Organic Syntheses

Discussion Addendum for:

Dibenzo[a,e]cyclooctene: Multigram Synthesis of a Bidentate Ligand

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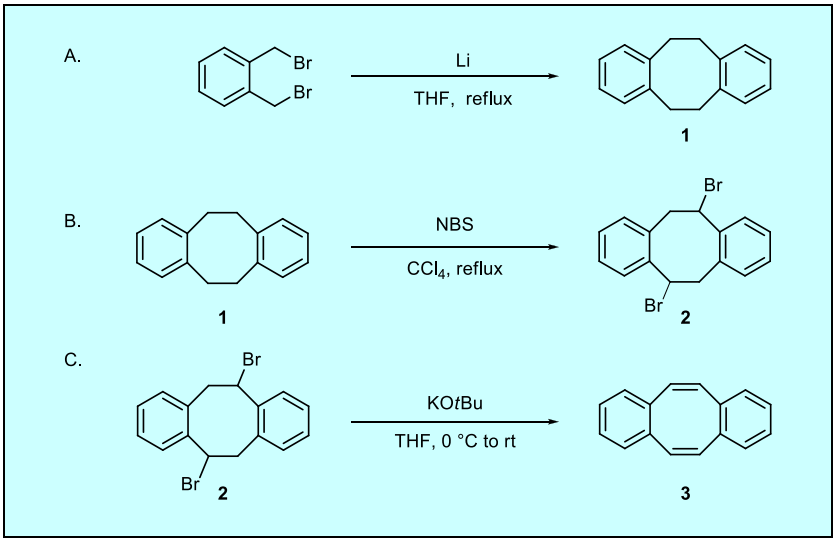

The title compound, henceforth designated dbcot, was first prepared in 1946.[2] It typically served to prepare analogs of cod-complexes of transition metals. Anton and Crabtree found that dbcot is bound more tightly and is more electron withdrawing than cod in complexes of low-valent transition metal ions.[3] This observation led to the first application of dbcot as a reagent, the Crabtree test (1983),[4] which was based on the finding that dbcot is an inhibitor of homo- but not heterogeneous transition metal catalysts. Perhaps due to difficulties associated with earlier syntheses, dbcot chemistry received

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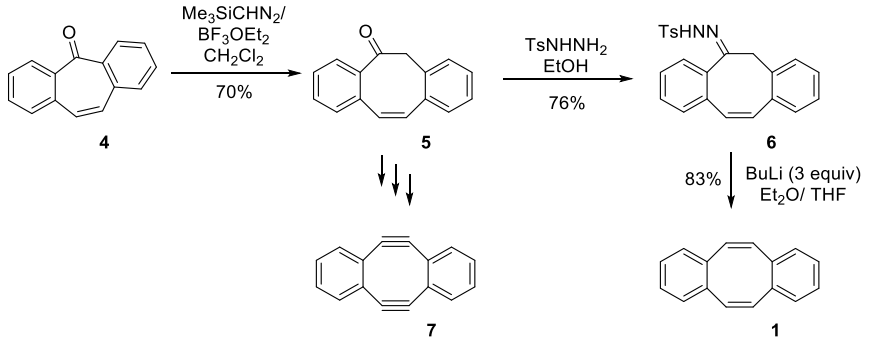
wider attention only after 2002, when Wudl et al.[5] reported a convenient synthesis, which was somewhat improved by our group.

This discussion addendum is focused on uses of dbcot and a few derivatives in catalysis. Useful procedures for preparation of these compounds are also outlined. Fundamental metalorganic and coordination chemistry of dbcot have been reviewed recently (2019)[6] and are here only discussed in conjunction with catalysis.

Preparation of Dbcot and Dbcot Derivatives

The procedures currently in use are all based on Wudl's work. The route to dbcot, as streamlined by us, has been used by several groups without problems. Nevertheless, members of one of the groups expressed concern about the lachrymatory effect of α,α'-dibromo-o-xylene and the use of carbon tetrachloride as solvent in the bromination step.[7]

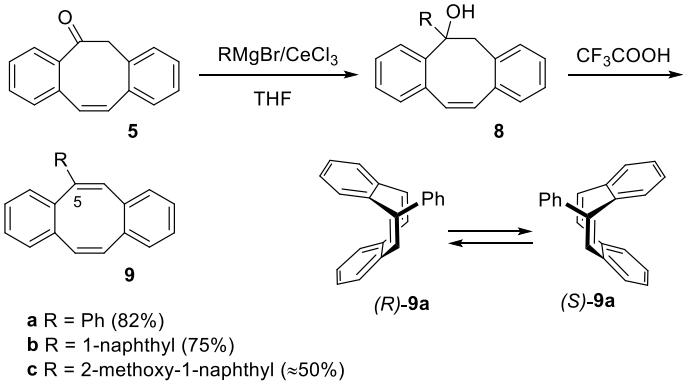
Wudl's work was also directed at the diyne **7** and included a ring enlargement of the commercially available dibenzosuberone (**4**) with trimethylsilyldiazomethane to give the ketone **5** (70%) (Scheme 1).[5] This ketone was used by Chen and Hartwig for the development of a second route to dbcot by adding a Shapiro reaction via the hydazone **6** to give dbcot (**1**) in 83% yield (Scheme 1).[8]



Scheme 1. A second practical route to dbcot (1)

Grützmacher et al.[9] prepared a series of 5-aryl-dbcot derivatives from the ketone **5** in two simple steps (Scheme 2) and used them as ligands of transition metal catalysts. A chiral Rh-complex of **9a**, obtained by resolution, gave promising results in an enantioselective Hayashi-Miyaura reaction. While the Rh-complex was stable against racemization, the free ligand (*R*)-**9a**

underwent complete racemization by tub to tub interconversion within > 3 h at room temperature.

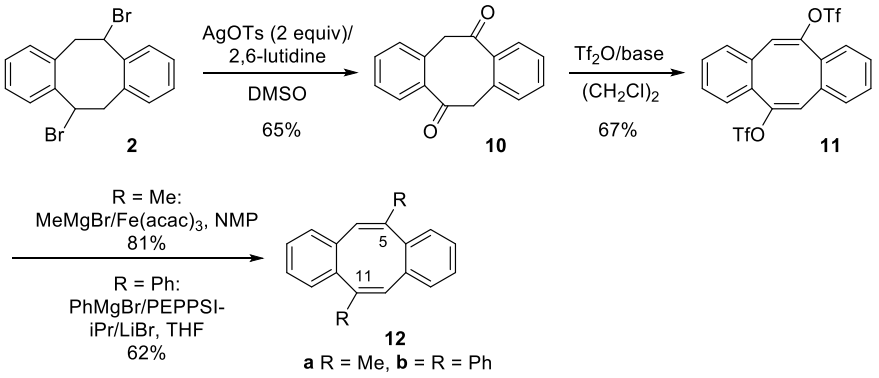


Scheme 2. A route to monoaryl substituted dbcot derivatives 9

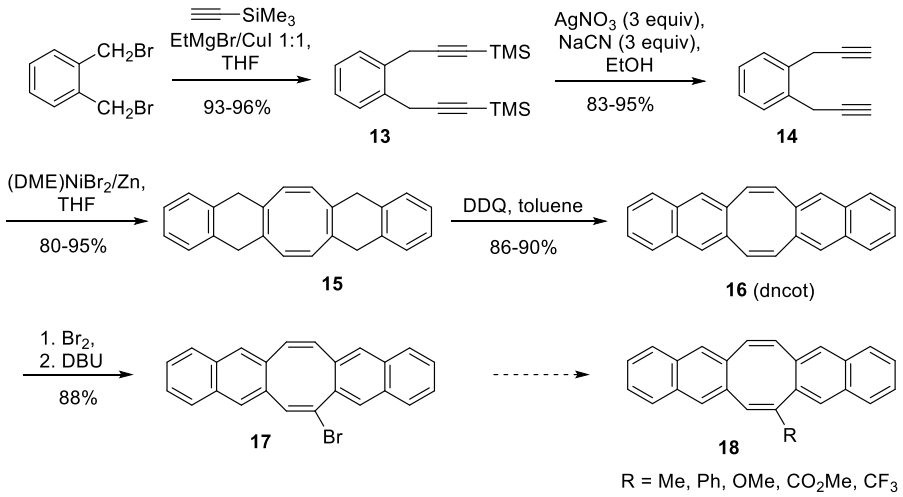
Strand et al.[10] advanced the topic of asymmetric catalysis by using C_2-symmetric derivatives **12** of dbcot (Scheme 3). Their synthesis commenced with the dibromide **2**, which was transformed into the dione **10** according to a known procedure (Kornblum oxidation),[11] which proceeded in good yield but required two equivalents of silver tosylate. The dione **10** was transformed into the bis-triflate **11** by treatment with Tf_2O. Finally, cross coupling using an Fe- and a Pd-catalyst, furnished 5,11-methyl- (**12a**) and 5,11-phenyl-dbcot (**12b**), respectively. Enantiomers of both **12a** and **12b** could be separated by semi-preparative chiral column chromatography. The enantiomers equilibrate by tub to tub isomerization with a barrier of ≈ 30 kcal/mol; accordingly, racemization at room temperature is slow.

The benzologue **16** (dncot) of dbcot was already prepared in 1990 in low yield.[12] A convenient high yield route was developed by Wender et al. (Scheme 4).[13] α,α'-Dibromo-o-xylene served as starting material; the reaction with ethynyltrimethysilane furnished the dialkyne **13** in almost quantitative yield. Subsequent deprotection to give **14** was carried out in excellent yield with 3 equivalents of silver cyanide. In the meantime, catalytic methods (10 mol% of $AgNO_3$) have been developed[14] that likely would allow simplification of the deprotection step. Nickel-catalyzed [2+2+2+2]-cycloaddition to give **15** followed by oxidation furnished crystalline dncot (**16**) in high overall yield. Addition of bromine followed by base-promoted elimination

gave the bromide **17**. This allowed preparation of a variety of further derivatives **18** of dncot by substitution or cross coupling reactions.



Scheme 3. Preparation of C_2-symmetric dbcot derivatives 12



Scheme 4. Preparation of dncot (15) according to Wender

Uses in Catalysis

Rhodium-Catalyzed 1,4- and 1,2-Additions of Arylboronic Acids

Interest in dbcot as a constituent of catalysts rather than as an inhibitor, cf the Crabtree test, began after Hayashi and Carreira in 2003 introduced chiral dienes **19** and **20**, respectively, as ligands of Rh-catalysts of the Hayashi-Miyaura reaction (Figure 1) [15,16a] and an Ir-catalyzed kinetic resolution allylic substitution.[16b]

Rh-Complexes of dienes such as cod, **19** and **20** are not very stable. This observation induced Grützmacher et al. (2005)[9] to employ Rh-complexes of the dbcot derivatives **9** as catalysts. The complex (*R*)-**21b** furnished excellent yield and modest but promising enantioselectivity for the 1,4-addition of phenylboronic acid to cyclohexen-2-one (Scheme 5).

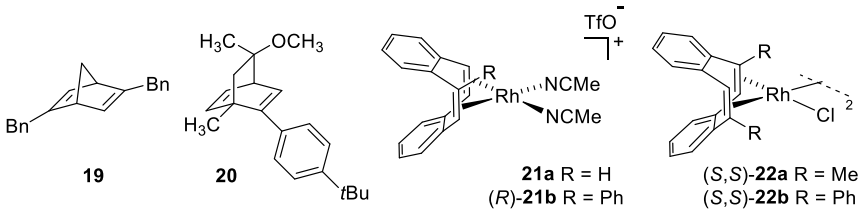
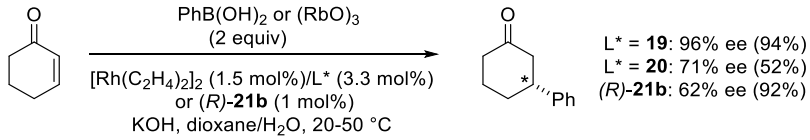
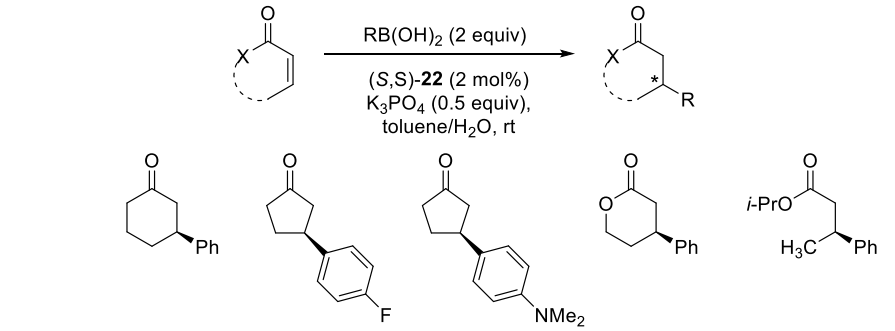


Figure 1. Chiral diene ligands and complexes



Scheme 5. Hayashi-Miyaura reaction

Following the rule that C_2-symmetry is an advantageous property of a chiral ligand, Strand and co-workers prepared the enantiomerically pure Rh-complexes (*S*,*S*)-**22a** and **–22b** (Figure 1) from the ligands **12a** and **12b**, respectively.[10] With these, the expected high enantioselectivities were indeed obtained with cyclic as well as acyclic enones and enoates (Scheme 6). In addition, highly enantioselective 1,2-additions of arylboronic acids to α-ketoesters were realized by the Strand group.[10]

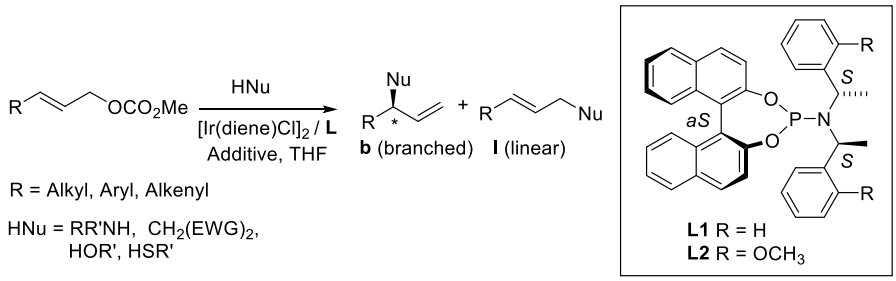


(*S*,*S*)-**22a**	98% ee (50%)	93% ee (66%)	96% ee (48%)	>99% ee (95%)	98% ee (82%)
(*S*,*S*)-**22b**	98% ee (80%)	>99% ee (quant)	>99% ee (38%)	>99% ee (quant)	99% ee (96%)

Scheme 6. Use of C_2-symmetric dbcot derivatives in the Hayashi-Miyaura reaction

Iridium-Catalyzed Allylic Substitutions

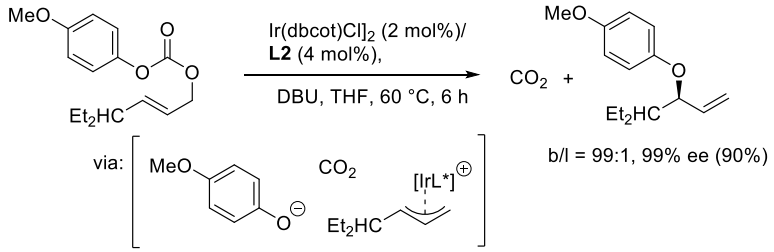
The Ir-catalyzed allylic substitution was introduced in 1997 and found immediate interest because of preference for the branched, chiral substitution product.[17] Continuous development has led to two very robust and highly regioselective as well as enantioselective versions (type I, Scheme 7,[18] and type II[19])[20] with many applications in the area of biologically active compounds.[21] Both versions rely on catalysts prepared from the complex $[Ir(cod)Cl]_2$ and a chiral phosphine. Earlier on it was not clear, whether cod was incorporated into the active catalyst. It turned out that cod is preserved in type I and lost in type II substitutions. This finding was an incentive to explore dbcot-derived catalysts in type I substitutions.



Scheme 7. Ir-catalyzed enantioselective allylic substitutions of type I

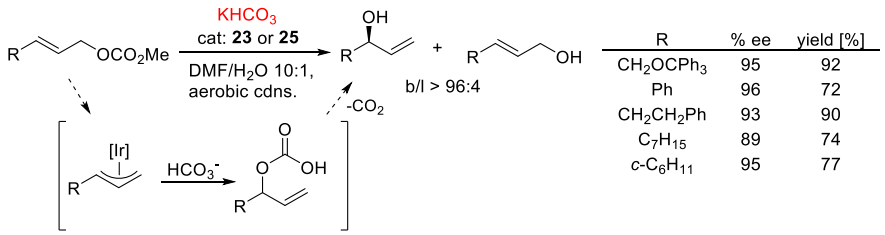
There are several improvements to be gained by using dbcot-complexes in type I allylic substitutions: (a) Dbcot-Ir-complexes display enhanced thermal stability, because dbcot is stronger bound to Ir^{I} than cod. (b) Reactions with cod-complexes as catalysts require strict exclusion of oxygen. In stark contrast, the corresponding reactions with dbcot-complexes can be run under air and with aqueous solvents. (c) With cod, reactions often display unsatisfactory regioselectivity in case of aliphatic substituents R. With dbcot improvement is gained because of its enhanced electron acceptor capacity.

An interesting example illustrating point (a) is due to Han et al. (Scheme 8).[22] This (Tsuji) reaction involves a decarboxylative allylic substitution as the key step. With cod as an ancillary ligand, the reaction did not proceed up to a temperature of 85 °C and a reaction time of 24 h, presumably because of decomposition of the catalyst. A highly selective reaction occurred with the corresponding dbcot derived catalyst at 60 °C within 6 h.



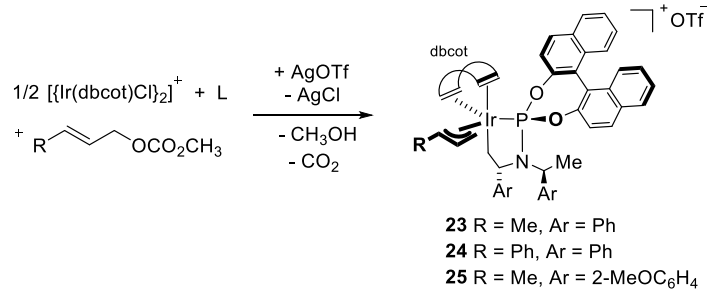
Scheme 8. Tsuji-type decarboxylative allylic etherification

Point (b), stability of the catalyst against air and water, is illustrated by Scheme 9.[23] Previous attempts to accomplish an allylic hydroxylation using cod containing Ir-complexes failed in our and another laboratory.[24] With dbcot as an ancillary ligand and bicarbonate as a nucleophile, the reaction could be performed with excellent results. The requisite Ir-complexes were obtained in a very convenient way as described in Scheme 10.[25]



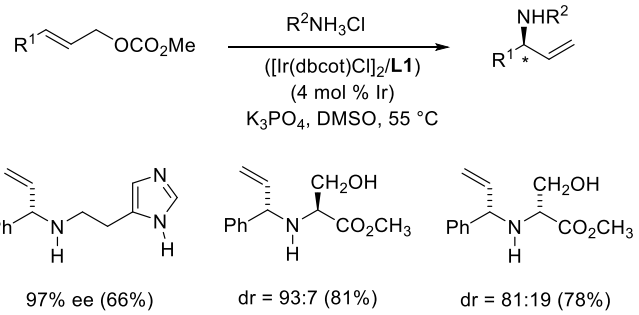
R	% ee	yield [%]
CH_2OCPh_3	95	92
Ph	96	72
CH_2CH_2Ph	93	90
C_7H_{15}	89	74
c-C_6H_{11}	95	77

Scheme 9. Enantioselective allylic hydroxylation



Scheme 10. One pot preparation of (allyl)Ir complexes

Tosatti et al. needed to employ similarly polar (DMSO) and aerobic conditions in the development of an array of drug lead-like highly polar amino acid derivatives.[26,27] Use of cod as ancillary ligand furnished yields below 5%. With dbcot excellent yields of the branched (exclusively) products were obtained (Scheme 11). Peters, et al. used the similarly polar solvent dimethylformamide in combination with the complex **24** successfully for a sequential allylic substitution/aza-Cope rearrangement process.[28]



Scheme 11. Aerobic allylic substitutions with highly polar amines in DMSO as a solvent

Improvement of regioselectivity, i. e. point (c) above, is another incentive for the replacement of cod by dbcot or dncot. Results, taken from reference 29 for cod/dbcot and reference 30 for dncot, are presented in Figure 2.[29,30] It is apparent that the latter ligands induce improved regioselectivity in favor of the branched products; this is likely due to their enhanced electron withdrawing capacity in comparison to that of cod. The (*R*)-enantiomer of the final product in Figure 2 was required as starting material for total syntheses of the natural products (+)-crypt- and (+)-infectocaryone.[31] Many further

examples concerning the influence of dbcot on regioselectivity have been reported by the You group.[32]

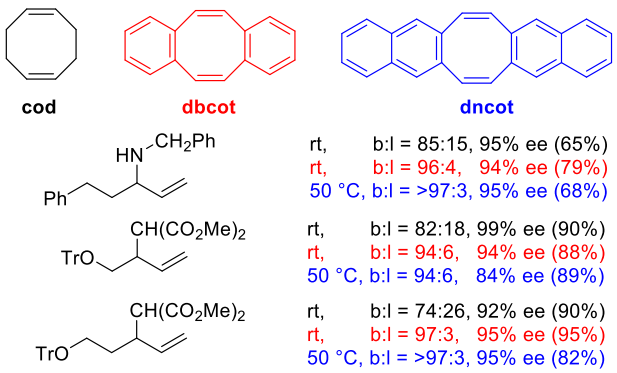


Figure 2. Results of reactions according to Scheme 7 using various diene ligands (ligand L2)

Miscellaneous reactions

Since 1995 Wender et al. have developed syntheses of cycloheptane derivatives via intra- and intermolecular Rh-catalyzed [5+2] cycloaddition reactions.[33] Over the years progress with respect to reactivity and regioselectivity was achieved by introducing new Rh-catalysts. Currently three catalysts are being used of which one contains dncot as a ligand (Scheme 12). The crucial problems for the intermolecular reaction are regioselectivity and rate (Figure 3).[13] The dncot-complex excelled particularly with respect to regioselectivity. The influence of the ligand was elucidated by dft calculations.[34]

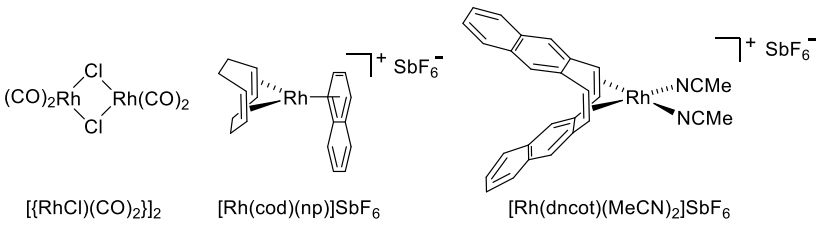
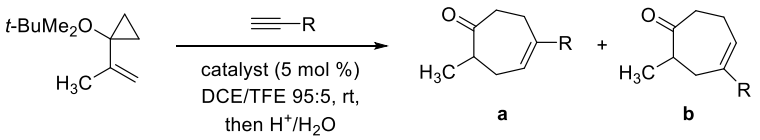


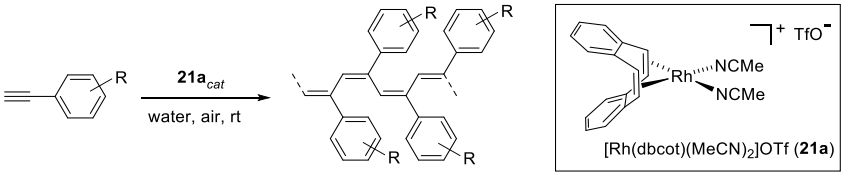
Figure 3. Catalysts used in [5+2] cycloaddition reactions



R	Catalyst	Ratio a:b	Yield a+b [%]
Ph	$[Rh(dncot)(MeCN)]_2SbF_6$	>20:1	95
Ph	$[Rh(cod)(np)]SbF_6$	6.8:1	68
n-Pr	$[Rh(dncot)(MeCN)_2]SbF_6$	5.4:1	74
n-Pr	$[Rh(cod)(np)]SbF_6$	1.1:1	57
COMe	$[Rh(dncot)(MeCN)_2]SbF_6$	1:20	96
COMe	$[Rh(cod)(np)]SbF_6$	1: >20	65

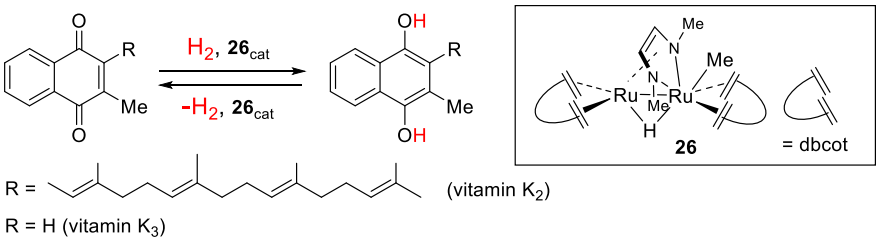
Scheme 12. [5+2] Cycloaddition reactions according to Wender et al. (DCE: 1,2-dichlorethane, TFE: 2,2,2-trifluoroethanol)

Zhang et al. have studied polymerization of phenylacetylenes with Rh-cod as well as Rh-dbcot-complexes as catalysts (Scheme 13).[35] Once more dbcot-complexes, such as **21a**, excelled, displaying higher stability and activity than cod-complexes due to stronger Lewis acidity caused by the high π-acidity of dbcot. Thus, on water polymerization under aerobic conditions became feasible. Facile recovery and re-use of the catalysts was possible due to their water-solubility.



Scheme 13. Use of a dbcot-complex as polymerization catalyst

Finally, Grützmacher et al.[36] have developed the Ru-catalyst **26**, which is a hydrogenase mimic in that it is able to both catalytically split and produce H_2 by stepwise release of electrons and protons (Scheme 14). Turnover numbers up to 252 were found for the hydrogenation of vitamin K_3; the quinoid moiety, rather than a double bond, was selectivity hydrogenated in the case of vitamin K_2.



Scheme 14. Hydrogenase mimic devised by Grützmacher et al.

References

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