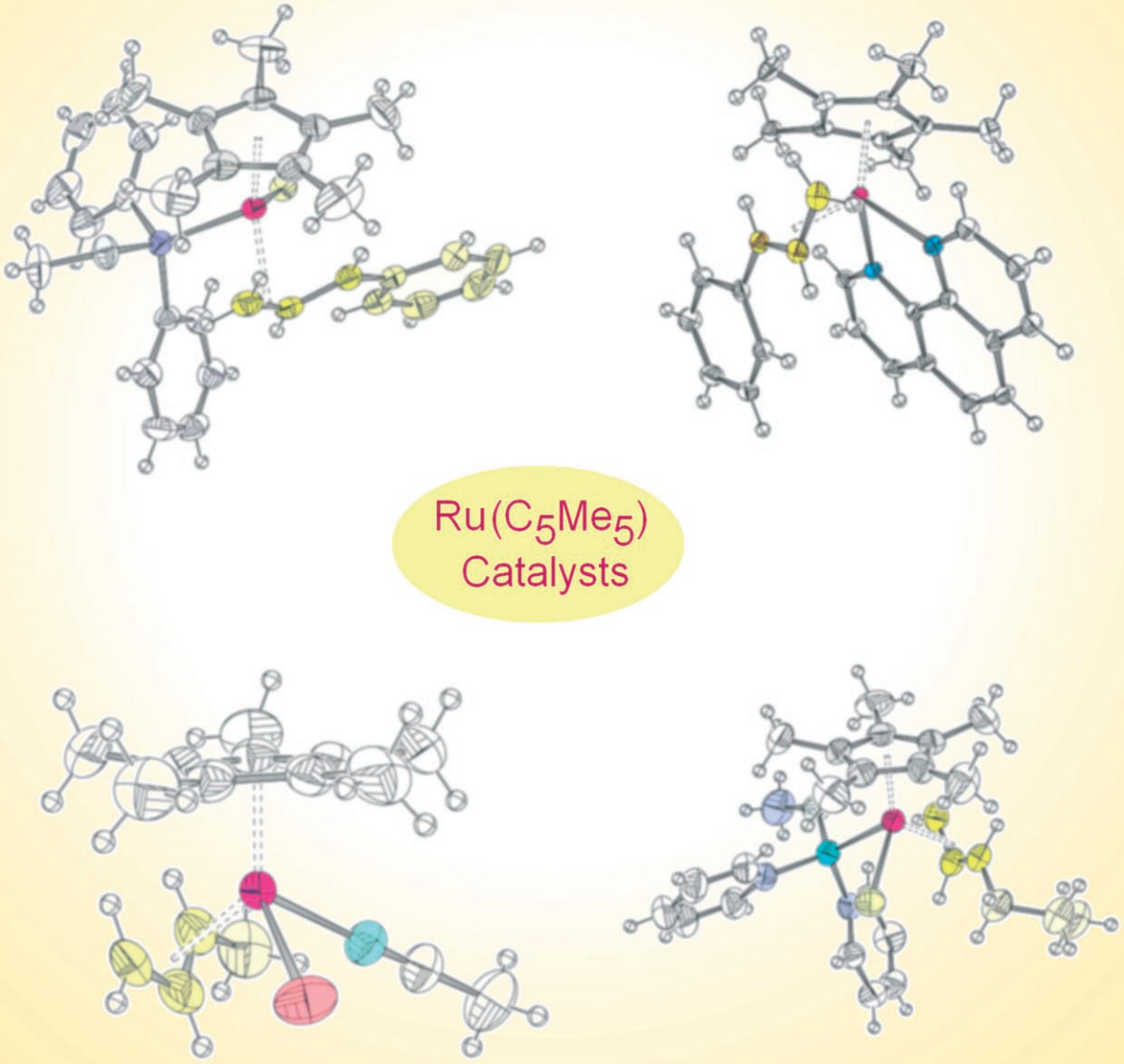
Pentamethylcyclopentadienyl–Ruthenium Catalysts for Regio- and Enantioselective Allylation of Nucleophiles

From regioselective allylation ...



... to enantioselective catalysis.

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Pentamethylcyclopentadienyl–Ruthenium Catalysts for Regio- and Enantioselective Allylation of Nucleophiles

Christian Bruneau,* Jean-Luc Renaud, and Bernard Demerseman[a]

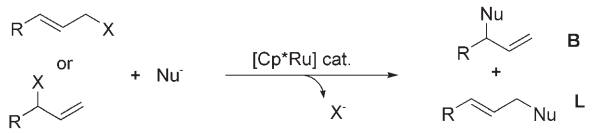
Abstract: Ruthenium(II) complexes containing the pentamethylcyclopentadienyl ligand efficiently perform the activation of allylic carbonates and halides to generate cationic and dicationic ruthenium(IV) complexes. This activation has been transferred as a key step to the catalytic allylation of nucleophiles. The structural and electronic properties of the allylic moieties lead to the regioselective formation of chiral products resulting from nucleophilic addition to their most substituted terminus. The catalytic activity of various Ru(Cp*) precatalysts in several allylic substitutions by C and O nucleophiles will be presented. The enantioselective version that has been demonstrated by using optically pure bisoxazoline ligands will also be discussed.

Keywords: allylation · enantioselectivity · nucleophilic substitution · regioselectivity · ruthenium

Introduction

Enantioselective nucleophilic substitution of allylic substrates catalysed by transition-metal complexes is a powerful method in organic synthesis. The palladium-catalysed reaction known as the Tsuji–Trost reaction[1] is one of the most popular model reactions for this type of substitution, which is used for the evaluation of the efficiency of chiral ligands. More recently, other transition-metal complexes based on molybdenum,[2] rhodium,[3] tungsten[4] and iridium[5] have shown high potential in this type of reaction. However, the nucleophilic allylic substitution has not been widely studied starting from unsymmetrically substituted substrates, and yet constitutes a challenging research area in asymmetric catalysis.

With the objective of preparing optically active compounds through the substitution of related unsymmetrical allylic substrates bearing an unsubstituted terminus, the first requirement is the regioselective formation of chiral branched isomers **B** (Scheme 1) via monosubstituted allylic



R= Ph, $PhCH_2$, *n*Pr ; NuH= alcohol, amine, phenol, $YCR'Z^1Z^2$
(Z^1= CO_2Me, Z^2=CO_2Me, COMe ; Z^1= Z^2= COMe ; R'= H, Me ; Y= H, Na)

Scheme 1. General scheme for the nucleophilic substitution of unsymmetrical allylic substrates leading to branched (**B**) and linear (**L**) regioisomers.

organometallic intermediates. To reach this purpose, some ruthenium complexes have shown potential and these will be presented in this paper.

Ru-Catalysed Nucleophilic Substitution Chronology

In the field of metal-catalysed allylic substitution, the catalytic activity of ruthenium complexes was first shown in 1985 by Tsuji, who used the ruthenium(II) dihydride complex $[RuH_2(PPh_3)_4]$ to perform the substitution of allyl and cinnamyl carbonates by stabilised carbon nucleophiles arising from β-ketoesters.[6] The reaction was carried out in pyridine as solvent, but led to the linear product starting from cinnamyl carbonate and methyl 2-methyl-3-oxobutanoate (Scheme 1, R′ = Me, Y = Na, $Z^1 = CO_2Me$, Z^2 = COMe). The substitution of cinnamyl carbonate was also performed with $[Ru^0(cod)(cot)]$ (cod = cyclooctadiene, cot = cyclooctatriene) as the catalyst precursor. Branched compounds were pro-

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duced from β-ketoesters, whereas no regioselectivity was obtained from malonate nucleophiles.[7]

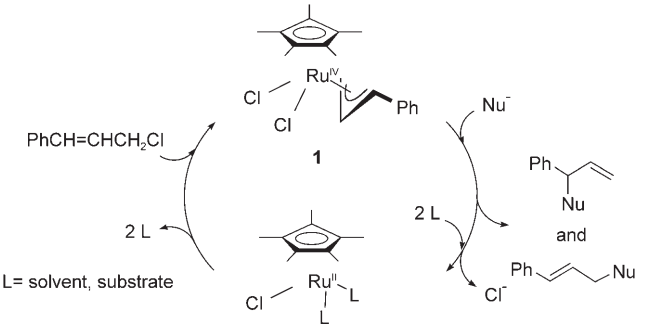
Neutral ruthenium complexes containing a Ru(Cp) (Cp = cyclopentadienyl) fragment, such as $[RuCl(Cp)(PPh_3)_2]$,[8] [RuCl(Cp)(cod)][9] are also able to provide the activation of allylic carbonates. The reactions require high temperature and lead to the formation of both branched and linear compounds without any regioselectivity. On the other hand, the cationic Ru(Cp)-containing precatalysts $[Ru(Cp)(PPh_3)(CH_3CN)_2]PF_6$,[10] and $[Ru(Cp)(CH_3CN)_3]PF_6$[11] performed the allylic activation under mild conditions (25–30 °C). Unfortunately, they provide a low regioselectivity in favour of the linear isomer, as exemplified by the reaction of *tert*-butyl cinnamyl carbonate with methyl sodium malonate in the presence of $[Ru(Cp)(CH_3CN)_3]PF_6$. Complete conversion with a **B**/**L** ratio of 1:2 was obtained in dimethylformamide at ambient temperature.[12]

A breakthrough in terms of regioselectivity in favour of the branched isomers was brought by the use of Ru(Cp*) (Cp* = pentamethylcyclopentadienyl) catalyst precursors. The Cp* ligand offers at the same time steric protection and electron richness to the metal centre. This was first shown by the utilisation of [RuCl(Cp*)(cod)] during the substitution of cinnamyl carbonate by piperidine; this reaction led to complete conversion in THF at 0 °C with a **B**/**L** ratio of 84:16.[13] Similarly, the reaction with sodium malonate at room temperature gave a **B**/**L** ratio of 88:12.[14] However, the regioselectivities that are obtained in the presence of this neutral ruthenium precursor strongly depend on the nature of the starting allylic substrates. Indeed, the formation of branched isomers is highly favoured when the allylic fragment is substituted by an aromatic group rather than an alkyl group. For instance, the substitution of the aliphatic *trans*-but-2-enyl methyl carbonate by piperidine produces a 56:44 **B**/**L** ratio,[13] and the substitution of butenyl methyl carbonates by pentanethiol leads to the linear compound as the major compound (**B**/**L** = 22:78).[15]

Based on the good results obtained with precatalysts featuring the Ru(Cp*) fragment, and the remarkable activities of enantiopure chiral nitrogen ligands already shown in enantioselective catalysis,[16] we investigated the potential of Ru(Cp*) complexes bearing nitrogen ligands with the objective of preparing new catalysts able to perform both regio- and enantioselective substitution of unsymmetrical allylic substrates. A variety of Ru(Cp*)-containing complexes were thus revealed as excellent precursors for the regioselective allylation of selected nucleophiles from cinnamyl derivatives, but also more challenging and innovative from aliphatic allylic substrates.

Structures of Neutral and Cationic η^3-Allyl Pentamethylcyclopentadienyl–Ruthenium(IV) Complexes

The pioneering study in which the pentamethylcyclopentadienyl–ruthenium complex [RuCl(Cp*)(cod)] was involved as a catalyst precursor for allylation reactions under mild conditions has undoubtedly initiated further efforts to take advantage of the interest of a regioselectivity favouring the formation of branched organic products.[13] The characterisation of the involved η^3-allyl ruthenium(IV) complex $[RuCl_2(Cp^*)(\eta^3\text{-}CH_2CHCHPh)]$ as depicted in Scheme 2, already



Scheme 2. Oxidative addition of allylic substrate as a key-step in ruthenium-catalysed allylic substitution reactions.

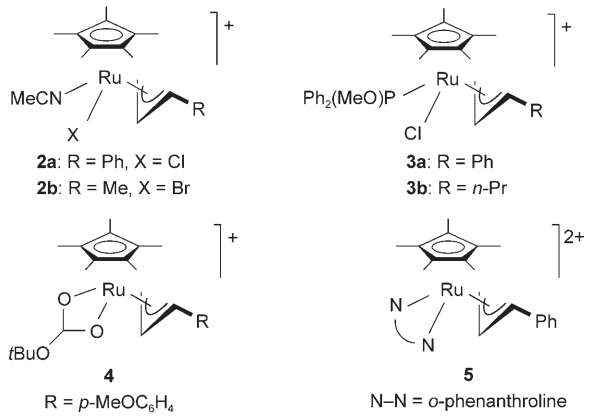
suggested that oxidative addition of allylic substrates to the ruthenium(II) centre would be a key step for related catalytic processes.[13]

From [RuCl(Cp*)(cod)], the easy removal of the 1,5-cyclooctadiene ligand allowing the formation of **1** might suggest a 14-electron RuCl(Cp*) fragment will account for the catalytic activity. However, the discovery of new Ru(Cp*)-based catalyst precursors indicated that the first requirement for catalytic activation was the ability of the ruthenium centre to generate a 16-electron ruthenium species able to coordinate the olefinic function from the allylic substrate. A subsequent intramolecular oxidative addition step completes the formation of η^3-allyl–ruthenium(IV) complexes.

In this way, not only the cationic $[Ru(Cp^*)(MeCN)_3]PF_6$ ruthenium(II) precursor bearing very labile acetonitrile ligands has conveniently allowed the synthesis of cationic $[RuX(Cp^*)(\eta^3\text{-}CH_2CHCHR)(MeCN)]PF_6$ complexes,[17,18] but also precursors such as $[Ru(Cp^*)(L)(MeCN)_2]PF_6$ and $[Ru(Cp^*)(bipy)(MeCN)]PF_6$, which have led to monocationic and dicationic η^3-allyl–ruthenium(IV) complexes, respectively (Scheme 3).[19,20]

Complexes **2a** and **2b** resulted from oxidative addition of the allylic halide to $[Ru(Cp^*)(MeCN)_3]PF_6$, and complex **4** is a rare example of a characterised η^3-allyl–ruthenium(IV) complex arising from oxidative addition of a cinnamyl carbonate.[21] Complexes **3a**, **3b** and **5** resulted from oxidative addition of allylic halides to $[Ru(Cp^*)(Ph_2POMe)(MeCN)_2]PF_6$ and $[Ru(Cp^*)(o\text{-phenanthroline})(MeCN)]PF_6$ in the presence of KPF_6, respectively. In the solid state, all these η^3-allyl–pentamethylcyclopentadienyl–ruthenium(IV) complexes have an *endo-trans*-CH_2CHCHR η^3-allyl ligand.

The selected data collected in Table 1 allow a comparison between the η^3-allyl–Ru fragments in complexes **1**–**5**. The examination of bond lengths emphasises for each complex a



Scheme 3. X-ray structurally characterised cationic pentamethylcyclopentadienyl–ruthenium(IV) complexes bearing an unsymmetrical η^3-allyl ligand.

Table 1. Selected bond lengths [Å] in [Ru(Cp*)(η^3-allyl)] complexes.

Complex	Ru–CH_2	Ru–CHR	Ru–CH	Δ[a]	Ref.
1	2.18(1)	2.35(2)	2.14(2)	0.17(3)	[13]
2a	2.192(3)	2.351(2)	2.162(3)	0.159(5)	[18]
2b	2.208(4)	2.280(5)	2.165(5)	0.072(9)	[17]
3a	2.182(5)	2.452(4)	2.210(4)	0.270(9)	[19]
3b	2.191(4)	2.339(4)	2.198(4)	0.148(8)	[19]
4	2.162(5)	2.303(5)	2.137(5)	0.14(1)	[21]
5	2.196(3)	2.398(3)	2.197(3)	0.202(6)	[20]

[a] $\Delta = (Ru–CHR) – (Ru–CH_2)$.

close as might be assumed for a true η^3-allyl ligand. Simple $^{13}C\{^1H\}$ NMR spectra allow us to distinguish the resonance corresponding to the $=CH_2$ carbon nucleus, whereas the resonances assigned to the two CH carbon nuclei (CH and CHR) occurred at neighbouring chemical shifts. In all cases, the resonance of the terminal CH_2 is located 20–40 ppm upfield with respect to the substituted terminal allylic end. For complexes **2a** and **2b** two species were observed in dichloromethane as monitored by NMR spectroscopy. This isomerism disappeared when a symmetrical allyl ligand was introduced, thus indicating a stereoisomerism that may be formally depicted as an exchange of position between the acetonitrile and the halide ligand. However, additional species believed to arise from *endo–exo* isomerism have been detected in acetone.[18] The substitution of the acetonitrile ligand by the more sterically demanding Ph_2POMe phosphorus ligand enhanced stereoselectivity as only one species was detected in the case of complexes **3a** and **3b**. In all cases, the allylic complexes contain a stereogenic ruthenium centre.

The study of these η^3-allyl–ruthenium(IV) complexes believed to be closely related to catalytic intermediates, was expected to provide a better mechanistic understanding for catalytic processes. Especially important at the synthetic point of view, but also intriguing, was the favoured formation of branched products when the allylic substrate generated an unsymmetrical η^3-CH_2CHCHR allyl ligand. The proposed formation of η^3-allyl–ruthenium(IV) intermediates as the first key step for ruthenium-catalysed allylation reactions is commonly accepted, as well as a subsequent addition of the nucleophile at one terminus carbon of the allyl ligand. From a kinetical point of view, both the preliminary η^2-olefinic coordination of the allylic substrate to the ruthenium(II) centre and the following intramolecular oxidative addition step might be of crucial importance during the allylic activation process. Thus, the allylation of the dimethyl malonate anion with *tert*-butyl cinnamyl carbonate was twice as fast by using **4** rather than $[Ru(Cp^*)(MeCN)_3]PF_6$ as the catalyst, owing to the coordinating ability of acetonitrile.[21] The rate of the catalytic process was also shown to depend on the linear or branched structure of the allylic carbonate, but in agreement with a mechanism involving the same η^3-allyl–ruthenium(IV) intermediate.

longer Ru–CHR bond relative to the Ru–CH_2 one ($0.072 < \Delta < 0.270$ Å).

The comparison of Ru–CH_2, and Ru–CH bond lengths in all the complexes reveals slight differences (maximum difference = 0.046, and 0.037 Å, respectively). The main variation concerns the Ru–CHR bond length. The Ru–CHAr bond lengths decreased from 2.452(4) Å in **3a** to 2.303(5) Å in **4**, thus remarkably following the order of decreasing steric requirement from Ph_2POMe, Cl (**3a**) > N–N chelate (**5**) > MeCN, Cl (**2a**) or Cl, Cl (**1**) > O–O chelate (**4**). However, the Ru–CHR bond is significantly shorter when R is an alkyl instead of an aryl group (2.280(5) Å in **2b** vs. 2.351(2) Å in **2a**; 2.339(4) Å in **3b** vs. 2.452(4) Å in **3a**), and thus becomes less distinct relative to the Ru–CH_2 bond length. Therefore, perhaps not surprisingly, moderate regioselectivities are reached in several catalytic systems starting from alkyl allylic substrates, whereas high regioselectivities were most often observed starting from cinnamyl substrates.

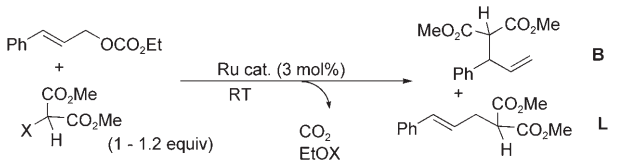
The structural details and $^{13}C\{^1H\}$ NMR spectroscopic data given in Table 2 are also specific of the allyl ligand. The CH–CH_2 and CH–CHR bond lengths are remarkably

Table 2. Bond lengths [Å], angles [°], and $^{13}C\{^1H\}$ NMR data for the allyl ligand in complexes **1**–**5**.

Complex	CH_2–CH	CH–CHR	H_2C-C-CHR	$\delta(CH_2)$	δ(CH)	Ref.
1	1.38(2)	1.43(2)	118(1)	62.9	90.4, 92.8	[13]
2a (major)	1.415(4)	1.412(4)	115.8(3)	67.7	91.4, 94.0	[17,18]
2a (minor)				59.8	93.2, 101.2	[17]
2b (major)	1.394(7)	1.403(5)	115.8(5)	66.9	86.4, 98.6	[17]
2b (minor)				62.0	94.1, 98.3	[17]
3a	1.398(6)	1.396(6)	119.5(4)	51.4	91.0, 103.4	[19]
3b	1.406(6)	1.395(6)	119.1(4)	53.3	96.1, 100.4	[19]
4	1.404(7)	1.397(7)	116.5(5)	65.3	93.2, 98.6	[21]
5	1.412(5)	1.402(5)	118.3(3)	67.0	92.7, 97.7	[20]

The data collected in Table 1 clearly indicate a longer Ru–CHR bond relative to the Ru–CH_2 one in η^3-allyl ruthenium(IV) complexes **1**–**5**, all bearing an unsymmetrical η^3-CH_2CHCHR allyl ligand. This observation might intuitively suggest a minor contribution of an η^2-CH_2=CH–$C^{(+)}$HR olefinic form to the coordination of the allyl ligand and this picture conveniently accounts for the observed regioselectivity. However, results from DFT calculations were more consistent with attack by a nucleophile at the less negative CHR carbon atom of a both geometrically and electronically distorded η^3-allyl ligand.[18]

Table 3. Ethyl cinnamyl carbonate substitution by carbonucleophiles.



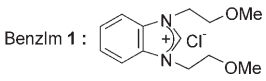
Catalyst precursor	X	Solvent	Reaction time [h]	Conv. [%]	**B**/**L** ratio	Ref.
[RuCl(Cp*)(cod)]	Na	THF	17	45	95:5	[26]
[RuCl(Cp*)(MesN=CHCH=NMes)]	Na	THF	17	85	65:35	[26]
$[Ru(Cp^*)(CH_3CN)(MesN{=}CHCH{=}NMes)]PF_6$	Na	THF	17	100	85:15	[26]
$[Ru(Cp^*)(CH_3CN)_2(PPh_2OMe)]PF_6$	Na	THF	16	100	92:8	[19]
$[Ru(Cp^*)(CH_3CN)_2(PPh_2(o\text{-tolyl})]PF_6$	Na	THF	16	100	90:10	[19]
$[Ru(Cp^*)(CH_3CN)(4,4'\text{-diMe-}2,2'\text{-bipy})]PF_6$	H	CH_3CN	17	100	96:4	[20]
$[Ru(Cp^*)(CH_3CN)(4,4'\text{-di}t\text{Bu-}2,2'\text{-bipy})]PF_6$	H	CH_3CN	17	100	95:5	[20]
$[Ru(Cp^*)(CH_3CN)_3]PF_6$/BenzIm **1**/*t*BuOK	H	CH_3CN	16	100	85:15	[27]
$[Ru(Cp^*)(CH_3CN)_3]PF_6$/BenzIm **2**/*t*BuOK	H	CH_3CN	16	100	88:12	[27]

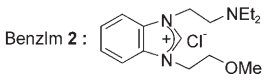
From the chirality point of view, stereospecific nucleophilic substitution starting from optically active substrates has been reported in the presence of $[Ru(Cp^*)(MeCN)_3]PF_6$ as catalyst.[12,37] However, it is very difficult to control the stereochemistry of the ruthenium centre and enantioselective catalytic processes have been achieved only with catalysts bearing an optically pure ligand. Examples based on the utilisation of $[Ru(Cp'\text{-}PR_2)(MeCN)_2]PF_6$[22,24] and $[Ru(Cp^*)(MeCN)_3]PF_6$[23] in the presence of a chiral bis-oxazoline ligand will be presented.

Pentamethylcyclopentadienyl–Ruthenium Catalysts for Regioselective Allylation of Nucleophiles

Allylation of stabilised carbon nucleophiles with cinnamyl carbonates: Stabilised carbon nucleophiles are usually generated from *gem*-diesters, *gem*-diketones, α-ketoesters, and related compounds upon deprotonation with NaH. Only in the case of allylic carbonates as starting substrates, in which the in situ formation of an alkoxide anion able to deprotonate the pronucleophile is observed, can the use of NaH be avoided. Examples of such a process have been observed in palladium-catalysed allylic substitution,[25] but with ruthenium catalysts the most common procedure includes previous generation of an anionic nucleophile. In the presence of neutral catalyst precursors featuring a labile bidentate ligand, such as [RuCl(Cp*)(cod)] and [RuCl(Cp*)(1,2-diimine)],[26] ethyl cinnamyl carbonate was substituted by sodium malonate with high regioselectivity but modest conversions (Table 3). On the other hand, no conversion was observed when the analogous neutral ruthenium complex containing the 1,3-bis(diphenylphosphino)propane ligand was used.[14] The corresponding cationic ruthenium complexes resulting from substitution of the chloride anion by acetonitrile were more efficient and led to complete conversion within 16 h with **B**/**L** ratios of about 85:15. $[Ru(Cp^*)(CH_3CN)_3]PF_6$ was shown to give complete conversion and the major formation of the branched isomer from *tert*-butyl cinnamyl carbonate and sodium malonate in a **B**/**L** ratio of 90:10.[12,21] Substitution of one acetonitrile ligand by the phosphane PPh_2(o-tolyl) or the phosphinite PPh_2OMe led to similar regioselectivities in THF at room temperature (Table 3).[19]

We have found that two types of catalysts were able to make the substitution of cinnamyl carbonate by diethyl malonate possible without previous deprotonation. One arises from an in situ generated catalytic system prepared by treatment of $[Ru(Cp^*)(CH_3CN)_3]PF_6$ with two equivalents of a benzimidazolium salt (BenzIm **1** or BenzIm **2**) and *t*BuOK



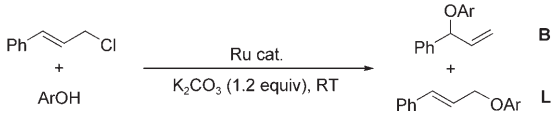


in THF at 50 °C for 2 h.[27] Even though, no well-defined complex could be isolated, this procedure is supposed to generate a [Ru(Cp*)(carbene)] species. The second family of catalyst precursors consists of well-characterised $[Ru(Cp^*)(CH_3CN)(bipyridine)]PF_6$ complexes, which produce dicationic ruthenium species $[Ru(Cp^*)(allyl)(bipyridine)]^{2+}$ upon activation of allylic substrates.[20] The formation of dicationic allylic intermediates would reinforce the electrophilic character of the intermediate allylic ligand and thus make the nucleophilic attack efficient even in the presence of a catalytic concentration of carbonucleophile. These catalytic systems not only make possible the direct reaction of malonates with allylic carbonates, but also lead to the highest regioselectivities in favour of the branched isomers (>95:5; Table 3). Similarly, the direct substitution of ethyl cinnamyl carbonate by pentane-2,4-dione is carried out with a **B**/**L** ratio of 98:2 in the presence of the extremely active $[Ru(Cp^*)(CH_3CN)(phenanthroline)]PF_6$ precursor.[20]

Allylation of phenols with cinnamyl chloride: Cinnamyl chloride reacts with methyl sodium malonate in the pres-

ence of $[Ru(Cp^*)(CH_3CN)_3]PF_6$ in DMF to form the expected branched and linear products. At room temperature, a poor regioselectivity is observed, whereas at −40 °C the branched product is obtained almost as the sole compound in more than 99 % relative yield.[12] We have investigated the use of cinnamyl chloride to perform the regioselective etherification by phenol derivatives, in the presence of K_2CO_3 as a base for the in situ formation of phenoxide anions, and various ruthenium catalysts (Table 4).

Table 4. Regioselective allylation of phenols by cinnamyl chloride.



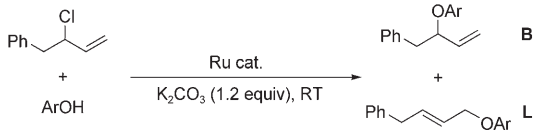
Catalyst precursor	Ar	Solvent	Reaction time [h]	Conv. [%]	**B/L** ratio	Ref.
$[Ru(Cp^*)(CH_3CN)_3]PF_6$	C_6H_5	CH_3CN	40	100	98:2	[17]
$[Ru(Cp^*)(CH_3CN)_3]PF_6$	4-$MeOC_6H_4$	CH_3CN	40	100	98:2	[17]
$[Ru(Cp^*)(CH_3CN)_3]PF_6$	4-MeC_6H_4	CH_3CN	40	100	97:3	[17]
$[Ru(Cp^*)(CH_3CN)_3]PF_6$	4-ClC_6H_4	CH_3CN	40	100	98:2	[17]
$[Ru(Cp^*)(CH_3CN)_3]PF_6$/BenzIm **1**/*t*BuOK	C_6H_5	CH_3CN	16	100	94:6	[27]
$[Ru(Cp^*)(CH_3CN)_3]PF_6$/BenzIm **1**/*t*BuOK	4-$MeOC_6H_4$	CH_3CN	16	100	94:6	[27]
$[Ru(Cp^*)(CH_3CN)_3]PF_6$/BenzIm **1**/*t*BuOK	4-ClC_6H_4	CH_3CN	16	100	89:11	[27]
$[Ru(Cp^*)(CH_3CN)_2(PPh_2OMe)]PF_6$	C_6H_5	CH_2Cl_2	16	100	85:15	[19]
$[Ru(Cp^*)(CH_3CN)_2(PPh_2OMe)]PF_6$	4-$MeOC_6H_4$	CH_2Cl_2	16	76	92:8	[19]
$[Ru(Cp^*)(CH_3CN)_2(PPh_2OMe)]PF_6$	4-MeC_6H_4	CH_2Cl_2	16	61	88:12	[19]

Very high regioselective substitutions took place when $[Ru(Cp^*)(CH_3CN)_3]PF_6$ was used in CH_3CN at room temperature.[17] When one acetonitrile ligand in complex $[Ru(Cp^*)(CH_3CN)_3]PF_6$ was exchanged by PPh_2OMe, no catalytic activity was observed neither in THF nor in acetonitrile. However, in dichloromethane, $[Ru(Cp^*)(CH_3CN)_2(PPh_2OMe)]PF_6$ led to the formation of the branched isomer as the major product at room temperature in 16 h, in a quantitative yield and a **B/L** ratio of 85:15.[19] The strong solvent influence seems to indicate that in the presence of the phosphinite ligand PPh_2OMe, THF and acetonitrile are strongly ligated to the [Ru(Cp*)] centre, thus precluding the coordination and activation of cinnamyl chloride. In dichloromethane, various aryl benzyl ethers were obtained with good regioselectivities, from *o*-, *m*- and *p*-cresols and *p*-methoxy- and *o*-chlorophenol (Table 4).[19] The [Ru(Cp*)(carbene)]-containing catalytic system was also found as an efficient catalytic system in terms of reactivity and regioselectivity. In acetonitrile, except for 2-chlorophenol which led to low regioselectivities with various types of benzimidazolylidene ligands, the best regioselectivities obtained from phenol, 4-methoxy-, and 4-chlorophenol corresponded to **B/L** ratios of 94:6, 94:6, and 89:11, respectively (Table 4).[27]

Allylation of phenols with allyl benzyl chloride: The substitution of 3-chloro-4-phenylbut-1-ene, as a typical branched substrate, by phenol in the presence of potassium carbonate and 3 mol % of $[Ru(Cp^*)(CH_3CN)_3]PF_6$ carried out at room temperature in acetonitrile or acetone led to complete conversion, but with a poor **B/L** ratio of 60:40 (Table 5).[19]

The catalyst generated in situ from the same ruthenium complex, a benzimidazolium chloride (BenzIm **1**) and *t*BuOK provided a complete reaction within 16 h and led to a better **B/L** ratio of 83:17.[27] Similar regioselectivities were obtained from 4-chlorophenol and 4-methoxyphenol with various benzimidazolium carbene sources (Table 5).[27] The best results from various phenols and 3-chloro-4-phenylbut-1-ene were obtained with $[Ru(Cp^*)(CH_3CN)_2(PPh_2OMe)]PF_6$ as the catalyst precursor, which provided high conversion in THF at room temperature with regioselectivities in favour of the branched isomer higher than 9:1 (Table 5).[19] The allylic substitution of 3-chloro-4-phenylbut-1-ene by phenoxides as nucleophiles appears to favour the formation of the branched isomers when at least one acetonitrile ligand of $[Ru(Cp^*)(CH_3CN)_3]PF_6$ is replaced by a benzimidazolylidene or a phosphinite ligand.

Table 5. Substitution of 3-chloro-4-phenylbut-1-ene by phenol derivatives.

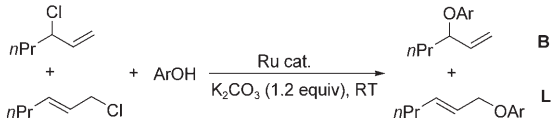


Catalyst precursor	Ar	Solvent	Reaction time [h]	Conv. [%]	**B/L** ratio	Ref.
$[Ru(Cp^*)(CH_3CN)_2(PPh_2OMe)]PF_6$	C_6H_5	THF	16	87	92:8	[19]
$[Ru(Cp^*)(CH_3CN)_2(PPh_2OMe)]PF_6$	4-$MeOC_6H_4$	THF	16	88	96:4	[19]
$[Ru(Cp^*)(CH_3CN)_2(PPh_2OMe)]PF_6$	4-MeC_6H_4	THF	16	93	91:9	[19]
$[Ru(Cp^*)(CH_3CN)_2(PPh_2OMe)]PF_6$	2-MeC_6H_4	THF	16	89	92:8	[19]
$[Ru(Cp^*)(CH_3CN)_3]PF_6$/BenzIm **1**/*t*BuOK	C_6H_5	CH_3CN	16	100	83:17	[27]
$[Ru(Cp^*)(CH_3CN)_3]PF_6$ + BenzIm **2** + *t*BuOK	4-$MeOC_6H_4$	CH_3CN	16	100	80:20	[27]
$[Ru(Cp^*)(CH_3CN)_3]PF_6$	4-ClC_6H_4	CH_3CN	16	100	83:17	[27]
$[Ru(Cp^*)(CH_3CN)_3]PF_6$	C_6H_5	CH_3CN	40	100	60:40	[17]

Allylation of phenols with aliphatic allylic chlorides: Isomeric hexenyl chlorides were used as allylic substrates to test the efficiency of ruthenium catalysts in the nucleophilic sub-

stitution. From phenol, $[Ru(Cp^*)(CH_3CN)_3]PF_6$ led to a **B/L** ratio of 63:37 in acetonitrile (Table 6), which represents a regioselectivity very comparable to that obtained from 3-chloro-4-phenylbut-1-ene.[17] The regioselectivity was slightly improve to a **B/L** ratio of 75:25, with the utilisation of $[Ru(Cp^*)(CH_3CN)_2(PPh_2OMe)]PF_6$ (Table 6).

Table 6. Etherification of aliphatic allylic halides by phenols.

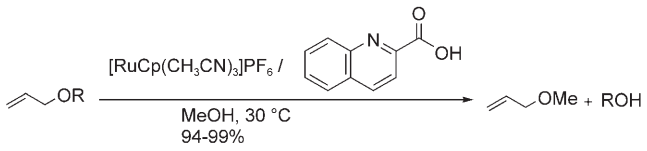


Catalyst precursor	Ar	Solvent	Reaction time [h]	Conv. [%]	**B/L** ratio	Ref.
$[Ru(Cp^*)(CH_3CN)_3]PF_6$	C_6H_5	CH_3CN	40	100	63:37	[17]
$[Ru(Cp^*)(CH_3CN)_3]PF_6$	C_6H_5	$(CH_3)_2CO$	40	100	70:30	[17]
$[Ru(Cp^*)(CH_3CN)_2(PPh_2OMe)]PF_6$	C_6H_5	THF	16	100	75:25	[19]
$[Ru(Cp^*)(CH_3CN)_2(PPh_2OMe)]PF_6$	$4\text{-}MeOC_6H_4$	THF	16	100	61:39	[19]
$[Ru(Cp^*)(CH_3CN)_2(PPh_2OMe)]PF_6$	$4\text{-}MeC_6H_4$	THF	16	88	75:25	[19]
$[Ru(Cp^*)(CH_3CN)_2(PPh_2OMe)]PF_6$	$4\text{-}ClC_6H_4$	THF	16	99	49:51	[19]

Applications of the Ruthenium-Catalysed Allylic Substitution Reaction

Protection and deprotection of alcohols: In organic chemistry, protection and deprotection of functionalised molecules require mild conditions with high reactivity and chemoselectivity. The allyloxycarbonyl function and the simple allyl group have demonstrated their efficiency for alcohol and amine protection. During the last five years, ruthenium-catalysed deprotection involving nucleophilic substitution by alcohol has been introduced as a simple method for carboxylate and hydroxy deprotection, with concomitant formation of an allyl ether. Thus, at room temperature, the use of $[Ru(Cp)(CH_3CN)_2(PPh_3)]PF_6$ proceeds with a high substrate/catalyst ratio from allyl carboxylates and methanol, and leads to the freed carboxylic acids and allyl methyl ether in quantitative yield.[10]

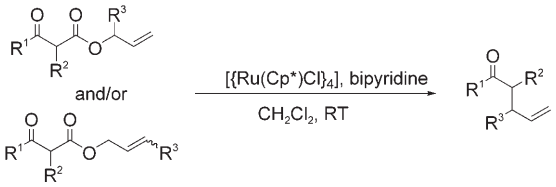
This ruthenium catalytic precursor is completely inert to deprotect allyl ethers. However, the addition of one equivalent of 2-quinolinecarboxylic acid to $[Ru(Cp)(CH_3CN)_3]PF_6$ provides a very efficient catalytic system to achieve the transetherification of various allyl ethers at 30 °C in methanol (Scheme 4).[11] Remarkably, the reverse reaction, the allylic alcohol etherification reaction, can be catalysed by the same ruthenium complex.[28]



R= Ph, $PhCH_2CH_2$, 2-indanyl, $PhCH_2(Me)_2C$, $CH_2{=}CH(CH_2)_3$, $HC{\equiv}C(CH_2)_3$

Scheme 4. Deprotection of alcohols.

Caroll rearrangement catalysed by ruthenium complexes: The decarboxylative allylic alkylation (namely, the Caroll rearrangement) is a [3,3]-rearrangement of allyl β-ketoesters which produces γ,δ-unsaturated ketones. The proposed mechanism for this catalysis mediated by transition metals involves an η^3-allyl intermediate. Saegusa et al. reported the first catalytic rearrangement of allyl β-ketoesters using a palladium complex.[29] However, the primary products were those of a [1,3]-rearrangement due to a nucleophilic attack at the less-substituted allyl terminus. The first [3,3]-rearrangement catalysed by ruthenium precursors $[\{Ru(Cp^*)(OCH_3)\}_2]$ and $[Ru(Cp^*)(\eta^3\text{-allyl})(\eta^2\text{-amidinate})][Cl, PF_6 \text{ or } BF_4]$ was reported by Nagashima et al.[30] Moderate to good selectivities were obtained with acyclic and cyclic compounds, respectively. Recently, Tunge and co-workers[31] reported that the [3,3]-Caroll rearrangement of allyl β-ketoesters could be catalysed by the $[RuCl(Cp^*)(bipy)]$ moiety, generated in situ by addition of bipyridine to $[\{RuCl(Cp^*)\}_4]$ (Scheme 5). Unsubstituted allyl β-ketoesters led almost exclusively to the branched ketone. Substituted β-ketoesters also reacted smoothly, but required longer reaction times and the diastereoselectivities were moderate.

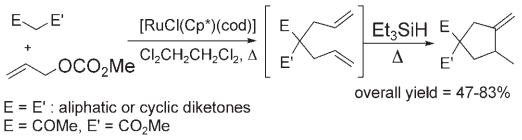


Scheme 5. Caroll rearrangement in the presence of $[Ru(Cp^*)(bipyridine)]$ catalysts.

This catalytic system was shown to be selective for the decarboxylative rearrangement of allyl β-ketoesters to γ,δ-unsaturated ketones in the presence of dimethyl malonate. The addition of the in situ generated enolate to the allyl ligand is then much faster than the deprotonation of malonate. Moreover, regioisomeric allyl β-ketocarboxylates provide the same product.[31a]

Tandem reactions catalysed by ruthenium complexes: Besides simple individual catalytic transformations, multiple catalytic transformations or cascade reactions in one pot have appeared.[32] Ruthenium catalysis has entered this field with a variety of cascade and sequential catalytic transformations.[33] The first tandem sequence, involving allylic substitution catalysed by a ruthenium complex, was described

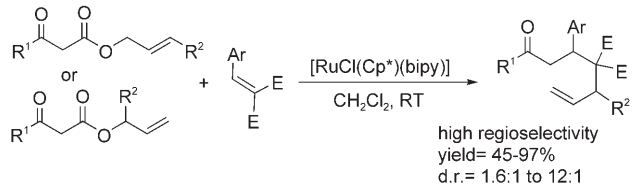
by Itoh et al. and provided *exo*-methylenecyclopentanes through a double allylation/cycloisomerisation from 1,3-diketones and β-ketoesters (Scheme 6).[34] The success of this



Scheme 6. Ruthenium-catalysed diallylation as the first step of a sequential transformation.

one-pot synthesis is based on the initial diallylation of malonates or β-ketoesters catalysed by [RuCl(Cp*)(cod)] followed by the additional use of a silane, which generates an active ruthenium–hydride species required for the second step.

A regioselective Michael addition/allylic alkylation was made possible by the decarboxylative activation of allyl β-ketoesters (Scheme 7).[35] The first step, catalysed by [RuCl(Cp*)(bipy)], regioselectively produced the enolate and an



Scheme 7. Tandem Michael addition/allylation.

electrophilic η^3-metal species. Enolate addition to the Michael acceptor produced a new stabilised enolate that served as nucleophile for the metal-catalysed allylic substitution. The regioselectivity of the last step is controlled by the ruthenium complex. By contrast, the analogous palladium-catalysed tandem reaction produced the opposite regioisomer. As observed for the Caroll rearrangement, the same product was isolated whatever the starting regioisomeric allyl β-ketocarboxylate.

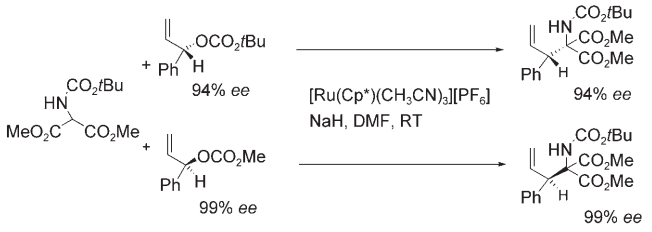
Even though tandem reactions are in the early stages, the above-mentioned examples demonstrate that Ru(Cp*) complexes are catalyst precursors of choice for regioselective control when a nucleophilic allylic substitution reaction is involved.

Asymmetric Allylation

Regio- and stereoselective formation of new bonds is a crucial issue in organic chemistry. Among the different methodologies, allylic substitutions represent a very useful and broadly explored transformation as a wide range of bond types can be created (C–C, C–S, C–N, C–O and C–H). The design of more and more active and selective ruthenium catalysts precursors for the allylic substitution reaction has led to the discovery of efficient catalytic systems giving highly regioselective reactions. This represents a main advantage, as the nature of the final compound is not dependent on the branched or linear nature of the unsymmetrical starting allylic substrate. It has been clearly shown that substitution at the more-substituted allylic terminus leading to chiral branched isomers is favoured, especially at the benzylic position of cinnamyl derivatives.

Stereoselectivity is another crucial problem to solve. Using allylic substitution, three classes of catalytic reaction can lead to the formation of optically pure compounds: 1) stereospecific reaction, 2) kinetic resolution and 3) enantioselective allylic substitution.

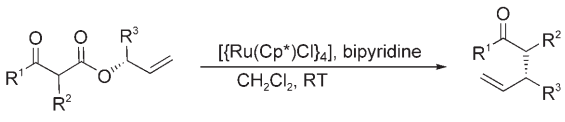
Stereospecific nucleophilic substitution: The complete transfer of chirality was observed during the substitution of the acyclic (*R*)- and (*S*)-1-phenylprop-2-enyl carbonates by a stabilised carbonucleophile (Scheme 8).[12]



Scheme 8. Stereospecific substitution of enantiopure allylic carbonates by carbonucleophiles.

It has been recently shown that nucleophilic addition of stabilised carbonucleophiles to cyclic allylic ruthenium complexes exclusively takes place from the *exo* face of the allylic ligand (opposite to metal coordination) according to an *anti* mechanism.[9,15,36] Then, the complete transfer of chirality proves that the addition of the nucleophile is faster than the equilibrium of the η^3-allyl–ruthenium intermediate and no racemisation was detected. The stereospecificity of the ruthenium-catalysed allylation was also demonstrated during the etherification of phenols starting from similar carbonates.[12]

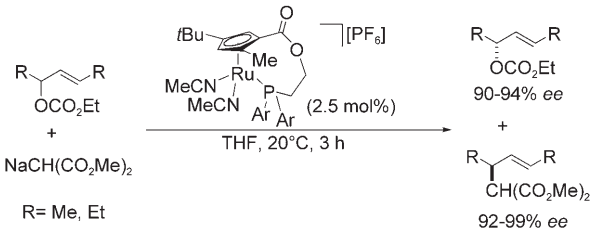
Decarboxylative allylation of ketone enolates using the [{RuCl(Cp*)}$_4$]/bipyridine catalytic system proceeds also in a stereospecific manner (Scheme 9).[37] Here again, the π–σ–π allyl interconversion is slow, and the rearrangement is highly stereospecific. The imperfect stereospecificity was attributed to a ruthenium-catalysed isomerisation of the starting material into the regioisomeric linear allyl β-ketoester, through reversible formation of η^3-allyl–ruthenium intermediate.



R^1 = Me, Bn, *i*Pr; R^2 = H, Me
R^3 = Ph, *p*-MeO-C_6H_4, *p*-Cl-C_6H_4, *p*-Me-C_6H_4, *p*-NO_2-C_6H_4

Scheme 9. Stereospecific allylation of enolates.

Kinetic resolution: Examples of kinetic resolution, in allylic substitution reaction, have been reported for palladium,[38] molybdenum[39] and iridium[40] catalysts. Using ruthenium catalysis, Onitsuka et al. have recently shown that planar chiral Ru(Cp′) complexes were effective catalysts for kinetic resolution of (*E*)-ethyl pent-3-en-2-yl carbonate during the substitution by malonate (Scheme 10, R = Me).[41] Extension

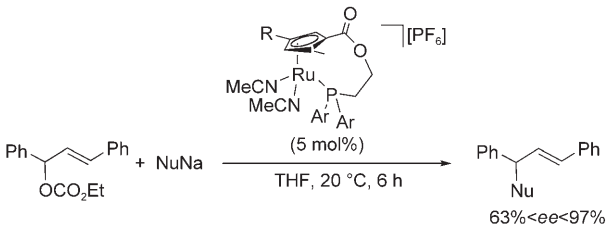


Scheme 10. Kinetic resolution of allylic carbonates by planar chiral cyclopentadienyl ruthenium catalysts.

of this reaction to other allylic carbonates (R = Et, Ph), which provides a symmetrical allylic organometallic intermediate, also leads to alkylated products in high *ee*'s (92–99%), and to the recovered carbonate in moderate to good *ee*'s (Scheme 10).

Enantioselective nucleophilic substitution: Enantioselective allylic substitution with nucleophiles is a powerful tool for the controlled formation of carbon–carbon and carbon–heteroatom bonds and opens efficient routes in total synthesis.[1b] Very few results have been reported on the enantioselective ruthenium-catalysed allylic nucleophilic substitution. The first examples were obtained with planar chiral cyclopentadienyl–ruthenium catalysts, which revealed high activity for the substitution of symmetrical allylic carbonates by di-*n*-propylamine and sodium malonates.[22] The allylic amination of *rac*-1,3-diphenylprop-2-enyl ethyl carbonate takes place at 20 °C in dichloromethane in the presence of 5 mol% of optically pure catalyst to give the allylated amine in quantitative yield with 20–74% *ee*. From sodium malonates, under similar conditions, optically active 1,3-diphenylprop-2-enyl malonates were obtained with high enantioselectivity (up to 97% *ee*) (Scheme 11).

We were interested in the development of a more straightforward route avoiding the preparation of planar chiral cyclopentadienyl–ruthenium complexes possessing an anchor phosphine ligand, but using optically pure bidentate nitrogen ligands for the enantioselective allylation from unsymmetrical substrates. Therefore, we are now developing a new catalytic system based on chiral bisoxazoline ligands and a Ru(Cp*) moiety for the regio- and enantioselective etherification of unsymmetrical allylic chlorides with phenols.[23] Among the chiral bisoxazolines, (4*R*,5*S*,4′*R*,5′*S*)-2,2′-methylenebis(4,5-diphenyl-2-oxazoline) led to the best enantioselectivities. Both regioselectivity and enantioselectivity of the O-allylation of phenol by cinnamyl chloride were found to be dependent on the nature of the solvent. In our

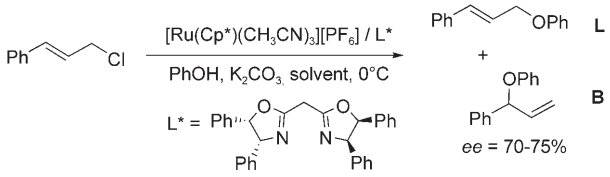


NuNa = $NaCH(CO_2Me)_2$, $NaCH(CO_2Et)_2$, $NaCMe(CO_2Me)_2$
R= Me, Ph, *t*Bu ; Ar= Ph, *o*-MeC_6H_4, 3,5-$Me_2C_6H_3$

Scheme 11. Enantioselective allylic substitution of carbonates with planar chiral ruthenium catalysts.

best reaction conditions, satisfactory regioselectivities (up to 4:1) and quite good enantioselectivities (70–75%) were obtained (Scheme 12).

Further studies with *para*-substituted phenols also provided good results, and demonstrated that this catalyst tolerates different substituents on the aromatic ring, and that the



Scheme 12. Enantioselective allylic substitution of cinnamyl chloride by phenol in the presence of optically pure [Ru(Cp*)(bisoxazoline)] catalysts.

electronic properties of the substituted phenols have little influence on the enantioselectivity (Table 7). Moreover, we have recently observed that this allylic etherification can be run at room temperature in acetone without any loss of enantioselectivity.

Table 7. Enantioselective allylic etherification of substituted phenols.

ArOH	Conversion [%]	Selectivity (**B**/**L**)	*ee* [%]
4-MeO-C_6H_4OH	75	2.2/1	81 (*R*)
4-Cl-C_6H_4OH	96	1.6/1	82 (*R*)
4-Me-C_6H_4OH	96	3/1	52 (*R*)

Conclusion and Outlook

Pentamethylcyclopentadienyl–ruthenium complexes bearing nitrogen ligands such as acetonitrile or bipyridine have revealed their ability to activate allylic halides and carbonates to generate [Ru(Cp*)(η^3-allyl)] complexes that can be isolated and fully characterised. Their structures exhibit common features:

- Formation of ruthenium complexes with a major *endo-trans*-coordinated allylic ligand.
- The allylic ligand shows two equivalent C–C bond lengths.
- The coordination of the allylic ligand is unsymmetrical in the sense that the ruthenium-unsubstituted carbon bond

length is always significantly shorter than the ruthenium-substituted carbon bond.

The catalytic allylation reactions take place at room temperature and are easy to transfer to applications in fine chemistry. The regioselectivity obtained for the allylation of various types of nucleophiles is in most cases in favour of the formation of the branched isomers, but strongly depends on the nature of the starting allylic substrate, the nucleophile, the catalyst precursor, the solvent and the temperature.

Satisfactory enantioselectivities have been obtained for the allylation of phenols in the presence of bisoxazoline ligands but to the detriment of regioselectivity. An objective is to find the family of ligands that will make possible the preparation of enantiomerically enriched allylic derivatives with high regioselectivity, and applicable to a large range of nucleophiles.

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