Lewis acid/CpRu dual catalysis in the enantioselective decarboxylative allylation of ketone enolates†

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The addition of a Lewis acidic metal triflate salt $Mg(OTf)_2$ as co-catalyst in the CpRu-catalyzed decarboxylative allylation of *in situ*-generated ketone enolates allows the reaction to proceed at lower temperature with higher regio- and enantioselectivity. Even so-far-unreactive substrates react.

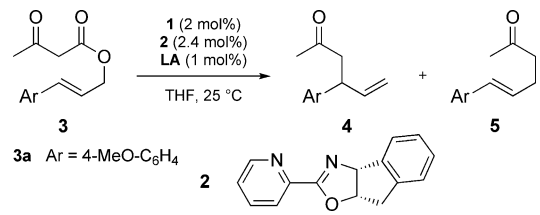
Introduction

Catalysts for enantioselective addition of nucleophiles are traditionally designed to activate the electrophilic reaction partner through Lewis or Brønsted acid activation.[1] Recently, following the work of Shibazaki,[2] bifunctional catalysts[3] or mixtures of catalysts[4] have been successfully developed to achieve the dual activation of both nucleophilic and electrophilic reaction partners.[5]

The catalytic *in situ* generation of nucleophiles and their participation in the C–C bond-forming processes is also a topic of sustained interest.[6] In this context, the fragmentation of allyl β-ketoesters and the subsequent condensation of the resulting unstabilized carbonyl nucleophiles and unsymmetrical allyl–metal fragments still represents a challenge to generate enantio- and regioselectively nonracemic γ,δ-unsaturated ketones.[7] Recently, combinations of a CpRu source (*e.g.* $[CpRu(\eta^6\text{-}C_{10}H_8)][PF_6]$ **1**)[8] and chiral diimine ligands[7f,g] were shown to catalyze this type of reaction with high selectivities, but with somewhat unsatisfactory reactivity; pyridine mono-oxazolines of type **2** (Table 1) being nevertheless better ligands than pyridine imines.[9]

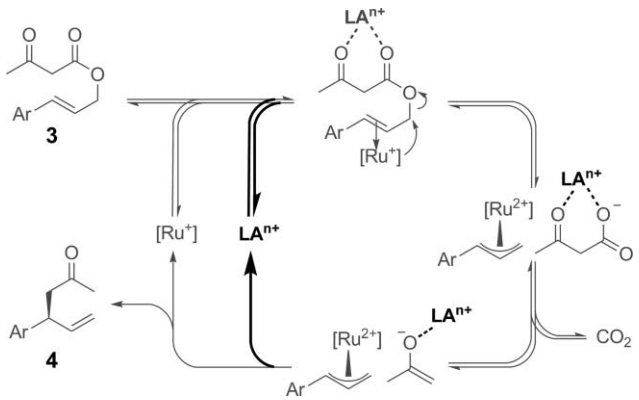
It is this lack of reactivity that we decided to tackle. Mechanistically, it is considered that, for CpRu allyl complexes, the ionization of the substrate to form a π-allyl metal complex, separated from the β-ketocarboxylate moiety, is the rate-determining step (Scheme 1, grey external cycle).[10] So, any process that would render the β-ketocarboxylate a better leaving group would be beneficial. As 1,3-dicarbonyl moieties are effective bidentate ligands for many metal ions,[11] the addition of a catalytic amount of an additional Lewis acid was considered.[12] It could ease the ionization step, facilitate the decarboxylation and even possibly organize the nucleophilic attack. Herein, we report that $Mg(OTf)_2$ is indeed an effective co-catalyst for the 'Carroll rearrangement' affording lower temperature conditions and overall higher reactivity and selectivity.

Table 1 Co-catalyst influence on the CpRu-catalyzed rearrangement of **3a**[a]



Entry	Ester	Lewis acid	Time/h[b]	Conv. (%)[c]	**4a** : **5a**[d]	ee (%)[e]
1	**3a**	—	48	<3	—	—
2	**3a**	$LiPF_6$	48	<3	—	—
3	**3a**	KPF_6	48	<3	—	—
4	**3a**	$Mg(OTf)_2$	24	>97	97 : 3	84
5	**3a**	$Zn(OTf)_2$	54	80	94 : 6	80
6	**3a**	$Cu(OTf)_2$	54	95	89 : 11	84
7	**3a**	TfOH[f]	48	<3[13]	—	—

[a] **1** (2 mol%), ligand **2** (2.4 mol%), THF, 25 °C, *c*(**3a**) 1 M; the results being the average of at least two runs. [b] Reaction time without 1 h induction time after which is added the substrate followed by the Lewis acid. [c] Determined by ^{1}H NMR (400 MHz). [d] Determined by GC-MS. [e] Determined by CSP-GC. **4a** is always levorotatory. [f] 2 mol% were used.



Scheme 1 Mechanistic rationale for a dual-catalysis approach.

Results and discussion

Lewis acid selection

To assess the feasibility of this dual-catalysis approach, cinnamyl ester **3a** (Ar = 4-MeO-C_6H_4) was treated with a preformed

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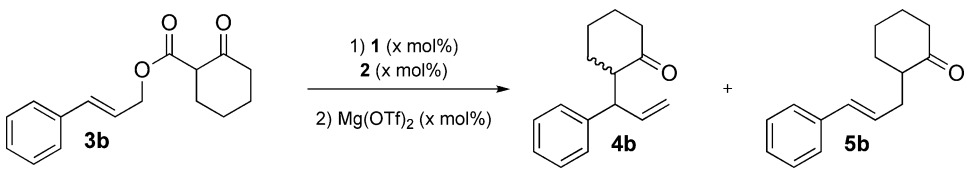
† Electronic supplementary information (ESI) available: ^{1}H NMR spectra of all substrates, ligand and catalyst precursor, and typical experimental and CSP separation procedures. See DOI: 10.1039/b910475e

Table 2 Optimal stoichiometry determination for the reaction of **3a**[a]

Entry	**1**	**2**	[Mg][b]	Temp/°C	Time/h[c]	Conv. (%)[d]	**4a** : **5a**[e]	ee (%)[f]
1	2	2.4	—	60	6	>97	99 : 1	79
2	2	2.4	—	25	48	<3	—	—
3	—	2.4	1	25	48	<3	—	—
4	2	—	1	25	24	<3	—	—
5	2	2.4	1	25	24	>97	97 : 3	84
6	2	2.4	2	25	24	>97	94 : 6	83
7	2	2.4	3	25	24	>97	90 : 10	78
8	2	3.4	1	25	24	>97	96 : 4	82
9	2	4.4	1	25	24	>97	96 : 4	82

[a] General conditions: THF, *c*(**3a**) 1 M; **1** and **2** in mol%; the results being the average of at least two runs. [b] $Mg(OTf)_2$, mol%. [c] Reaction time after the addition of **3a** and $Mg(OTf)_2$ (not including the 1 h mixing time of **1** and **2** at 60 °C). [d] Determined by ^1H NMR (400 MHz). [e] Determined by GC-MS. [f] Determined by CSP-GC. **4a** is always levorotatory.[16]

Table 3 Stoichiometry determination for the reaction of **3b**[a]



Entry	**1** (mol%)	**2** (mol%)	$Mg(OTf)_2$ (mol%)	T/°C	Time/h[b]	Conv. (%)[c]	**4b** : **5b**[d]	ee (%)[e]	dr[d,f]
1	2	2.4	—	60	9	>97	86 : 14	77,77	64 : 36
2	2	2.4	—	25	48	<3	—	—	—
3	—	2.4	1	25	48	<3	—	—	—
4	2	—	1	25	48	<3	—	—	—
5	2	2.4	1	25	24	>97	81 : 19	87,87	58 : 42
6	2	2.4	2	25	24	>97	72 : 28	84,82	57 : 43
7	2	2.4	3	25	24	>97	70 : 30	84,81	56 : 44
8	2	3.4	1	25	24	>97	85 : 15	86,86	59 : 41
9	2	4.4	1	25	24	>97	91 : 09	87,88	61 : 39

[a] General conditions: THF, *c*(**3b**) 1 M; the results being the average of at least two runs. [b] Reaction time after the addition of **3b** and $Mg(OTf)_2$ (not including the 1 h mixing time of **1** and **2** at 60 °C). [c] Determined by ^1H NMR (400 MHz). [d] Determined by GC-MS. [e] Enantiomeric excess for the *syn* and *anti* stereoisomers of **4b**; determined by CSP-GC. No peak separation was achieved for linear **5b**. [f] Ratio between the *syn* and *anti* stereoisomers of product **4b**.

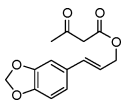
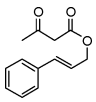
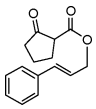
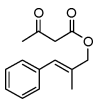
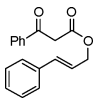
combination of CpRu **1** and ligand **2**. At room temperature, no conversion was obtained without a co-catalyst (Table 1, entry 1). The use of additional cationic alkali metal sources as $LiPF_6$ or KPF_6 (entries 2 and 3) provided no reaction.

On the other hand, $Mg(OTf)_2$ afforded a clean reaction at room temperature (entry 4). The products were obtained with a higher enantiomeric excess but a slightly lower regioselectivity (**4a** ee 84%, **4a** : **5a** 97 : 3) than under the classical reaction conditions (60 °C, no co-catalyst, ee 79%, **4a** : **5a** 99 : 1, Table 2, entry 1). $Zn(OTf)_2$ and $Cu(OTf)_2$ (entries 5 and 6) were also tested. In both cases, the reactions were noticeably slower (incomplete reaction after 54 h) and the regio- and/or enantioselectivities were lower. $Mg(OTf)_2$ salt then appeared as the best candidate for further screening.[14]

Stochiometry determination

The next step necessary was the determination of the optimal three-component combination of CpRu **1**, ligand **2** and Lewis acid $Mg(OTf)_2$. Screening was performed with two rather different substrates **3a** and **3b** (Tables 2 and 3 respectively). The reactions of these compounds at 60 °C in the absence of a Lewis acid are provided as references (Tables 2 and 3, entry 1). The results of the two assays point towards the same conclusions. At 25 °C, all reagents are clearly indispensable to promote the desired reaction of **3a** or **3b**: no reactivity is observed with any lack of **1**, **2** or $Mg(OTf)_2$ (entries 2 to 4, both tables). Then, when all three reagents are present in a 2 : 2.4 : 1 ratio, better enantioselectivities are obtained at room temperature than at 60 °C (Tables 2 and 3 entries 5, 84 and 87% ee for **4a** and **4b** respectively). Increasing the amount of $Mg(OTf)_2$ from 1 to 3 mol% has a negative influence both on the regioselectivity (branched-to-linear ratio, **4** : **5**) and on the enantioselectivity of the reaction (entries 6 to 7). Since the catalytically active Ru species can only bear a single ligand **2**, the use of an overstoichiometric amount of ligand might lead to coordination of the free ligand onto to the additional metal salt and thus modify its Lewis acidity. The influence of the ligand stoichiometry was thus assessed by increasing the amount of ligand **2** from 2.4 to 4.4 mol%. Little influence on the reactions of **3a** was observed but results were nicely improved with **3b**—the regioselectivity of the reaction in particular. Unfortunately, no positive effect was observed on the *syn*-to-*anti* ratio for the diastereoisomers of **4b** (Table 3, entries 8 and 9).[15]

Table 4 Substrate scope of CpRu-catalyzed rearrangements

Entry	Ester		Time/h[a]	Conv. (%)[b]	**4** : **5**[c]	ee (%)[d]
1		**3c**	24[e]	>97	98 : 2	83
2		**3d**	24[e]	>97	93 : 7	82
3		**3e**	24[e]	>97	92 : 8	nd, 88 (57 : 43)[f]
4		**3f**	24[g]	<3	—	—
		3f	24[h]	>97	70 : 30	nd
5		**3g**	24[g]	<3	—	—
		3g	24[h]	40	9 : 91	nd
6		**3h**	64[i]	>97	95 : 5	86
		3h	24[e]	>97	93 : 7	80

[a] Reaction time without the 1 h induction time after which the substrate and $Mg(OTf)_2$ are added. [b] Determined by ^1H NMR (400 MHz). [c] Branched-to-linear ratio determined by GC-MS. [d] Determined by CSP-GC or CSP-HPLC. Products **4c**, **4d**, **4f** and **4h** being levorotatory.[16] [e] **1** (2 mol%), **2** (4.4 mol%), $Mg(OTf)_2$ (1 mol%), THF, 24 °C, **3**: *c* 1 M. [f] Diastereomeric ratio given in brackets. [g] Classical conditions: **1** (10 mol%), **2** (13 mol%), THF, 60 °C, **3**: *c* 1 M. [h] Above classical conditions with $Mg(OTf)_2$ (5 mol%) extra. [i] **1** (2 mol%), **2** (2.4 mol%), THF, 25 °C, **3h**: *c* 2 M.

Substrate scope

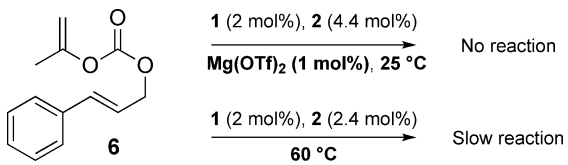
With the resulting 2 : 4.4 : 1 stoichiometry of **1** : **2** : $Mg(OTf)_2$ in hand, the scope of the reaction was studied (Table 4). Two rather classical substrates were first used, compounds **3c** and **3d** bearing different substituents on the aromatic nucleus of the allyl moiety. As expected, these compounds reacted at 25 °C under the new set of conditions to afford the branched regioisomer with excellent regioselectivity and ee values of 83 and 82% for **4c** and **4d**, results better than those at 60 °C (ee 77% in both cases).[9] In the case of substrate **3e** similar results to **3b** were, not too surprisingly, obtained due to their structural similarities (entry 3).[9]

Maybe more importantly, experiments with substrates **3f** and **3g** were also performed. These compounds, which did not afford any conversion under previous (non co-catalized) conditions at 60 °C, now reacted in the presence of $Mg(OTf)_2$ as co-catalyst. For instance **3f** yielded, at 60 °C, the corresponding branched product **4f** with decent regioselectivity; no conditions being found for the analytical separation of the enantiomers and the measurement of the enantiomeric purity. The previously unreactive aliphatic **3g** also provided a reaction. The linear product **5g** was obtained predominantly in the crude reaction mixture (**4g** : **5g**, 9 : 91); this result, however, being in line with previous observations from the groups of Bruneau and Pregosin with Cp*Ru catalysts.[10]

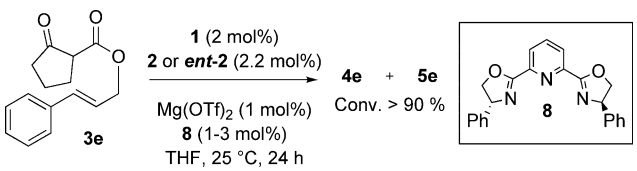
Overall, looking at the results of the reactions of **3a**–**3e**, better enantioselectivity is afforded for the branched products of type **4** under dual-catalysis conditions. We wondered about the generality of this observation and about the origin of this increase in enantioselectivity; the better selectivity being possibly a result of the lowering of the reaction temperature only. Substrate **3h** was therefore selected. This allylic benzoylester is more reactive and known to react already at 25 °C without any Lewis acid additive.[9] Significantly, it was observed that the presence of $Mg(OTf)_2$ lowers the enantioselectivity of the reaction of **3h** quite substantially (ee 80 *vs.* 86%, entry 6, Table 4). Clearly, temperature is not the only parameter to be considered: the higher reactivity with the co-catalyst being, at the same temperature, detrimental to the selectivity.

Mechanistic insight

With these results in hand, preliminary experiments were performed to try to understand the role of the Lewis acid during the reaction. First, a stoichiometric amount of $Mg(OTf)_2$ was added to allylic ester **3a** and no change was observed in the attenuated total reflection (ATR)-IR spectrum ($\nu_{C=O} = 1714, 1738\ cm^{-1}$). This lack of perturbation suggested an absence of Lewis interaction between the metal and the substrate at the start of the reaction and a role for the Mg salt at a later stage of the mechanism. This assumption was tested with cinnamyl isopropenyl carbonate **6**. Importantly, no reaction was obtained under dual-catalysis reaction conditions whereas a slow but detectable reaction was obtained under classical conditions (Scheme 2, <15% conv. after 24 h). This result clearly shows the importance of the ketoester moiety in the activation process despite the lack of evidence in ATR-IR spectroscopy for its interaction with $Mg(OTf)_2$.



Scheme 2 Reaction of cinnamyl isopropenyl carbonate **6** under dual–catalysis (top) and classical (bottom) conditions.

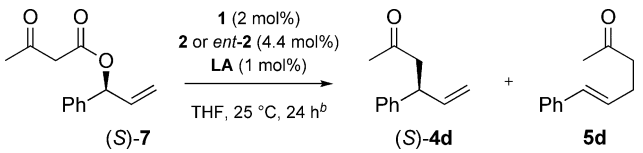


Scheme 3 Use of preformed chiral Lewis acidic co-catalyst.

This assertion was verified by looking at the reactivity of chiral secondary allylic ester **7**[17] (Table 5). Traditionally, this type of substrate reacts faster than the corresponding primary linear adducts of type **3** in allylation reactions mediated by CpRu or Cp*Ru moieties.[18,7b,f] This higher reactivity is considered to be linked to a better accessibility of the metal fragment to the monosubstituted olefin.

For the rearrangement of enantiopure (*S*)-**7** to occur at room temperature, as for the linear substrates, the use of the additional

Table 5 Enantiospecific CpRu-catalyzed rearrangement of **7**[a]



(*S*)-**7** (*S*)-**4d** **5d**

Entry	L	Lewis acid	Conv. (%)[c]	**4d** : **5d**[d]	Diallylated (%)[d]	ee (%)[e]
1	**2**	—	<3	—	—	—
2	***ent*-2**	$Mg(OTf)_2$	>97	93 : 7	5	(*S*)-93
3	***ent*-2**	$Zn(OTf)_2$	>97	91 : 9	7	(*S*)-95
4	***ent*-2**	$Cu(OTf)_2$	>97	71 : 29	7	(*S*)-97
5	**2**	$Mg(OTf)_2$	>97	89 : 11	9	(*S*)-40
6	**2**	$Zn(OTf)_2$	>97	86 : 14	10	(*S*)-50
7	**2**	$Cu(OTf)_2$	>97	51 : 49	16	(*S*)-70

[a] **1** (2 mol%), ligand (4.4 mol%), THF, 25 °C, *c*(**7**) 1 M. [b] Reaction time without the 1 h induction time after which is added the substrate followed by the *Lewis* acid. [c] Determined by ^{1}H NMR (400 MHz). [d] Sum of diallylated isomeric products determined by GC-MS. [e] Determined by CSP-GC; absolute configuration deduced from the optical rotation sign.[7b]

Lewis acid was necessary (entry 1). Using ***ent*-2**[19] as ligand and $Mg(OTf)_2$ as Lewis acid, (*S*)-**7** yielded the corresponding ketone (*S*)-**4d** (global retention of configuration) with good regio- and high enantioselectivity (entry 2, **4d** : **5d**, 93 : 7, ee 93%). But contrary to what had been previously observed,[7b,f] a complex mixture of diallylated regioisomeric products was obtained along with **4d** and **5d**. Once again the use of $Zn(OTf)_2$ or $Cu(OTf)_2$ afforded lower regioselectivity but higher enantioselectivity was interestingly obtained (entries 3 and 4, up to ee 97% for **4d** with $Cu(OTf)_2$). Using **2** as ligand, a clear mismatched effect was obtained in all cases with lower enantioselectivity but also poorer regioselectivity and more diallylated products (entries 5 to 7). Since (*S*,+)-**4d** was obtained in all reactions, and this with both enantiomers **2** and ***ent*-2** of the ligand, it is clear that the stereogenic information within the substrate (*S*)-**7** remains overall predominant. This tends to show that a possible isomerization of the transient π-allyl complex is slow on the timescale of the reaction. As such, the imperfect stereospecificity of the reaction is most probably, as hypothesized by Tunge,[7b] due to the partial isomerization of branched **7** into linear **3d** resulting in a loss of initial stereochemical information.

On the possibility of using a chiral Lewis acid

Finally, in view of the probable role of $Mg(OTf)_2$ as Lewis acid activator of the ketoester functional group, we entertained the idea of finding a chiral ligand that would be selective for the magnesium ion in the presence of **1** and **2**. It would generate, *in situ*, a chiral Lewis acid specific for the nucleophilic fragment able to reinforce possibly the enantio- and/or diastereoselectivity of the reactions. In a very preliminary study, the influence of 2,6-bis((*R*)-4-phenyl-4,5-dihydrooxazol-2-yl)pyridine **8** was tested (Scheme 3).

First, it was verified that **8** is not an efficient ligand in conjunction with CpRu **1** for the Carroll rearrangement. Indeed, no reactions occurred in the presence of **8** under classical conditions. Then, various amounts of **8** (1 to 3 mol%) were premixed with $Mg(OTf)_2$ (1 mol%) and the mixtures were added to reactions of **3e**. In all cases, the reactions performed well but essentially no influence of **8** was found on the selectivity ratios (**4e** : **5e,** 95 : 5, dr, 55 : 45, 87% ee), and this with both enantiomers of the pymox ligand (***ent*-2** and **2**, see Table 4, entry 3 for comparison). Only a slight increase in the branched-to-linear ratio was noticed. The observed enantioselectivity is only due to the effect of ligand **2**.

Conclusions

In conclusion, dual-catalysis with $Mg(OTf)_2$ allows a wider scope of substrates. The results show that the Lewis acidic metal cation plays a role in the activation of one of the intermediates prior to the decarboxylation—and the β-ketoacetate leaving group in particular.[20] In addition, the metal cation influences the nature of the nucleophilic species since a clear effect on the regioselectivity of the reaction is observed by varying the nature of the metal or its ligands. Current studies are pursing the identification of effective chiral Lewis acidic complexes able to act in synergy with a CpRu-based catalyst.

Experimental

General remarks

Unless otherwise stated, solvents and chemicals were purchased and used as received. Deuterated chloroform was filtered through a plug of basic alumina prior to use. NMR spectra were recorded on Brucker ARX-400 and AMX-500 spectrometers. ^{1}H NMR chemical shifts are given in ppm relative to Me_4Si with solvent resonances used as internal standards. Data are reported as follows: chemical shift (δ) in ppm on the δ scale, multiplicity (s = singlet, d = doublet, t = triplet, h = septuplet, dd = doublet of doublet, dt = doublet of triplet, and m = multiplet), coupling constant (*J*) in Hz. Electrospray ionization mass spectra were obtained on a Finnigan SSQ 7000 spectrometer at the Department of Mass Spectroscopy of the University of Geneva. Optical rotations were measured by optical rotary dispersion (ORD) on a JASCO P-1030 polarimeter in a thermostated (20 °C) 10.0 cm-long microcell with high-pressure sodium lamps. Determination of the enantiomeric purity of compounds was achieved by chiral stationary phase (CSP) high-performance liquid chromatography (CSP-HPLC) on an Agilent LC-1100 HPLC equipped with a binary pump, an autosampler, a column thermostat and a diode

array detector, or by CSP-GC on a Hewlett Packard 6890 GC equipped with an autosampler and a flame ionization detector. Determination of the branched-to-linear ratios was achieved by GC-MS on a Agilent 6890 GC-MS using a capillary column HP-5. ATR-IR spectra were recorded with a Perkin-Elmer 1650 FT-IR spectrometer using a diamond ATR Golden Gate sampler.

β-Ketoesters **3a**, **3c**, **3d**, **3f** and **3g** were prepared by DMAP-catalyzed addition of the corresponding allylic alcohols to diketene.[21] β-Ketoesters **3b**, **3e** and **3h** were prepared using a transesterification procedure. A scheme showing the preparation of these starting materials is included in the ESI.†

Compounds **3a**–**3h** and **7** have spectral characteristics identical to those already described in the literature.[7a,f]

Cinnamyl prop-1-en-2-yl carbonate (6). Cinnamyl prop-1-en-2-yl carbonate (**6**) was synthesised following a literature procedure[22] and obtained as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.50–7.30 (m, 5H), 6.80 (d, ^3J(H–H) = 16 Hz, 1H), 6.40 (dt, ^3J(H–H) = 16 Hz, ^3J(H–H) = 6.5 Hz, 1H), 4.93 (d, ^2J(H–H) = 1.5 Hz, 1H), 4.88 (dd, ^3J(H–H) = 7 Hz, ^4J(H–H) = 1 Hz, 2H), 4.82–4.76 (m, 1H), 2.07 (d, ^2J(H–H) = 1 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.0 (1C), 152.9 (1C), 136.0 (1C), 135.2 (1C), 128.7 (2C), 128.3 (1C), 126.8 (2C), 122.1 (1C), 102.0(1C), 68.7 (1C), 19.2(1C). MS (EI): 218 (1), 174 (3), 117 (100), 115 (25). ATR-IR (neat): 1747, 1672, 1447, 1378, 1269, 1198 966, 931, 741, 691 cm^{-1}. Low-resolution ESI-MS: 218 (1%), 117 (100%). Please see the ESI for the GC-MS trace and ^{1}H and ^{13}C NMR spectra.†

CpRu-Catalyzed Carroll rearrangement—dual-catalysis procedure

In a typical procedure, in a 2 mL screw-cap vial equipped with a magnetic stirring bar, [CpRu(η^6-naphthalene)][PF_6] **1** (5.3 mg, 0.012 mmol, 2 mol%) and ligand **2** (8.1 mg, 0.033 mmol, 4.4 mol%) were dissolved in 0.6 mL dry THF. The vial was flushed with argon and capped. After heating for 1 h at 60 °C, the vial was cooled to room temperature (~25 °C) and allyl β-ketoester **3a** (150 mg, 0.6 mmol) was added in one portion followed by $Mg(OTf)_2$ (2.0 mg, 0.006 mmol, 1 mol%) and the vial was flushed again with argon and stirred at room temperature for 24 h. The cooled reaction mixture was diluted with 1.5 mL of ether–pentane (60 : 40). After precipitation, the metal salts were filtered off on a short SiO_2 column (0.5 cm × 4 cm, elution ether–pentane, 60 : 40); the solvents were then evaporated under reduced pressure to afford the crude reaction mixture (**4a** + **5a**) as a pale yellow oil which was analysed (^{1}H NMR, GC-MS, CSP-GC, ORD) without further purification. Compounds **4a**–**4f**, **5g** and **4h** have already been reported in the literature and all general data collected fit the previous description.[7,23]

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