ENANTIOSELECTIVE [2+2+2] ANNULATIONS

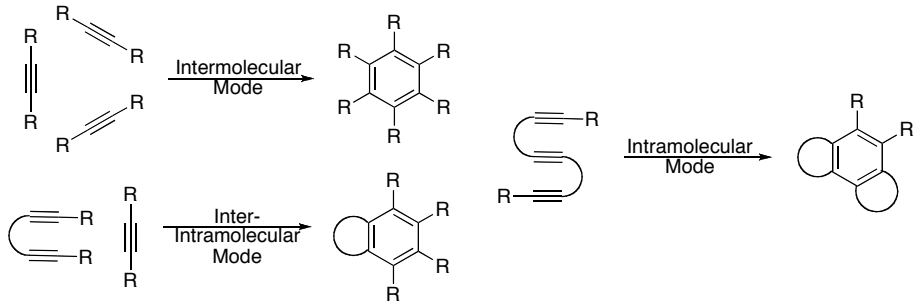
Reported by Nicholas Anderson October 2, 2008

INTRODUCTION

Although the trimerization of acetylene to form benzene has been known for almost 150 years,[1] efficient catalytic methods for this process have only recently been developed. While the conversion of three acetylene molecules into a molecule of benzene is a highly exothermic reaction (ΔH° = –594 kJ/mol),[2] a surprisingly high activation energy is required for the uncatalyzed process ($\Delta G^\ddagger$ = 242 kJ/mol).[3] This high kinetic barrier requires that the uncatalyzed reaction be executed at high temperatures, often in excess of 400 ˚C. Such a high reaction temperature makes [2+2+2] cycloadditions synthetically unattractive; however, the development of catalysts for the [2+2+2] cycloaddition allows for reactions that occur under milder conditions.

A number of catalytic [2+2+2] cycloadditions have been developed using a variety of metals.[4] The first report of catalysis of the trimerization of acetylene, reported 60 years ago,[5] showed that a variety of nickel complexes can effect the transformation. Subsequently, studies have shown that complexes of many other metals are superior catalysts for this process, including Co, Fe, Ir, Mo, Pd, Rh, Ru, Ta, and Ti.[2] Complexes of cobalt,[6] iridium,[7] nickel,[8] and rhodium[9] are the most studied catalysts, with many experimental and computational studies reported. There are three possible modes for [2+2+2] cycloaddition shown in Scheme 1, defined by the number of molecules involved in the cycloaddition. Most studies have focused on the inter-intramolecular mode, with three alkynes residing in two distinct molecules. The inter-intramolecular mode has also been the most extensively developed into enantioselective reaction. An enantioselective reaction in intramolecular mode has also been developed although with much more limited substrate scope.

Scheme 1. Possible Modes of [2+2+2] Cycloaddition.



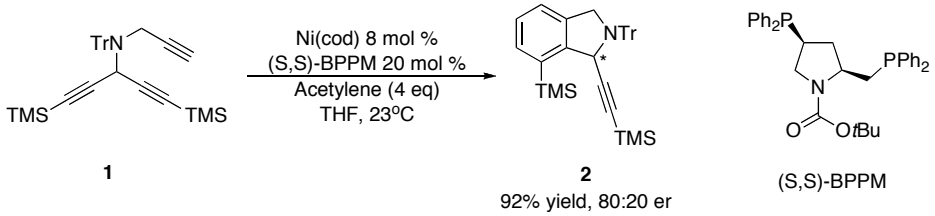
The past decade has witnessed the development of enantioselective cycloadditions catalyzed mainly by chiral cobalt, iridium, and rhodium complexes.[10] The asymmetric reactions developed enable

the construction of a variety of chiral molecules including simple aromatics, biaryls, aryl amides, helicenes[11] and cyclophanes.[12] The generation of an arene with a benzylic stereogenic center is the most well developed asymmetric [2+2+2] process, followed closely by the formation of chiral biaryls; these two approaches will be discussed in detail, while only a brief mention of the less developed helicene and cyclophane forming reactions will be presented.

BENZYLIC STEREOGENIC CENTERS

The first successful asymmetric [2+2+2] cyclization that generates an sp^3 hybridized stereogenic carbon involves the desymmetrization of triyne **1** through reaction with acetylene in the presence of a chiral nickel catalyst (Scheme 2).[13] The use of the TMS protected alkynes is critical, as the terminal alkyne gives a lower yield, 82%, and only 73:27 er. More importantly, the large trityl protecting group on nitrogen is required for enantioselectivity, as the benzyl protected substrate gives only 52:68 er.

Scheme 2. Desymmetrization of Triyne 1.



1 **2** (S,S)-BPPM

92% yield, 80:20 er

While the nickel-catalyzed reaction provided the first insight into the asymmetric [2+2+2] cyclizations, the low enantioselectivities and requirement of such a bulky trityl substituent reduces the usefulness of this process in synthetic endeavors.

The rhodium-catalyzed desymmetrization of diynyl phosphine oxides (Scheme 3) greatly improve on the scope of [2+2+2] cycloadditions and gives synthetically useful products (Table 1).[14] A phenyl-substituted alkyne gives better yields and much better enantioselectivities (entry 1) than an alkyl-substituent substrate (entry 3). Whereas the size of the substituent seems to affect the enantioselectivities, the electronic nature of the substituents exerts a negligible effect (entries 4 and 5). Additionally, catalyst loading has no effect on the enantioselectivity of the reaction (entry 2). Finally, the identity of the linker in **3**, methylene, oxygen, or tosyl amine does not influence yields and enantioselectivities of the corresponding products **5** (entries 1, 6, and 7).[14] Although these chiral phosphine oxides are interesting, molecules containing benzylic carbon centers are more common than the phosphine oxides and a method for their enantioselective formation would therefore be more useful.

Scheme 3. Desymmetrization of Diyne 4.

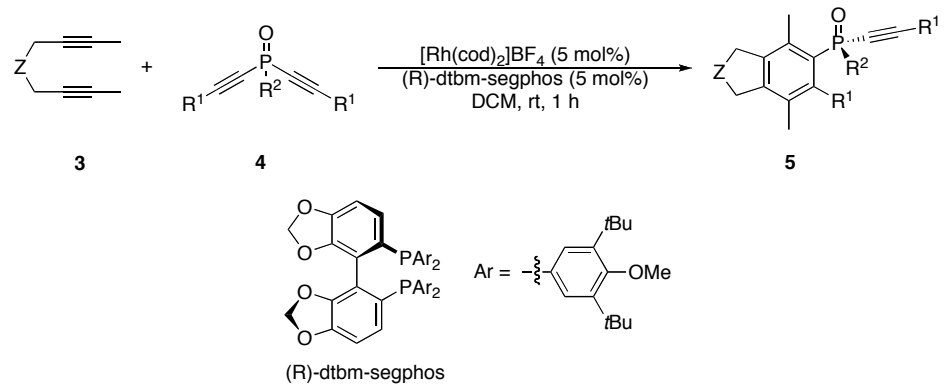


Table 1. Effect of Substituents on Desymmetrization of 4.

entry	Z	R^1	R^2	yields (%)	er
1	O	Ph	Me	>99	96.5 : 3.5
2[a]	O	Ph	Me	91	96.5 : 3.5
3	O	*n*-Bu	Me	71	67.5 : 32.5
4	O	4-$MeOC_6H_4$	Me	96	97.5 : 2.5
5	O	4-$F_3CC_6H_4$	Me	83	95.5 : 4.5
6	CH_2	Ph	Me	98	96.5 : 3.5
7	NTs	Ph	Me	>99	92.5 : 7.5

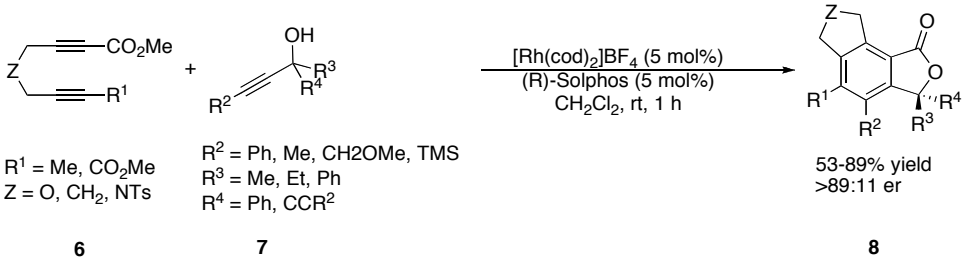
[a] 1 mol % of catalyst used

The development of a similar catalytic system for the construction of molecules containing benzylic stereogenic carbon centers is achieved through the modification of the ligand and substrate. Desymmetrization of a diynyl tertiary alcohol can set a benzylic stereocenter as shown in Scheme 4 when $R^4 = C{\equiv}CR^2$. More interesting than the desymmetrization however, is the kinetic resolution of a racemic propargylic alcohol developed by Tanaka et al.[15] The inter-intramolecular [2+2+2] between the diyne, **6**, and propargylic alcohol, **7**, give a stereodefined benzylic alcohol which closes to phthalide **8**. The expected benzylic alcohol is not isolated from the reaction mixture, but rather, only phthalide **8** was observed. High enantioselectivities are observed in the presence of excess propargylic alcohol indicating that the reaction proceeds through an inter-intramolecular mode. However, the hydroxyl group is still necessary for reactivity, isolated alkynes being unreactive.

Terminal alkynes give poor enantioselectivities and an ester substituent on one of the acetylene units of the diyne is required for good yields and selectivities.[15] Moreover, a free propargylic alcohol is needed for reaction to occur. It is currently unclear why these functional groups are required and if the

formation of benzylic stereogenic centers is to become synthetically useful, further study is needed to resolve these two major problems.

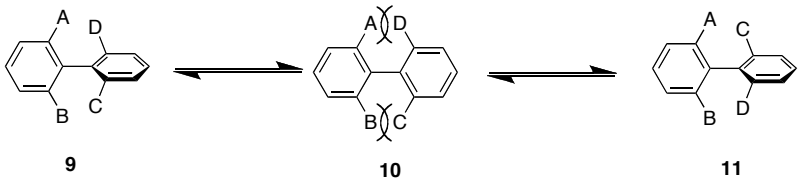
Scheme 4. Kinetic Resolution of Propargyl Alcohol by [2+2+2] Cyclization



APPLICATION TO ATROPISOMERIC COMPOUNDS

Atropisomerism is defined as the restricted rotation around a single bond that prevents two conformers from interconverting.[16] The prototypical example is a biaryl (**9**) and its enantiomer (**11**) with four different *ortho* substituents that prevent rotation around the biaryl bond (Scheme 5). If the steric interactions in transition structure **10** are large enough, **9** and **11** can be isolated. However, if two of the four substituents (A, B, C, and D) are hydrogen, fluorine, or methoxy, the racemization takes place at room temperature.[16] Additionally, some 2,2'-bipyridines and 2-arylpyridines can be resolved and can be configurationally stable.[16] The synthesis of axially chiral biaryls can be envisioned to occur through either the formation of one aromatic ring with the second preformed or the formation of both rings at the same time.

Scheme 5. Atropisomerism in a Substituted Biaryl.

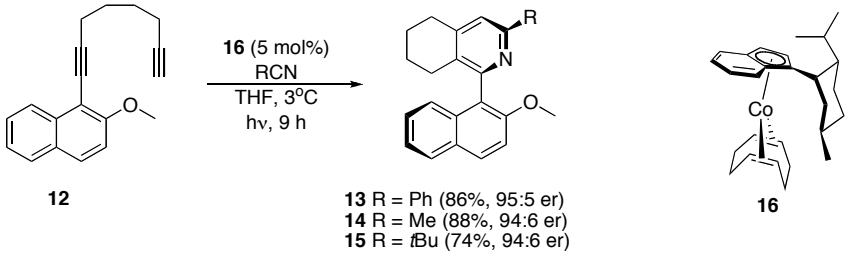


Cobalt-Catalyzed Formation of Biaryls

The construction of a single ring was first realized by Gutnov et. al. in the construction of chiral 2-arylpyridines.[17] Previous studies showed that the [2+2+2] cycloaddition of a nitrile with two alkynes yielded the pyridine derivative and thus prompted the study of an asymmetric variant.[18] A variety of chiral cyclopentadienyl-derived cobalt catalysts were evaluated in the reaction of naphthyl nitriles with alkynes. While the reaction did afford 2-naphtylpyridines, the yields were typically very low (<15%) and the enantioselectivities were moderate (ca. 83:17 er). Interestingly, the chiral ligands used are

responsible for the low yields, as the achiral CpCo(cod) complex provided much higher yields under identical reaction conditions. Changing from a naphthyl nitrile to an alkynyl naphthalene (**12**) allowed for the construction of 2-napthylpyridines in good yield and enantiopurity (Scheme 6).[17]

Scheme 6. Enantioselective Formation of 2-(1-Naphthyl)pyridine.



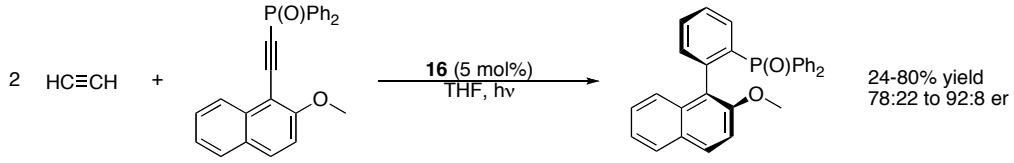
12

13 R = Ph (86%, 95:5 er)
14 R = Me (88%, 94:6 er)
15 R = *t*Bu (74%, 94:6 er)

16

Gratifyingly, 1-naphthylarenes are accessible using the same catalyst (**16**) through the reaction of a 1-alkynylnaphthalene with acetylene (Scheme 7).[19] A very large substituent on the alkyne of the alkynylnaphthalene is required for reasonable enantioselectivities. The diphenylphosphinoyl group, utilized in compound **17**, allows for access of biaryl phosphineoxides (**18**) in moderate to good enantioselectivity, up to 92:8 er. An additional benefit to the phosphinoyl substituent is the formation of biaryl phosphine oxide. Reduction of the oxide with AlH_3 allows for the facile production of chiral monodentate biaryl phosphines. The use of cobalt complexes as catalysts for the [2+2+2] reaction allows for the formation of a wide variety of chiral biaryls with typically moderate yields, it has been shown that rhodium complexes catalyze the [2+2+2] reaction with higher enantioselectivities although with a slightly more limited substrate scope.

Scheme 7. Enantioselective Formation of 1-Arylnaphthalene.

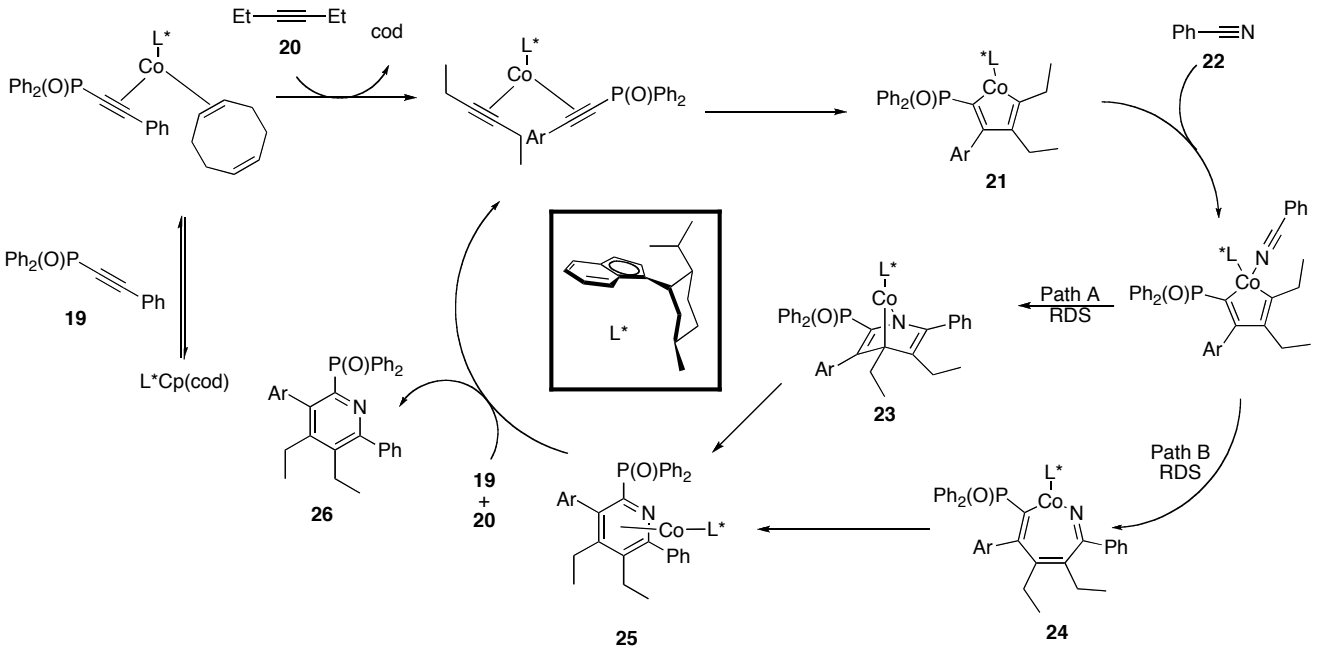


17 **18**

A catalytic cycle (Scheme 8) has been proposed on the basis of theoretical[20] and experimental studies. Calculation of both ground and transition state energies at the DFT level[20] supports the pre-coordination of two alkynes, followed by cycloisomerization to give the Co(III) cobalacyclopentadiene. Experimentally, a 1:1:1 mixture of phosphine oxide **19**, 3-hexyne (**20**), and benzonitrile (**22**) generates predominantly the substituted pyridine (**26**).[19] This observation supports the intermediacy of **21**, the formation of any constitutional isomer of **21** as an intermediate would lead to different products. Presumably, the electron poor **19** binds to the Co(I), deactivating the cobalt towards another electron

deficient alkyne, but allowing the binding of the more electron rich 3-hexyne. The cycloisomerization to **21** is supported by the lack of affinity between the free nitrile and the Co(I) center. Only by oxidative coupling to give **21** with an electron poor Co(III) center can the coordination of the nitrile be rationalized. The next step in the cycle is currently ambiguous due to a lack of experimental data to support the formation of the [2.2.1]cobaltabicycloheptane, **23**, or the cobaltacycloheptatriene, **24**. Computational studies of the trimerization of acetylene with a CpCoL catalyst have not found any low energy pathways through a cobaltacycloheptatriene, while favorable pathways through a [2.2.1]cobaltabicycloheptane have been shown.[20] Interestingly, no minimum corresponding to a cobaltacycloheptatriene was found, suggesting while the mechanism may proceed through Path A, **23** is not an energy minimum but rather a transition state.

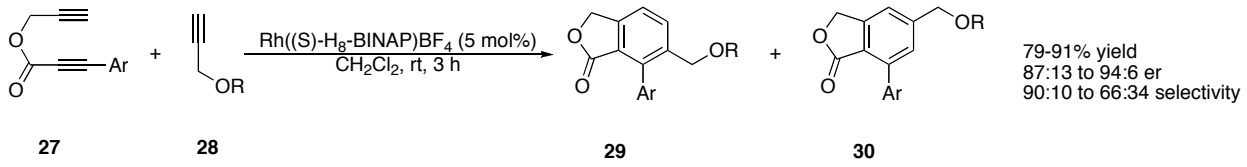
Scheme 8. Proposed Catalytic Cycle for the Cobalt-Catalyzed, Enantioselective [2+2+2] Cyclization.



Rhodium-Catalyzed Biaryl Formation

An alternative to the use of cobalt cyclopentadienyl complexes, which must be prepared prior to use, is the cationic Rh(I) phosphine complexes which allow the use of commercially available ligands. Tanaka et. al. have recently shown that a suitable alkyne and α,ω-diyne will combine in the presence of $[Rh(H_8\text{-binap})]BF_4$ to give aryl phthalides with moderate to good enantioselectivities (Scheme 9).[21] The rhodium-catalyzed reaction displays higher regioselectivities compared to the cobalt catalyzed process. When a symmetrically substituted alkyne is employed, the yields decrease to 45-73% but excellent enantioselectivities are observed in most cases.

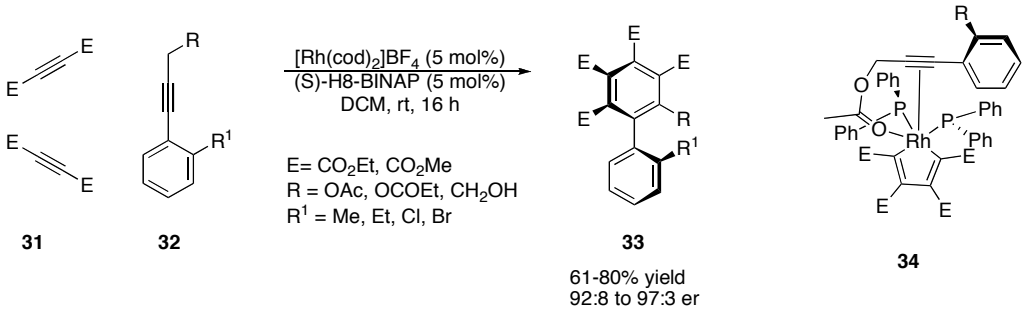
Scheme 9. Cationic Rhodium-Catalyzed [2+2+2] Cycloadditions.



27 28 29 30

The rhodium complex can catalyze the double intramolecular cyclization to combine three alkynes to give enantioenriched biaryls (Scheme 10).[22] Unfortunately, two of the alkynes (**23**) must be electron deficient as the only known examples involve the diesters. Although in-depth mechanistic studies have not been done, it is generally assumed that the rhodium-catalyzed [2+2+2] cyclization occurs by a similar mechanism as the cobalt-mediated reaction. A metalacyclopentadiene is formed by electrocyclization of two electron deficient alkynes coordinated to the metal center, which then coordinates the more electron rich alkene, followed by electrocyclization and reductive elimination.[23] On the basis of this assumption, a model has been proposed for the enantioselectivity of the reaction, formation of complex **26** being the stereo-determining step of the catalytic cycle. In addition to these advantages compared to the cobalt-catalyzed cyclization, the rhodium system can also catalytically form achiral arylpyridines[24] with good regioselectivity and 2-phosphinobiaryls[25] in similar yields and selectivities.

Scheme 10. Double Intermolecular Enantioselective Biaryl Synthesis and Proposed Intermediate.



31 32 33 34

CONCLUSION

In recent years, the development of enantioselective [2+2+2] cyclizations have allowed for the preparation of a variety of different types of chiral compounds. The two most important types of compounds are molecules bearing benzylic stereogenic centers and stereogenic axes. The optimization of reaction conditions and ligands is well underway and while the task is far from over, much success has been realized. A solid mechanistic foundation is currently lacking and would allow for better ligand

design. Ultimately, the ability to develop highly chemo- and regioselective catalysts will make the [2+2+2] manifold more attractive to synthetic chemists.

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