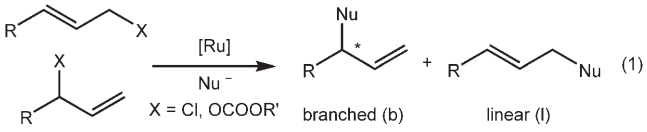
Synthetic Methods

DOI: 10.1002/anie.200604573

An Enantioselective CpRu-Catalyzed Carroll Rearrangement**

*Samuel Constant, Simone Tortoioli, Jessica Müller, and Jérôme Lacour**

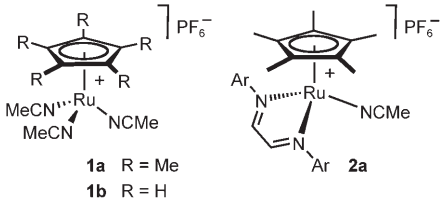
Easy and direct access to enantioenriched molecules is essential for the construction of complex molecular structures. Among the wide variety of methods, one of the most documented is the attack of a nucleophile onto an allyl–metal intermediate to yield chiral allylic compounds with high enantiomeric excess. 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. In this respect, several ruthenium derivatives have proven to be largely effective for the introduction of nucleophiles at the more substituted position, thus leading to branched (b) rather than linear (l) products [Eq. (1)].[1]

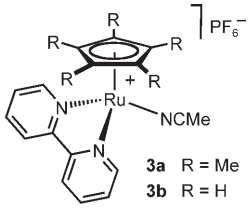


(1)

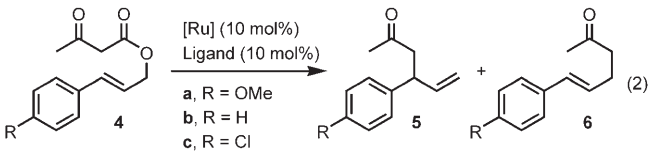
These metal derivatives include, among others, the tris(acetonitrile) complex $[Cp^*Ru(CH_3CN)_3][PF_6]$ (**1a**; $Cp^* = C_5Me_5$) from Trost et al.,[2] diazabutadiene (dab) and 2,2′-bipyridine (bpy) complexes from Bruneau, Demerseman, Renaud and co-workers (**2a** and **3a**),[3] 1,5-cyclooctadiene (1,5-cod) complexes from Kondo, Mitsudo, et al,[4] amidinate derivatives from Nagashima and co-workers,[5] and Ru^{IV} carbonate derivatives from Pregosin and co-workers.[6]

Typical substrates are allyl carbonates and allyl chlorides (primary or secondary), and effective allylic alkylation, amination, and etherification reactions have been developed.[2–6] If nonracemic secondary allyl carbonates are used, the reactions proceed stereospecifically with possibly complete transfer of chirality.[2] Cp*Ru derivatives are largely preferred over CpRu moieties (for example, **1a** over $[CpRu(CH_3CN)_3][PF_6]$ (**1b**); $Cp = C_5H_5$) as the more electron-rich metal fragment is catalytically more active and leads to higher b/l ratios. Recently, an intramolecular variant of allylic alkylation was described in the context of regioselective (and stereospecific) Carroll-type rearrangements.[7] Allyl β-





ketoesters of type **4** [Eq. (2)] were shown to react smoothly in the presence of $[\{Cp^*RuCl\}_4]$ (**1c**) and bpy to form γ,δ-unsaturated ketones **5** in high yields and excellent b/l ratios.[7a]



(2)

The conditions were particularly mild (CH_2Cl_2, room temperature). This result is in sharp contrast with that of classical (thermal) decarboxylative [3,3] sigmatropic Carroll reactions that require elevated temperatures to proceed (typically 140–180 °C);[8] the Carroll rearrangement is nevertheless a highly useful concerted reaction used for a variety of synthetic applications.[9,10]

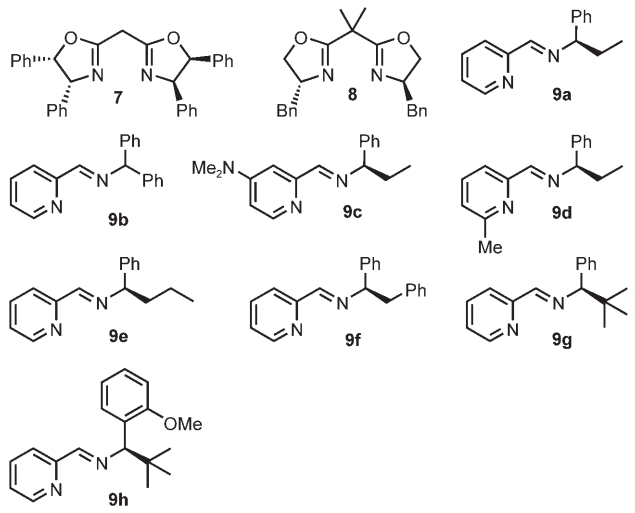
Despite all these advantages, Ru-catalyzed enantioselective allylic substitutions are rare.[11,12] To our knowledge, the etherification of allyl chlorides with phenols using, as catalyst, combinations of Cp*Ru (as in **1a**) and bisoxazoline ligands (for example, **7**; Scheme 1) is the single reported example of enantioselective Ru-catalyzed allylic substitution reaction, with good enantioselectivity (up to 80% *ee*) and decent regioselectivity (d.r. 62:38 to 87:13) being achieved.[13] Herein we report that the conjunction of simple-to-make unsymmetrical pyridine–imine ligands and the CpRu derivative **1b** affords highly regio- and enantioselective Carroll rearrangements, this being the first example of Ru-catalyzed asymmetric C–C bond-forming allylic substitution.

In view of the previously mentioned results, initial experiments on the enantioselective variant of the Carroll rearrangement were conducted by the treatment of allylic ester **4a** [Eq. (2), R = OMe] with catalytic amounts of **1c** (2.5 mol% of

[*] S. Constant, Dr. S. Tortoioli, J. Müller, Prof. J. Lacour
Département de Chimie Organique
Université de Genève
quai Ernest Ansermet 30, 1211 Genève 4 (Switzerland)
Fax: (+41) 22-379-3215
E-mail: jerome.lacour@chiorg.unige.ch

[**] We are grateful for financial support of this work by the Swiss National Science Foundation and the State Secretariat for Education and Science. We thank Prof. Dr. Klaus Ditrich (BASF) for generous gifts of chiral amines and epoxides.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 1. Diimine and pyridine–imine ligands.

Table 1: Ru-catalyzed rearrangement of allylic esters **4**.[a]

Ester	Ligand	*t* [h]	Conv. [%]	*ee* [%]	Conf.[b]	b/l Ratio[c]
4a	–	48	0	–	–	–
4a	**9a**	20	100[d]	56	(+)	>99:1
4a	bpy	4	100	–	–	>99:1
4a	**9b**	30	100	–	–	>99:1
4a	**9c**	13	97	50	(+)	>99:1
4a	**9d**	92	47	20	(+)	>99:1
4a	**9e**	24	100	58	(+)	>99:1
4a	**9f**	22	100	66	(+)	>99:1
4a	**9g**	20	100	72	(+)	>99:1
4a	**9h**	24	100	80	(+)	>99:1
4b	**9h**	24	100	74	(+), *S*	94:6
4c	**9h**	120	75	66	(+)	95:5

[a] Reaction conditions: **1b** (10 mol%), ligand (10 mol%), THF, 60°C, 0.5 M; the results are the average of at least two runs. [b] Sign of the optical rotation and absolute configuration when known. [c] Ratios of branched (**5**) to linear (**6**) products were determined at complete conversion. [d] 95% yield of isolated product.

the tetramer) and bisoxazoline ligand **8** (10 mol%) in CH_2Cl_2 at room temperature. Unlike the reaction performed in the presence of bpy (15 min, 100% conversion), poor reactivity was observed in the presence of this ligand (15% conversion after 7 days), and no enantioselectivity was achieved (0% *ee*).

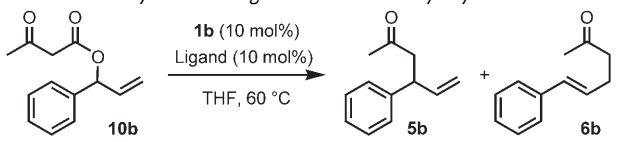
Obviously, ligand **8** did not possess the (stereo)electronic requirements for the activation of the ruthenium catalyst. To generate some reactivity, the presence of a pyridine moiety within the framework of the chiral diimine ligand was deemed necessary. Ligand **9a**, readily synthesized by the condensation of 2-pyridine-carboxaldehyde and (*R*)-1-phenyl-propylamine, was prepared and submitted to the reaction conditions. Although very modest, the result was better (45% conversion after 5 days, 13% *ee*) than that of ligand **8**. Intensive screening of solvent, temperature, concentration, and metal source (**1b** and **1c**) afforded effective conditions for the "Carroll" rearrangement. A combination of CpRu complex **1b** and ligand **9a** (10 mol% each) in THF at 60°C allowed the reaction to proceed with good yield and a first decent enantioselectivity (**5a**: 56% *ee*, 20 h, 100% conversion, 95% yield).[14] Significantly, no trace of the linear product **6a** was found using the CpRu catalyst **1b** (NMR and GC–MS monitoring). The occurrence of a perfect b/l ratio under the optimized conditions was confirmed in reactions performed with bpy and achiral iminopyridine ligand **9b** (Scheme 1). The results are summarized in Table 1.

At this stage, a rather intensive screening of chiral ligands was performed; a selection of these ligands is presented in Scheme 1. To begin, the nature of the pyridine moiety was varied as substituents were introduced on the aromatic nucleus (**9c**: *p*-NMe_2, **9d**: *o*-Me). Whereas the dimethylamino substituent enhanced the reactivity of the catalyst, the presence of the methyl group in the proximity of the coordinating nitrogen atom strongly decreased the reactivity; both modifications came at the expense of the enantioselectivity. A series of chiral ligands (**9e–h**) was then prepared by condensation of 2-pyridine-carboxaldehyde and other chiral benzylic primary amines.[15] From **9e** to **9g**, a gradual increase in the enantioselectivity of the allylic substitution was noticed (up to 72% *ee*), which is most probably related to the increase in size of the benzylic α substituent (from Et (**9a**) to Pr, Bn, and then *t*Bu). Finally, a useful level of enantioselectivity was obtained (80% *ee*) when the reaction was performed in the presence of ligand **9h** prepared from (*R*)-1-(2-methoxyphenyl)-2,2-dimethylpropan-1-amine.[16,17] Importantly, in all these examples with the Cp catalyst, the b/l ratio remained excellent as no trace of compound **6a** could be observed.

With this result in hand, we extended the asymmetric protocol to allylic esters **4b** and **4c** [Eq. (2); R = H and Cl, respectively]. The reaction with unsubstituted **4b** proceeded somewhat less selectively in terms of enantio- and regiochemistry (74% *ee* and b/l 94:6). With ligand **9h**, (+)-**5b** was obtained, for which an *S* configuration could be determined by hydrogenation to produce (*S*)-(2)-4-phenyl-2-hexanone.[7b,18] With **4c** bearing a chlorine atom, the reaction was much slower than with **4a** and **4b**, as five days were necessary to reach a decent conversion (75%); however, the regio- and enantioselectivity remained strong (66% *ee* and b/l 95:5). The effect of the electron-withdrawing atom on the reactivity is in line with the results of the Bruneau and Tunge groups.[3,7b]

To gain some insight on the nature of the asymmetric transformation and achieve possibly higher levels of selectivity, care was taken to perform the asymmetric Carroll rearrangement on an enantioenriched secondary allyl ester to determine 1) whether the reaction still occurred stereospecifically under our set of conditions and 2) whether chiral ligands could positively affect the subsequent selectivity. We selected compound **10b** (Table 2) for our study since the configurations of both starting material and product are known. The *R* and *S* enantiomers were prepared by olefination of commercially available enantiopure styrene oxide by using the protocol developed by Mioskowski and co-workers and then esterification with acetyl diketene (**10b**, *R* and *S*, >99% *ee*, CSP-GC).[19]

Table 2: Ru-catalyzed rearrangement of secondary allylic ester **10b**.[a]



Ester	Ligand	*t* [h]	*ee* [%]	Conf.[b]	b/l Ratio[c]
(*S*)-**10b**	bpy	2	48	(+), *S*	94:6
(*S*)-**10b**	**9b**	6	72	(+), *S*	94:6
(*S*)-**10b**	**9a**	10	84	(+), *S*	92:8
(*S*)-**10b**	**9h**	10	92	(+), *S*	93:7
(*R*)-**10b**	bpy	2	46	(−), *R*	93:7
(*R*)-**10b**	**9b**	6	72	(−), *R*	94:6
(*R*)-**10b**	**9a**	6	68	(−), *R*	94:6
(*R*)-**10b**	**9h**	6	70	(−), *R*	>99:1

[a] All reactions reached complete conversion by the reported time. Reaction conditions: **1b** (10 mol%), ligand (10 mol%), THF, 60°C, 0.5 M; the results are the average of at least two runs. [b] Sign of the optical rotation and absolute configuration. [c] Ratios of branched (**5b**) to linear (**6b**) products were determined at complete conversion.

Both enantiomers of **10b** reacted faster than their linear analogue **4b**,[6a] and all reactions were complete in less than 10 hours in the presence of achiral (bpy, **9b**) or chiral ligands (**9a**, **9h**). The results are summarized in Table 2. First, as in the case of **4b**, nonnegligible amounts of linear product **6b** could be observed in most of these reactions; the ratios, from 93:7 to better than 99:1, remain however in line with the result obtained with the linear ester. In all cases, the reactions were stereospecific and a net retention of configuration was observed as (*R*)- and (*S*)-**10b** afforded (*R*)- and (*S*)-**5b**, respectively.

When achiral bpy was used as the ligand, a rather strong loss of selectivity was observed in our case (46–48% *ee*), a result substantially different from that observed by Burger and Tunge on the same substrate and different reaction conditions (83–87% *ee*).[7b] Interestingly, iminopyridine **9b** (Scheme 1) led to a better conservation of chiral information (72% *ee*). In the reactions performed with (*R*)- and (*S*)-**10b** in the presence of chiral ligands, **9a** and **9h**, a rather distinct behavior was noticed. In the case of (*S*)-**10b**, a "matched" diastereomeric effect was observed as the reaction was influenced positively by the chiral ligands, (+)-(*S*)-**5b** being isolated in much better enantiomeric purity (up to 92% *ee*) than in the reaction performed with achiral **9b**. This result was not completely unanticipated in view of the tendency of ligands **9a** and **9h** to favor the formation of the (+),*S* enantiomer starting from **4b**. However, more surprising was the overall lack of (mismatched) influence of the chiral ligands on the reaction with (*R*)-**10b**, as (−)-(*R*)-**5b** was isolated with essentially the same enantiomeric purity as in the reaction performed with achiral **9b**. The origin of this difference and the fact that this enantiomer reacts faster than (*S*)-**10b** remain unclear at this stage.

In conclusion, we describe the first Ru-catalyzed asymmetric Carroll rearrangement using simple-to-make unsymmetrical pyridine–imine ligands and a Cp rather than a Cp* source of ruthenium. Further studies are being performed to understand the intricate details of the unusual aspects of this transformation and extend the results to other useful processes.

Received: November 8, 2006
Published online: February 5, 2007

Keywords: C–C coupling · enantioselectivity · N ligands · rearrangement · ruthenium

[1] C. Bruneau, J. L. Renaud, B. Demerseman, *Chem. Eur. J.* **2006**, *12*, 5178–5187.
[2] B. M. Trost, P. L. Fraisse, Z. T. Ball, *Angew. Chem.* **2003**, *114*, 1101–1103; *Angew. Chem. Int. Ed.* **2002**, *41*, 1059–1061.
[3] M. D. Mbaye, B. Demerseman, J. L. Renaud, L. Toupet, C. Bruneau, *Angew. Chem.* **2003**, *115*, 5220–5222; *Angew. Chem. Int. Ed.* **2003**, *42*, 5066–5068; J. L. Renaud, C. Bruneau, B. Demerseman, *Synlett* **2003**, 408–410; M. D. Mbaye, B. Demerseman, J. L. Renaud, L. Toupet, C. Bruneau, *Adv. Synth. Catal.* **2004**, *346*, 835–841; M. D. Mbaye, B. Demerseman, J. L. Renaud, C. Bruneau, *J. Organomet. Chem.* **2005**, *690*, 2149–2158; B. Demerseman, J. L. Renaud, L. Toupet, C. Hubert, C. Bruneau, *Eur. J. Inorg. Chem.* **2006**, 1371–1380.
[4] T. Kondo, H. Ono, N. Satake, T.-a. Mitsudo, Y. Watanabe, *Organometallics* **1995**, *14*, 1945–1953; T. Kondo, Y. Morisaki, S.-y. Uenoyama, K. Wada, T.-a. Mitsudo, *J. Am. Chem. Soc.* **1999**, *121*, 8657–8658; Y. Morisaki, T. Kondo, T. Mitsudo, *Organometallics* **1999**, *18*, 4742–4746.
[5] H. Kondo, Y. Yamaguchi, H. Nagashima, *Chem. Commun.* **2000**, 1075–1076; H. Kondo, A. Kageyama, Y. Yamaguchi, M.-A. Haga, K. Kirchner, H. Nagashima, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1927–1937; H. Nagashima, H. Kondo, T. Hayashida, Y. Yamaguchi, M. Gondo, S. Masuda, K. Miyazaki, K. Matsubara, K. Kirchner, *Coord. Chem. Rev.* **2003**, *245*, 177–190.
[6] a) R. Hermatschweiler, I. Fernandez, F. Breher, P. S. Pregosin, L. F. Veiros, M. J. Calhorda, *Angew. Chem.* **2005**, *117*, 4471–4474; *Angew. Chem. Int. Ed.* **2005**, *44*, 4397–4400; b) R. Hermatschweiler, I. Fernandez, P. S. Pregosin, E. J. Watson, A. Albinati, S. Rizzato, L. F. Veiros, M. J. Calhorda, *Organometallics* **2005**, *24*, 1809–1812; c) I. Fernandez, R. Hermatschweiler, F. Breher, P. S. Pregosin, L. F. Veiros, M. J. Calhorda, *Angew. Chem.* **2006**, *118*, 6535–6540; *Angew. Chem. Int. Ed.* **2006**, *45*, 6386–6391; d) I. Fernandez, R. Hermatschweiler, P. S. Pregosin, A. Albinati, S. Rizzato, *Organometallics* **2006**, *25*, 323–330; e) I. Fernandez, P. S. Pregosin, A. Albinati, S. Rizzato, *Organometallics* **2006**, *25*, 4520–4529; f) R. Hermatschweiler, I. Fernandez, P. S. Pregosin, F. Breher, *Organometallics* **2006**, *25*, 1440–1447.
[7] a) E. C. Burger, J. A. Tunge, *Org. Lett.* **2004**, *6*, 2603–2605; b) E. C. Burger, J. A. Tunge, *Chem. Commun.* **2005**, 2835–2837; c) C. Wang, J. A. Tunge, *Org. Lett.* **2005**, *7*, 2137–2139; d) J. A. Tunge, E. C. Burger, *Eur. J. Org. Chem.* **2005**, 1715–1726.
[8] M. F. Carroll, *J. Chem. Soc.* **1940**, 1266–1268; M. F. Carroll, *J. Chem. Soc.* **1940**, 704–706; M. F. Carroll, *J. Chem. Soc.* **1941**, 507–511.
[9] M. Defosseux, N. Blanchard, C. Meyer, J. Cossy, *Org. Lett.* **2003**, *5*, 4037–4040; M. E. Jung, B. A. Duclos, *Tetrahedron Lett.* **2004**, *45*, 107–109; W. Bonrath, T. Netscher, *Appl. Catal. A* **2005**, *280*, 55–73, and references therein.
[10] For a Pd-catalyzed enantioselective Carroll rearrangement, see: R. Kuwano, N. Ishida, M. Murakami, *Chem. Commun.* **2005**, 3951–3952.
[11] For a general review on asymmetric allylic alkylation, see: B. M. Trost, *J. Org. Chem.* **2004**, *69*, 5813–5837.

[12] Planar-chiral CpRu complexes with tethered phosphine ligands are effective catalysts for the kinetic resolution of racemic allyl carbonates: Y. Matsushima, K. Onitsuka, T. Kondo, T. Mitsudo, S. Takahashi, *J. Am. Chem. Soc.* **2001**, *123*, 10405 – 10406; Y. Matsushima, K. Onitsuka, S. Takahashi, *Organometallics* **2005**, *24*, 2747 – 2754.
[13] M. D. Mbaye, J. L. Renaud, B. Demerseman, C. Bruneau, *Chem. Commun.* **2004**, 1870 – 1871.
[14] Ligand **8** did not accelerate the reaction catalyzed by **1b** under the optimized conditions (0% conversion, 7 days, THF, 60°C, 0.5 M); compound **1b** was prepared by using Kündig's protocol: E. P. Kündig, F. R. Monnier, *Adv. Synth. Catal.* **2004**, *346*, 901 – 904.
[15] The enantiopure primary amines were commercially available or readily prepared following literature precedents. (*R*)-1,2-Diphenylethanamine was obtained from the racemate by using a semipreparative CSP-HPLC resolution (Chiralpak IA). For the synthesis and absolute configuration assignment, see: T. Asai, T. Aoyama, T. Shioiri, *Synthesis* **1980**, 811 – 812; M. Cinquini, S. Colonna, F. Cozzi, *J. Chem. Soc. Perkin Trans. 1* **1978**, 247 – 249; (*R*)-2,2-dimethyl-1-phenylpropan-1-amine: M. E. Warren, H. E. Smith, *J. Am. Chem. Soc.* **1965**, *87*, 1757 – 1764; V. V. Dunina, M. Y. Kazakova, Y. K. Grishin, O. R. Malyshev, E. I. Kazakova, *Russ. Chem. Bull.* **1997**, *106*, 1321 – 1330.
[16] G. Bernardinelli, D. Fernandez, R. Gosmini, P. Meier, A. Ripa, P. Schupfer, B. Treptow, E. P. Kündig, *Chirality* **2000**, *12*, 529 – 539.
[17] The *o*-MeO substituent in **9h** creates an A(1,3) strain situation with the neighboring stereogenic center; the increased rigidity of **9h** versus **9g** is possibly the reason for the better selectivity. With the MeO group, **9h** is also potentially a tridentate ligand; the ether linkage functions possibly as an "on/off" ligand, thus allowing for the formation of a σ-allyl Ru intermediate. We thank a referee for this latter suggestion.
[18] K. Soai, S. Yokoyama, T. Hayasaka, K. Ebihara, *J. Org. Chem.* **1988**, *53*, 4148 – 4149; A. Hajra, N. Yoshikai, E. Nakamura, *Org. Lett.* **2006**, *8*, 4153 – 4155.
[19] L. Alcaraz, J. J. Harnett, C. Mioskowski, J. P. Martel, T. Legall, D. S. Shin, J. R. Falck, *Tetrahedron Lett.* **1994**, *35*, 5449 – 5452.

