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Enantioselective CpRu-Catalyzed Carroll Rearrangement – Ligand and Metal Source Importance

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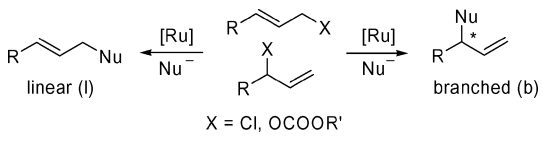
The addition of unstabilized carbonyl nucleophiles to unsymmetrical allyl-metal fragments still represents a challenge to generate stereogenic centers enantio- and regioselectively. In this context, the decarboxylative Carroll rearrangement of allyl β-keto esters is particularly interesting, since chiral γ,δ-unsaturated ketones are obtained. Herein, we show that CpRu half-sandwich complexes can, with selected enantiopure pyridine-monooxazoline ligands, catalyze this transformation and afford complete conversions along with good levels of regioselectivity and enantioselectivity. Even more challenging (electron-poor) substrates react (up to 86 % *ee*, branched/linear ratio ≥ 97:03). In addition, the use of an air-stable metal precursor, namely [CpRu(η^6-naphthalene)][PF_6], allows the reaction to be carried out reproducibly even in non-anhydrous THF with a catalyst loading as low as 2 mol-%.

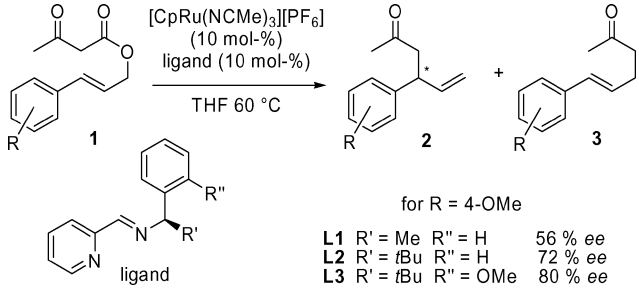
Introduction

The construction of complex, three-dimensional, molecular structures requires straightforward access to enantioenriched or enantiopure building blocks. Among the wide variety of synthetic methodologies available, the attack of a nucleophile onto allyl-metal intermediates yielding chiral allylic compounds with high enantiomeric excess is among the most documented.[1] With unsymmetrical allyl-metal intermediates, the regioselectivity of the nucleophilic attack is of crucial importance and can be controlled by the nature of the metal.[2] In this context, several Ru complexes have proven to be largely effective for the addition of nucleophiles onto the most highly substituted position, thus leading to branched (b) rather than linear (l) products (Scheme 1).[3] The most common substrates for Ru-catalyzed allylic substitutions are allyl carbonates and chlorides (primary or secondary), for which effective allylic alkylation, amination and etherification reactions have been developed.[4–6]

Overall, Cp*Ru derivatives have largely been preferred over CpRu moieties (Cp* = C_5Me_5, Cp = C_5H_5), as the more electron-rich Cp* metal fragment is usually catalytically more active and leads to higher b/l ratios. With secondary non-racemic allyl carbonates, reactions proceed stereospecifically with possibly a complete transfer of the stereochemical information.[4] Recently, an "intramolecular" variant of allylic alkylation was described in the context of regioselective (and stereospecific) Carroll-type rearrangements. Allyl β-keto esters of type **1** (Scheme 2) reacted smoothly with a catalytic amount of [{Cp*RuCl}$_4$] and 2,2′-bipyridine (bpy) to form selectively branched γ,δ-unsaturated ketones **2** in high yield. The linear regioisomer **3** was formed only in trace amounts.[7,8] The particularly mild reaction conditions (CH_2Cl_2, room temperature), in sharp contrast with those of thermal decarboxylative [3,3]-sigmatropic Carroll reactions (140–180 °C),[9,10] were particularly interesting. The involvement of the metal moiety was key to the observed enhanced reactivity and augured well for the development of an enantioselective version of the reaction.



Scheme 1. Allylic substitution of unsymmetrical substrates.



Scheme 2. CpRu-catalyzed rearrangement of primary esters with ligands **L**.

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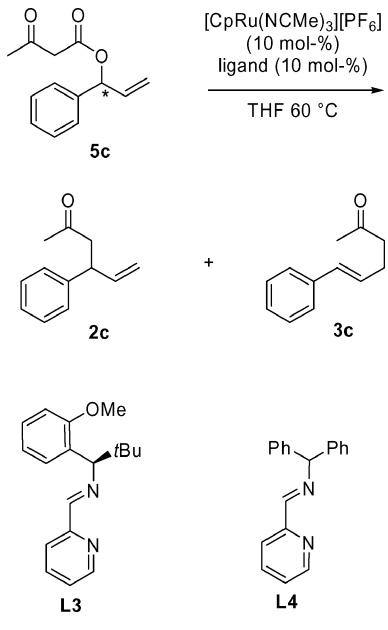
Ru-catalyzed enantioselective allylic substitutions remain rare, however. Planar, chiral, Cp′Ru complexes with tethered phosphane ligands have been described by Takahashi as effective catalysts for the kinetic resolution of racemic "symmetrical" allyl carbonates.[11] With unsymmetrical substrates, Bruneau reported the first example of a Cp*Ru-catalyzed enantioselective reaction in the context of the etherification of allylic chlorides with phenols;[12] this reaction was also effectively catalyzed by the above-mentioned Cp′Ru complexes, as described by Onitsuka.[13]

In view of this relative lack of asymmetric examples of Ru-catalyzed allylic substitutions in general, and C–C bond forming reactions in particular, we thought that the development of a Ru-catalyzed enantioselective version of the Carroll rearrangement would be of particular interest. This was achieved recently with a combination of [CpRu(NCMe)$_3$][PF$_6$] (**4a**)[14] and enantiopure pyridine-imine ligands (Scheme 2, **L1**–**L3**).[15] The branched isomer **2** was obtained selectively (b/l up to 99:1) with a decent level of enantioselectivity (up to 80% *ee* with **L3**); the presence of pyridine-imine ligands allowed a reversal of the preferential "linear" regioselectivity induced by **4a** as the catalyst.[4] Unfortunately, these reported conditions require rather large amounts of metal precursor (10 mol-% of **4a**). Long reaction times are also needed (20 h to several days), especially with substrates bearing electron-withdrawing substituents (e.g. a *p*-Cl).[6f] An acute sensitivity to several reaction parameters, including temperature and solvent, was noticed, diminishing somewhat the scope of this process. With secondary allylic esters (*R*)- and (*S*)-**5c** and **L3** as the ligand, a complicated "matched/mismatched" situation was also observed (Scheme 3). The "matched" reaction was quite slower than the "mismatched", and less effect on the enantioselectivity was seen in the latter case than in the reaction with achiral **L4**. The conformational lability of pyridine-imine ligands of type **L** also made rationalizing the stereochemical outcome difficult. The relatively moderate enantioselectivity obtained was also possibly a consequence of this conformational flexibility.



Scheme 3. CpRu-catalyzed rearrangement of secondary esters with ligands **L**.

A new generation of ligands was obviously needed to overcome these limitations associated with the use of pyridine-imine ligands **L1**–**L4**. Herein, we report that simple-to-make pyridine-mono-oxazoline moieties (pymox, **6**) are effective ligands leading to better overall results. We also demonstrate that, to obtain reproducible results, care must be taken in the choice of the Ru source and detail an air-stable alternative to **4a** that affords highly regio- and enantioselective Carroll rearrangement reactions even under non-inert conditions. In addition, quite a few experiments were performed with more elaborate substrates to shed some light on the mechanism at play.

Results and Discussion

To circumvent the drawbacks detailed above, the use of a more rigid structural scaffold was considered and that of the pymox ligands in particular.[16] In the context of arene-metal coordination chemistry, this ligand family has been successfully used by Brunner[17] and Davies[18] to control the configuration of pseudo-tetrahedral Cp and η^6-arene-Ru piano-stool complexes, respectively. Several pymox ligands were synthesized following the procedure of Bolm and co-workers by condensing commercially available enantiopure 1,2-amino alcohols onto 2-cyanopyridine with a catalytic amount of $ZnCl_2$.[19]

This series of ligands was subjected to the standard allylation reaction conditions developed for the pyridine-imine ligands.[15] The results are summarized in Table 1. Ligand **6a**, bearing the same oxazoline as the most selective ligand of Bruneau,[12] proved to be quite efficient; the Carroll rearrangement of **1a** yielded the expected product **2a** with full conversion and a perfect b/l ratio in less than 2 h with a decent *ee* value of 53%. A gradual increase of the bulk of the substituent α to the N atom improved the enantiomeric excess up to 72% with the valinol-derived pymox **6d** without any loss of regioselectivity. Surprisingly, ligand **6e**, derived from *tert*-leucinol, displayed no catalytic activity whatsoever. The completely rigid ligand **6f**, derived from (1*R*,2*S*)-*cis*-1-amino-2-indanol, afforded solely the desired branched product **2a** with an enantioselectivity of 80% at full conversion. Thus, ligand **6f** performed as regio- and enantioselectively as the most efficient pyridine-imine ligand **L3** but with a much higher catalytic activity (2 h and 24 h for **6f** and **L3**, respectively). In order to further optimize the structure of the ligand, variations on the substitution pattern of the pyridine part were undertaken. Electron-poor pyrimidine- and pyrazine-derived ligands (**6g** and **6h**,

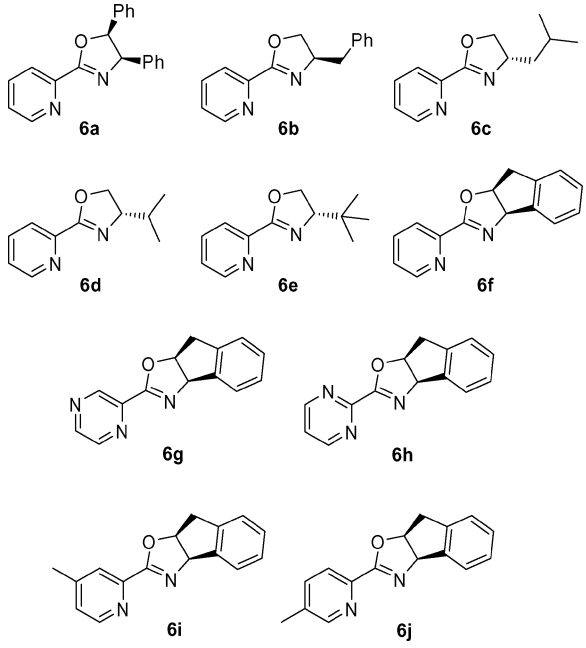
respectively) were thus synthesized in a similar manner to **6f**. These two ligands afforded solely the branched product **2a** with the same *ee* value of 78%. However, the reactions with these two electron-poor ligands were noticeably slower than those with unsubstituted pyridine ligand **6f** (Table 1, Entries 7 and 8). On the other hand, ligand **6i**, bearing an electron-donating methyl group *para* to the N atom of the pyridine, afforded a faster reaction with excellent regioselectivity but a lower enantioselectivity (73% *ee* in 1.5 h for **6i** vs. 80% *ee* in 2 h for **6f**). Electronic factors on the pyridine side of the ligand seemed to play a crucial role in the kinetics of the reaction (electron-poor ligands affording slower reactions) but accelerating the reaction seemed detrimental to the enantioselectivity.[15] In addition, the 5-methyl-substituted pyridine ligand **6j** allowed for full conversion of **1a** into **2a** but with a strongly detrimental effect on the kinetics (76% *ee* in 4 h for **6j** vs. 80% *ee* in 2 h for **6f**). The additional methyl group, in the latter case, was probably sterically interacting with the π-allyl fragment and slowing down the reaction. A "naked" pyridine moiety on the ligand thus seemed a good compromise to fulfill the stereoelectronic requirements. Ligand **6f** then appeared as the most suitable candidate for further screening.[20]

Using ligand **6f** and "classical" conditions (THF, 60 °C, 0.5 M of substrate **1**, 10 mol-% of **4a** and 10 mol-% **6f**), the scope of the reaction was investigated with a variety of substrates (compounds **1a**–**g**, Table 2). The regioisomeric anisyl derivatives **1a** and **1b** (*o*- or *p*-OMe) and **1f**, bearing a 3,4-methylidene dioxy group, reacted equally well when submitted to the reaction conditions yielding the corresponding branched products with about 80% *ee* in all cases. As observed with the pyridine-imine ligands,[15] the reactions were slower with the more challenging substrates bearing no substituent or an electron-withdrawing group (**1c**–**e**). However, with **6f** as the ligand, reactions occurred within a few days even with **1e** bearing a *p*-NO_2 group. A low b/l ratio of 76:24 was only obtained for this particular substrate, which was in good agreement with the previously described reactivity of such electron-poor substrates.[6f] Contrary to what had been previously observed with **L3** as ligand, for which the enantioselectivity was lower when longer reaction times were needed (80, 74 and 66% *ee* for **1a**, **1c** and **1d**, respectively),[15] only the b/l ratio was significantly influenced by the electronic properties of the cinnamyl fragment (Table 2, Entries 1, 4 and 5). No important effect on the enantioselectivity was observed in this series. This observation indicates that the enantio- and the regiodetermining steps of this reaction are probably distinct and independent. The configuration of the substrate was also important. For instance, compound **1g**, the *Z* isomer of **1a**, reacted to form **2a** as the major product. However, the reaction was significantly slower (7 h vs. 2 h) and much less selective (15 vs. 80% *ee*) than that with **1a**; the same levorotatory enantiomer of **2a** was predominant in both cases.[21,22]

With this catalytic system in hand, we decided to revisit the rearrangement of the secondary acetoacetates **5**, for which no obvious matched/mismatched effect could be observed with **L3** as the ligand.[15] In the case of **6f**, a clear matched/mismatched situation was observed as *ee* values of 45 and 87% were obtained with (*S*)-**5c** and (*R*)-**5c**, respectively (Table 3). In addition, in the mismatched series, the reaction was slower, and the b/l ratio was noticeably lower. When racemic **5c** was submitted to the reaction conditions, a slightly enantio-enriched product was obtained at 86% conversion [15% *ee* in favor of the (–)-(*R*) enantiomer] in good accordance with the results obtained in both enantiopure series and the fact that the reaction is globally stereospecific with branched secondary allylic substrates.[4,7b]

Due to the higher reactivity of the catalytic system derived from ligand **6f**, we then investigated lowering the catalyst loading towards a more practical level. Interestingly, only 2 mol-% of **4a** and 2.4 mol-% of **6f** were necessary to maintain the level of conversion and stereochemical outcome if the concentration of the substrates was increased to 2.0 M. Details are given in the Supporting Information.

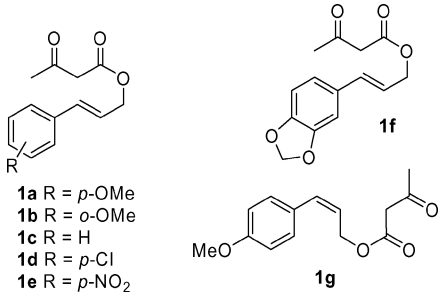
Table 1. CpRu-catalyzed rearrangement of allylic ester **1a**.[a]



Entry	Ester	Ligand	Time [h]	Conv. [%]	*ee* [%]	Optical rotation[b]	b/l[c]
1	**1a**	**6a**	2	>97	53	(–)	>97:3
2	**1a**	**6b**	2	>97	56	(–)	>97:3
3	**1a**	**6c**	2	>97	63	(+)	>97:3
4	**1a**	**6d**	2	>97	72	(+)	>97:3
5	**1a**	**6e**	48	<3	–	–	–
6	**1a**	**6f**	2	>97	80	(–)	>97:3
7	**1a**	**6g**	3.5	>97	78	(–)	>97:3
8	**1a**	**6h**	3.5	>97	78	(–)	>97:3
9	**1a**	**6i**	1.5	>97	73	(–)	>97:3
10	**1a**	**6j**	4	>97	76	(–)	>97:3

[a] Fresh **4a** (10 mol-%), ligand **6** (10 mol-%), THF, 60 °C, and **1a** (0.5 M); the results are the average of at least two runs. [b] The sign of the optical rotation of **2a**. [c] Ratios of branched (**2**) to linear (**3**) products were determined at complete conversion by ^{1}H NMR (400 MHz) spectroscopy.

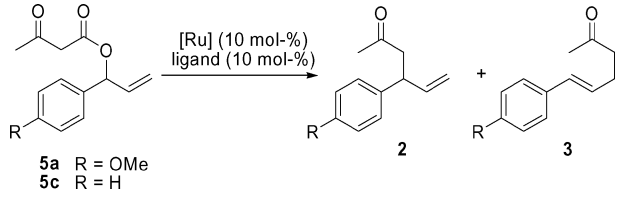
Table 2. CpRu-catalyzed rearrangement of allylic esters **1**.[a]



Entry	Ester	Time [h]	Conv. [%]	*ee* [%]	Optical rotation[b]	b/l[c]
1	**1a**	2	>97	80	(–)	>97:3
2	**1b**	3	>97	78	(–)	>97:3
3	**1c**	7	>97	77	(–)-(*R*)	95:5
4	**1d**	24	>97	77	(–)	93:7
5	**1e**	120	>97	75	(–)	76:24
6	**1f**	1.5	>97	77	(–)	>97:3
7	**1g**	7	>97	15	(–)	95:5

[a] Fresh **4a** (10 mol-%), ligand **6f** (10 mol-%), THF, 60 °C, and **1** (0.5 M); the results are the average of at least two runs. [b] The sign of the optical rotation of **2** and the absolute configuration, when known. [c] Ratios of branched (**2**) to linear (**3**) products were determined at complete conversion by ^{1}H NMR (400 MHz) spectroscopy.

Table 3. Rearrangement of secondary substrates.[a]



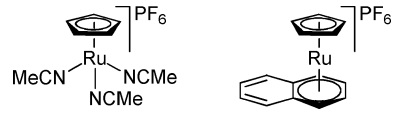
Entry	Ester	Time [h]	Conv. [%]	*ee* [%]	Optical rotation[b]	b/l[c]
1	(*R*)-**5c**	2.5	>97	87	(–)-*R*	95:5
2	(*S*)-**5c**	3	85	45	(+)-*S*	90:10
3	*rac*-**5c**	3	86	23	(–)-*R*	88:12

[a] Fresh **4a** (10 mol-%), ligand **6f** (10 mol-%), THF, 60 °C, and **5c** (0.5 M); the results are the average of at least two runs. [b] The sign of the optical rotation of **2**. [c] Ratios of branched (**2**) to linear (**3**) products were determined at complete conversion by ^{1}H NMR (400 MHz) spectroscopy.

Importantly, we observed during the initial screening process that the enantioselectivity with **1a** varied from one reaction to the next under the same conditions. After extensive investigation of reaction parameters, this phenomenon was correlated to a change of aspect of the [CpRu(NCMe)$_3$][PF$_6$] salt and to the shelving time of **4a** in the freezer, in particular. Indeed, the color of this precatalyst, although kept under an argon atmosphere at –20 °C, gradually changed from bright yellow (when fresh) to brown-orange after a few weeks. A gradual decrease of the enantioselectivity was observed from 80% *ee* with freshly prepared **4a** to 69% *ee* with a five-week-old sample. Interestingly, neither the b/l ratio nor the conversion after 2 h was affected by the condition of **4a**.[20] Needless to say, all the previously described experiments were carried out with freshly prepared precatalyst **4a** (less than one week old).

To circumvent this problem, we envisaged a different source of metal precursor, the [CpRu(η^6-naphthalene)][PF$_6$] complex **4b** in particular (Table 4).[14] As reported recently by Hintermann and Bolm,[23] this air-stable complex can be used as a precatalyst for the hydration of terminal alkynes. Initial experiments validated this choice, as salt **4b** was indeed able, with ligand **6f**, to provide the desired product **2a** with excellent regioselectivity. However, in experiments performed under standard conditions, a quite lower enantioselectivity value was obtained (71% *ee* with **4b**, Table 4, Entry 2 vs. 80% *ee* with **4a**, Table 2, Entry 1). We reasoned that the presence of the substrate during the displacement of the η^6-naphthalene by the pymox ligand was perturbing the outcome of the reaction. This problem was then overcome by treating complex **4b** with the ligand prior to the addition of the substrate. To determine the optimal induction period, reactions were performed with an initiation time of 30, 60 or 90 min before introducing the allylic ester. In the latter two cases, the enantioselectivity was essentially restored (79% *ee*, Table 4, Entries 3 and 4). Whether the liberated naphthalene moiety was involved in the reaction after its displacement is debatable; it was almost quantitatively recovered at the end of the reaction, and thus, provided an internal reference for approximate GC-yield calculations.

Table 4. Initiation-time effect with **4b**.[a]



Entry	Ligand	Initiat. time [min]	Time [h]	Conv. [%]	*ee* [%]	Optical rotation[b]	b/l[c]
1	–	0	48	<3	–	–	–
2	**6f**	0	6	>97	71	(–)	>97:3
3	**6f**	30	6	>97	74	(–)	>97:3
4	**6f**	60	6	>97	79	(–)	>97:3
5	**6f**	90	6	>97	79	(–)	>97:3

[a] **4b** (2.5 mol-%), ligand **6f** (3 mol-%), THF, 60 °C, and **1a** (2 M); the results are the average of at least two runs. [b] The sign of the optical rotation of **2**. [c] Ratios of branched (**2**) to linear (**3**) products were determined at complete conversion by ^{1}H NMR (400 MHz) spectroscopy.

The generality of this catalytic combination was then tested with some of the substrates described previously. The results are detailed in Table 5. For all tested substrates, the catalyst generated in situ from **4b** performed as selectively as the one derived from **4a**. In the particular case of the less active substrates (Table 5, Entries 3 and 4), regio- and enantioselectivities were even slightly better. Importantly, complex [CpRu(η^6-naphthalene)][PF$_6$] could be stored at ambient temperature under ambient atmosphere in a screw-cap vial for over 6 months without any noticeable erosion

of reactivity or selectivity. However, due to the photosensitivity of [CpRu(η^6-naphthalene)][PF_6],[24] **4b** must be stored in the dark.

Table 5. CpRu-catalyzed rearrangement of allylic esters **1** with **4b**.[a]

Entry	Ester	Time[b] [h]	Conv. [%]	*ee* [%]	Optical rotation[c]	b/l[d]
1	**1a**	6	>97	79	(–)	>97:3
2	**1c**	25	>97	77	(–)	95:5
3	**1d**	120	>97	81	(–)	93:7
4	**1e**	400	>97	79	(–)	79:21

[a] **4b** (2.5 mol-%), ligand **6f** (3 mol-%), THF, 60 °C, and **1** (2 M); the results are the average of at least two runs. [b] Reaction time without 1 h of initiation time. [c] The sign of the optical rotation of **2**. [d] Ratios of branched (**2**) to linear (**3**) products were determined at complete conversion by ^{1}H NMR (400 MHz) spectroscopy.

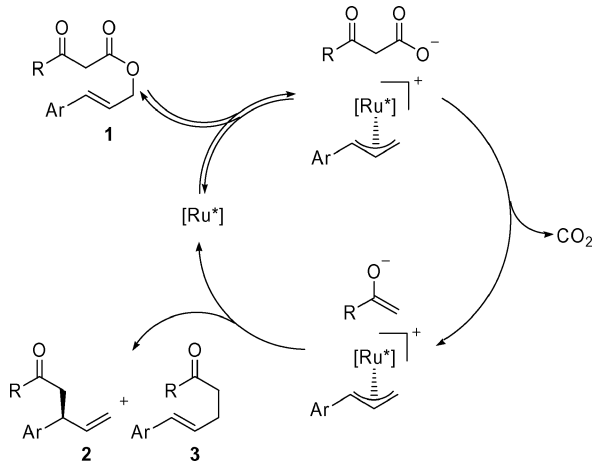
The robustness of this catalytic system was further assessed by performing the rearrangement of allylic ester **1a** in non-anhydrous conditions. The results of the reactions performed with various amounts of water are reported in Table 6. We observed no effect on the regioselectivity (>97:3) and only a very small effect on the enantioselectivity (78 vs. 79% *ee*) of the process with 10, 300 and 2100 ppm of water in THF (Table 6, Entries 1–3). When the amount of water was raised to approximately 0.3% (v/v), the branched product was still exclusively obtained but with a slightly lower enantioselectivity (Table 6, 75 vs. 79% *ee*, Entry 4). Thus, this reaction can also be performed under non-anhydrous conditions with standard bottled solvent (typically less than 50 ppm of water for commercially available, analytical-grade THF) with virtually no effect on the stereochemical outcome of the reaction.

Table 6. CpRu-catalyzed rearrangement of allylic ester **1a** with **4b** in non-anhydrous THF.[a]

Entry	Water[b] [ppm]	Time[c] [h]	Conv. [%]	*ee* [%]	Optical rotation[d]	b/l[e]
1	10	8	>97	79	(–)	99:1
2	300	8	>97	78	(–)	98:2
3	2100	8	>97	78	(–)	98:2
4	11600	8	>97	75	(–)	97:3

[a] **4b** (2 mol-%), ligand **6f** (2.4 mol-%), THF, 60 °C, and **1a** (2 M); the results are the average of at least two runs. [b] Measured with a Karl Fischer apparatus. [c] Reaction time without a 1 h initiation time. [d] The sign of the optical rotation of **2**. [e] Ratios of branched (**2**) to linear (**3**) products were determined at complete conversion by GC-MS.

Finally, a series of experiments (and the synthesis of new substrates) were performed to gain some insight into the reaction mechanism. Generally, Cp*Ru- and CpRu-catalyzed allylation reactions are believed to proceed through the formation of Ru-π-allyl complexes with leaving group release,[5,6] and the decarboxylative addition of enolates is no exception.[7] In this latter case (Scheme 4), the oxidative addition of the metal complex to the substrate leads to the release of a keto acetate moiety, which upon decarboxylation, generates an "unstabilized" enolate. This nucleophilic enolate subsequently adds to the π-allyl complex to regenerate the catalytically active Ru complex and furnishes the γ,δ-unsaturated ketone.

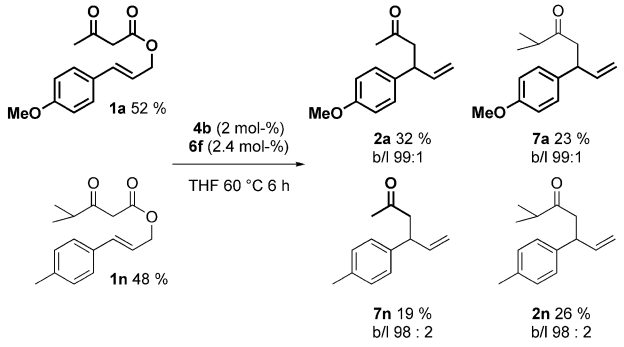


Scheme 4. Postulated mechanistic rational.

To confirm the nature of the nucleophilic intermediate, we attempted to intercept the transient species. When the reaction of **1c** was conducted with 1 equiv. of dimethylmalonate,[7a] no incorporation of the malonate fragment onto the allyl fragment was observed (GC-MS). This suggests that the addition of the alleged "unstabilized" enolate onto the allyl fragment is much faster than the deprotonation of the acidic malonic ester. Moreover, in contrast to the observation of Tunge with a Cp*Ru-based catalyst,[7c] the enolate could not be trapped by a Michael acceptor (typically substituted methylenemalononitriles) under the standard reaction conditions. In view of the lack of interception of the nucleophilic species, it was then debatable whether the reaction proceeded intramolecularly rather than intermolecularly.

To solve this issue, a double-crossover experiment was performed with a ca. 1:1 mixture of **1a** and **1n** (Scheme 5). After 6 h, GC and MS analysis of the resulting crude reaction mixture showed the formation of all possible branched and linear products compatible with intermolecular processes (**2a**, **3a**, **2n** and **3n** and crossover products **7a**, **8a**, **7n** and **8n**, Scheme 5). This result indicated that the alkylation reaction clearly proceeded through the fragmentation of substrates into nucleophilic and electrophilic species, which resulted in crossover.[25]

To further characterize the nucleophilic species and probe the generality of the reaction, several more elaborate cinnamyl keto esters were synthesized (**1h**–**m**). Their reactions are summarized in Table 7.[26] Substrates **1h**–**j**, bearing an α substituent between the carbonyl moieties, reacted with similar kinetics and enantioselectivities to those of unsubstituted **1c** (Table 2, Entry 3 vs. Table 7, Entries 1–3). However, the regiochemistry favored the branched adducts noticeably less (down to 81:19). Clearly, the bulkier the nucleophile, the more of the linear product was provided.

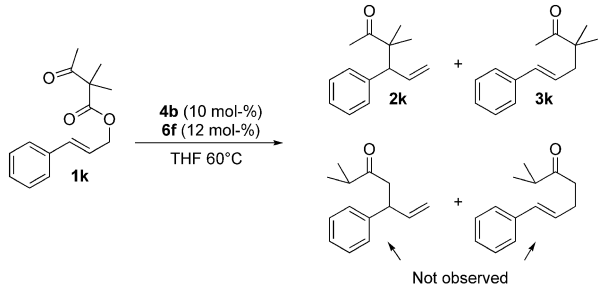


Scheme 5. Double-crossover experiment (linear products **3** and linear crossover products **8** are omitted for clarity; ratios were measured by GC-MS).

Furthermore, the presence of an α substituent led to the introduction of a stereogenic centre and, as a result, four stereoisomers of compounds **2** and two enantiomeric linear adducts **3** were obtained.

For branched derivative **2h**, GC analysis indicated that the diastereoselectivity linked to the presence of the new stereocenter was low (ca. 2:1).[27] As a similarly low selectivity was also observed for (cyclic) **2i** and **2j**, it was probably not due to a lack of control of the *E*/*Z* geometry of the postulated enolate intermediate. Interestingly, and in slight contrast to these results, the chiral linear products **3h** and **3i** were obtained with a decent enantioselectivity (67% and 79% *ee*, respectively). This shows that the facial approach of the alleged enolate was better controlled when the attack onto the electrophilic fragment occurred at the unsubstituted, allylic, terminal position rather than α to the aromatic moiety.[2,28]

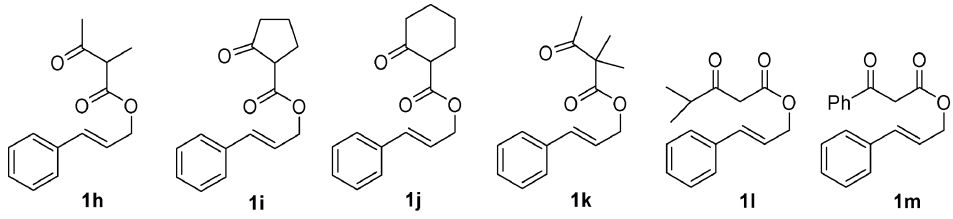
Substrates **1h**, **1k** and **1l**, designed to probe the existence of enolate intermediates and their regioisomeric stability, reacted smoothly under the reaction conditions. In the particular case of **1k**, as there are no α hydrogen atoms between the two carbonyl groups, the selective formation of **2k** indicated that the decarboxylation of the corresponding keto acetate occurred necessarily prior to the attack onto the π-allyl complex. In addition, the fact that the new C–C bonds in **2h** to **2l** and **3h** to **3l** (Scheme 6) resulted solely from the attack of the carbon previously bearing the carboxylate moiety is compatible with the formation of enolates whose regiochemistry is preserved throughout the catalytic cycle.[7]



Scheme 6. Conservation of the enolate regiochemistry for **1k**.

Finally, the benzoyl-substituted substrate **1m** reacted smoothly with faster kinetics but the same selectivity as those of **1c** under the same conditions.[8a] The faster reaction for this substrate allowed the temperature to be lowered to 25 °C, and **2m** was obtained in 86% *ee* and a b/l ratio of 95:5 within 64 h. These results confirmed that better *ee* values were obtained at a lower temperature.[29]

Table 7. CpRu-catalyzed rearrangement of allylic esters **1**.[a]



Entry	Ester	Time[b] [h]	Conv.[c] [h]	b/l[d]	*dr*[d]	*ee* (**b**$_1$, **b**$_2$, **l**)[e,f] [%]	Optical rotation[g]
1	**1h**	9	>97	81:19	68:32	72, n.d., 67	(–)
2	**1i**	9	>97	87:13	64:36	n.d., 81, 79	(–)
3	**1j**	9	>97	86:14	64:36	77, 77, n.d.	(–)
4	**1k**	9	>97	83:17	–	57	(–)
5	**1l**	9	>97	85:15	–	67	(–)
6	**1m**	5	>97	92:8	–	78	(–)
7	**1m**[h]	24	>97	95:5	–	83	(–)
8	**1m**[i]	64	>97	95:5	–	86	(–)

[a] **4b** (10 mol-%), ligand **6f** (12 mol-%), THF, 60 °C, and **1** (2 M); the results are the average of at least two runs. [b] Reaction time without 1 h of initiation time. [c] Determined by ^{1}H NMR (400 MHz) spectroscopy. [d] Ratios of branched (**2**) to linear (**3**) products and diastereomeric ratios among compounds **2** (*dr*) were determined at complete conversion by GC-MS. [e] The *ee* value of the first and second eluted branched stereoisomers of **2** and of the linear **3**, respectively. [f] n.d.: nothing detected. [g] The sign of the optical rotation of **2**. [h] Reaction was performed at 40 °C. [i] Reaction was performed at 25 °C.

Conclusions

Herein, we reported that the conjunction of simple-to-make and readily available, enantiopure, pymox ligands (in one step from commercially available sources) and a CpRu precatalyst provided an efficient catalytic system for Carroll-type rearrangements of allyl-β-keto esters of type **1** with good to perfect regioselectivity and good enantiomeric control. Even challenging substrates bearing strongly electron-withdrawing groups reacted with catalyst loadings as low as 2 mol-%. In addition, to avoid the phenomenon of catalyst aging, which is detrimental to selectivity, an alternative catalytic combination was developed composed of air-stable [CpRu(η^6-naphthalene)][PF_6] **4b** and indanyl-pymox ligand **6f**, which provided reproducibly high selectivities even in non-anhydrous media.

Experimental Section

CpRu-Catalyzed Carroll Rearrangement. Improved Procedure (Typical Procedure): In a 2 mL screw-cap vial equipped with a magnetic stirring bar, [CpRu(η^6-naphthalene)][PF_6] (6.6 mg, 0.015 mmol, 2.5 mol-%) and **6f** (4.3 mg, 0.018 mmol, 3 mol-%) were dissolved in dry THF (0.3 mL). The vial was flushed with argon and capped. After 1 h of heating at 60 °C, allyl β-keto ester **1a** (150 mg, 0.6 mmol) was added in one portion, and heating was continued for another 6 h. The cooled reaction mixture was diluted with diethyl ether/pentane (60:40, 1.5 mL). After precipitation, the metal salts were filtered through a short SiO_2 column (0.5 cm × 4 cm, elution diethyl ether/pentane, 60:40). The solvents were then evaporated under reduced pressure to afford the crude reaction mixture as a pale yellow oil.

Supporting Information (see also the footnote on the first page of this article): Experimental procedures, spectroscopic and analytical data (^{1}H, ^{13}C, and HRMS) for new compounds, and Chiral Stationary-Phase-GC or HPLC separation methods for all chiral products.

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