SYNTHESIS OF CHIRAL 2-CYANOMETHYL OXAZOLINES AND THEIR APPLICATIONS IN RUTHENIUM-CATALYZED ALLYLIC SUBSTITUTION

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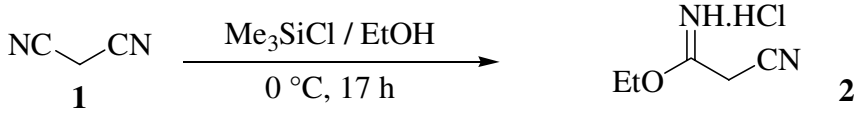
ABSTRACT: 2-Cyanomethyl oxazolines have been prepared in good yields from optically pure amino alcohols and ethyl cyanoacetimidate hydrochloride. They have been evaluated as new bidentate ligands in the ruthenium-catalyzed allylic substitution reaction, on association with the complex $[RuCp^*(MeCN)_3][PF_6]$. This association leads to the favoured formation of the linear allylic product

Key words: Chiral mono(oxazolines), ruthenium, catalysis, allylation

Optically pure chelating ligands featuring the oxazoline structure have recently revealed a very high potential in enantioselective molecular catalysis with transition metals, leading to optically active products of biological interest [1]. Besides bis(oxazoline) ligands, most of the other efficient bidentate ligands contain a phosphino group as the other chelating arm [2]. Bidentate monooxazoline *N,N*-ligands are mainly represented by oxazoline-pyridine compounds, which have also found interesting properties [3]. No oxazoline with an additional coordinating nitrile side group have been reported up to now. They also offer an easy further possibility of functionalization by classical modification of the nitrile group. On the other hand, we have recently found that chiral bis(oxazoline) ligands associated to $[RuCp^*(MeCN)_3][PF_6]$ as catalyst precursor, provided efficient catalytic systems for the enantioselective allylation of phenols from unsymmetrical cinnamyl derivatives [4].
We now report the one-step preparation of chiral 2-cyanomethyl oxazolines and their use as ligand in the ruthenium-catalyzed nucleophilic substitution reaction.

Synthesis of new 4,5-dihydro-2-oxazolylacetonitrile (or 2-cyanomethyl oxazolines)

The direct synthesis of 2-cyanomethyl-4-ethyl-oxazoline has been carried out from malonitrile and α-amino alcohol under acidic conditions but in moderate yield [5a]. The use of $Zn(OAc)_2$ as catalyst has made possible the preparation of related 2-cyanomethyl oxazolines from 2,2-dimethylmalonitrile and amino alcohols in better yields[5b]. Our strategy to produce chiral 2-cyanomethyl oxazolines is based on the reaction of ethyl cyanoacetimidate hydrochloride with α-amino alcohols in refluxing dichloromethane. The ethyl cyanoacetimidate hydrochloride **2** is previously prepared in quantitative yield from malonitrile **1** and trimethylsilylchloride in ethanol at 0°C for 17 h (equation 1) [6].



Equation 1

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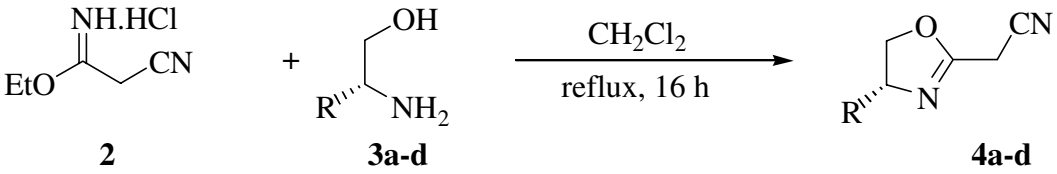
Then, the 2-cyanomethyl oxazoline formation conditions were studied from reagent **2** and (*R*)-2-aminobutanol **3a**. Following our best conditions, 10 mmol of **2** reacted with 10 mmol of (*R*)-2-aminobutanol **3a** in refluxing anhydrous dichloromethane for 16 h. After purification by chromatography on silica the 2-cyanomethyl oxazoline **4a** was isolated in 90% yield according to equation 2.



2 **3a-d** **4a-d**

R= Et(**a**), ^{i}Pr(**b**), Ph(**c**), Bn(**d**)

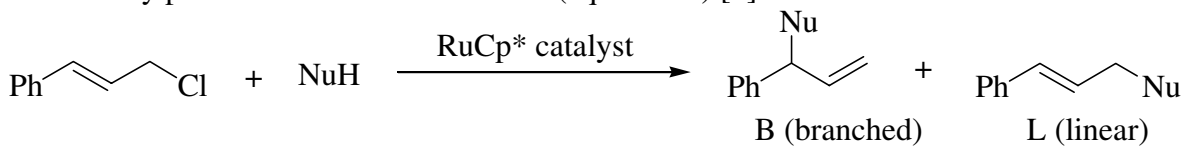
4a 90%
4b 85%
4c 90%
4d 85%

Equation 2

The reaction was extended to three other optically active α-amino alcohols **3b-d**, which led to the corresponding 2-cyanomethyl oxazolines **4b-d** in 85-90% yields.
In ^{13}C NMR spectrscopy, these compounds showed characteristic signals at 113.6 (±1) ppm for the cyano carbon atom, and in the range 157.2-158.4 ppm for the sp^{2}C=N carbon atom.

Application in catalysis: Ruthenium-catalyzed nucleophilic substitution of cinnamyl chloride by phenols

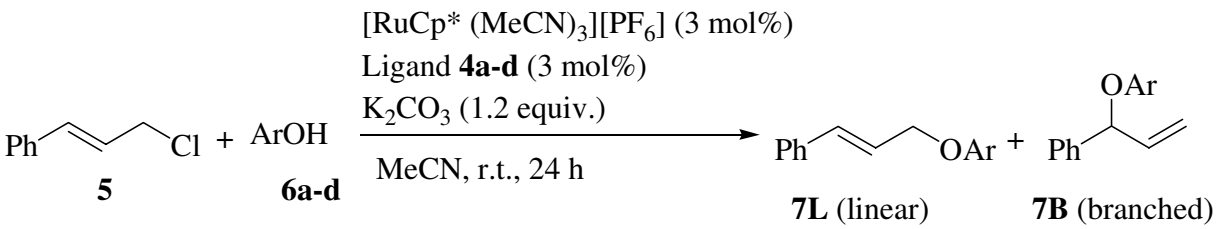
We have recently shown that Cp*Ru-containing complexes were able to perform the regioselective allylation of various nucleophiles from cinnamyl chloride or carbonate to regioselectively produce the branched isomers (equation 3) [7].



B (branched) L (linear)

Equation 3

Generation of active catalysts by substitution of acetonitrile ligands from [RuCp*(MeCN)$_3$][PF$_6$] with a bidentate bis(oxazoline) [4] or monodentate carbine [8] ligand has already been successfully performed. The substitution of cinnamyl chloride by phenol was thus investigated in the presence of catalyst arising from the *in situ* association of [RuCp*(MeCN)$_3$][PF$_6$] with the 2-cyanomethyl oxazolines **4a-d**. Treatment of 1 mmol de cinnamyl chloride with 1.2 mmol of phenol, 1.2 mmol of K_2CO_3, 3 mol% of [RuCp*(MeCN)$_3$][PF$_6$], and 3 mol% of ligand **4**, in acetonitrile at room temperature for 24 h led to complete conversion of the substrates according to equation 4.



5 **6a-d** **7L** (linear) **7B** (branched)

Ar= Ph (**a**), *p*-MeC$_6$H$_4$ (**b**), *m*-MeC$_6$H$_4$ (**c**), *o*-MeC$_6$H$_4$ (**d**)

Equation 4

The reaction led to both linear **7L** and branched **7B** products in proportion depending on the ligand nature. The results are gathered in Table 1.

Table 1. Allylation of ArOH with cinnamyl chloride in the presence of $[RuCp^*(MeCN)_3][PF_6]$ / **4a-d**[a]

Ligand	Ar OH	Yield (%)[b]	L/B ratio[c]
4a	**6a**	70	70/30
4a	**6b**	75	97/3
4a	**6c**	65	87/13
4a	**6d**	70	96/4
4b	**6a**	75	97/3
4b	**6b**	85	96/4
4b	**6c**	80	92/8
4b	**6d**	90	98/2
4c	**6a**	60	82/18
4c	**6b**	55	52/48
4c	**6c**	65	48/52
4c	**6d**	90	97/3
4d	**6a**	70	94/6
4d	**6b**	50	88/12
4d	**6c**	67	95/5
4d	**6d**	95	89/11

[a]General conditions: Phenol (1.2 mmol), cinnamyl chloride (1 mmol), K_2CO_3 (1.2 mmol), $[RuCp^*(MeCN)_3][PF_6]$ (0.03 mmol), **4** (0.03 mmol), acetonitrile (4 ml), room temperature, 24 h. [b]Isolated yield. [c]ratio determined by ^1H NMR of the crude mixture.

In most cases, the reaction led to high conversion and high regioselectivity in favour of the linear products **7L**. This is an indication that the coordination of ligands **4a-d** took place as the $[RuCp^*(MeCN)_3][PF_6]$ precursor is a very efficient catalyst for the formation of branched aryl allyl ethers of type **7B** under similar catalytic conditions.[7a] The formation of the achiral linear products **7L** as major isomers shows that 2-cyanomethyl oxazoline associated to ruthenium catalysts more or less prevents the formation of the chiral product **7B**. For this reason, the 2-cyanomethyl oxazoline-ruthenium catalysts have not a good future in enantioselective catalysis. In addition, the determination of the enantiomer excesses in the reactions, where the formation of the branched isomer was acceptable (**7bB** (48%) and **7cB** (52%) in the presence of the ligand **4c**), revealed modest enantioselectivity (30 and 60% e.e., respectively). This is likely due to the too weak interaction of the nitrile group with the ruthenium site in the catalyst.

In conclusion, we have developed a straightforward and efficient synthesis of 2-cyanomethyl oxazolines from optically pure α-amino alcohols. These bidentate functional ligands are able to coordinate the RuCp* fragment and lead to *in situ* generated active catalysts for the regioselective preparation of linear prop-2-enyl aryl ethers upon nucleophilic substitution of cinnamyl chloride.

Experimental section

^1H and ^{13}C NMR spectra were recorded on an AC 300 FT Bruker instrument (^1H: 300 MHz, ^{13}C: 75 MHz) and referenced internally to tetramethylsilane. IR spectra were recorded with a Perkin Elmer 298 spectrometer. All solvents have been distilled according to usual methods, dichloromethane over CaH_2, ether and THF over sodium in the presence of benzophenone.

General procedure for the synthesis of 4,5-dihydro-2-oxazolylacetonitrile

In a 50 ml Schlenk tube (or in a closed glass reactor) were introduced 10 mmol of ethyl cyanoacetimidate hydrochloride **2,** prepared as reported in the literature [6], and 10 mmol of α-amino alcohol in 20 ml of anhydrous dichloromethane. The mixture was refluxed under an inert

atmosphere of nitrogen during 16 h until complete conversion. After removal of the salt (NH_4Cl) by filtration, the organic phase was concentrated under vacuum, and the product was purified by chromatography over silica with a (100/1) CH_2Cl_2/MeOH mixture as eluent.

• (4*R*)-4-ethyl-4,5-dihydro-2-oxazoleacetonitrile : 4a

Yield: 90% ; IR ($CHCl_3$) : 2220, 1646, 1596, 1577, 1525 cm^{-1} ; ^1H NMR ($CDCl_3$, 300MHz) : δ (ppm) : 0.98 (t, 3 H, J= 7.4 Hz, $C\underline{H}_3CH_2$) ; 1.63-1.74 (m, 2 H, CH_3-$C\underline{H}_2$) ; 3.45 (s, 2 H, CH_2-CN) ; 3.96-4.16 (m, 2 H, CH-O and CH-N) ; 4.46 (dd, 1 H, J= 7.8 Hz, J= 6.6 Hz, CH-O).

^{13}C NMR (50 MHz, $CDCl_3$) : δ (ppm) : 9.6 ($\underline{C}H_3$) ; 18.0 (CH_3-$\underline{C}H_2$) ; 28.0 ($\underline{C}H_2$-CN) ; 67.7($\underline{C}$H-N) ; 73.8($\underline{C}H_2$-O) ; 114.3 (C≡N) ; 157.9(C=N).

• (4*R*)-4-(isopropyl)-4,5-dihydro-2-oxazoleacetonitrile : 4b

Yield : 85% ; IR ($CHCl_3$): 2225, 1649, 1601, 1579, 1522 cm^{-1} ; ^1H NMR ($CDCl_3$, 300MHz) : δ (ppm) : 0.87 (d, 3 H, J= 6.9 Hz, $C\underline{H}_3$-CH) ; 0.95 (d, 3 H, J= 6.6 Hz, $C\underline{H}_3$-CH) ; 1.73-1.81 (m, 1 H, $(CH_3)_2C\underline{H}$) ; 3.45 (s, 2 H, $C\underline{H}_2$-CN) ; 3.91-3.99 (m, 1 H, CH-N) ; 4.06(t, 1 H, J= 8.4 Hz, CH_2-O) ; 4.36(dd, 1 H, J= 9.6 Hz, J= 8.3 Hz, $C\underline{H}_2$-O) ; ^{13}C NMR ($CDCl_3$, 75 MHz) : δ (ppm) : 18.1 ($\underline{C}H_3$-CH) ; 18.2 ($\underline{C}H_3$-CH) ; 29.0 ($\underline{C}H_2$-CN) ; 33.0 (($CH_3)_2\underline{C}$H); 71.6 (CH-N) ; 72.5 (CH_2-O) ; 113.8 (C≡N) ; 157.2(C=N).

• (4*R*)-4-phenyl-4,5-dihydro-2-oxazoleacetonitrile : 4c

Yield : 90% ; IR ($CHCl_3$): 2216, 1652, 1601, 1562, 1526 cm^{-1} ; ^1H NMR ($CDCl_3$, 300MHz): δ (ppm) : 3.44 (s, 2 H, $C\underline{H}_2$-CN) ; 4.13 (dd, 1 H, J= 8.4Hz, J= 0.9Hz, $C\underline{H}_2$-O) ; 4.64 (dd, 1 H, J= 10.5 Hz, J = 0.9 Hz, $C\underline{H}_2$-O); 5.12-5.20 (dd, 1 H, J= 9.9 Hz and J= 10.5 Hz, $C\underline{H}$-N) ; 7.11-7.31 (m, 5 H, Ph) ; ^{13}C NMR ($CDCl_3$, 75 MHz,) : δ (ppm) : 17.3 ($\underline{C}H_2$-CN) ; 68.7 (CH-N) ; 74.9 (CH_2-O) ; 112.8 (C≡N) ; 125.5, 126.9, 127.6 and 127.9 (aromatic C) ; 139.8 (aromatic C) ; 157.8 (C=N).

• (4*R*)-4-benzyl-4,5-dihydro-2-oxazoleacetonitrile : 4d

Yield : 85% ; IR ($CHCl_3$): 2218, 1655, 1607, 1580, 1529 cm^{-1} ; ^1H NMR ($CDCl_3$, 300MHz) : δ (ppm) : 2.64 (dd, 1 H, J= 14.1 Hz, J= 8.1 Hz, CH_2-Ph) ; 3.07 (dd, 1 H, J= 13.8 Hz, J= 5.4 Hz, CH_2-Ph) ; 3,31 (s, 2 H, CH_2-CN) ; 4.11 (dd, 1 H, J= 8.4 Hz, J= 7.5 Hz, CH_2-O) ; 4.23 (t, 1 H, J= 8.7 Hz, CH_2-O) ; 4.35-4.39 (m, 1 H, CH-N) ; 7.05-7.25 (m, 5 H, Ph) ; ^{13}C NMR ($CDCl_3$, 75 MHz,) : δ (ppm) : 18.7 ($\underline{C}H_2$-CN) ; 41.6 ($\underline{C}H_2$-Ph) ; 67.9 (CH-N) ; 73.5 (CH_2-O) ; 114.2 (C≡N) ; 127.2, 129.1, 129.4 and 129,6 (aromatic $\underline{C}$H) ; 137.5 (aromatic $\underline{C}$H) ; 158.4 (C=N).

General procedure for the catalytic allylation reaction

In a Schlenk type flask equipped with a magnetic stirrer were successively added under nitrogen atmosphere, 0.03 mmol of $[RuCp^*(MeCN)_3][PF_6]$, 0.03 mmol of ligand **4**, 4 ml of acetonitrile, 1.2 mmol of K_2CO_3, 1 mmol de cinnamyl chloride, and 1.2 mmol of phenol susbtrate. The reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and the residue was extracted with 50 ml of diethyl ether. After filtration, the organic phase was concentrated under vacuum and chromatographied through a silica column eluted with a (90/10) hexane/ diethyl ether mixture. The ratio of branched and linear products was determined by ^1H NMR of the crude mixture before chromatography.

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