

Control of the Regioselectivity in Cobalt- versus Ruthenium-Catalyzed Alder-ene Reaction of Unsymmetrical 1,3-Diynes

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(5) Supporting Information



ABSTRACT: The Alder-ene reaction of trialkylsilyl-substituted 1,3-butadiynes with terminal alkenes was investigated utilizing a cobalt-based catalyst, and the results were compared with Alder-ene rections catalyzed by the $[CpRu(H_3CCN)_3]PF_6$ catalyst. Obviously, the two catalysts gave complementary results of yn-dienes differing in the site where the new carbon–carbon bond was formed. Of particular interest are observations concerning the double bond migration within the alkene component. While simple alkenes gave exclusively the *E*-configuration, the application of 3-buten-1-ol resulted in the corresponding *Z*-double bond, indicating that the hydroxyl group acts as donor coordinating to the cobalt center and thereby altering the reaction pathway.

In organic synthesis the control of a regioselective addition of an atom or a group of atoms to an unsaturated carboncarbon double or triple bond is a very basic problem to solve. In this respect, the overall addition can either generate the Markovnikov or the *anti*-Markovnikov orientation. Many examples for such regioselective carbon-heteroatom bond formations can be found in the literature.

When carbon–carbon bonds are formed in such reactions, meaning that the formal addition of a CH-bond to another unsaturated functionality is realized, the examples are far scarce.¹ In recent years, we reported a number of cobalt-catalyzed transformations where the regiochemistry of such formal CH-addition reactions can be controlled by either altering reaction conditions, such as the solvent, or just altering the ligand on the transition metal.² Among these reactions we described the cobalt-catalyzed Alder-ene reaction of internal alkynes, such as propiolate 1, with terminal alkenes (Scheme 1) for the regio- and stereoselective synthesis of *E*,*E*-1,4-diene (2).³

This reaction is highly complementary to the rutheniumcatalyzed Alder-ene reaction which led exclusively to products of type 3.⁴ Most importantly, both types of products 2 and 3are of interest, as they can be utilized for the synthesis of natural products.⁵

Scheme 1. Regiocontrol of Transition Metal Catalyzed Alder-ene Reactions of Propiolates

previous work



In this report, we describe the complementary Alder-ene reaction of 1,3-butadiynes with terminal alkenes catalyzed by either a cobalt-based catalyst system comprising $CoBr_2dppp$, zinc powder, and ZnI_2 or the ruthenium-based catalyst $[CpRu(H_3CCN)_3]PF_6$ applied excessively by Trost (Scheme 2). The possible number of products considering carbon–

Scheme 2. Ruthenium-Catalyzed Alder-ene Reaction of Silyl-Protected 1,3-Butadiynes



carbon bond formations at all four carbons (C1–C4) on the butadiyne system adds up to 16. *E/Z*-Mixtures at the α - and β - double bond (see in 5) are possible.

In 2007 Lee reported the ruthenium-catalyzed Alder-ene reaction of 1,3-butadiynes with terminal alkenes and observed that unsymmetrical 1,3-butadiynes bearing one bulky trialkyl-silyl group, such as triethylsilyl, react chemoselectively at C3 of the other triple bond to form products of type 4 in good yields (60-85%).⁶

Based on our investigation with internal alkynes (Scheme 1), we reasoned that the cobalt catalyst could alter the

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^{*a*}Reaction conditions: CoBr₂(dppp) (10 mol %), Zn, ZnI₂ (20 mol % each), butadiyne (0.5 mmol, 1.0 equiv), alkene (0.75 mmol, 1.50 equiv), CH₂Cl₂ (0.5 mL), ambient temperature. ^{*b*}The E/Z ratios of the β -double bond were determined by ¹H NMR spectroscopy. ^{*c*}Accompanied with the corresponding conjugated 1,3,5-yne-diene isomer (ratio: 86:14).

regiochemistry of the Alder-ene reaction so that the carbon– carbon bond formation takes place at C4 of the butadiyne next to the substituent R^1 to form products of type 5 instead. Accordingly, unsymmetrical butadiynes were synthesized with a trialkylsilyl-substituted alkyne subunit and either an aromatic or an aliphatic substituent (R^1) at C4; see Supporting

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Information (SI). These diynes were subjected to a cobaltcatalyzed Alder-ene reaction with terminal alkenes, and in all cases an exclusive chemoselective reaction was observed. The trialkylsilyl-substituent efficiently directed the cobalt catalyst toward the other triple bond, and the carbon—carbon bond formation was also exclusively observed at C4 in the products of type **5**. If no trialkylsilyl substituent was used, a mixture of both possible regioisomers was isolated, where the carbon carbon bond formation predominantly takes place at the less hindered carbon atom (C1 or C4) of the 1,3-diyne (Table 1, entry 16).

Based on the reaction mechanism for ruthenium- and cobaltcatalyzed Alder-ene reactions, the stereochemistry of the double bond (α) bearing substituent R¹ is controlled via a metallacycle and is therefore exclusively configured as shown in Scheme 2. The stereochemistry of the β -double bond, generated by β hydride elimination from this metallacycle, is believed to be mostly sterically controlled to produce preferentially the *E*configured double bond. The results of these reactions are summarized in Table 1 showing the main product 5 with the preferentially formed stereochemistry of the β -double bond.

Unlike the ruthenium catalyst, the cobalt catalyst system is also capable of catalyzing an alkyne trimerization reaction and suppressing the formation of these side products; the alkene was used in excess, and the butadiynes were added slowly in small portions.⁷ Accordingly, two concurring reaction pathways exist and the yields of the Alder-ene products, which are reported in Table 1, vary because of different relative rates of the reaction depending of the reactivity of the alkene component.

Scheme 3. Cobalt-Catalyzed Alder-ene Reaction between 1,3-Butadiyne and TBS-Protected Homoallylic Alcohol 7



As terminal alkenes, we choose 1-octene, allyltrimethylsilane, allylbenzene derivatives, and 3-buten-1-ol to cover different types of alkenes. The 1,3-butadiynes were substituted by either a trimethylsilyl or a triisopropylsilyl group, whereas the other substituent on the diyne was a methoxybenzene moiety or a simple alkyl chain. The methoxy group increased the polarity of the products, so that **5** could be more easily separated by column chromatography from the above-mentioned cyclo-trimerization side products.

The reactions of methoxybenzene substituted 1,3-butadiynes gave higher yields in the case of the *para-* and *meta-*substituted educts (entries 1, 4), while the yield of the more hindered *ortho-*methoxy substituent diyne (entry 7) is significantly reduced. The application of allyltrimethylsilane as an alkene component led to a significantly lower E/Z ratio concerning the

Table 2. Results of the Ruthenium-Catalyzed Alder-eneReaction for the Synthesis of Products of Type 4



^{*a*}Reaction conditions: $[CpRu(MeCN_3)]PF_6$ (10 mol %), 1,3-diyne (0.5 mmol, 1.0 equiv), alkene (1.0 mmol, 2.0 equiv) in acetone (3.0 mL). The regioisomeric ratios were determined by ¹H NMR spectroscopy. ^{*b*}Accompanied by the side product with the carbon– carbon bond formation at C2 (see SI).

 β -double bond. Surprisingly, the ¹H NMR data support the formation of the product **5m** mainly as the *Z*-isomer of the β -double bond. Unfortunately, we have no rationale for this behavior at the present time. Also the application of allylbenzene derivatives gave different results (compare entries 3 and 11). The significantly different yields are caused by the higher tendency of the TMS-substituted diyne to undergo the cyclotrimerization compared to the more hindered triisopropyl-substituted diyne. In the case of a higher reactivity of the alkene

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component, such as allyl trimethylsilane (entries 2 and 9), comparable yields are obtained.

Of considerable interest are entries 14 and 15 because with 3buten-1-ol the double bond geometry of the β -double bond was inverted. Probably, the coordination of the oxygen to the cobalt may be relevant which was observed for other oxygen-bearing functionalities in the past as well.^{3b}

In order to reduce the coordination of the oxygen and invert the double bond of the β -double bond toward an *E*-configured geometry, we repeated entry 15 with the TBS-protected alcohol 7 (Scheme 3).

The reaction resulted in a product mixture, consisting of the "undesired" product **8a**, which still had the *Z*-configured β -double bond and two new products which had not been observed in the previous reactions. First, we identified the conjugated 1,3-diene **8b**, which could result from a β -hydride elimination "the other way" from the proposed intermediate **A**, as was observed from ruthenium-catalyzed Alder-ene reactions.⁸ Second, an unusual 1,5-diene, product **8c**, was observed, which results from an additional double bond shift from **8a** to **8c**. Despite our extended knowledge in double bond isomerization and translocation with cobalt and nickel based catalysts,⁹ we were not able to shift the ratio of **8a:8c** by applying our catalysts. Accordingly, a different mechanism might be in action and we intend to investigate this phenomenon in more detail in the future.

The final set of experiments was conducted with the ruthenium-based catalyst system (compare Scheme 2) to compare the results and to illustrate the straightforward compatibility of the catalyst systems. Accordingly, a number of the 1,3-butadiynes were reacted with terminal alkenes according to the protocol reported by Lee.⁶ The results are summarized in Table 2.

All ruthenium-catalyzed reactions gave exclusively the branched product 4, where the carbon–carbon bond formation takes place at C3. In contrast to Lee et al. the subjected 1,3-diynes needed longer reaction times and in the case of the aryl-substituted alkenes higher reaction temperatures were needed to reach complete conversion of the starting materials. Unfortunately, 3-buten-1-ol gave no complete conversion even at 60 °C or with a higher catalyst loading. In the case of the TBS-protected alcohol 7 (entry 10), we were able to isolate the desired product as a single isomer.

In conclusion, we were able to apply the cobalt- and ruthenium-catalyzed Alder-ene reaction of unsymmetrical silylsubstituted 1,3-butadiynes with terminal alkenes in a complementary fashion. While the α -double bond configuration is controlled by the reaction mechanism, the configuration of the β -double bond can be controlled by the substituent on the alkene component. Those substrates without a donor functionality prefer the *E*-configuration, whereas the *Z*configuration is generated when 3-buten-1-ol is applied. Accordingly, the usefulness of the Alder-ene reaction is considerably increased via our new protocol.

ASSOCIATED CONTENT

S Supporting Information

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Notes

The authors declare no competing financial interest.

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Synthesis, analytical data, NMR spectra (PDF)