DOI: 10.1002/adsc.200900498

Ruthenium Catalysts for Controlled Mono- and Bis-Allylation of Active Methylene Compounds with Aliphatic Allylic Substrates

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Received: July 16, 2009; Published online: October 22, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900498.

Abstract: The allylation of 1,3-dicarbonyl compounds and malononitrile with aliphatic allylic substrates is achieved under mild conditions in the presence of new ruthenium catalysts. The ruthenium complex [Ru(C_5Me_5)(2-quinolinecarboxylato)(CH_2CHCH-*n*-Pr)][BF_4] as a precatalyst, allows the synthesis of mono-allylated branched derivatives. On the other hand, the parent complex [Ru(C_5Me_5)(MeCN)$_3$][PF_6] as a precatalyst, straightforwardly favours the bis-allylation of the procarbonucleophiles leading to bis-allylated bis-linear products. The involvement of the two precatalysts provides a sequential synthesis of unsymmetrical mixed linear-branched bis-allylated derivatives.

Keywords: allylation; C−C bond formation; homogeneous catalysis; regioselectivity; ruthenium

Introduction

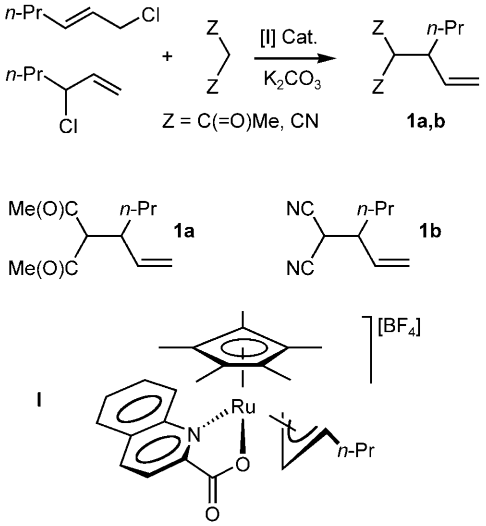
Ruthenium complexes have recently attracted an increasing interest as catalysts in allylic substitution reactions,[1] a versatile tool to form carbon-carbon and heteroatom-carbon bonds.[2] Furthermore, the reaction of malonate-type anions with allylic substrates has been largely employed as a useful test for the discovery of new catalysts and the investigation of their catalytic properties.[3] By contrast, little attention has been paid to the formation of 1,6-dienes through ruthenium-catalyzed double allylation of active methylene compounds, and especially to the regioselectivity of this transformation. However, 1,6-dienes are valuable building blocks and their cycloisomerization with various organometallic catalysts has been extensively studied.[4] The double allylation of 1,3-dicarbonyl compounds has been achieved using the ruthenium(0) complex Ru(cod)(cot) (cod = 1,5-cyclooctadiene, cot = 1,3,5-cyclooctatriene) as precatalyst.[5] The bis-allylation reaction was achieved at 80 °C using *N*-methylpiperidine as solvent, and a similar procedure was recently used for the first step in a "one-pot" double allylation/cycloisomerization of 1,3-dicarbonyl compounds using the RuCl(Cp*)(cod) precatalyst (Cp* = pentamethylcyclopentadienyl).[6]

We report herein a sequential access to novel unsymmetrical bis-allylated linear-branched derivatives from active methylene compounds and aliphatic allylic substrates, using the ruthenium complexes [Ru(Cp*)(2-quinolinecarboxylato)(η^3-CH_2CHCH-*n*-Pr)][BF_4] and [Ru(Cp*)(MeCN)$_3$][PF_6] as precatalysts. The former allowed the regioselective formation of mono-allylated branched derivatives whereas the latter provided an access to bis-allylated bis-linear derivatives under very mild conditions.

Results and Discussion

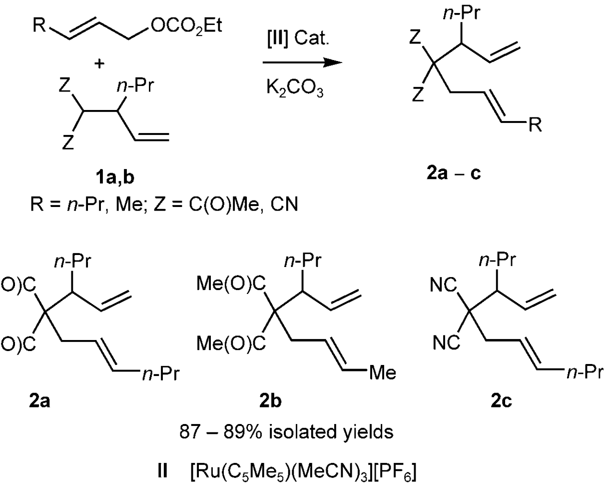
Since the [Ru(Cp)(2-quinolinecarboxylato)(η^3-allyl)][PF_6] complex has disclosed efficiency as precatalyst for nucleophilic allylic substitution with *O*-nucleophiles,[7] [Ru(Cp*)(2-quinolinecarboxylato)(η^3-allyl)][PF_6 or BF_4] ruthenium(IV) precatalysts have allowed highly regioselective nucleophilic substitution of aliphatic allylic substrates in favour of branched products,[8] and recently provided a novel access to functionalized vinylsilanes.[9] To extend the scope of ruthenium-catalyzed allylation reactions using catalysts based on a (Cp*)Ru fragment, the allylation of 2,4-pentanedione and malononitrile with hexenyl chloride was investigated. Hexenyl chloride was involved as a 4:1 mixture of linear n-PrCH=CHCH$_2$Cl and branched n-PrCH(Cl)CH=CH$_2$ isomers resulting from the reaction between PCl$_3$ and 2-*(E)*-hexen-1-ol.[10] Using the ruthenium complex [Ru(Cp*)(2-quinolinecarboxylato)(η^3-CH$_2$CHCH-n-Pr)][BF$_4$] **I** as a precatalyst in the presence of potassium carbonate as a base, the reaction occurred at room temperature. Starting from equimolar mixtures of hexenyl chloride, procarbonucleophile, and potassium carbonate in acetonitrile as solvent, complete conversion of the procarbonucleophile was reached in the presence of 3 mol% of **I** at room temperature (Scheme 1).

Starting from 2,4-pentanedione and malononitrile, the mono-allylated branched derivatives **1a** and **1b** were formed with an excellent selectivity (>95%) as monitored by GC analysis. Bis-linear and mixed linear-branched bis-allylated derivatives (*vide infra*) appeared as minor products. The pure mono-allylated branched derivatives **1a** and **1b** were obtained after chromatographic work-up as colourless oils in 82% and 53% yields, respectively. These selectivities are in line with our previous results obtained from the reaction of dimethyl malonate with hex-2-en-1-yl carbonate, and thus confirm the high regioselectivity in favour of the branched isomers using catalysts based on a Ru(Cp*)(2-quinolinecarboxylato) fragment, starting from aliphatic allylic substrates.[8]



Scheme 1. Synthesis of mono-allylated branched products **1a** and **b**. *Experimental conditions:* pronucleophile: 0.5 mmol, hexenyl chloride: 0.5 mmol, base: 0.5 mmol, catalyst **I**: 3 mol%, acetonitrile (4.0 mL) as solvent, room temperature, 16–18 h.

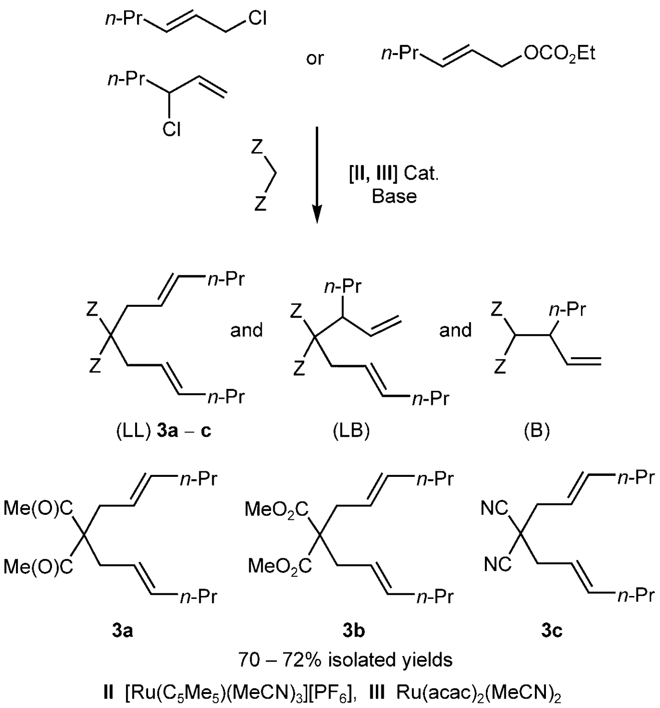
Whereas the second allylation of the mono-allylated derivatives **1a** and **1b** was negligible in the presence of the catalyst precursor **I**, it was made successful using hex-2-en-1-yl ethyl carbonate as allylic substrate in the presence of the ruthenium complex [Ru(Cp*)(MeCN)$_3$][PF$_6$] as a distinct precatalyst **II** (Scheme 2).



Scheme 2. Synthesis of unsymmetrical linear-branched bis-allylated products **2a–c**. *Experimental conditions:* **1a** or **b**: 0.5 mmol, allylic carbonate: 0.5 mmol, K$_2$CO$_3$: 0.5 mmol, catalyst **II**: 3 mol%, acetonitrile (4.0 mL) as solvent, 40°C, 2 days.

This second allylation step was, however, more difficult as compared to the first one. The presence of a mineral base (K$_2$CO$_3$) to stimulate the formation of the anionic carbonucleophile species was required although a carbonate was used as allylic substrate. Furthermore, a longer reaction time of 2 days and a slight thermal activation (40°C) were also needed to reach completion of the reaction. The unsymmetrical linear-branched bis-allylated products **2a** and **2c** were formed with excellent regio- and stereoselectivities and subsequently isolated as colourless oils in 89% and 87% yields, respectively. The bis-allylated product **2b** bearing distinct n-propyl and methyl groups in the branched and linear chains, respectively, was similarly prepared starting from **1a** and crotyl ethyl carbonate.

Starting directly from the initial procarbonucleophile, precatalyst **II** allowed the straightforward bis-allylation of active methylene compounds even at room temperature. In this case, however, the reaction led to the major formation of bis-linear products. In contrast, some experiments using cinnamyl instead of hexenyl allylic substrates showed a highly favoured formation of mono-allylated branched derivatives as might be expected from previous studies using precatalyst **II**.[3a] Typically, the reaction of 2.2 equivalents of hexenyl chloride with 2,4-pentadione, dimethyl malonate, or malononitrile, resulted in the consumption of these procarbonucleophiles and the formation of symmetrical bis-allylated bis-linear (LL) derivatives as major products (Scheme 3). The conversion into the (LL) bis-allylated bis-linear products was close to 85% as indicated by GC analysis, independently of the nature of the procarbonucleophile. Moreover, very similar results were obtained using hex-2-en-1-yl ethyl carbonate instead of hexenyl chloride as allylic substrate. The bis-allylation of 2,4-pentadione or malononitrile was achieved using K_2CO_3 as a base. Starting from dimethyl malonate, completion of the reaction was reached using Cs_2CO_3 as a base. We found that the ruthenium complex $Ru(acac)_2(MeCN)_2$ (acac = acetylacetonato) **III**,[11] which contains no cyclopentadienyl ligand was also efficient for the bis-allylation of malononitrile with hexenyl chloride in the presence of K_2CO_3, and led to the favoured formation of bis-linear product **3c** with the same activity as complex **II**. The concomitent minor formation (around 15%) of bis-allylated (LB) and mono-allylated (B) derivatives in a variable ratio depending on the procarbonucleophile was observed, but it was possible to separate and isolate the pure bis-allylated bis-linear (LL) products **3a–c** as colourless oils in 70–72% yields by chromatography on silica gel.

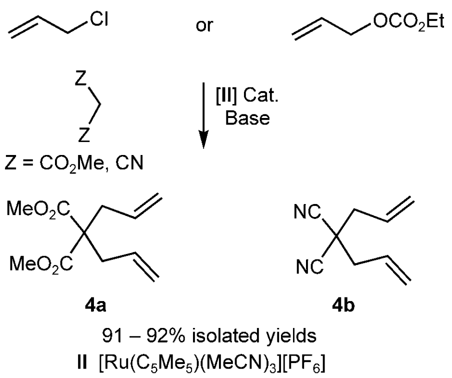


Scheme 3. Synthesis of symmetrical bis-allylic bis-linear derivatives **3a–c**. *Experimental conditions:* pronucleophile: 0.5 mmol, hex-2-en-1-yl ethyl carbonate or hexenyl chloride: 1.1 mmol, base: 1.1 mmol, catalyst: 3 mol%, acetonitrile (4.0 mL) as solvent, room temperature, 16–18 h.

Of interest, the formation of bis-allylated bis-branched products was not detected. This observation suggested that the presence of a branched chain in mono-allylated intermediates forced the second allylation towards the formation of the linear allylic fragment. This might account for the highly regioselective formation of unsymmetrical linear-branched bis-allylated products **2a–c** starting from mono-allylated branched derivatives **1a** and **1b** in the presence of precatalyst **II**.

The conversion of active methylene compounds into bis-allylated bis-linear (LL) derivatives obviously involved a transient formation of the corresponding mono-allylated linear products. These intermediates were more easily detected starting from an equimolar pronucleophile/allylic substrate ratio. However, their formation remained not selective enough to subsequently attempt separation from the simultaneously formed bis-allylated products and unreacted procarbonucleophile substrates. The synthesis of mono-allylated derivatives was nevertheless possible using a large excess of procarbonucleophile. Thus, using catalyst **III** and starting from malononitrile and hexenyl chloride in a 3:1 molar ratio, the reaction mainly afforded the mono-allylated 2-[*(E)*-hex-2-en-1-yl]malononitrile derivative that was separated from minor products and unreacted malononitrile by chromatography and isolated as a colourless oil in 71% yield, relative to the allylic substrate.

Allyl chloride and allyl ethyl carbonate were involved as unsubstituted allylic substrates leading to only one type of allylated products with no possible regioisomers. The bis-allylation of dimethyl malonate and malononitrile with these simple allylic substrates was achieved using precatalyst **II** to afford dimethyl diallylmalonate **4a**, and diallylmalononitrile **4b**, respectively (Scheme 4). The complete conversion of dimethyl malonate or malononitrile into **4a** and **4b**, re-



Scheme 4. Synthesis of bis-allyl derivatives **4a** and **b**. *Experimental conditions:* pronucleophile: 0.5 mmol, allyl ethyl carbonate: 1.1 mmol or allyl chloride: 1.5 mmol, base: 1.1 mmol, catalyst **II**: 3 mol%, acetonitrile (4.0 mL) as solvent, room temperature, 16–18 h.

spectively, was reached at room temperature using Cs_2CO_3 as a base, indistinctly starting from a slight excess of allyl chloride or allyl ethyl carbonate. The unsubstituted allyl substrate offers no steric hindrance and high yields in bis-allylated isolated products (91–92%) were obtained. Note also that no reaction was detected in the absence of appropriate ruthenium precatalyst.

Conclusions

The examples developed in this study highlight a new catalytic route to achieve the bis-allylation of active methylene compounds such as 1,3-dicarbonyl compounds and malononitrile. Mainly based on pentamethylcyclopentadienyl-ruthenium catalysts, allylation reactions occurred under very mild conditions in the presence of innocuous bases. A [Ru(Cp*)(2-quinolinecarboxylato)(CH_2CHCH-*n*-Pr)][BF_4] precatalyst allowed the regioselective synthesis of mono-allylated branched products starting from unsymmetrical aliphatic allylic substrates. The complex [Ru(Cp*)-(MeCN)$_3$][PF_6] catalyzed the formation of bis-allylated derivatives but with preferential formation of linear products. This catalyst is efficient for the synthesis of unsubstituted bis-allyl derivatives, and especially appropriate for the preparation of mixed branched-linear bis-allylated products starting from branched mono-allylated substrates. We have thus shown that the selection of the appropriate precursor in the ruthenium catalysts toolbox makes possible the preparation of a variety of differently substituted 1,6-dienes resulting from regioselective allylation upon substitution of the two protons of soft procarbonucleophiles.

Experimental Section

General Considerations

The reactions were carried out under an inert atmosphere of argon according to Schlenk techniques. HPLC grade acetonitrile was used as purchased. ^1H and ^{13}C NMR spectra were recorded at 297 K on a Bruker DPX 200 instrument and referenced internally to the solvent peak. HR-MS were recorded on Varian MAT 311 with EI source or on ZAB Spec TOF with ESI source mass spectrometers at the "Centre Régional de Mesures Physiques de l'Ouest" (Rennes). The [Ru(Cp*)(2-quinolinecarboxylato)(η^3-CH_2CHCH-*n*-Pr)] [BF_4][8] and [Ru(Cp*)(MeCN)$_3$][PF_6][12] precatalysts were prepared as reported previously.

General Procedure for the Synthesis of Allylated Compounds

As a general procedure for catalytic experiments, the pronucleophile and the catalyst were added to a stirred mixture of allylic substrate and base in acetonitrile (amounts, reaction time and temperature as indicated in captions of the Schemes). After completion of the reaction, the slurry was filtered through a plug of silica gel and the filtrate was concentrated under reduced pressure. The resulting crude oil was purified by column chromatography using silica gel and petroleum ether/diethyl ether (10:1–20:1) as eluent.

Characterization of Compounds

HR-MS determinations and characteristic NMR spectra and spectroscopic data are given in the Supporting Information.

Acknowledgements

H.J.Z. is grateful to the Ambassade de France in China and to the International Program of the Natural Science Foundation of China for a Ph. D. financial support.

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