COMMUNICATION

ChemComm
www.rsc.org/chemcomm

First enantioselective allylic etherification with phenols catalyzed by chiral ruthenium bisoxazoline complexes

Mbaye D. Mbaye, Jean-Luc Renaud,* Bernard Demerseman and Christian Bruneau*
Institut de Chimie, UMR 6509, Organométalliques et Catalyse, Université de Rennes 1, Campus de Beaulieu-35042, Rennes, Cedex, [France]. E-mail: christian.bruneau@univ-rennes1.fr; jean-luc.renaud@univ-rennes1.fr; Fax: 33(0)223236939; Tel: 33(0)223236283

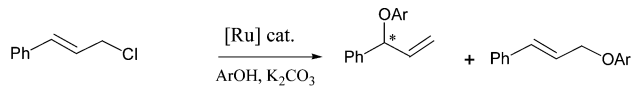
Received (in Cambridge, UK) 22nd April 2004, Accepted 1st June 2004
First published as an Advance Article on the web 2nd July 2004

Regio- and enantioselective substitution of cinnamyl chloride by phenols has been achieved with up to 82% enantiomeric excess, using a ruthenium catalyst prepared from [Cp*(CH$_3$CN)$_3$Ru][PF$_6$] and a chiral bisoxazoline ligand.

Allylic aryl ethers are suitable precursors for the Claisen rearrangement and useful intermediates for access to biologically active natural compounds.[1] They have been prepared *via* palladium-catalyzed allylation of phenols[2,3] and the stereospecificity of the allylic etherification has been demonstrated with catalyst precursors based on palladium,[4] rhodium,[5] and ruthenium.[6] Enantioselective allylations of phenols have been successfully performed with palladium catalysts containing chiral bis-diphenylphosphinobenzamide ligands[7,8] and has provided elegant routes to the synthesis of optically active natural compounds.[8] Recently, an iridium catalyst containing a chiral monophosphoramidite ligand has revealed a high efficiency for the enantioselective etherification of phenoxides with allylic carbonates.[9] Ruthenium catalysts are also known to promote the regioselective formation of chiral branched compounds *via* allylic substitution from unsymmetrical carbonates,[10] but apart from the C–C bond formation from 1,3-diphenyl-2-propenyl ethyl carbonate and sodiomalonate derivatives in the presence of planar-chiral cyclopentadienylruthenium catalysts,[11] no example of enantioselective substitution of achiral allylic derivatives has been reported.

We wish to report that new catalytic systems based on chiral dinitrogen chelating ligands and a pentamethylcyclopentadienylruthenium moiety provide the first examples of ruthenium-catalyzed regio- and enantioselective etherification of allylic chlorides with phenols.

We have previously reported that ruthenium complexes containing chelating dinitrogen ligands such as bis-imines[12] or 2,2′-bipyridines[13] are useful catalysts for the regioselective nucleophilic substitution of unsymmetrical allylic carbonates. Of peculiar interest, the study of [Cp*(bipy)(CH$_3$CN)Ru][PF$_6$]-catalyzed reactions emphasized the key role of [Cp*(η^3-allyl)(bipy)Ru(IV)]$^{2+}$ intermediates, still bearing a dinitrogen chelating bipyridine ligand, in the catalytic process.[13] More recently, we have also shown that the reaction of cinnamyl chloride **1** with phenols and potassium carbonate in the presence of [Cp*(CH$_3$CN)$_3$Ru][PF$_6$] as catalyst, regioselectively afforded the allyl aryl ethers **2–3** in a branched : linear ratio higher than 40 : 1 (Scheme 1).[14]



1 **2** **3**

Scheme 1

These results provided impetus to study the enantioselective reaction in the presence of chiral dinitrogen ligands. Our first attempts with enantiomerically pure bis-imines were unsuccessful. The use of bisoxazolines (See Fig. 1) which are efficient chiral ligands in many asymmetric catalytic reactions, was then investigated.[15]

At room temperature, the reaction of 0.5 mmol of cinnamyl chloride with 0.75 mmol of phenol in the presence of 0.015 mmol (3 mol%) of [Cp*Ru(CH$_3$CN)$_3$][PF$_6$] and 0.015 mmol of bisoxazoline ligand in acetone led to poor regioselectivities, and the branched ether **2** was merely obtained as a racemate. Enantioselectivity of the allylic etherification was reached when the reactions were carried out at 0 °C (Table 1).† Decreasing the temperature below 0 °C does not improve the regio- or the enantioselectivity.

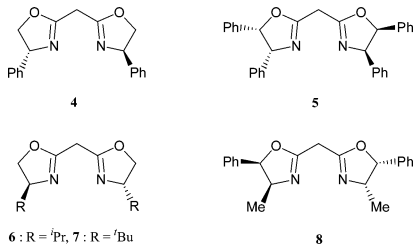


Fig. 1

Table 1 Influence of the nature of the bisoxazoline ligand on the etherification of cinnamyl chloride with phenol[a]

Ligand	Conversion (%)[b]	Selectivity (**2**/**3**)[b]	e.e.(%)[c,d]
4	82	9/1	27 (*R*)
5	70	2/1	77 (*R*)
6	76	7.5/1	7.5 (*S*)
7	38	5/1	0
8	70	8/1	10 (*S*)

[a] conditions : 0.75 mmol of phenol, 0.75 mmol of K_2CO_3, 0.5 mmol of cinnamyl chloride **1**, 0.015 mmol of [Cp*Ru(CH$_3$CN)$_3$][PF$_6$] and ligand (3 mol%) in 4 mL of acetone, 0 °C, 40 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC. [d] Absolute configuration of the products were established by correlation with previous data.[9]

Among the chiral bisoxazolines, it appeared that the enantioselectivity was enhanced by the presence of a phenyl group at the C(4)-position of the oxazoline rings (Table 1, Fig. 1). Thus, ligands **4** and **5** provided moderate to good enantioselectivities (27 and 77%, respectively), whereas low enantioselectivities were obtained from ligands **6–8**, with Me, ^{i}Pr or ^{t}Bu groups as substituents at the C(4)-position. Furthermore, the additional presence of a phenyl group at the C(5)-position in **5** (as compared to **4**) resulted in a markedly enhanced enantioselectivity (77 e.e. with **5** *vs*. 27% e.e. with **4**).

Both regioselectivity and enantioselectivity of the *O*-allylation of phenol by cinnamyl chloride in the presence of ligand **5** were found to be dependent on the nature of the solvent (Table 2). Coordinating solvents (acetone, acetonitrile, THF) led to good enantiomeric excesses (63–80%) but with moderate regioselectivities (2–2.5/1). Dichloromethane provided a significantly increased regioselectivity (6.5/1) but a lower enantioselectivity (53%). Finally, good regioselectivities (4/1) and satisfactory enantioselectivities (70–75%) were reached when THF–CH_2Cl_2 (1 : 1) or acetone–CH_2Cl_2 (1 : 1) mixtures were used as solvent.

The scope of the allylic substitution of cinnamyl chloride **1** by *para*-substituted phenols catalyzed by ruthenium complexes in the presence of K_2CO_3 was studied in acetone at 0 °C in the presence of the bisoxazoline **5** (Table 3). Very good conversions and enantioselectivities were obtained, which showed that the catalyst

DOI: 10.1039/b406039c

Table 2 Solvent effects in allylic etherification of phenol[a]

Solvent	Conversion (%)[b]	Selectivity (**2**/**3**)[b]	e.e.(%)[c]
Acetone	70	2/1	77
Acetonitrile	88	2.2/1	63
THF	88	2.5/1	80
CH_2Cl_2	70	6.5/1	53
Acetone/CH_2Cl_2	96	4/1	70
THF/CH_2Cl_2	90	4/1	75

[a] conditions : 0.75 mmol of phenol, 0.75 mmol of K_2CO_3, 0.5 mmol of cinnamyl chloride, 0.015 mmol of $[Cp^*Ru(CH_3CN)_3][PF_6]$ and **5** (3 mol%) in 4 mL of solvent, 0 °C, 40 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC.

tolerated the presence of methoxy and chloro substituents at the phenyl ring. Moreover, changing the electronic properties of the substituted phenol has little influence on the enantioselectivity. On the other hand, cinnamyl carbonate was found to be much less reactive than **1**.

Table 3 Allylic etherification of substituted phenols[a]

ArOH	Conversion (%)[b]	Selectivity (**2**/**3**)[b]	e.e.(%)[c,d]
4-MeO–C_6H_4	75	2.2/1	81 (*R*)
4-Cl–C_6H_4	96	1.6/1	82 (*R*)
4-H–C_6H_4	70	2/1	77 (*R*)

[a] Conditions : 0.75 mmol of ArOH, 0.75 mmol of K_2CO_3, 0.5 mmol of cinnamyl chloride **1**, 0.015 mmol of $[Cp^*Ru(CH_3CN)_3][PF_6]$ and **5** (3 mol%) in 4 mL of acetone, 0 °C, 40 h. [b] as determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC. [d] Absolute configuration of the products were established by correlation with previous data.[9]

In conclusion, we developed the first enantioselective allylic etherification with phenols catalyzed by a system based on the association of a (pentamethylcyclopentadienyl)ruthenium precursor and a chiral bisoxazoline. This catalytic system favoured the formation of branched allyl aryl ethers starting from cinnamyl chloride and provided good enantioselectivities with highly substituted chiral bisoxazoline ligands. The scope of the method when starting from other types of nucleophiles and other allylic substrates, as well as the elucidation of the structure of the ruthenium catalyst are now under investigation.

The authors wish to thank the European Union COST Programme D24/0005/02 for support.

Notes and references

† After stirring 0.015 mmol (3 mol%) of $[Cp^*Ru(CH_3CN)_3]PF_6$ and 0.015 mol (3 mol%) of bisoxazoline ligand in acetone at room temperature for one hour, 0.75 mmol of potassium carbonate and 0.5 mmol of cinnamyl chloride were added and the mixture was cooled to 0 °C. After 15 min., 0.75 mmol of phenol was added and the mixture was stirred at 0 °C for 40 hours, then filtered on silica and concentrated. The resulting oil was analyzed by ^{1}H NMR spectroscopy and the enantiomeric excess was determined by HPLC.

1 B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921.
2 (*a*) B. M. Trost and C. Lee, in *Catalytic Asymmetric Synthesis*, I. Ojima, Ed., Wiley, 2000, pp. 593–649; (*b*) A. Pfaltz and M. Lautens in *Comprehensive. Asymmetric Catalysis*, E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Eds.; Springer: Berlin, 1999, p. 833.
3 (*a*) C. Goux, P. Lhoste and D. Sinou, *Synlett*, 1992, 725; (*b*) S. Cacchi, G. Fabrizi and L. Moro, *Synlett*, 1998, 741; (*c*) B. Nay, J.-F. Peyrat and J. Vercauteren, *Eur. J. Org. Chem.*, 1999, 2231; (*d*) M. Massacret, P. Lhoste, R. Lakhmiri, T. Parella and D. Sinou, *Eur. J. Org. Chem.*, 1999, 2665.
4 C. Goux, M. Massacret, P. Lhoste and D. Sinou, *Organometallics*, 1995, **14**, 4585.
5 (*a*) P. A. Evans and D. K. Leahy, *J. Am. Chem. Soc.*, 2000, **122**, 5012; (*b*) P. A. Evans and D. K. Leahy, *J. Am. Chem. Soc.*, 2002, **124**, 7882.
6 B. M. Trost, P. L. Fraisse and Z. T. Ball, *Angew. Chem. Int. Ed.*, 2002, **41**, 1059.
7 (*a*) A. Iourtchenko and D. Sinou, *J. Mol. Catal. A: Chem.*, 1997, **122**, 91; (*b*) J.-R. Labrosse, C. Poncet, P. Lhoste and D. Sinou, *Tetrahedron: Asymmetry*, 1999, **10**, 1069.
8 (*a*) B. M. Trost and F. D. Toste, *J. Am. Chem. Soc.*, 2000, **122**, 11262and references cited therein (*b*) B. M. Trost, H. C. Shen, L. Dong and J.-P. Surivet, *J. Am. Chem. Soc.*, 2003, **125**, 9276.
9 F. Lopez, T. Ohmura and J. F. Hartwig, *J. Am. Chem. Soc.*, 2003, **125**, 3426.
10 T. Kondo, H. Ono, N. Satabe, T. Mitsudo and Y. Watanabe, *Organometallics*, 1995, **14**, 1945.
11 Y. Matsushima, K. Onitsuka, T. Kondo, T. Mitsudo and S. Takahashi, *J. Am. Chem. Soc.*, 2001, **123**, 10405.
12 J.-L. Renaud, C. Bruneau and B. Demerseman, *Synlett*, 2003, 408.
13 M. D. MBaye, B. Demerseman, J.-L. Renaud, L. Toupet and C. Bruneau, *Angew. Chem. Int. Ed.*, 2003, **42**, 5066.
14 M. D. MBaye, B. Demerseman, J.-L. Renaud, L. Toupet and C. Bruneau, *Adv. Synth. Catal.*, 2004, **346**, in press.
15 A. K. Ghosh, P. Mathivanan and J. Cappiello, *Tetrahedron: Asymmetry*, 1998, **9**, 1.