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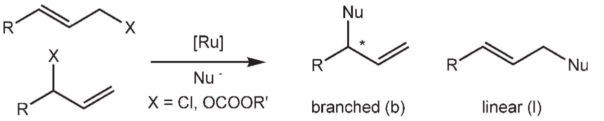
VIP Homogeneous Catalysis

Air- and Microwave-Stable (C_5H_5)Ru Catalysts for Improved Regio- and Enantioselective Carroll Rearrangements**

*Samuel Constant, Simone Tortoioli, Jessica Müller, David Linder, Frédéric Buron, and Jérôme Lacour**

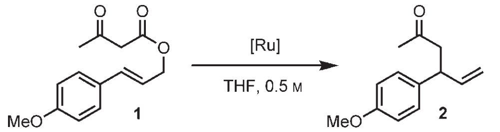
Among the wide variety of synthetic methods allowing the construction of complex molecular structures, one of the best documented is the attack of a nucleophile at an allyl metal fragment, yielding chiral allylic compounds in (virtually) enantiopure form. One of the benefits of such substitution is that the regioselectivity of the reaction with unsymmetrical allyl substrates can be controlled by the metal catalyst.[1] In this respect, several ruthenium-based compounds, in particular Cp*Ru derivatives (Cp* = C_5Me_5), have proven to be largely effective for the introduction of nucleophiles at the more substituted position, leading to branched (b) rather than linear (l) products [Eq. (1)].[2] Typical substrates are allyl carbonates and allyl chlorides (primary or secondary), and efficient allylic alkylation, arylation, amination, and etherification reactions have been developed.[3–6]



(1)

Although useful, these reactions are, however, usually performed with large amounts of ruthenium catalysts (ca. 10 mol %), and the active complexes are not recovered at the end of the reaction owing to their sensitivity to moisture, oxygen, and isolation conditions. To our knowledge, only Bruneau, Renaud, and co-workers have been able to perform multiple catalytic cycles by immobilizing a cationic Cp*Ru catalyst in an ionic liquid phase.[7] Cyclopentadienyl Ru derivatives that would be 1) air-insensitive, 2) easily synthesized and purified, 3) catalytically active, and 4) possibly reusable would thus be important novelties in this field. Herein, we report that such species can indeed be made through the use of an anionic monodentate ligand. Several beneficial aspects are presented, including improved regio- and enantioselectivity in the Carroll rearrangement of allyl-β-ketoesters in direct comparison studies with the classical $[PF_6]^-$ analogues of the catalytic species.

Allyl-β-ketoesters of type **1** [Eq. (2)] are known to react smoothly in the presence of cyclopentadienyl Ru moieties and 2,2′-bipyridine (bpy) to form γ,δ-unsaturated ketones (e.g. **2**) in high yields and excellent b/l ratios.[6] Recently, an enantioselective version of this Carroll rearrangement was developed that required the combined use of $[CpRu(NCCH_3)_3][PF_6]$ and enantiopure pyridine imine ligands (Cp = C_5H_5).[8] These allylic substitution reactions, utilizing rather large amounts of non-recoverable ruthenium catalysts (10 mol %), thus constituted an ideal framework for the purposed study.



(2)

Recently, a novel hexacoordinated phosphorus anion, TRISPHAT-N (**3**, Figure 1), was also described and demonstrated to be an efficient counterion and ligand altogether able to enter the first coordination sphere of metal complexes.[9,10] Furthermore, it was shown that the derived zwitterionic metal complexes possess interesting chromatographic, air, and moisture stability. The possibility that **3** would form a stable complex with the mixture of $[CpRu(NCCH_3)_3][PF_6]$ and bpy was therefore particularly interesting for the Carroll rearrangement.

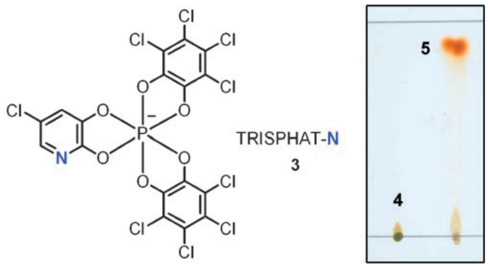


Figure 1. Hexacoordinated phosphorus anion TRISPHAT-N **3** and thin-layer chromatographic behavior (SiO_2, CH_2Cl_2) of salt **4** and of the crude reaction mixture of **4** and $[Bu_3NH][\mathbf{3}]$ leading to **5**.

The viability of this strategy was readily assessed by dissolving $[CpRu(NCCH_3)_3][PF_6]$[11] and bpy (1.0 equiv each)

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[*] S. Constant, Dr. S. Tortoioli, J. Müller, D. Linder, Dr. F. Buron, Prof. J. Lacour
Département de Chimie Organique
Université de Genève
quai Ernest Ansermet 30, 1211 Genève 4 (Switzerland)
Fax: (+41) 223-793-215
E-mail: jerome.lacour@chiorg.unige.ch
Homepage: http://www.unige.ch/sciences/chiorg/lacour/

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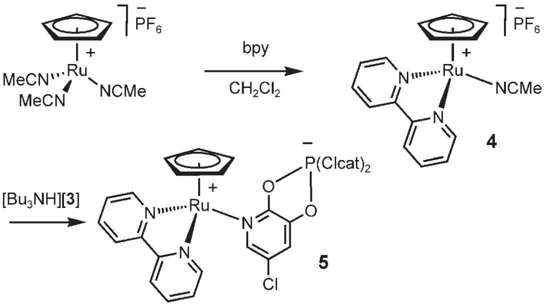
in N_2-saturated CH_2Cl_2 to yield air-sensitive [CpRu(bpy)-($NCCH_3$)][PF_6] (**4**, Scheme 1). Subsequent addition of [Bu_3NH][**3**] (1.0 equiv)[9] to the solution of salt **4** led, as desired, to the formation of zwitterionic adduct **5**.[12] This resulting molecule was readily isolated by column chromatography owing to the remarkable elution properties bestowed by **3** (Figure 1, $R_f = 0.85$ (SiO_2, CH_2Cl_2), 76 %). As expected, **5** turned out to be completely air- and moisture-stable.[13] With zwitterion **5** in hand, we turned our attention to its reactivity.



Scheme 1. Synthesis of salt **4** and zwitterionic complex **5**; P(Clcat)$_2$ represents the fragment constituted by the hexacoordinated phosphorus atom and the two tetrachlorocatecholate ligands.

Initial experiments on the Carroll rearrangement were conducted by the treatment of allylic ester **1** with catalytic amounts of **4** or **5** (10 mol %) in THF at 60 °C. The reactions proceeded smoothly to generate, in both cases, the branched adduct **2** exclusively. Not surprisingly, a longer reaction time was necessary with complex **5** (**4**: 100 % conv, 4 h; **5**: 100 % conv, 48 h). However, thin-layer chromatographic monitoring of the reactions revealed that **5**, unlike **4**, was surviving the reaction conditions. Moreover, zwitterion **5** was readily recovered from the crude mixture by column chromatography (SiO_2, CH_2Cl_2, 85 %). The possibility of reusing the isolated complex as catalyst was tested, and subsequent reactions occurred without any loss of efficiency or regioselectivity (five consecutive runs, b/l > 99:1, 84 to 90 % recovery per run).

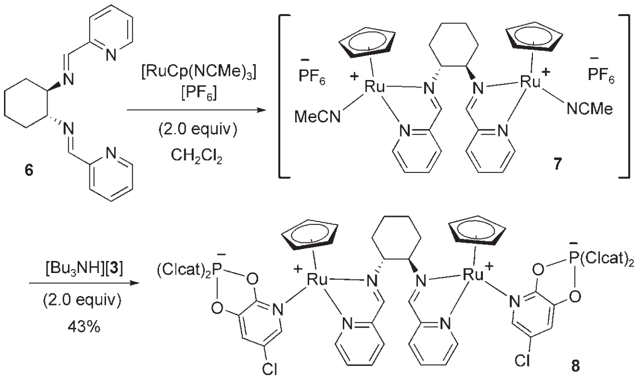
The longer reaction time required with complex **5** was, however, of concern. Conditions that would improve the kinetics were looked for. Higher temperatures were considered, despite the fact that treatment of **1** at 140 °C in a sealed vessel under microwave irradiation yielded the rearrangement product with a noticeably lower regioselectivity (b/l = 4.9:1, Table 1, entry 2), albeit with only 2 mol % **4** and 60 min reaction time. Considering that the lower selectivity might be the result of an in situ degradation of **4** into a less selective entity, the reaction was tested with **5**.[14] The results are reported in Table 1. The reactions proceeded with perfect regioselectivity in favor of the branched isomer, in sharp contrast to the reaction with **4**. Relatively short reaction times (30 min) were needed with a catalyst loading of 10 mol %. Ultimately, catalyst loading could be lowered to 2 mol % without impacting the outcome (95 % conv, b/l > 99:1, 60 min).

Table 1: Microwave-assisted rearrangement of allylic ester **1**.[a]

Entry	[Ru]	Cat. loading [mol %]	Conv [%]	*t* [min]	b/l
1	–	–	0	120	–
2	**4**	2	100	60	4.9:1
3	**5**	10	100	30	> 99:1
4	**5**	5	100	30	> 99:1
5	**5**	2	90	30	> 99:1
6	**5**	2	95	60	> 99:1

[a] **4** or **5** (2–10 mol %), THF, 140 °C, *c* = 0.5 M, sealed vessel (microwave irradiation); the results are the average of at least two runs.

The benefit of the increased stability given by anion **3** became further apparent in the following preliminary study. As mentioned above, an enantioselective variant of this reaction was recently developed using a 1:1 combination of [CpRu($NCCH_3$)$_3$][PF_6] and enantiopure pyridine imine ligands;[8] these ligands are readily synthesized by the condensation of 2-pyridine-carboxaldehyde and α-branched benzylic amines. In an effort to extend the pool of ligands and to determine if a dinuclear catalyst would be beneficial,[15] [CpRu($NCCH_3$)$_3$][PF_6] (2.0 equiv) was treated with the tetradentate ligand *N,N'*-bis(2-pyridylmethylidene)-1,2-(*R,R*)-cyclohexanediamine (**6**, Scheme 2) derived from commercially available 1,2-(*R,R*)-cyclohexanediamine and 2-pyridine-carboxaldehyde.[16] ^{1}H NMR spectroscopic monitoring of this experiment indicated the formation of a complex mixture of several CpRu species, including three stereoisomeric dinuclear complexes **7** (Scheme 2), which could not be isolated from the crude mixture. Addition of two equivalents of [Bu_3NH][**3**] led to the formation of zwitterions **8**, which were isolated by chromatography in modest yield (43 %, SiO_2, CH_2Cl_2).[17] ^{1}H and ^{31}P NMR spectroscopy revealed the direct coordination of the anions **3** to the Ru centers[9] and confirmed, along with ESI-MS measurements, the formation of the proposed structure **8** as a complex mixture of stereoisomers.[10]



Scheme 2. Synthesis of dinuclear zwitterionic complexes **8**.

The asymmetric protocol was then tested with mixtures **7** and **8** (5 mol %) under the classical conditions (THF, 60 °C, 0.5 M, 48 h). Compound **1** reacted to form (+)-**2** with, in both cases, excellent regioselectivity (b/l > 49:1) and good conversion (100 % and 85 % for **7** and **8**, respectively). The enantioselectivity was, however, very different, as *ee* values of 57 % and 85 % were obtained for **7** and **8**, respectively.

Considering that the much lower selectivity in the case of **7** might be the result of in situ degradation of the dinuclear catalysts or of the activity of other species initially present in the mixture,[17] care was taken to follow the selectivity as a function of time (Figure 2). A strong time dependence was observed in the case of **7**; the enantioselectivity was much lower at the start of the reaction (18 % *ee* after one hour) and reached essentially the maximal value after 24 h (56 % *ee*). In the case of the TRISPHAT-N adducts **8**, monitoring revealed an essentially constant selectivity throughout the reaction, thus indicating, most probably, that the obtained results are due to the dinuclear catalysts and not to other species.

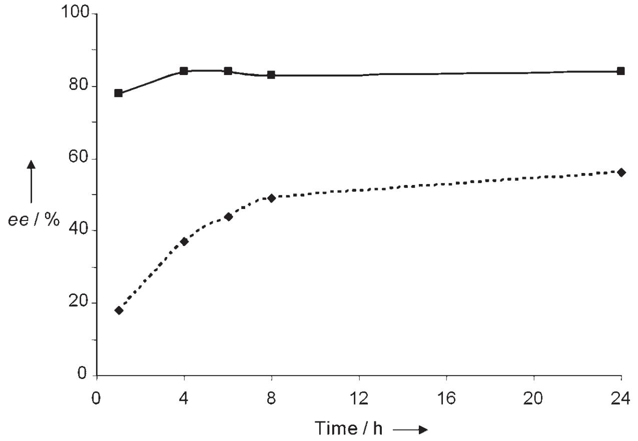


Figure 2. Enantioselectivity of **2** as a function of time in the reactions catalyzed by **7** (-----) and **8** (——).

In conclusion, we report herein the first synthetic application of a hexacoordinated phosphorus anion able to stabilize catalytically active metallic species. The added stability towards oxygen and moisture allows the isolation and characterization of complexes in ambient atmosphere. The important lipophilicity given by the phosphate allows the ready separation of zwitterionic adducts, which in some instances can permit catalyst reuse after isolation. Furthermore, in the context of the Carroll rearrangement, it is shown that this increased stability improves the regioselectivity of reactions performed under harsh conditions; the enantioselectivity in the case of **8** (85 % *ee*) is the highest reported to date in a Ru-catalyzed enantioselective Carroll rearrangement.[18] This methodology of stabilization of unstable reactive species is currently being extended to other organometallic complexes.

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[10] TRISPHAT-N: bis(tetrachlorobenzenediolato)mono(5-chloropyridine-2,3-diolato) phosphate(V). This anion (**3**) is chiral and was used as a racemate throughout this study.

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[12] Interestingly, no stable complex is formed by the addition of $[Bu_3NH][\mathbf{3}]$ to $[Cp^*Ru(bpy)(NCCH_3)][PF_6]$.

[13] Compound **5** has been characterized using classical spectroscopic and spectrometric means (see the Supporting Information). It is stable for weeks as a solid in ambient atmosphere.

[14] In the absence of **4** or **5**, allylic ester **1** is thermally stable at 140 °C for at least 2 h with no trace of **2** or other isomers being observed (Table 1, entry 1).

[15] Dinuclear complexes can be extremely effective catalysts in a variety of processes, see: B. Coq, F. Figueras, *Coord. Chem. Rev.* **1998**, *178–180*, 1753–1783; E. K. Van Den Beuken, B. L. Fer-

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[16] Compound **6**, its enantiomer, or the racemate, have been used successfully as ligands in many metal-catalyzed processes, see: T. J. Goodwin, R. S. Vagg, P. A. Williams, *J. Proc. R. Soc. N. S. W.* **1984**, *117*, 1–6; G. C. Van Stein, G. Van Koten, K. Vrieze, C. Brevard, A. L. Spek, *J. Am. Chem. Soc.* **1984**, *106*, 4486–4492; P. K. Bowyer, K. A. Porter, A. D. Rae, A. C. Willis, S. B. Wild, *Chem. Commun.* **1998**, 1153–1154; C. R. Baar, L. P. Carbray, M. C. Jennings, R. J. Puddephatt, J. J. Vittal, *Organometallics* **2001**, *20*, 408–417; Y. N. Belokon, M. North, T. D. Churkina, N. S. Ikonnikov, V. I. Maleev, *Tetrahedron* **2001**, *57*, 2491–2498; S. Kano, H. Nakano, M. Kojima, N. Baba, K. Nakajima, *Inorg. Chim. Acta* **2003**, *349*, 6–16; M. Klopstra, R. Hage, R. M. Kellogg, B. L. Feringa, *Tetrahedron Lett.* **2003**, *44*, 4581–4584; S. Schoumacker, O. Hamelin, J. Pecaut, M. Fontecave, *Inorg. Chem.* **2003**, *42*, 8110–8116; Q. T. Nguyen, J. H. Jeong, *Polyhedron* **2006**, *25*, 1787–1790; A. Ouali, M. Taillefer, J.-F. Spindler, A. Jutand, *Organometallics* **2007**, *26*, 65–74; J. Song, Q. Shen, F. Xu, X. Lu, *Tetrahedron* **2007**, *63*, 5148–5153.

[17] This result reflects the intrinsic instability of ligand **6** and its complexes **7**. For this reason, recycling of complexes **8** and reactions under microwave irradiation were not attempted.

[18] Enantioselective iridium-catalyzed Carroll or Carroll-like processes that occur with excellent control over the stereocenters created on the allylic fragment have recently been reported, see: D. J. Weix, J. F. Hartwig, *J. Am. Chem. Soc.* **2007**, *129*, 7720–7721; H. He, X.-J. Zheng, Y. Li, L.-X. Dai, S.-L. You, *Org. Lett.* **2007**, *9*, 4339–4341.