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Allylic Alkylation

[(*p*-Cymene)$RuCl_2$]$_2$: An Efficient Catalyst for Highly Regioselective Allylic Alkylations of Chelated Amino Acid Ester Enolates

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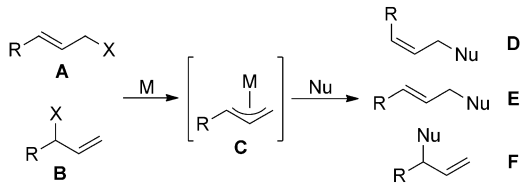
Abstract: Chelated amino acid ester enolates are excellent nucleophiles for ruthenium-catalyzed allylic alkylations. Although [Cp*Ru(MeCN)$_3$]PF_6 was found to be the most reactive catalyst investigated, with the resulting allyl complexes reacting at temperatures as low as −78 °C, unfortunately the process took place with only moderate regio- and diastereoselectivity. In contrast, [(*p*-cymene)$RuCl_2$]$_2$ allowed allylations to be performed with a high degree of regioretention. Secondary allyl carboxylates with a terminal double bond were found to be the most reactive substrates, giving rise to the branched amino acids with perfect regioretention and chirality transfer. In this case, no isomerization of the Ru–allyl complex formed in situ was observed, in contrast to the analogues palladium complexes. This isomerization-free protocol can also be used for the synthesis of (*Z*)-configured γ,δ-unsaturated amino acid derivatives, starting from (*Z*)-allylic substrates. Here, the more reactive phosphates were found to be superior to the carboxylates, providing the required amino acids in almost quantitative yield with perfect regio- and stereoretention. Therefore, the Ru-catalyzed allylation reactions are well positioned to overcome the drawbacks of Pd-catalyzed processes.

Introduction

Transition-metal-catalyzed allylic alkylations have become powerful and efficient tools in organic synthesis, allowing a wide range of C–C and C–heteroatom couplings.[1] Although, in earlier days the scenery was clearly dominated by the Pd-catalysts, during the last one or two decades a range of other late-transition-metals have made their way into the limelight.[1,2] This significantly increased the synthetic potential of this protocol, because each transition metal has its own characteristics and can show different reaction behavior compared with palladium. For examples, if terminal allyl complexes (**C**) are formed, either from linear (**A**) or from branched substrates (**B**), the regioselectivity of the nucleophilic attack on the allyl complex strongly depends on the transition metal used (Scheme 1). Whereas π-allyl palladium complexes are generally attacked at the sterically least hindered position (generating the linear products **D** and **E**), other metals such as Mo, W, or Ir give rise to the branched product **F** preferentially.[2] In contrast, Rh[3] or Ru[4] show a high tendency for regioretention, although especially in case of Ru, the regioselectivity strongly depends on the Ru-catalyst used.[4] Considering that the Ru-catalyzed process does not necessarily require the conversion of an allylic alcohol into a better leaving group, but can be used directly,[5] the Ru-catalyzed allylation is still rather underdeveloped.



Scheme 1. Transition-metal-catalyzed allylic substitution.

In their pioneering work, Tsuji et al. investigated allylations of β-ketoesters using branched allyl carbonate **B** (Scheme 1, R = Me, X = OCOOEt).[6] They found [$RuH_2(PPh_3)_3$] to be a highly active catalyst, giving rise to a mixture of substitution products (**D**/**E**/**F** = 10:58:32) that was similar to the ratio obtained with Pd- and Ni-complexes, but contrary to Rh-catalysts, which delivered the branched product **F** preferentially. Watanabe observed a "Rh-type" regioselectivity when using [Ru(cod)(cot)] (cod: cyclooctadiene, cot: cyclooctatriene).[7] They also observed, that complexes such as [(η^3-allyl)$Ru(CO)_3Br$] show ambiphilic behavior, reacting both as electrophiles (in allylic alkylations) and as nucleophiles (in carbonyl additions).[8]

In general, a high tendency towards the branched product is observed for Ru-complexes containing Cp* as an electron-donating, sterically demanding ligand.[8b] Excellent reactivities and selectivities were described for [Cp*Ru(MeCN)$_3$]PF_6 by Trost et al. in 2002.[9] Independent of the substrates (**A** or **B**) used, almost identical yields and regioselectivities were obtained, clearly indicating that the same π-allyl-Ru-complex **C** (M = Ru) is formed. This situation is comparable to the Pd-catalyzed reactions, although the nucleophilic attack occurs preferentially

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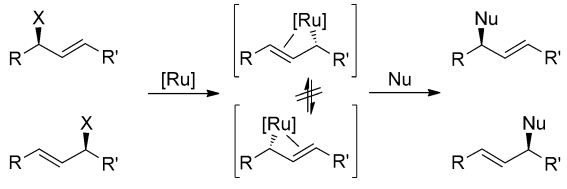
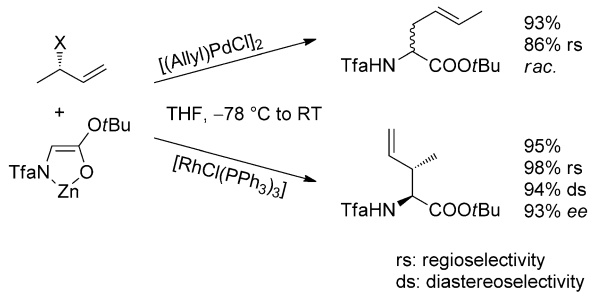
at the sterically more hindered position (comparable to Ir, Mo and W-catalysts). When optically pure substrates of type **B** were used, complete chirality transfer into the product was observed, indicating that the Ru-π-allyl-complexes do not undergo π-σ-π-isomerization as the Pd-complexes do. Based on these observations, a range of different Cp*-Ru-complexes have been developed and evaluated, especially by the groups of Bruneau[10] and Pregosin.[11] The high regioselectivity obtained with these types of complexes can be explained by the formation of an unsymmetric π-allyl-Ru-complex and a strong shielding effect of the Cp* ligand.[12] Enantiomerically enriched branched alkylation products **F** can not only be obtained from enantiomerically pure **B**, but also from the linear substrates **A** by using chiral ligands on Ru.[13] Interestingly, the opposite regioselectivities were observed with $[Ru_3(CO)_{12}]$ and the bidentate diphenylphosphinylbenzoic acid (DPPBA) ligand, which gives rise to the linear products almost exclusively.[14]

A different reaction behavior is found in allylations catalyzed by $[(p\text{-cymene})RuCl_2]_2/PPh_3$ as reported by Kawatsura.[15] With this catalyst, a high degree of regioretention is observed with linear as well as with branched allylic substrates. This effect is not only observed with terminal allylic substrates such as **A** and **B**, but also with 1,3-disubstituted systems, and a perfect chirality transfer (retention) is found with this catalyst. However, the catalytic activity of the cymene–Ru complex is lower compared with the Cp* system. Although these substrates undergo allylic substitution with most nucleophiles at room temperature, the cymene complex requires higher temperatures for allylations of the "standard nucleophile" malonate.[16] Although the mechanistic details of this divergent reaction behavior is not yet understood, it could be assumed that the cymene–Ru complexes do not react via a (unsymmetrical) π-allyl-intermediate, but more via a (σ-π)-enyl-type complex, as proposed for Rh-catalyzed reactions.[3] In this case, the regio- and stereoretention can be explained by an *anti*-S_N2' formation of the (σ-π)-enyl-Ru complex, which is also attacked in an *anti*-S_N2' mode by the nucleophile, resulting in overall retention (Scheme 2).

In the previously reported allylations using Ru-complexes, mainly stabilized carbanions such as malonates and β-ketoesters have been used, as well as several hetero-nucleophiles such as amines,[14b,17] alcohols,[18] or thiols.[5c,19] Recently, we reported the Ru-catalyzed allylic alkylations of chelated amino acid ester enolates leading to γ,δ-unsaturated amino acid derivatives.[20] Our group has been investigating reactions of chelated enolates of amino acids[21] and peptides[22] with π-allyl complexes for several years and observed a number of interesting effects.[23] Compared with the standard nucleophiles (malonates, etc.) the chelated enolates show the high reactivity of "nonstabilized" enolates combined with a (thermal) stabilization through the chelating metal salt. Thus, these enolates do not need to be reacted at 0 °C or room temperature (as is the case for malonates) but can be allylated at temperatures as low as −78 °C or even lower. This allows isomerization processes in Pd-catalyzed reactions to be suppressed,[22d,24] and results in excellent selectivities in Rh-catalyzed processes (Scheme 3).[25] Herein, we describe in detail the evaluation of Ru-catalyzed allylations of chelated glycine enolates.



Scheme 2. Proposed reaction mode of $(cymeneRuCl_2)_2$-catalyzed allylations with regio- and stereoretention ([Ru] = $cymeneRuL_2$).



Scheme 3. Allylic alkylations of chelated enolates (Tfa = trifluoroacetyl).

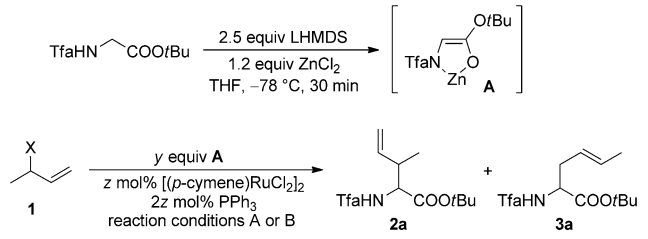
Results and Discussion

We started our investigations under the optimized conditions found in Pd- and Rh-catalyzed reactions. Trifluoroacetic acid (TFA)-protected *tert*-butylglycinate (TfaGlyO*t*Bu) was used as a Zn-chelated enolate, because this enolate gave by far the best yields and selectivities (Scheme 3). The allyl substrate was used in excess to favor complete conversion of the enolate. As catalyst, we used Kawatsura's $[(p\text{-cymene})RuCl_2]_2/PPh_3$ (5 mol%) because of its high regioretention and chirality transfer. We used several leaving groups that gave good results in previous investigations. Whereas allyl carbonates and carboxylates were excellent substrates in Pd-catalyzed allylations, phosphates have been found to be superior in Rh-catalyzed processes. The results are summarized in Table 1.

Surprisingly, the yields obtained were only moderate, and were, in all cases, in the range of 16 to 20%, independent of the leaving group. The regioselectivity towards the branched product **2a**[23d] was excellent for allyl carbonate **1a** and carboxylates **1b** and **1c** (Table 1, entries 1–3), but was significantly lower with phosphate **1d** (entry 4). Even more surprising was the completely unselective formation of **2a** observed with this leaving group, whereas good selectivities were obtained with the carboxylates (entries 2 and 3).

To increase the yield, we decided to take advantage of the thermal stability of the chelated enolates. In contrast to normal, nonchelated ester enolates, which decompose during warming to temperatures higher than −20 °C, the chelated enolates can be heated in tetrahydrofuran (THF) to reflux for several hours without decomposition. Therefore, after warming the reaction mixtures to room temperature overnight (Meth-

Table 1. Ru-catalyzed allylic alkylations using secondary allyl carboxylates and phosphates.



Entry	1	X	y	z	Method[a]	Yield [%][b]	Ratio[c] 2a/3a	Ratio 2a[c] anti/syn
1	1a	OCOOEt	0.5	2.5	A	16	98:2	78:22
2	1b	OAc	0.5	2.5	A	20	99:1	90:10
3	1c	OBz	0.5	2.5	A	20	99:1	89:11
4	1d	$OPO(OEt)_2$	0.5	2.5	A	18	88:12	52:48
5	1b	OAc	0.5	2.5	B	33	99:1	89:11
6	1c	OBz	0.5	2.5	B	50	98:2	87:13
7	1d	$OPO(OEt)_2$	0.5	2.5	B	70	88:12	49:51
8	1c	OBz	1.2	5	A	76	98:2	88:12
9	1c	OBz	1.5	5	A	83	98:2	88:12
10	1e	OCOO*t*Bu	1.5	5	A	81	99:1	89:11
11	1e	OCOO*t*Bu	1.5	2	A	82	99:1	90:10
12	1e	OCOO*t*Bu	1.5	1	A	73	99:1	89:11

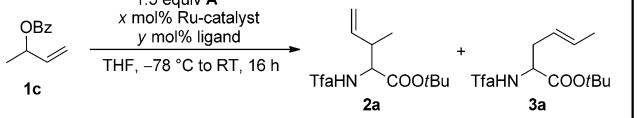
[a] Reaction conditions: Method A: THF, −78 °C to RT, 16 h; Method B: THF, −78 °C to RT, 16 h, 60 °C, 3 h. [b] Yield calculated based on the minor component. [c] Ratios determined by GC analysis (ChiraSil-Val). LHMDS = lithium hexamethyl disilazide; Bz = benzoyl.

od A) they were then heated to 60 °C for 3 h (Method B). Indeed, under these conditions, the yields could be increased significantly without affecting the regio- and stereoselectivity (Table 1, entries 5–7). With phosphate **1d**, a yield of 70% could be obtained, which is acceptable (entry 7), but the yields of the carboxylates were still moderate. Therefore, we next varied the substrate/enolate ratio to investigate this influence. Allylbenzoate **1c** was used as substrate, and a strong increase of the yield was observed when the enolate was used in (slight) excess (entries 8 and 9) even under the milder reaction conditions A. In this case, 5 mol% Ru-catalyst/**1c** was used. The best results were obtained with 1.5 equiv enolate, and the use of a higher excess resulted in no further improvement. A comparable result was obtained with carbonate **1e** (entry 10), and this substrate was also used to also investigate the amount of catalyst required (entries 10–12). With 2 mol% catalyst almost the same yields and selectivities were obtained, whereas reducing the amount to only 1 mol% resulted in a slight drop to 73%, but was still in a preparatively useful range. Based on these results, we used 1.2–1.5 equiv enolate/substrate and 2 mol% catalyst for our further investigations.

In a second set of experiments, we investigated the influence of the catalyst/ligand system on the regio- and stereoselective outcome of the reaction.

According to Kawatsura and Itoh,[15] added PPh_3 initiates the dissociation of the dimeric Ru-complex through formation of $[(cymene)RuCl_2(PPh_3)_3]$,[26] which actually enters the catalytic cycle. Therefore, because one might expect an influence of this dissociating ligand on the reaction, we screened a set of phosphanes, phosphites as well as carbene ligands (Table 2).

Table 2. Influence of ligands on Ru-catalyzed allylic alkylations of secondary allyl benzoate **1c**.



Entry	Ru catalyst	x	ligand	y	Yield [%]	Ratio[d] 2a/3a	Ratio 2a[d] anti/syn
1	$[(p\text{-cymene})RuCl_2]_2$	5	PPh_3	10	83	98:2	88:12
2	$[(p\text{-cymene})RuCl_2]_2$	5	P(2-furyl)$_3$	10	83	98:2	88:12
3	$[(p\text{-cymene})RuCl_2]_2$	5	P(*o*-tolyl)$_3$	10	55	98:2	86:14
4	$[(p\text{-cymene})RuCl_2]_2$	5	PCy_3[a]	10	71	95:5	72:28
5	$[(p\text{-cymene})RuCl_2]_2$	5	$P(OMe)_3$	10	62	98:2	87:13
6	$[(p\text{-cymene})RuCl_2]_2$	5	$P(OEt)_3$	10	82	98:2	84:16
7	$[(p\text{-cymene})RuCl_2]_2$	5	$P(OPh)_3$	10	46	90:10	75:25
8	$[(p\text{-cymene})RuCl_2]_2$	5	MeCN	10	54	91:9	79:21
9	$[(p\text{-cymene})RuCl_2]_2$	2	SIMes·HCl[b]	4	75	96:4	81:19
10	$[(p\text{-cymene})RuCl_2]_2$	2	SIPr·HCl[c]	4	82	95:5	78:22
11	$[RuCl_2(PPh_3)_3]$	2	–		36	90:10	54:46
12	$[Cp^*Ru(MeCN)_3]PF_6$	2	–		92	73:27	82:18

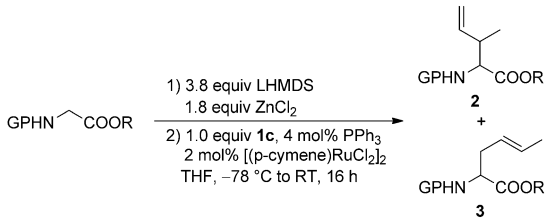
[a] Cy = cylohexyl. [b] SIMes = *N*,*N*′-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene. [c] SIPr = *N*,*N*′-bis(2,6-diisopropyl)imidazolin-2-ylidene. [d] Ratios determined by GC analysis (ChiraSil-Val).

Replacing PPh_3 by P(furyl)$_3$ had no influence on the reaction at all. Probably for steric reasons, the catalyst obtained with P(*o*-tolyl)$_3$ was slightly less active, although the selectivity was unchanged, indicating that the attack of the nucleophile on the Ru-allyl intermediate is subject to electronic rather than steric control.[27] Interestingly, a significant drop in the diastereoselectivity was observed in the presence of PCy_3. With phosphite ligands, a comparable degree of regioretention was found (Table 2, entries 5 to 7). The diastereoselectivity decreased with increasing steric demand of the ligand. Addition of the bidentate ligand dppe completely suppressed the reaction, probably by blocking the free coordination side on the catalyst.

The dissociating ligand does not necessarily have to be a P-ligand. Acetonitrile does the same job, and the results obtained herewith were comparable to those obtained with $P(OPh)_3$ (Table 2, entry 8). This forced us to investigate also the influence of some carbene ligands, as well as other Ru-catalysts. The carbene complexes were found to be nearly as active as the PPh_3 complex but slightly less regioselective; the diastereoselectivity was worse (entries 9 and 10). A significant drop in both yield and diastereoselectivity was observed when $[RuCl_2(PPh_3)_3]$ was used (entry 11). By far the most active catalysts were the RuCp* complexes, which all gave excellent yield, but unfortunately by far the lowest regioselectivity (entry 12). Therefore, we used the original $[(cymene)RuCl_2]_2/PPh_3$ catalyst for subsequent investigations. It should be mentioned that, in all cases, the linear product (*E*)-**3** was formed exclusively.

Besides the catalyst, the structure of the attacking nucleophile should also have a strong influence. With this assumption, we also varied the protecting groups on the glycine (Table 3). In analogy to Pd- and Rh-catalyzed allylations, by far the most selective reactions were observed with the *N*-Tfa-pro-

Table 3. Influence of the protecting groups (PG) on the chelated enolate.



Entry	PG	R	Yield [%]	Major product	Ratio[a] 2/3	Ratio 2[a] *anti*/*syn*
1	Tfa	*t*Bu	83	**2a**[23d]	98:2	88:12
2	Tfa	Me	74	**2b**[28]	99:1	74:26
3	Boc	*t*Bu	86	**2c**	99:1	60:40
4	Cbz	*t*Bu	79	**2d**	99:1	71:29
5	Cbz	Me	74	**2e**[28]	99:1	40:60
6	Ts	Me	57	**2f**[28]	99:1	33:67

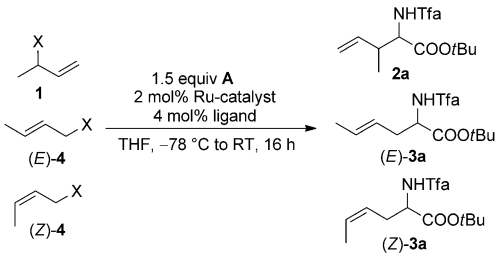
[a] Ratios determined by GC analysis (ChiraSil-Val). Boc = *tert*-butoxycarbonyl; Cbz = carbobenzyloxy.

tected *t*-butyl glycinate (entry 1) used in the optimization studies. The corresponding methyl ester (entry 2) was significantly less diastereoselective. Even worse was the situation with the carbamate protecting groups (entries 3–5). The Boc-protected *t*-butyl ester gave the branched product as an almost 1:1 mixture. With the Cbz-protected derivative, the *anti*-selectivity was slightly better, but the corresponding methyl ester provided even the *syn* diastereomer preferentially (entries 4 and 5). So far, the highest *syn*-selectivity was obtained with the N-tosylated methyl ester. From these results, a clear tendency can be observed: The *anti*-isomer is favored by small N- and large O-protecting groups, and vice versa for the *syn*-isomer. The yields obtained were generally good, and the regioselectivity was almost perfect, irrespective of the glycine derivative used.

Although no influence of the nucleophile on the degree of regioretention was found, there should be an influence by the allylic substrate used. The position of the leaving group on the allyl moiety might have an influence, as well as the nature of the substituents (aliphatic or aromatic). Therefore, we compared the results obtained with branched **1c** with those obtained with the linear crotyl derivatives (*E*)- and (*Z*)-**4c** (Table 4). Whereas the reaction of the branched substrate **1c** started at −55 °C to give the branched product **2c** in good yield and excellent regioselectivity (entry 1), the linear substrates were found to be significantly less active. Here, the temperature needed to be increased to −35 °C to initiate the reaction. The yields obtained were also much lower, even when the reaction mixture was warmed to room temperature (entries 2 and 3). Whereas **1c** and (*E*)-**4c** gave the branched product **2c** with almost the same *anti*/*syn*-selectivity, the (*Z*)-substrate reacted almost completely unselectively. In contrast, the regioselectivity was better in the case of (*Z*)-**4c** (compared with (*E*)-**4c**). Interestingly, absolutely no isomerization was observed. Application of **1c** and (*E*)-**4c** resulted in the formation of (*E*)-**3a** exclusively, whereas only (*Z*)-**3a** was obtained from (*Z*)-**4c**. The allyl-Ru complex formed in situ from the (*Z*)-substrate clearly differs significantly from complexes formed from (*E*)-**4c** and **1c**, which might be similar (same diastereoselectivity for **2c**). The different degree of regioretention (88 vs. 72%) might be a result of the higher reaction temperature required for the reaction of (*E*)-**4c**. To test this conclusion, we also investigated the corresponding phosphates, which we found to be more reactive, although less selective, at least in the case of branched substrate **2d**. Indeed, all the substrates reacted smoothly at −78 °C, albeit without any diastereoselectivity.

As observed previously, the branched substrate **2d** also reacted without significant regioretention, whereas the regioselectivity of the linear substrates increased, probably because of the lower reaction temperature. Especially the (*Z*)-configured phosphate provided (*Z*)-**3a** almost exclusively (Table 4, entry 6).

Table 4. Allylic alkylations using primary and secondary allylic substrates.



Entry	Substrate	X	Cat.[a]	Ligand	Yield [%]	Ratio[b] 2/(*E*)-3/(*Z*)-3	Ratio 2[b] *anti*/*syn*
1	**1c**	OBz	A	PPh_3	83	98:2:0	88:12
2	(*E*)-**4c**	OBz	A	PPh_3	43	28:72:0	88:12
3	(*Z*)-**4c**	OBz	A	PPh_3	34	12:0:88	41:59
4	**1d**	$OPO(OEt)_2$	A	PPh_3	90	64:36:0	39:61
5	(*E*)-**4d**	$OPO(OEt)_2$	A	PPh_3	93	20:80:0	55:45
6	(*Z*)-**4d**	$OPO(OEt)_2$	A	PPh_3	85	1:0:99	n.d.
7	**1c**	OBz	A	SIPr	75	96:4:0	81:19
8	(*E*)-**4c**	OBz	A	SIPr	44	40:60:0	90:10
9	(*Z*)-**4c**	OBz	A	SIPr	30	13:0:87	44:56
10	**1c**	OBz	A	SIMes	82	95:5:0	78:22
11	(*E*)-**4c**	OBz	A	SIMes	20	19:81:0	75:25
12	(*Z*)-**4c**	OBz	A	SIMes	21	16:0:84	51:49
13	**1c**	OBz	B	–	92	73:27:0	82:18
14	(*E*)-**4c**	OBz	B	–	41	45:55:0	86:14
15	(*Z*)-**4c**	OBz	B	–	13	49:0:51	36:64

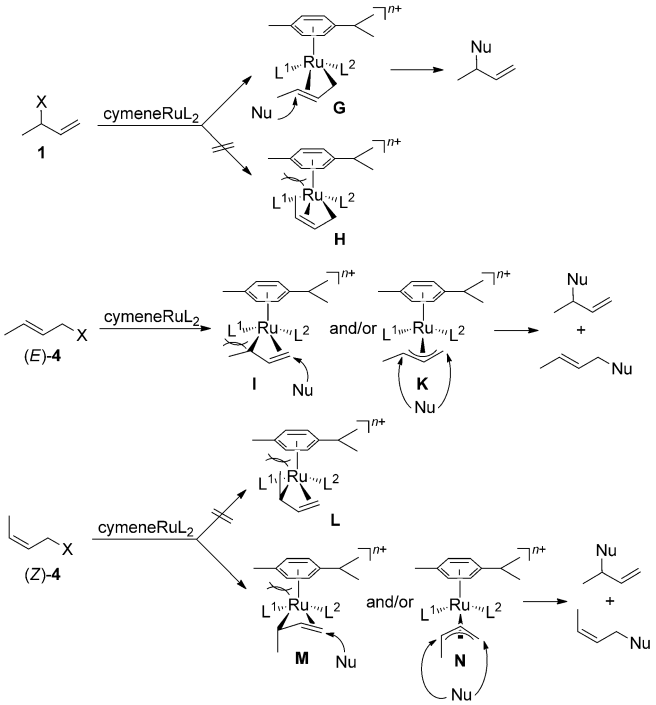
[a] Catalyst A: $[(p\text{-cymene})RuCl_2]_2$; Catalyst B: $[Cp^*Ru(MeCN)_3]PF_6$. [b] Ratios determined by GC analysis (ChiraSil-Val). n.d. = not determined.

These results clearly indicate that **1d** and (*E*)-**4d** do not form the same allyl-Ru-intermediate, otherwise the regioselectivity should be similar. For comparison, we also investigated the influence of the ligand, using the carbene ligands SIPr and SIMes (entries 7–12). The same tendency was observed as with PPh_3. The branched substrate **1c** was the most reactive and most regioselective, although the diastereoselectivity was slightly lower compared with the phosphane catalyst. The linear substrates gave only very moderate yields, especially in the case of the SIMes-ligand, for which the yield dropped to 20%, whereas 80% yield was obtained with **1c** (entries10–12). The same effect was also observed in reactions catalyzed by the Trost catalyst (entries 13–15), which was also the least selective. In this case, a large difference in the reactivity was observed between (*E*)-**4c** and (*Z*)-**4c**. Whereas the (*E*)-isomer already started to react at $-78\,^{\circ}C$, the (*Z*)-isomer required warming to $-15\,^{\circ}C$, and even then the yield was only 13% (entry 15).

These studies clearly indicate that branched allylic alcohols should be activated as carboxylates such as benzoate (**1**), and that phosphates are the leaving group of choice for linear substrates **4**, especially the (*Z*)-isomers. In these cases, an excellent degree of regioretention can be obtained, in combination with good yield and diastereoselectivity. With respect to selectivity, the cymene-catalyst is superior to the Cp* complex, while this is the more reactive one. The diastereoselectivities of the reaction leading to **2a** from **1c** and (*E*)-**4c** are comparable, whereas the degree of regioretention differed significantly.

The high levels of regioretention obtained with **1c** can be nicely explained by a double S_N'-type mechanism (Scheme 4). Nucleophilic attack of the sterically demanding Ru-complex on the sterically unhindered terminal position of **1c** should provide an σ-allyl-Ru complex. Coordination of the (*E*)-double bond towards the Ru generates an $(\sigma+\pi)$-enyl complex **G**, which is attacked by the nucleophile in a S_N'-mode. In principle, a (*Z*)-double bond can also be formed in the S_N' step, but, in this case, the methyl substituent should interact with the cymene ring on the Ru (**H**). This would explain why no (*Z*)-**3c** is formed from **1c**. In principle, the scenario should be comparable for the linear substrates **4**, although a nucleophilic attack of the Ru complex on the substituted double bond should be sterically hindered, which can explain the higher reaction temperatures required and the lower yields. Reaction of (*E*)-**4c** should give rise to a secondary σ-Ru bond with significant interactions of the methyl substituent and the ligands on Ru. This steric repulsion should extend the σ-bond, and shorten the π-bond (**I**), generating a situation very close to a π-allyl complex (**K**). Nucleophilic attack on such an intermediate should be less regioselective compared with the "unhindered" $(\sigma+\pi)$-enyl complex **G**. Nevertheless, such a π-allyl complex **K** should be structurally rather similar to **G**, and nucleophilic attack at the sterically more hindered positions should proceed in a similar way. This would explain the comparable diastereoselectivities obtained for **2a**.

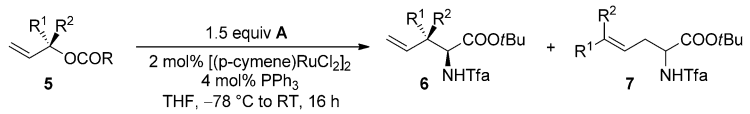
The situation is different in the case of (*Z*)-**4c**. If this substrate reacts in an analogous fashion to those of the two other substrates, a $(\sigma+\pi)$-enyl complex **L** should be formed with an axial methyl group interacting directly with the cymene ligand, comparable to intermediate **H**. The fact that no (*Z*)-**3a** is formed from **1c** indicates that such a scenario probably does not occur. This might explain the lower reactivity of the (*Z*)-substrates compared with the (*E*)-isomers. Probably the allyl ligand coordinates the other way round with the methyl-substituent distal to the cymene ligand (**M**, **N**). The resulting different complex geometry might explain the completely different reaction behavior of the (*Z*)-substrate. Probably, the $(\sigma+\pi)$-enyl complex is formed first, as indicated by the excellent regioselectivity observed with (*Z*)-**4a** at $-78\,^{\circ}C$. During warm-up, isomerization towards a π-allyl complex becomes reasonable, resulting in a drop of regioselectivity.



Scheme 4. Mechanistic proposal for Ru-catalyzed allylic alkylations.

To evaluate the scope and limitations of this protocol, we subjected a range of branched allylic acetates and benzoates **5** to our optimized reaction conditions (Table 5).[20] Replacing the methyl group of **1a** (entry 1) by a linear alkyl chain or by an isopropyl substituent resulted in a decrease of regio- and stereoselectivity (entries 2 and 3). In contrast, good regioselectivities were obtained with tertiary benzoates (entry 4) and aryl-substituted substrates (5 and 6). An excellent yield was obtained with the *p*-brominated substrate **5e**, and the halogenated amino acid **6e** should be a suitable substrate for further modifications through cross-coupling reactions. Considering that no isomerizations were observed during our previous studies, we also subjected some enantiomerically enriched allylic substrates to our reaction conditions to investigate the chirality transfer (entries 7–9). In all examples, perfect chirality transfer was observed, indicating that the Ru-catalyzed process is an important alternative to the Pd-catalyzed reactions, which result in complete loss of the stereogenic information if terminal π-allyl complexes are formed.

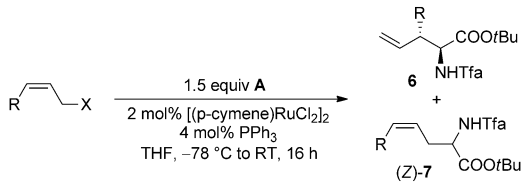
Table 5. Allylic alkylations using secondary allyl carboxylates **5**.



Entry	Substrate	Config.	*ee* [%]	R	R^1	R^2	Yield [%]	Major product	Ratio[a] **6**/**7**	Ratio **6**[a] *anti*/*syn*	Config. **6**	*ee* [%]
1	**1c**	(*R*/*S*)	–	Ph	Me	H	83	**2a**	98:2	88:12	(*R*/*S*)	–
2	**5a**	(*R*/*S*)	–	Me	Pent	H	90	**6a**	89:11	83:17	(*R*/*S*)	–
3	**5b**	(*R*/*S*)	–	Ph	*i*Pr	H	87	**6b**	84:16	40:60	(*R*/*S*)	–
4	**5c**	(*R*/*S*)	–	Ph	Me	Me	86	**6c**	98:2	–	(*R*/*S*)	–
5	**5d**	(*R*/*S*)	–	Me	Ph	H	75	**6d**	96:4	81:19	(*R*/*S*)	–
6	**5e**	(*R*/*S*)	–	Ph	*p*-BrPh	H	98	**6e**	96:4	71:29	(*R*/*S*)	–
7	**1c**	(*S*)	96	Ph	Me	H	87	**2a**	97:3	83:17	(2*S*,3*S*)	96
8	**5d**	(*R*)	97	Me	Ph	H	97	**6d**	97:3	82:18	(2*S*,3*R*)	97
9	**5f**	(*S*)	95	Ph	Et	H	83	**6f**	97:3	76:24	(2*S*,3*S*)	95

[a] Ratios determined by GC analysis (ChiraSil-Val).

Table 6. Allylic alkylations using (*Z*)-allyl substrates **4**.



Entry	Substrate	X	R	Yield [%]	Ratio[a] **6**/(*Z*)-**7**	Product
1	(*Z*)-**4f**	OBz	Et	56	7:93	**7f**[25]
2	(*Z*)-**4g**	OBz	$CH_2OTBDMS$	40	3:97	**7g**[24d]
3	(*Z*)-**4h**	$OPO(OEt)_2$	CH_2OPMP	95	1:99	**7h**[24d]
4	(*Z*)-**4i**	$OPO(OEt)_2$	CH_2OBn	98	1:99	**7i**[24d]

[a] Ratios determined by GC analysis (ChiraSil-Val). TBDMS = tert-butyldimethylsilyl; PMP = *p*-methoxphenyl.

The second big advantage of the Ru-catalyzed process compared with the Pd-protocol is the isomerization-free allylation with the (*Z*)-configured allylic substrates. To establish whether the excellent results observed especially with (*Z*)-**4d** are general, we subjected a range of functionalized substrates to our reaction conditions (Table 6). The general trend that allylic phosphates are superior to benzoates was confirmed. The ethyl substituted benzoate (*Z*)-**4f** gave better results than the previously investigated (*Z*)-**4c**. The functionalized substrates (*Z*)-**4g–i** reacted with perfect regioretention, providing the (*Z*)-configured linear products (*Z*)-**7** exclusively. With the phosphates, almost quantitative yield was obtained.

Conclusion

We have shown that $[(cymene)RuCl_2]_2$-catalyzed allylic alkylations are a powerful alternative to Pd-catalyzed reactions. Especially with highly reactive chelated enolates, the reactions take place free of isomerization with excellent regioretention and chirality transfer. This allows the stereoselective synthesis of β-branched amino acids from secondary allyl carboxylates, whereas linear (*Z*)-configured amino acids are obtained from the corresponding phosphates. Applications of these reactions for the modification of peptides and natural products are under investigation.

Experimental Section

General remarks

All air- or moisture-sensitive reactions were carried out in dried glassware (>100 °C) under an atmosphere of nitrogen. Dried solvents were distilled before use: THF was distilled from $LiAlH_4$, CH_2Cl_2 was dried with CaH_2 before distillation. The products were purified by flash chromatography on silica gel columns (Macherey–Nagel 60, 0.063–0.2 mm). Mixtures of ethyl acetate and hexane were generally used as eluents. Analytical TLC was performed on pre-coated silica gel plates (Macherey–Nagel, Polygram SIL G/UV254). Visualization was accomplished with UV-light and $KMnO_4$ solution. Melting points were determined with a MEL-TEMP II apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a Bruker AC-400 [400 MHz (^1H) and 100 MHz (^{13}C)] spectrometer in $CDCl_3$. Chemical shifts are reported in ppm relative to TMS, and $CHCl_3$ was used as the internal standard. Selected signals for the minor regio- and diastereomers are extracted from the spectra of the isomeric mixture. Regioisomeric and diastereomeric ratios were determined by GC analysis using an L-ChiraSilVal capillary column (25 m × 0.25 mm). Nitrogen was used as carrier gas. Mass spectra were recorded with a Finnigan MAT 95 spectrometer using the CI technique. Elemental analyses were performed at Saarland University. All compounds not described here have been reported previously.[20,23d,24d,27]

Synthesis of starting materials

Allylic alcohols as precursors for **1a–e** and **5c** were purchased from commercial suppliers. The racemic precursors for the other esters **5**, were prepared by addition of vinylmagnesiumbromide to the corresponding aldehyde. The (*Z*)-configured alcohol required for the (*Z*)-substrates (*Z*)-**4c** and (*Z*)-**4d** was obtained by ether cleavage of 2,5-dihydrofuran[29] and the (*E*)-isomer was obtained by reduction of (*E*)-crotyl ethyl ester.[30] The racemic allylic alcohols were converted into the benzoates, acetates, carbonates, and phosphates by standard methods. Compounds (*Z*)-**4h** and (*Z*)-**4i** were prepared as described previously.[24d] Compounds (*S*)-**1c** and (*S*)-**5f** were obtained by the method described by Feringa et al.[31] The enzymatic racemic resolution of **5d** using the immobilized lipase Novozyme 450 gave allylic acetate (*R*)-**5d**.[32]

Ruthenium-catalyzed allylic alkylations; General procedure

A solution of hexamethyldisilazane (335 mg, 2.07 mmol) in THF (2.0 mL) was prepared in a Schlenk flask under nitrogen. After the solution was cooled to −20 °C, a solution of *n*-butyllithium (1.6 M in hexanes, 1.17 mL, 1.88 mmol) was added slowly, the cooling bath was removed, and stirring was continued for 10 min. The solution was cooled to −78 °C and the TFA-protected *tert*-butyl glycinate (171 mg, 0.75 mmol), dissolved in THF (1 mL), was added to

the freshly prepared LHMDS solution. After 10 min, a solution of dried $ZnCl_2$ (123 mg, 0.90 mmol) in THF (1.0 mL) was added and stirring was continued for 30 min at −78 °C.

A solution was prepared from $[(p\text{-cymene})RuCl_2]_2$ (6.4 mg, 0.01 mmol) and triphenylphosphane (5.2 mg, 0.02 mmol) in THF (1 mL), and stirred for 5 min at RT, during which time it became red. The allyl substrate (0.50 mmol) was added and the resulting solution was added slowly to the chelated enolate at −78 °C. The mixture was allowed to warm to RT overnight. The solution was diluted with diethyl ether (20 mL) before 1 M $KHSO_4$ (10 mL) was added. After separation of the layers, the aqueous layer was extracted twice with diethyl ether and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude product was purified by flash chromatography (SiO_2). The isomeric ratios were determined by CG analysis of the crude product (before chromatography). The configuration was assigned according to reported data of the predominant, known compounds.

***tert*-Butyl 2-(*N*-*tert*-butyloxycarbonylamino)-amino-3-methyl-4-pentenoate (2c)**: According to the general procedure for ruthenium-catalyzed allylic alkylations *N*-Boc-protected *tert*-butyl glycinate (171 mg, 0.75 mmol) was reacted with allyl benzoate **1c** (88 mg, 0.50 mmol). Flash chromatography (silica gel; hexanes/ethyl acetate, 95:5) gave rise to a diastereomeric mixture (*anti*/*syn*, 6:4) of **2c** in 86% yield (123 mg, 0.43 mmol) as a colorless oil and as a single regioisomer (rs: 99:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ (*anti*-**2c**, 60%) = 1.08 (d, J = 6.9 Hz, 3H; CHCH_3), 1.44 (s, 9H; CCH_3), 1.46 (s, 9H; CCH_3), 2.72 (m, 1H; C*H*CH$_3$), 4.17 (m, 1H; C*H*NH), 4.92 (d, J = 8.5 Hz, 1H; NH), 5.04–5.12 (m, 2H; CHCH_2), 5.72 ppm (m, 1H; C*H*CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0 (q, CHCH_3), 28.0 (q, CCH_3), 28.3 (q, CCH_3), 40.4 (d, *C*HCH$_3$), 58.0 (d, *C*HNH), 79.6 (s, OCCH$_3$), 81.8 (s, OCCH$_3$), 116.3 (t, CHCH$_2$), 138.0 (d, *C*HCH$_2$), 155.7 (s, NCO), 170.9 ppm (s, *C*OO); ^{1}H NMR (400 MHz, $CDCl_3$): δ (*syn*-**2c**; 40%, selected signals) = 1.04 (d, J = 7.0 Hz, 3H; CHCH_3), 2.62 (m, 1H; C*H*CH$_3$), 5.02 ppm (d, J = 8.5 Hz, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3 (q, CHCH$_3$), 40.9 (d, *C*HCH$_3$), 57.7 (d, *C*HNH), 81.9 (s, OCCH$_3$), 115.7 (t, CHCH$_2$), 139.0 (d, *C*HCH$_2$), 155.4 (s, NCO), 170.7 (s, *C*OO); GC (L-Chirasil-Val; 80 °C, 10 min, 80 °C to 180 °C, 1 °C min^{-1}, 20 min): t_R = 47.93 (2*R*,3*R*), 49.15 (2*R*,3*S* + 2*S*,3*S*), 50.15 (2*S*,3*R*) min; HRMS (CI): m/z calcd for $C_{15}H_{28}NO_4$: 286.2013 $[M+H]^+$; found: 286.2021.

***tert*-Butyl 2-(*N*-benzyloxycarbonylamino)-amino-3-methyl-4-pentenoate (2d)**: According to the general procedure for ruthenium-catalyzed allylic alkylations, *N*-Cbz-protected *tert*-butyl glycinate (199 mg, 0.75 mmol) was reacted with allyl benzoate **1c** (88 mg, 0.50 mmol). Flash chromatography (silica gel; hexanes/ethyl acetate, 95:5) gave rise to a diastereomeric mixture (*anti*/*syn*, 71:29) of **2d** in 79% yield (126 mg, 0.39 mmol) as a colorless oil and as a single regioisomer (rs: 99:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ (*anti*-**2d**; 71%) = 1.09 (d, J = 6.9 Hz, 3H; CHCH_3), 1.46 (s, 9H; CCH_3), 2.76 (m, 1H; C*H*CH$_3$), 4.27 (dd, J = 8.8, 4.5 Hz, 1H; C*H*NH), 5.04–5.10 (m, 2H; CHCH_2), 5.11 (m, 2H; CH_2Ph), 5.18 (d, J = 8.7 Hz, 1H; NH), 5.67 (m, 1H; C*H*CH$_2$), 7.27–7.37 ppm (m, 5H; Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9 (q, CHCH$_3$), 28.0 (q, CCH$_3$), 40.3 (d, *C*HCH$_3$), 58.4 (d, *C*HNH), 66.9 (t, CH$_2$Ph), 82.1 (s, OCCH$_3$), 116.6 (t, CHCH$_2$), 128.1 (d, Ar*C*), 128.1 (d, Ar*C*), 128.5 (d, Ar*C*), 136.3 (d, *C*HCH$_2$), 137.7 (s, Ar*C*), 156.2 (s, NCO), 170.5 ppm (s, *C*OO); ^{1}H NMR (400 MHz, $CDCl_3$): δ (*syn*-**2d**; 29%, selected signals) = 1.06 (d, J = 7.0 Hz, 3H; CHCH_3), 2.65 (m, 1H; C*H*CH$_3$), 5.28 ppm (d, J = 9.0 Hz, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2 (q, CHCH$_3$), 40.9 (d, *C*HCH$_3$), 58.1 (d, *C*HNH), 116.0 (t, CHCH$_2$), 138.7 ppm (d, *C*HCH$_2$); GC (Chirasil-Val; 80 °C, 10 min, 80 °C to 180 °C, 1 °C min^{-1}, 20 min): t_R = 106.54 (34%; 2*R*,3*R*), 107.33 (14%; 2*R*,3*S*), 107.61 (36%; 2*S*,3*S*), 108.19 (15%; 2*S*,3*R*) min; (*E*)-**3d**: t_R = 113.87 (< 1%; 2*R*), 115.09 (< 1%; 2*S*) min; elemental analysis calcd (%) for $C_{18}H_{25}NO_4$ (319.40): C 67.69, H 7.89, N 4.38; found: C 67.51, H 7.92, N 4.48.

***tert*-Butyl 3-isopropyl-2-(trifluoroacetamido)pent-4-enoate (6b)**: According to the general procedure for ruthenium-catalyzed allylic alkylations *N*-TFA-protected *tert*-butyl glycinate (171 mg, 0.75 mmol) was reacted with allyl benzoate **5b**[33] (79 mg, 0.39 mmol). Flash chromatography (silica gel; hexanes/ethyl acetate, 98:2) gave rise to a mixture of **6b** (*anti*/*syn*, 40:60) and **7b** (**6b**/**7b**, 84:16) in 87% yield (105 mg, 0.34 mmol) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (*syn*-**6b**; 60%) = 0.89 (d, J = 6.9 Hz, 3H; CHCH_3), 1.10 (d, J = 6.6 Hz, 3H; CHCH_3), 1.49 (s, 9H; CCH_3), 1.78 (m, 1H; CCH_3), 2.04 (ddd, J = 10.4, 9.1, 5.3 Hz, 1H; NCHC*H*), 4.68 (dd, J = 8.2, 5.2 Hz, 1H; NC*H*), 5.07 (dd, J = 16.9, 1.8 Hz, 1H; CHCH_2), 5.22 (dd, J = 10.1, 1.8 Hz, 1H; CHCH_2), 5.47 (ddd, J = 16.9, 10.4 Hz, 10.4 Hz, 1H; C*H*CH$_2$), 6.81 ppm (br s, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.6 (q, CHCH$_3$), 28.0 (q, CHCH$_3$), 28.4 (d, *C*HCH$_3$), 53.4 (d, *C*HNH), 55.0 (d, NCHCH), 83.4 (s, *C*CH$_3$), 115.7 (q, J = 287.9 Hz, *C*F$_3$), 120.0 (t, CHCH$_2$), 135.0 (d, *C*HCH$_2$), 156.7 (s, $J_{8,F}$ = 37.7 Hz; CF$_3$*C*O), 169.4 ppm (s, *C*OO); ^{1}H NMR (400 MHz, $CDCl_3$): δ (*anti*-**6b**; 40%, selected signals) = 0.90 (d, J = 7.0 Hz, 3H; CHCH_3), 1.02 (d, J = 6.6 Hz, 3H; CHCH_3), 1.47 (s, 9H; CCH_3), 1.66 (m, 1H; CCH_3), 2.28 (ddd, J = 9.7, 8.0, 4.7 Hz, 1H; NCHC*H*), 4.70 (dd, J = 8.7, 5.1 Hz, 1H; NC*H*), 5.11 (dd, J = 16.6, 1.7 Hz, 1H; CHCH_2), 5.23 (dd, J = 10.3, 1.8 Hz, 1H; CHCH_2), 5.55 (dd, J = 16.7, 10.3, 9.6 Hz, 1H; C*H*CH$_2$), 6.55 (br s, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2 (q, CHCH$_3$), 19.7 (q, CHCH$_3$), 28.1 (d, *C*HCH$_3$), 53.9 (d, *C*HNH), 54.4 (d, NCHCH), 83.1 (s, *C*CH$_3$), 120.0 (t, CHCH$_2$), 134.0 (d, *C*HCH$_2$), 168.6 ppm (s, *C*OO). ^{1}H NMR (400 MHz, $CDCl_3$): δ [(*E*)-**7b**; selected signals] = 2.54 (m, 2H; NCHCH_2), 4.50 (dt, J = 7.5, 5.3 Hz, 1H; NC*H*), 5.19 (m, 1H; CH$_2$C*H*CHCH), 5.51 (m, 1H; CH$_2$CHC*H*CH), 6.81 ppm (br s, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.8 (t, NCHCH$_2$), 52.7 (d, NCH), 119.1 (d, CH$_2$CHCH), 132.8 (d, CH$_2$CHCH); GC (L-Chirasil-Val; 80 °C, 10 min, 80 °C to 180 °C, 1 °C min^{-1}, 20 min): t_R = 28.39 (**6b**, 2*R*,3*R*), 29.21 (**6b**, 2*R*,3*S*), 34.10 (**6b**, 2*S*,3*R*), 34.64 (**6b**, 2*S*,3*S*), 37.71 [(*E*)-**7b**, 2*R*], 42.45 [(*E*)-**7b**, 2*S*] min; HRMS (CI): m/z calcd for $C_{14}H_{22}F_3NO_3$: 309.1552 $[M]^+$; found: 309.1468.

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Keywords: allylation · amino acids · enols · regioselectivity · ruthenium

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