ORGANIC LETTERS

2010
Vol. 12, No. 21
4960−4963

Highly Regioselective Ruthenium-Catalyzed Allylic Alkylations of Chelated Enolates†

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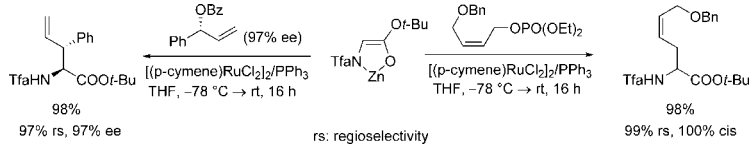
Received September 3, 2010

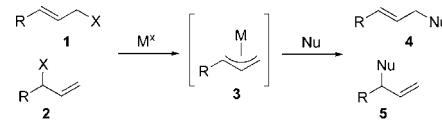
ABSTRACT



Ru-catalyzed allylic alkylations are a highly interesting alternative to Pd-catalyzed reactions. Ru complexes show a high tendency for regioretention, especially for branched and (*Z*)-configured substrates, and they do not undergo isomerization of the allyl intermediates formed. Therefore, (*Z*)-substrates conserve their olefin geometry, and a perfect chirality transfer is observed with optically active substrates.

π-Allyl metal complexes play a major role in modern organic synthesis as key intermediates of a wide range of C−C and C−heteroatom couplings.[1] The scenery is clearly dominated by Pd catalysts, but during the last years a range of other metals, especially late transition metals, made their way into the limelight.[2] This clearly increases the potential of allylation chemistry because these metals show significantly different reaction behavior compared to palladium (Scheme 1). For example, if terminal π-allyl complexes (**3**) are formed either from linear (**1**) or from branched substrate (**2**), the Pd-catalyzed allylation provides the linear substitution product (**4**) preferentially, while Mo, W, and Ir give rise to the branched product (**5**).[2] However, especially with Pd catalyst, the control of the regioselectivity (rs) is not a trivial issue.[3] On the other hand, Rh shows a high degree of regioretention,

Scheme 1. Transition Metal Catalyzed Allylic Alkylations



although with a tendency toward the branched product.[4] A similar behavior is also observed for Ru complexes. With respect, that with these catalysts allylic alcohols can be used without further activation[5] and that besides C-nucleophiles also amines,[6] alcohols,[7] or thiols[8] can be allylated, the Ru-catalyzed allylations are still rather underdeveloped.[9]

Trost et al.[10] and Bruneau et al.[11] reported regio- and stereoselective allylations of various nucleophiles at room temperature using $[Cp^*Ru(NCCH_3)]PF_6$ as a catalyst, which

† Dedicated to Prof. Dr. G. Helmchen on the occasion of his 70th birthday.

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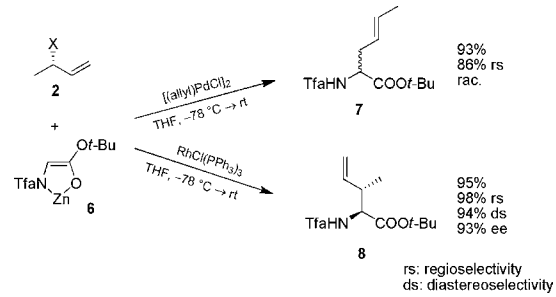
10.1021/ol102106v
Published on Web 09/24/2010

proved to be superior compared to the sterically less demanding [CpRu(NCCH$_3$)]PF$_6$ catalyst. Comparable product ratios (**4**/**5**) were obtained, independent of the substrate used (**1** or **2**), indicating that the reaction proceeds via a π-allyl complex, comparable to the Pd-catalyzed process. The formation of π-allyl intermediates was also confirmed by detailed mechanistic work from the Pregosin group.[12] The stereochemical outcome of the reaction can be explained by a double inversion mechanism, as discussed for Pd complexes,[1] but in contrast to the Pd-catalyzed process, a complete chirality transfer can be observed in reactions of optically pure substrates **2**. Obviously, the Ru$-\pi$-allyl complexes do not undergo $\pi-\sigma-\pi$-isomerization as do the Pd complexes.[12] Although Tunge et al. observed a partial racemization in decarboxylative allylations of optically active β-keto allylic esters, in this case an isomerization of the allylic substrate (**2** → **1**) was responsible for the fading ee and not a $\pi-\sigma-\pi$ isomerization.[13]

Obviously, the effect of ligands is tremendous in this reaction. The product ratio can be shifted nearly completely to the linear product **4**, if *o*-phosphinobenzoic acid/Ru$_3$(CO)$_{12}$ is used as catalyst,[14] while [RuCl$_2$(*p*-cymene)]$_2$ shows excellent regioretention.[15] This allows a clean conversion of the linear substrate **1** into the linear product **4** and branched **2** into **5**. This outcome can not be explained via a common π-allyl intermediate (**3**) but is an indication for a σ-allyl- or a σ-enyl-complex, as also discussed in Rh-catalyzed processes.[4]

For some time, our group has investigated Pd-catalyzed allylic alkylations of chelated enolates such as **6** (Scheme 2), obtained from amino acid esters[16] and peptides.[17] On the basis of their high reactivity, these enolates react under much milder conditions compared to the generally used stabilized enolates, offering new synthetic options.[18] For example, at

Scheme 2. Transition Metal Catalyzed Allylic Alkylations of Chelated Enolates

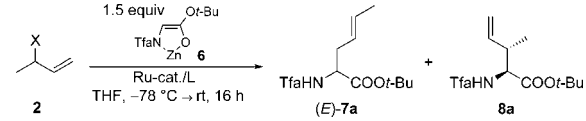


−78 °C the $\pi-\sigma-\pi$ isomerization of the π-allyl Pd intermediates can be suppressed almost completely,[19] allowing regioselective attack at the different allylic positions[20] and the more or less isomerization-free reaction of (*Z*)-substrates.[21] Nevertheless, substrates forming terminal allyl complexes are critical candidates. If optically active substrates **2** are used, complete epimerization is observed, as a consequence of the fast $\pi-\sigma-\pi$-isomerization.

This forced us to focus our efforts also on the Rh-catalyzed version. And indeed, with Wilkinson's catalyst the branched product **8** was obtained preferentially, and a nearly perfect chirality transfer was obtained with optically active substrates.[22] However, herewith, only terminal, monosubstituted allyl substrates **2** showed good conversion, and good branched-selectivities were only observed for allylic substrates with small substituents, such as **2a**. With sterically more demanding substrates also the linear product is formed, clearly indicating that in Rh-catalyzed a π-allyl complex formation can not be neglected.

Therefore, we were interested to find an alternative catalytic system showing a broader substrate spectrum but with properties similar to the Rh catalysts, and we investigated the allylic alkylation of our chelated enolates in the presence of various Ru catalysts using racemic butenyl-3-benzoate **2a** as a model

Table 1. Optimization of Ru-Catalyzed Allylic Alkylations



entry	subs.	X	Ru cat./ L[a]	yield [%]	ratio **7a**:**8a**	ratio (**8**) *anti*:*syn*
1	**2a**	OBz	4% cat. A	36	10:90	54:46
2	**2a**	OBz	2% cat. B	92	27:73	82:18
3	**2a**	OBz	2% cat. B 2% PPh$_3$	98	22:78	79:21
4	**2a**	OBz	2% cat. C	83	2:98	88:12
5	**2b**	OAc	2% cat. C	88	4:96	89:11
6	**2c**	OCOO*t*Bu	2% cat. C	81	1:99	90:10

[a] Catalyst systems: cat. A: RuCl$_2$(PPh$_3$)$_3$; cat. B: [Cp*Ru(MeCN)$_3$]PF$_6$; cat. C: [(*p*-cymene)RuCl$_2$]$_2$/2 PPh$_3$.

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(14) Kawatsura, M.; Ata, F.; Wada, S.; Hayase, S.; Uni, H.; Itoh, T. *Chem. Commun.* **2007**, 298–300.

(15) Kawatsure, M.; Ata, F.; Hayase, S.; Itoh, T. *Chem. Commun.* **2007**, 4283–4285.

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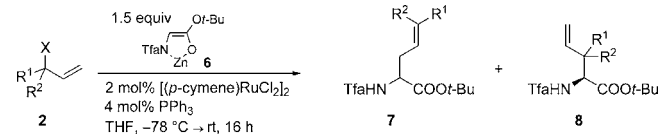
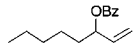
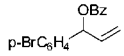
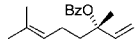
Table 2. Ru-Catalyzed Allylic Alkylations of Chelated Enolates **6**



2 7 8

entry	substrate	ee [%]	yield [%]	major product	ratio 7:8	ratio (8) *anti*:*syn*	ee (8) [%]	chirality transfer [%]
1	(*S*)-**2a** 	96	87	(2*S*,3*S*)-**8a**	3:97	83:17	95	99
2	(*S*)-**2d** 	95	83	(2*S*,3*S*)-**8d**	3:97	76:24	95	100
3	(±)-**2e** 	--	92	(±)-**8e**	6:94	86:14		
4	(*R*)-**2f** 	97	98	(2*S*,3*R*)-**8f**	3:97	82:18	97	100
5	(±)-**2g** 	--	98	(±)-**8g**	4:96	71:29		
6	**2h** 	--	66	(±)-**8h**	2:98	--		
7	(*S*)-**2i** 	96	55	(2*S* /*R*,3*S*)-**8i**	5:95	50:50	95	99

substrate (Table 1). A slight excess of the enolate was used to allow a complete consumption of the allylic substrate. First, reactions were carried out with $RuCl_2(PPh_3)_3$ (cat. A) which showed that, in principle, the reaction is possible and that the branched product is formed preferentially, but the yield and diastereoselectivity were low (entry 1). Therefore, we next switched to the Cp*−Ru complex (cat. B) introduced by Trost,[10] which provided the allylation product in excellent yield and good diastereoselectivity, although in this case the regioselectivity dropped to 73% (entry 2). Addition of phosphines such as PPh_3 had only a marginal effect, both on the yield and selectivities (entry 3).

The best results were obtained with $[(p\text{-cymene})RuCl_2]_2$/2 PPh_3 (cat. C) which provided the branched product nearly exclusively with high *anti*-selectivity and in good yield (entry 4). The yield was a little lower compared to the Cp* complexes (cat B), probably because of a slightly lower reactivity of the cymene complex. Other leaving groups, such as the corresponding acetate (**2b**) or carbonate (**2c**) can be used as well, without significant influence on the yield and selectivity (entries 5 and 6). It should be mentioned that in all examples investigated the (*E*)-configured linear product (*E*)-**7a** was formed exclusively.

To prove the generality of these observations and to evaluate the scope and limitations of this protocol, we subjected a wide range of other allylic substrates **2** (including optically active ones) to our optimized reaction conditions (Table 2). With all optically active substrates used, a perfect chirality transfer was observed. This clearly indicates that no epimerization occurs under the reaction conditions used.

This is a great advantage compared to the Pd-catalyzed processes and comparable to the Rh-catalyzed reactions. Prolonging the side chain had no great influence on the yield and selectivities (entries 1−3). Excellent results were obtained with aryl-substituted substrates (entries 4 and 5) providing the branched product nearly exclusively in almost quantitative yield. A comparable regioselectivity was also observed with substrates with the leaving group at a quaternary center (entries 6 and 7). In this case, the yield dropped to 50−60%, probably because of sterical hindrance in the Ru-coordination step. However, it should be mentioned that no reactions are observed with these substrates under Rh-catalyzed conditions.

As another interesting substrate, we investigated dienoate **2k** (Scheme 3). This type of substrate gives mixtures of products under Pd-catalyzed conditions because both double bonds can form π-allyl complexes and the complexes can easily isomerize. Therefore, in general the conjugated dienes are formed preferentially, even with the highly reactive chelated enolates.[23] However, with the Ru catalyst also a

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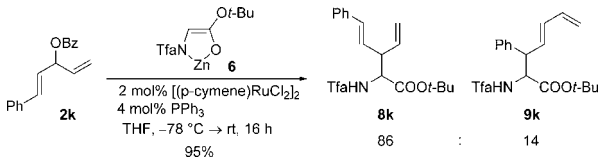
Scheme 3. Ru-Catalyzed Allylic Alkylations Using Dienoates



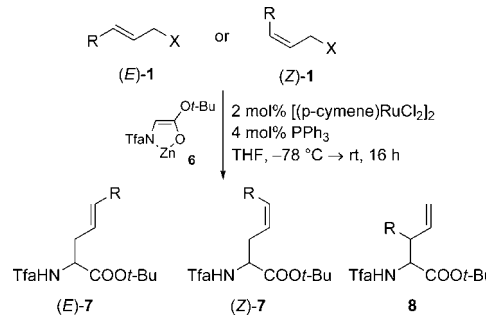
high degree of regioretention was observed, combined with an excellent yield. The conjugated product **9k** was formed only in 14% yield. The unbranched, linear product (**7k**) was not formed at all.

Last but not least, we focused our interest also on linear allylic substrates **1**. In general, under Pd-catalyzed conditions these substrates give the linear substitution products preferentially as an (*E*/*Z*)-mixture, with the (*E*)-product as the major one. Under certain circumstances, we were able to conserve the (*Z*)-olefin geometry (at least in part) in reactions of (*Z*)-substrates,[21] but this is still not a trivial issue and requires careful optimizations of the reaction conditions. Therefore, the Ru-catalyzed process would fill an important synthetic weak spot.

On the basis of the results obtained with the benzoates, we subjected linear (*E*)- and (*Z*)-configured substrates **1a** to the usual reaction conditions (Table 3, entries 1 and 2). Compared to the terminal substrate **2a**, the reactions were much slower, and the yields dropped dramatically, down to 15% in the case of the (*Z*)-substrate (entry 2). However, out of three possible products, only two were formed in each reaction. The substitution product obtained by regioretention was the major product. This clearly indicates that no isomerization had occurred. With respect to our previous good experience in Rh-catalyzed reactions with allylic phosphates, we tried to increase the yields by using these leaving groups. Indeed, the corresponding phosphates **1b** gave the required substitution product **7a** in much better yields and selectivities compared to the benzoates (entries 3 and 4). Especially the (*Z*)-substrate (*Z*)-**1b** provided nearly exclusively the product (*Z*)-**7a** with complete retention of the substitution position and olefin geometry.[24] This general trend could be confirmed with further, also functionalized,

(24) All isomeric ratios and ee values were determined by GC using the chiral column Chira-Si-*L*-Val.

Table 3. Ru-Catalyzed Allylic Alkylations Using Linear Substrates **9**



entry	substrate	R	X	yield [%]	ratio (*E*)-**7**:(*Z*)-**7**:**8**
1	(*E*)-**1a**	Me	OBz	32	68:0:32
2	(*Z*)-**1a**	Me	OBz	15	0:84:16
3	(*E*)-**1b**	Me	$OPO(OEt)_2$	93	80:0:20
4	(*Z*)-**1b**	Me	$OPO(OEt)_2$	85	1:98:1
6	(*Z*)-**1l**	CH_2OPMP	$OPO(OEt)_2$	95	0:98:2
7	(*Z*)-**1m**	CH_2OBn	$OPO(OEt)_2$	98	0:99:1

examples, such as the *p*-methoxyphenyl (pmp) ether **1l** or the benzylated derivative **1m** (entries 5 and 6).

In conclusion, we could show that Ru-catalyzed allylic alkylations are a highly interesting alternative to Pd- or Rh-catalyzed reactions. The investigated Ru complexes show a high tendency for regioretention, especially with (*Z*)-configured substrates, which are critical candidates in Pd-catalyzed reactions. The allyl intermediates formed do not undergo isomerization, comparable to Rh complexes, but the Ru complexes show a larger substrate spectrum. Further investigations with other allylic substrates as well as synthetic applications are currently underway.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft (Ka 880/8-2) and by the Fonds der Chemischen Industrie.

Supporting Information Available: Experimental procedures as well as analytical and spectroscopic data of all allylation products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102106V