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

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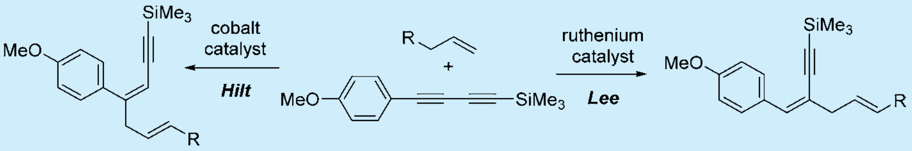
Supporting Information



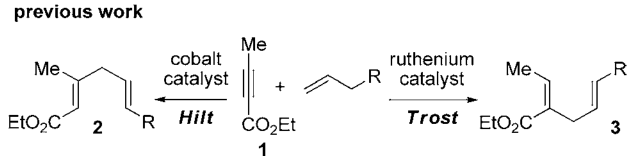
ABSTRACT: The Alder-ene reaction of trialkylsilyl-substituted 1,3-butadiynes with terminal alkenes was investigated utilizing a cobalt-based catalyst, and the results were compared with Alder-ene rections catalyzed by the $[CpRu(H_3CCN)_3]PF_6$ catalyst. Obviously, the two catalysts gave complementary 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 carbon−carbon 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]

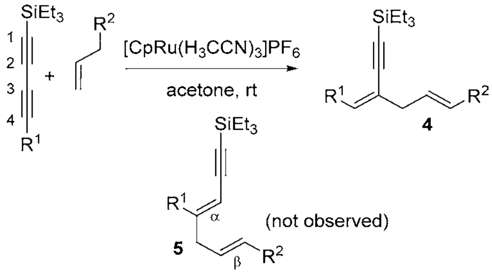
This reaction is highly complementary to the ruthenium-catalyzed Alder-ene reaction which led exclusively to products of type **3**.[4] Most importantly, both types of products **2** and **3** are of interest, as they can be utilized for the synthesis of natural products.[5]

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



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−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.

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



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 trialkylsilyl 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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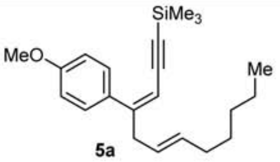
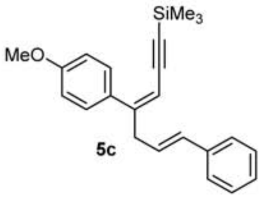
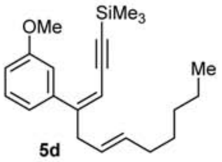
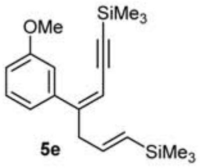
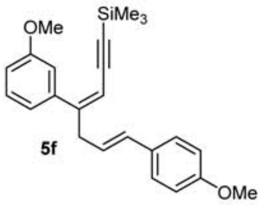
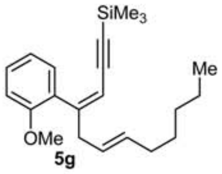
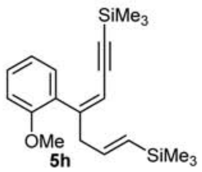
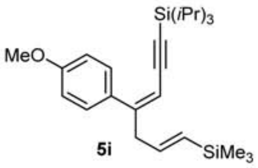
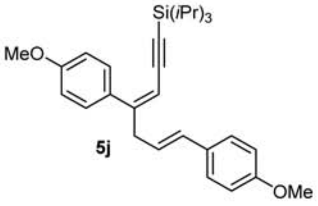
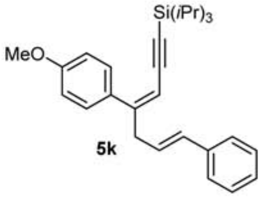
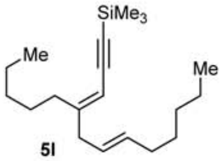
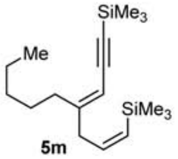
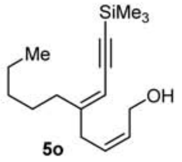
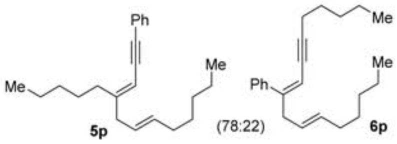
Table 1. Results of the Cobalt-Catalyzed Alder-ene Reaction of 1,3-Butadiynes

no.	main product 5[a]	yield time *E*/*Z* ratio[b]
1	 **5a**	65% 18 h 99:1
2	 **5b**	64% 22 h 75:25
3	 **5c**	31% 72 h 99:1
4	 **5d**	67% 20 h 99:1
5	 **5e**	71% 20 h 84:16
6	 **5f**	40% 72 h 99:1
7	 **5g**	33% 18 h 99:1
8	 **5h**	34% 18 h 80:20
9	 **5i**	62% 7 d 85:15
10	 **5j**	52% 72 h 99:1
11	 **5k**	65% 72 h 99:1
12	 **5l**	86% 36 h 99:1
13	 **5m**	67% 36 h 25:75
14	 **5n**	19% 16 h 1:99
15	 **5o**	61%[c] 16 h 1:99
16	 **5p** (78:22) **6p**	46% 42 h 99:1

[a] Reaction conditions: CoBr$_2$(dppp) (10 mol %), Zn, ZnI$_2$ (20 mol % each), butadiyne (0.5 mmol, 1.0 equiv), alkene (0.75 mmol, 1.50 equiv), CH$_2$Cl$_2$ (0.5 mL), ambient temperature. [b] The *E*/*Z* ratios of the *β*-double bond were determined by ^{1}H 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

Information (SI). These diynes were subjected to a cobalt-catalyzed 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 cobalt-catalyzed Alder-ene reactions, the stereochemistry of the double bond (α) bearing substituent R^1 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

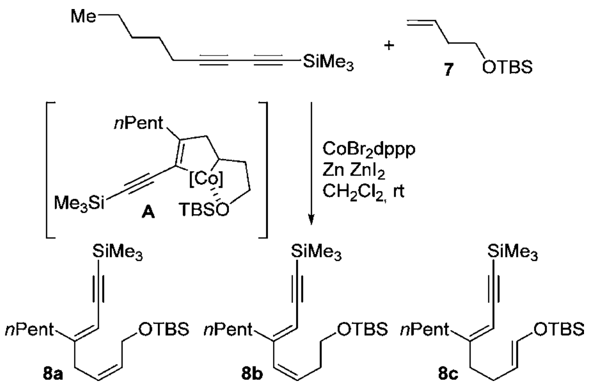
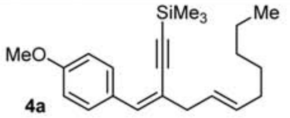
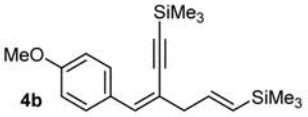
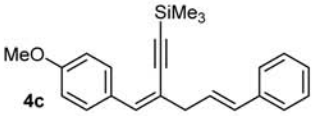
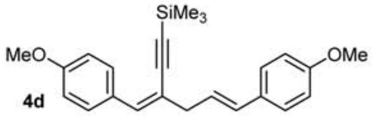
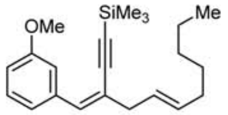
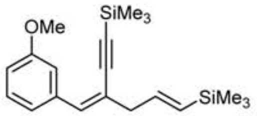
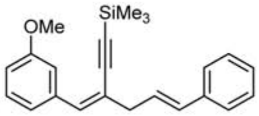
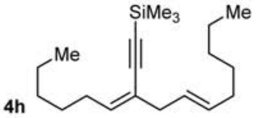
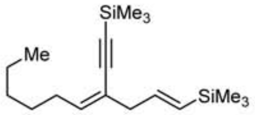
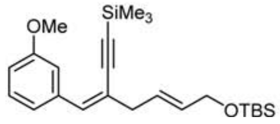


Table 2. Results of the Ruthenium-Catalyzed Alder-ene Reaction for the Synthesis of Products of Type 4

no.	products of type 4[a]	yield temp / time
1	 4a	65% rt / 3 h
2	 4b	78%[b] rt / 18 h
3	 4c	47% 60 °C / 72 h
4	 4d	60%[b] 60 °C / 72 h
5	 4e	55% rt / 24 h
6	 4f	80%[b] rt / 96 h
7	 4g	66% 60 °C / 72 h
8	 4h	51% rt / 72h
9	 4i	60% rt / 72h
10	 4j	28% 60 °C / 5 d

[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).

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

Of considerable interest are entries 14 and 15 because with 3-buten-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 silyl-substituted 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

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03729.

Synthesis, analytical data, NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(7) All cobalt-catalyzed Alder-ene reactions are complete after the given reaction times. Besides the Alder-ene products of type **4** only cyclotrimerization products were found. For cobalt-catalyzed cyclotrimerization of alkynes, see: (a) Gandon, V. In *Transition Metal-Mediated Aromatic Ring Construction*, 1st ed.; Tanaka, K., Ed.; Wiley: NJ, 2013; pp 3−35. (b) Gandeepan, P.; Cheng, C.-H. *Acc. Chem. Res.* **2015**, *48*, 1194−1206. (c) Dominguez, G.; Perez-Castells, J. *Chem. Soc. Rev.* **2011**, *40*, 3430−3444. (d) Weding, N.; Hapke, M. *Chem. Soc. Rev.* **2011**, *40*, 4525−4538.

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