Regiodiverse Three-Component Synthesis of Arenes

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Abstract: A ruthenium-catalyzed enyne metathesis reaction followed by a cobalt-catalyzed Diels–Alder reaction and oxidation of the dihydroaromatic intermediate generates the two regioisomeric aromatic products in good overall yields in a one-pot procedure. The regiochemistry of the cycloaddition can be controlled by the ligand choice on the cobalt catalyst to generate the product with the 1,3,5- or the 1,2,4-substitution pattern predominantly. The high functional group tolerance was used to generate bifunctionalized building blocks and finally an unprecedented regioselective Scholl reaction is described.

Keywords: alkynes; arenes; cobalt; metathesis; regioselectivity

The synthesis of highly substituted aromatic compounds is an issue of great interest in pharmaceutical as well as in material science. The alternative to traditional functionalizations of an already existing aromatic backbone by cross-coupling reactions, Friedel-Crafts functionalizations and so on is the generation of the aromatic core by transition metal catalysis from functionalized alkynes or enynes. In particular, the cobalt-catalyzed cyclotrimerization of alkynes is a powerful tool for this purpose.^[1] Although quite a number of transition metal catalysts exist to realize this transformation, to date it has not been possible to perform a cyclotrimerization of three different alkynes in an intermolecular fashion without tethering of the starting materials to generate a single product.^[2] Accordingly, the cyclotrimerization of three different alkynes in an intermolecular fashion leads to up to 37 isomers (Scheme 1) which are formed in a more or less statistical mixture. In many cases only the regiochemistry of the products can be controlled, leading either to preference for the 1,3,5- or the 1,2,4substitution pattern and thereby reducing the number of possible products.^[3]



Scheme 1. Intermolecular trimerization of alkynes.

An alternative to the cyclotrimerization of alkynes is the cobalt-catalyzed Diels–Alder reaction of alkynes with 1,3-dienes followed by oxidation of the dihydroaromatic intermediate.^[4]

Thereby, excellent regiocontrol can be obtained and the dienophile is not limited to acceptor-substituted educts as in thermal Diels–Alder reactions with normal electron demand. In the past we were able to show that the neutral Diels–Alder reaction can be efficiently catalyzed by low valent cobalt complexes under ambient temperature. The products can be obtained in excellent yields and depending on the ligand on the cobalt centre the 1,4- (*para*) or the 1,3-substitution (*meta*) regioisomer can be selectively addressed.^[5]

To overcome the limitations of the cyclotrimerization of three different alkynes we investigated a strategy by which the first alkyne is converted, in the presence of an alkene under ruthenium-catalyzed enyne metathesis conditions, to a 1,3-diene.^[6]

This intermediate is then applied in a cobalt-catalyzed Diels–Alder reaction with the second alkyne to generate the dihydroaromatic intermediate so that the desired aromatic product can be obtained after oxidation with DDQ.

We envisaged that this approach could be realized as a reaction sequence without isolation of the intermediates by chromatography. This would be of advantage because the isolation of volatile 1,3-diene intermediates can be circumvented and the tendency of 1,3-dienes to polymerize when concentrated can be reduced. In addition, flexibility is easily introduced into the reaction sequence leading to 3 as two different routes are available by simply exchanging the order at which the respective alkynes 1 and 2 are applied. The two routes exhibit different yields to generate the identical product 3 (Scheme 2) and later on regioselectivi-



Scheme 2. Flexible approach to 3 by enyne metathesis, cobalt-catalyzed Diels-Alder reaction and DDQ oxidation.

ties in the Diels–Alder reaction can be controlled when unsymmetrical starting materials are applied.

The results for the reaction sequence are summarized in Table 1 and we would like to emphasise that all products are obtained without isolation of intermediates over three steps.

In entries 1–7 at least one symmetrical alkyne was used and tri- and tetrasubstituted aromatic compounds were obtained without addressing the problem of regioisomers. In the following reactions (entries 8-17) two different unsymmetrical alkynes were used and the control of the regiochemistry of the products of type 7 was then controlled by the application of two different cobalt catalyst systems bearing either dppe or 8 as ligands. Catalyst system A {CoBr₂ $[1,2-bis(diphenylphosphino)ethane] = CoBr_2(dppe)],$ ZnI_2 generates predominantly products Zn. with a 1,4-substitution pattern, while catalyst system В {CoBr₂[2,4,6-trimethyl-*N*-(pyridin-2-ylmethylene)amine] $[=CoBr_2(8), Zn, Fe, ZnI_2]$ prefers to form the regioisomeric 1,3-substituted products as described earlier.^[5c]

Utilizing these two catalysts, good to excellent regioselectivities were obtained and the two regioisomers were obtained in good yields (entries 8–17). The choice of the alkyne used in the initial transformation of the reaction sequence has a profound influence upon the regioselectivity of the products formed in the Diels–Alder reaction. This can be visualized particularly well in entries 14–17. Using catalyst A the regioselectivity of the sequence utilizing the two alkynes 1-phenyl-1-hexyne and 4-methoxyphenylacetylene led to a higher regioselectivity (78:22, entry 16) when 1-



Scheme 3. Selected follow-up reactions utilizing functionalized arene derivatives.

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Table 1. Results for the enyne metathesis/Diels-Alder/oxidation reaction sequence.



Ligand:

$$Ph_2P$$
 PPh_2 (= dppe) or N_N N_N

Entry	Alkyne A (4)	Alkyne B (6)	Product 7	Yield ^[j]
1	MeO-	<i>n</i> -Pr——— <i>n</i> -Pr	<i>n</i> -Pr	70%
2	n-Pr────n-Pr	MeO-	MeO 7a	87%; 86% ^[b]
3	n-Pr───_n-Pr	MeOOOMe	n-Pr OMe OMe 7b	76%; 85% ^[c]
4	n-Pr────n-Pr	TMS- <u>—</u> TMS	n-Pr n-Pr 7c	89%; 94% ^[c]
5	<i>n</i> -Pr ──── <i>n</i> -Pr	PhPh	n-Pr Ph n-Pr 7d	41%
6	n-Pr───_n-Pr	≡ —	n-Pr n-Pr 7e	80%
7	n-Pr────n-Pr	PhB(Pin)	n-Pr Ph B(Pin) 7f	83% ^[c]
8	MeO-	<u></u> —n-Hex	MeO 7g	72% (96:4)
9	MeO-	── <i>t-</i> Bu	MeO 7h	72% (92:8)
10			MeO 7i	73% (91:9)
11	MeO-	──TMS	MeO TMS	61% ^[d,e] (11:89)
12			Meo 7k Me	61% (88:12)

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 Table 1. (Continued)



[a] First step: 1.0 equiv. alkyne A, 7.5 bar ethene, Grubbs II catalyst (2 mol%), CH₂Cl₂; second step: 1.2 equiv. alkyne B, CoBr₂(dppe) (10 mol%), ZnI₂ (20 mol%), Zn powder (20 mol%); third step: 1.2 equiv. DDQ, toluene.

- ^[b] CoBr₂(dppe) (5 mol%), ZnI₂ (10 mol%), Zn powder (10 mol%).
- ^[c] CoBr₂(dppe) (20 mol%), ZnI₂ (40 mol%), Zn powder (40 mol%).
- ^[d] 1.5 equiv. alkyne B.

^[e] CoBr₂(8) (10 mol%), ZnI₂ (20 mol%), Zn powder (20 mol%), Fe powder (20 mol%).

- ^[f] CoBr₂(8) (20 mol%), ZnI₂ (40 mol%), Zn powder (40 mol%), Fe powder (40 mol%).
- ^[g] 1.5 equiv. alkyne A, 1.0 equiv. alkyne B.
- ^[h] Enyne-metathesis in C_6F_6 , Grubbs II catalyst (5 mol%).
- ^[i] 2.0 equiv. alkyne B.
- [j] Ratio of regioisomers are given in brackets.

phenyl-1-hexyne was used first in the metathesis reaction as compared to 60:40 (entry 14) when 4-methoxyphenylacetylene was the alkyne applied first. On the other hand, when catalyst B was used in the Diels– Alder reaction the higher regioselectivity was observed when 4-methoxyphenylacetylene was used first in the metathesis reaction (7:93 in entry 15 *versus* 43:57 obtained in entry 17).

The tolerance of the reaction sequence towards functional groups was demonstrated in entries 6 and 7



catalyst A: 82% 14:15 = 78:22 catalyst B: 72% 14:15 = 8:9 Scheme 4. Synthesis of bifunctionalized terphenylenes.

B(Pin) Ph catalyst B: 72% 14:15 = 8:92

Scheme 5. Reaction sequence utilizing 1-hexene as alkene component.

reported by Mori.^[6e] Our previous work has shown that the cobalt-based systems show a high tolerance for a broad range of functional groups besides the two shown in this work.^[4,5] Therefore, a bromo-functionalized building block **7e** can be generated and converted in a Sonogashira reaction to the alkyne **9** in excellent yield

in the synthesis of more complex aryl bromide and ar-

ylboronic ester derivatives. Both functionalities are

well accepted and remain unaltered in the products

which were obtained in high yields. Electron-deficient

alkynes such as propiolic esters were not utilized as

starting materials in the ruthenium-catalysed enyne

metathesis based on the low reactivity of such educts



(Scheme 3). In addition, the boronic ester 10 was successfully reacted to the phenol derivative 11 in 86% yield by oxidation. The double Suzuki-coupling reaction of **7f** with 1,4-dibromobenzene gave the quinquephenylene product 11 in 86% yield. Under the dehydrative conditions applied in the Scholl reaction^[7] utilizing FeCl₃ the tribenzo[fg,ij,rst]pentaphene derivative 13 was exclusively isolated in good yield while the corresponding tribenzo[f,k,m]tetraphene derivative 12 was not observed. A quantum mechanical calculation of the proposed radical cation intermediate suggested unequal orbital coefficients at the two carbon atoms (carbon a and carbon b in 11) relevant for the regiodivergent carbon-carbon bond formation. This could explain why product 13 was formed exclusively. Further investigations towards regioselective Scholl reactions are underway.^[7b]

Bifunctionalized building blocks are also easily accessible. This was exemplified in the regiodiverse synthesis of **14** and **15** (Scheme 4) starting from two different mono-functionalized alkynes and ethene utilizing either catalyst A in the Diels–Alder reaction to predominantly generate the terphenylene regioisomer **14** (**14**:**15**=78:22) or by applying catalyst B to generate the bifunctionalized terphenylene **15** as the major product (**14**:**15**=8:92).

As in the case for the synthesis of product 9 debromination of 14 or 15 by the cobalt catalysts or the zinc powder was not observed. The follow-up chemistry of these bifunctionalized building blocks is under investigation.

For the expansion of the reaction sequence towards the regiodiverse synthesis of products having three substituents, a terminal alkene was used in place of ethene. As the prototype reagent 1-hexene was used in the enyne-metathesis reaction with phenylacetylene to generate an intermediate 1,3-disubstituted 1,3diene (16, Scheme 5). The intermediate was then converted in a regiodiverse cobalt-catalyzed Diels–Alder reaction with trimethylsilylacetylene utilizing catalyst A or catalyst B leading to the synthesis of the 1,2,4trisubstituted benzene derivative 17 or alternatively to the 1,3,5-trisubstituted derivative 18.

Both regioisomers are addressable by the cobalt catalysts systems A or B to predominantly generate the desired regioisomer in good overall yields.

In conclusion, we have demonstrated that a reaction sequence consisting of an enyne metathesis and a cobalt-catalyzed Diels–Alder reaction is a versatile tool for the synthesis of complex arene derivatives in a modular fashion. Yields and regioselectivities are sufficiently high to allow utilization of the reaction sequence in the future to address a broad range of complex molecules.

Experimental Section

Representative Procedure (Table 1, entry 2)

4-Octyne (110 mg, 1.0 mmol, 1 equiv.) and Grubbs II catalyst (17 mg, 0.02 mmol, 2 mol%) were dissolved in 2 mL dry dichloromethane and were reacted in a glass autoclave with ethene (7.5 bar) at 60 °C for 5 h. Then argon was bubbled through the solution and added to a flask containing anhydrous zinc iodide (64 mg, 0.2 mmol, 20 mol%), zinc powder (13 mg, 0.2 mmol, 20 mol%), $CoBr_2(dppe)$ (62 mg, 0.1 mmol, 10 mol%) and 4-methoxyphenylacetylene (159 mg, 1.2 mmol, 1.2 equiv.) under an argon atmosphere. The reaction mixture was stirred over night at ambient temperature and filtered over a small plug of silica gel (eluent: pentane/diethyl ether 1:1). The solvent was removed and the dihydroaromatic intermediate was oxidized with DDQ (272 mg, 1.2 mmol, 1.2 equiv.) in 15 mL toluene. After filtration over a small plug of deactivated silica gel (eluent: pentane/diethyl ether 1:1) the solvent was removed and the residue was purified by column chromatography on silica gel (eluent: pentane/diethyl ether=30:1). The product 7a was obtained as yellow solid; yield: 233 mg (0.87 mmol, 87%). ¹H NMR (CDCl₃, 300 MHz): $\delta = 7.57 - 7.51$ (m, 2H), 7.38-7.31 (m, 2H), 7.21 (d, J=7.7 Hz, 1H), 7.01–6.95 (m, 2H), 3.86 (s, 3H), 2.70-2.60 (m, 4H), 1.75-1.59 (m, 4H), 1.04 (t, J = 7.2 Hz, 6H); ¹³C NMR (CDCl₃, 75 MHz): $\delta = 158.9$, 140.7, 138.9, 138.2, 134.0, 129.5, 127.9, 127.5, 124.1, 114.1, 55.3, 35.0, 34.4, 24.4, 24.4, 14.3. IR: 2957, 2931, 2869, 1610, 1519, 1492, 1464, 1377, 1274, 1247, 1180, 1044, 1029, 822; MS (EI): m/z = 268 (M⁺, 100), 239 (89), 224 (14), 211 (16), 195 (14), 179 (11), 165 (20), 152 (16); HR-MS (EI): m/z =268.1833, calcd. for $C_{19}H_{24}O: m/z = 268.1827$.

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