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Carbon-Carbon Bond Formation Facilitated by π -Complexed Organometallic Auxiliaries: An Overview

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A Review:

Organometallic moieties attached to substrates via π -complexation play an important role as auxiliaries. As described in the present review, η -linked auxiliaries have been employed to overcome numerous synthesis obstacles that continue to present significant challenges for catalyzed reactions. This has been particularly true in carbon-carbon bond forming reactions involving highly unsaturated systems such as arenes, dienes and allenes, which are emphasized here.

1. INTRODUCTION

While the development of catalyzed reactions continues at an unabated pace, auxiliary-assisted carbon-carbon bond formation remains an important synthesis strategy. In this vein, organometallic complexes attached to substrates via π -complexation have proven particularly attractive as auxiliaries since upon removal they leave no trace of their attachment. These auxiliaries have been employed to overcome numerous synthesis obstacles that present significant challenges for catalyzed reactions. The present review is concerned mainly with π -complexed auxiliaries that do not directly intervene [1] in the bond-forming step of a given chemical transformation. The focus is on organometallic entities that, through steric interactions or indirect electronic influence, lead to desired bond formation that is not otherwise possible or favorable without the auxiliary. Importantly, these traceless auxiliaries are removed under mild reaction conditions (Scheme 1).

Except for an excellent summary by Paley that discussed planar chiral organometallic complexes, [2] there have been no reviews since 2007 [3] that have summarized developments involving π -complexed non-intervening organometallic auxiliaries [4]. The

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aim of this review is to highlight representative reactions involving such auxiliaries though this coverage is not intended to be exhaustive.

2. CHROMIUM AUXILIARIES

Functionalization of simple arenes is challenging due to their poor reactivity. A well-developed strategy is to utilize low-valent chromium carbonyls, which form stable η^6 -complexes with arenes. We summarize here several key strategies that illustrate their utility as mainly non-intervening auxiliaries. Chromium tricarbonyl is a versatile auxiliary group as it can be easily attached and removed under mild conditions and is compatible with a wide variety of reagents except oxidizers. Chromium tricarbonyl complexes are generally easy to handle, air stable, and can be stored for long periods away from light. Several methods are available for complexation depending upon the substitution present on the arene group. The preferred method is prolonged (4 days) thermolysis of $\text{Cr}(\text{CO})_6$ with an excess of the arene under an inert atmosphere.

Chromium auxiliaries have been utilized to functionalize arenes via a nucleophile addition/oxidation sequence pioneered by Semmelhack [5]. This is an example of an auxiliary that intervenes in relatively direct way in bond formation, an aspect that has been previously reviewed [3]. However, the chromium tricarbonyl auxiliary is also useful in synthesizing various natural products due to their ability to impart a chirality to aryl rings (planar chirality) temporarily allowing these entities to serve as chiral auxiliaries. For example, enantioenriched planar chiral complex **1** was obtained through complexation with $\text{Cr}(\text{CO})_6$ at 140°C followed by resolution and utilized in the synthesis of (–)-lasubine (Scheme 2) [6]. The key step of this synthesis involved a Lewis acid-mediated diastereoselective aza-Diels-Alder reaction of imine **1** with Danishefsky's diene. The chromium auxiliary provided a facial selectivity in the concerted addition step to afford pyridinone intermediate **2**. Further elaboration of **2** to the natural product via the intermediacy of **3** involved an intermolecular radical cyclization.

Chromium tricarbonyl has been used in the preparation of axially chiral biaryls via a Suzuki coupling. In this approach, biaryl axial chirality is induced by the planar chirality present in arene-chromium complex **4**. The potency of this concept was validated by its successful application to the formal and total syntheses of (–)-steganone, [7] the synthesis of the AB ring system of vancomycin, [8] and the total synthesis of korupensamines A and B [9]. For instance, the synthesis of korupensamine A began with the lithiation and bromination of chromium arene complex **4** to furnish non-racemic intermediate **5** (Scheme 3). A subsequent Suzuki-Miyaura coupling of **5** with a naphthylboronic acid in refluxing methanol produced axially chiral biaryl chromium complex **6**. This intermediate was subsequently elaborated to korupensamine A, which included decomplexation under relatively mild conditions of 10% HCl_{aq} in THF at room temperature in air.

3. IRON AUXILIARIES

Relative to its chromium cousin, π -complexes of iron tricarbonyl have been utilized infrequently in organic synthesis. Neutral iron tricarbonyl auxiliary has been primarily

exploited to promote facial selectivity in diene systems and its reactive cationic form for regioselective bond formation. Typically a diene is treated with iron pentacarbonyl to produce a neutral tricarbonyl(cyclohexa-1,3-diene)iron complex such as **7** (Scheme 4). Exposure of **7** to triphenylmethyl tetrafluoroborate leads to electrophilic species such as **8** via hydride abstraction.

Cationic complexes such as **8** may act as a cyclohexanone γ -cation synthon when a directing group (-OMe) is present. Nucleophilic addition to this system occurs exclusively at the more hindered γ -carbon center, away from the directing group. Being adjacent to the -OMe group, the α -carbon center is electron rich and thus discourages nucleophilic addition at that position. Several carbon nucleophiles have been used in this system resulting in γ -addition products [10].

The Ong group has explored the utility of cyclohexadienylium-Fe(CO)₃ salts as intermediates in complex synthesis (Scheme 5). Utilizing TMS-CN, [11] a cyano-substituted quaternary center was installed to give intermediate **9**. Further manipulation of this cyano group produced late-stage intermediate **10**, important in the synthesis of nitraria alkaloids [12]. This method has also been applied to obtain *cis*-fused perhydroisoquinoline ring systems [13] as well as spiro-oxaquinolizinone (ABC ring) core of upenamide [14].

Iron tricarbonyl can also act as a diene protecting group. Olefinic bonds can be functionalized selectively in the presence of the alkenes complexed with Fe(CO)₃ groups. For instance the C₂₂-C₂₃ double bond of ergosteryl acetate **11** was selectively hydrogenated with the B-ring diene protected by Fe(CO)₃ [15]. Surprisingly, the complex is also compatible with oxidative conditions. Thus, using osmium tetroxide, the exocyclic C₂₂-C₂₃ double bond was transformed to the corresponding diol, though the authors do not comment on the diastereoselectivity of this reaction (Scheme 6) [16].

The planar chirality of enantiopure iron-tricarbonyl complexes has been utilized as a strategy for stereoselective bond formation. For example, in the presence of (*R*)-*p*-tolyl sulfoxide, the Fe(CO)₃ auxiliary complexes the diene face opposite the sulfoxide oxygen to give intermediate **12** (Scheme 7) [17]. Similar diastereoselective complexations have been observed with other chiral auxiliaries [18]. Subsequent allylation of the nearby aldehyde carbonyl in complex **12** was achieved in relatively high diastereoselectivity. Further elaboration led to a medium sized carbocycle (Scheme 7) [17].

4. MOLYBDENUM AUXILIARIES

Organomolybdenum species have found applications as auxiliaries in the synthesis of complex polyfunctional small molecules. In particular, their planar chiral cationic η^3 -complexes have proven useful in the derivatization of allyl systems. These complexes are usually prepared by the reaction of an allyl electrophile with a suitable Mo(0) source (Scheme 8). The oxidative addition of Mo(CO)₃(L)₃ type complexes with an allylic halide or ester followed by ligand exchange with LiCp produces neutral complexes **13**, which are stable 18-electron species and unreactive toward nucleophiles.

These are not strictly non-intervening organometallic auxiliaries since the molybdenum of **13** must be activated by treatment with nitrosonium tetrafluoroborate to give electrophilic complex **14**. The most common Mo(0) source is Mo(CO)₃(MeCN)₃ [19]; however, other variants including Mo(CO)₃(DMF)₃, Mo(CO)₃(PhMe), Mo(CO)₃(diglyme) have also been used. The complexation step relies on several factors such as leaving group, allylic substitution, nature of the Mo ligand, and heteroatom substituents on the substrate.

Additions to substrates bearing a molybdenum auxiliary have been investigated with enantiomerically pure benzoate (*S*)-**15**. Liebeskind has suggested that coordination with an ester carbonyl group takes place as a first step followed by the loss of a carbonyl group [20]. After losing another CO and coordinating with the nearby carbon-carbon double bond, neutral Mo(II) complex **16** is produced with overall retention of configuration from benzoate **15** (Scheme 9) [21].

However, the stereochemistry of the oxidative addition of various Mo(0) species depends on the concentration of the Mo source and the nature of its associated ligands. The structure of the substrate itself can also influence product configuration. For example, enantiopure substrate **17** led to a 92:8 mixture of inversion and retention products with Mo(CO)₃(DMF)₃. By contrast, exclusive retentive product was produced using Mo(CO)₃(PhMe) as the Mo(0) source (Scheme 10).

Importantly, organomolybdenum auxiliaries have been used to install carbon-carbon bonds in a regio- and stereoselective manner. For example, acyclic Mo(II) complex **18** pioneered by Faller [22] when exposed to a nucleophilic addition reaction with sodium diethyl malonate resulted in enantiomerically pure regioisomers though with poor (3:2) regioselectivity (Scheme 11). However, when larger nucleophile **19** was used, the regioselectivity improved substantially [23]. Subsequent demetalation of the product was accomplished by mild oxidation with ceric ammonium nitrate or, in some cases, by exposure to air.

The utility of enantiomerically enriched planar chiral substrates containing the molybdenum auxiliary was nicely demonstrated by Liebeskind in his stereospecific synthesis of *cis* and *trans*-2,6-disubstituted pyran compounds (Scheme 12) [24]. Neutral air-stable complex **21** was prepared in one pot by reacting **20** with Mo(CO)(MeCN)₃ followed by ligand exchange with CpLi with retention of the original allylic acetate configuration [25]. Compound **20** can be easily accessed from commercially available enantiopure tri-O-acetyl-glucal [26]. Cationic 2H-pyran complex **22** was then obtained via an ionization reaction with Et₃O⁺PF₆⁻. Guided by the molybdenum auxiliary, substrate **22** underwent *anti*-selective addition reactions. For example, the treatment of **22** with a Grignard reagent led to product **23** in which the nucleophilic group was added to the face opposite to the auxiliary. The resulting neutral complex **23** was further activated by ionizing the ethoxy group with Ph₃C⁺PF₆⁻ followed by nucleophilic hydride delivery with NaBH₃CN to furnish *trans*-2,6-disubstituted pyranymolybdenum complexes **25**. Isomeric *cis*-2,6-disubstituted complexes **25** were obtained easily by reversing the order of nucleophile addition. The metal auxiliary was removed in excellent yield by treating with trifluoroacetic acid.

Subsequently, the Liebeskind group developed a one-pot scalable protocols to access various η^3 -pyranyl and η^3 -pyridinyl building blocks from furfuryl alcohols or *N*-protected furfuryl amines (Scheme 13) [27]. Pyranyl or pyridinyl scaffolds **26** containing a molybdenum auxiliary were obtained non-racemically using modified oxa- and aza-Achmatowicz reactions in the presence of a chiral auxiliary.

These air- and moisture-stable pyranyl and pyridinyl molybdenum complexes have been used in the enantio-controlled construction of a diverse set of heterocyclic organic systems. The η^3 -molybdenum and its auxiliary ligands provide a regio- and stereocontrol element on the pyran ring template that allows introduction of three new stereocenters and makes possible novel and strategic reaction pathways that are not achievable with traditional organic systems. This organometallic scaffolding strategy was elaborated on η^3 -piperidinyl molybdenum building blocks to access natural product bearing a piperidine ring such as product **28** [27b]. This natural product was obtained from the complex **26** via sequential addition of three functional groups through complete regio- and stereoselective fashion guided by the Mo(CO)Tp auxiliary to furnish the advanced piperidine intermediate (–)-**27**. Further elaboration of the compound **27** completed the synthesis of (–)-6,7-dehydro-indolizidine 233E, **28** (Scheme 14).

Similarly, the natural product (–)-andrachcinidine (**30**) was obtained via a pseudodesymmetrization approach involving a highly diastereoselective methoxide replacement from an η^3 -piperidineyl molybdenum building blocks (+)- or (–)-**29**. In this approach, an enantiocontrolled methoxide-abstraction/nucleophilic addition strategy was developed in the presence of a chiral auxiliary (*trans*-2-(*R*-cumyl)cyclohexyl) to obtain 2,6-disubstituted piperidine adduct, which was ultimately converted to natural product **30** (Scheme 15) [28].

5. MANGANESE AUXILIARIES

The methylcyclopentadienylmanganesedicarbonyl (MMD) moiety forms stable neutral complexes when appended to alkenes and allenes. One of the attractive features of the MMD auxiliary is that the precursor material MeCpMn(CO)₃ (MMT) is a relatively inexpensive and widely available gasoline additive. Substrates possessing the MMD auxiliary are prepared by a ligand exchange reaction of MMT under UV photolysis with electrophilic olefins or alkynes in coordinating solvents such as THF (Scheme 16). It has been suggested that, after carbonyl loss, the coordinately unsaturated species **31** initially establishes an η^1 -bond with the carbonyl oxygen of a substrate (as in **32** for example). Over time, this complex isomerizes to form a more stable π -alkene linkage (η^2 -bond) [29]. In dienal systems, the MMD auxiliary binds exclusively to the α,β -double bond as in **33** [29a, 30].

Taking advantage of MMD as an alkene-connected auxiliary, polystyrene resin **34** was created to contain a cyclopentadienylmanganesetricarbonyl unit through an amide bond. In a proof-of-concept study, resin **34** was then used to link and unlink a series of simple electron deficient alkenes (Scheme 17) [31].

The MMD auxiliary has found more extensive application in facilitating the synthesis of allenes and in their subsequent elaboration. Pioneering efforts by Franck-Neumann involved an initial complexation of alkynals **35** ($R^1 = H$) under UV irradiation to form MMD-allenyl intermediate **36** (Scheme 18). Subsequent treatment of **36** with DBU led to MMD-complexed allene **37a** as the *exo*-diastereomer in which the metal auxiliary is “*trans*” to the γ -substituent [32]. The use of Al_2O_3 as a base in this isomerization completely eroded the *exo*-selectivity. It has been proposed that the role of the manganese auxiliary is to reverse the thermodynamic preference for the alkyne in favor of the allene in the isomerization reaction [33]. The importance of the use of the MMD auxiliary to alter the thermodynamic preference for alkyne is highlighted by failed attempts to isomerize alkynyl **35** ($R_1 = -OCH_3$) to the corresponding allene **38** using DBU in the absence of the auxiliary even after a prolonged reaction time (4 days) [33].

The MMD auxiliary also serves as a protecting group for allenals, which are otherwise prohibitively reactive at their sp-centers towards nucleophiles. Thus, allenal **39**, obtained via an alkyne isomerization strategy, was coupled with a non-racemic hydrazine and the resulting diastereomers separated to give (*S*)-(+)-**40** (Scheme 19). Hydrazone **40** was hydrolyzed in good yield to reveal enantiomerically enriched allenal **41**. Further elaboration of **41** led to the synthesis of insect pheromone **42** in high enantiomeric purity [34].

The MMD auxiliary has also been used to promote stereoselectivity in aldol reactions leading to allenyl α -carbinols [35]. MMD-complexed alkynyl ketones **43** readily underwent aldol reactions with aromatic aldehydes to afford products **46** after MMD-removal with high diastereoselectivity and complete regioselectivity. The preference for the major diastereomer in these reactions was rationalized on the basis of selective formation of *E*-(*O*)-cumulenolate intermediate **44** (Scheme 20). Specifically, the terminal substituents on this cumulated enolate are four carbons away from each other thus posing a significant challenge to control the geometry of this intermediate. This problem was mitigated by the MMD unit whose steric bulk promotes an *E*-(*O*)-cumulenolate in which the two substituents lie in an *anti* arrangement to the auxiliary. The cumulenolate then underwent an aldol reaction with aldehyde most likely via closed transition state **TS45** promoting a (*Re*)-face addition to aldehyde. A final MMD-removal step under mild conditions using $PhI(OAc)_2$ afforded allene products **46**. Importantly, the direct conversion of alkynyl ketones to allene products **46** is not possible with any useful level of diastereo- and regioselectivity.

The MMD auxiliary also proved critical to the successful production of non-racemic allenyl aldehydes using a chiral ammonium phase transfer isomerization protocol. As discussed, conjugated alkynyl aldehydes such as **47** normally do not isomerize to their thermodynamically less stable allene isomers. However, with a manganese auxiliary in place, non-racemic allenyl aldehyde **48** was obtained (along with seven other examples) in good enantioselectivity (Scheme 21) [36].

The MMD auxiliary is thought to magnify the axial chirality of the allene moiety, allowing for highly diastereoselective additions to the aldehyde carbonyl of **47** [37]. Using this strategy, nitrile-substituted allenyl carbinol **49** was prepared and subsequently converted to Hagen's gland lactone **50** in four steps (Scheme 22). This total synthesis, one of the most

succinct for Hagen's gland lactone to date, highlights the utility of MMD as a multipurpose auxiliary in complex small molecule construction.

6. CONCLUSION

From the standpoint of atom-economy, bond-forming reactions that give useful results without auxiliaries (or even catalysts) are most ideal. However, as briefly described in this review, π -complexed organometallic auxiliaries have been employed in specialized cases to overcome longstanding synthesis obstacles that present significant challenges for catalyzed reactions. The auxiliaries discussed here exert their synthetically useful effect mainly through steric interactions or indirect electronic influence. Though this synthetic strategy will always entail the use of stoichiometric organometallic entities, they offer the benefit of removal usually under mild conditions leaving no trace of their attachment. It is hoped that progress in this area will continue thus providing valuable alternative tools for synthesis chemists as they undertake ever more challenging complex synthesis endeavors.

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Scheme 1.
Organometallic auxiliary concept.

Scheme 2.
Synthesis of (-)-lasubine

Scheme 3.

Access to axially chiral biaryls; key steps in the total synthesis of korupensamine A.

Scheme 4.
Remote functionalization on cyclohexanone system

Scheme 5.
Preparation of spirocycles.

Scheme 6.
Iron tricarbonyl as diene protecting group.

Scheme 7.
Iron tricarbonyl as a steric directing group.

Scheme 8.
Complexation with molybdenum tricarbonyl.

Scheme 9.
Stereospecific complexation with molybdenum.

Scheme 10.
Complexation of a molybdenum auxiliary.

Scheme 11.

Regioselective additions in acyclic and cyclic systems.

Scheme 12.
Regiodiverse syntheses of disubstituted dihydropyrans.

Scheme 13.

One pot access to molybdenum building blocks.

Scheme 14.
Construction of a dehydroindolizidine.

Scheme 15.
Synthesis of (-)-andrachcinidine.

Scheme 16.
Complexation of the CpMn(CO)₂ auxiliary.

Scheme 17.

Polymer supported MMD auxiliary as an alkene linker.

Scheme 18.

MMD auxiliary promotes alkyne to allene isomerization.

Scheme 19.

MMD as allenal protecting group in pheromone synthesis.

Scheme 20.
Diastereoselective formation of allenyl carbinols.

Scheme 21.
Enantioselective isomerization of MMD-alkyne.

Scheme 22.

Stereoselective synthesis of a natural product using MMD-allene building block.