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Authors: Bernhard Breit and Lukas Hilpert

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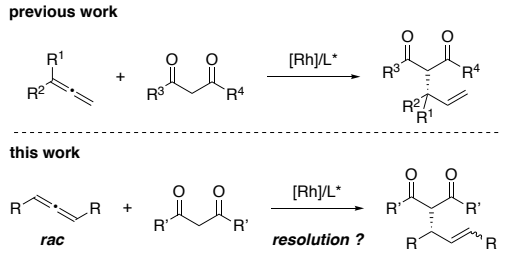
Rhodium-Catalyzed Parallel Kinetic Resolution of Racemic Internal Allenes Towards Enantiopure Allylic 1,3-Diketones

Lukas J. Hilpert and Bernhard Breit*

Abstract: *A rare case of a parallel kinetic resolution of racemic 1,3-disubstituted allenes by means of a rhodium-catalyzed addition to 1,3-diketones furnishing enantiopure allylic 1,3-diketones is described. Mechanistic experiments demonstrate that the different allene enantiomers react to either the diastereomeric E- or Z-allylic 1,3-diketones with the same absolute configuration of the newly formed stereogenic center. A broad substrate scope demonstrates the synthetic utility of this new method.*

The development of novel catalytic and atom efficient C-C and C-heteroatom-bond forming reactions is fundamental to propel a more sustainable catalytic organic synthesis. We recently reported on a series of catalytic addition reactions of pronucleophiles to allenes and alkynes,[1-3] which can be seen as atom economic variants[4] of the Tsuji-Trost reaction.[5-9] In this context we developed a regio- and enantioselective addition of 1,3-diketones to terminal allenes to form tertiary and quaternary stereocenters in high yields as well as regio- and enantioselectivities (Scheme 1).[10] Upon studies towards the extension of the substrate scope to racemic 1,3-disubstituted allenes we now came across an interesting phenomenon reported herein.



Scheme 1. Previous work on the Rh-catalyzed addition of 1,3-dicarbonyl compounds to allenes in contrast to the addition to internal allenes.

Thus, the reaction of racemic internal allene **1** with acetylacetone in the presence of a rhodium-catalyst modified with phosphoramidite **L1** and TFA as a Brønsted acid co-catalyst at room temperature furnished the addition product **4** in quantitative yield as a mixture of *E*- and *Z*-stereoisomers both in high enantioselectivities (Scheme 2).[11,12]

[*] Lukas J. Hilpert, Prof. Dr. Bernhard Breit
Institut für Organische Chemie
Albert-Ludwigs-Universität Freiburg
Albertstraße 21, 79104 Freiburg im Breisgau (Germany)
E-mail: bernhard.breit@chemie.uni-freiburg.de

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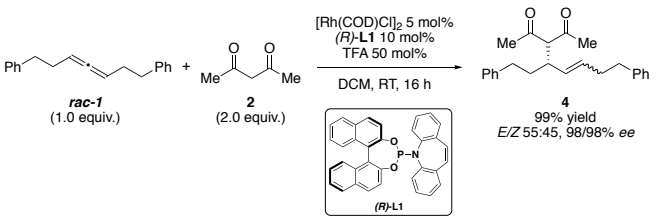
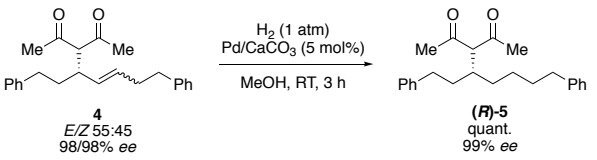


Scheme 2. Optimized reaction conditions for the rhodium-catalyzed addition of acetylacetone (**2**) to racemic internal allene ***rac*-1** using the depicted (*R*)-P-amidite ligand. Reaction was performed on a 0.25 mmol scale; DCM (c = 0.2 M). X/Y % *ee* (X: *E*-isomer, Y: *Z*-isomer). *E/Z*-value was determined by crude ^{1}H-NMR. The enantiomeric excess (*ee*) was determined by chiral HPLC. The absolute configuration of the product was determined by structural modification and comparison with previously reported literature.

Hydrogenation of **4** delivered the single enantiomer ***(R)*-5** as evidenced by chiral HPLC, proving that the absolute configuration of the newly formed stereocenter of ***E*-** and ***Z*-4** was the same (Scheme 3).



Scheme 3. Hydrogenation reaction to prove absolute configuration of ***E*-** and ***Z*-4**. *E/Z*-ratio was determined by crude ^{1}H-NMR. The enantiomeric excess (*ee*) was determined by chiral HPLC.

However, given the fact that our earlier studies on addition reactions of pronucleophiles to internal allenes showed that either *E*- or *Z*-allylic products were obtained selectively, we were curious about the origin of this low *E/Z*-selectivity. One possibility was that an *E/Z*-isomerization during the reaction could occur. Therefore we analyzed the products' *E/Z*-ratio at different levels of reaction progress (Scheme 4). Interestingly, at 10 min reaction time, product **4** was already formed in 51 % yield in an *E/Z*-ratio of 13:87 and with 99/98 % *ee*. After 16 h and even 48 h the same results as displayed in Scheme 2 were obtained (99 % yield, *E/Z* 55:45, 98/98 % *ee*). This suggested that either a subsequent slower isomerization of the *Z*-product to the *E*-isomer occurred or that there were different reaction pathways for each allene enantiomer. To exclude an isomerization process we subjected isolated product **4** (*E/Z* 15:85) to the same catalysis conditions and as the *E/Z*-ratio remained unchanged after a reaction time of 16 h, we could rule out the scenario of a subsequent alkene isomerization.

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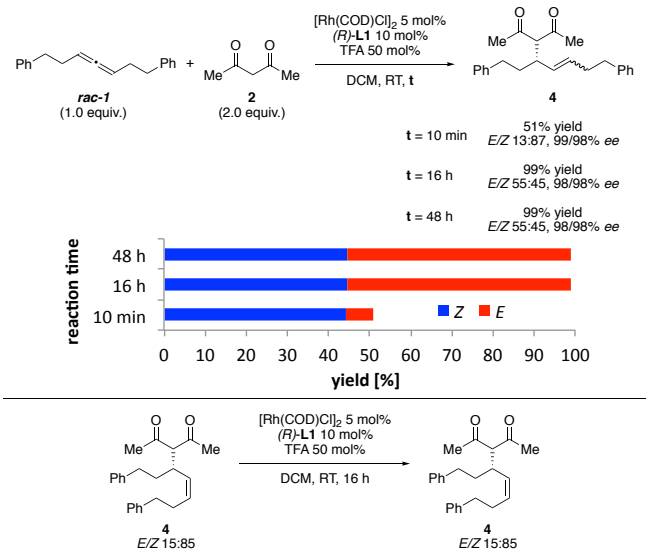
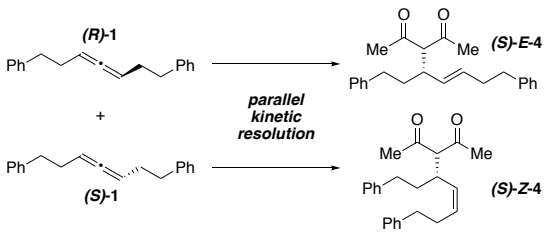


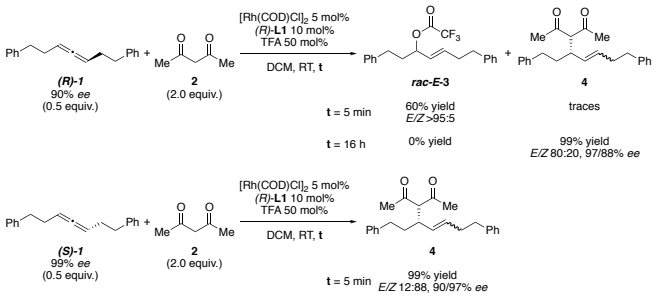
Scheme 4. Time-dependent *E/Z*-ratios for the rhodium-catalyzed addition of acetylacetone (**2**) to racemic internal allene ***rac*-1**. Reaction was performed on a 0.25 mmol scale; DCM (c = 0.2 M). Additional experiment with acetylacetone (**2**) (1.0 equiv.) showed the same result. X/Y % *ee* (X: *E*-isomer, Y: *Z*-isomer). *E/Z*-ratio was determined by crude ^{1}H-NMR. The enantiomeric excess (*ee*) was determined by chiral HPLC.

Hence, the only possible interpretation was a selective reaction pathway for each allene enantiomer to form one product diastereomer (Scheme 5). In such a scenario, the racemic substrate would undergo a rhodium-catalyzed *parallel kinetic resolution* (*PKR*). *PKR* is a rarely observed phenomenon in synthetic organic chemistry.[13,14]



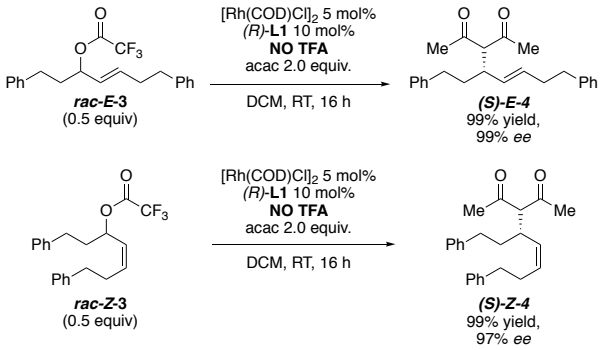
Scheme 5. Proposed *parallel kinetic resolution* for the rhodium-catalyzed addition of acetylacetone (**2**) to racemic internal allene ***rac*-1**.

To gain deeper insights into the reaction mechanism, enantiopure allenes ***(R)*-1** and ***(S)*-1** were prepared and subjected to the catalysis conditions respectively (Scheme 6). After 5 min ***(R)*-1** was converted to TFA-ester ***rac-E*-3,** whereas ***(S)-Z*-4** (*E/Z* 12:88) was formed starting from ***(S)*-1**. After 16 h TFA-ester ***rac-E*-3** was completely transformed to the final product ***(S)-E*-4** (*E/Z* 80:20).



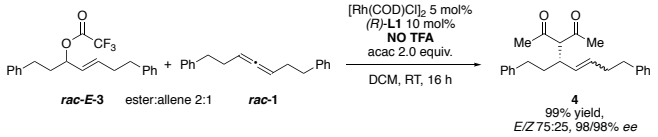
Scheme 6. Addition of acetylacetone (**2**) to enantioenriched allene ***(R)*/*(S)*-1**. Reactions display a cutout of actual catalyses starting from racemic allene **1**. 0.5 equivalents of enantioenriched allene **1** correspond to the concentration in actual catalysis starting from racemic allene **1**. Yield is based on 0.5 equiv. starting material.

This result suggested that TFA-esters could be intermediates in this reaction. For this reason, ***rac-E*-3** and ***rac-Z*-4** were prepared separately and were subjected to the catalysis reaction conditons respectively (Scheme 7). Notably, ***rac-E*-3** was transformed quantitatively and with high enantioselectivity to ***(S)-E*-4**, while ***rac-Z*-3** reacted cleanly to give ***(S)-Z*-4**.



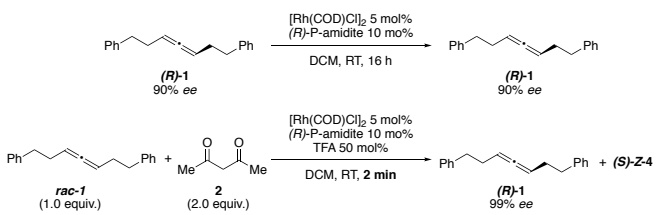
Scheme 7. Reactions to prove and clarify the role of TFA-ester **3**. Reactions display a cutout of actual catalysis starting from racemic allene **1**. 0.5 Equivalents of TFA-esters correspond to concentration in actual catalysis starting from racemic allene **1**. Yield is based on 0.5 equiv. starting material.

An additional control experiment starting from allene **1** in the absence of TFA showed no product formation. To further clarify the role of TFA, a mixture of the corresponding TFA-ester **3** and allene **1** was subjected to the catalysis conditions without adding additional TFA (Scheme 8). After 16 h reaction time, both TFA-ester and allene were completely converted to the allylation product **4**. This indicates that the TFA-ester **3** is an intermediate and the TFA is released as a leaving group to serve as the co-catalyst upon reaction with allene *rac*-**1**.



Scheme 8. Reaction to prove and clarify the role of TFA as additive. Reactions were performed in 0.25 mmol scale, DCM (c = 0.2 M). *E/Z*-value was determined by crude ^{1}H-NMR. The enantiomeric excess (*ee*) was determined by chiral HPLC.

To check whether the allene substrate is racemized in a background isomerization, we performed the catalysis with enantioenriched allene ***(R)*-1** (Scheme 9). As expected no racemization occured.[15] In an additional experiment ***rac*-1** reacted with acetylacetone (**2**) and the reaction was stopped after 2 min. This allowed to isolate remaining allene, which was essentially enantiopure with *R*-configuration.



Scheme 9. Experiments to exclude background racemization. Reactions were performed in 0.25 mmol scale, DCM (c = 0.2 M). *E*/*Z*-ratio was determined by crude ^{1}H-NMR. The enantiomeric excess (*ee*) was determined by chiral HPLC.

To get further mechanistic insights we performed the reaction in an NMR tube to monitor the reaction progress by ^{1}H-NMR spectroscopy. Under such diffusion-controlled conditions (no stirring) the reaction was significantly slower. Thus, a conversion reached in the flask experiment after 5 min reaction time needed 140 min in the NMR tube experiment.[16] The observed reaction profile is depicted in Figure 1. Indeed we were able to observe now both allylic TFA-esters ***rac*-Z-3** and ***rac*-E-3** as intermediates during catalysis. Thus, ***rac*-Z-3** is formed rapidly and reacts fast to the C-C-coupling product ***(S)*-Z-4**. Conversely, the *E*-TFA-ester is formed somewhat slower, and reacts much slower to the C-C-coupling product ***(S)*-E-4**.

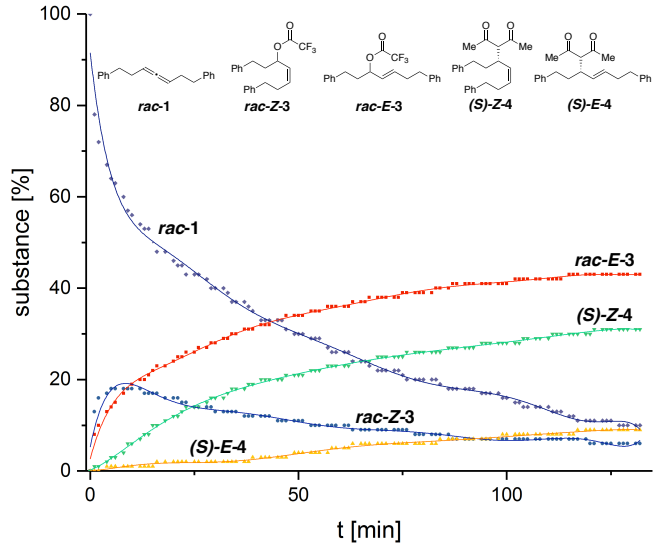
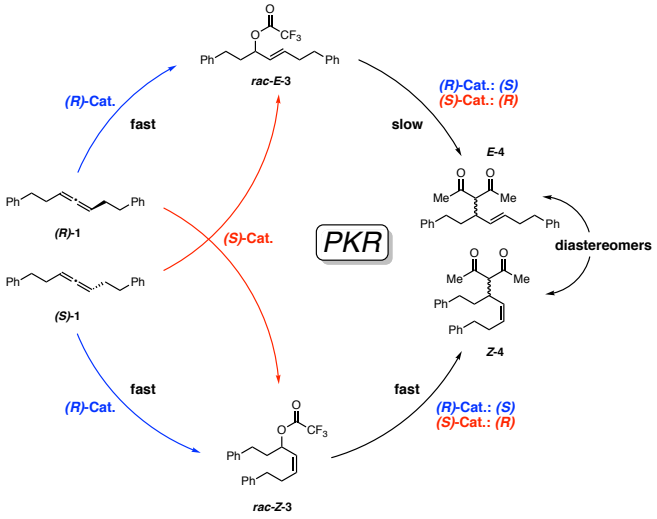


Figure 1. Reaction profile to show time depending interconversion of allene **1** and intermediates towards product **4**.

Merging all experimental data allowed to draw the mechanistic scenario depicted in Scheme 10. Thus, allene **(*R*)-1** was converted via the TFA-ester ***rac*-E-3** to ***(S)*-E-4** in 98% *ee* by the (*R*)-catalyst system **(*R*-Cat)**. In a parallel pathway the allene **(*S*)-1** reacted via the TFA-ester ***rac*-Z-3** furnishing the C-C-coupling product ***(S)*-Z-4** in 98% *ee*. Switching the stereochemistry of the P-amidite ligand of the rhodium catalyst from (*R*) to (*S*) led via the opposite diastereomeric intermediates and to the opposite absolute configuration in the final product.

Hence, the first step, the rhodium-catalyzed addition of TFA to internal allene, determined the olefin geometry but delivered TFA-esters **3** as racemates. Only the second step, the rhodium-catalyzed allylic substitution of the TFA-esters with acetylacetone determined the absolute configuration C-C coupling products in high enantioselectivity while preserving alkene geometry (see experiments shown in Scheme 7).



Scheme 10. Summarizing flow chart of *PKR* to highlight selectivity aspects depending on absolute configuration of P-amidite-ligand.

With a detailed mechanistic understanding and optimized reaction conditions in hand we explored the substrate scope (Table 1). Variations in the 1,3-diketone backbone were well tolerated. Both aliphatic (**4-8**), aromatic (**9-17**) and heteroaromatic (**18**) substituents were incorporated. Conspicuously, the *E*/*Z*-ratio was heavily depending on the obtained yield, highlighting that the formation of *E*- and *Z*-product must proceed through different pathways. Only if a ratio of nearly 50:50 is reached a quantitative yield could be achieved (cf. formation of **4**). Steric hindrance was a determining factor. Increase of hindrance from methyl- (**3**) to *t*Bu-substitution (**8**) decreased the yield from 99 % to 24 %. Relating thereto, **8** was received only as *Z*-diastereomer since the reaction pathway towards the *Z*-product is in all cases significantly faster, and less susceptible to less steric factors. For diaryl-substituted 1,3-diketones both electron-rich (**10**) and electron-poor (**11**) as well as halogen substituents (**11-14**) were well tolerated. A methyl substitutuent is well tolerated in *para*, *meta* and even *ortho* position (**15-17**). Furthermore, several other 1,3-disubstituted allenes could serve as reaction partners (**19-24**) including a macrocyclic allene substrate (**21**).

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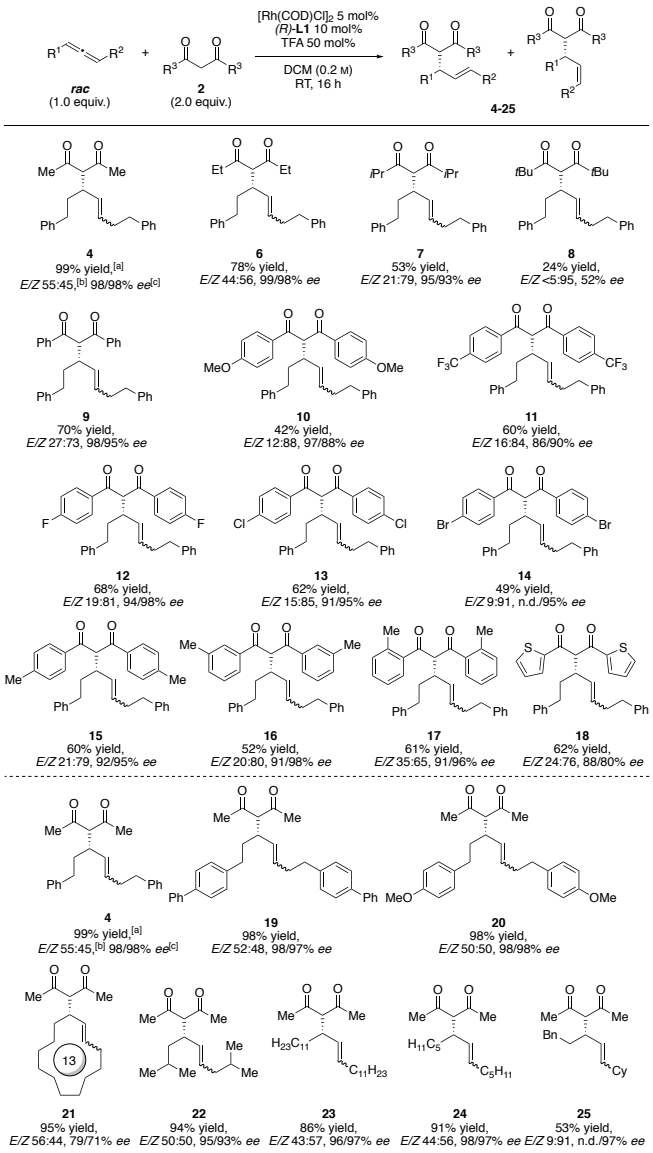
Table 1. Scope of the Rh-catalyzed *PKR* of 1,7-diphenyl-hepta-3,4-diene (**1**) with different 1,3-diketones and *PKR* of different internal allenes with acetyl acetone (**2**).



[a] Reported yields are of isolated 1,3-diketones. For substrates with steric hindrance the lower yields were accompanied by full conversion of allene **1** and detection of the *E*-TFA-ester **3** in the crude ^{1}H-NMR. [b] *E*/*Z*-ratio was determined by crude ^{1}H-NMR. [c] *ee* was determined by chiral HPLC; X/Y % *ee* (X: *E*-isomer, Y: *Z*-isomer).

To conclude, we herein described a rare case of a *parallel kinetic resolution* in the course of a rhodium-catalyzed addition of 1,3-diketones to racemic allenes. Mechanistic investigations revealed that allylic TFA-esters are passed as intermediates. In this first step alkene geometry is controlled while the second step occurs as an allylic substitution and controls the enantioselectivity in this process while preserving alkene geometry.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Parallel Kinetic Resolution • Rhodium • Asymmetric Catalysis • 1,3-Diketones • Allenes

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[11] For optimization and screening tables, see the Supporting Information.

[12] For determination of absolute configuration, see the Supporting Information.

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[15] For further experiments, see supporting information.

[16] For detailed overview about NMR-spectra monitoring the reaction, see supporting information.

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Layout 2:

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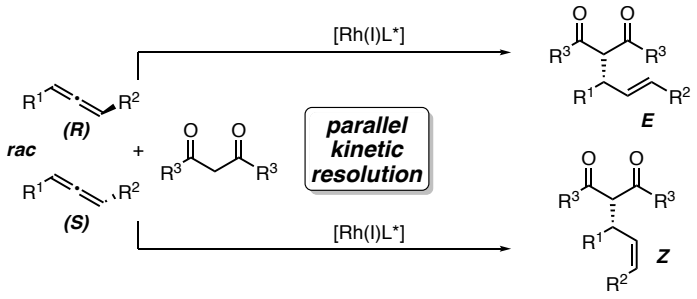

*Lukas J. Hilpert and Bernhard Breit**

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Rhodium-Catalyzed Parallel Kinetic Resolution of Racemic Internal Allenes Towards Enantiopure Allylic 1,3-Diketones

A rare case of a *parallel kinetic resolution* in the course of a rhodium-catalyzed addition of 1,3-diketones to racemic allenes is reported. Mechanistic analysis shows that each allene enantiomer reacts in parallel to either the *E*- or *Z*-allylation product in high enantioselectivity with the same absolute configuration of the newly formed stereocenter.