.9 (s), 67.9 (s), 61.5 (s), 30.1 (s), 13.2 (s); MS (70 eV): *m/z* (%): 306.1 (40) $[M^+]$; HRMS (EI (+), 70 eV): $[C_{14}H_{14}N_2O_6]^+$: calcd 306.0852, found 306.0823.

(+)-Ethyl 3-(2-(3,5-bis(trifluoromethyl)phenyl)oxazol-5-yl)-2-hydroxypropanoate (4c)



4c

Prepared according to **GP2** from N-(prop-2-yn-1-yl)-3,5-bis(trifluoromethyl)benzamide **1d** (0.05 g. 0.169 mmol), ethyl glyoxylate (0.034 g, 0.338 mmol), dry CH_2Cl_2 (4.0 mL), $Ph_3PAuNTf_2$ (6.26 mg, 0.0084 mmol), $Cu(OTf)_2$ (3.06 mg, 0.0084 mmol) and (*S*,*S*)-2,2`-Isopropylidene-bis(4-phenyl-2-oxazoline) (2.83 mg, 0.0084 mmol). Purification *via* flash column chromatography (1 : 2, EtOAc/petrol) afforded the title compound **4c** (53.0 mg, 80%) as a colourless solid.

$[\alpha]_D^{20}$ +5.2 (*c* 1.0, $CHCl_3$); 84% ee; HPLC DAICEL CHIRALCEL AS-H, *n*-hexane/2-propanol (90:10), flow rate = 0.7 mL/min, area: 354.249 (minor) and 3268.88 (major), retention time: 7.5 min (minor) and 8.0 min (major); R_f = 0.51 (1 : 1, EtOAc/petrol); M.p = 60 – 62 °C; IR (neat, ν_{max}/cm^{-1}): 3430, 2988, 1740, 1621, 1553, 736; ^1H NMR (400 MHz, CD_2Cl_2): δ 8.35 (s, 2H), 7.85 (s, 1H), 6.97 (s, 1H), 4.43 (t, *J* = 5.2 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.14 (qd, *J* = 6.4, 15.2 Hz, 2H), 3.10 (s, 1H), 1.19 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 173.8 (s), 158.7 (s), 150.3 (s), 132.4 (q, *J* = 33.5 Hz, 2C), 129.9 (s), 126.4 (d, *J* = 3.2 Hz), 124.8 (q, *J* = 271.0 Hz, 2C), 123.6 (qu, *J* = 3.7 Hz, 2C), 69.0 (s), 62.6 (s), 31.2 (s), 14.3 (s); MS (70 eV): *m/z* (%): 397.0 (25) $[M^+]$; HRMS (EI (+), 70 eV): $[C_{16}H_{13}NO_4F_6]^+$: calcd 397.0734, found 397.0738.

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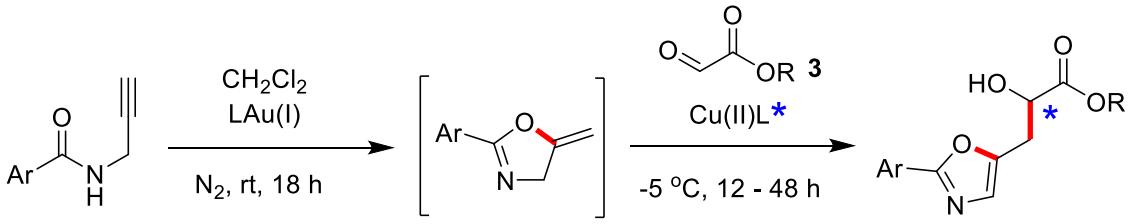
TOC graphic



R = Et, Bn
yield = up to 93%
ee = up to 86%