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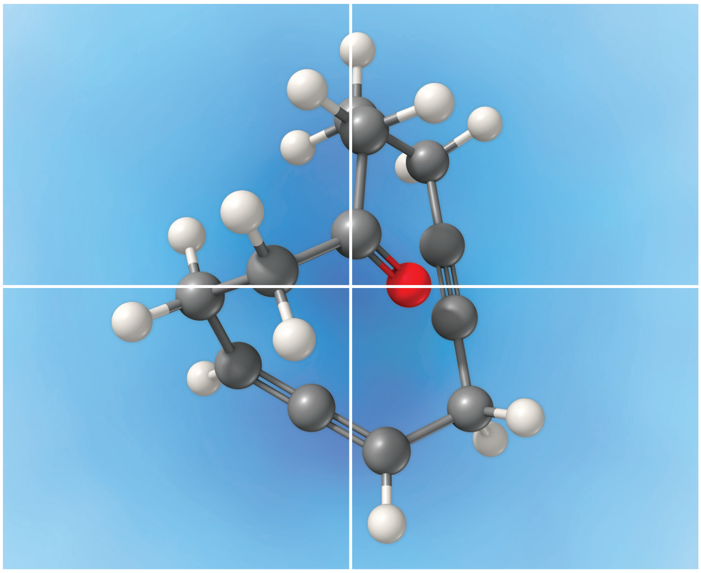

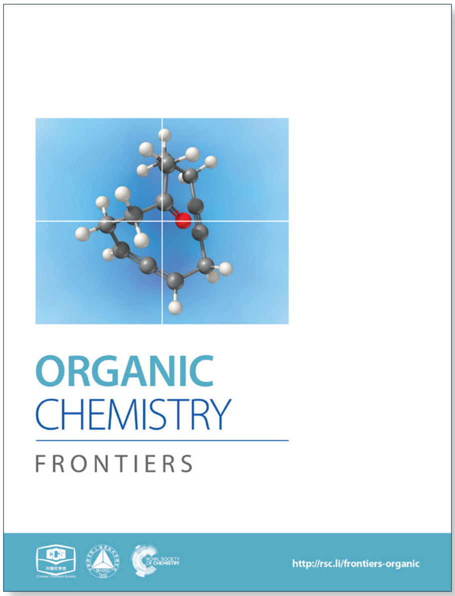

Organometallic Intermediate-Based Organic Synthesis: Organo-di-Lithio Reagents and Beyond

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Dedicated to Prof. Ei-ichi Negishi on the occasion of his 80th birthday

Supporting Information Placeholder

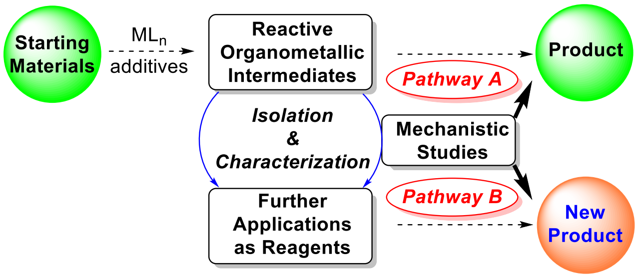
ABSTRACT: Metal-mediated organic reactions have become one of the great frontiers of organic synthesis. These processes usually involve multiple transient or unobservable reactive intermediates. The isolation and study of these reactive organometallic intermediates would not only lead to a better understanding of their reactivity, but can also guide the discovery of new reactions, culminating in the advancement of novel synthetic methods. Herein we provide a perspective of research strategy, which focuses on organometallic intermediate-based organic synthesis. Specifically, we highlight the applications of our organo-di-lithio reagents to the synthesis of a diverse range of reactive intermediates and small molecules. A series of organo-di-lithio reagents has been synthesized, isolated, and applied in organic and organometallic synthesis. These isolated dilithio reagents can be transformed into a variety of organo-di-metallic or metallacyclic compounds via transmetallation, which in turn provides access to organic and organometallic compounds with interesting and useful properties. Selected examples by other research groups are also briefly mentioned, in which reactive organometallic intermediates are isolated for a better understanding of reaction mechanisms, and in some cases are further applied to synthesis.

1. ORGANOMETALLIC INTERMEDIATE-BASED ORGANIC SYNTHESIS: THE STRATEGY

Organometallic compounds, either as reagents or catalysts, are widely applied in synthetic chemistry.[1] Traditionally, the synthesis, isolation, spectroscopic properties, and structural characterization of organometallic compounds are the main interests of inorganic chemists. On the other hand, organic chemists are more generally concerned with the application of inorganic and organometallic complexes to mediate or catalyze organic transformations. Despite what appears to be a fruitful middle ground for research between these two areas, there is limited activity in organometallic intermediate-based organic synthesis in recent years. The identification of many of the intermediates in metal-mediated and catalyzed organic reactions have fallen between the cracks. Filling this gap should benefit both areas and advance the development of synthetic chemistry as a whole.[2]

Usually, as illustrated in Scheme 1, after the discovery of a new reaction, the researchers would (or should) have interest in the reaction mechanism. They may try to isolate and characterize the reactive organometallic intermediates, in addition to other ways to investigate the reaction mechanism. Elucidating a mechanism in most cases is much more challenging and may require much more diversified skills. Based on the study of organometallic intermediates and other mechanistic evidence, a possible reaction pathway will be formulated, and perhaps further improvement of the efficiency of catalysts and reactions of existing catalytic reactions will be made (***Pathway A***), as exemplified in many important catalytic processes developed over the years.[3-11] Alternatively or ideally, further synthetic application of the isolated reactive organometallic intermediates, particularly when they are unprecedented ones, would lead to the development of completely new reactions and synthetic methods (***Pathway B***).

Scheme 1. Organometallic Intermediate-based Organic Synthesis: The Strategy

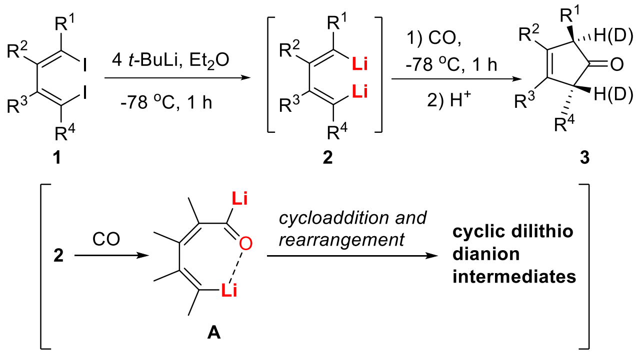


Metal-mediated stoichiometric reactions are widely applied in synthetic chemistry and chemical industry. Thus, in this Perspective, we focus on metal-mediated stoichiometric reaction patterns to introduce the research strategy, using the isolated reactive organometallic intermediates as reagents (Scheme 1, ***Pathway B***). The synthesis, structure and applications of organo-di-lithio reagents will be highlighted. Transmetallation of these dilithium compounds leads to second-generation organometallic intermediates as reagents, which have also been applied to organic synthesis.

2. REACTION OF DILITHIO REAGENTS WITH CO: DISCOVERY OF A NEW REACTION, ISOLATION OF REACTIVE ORGANOMETALLIC INTERMEDIATES, AND FURTHER APPLICATION

Dicovery of a New Reaction. 1,4-Dilithio-1,3-butadiene derivatives (**2**: dilithio reagents for short) shown in Scheme 2 have been known for a long time.[12,13] Although some heterocycles (mainly metallacyclopentadienes) were prepared from dilithio reagents and metal salts,[14,15] organic tranformations and synthetic applications of dilithio reagents had been rarely investigated piror to our studies, which demonstrated unique reactivity and useful synthetic applications, when treated with various organic substrates.[16,17] In the early 2000s, we found that the reaction of dilithio reagents **2** with CO afforded *trans*-3-cyclopenten-1-ones **3** (Scheme 2).[18] This reaction featured high efficiency, regio- and stereoselectivity, and was an unprecedented carbonylation of organolithium reagents.

Scheme 2. *in situ* Generation of Dilithio Reagents 2 and Their Reaction with CO



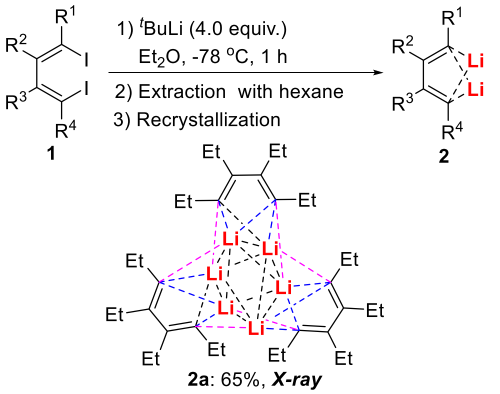
Initially, a reaction mechanism was proposed (Scheme 2) without the structural information of the dilithio intermediates **2** and their carbonylation reaction intermediates. This was based on the structures of the products **3** and the hypothesis that carbonylation of one C-Li bond in **2** would form the acyllithium intermediate **A**.[19] It was also reasonable to propose an intramolecular stabilization of this entity by chelation. This intermediate **A** could undergo cycloaddition reaction/rearrangement to afford cyclic dilithio dianions. To shed light on the reaction pathway from the diiodo reagents, next we set out to isolate the reactive organometallic intermediates.

Isolation and Characterization of Dilithio Reagents 2 and Oxy-cyclopentadienyl Dilithium Intermediates 4. Attempts to isolate the intermediates formed between dilithio reagents **2** and CO directly from the reaction mixture generally failed, primarily due to the presence of a complicated reaction mixture, and the existence of LiI salts that prevented the isolation, purification, and crystallization of reactive intermediates. We, therefore, tried to establish a method of obtaining pure dilithio compounds **2** (Scheme 3) without the complication from LiI.[13] Compound pure **2a** was obtained in 65% isolated yield by extraction of **2a** from the reaction mixture with hexane, filtration to remove LiI, and recrystallization in hexane.[20] The X-ray structure determination indicated **2a** was a trimer with a Li_6 pseudooctahedron.[20a] A variety of dilithio reagents **2** could be obtained as crystalline compounds on a gram-scale. They are stable as long as stored dry under N_2 and can be directly used as reagents.

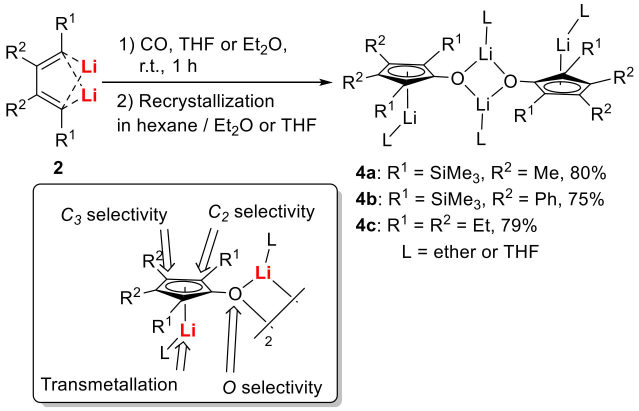
With pure isolated dilithio reagents **2** in hand, we then successfully isolated and characterized the reaction intermediate between the dilithio reagents **2** and CO. Thus, the oxy-cyclopentadienyl dilithium intermediates **4** (OCp for short) were obtained (Scheme 4).[21] X-ray structural analysis showed that it is a dimer in the solid state and two Cp rings are connected through a "Li_2O_2" four-membered ring. Each Cp ring is coordinated to a lithium atom in an η^5-fashion.

These OCp dianions **4** are structurally unique (Scheme 4). There are two reactive sites: the CpLi moiety and the exocyclic OLi group. In addition, the CpLi moiety may have an issue of site-selectivity, *eg*. C-2 or C-3 selectivity. Therefore, treatment of **4** with organic substrates or organometallic compounds might lead to interesting chemo- and regio-selectivity.[21] Thus, the reaction chemistry and applications of the isolated intermediates **4** were subsequently investigated.

Scheme 3. Isolation and Characterization of Pure Organo-di-lithio Reagents 2



Scheme 4. Isolation and Characterization of Dilithio OCp Dianions 4

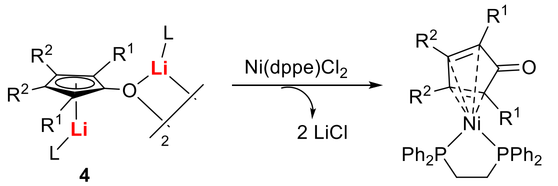


Application of Oxy-cyclopentadienyl Dilithium Intermediates 4 (OCp Dianions). Since these OCp dianions **4** could be expected to act as precursors or ligands for transition metal complexes, we investigated the reactivity of dianions **4** with transition metal compounds. For example, treatment of **4** with $Ni(dppe)Cl_2$ afforded the cyclopentadienone-nickel complexes **5** in good isolated yields (Scheme 5), demonstrating the unique utility of OCp dianions **4**.[21]

It was also found that the reaction of **4** with electrophiles was dependent on the nature of electrophiles and the reaction conditions (Scheme 6).[18,21] When **4** was treated with 2 equiv of MeI, Me_2SO_4, benzyl halides, or propargyl halides, *trans*-3- C-2-alkylated cyclopentenone derivatives **6** were obtained with perfect chemo-, regio- and stereo-selectivity. When acid chlorides (RCOCl) were used, the reaction afforded double acylated cyclopentadienes **7a–c**. When ^{t}BuCOCl/RCOCl was sequentially added to OCp dianions **4**, mixed double acylated products such as **7d,e** were obtained as the only products. These studies indicate *O*-acylation is faster than C-acylation with ^{t}BuCOCl.

The high-yielding mono *O*-acylation intermediate **8** was especially interesting, since it might provide otherwise unavailable ester-substituted CpLi compounds.

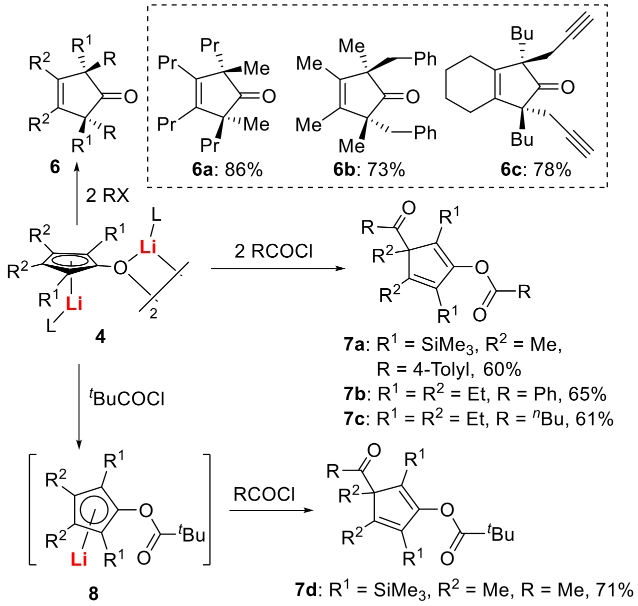
Scheme 5. Application of OCp Dianions 4: Synthesis of η^4-Cyclopentadieneone-Ni(0) Complexes 5



4

5a: R^1 = $SiMe_3$, R^2 = Me, 70%
5b: R^1 = R^2 = Et, 61%

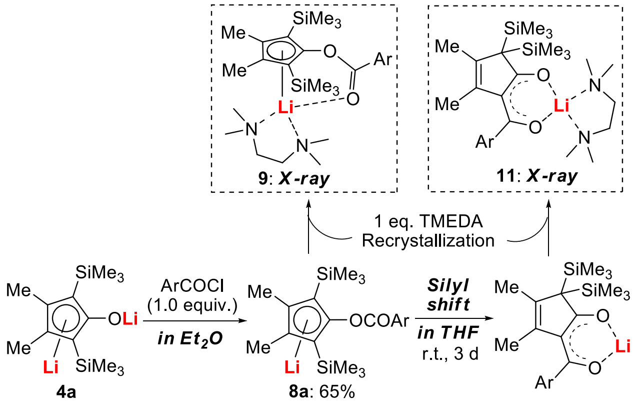
Scheme 6. Site-selective Reaction and Synthetic Applications of OCp Dianions 4



6
6a: 86% **6b**: 73% **6c**: 78%
4
7a: R^1 = $SiMe_3$, R^2 = Me, R = 4-Tolyl, 60%
7b: R^1 = R^2 = Et, R = Ph, 65%
7c: R^1 = R^2 = Et, R = ^{n}Bu, 61%
8
7d: R^1 = $SiMe_3$, R^2 = Me, R = Me, 71%
7e: R^1 = R^2 = Et, R = Ph, 69%

Isolation and Application of the Monoacylated Cyclopentadienyllithium Intermediates 8. The *O*-acylated intermediate **8a** was isolated successfully (Scheme 7).[22] The structure of **8a** was supported by X-ray structural analysis of its TMEDA-coordinated complex **9**. Furthermore, it was found that THF solvent triggered the silyl-shift of **8a** to give the *gem*-bis(trimethylsilyl) complex **10**, whose structure was also confirmed by X-ray structural analysis of the TMEDA-coordinated complex **11**. Application of **8** for the synthesis of substituted metallocene type complexes is on-going research in our laboratory.[23]

Scheme 7. Isolation and Reactivity of Monoacylated Intermediates 8



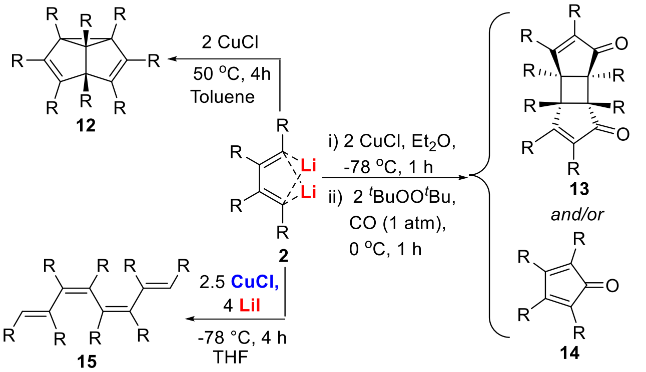
9: *X-ray* **11**: *X-ray*
4a **8a**: 65% **10**: *quant. yield*

3. TRANSMETALLATION OF DILITHIO REAGENTS TO COPPER: DISCOVERY OF NEW REACTIONS, ISOLATION OF REACTIVE ORGANOMETALLIC INTERMEDIATES, AND FURTHER APPLICATIONS

Discovery of New Reactions. The dilithio reagents **2** were expected to undergo transmetallation reactions to afford other organo-di-metallic or metallacyclic compounds.[24] When dilithio reagents **2** were treated with CuCl, semibullvalene derivatives **12** were generated via a CuCl-promoted cyclodimerization (Scheme 8).[25] This method provided the first practical synthesis of semibullvalenes using the metal-mediated C–C bond forming approach. Butadienyl dicopper intermediate was proposed as the first key intermediate upon transmetallation. When carbon monoxide was added, an unprecedented cycloaddition reaction was observed to afford head-to-head dimers **13** as well as the expected cyclopentadienones **14** (Scheme 8).[26] It was also found that the proposed butadienyl dicopper intermediates underwent thermal decomposition-linear dimerization in the presence of additional LiI, providing octa-alkyl substituted all-*cis* octatetraene derivatives **15** following hydrolysis (Scheme 8).[27]

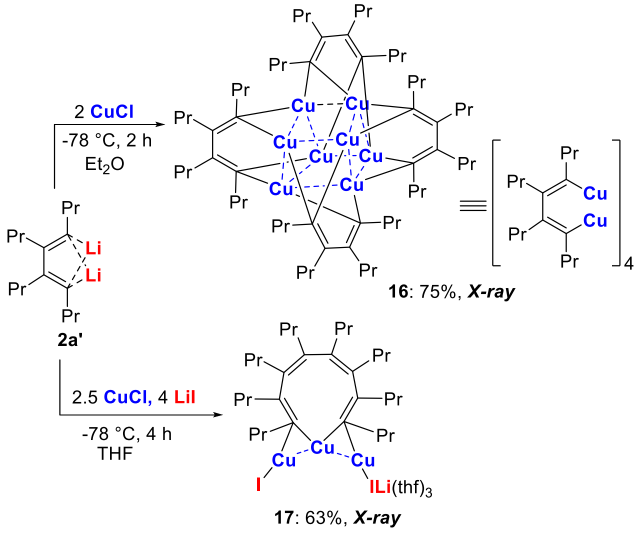
Organocopper compounds are structurally interesting and synthetically useful. However, very few isolable and structurally well-defined alkenyl organocopper(I) compounds were known before our studies.[28] The new reactions in Scheme 8 suggested the possibility of unique structures of the proposed butadienyl dicopper(I) intermediates.

Scheme 8. Transmetallation of Dilithio Reagents 2 to Copper: New Reactions



Isolation of Copper Intermediates. Treatment of the dilithio reagent **2a'** (R = Pr) with 2.0 equiv of CuCl in Et_2O at –78 °C for 2 h afforded the complex **16** (Scheme 9).[29] The X-ray structural analysis of **16** revealed a tetrameric organodicopper aggregate. The four butadienyl moieties are linked to the copper cluster via two three-center-two-electron (3c-2e) bonds. The Cu-Cu stacking interaction stabilizes the organodicopper complex. In contrast, when **2a'** was treated with 2.5 equiv of CuCl and 4.0 equiv of LiI in THF, 1,8-dicopper-1,3,5,7-octatetraene **17** was obtained.[29] The solid state structure shows three copper atoms forming a linear Cu-Cu-Cu geometry. Each terminal carbon is linked to two copper atoms, forming three-center-two-electron (3c-2e) bonds.

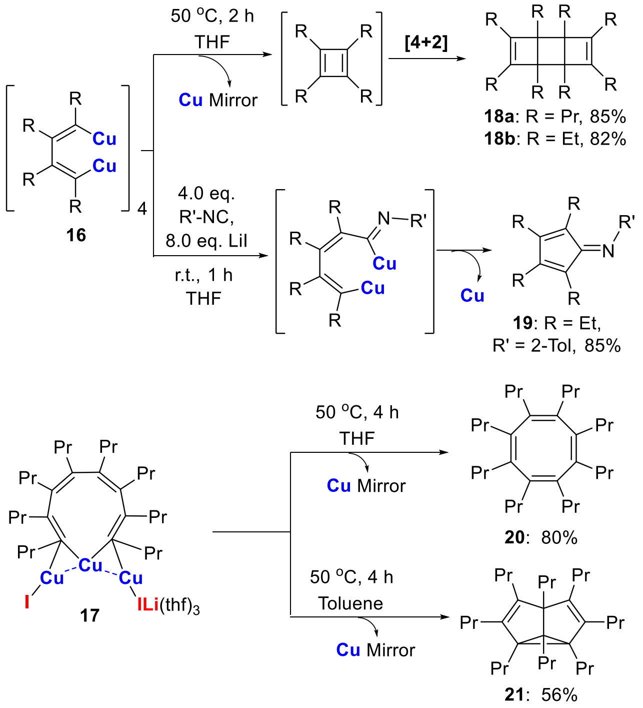
Scheme 9. Isolation and Characterization of 1,4-Dicopper 16 and 1,8-Dicopper 17



Application of the Copper Intermediates. The reactivity of isolated copper intermediates **16** and **17** was explored next. Intramolecular homo-coupling of compounds **16** and subsequent [4+2] cycloaddition gave tricycle[4.2.0.$0^{2,5}$]octa-3,7-dienes **18** (Scheme 10).[29] In the presence of LiI, compound **16** reacted with 2-methylphenyl isocyanide to give the iminocyclopentadiene **19** via 1,1-insertion/intramolecular coupling. When the aggregate **17** was dissolved in THF (Scheme 10), an intramolecular C–C coupling reaction afforded the cyclooctatetraene **20**. Interestingly, when the solvent was switched from THF to toluene, the semibullvalene derivative **21** was obtained.[25,29]

Since these organocopper(I) compounds are structurally very interesting, the Cu-Cu interaction might result in novel applications when treated with organic substrates and small molecules in particular. Further applications are currently under investigation.

Scheme 10. Applications of Isolated Copper Aggregates

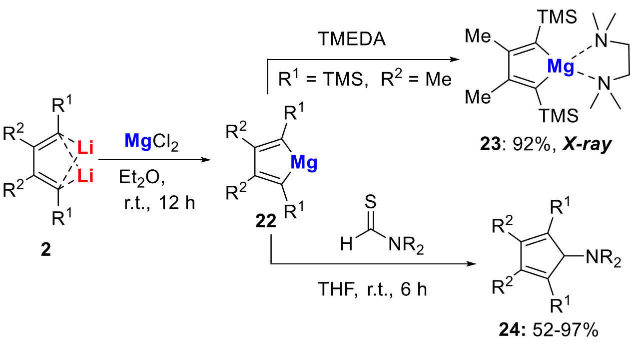


4. SYNTHESIS, STRUCTURAL CHARACTERIZATION, AND SYNTHETIC APPLICATION OF REACTIVE ORGANOMETALLIC INTERMEDIATES

The above research has generally followed the strategy of organometallic intermediate-based organic synthesis, in the order of discovery of new reactions, isolation of reactive organometallic intermediates, and further applications of these organometallic intermediates to new processes. In addition, dilithio reagents have been also directly applied for the synthesis of different organometallic species for the opportunities of developing novel chemistry and synthetic methods. Two recent examples from our group are presented below.

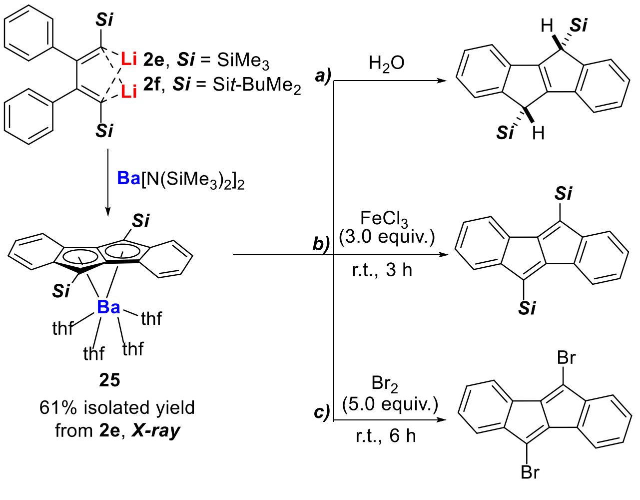
Synthesis, Characterization and Application of Magnesiacyclopentadienes. Metallocyclopentadienes are a class of important organometallic compounds because they are very useful building blocks for synthetic chemistry, and often proposed as key intermediates in metal-mediated or catalyzed reactions. However, metallocyclopentadienes of the alkaline-earth metals were not known until our study. When the dilithio reagent **2b** (R^1 = TMS, R^2 = Me) was treated with one equiv of $MgCl_2$ in Et_2O at room temperature for 12 h, the magnesiacyclopentadiene **22** was formed cleanly (Scheme 11).[30] The structure of **22** was confirmed by X-ray structural analysis of its TMEDA-coordinated complex **23**. As a nearly coplanar, the angle of C1-Mg-C4 (91.54°) is much smaller than the classic C-Mg-C angles in usual tetracoordinate magnesium compounds (115-130°). These magnesiacyclopentadienes showed excellent reactivity towards thioformamides, which provided an efficient synthetic method for the preparation of amino cyclopentadienes **24**. In comparison, when the pure dilithio reagents **2** were treated with thioformamides, a mixture of unidentified products and amino cyclopentadienes were observed. This result demonstrated the unique reactivity of magnesiacyclopentadienes.

Scheme 11. Synthesis, Characterization and Application of Magnesiacyclopentadienes 22



Synthesis, Characterization and Application of Barium Dibenzopentalenides. The first main-group metal η^8 complex coordinated with a dibenzopentalene dianion was recently synthesized and structurally characterized by our group.[31] The barium dibenzopentalenides **25** (Scheme 12), in which the single barium atom is coordinated to the parent pentalene in an η^8 fashion as revealed by their X-ray structural analysis, were synthesized from 2,3-diphenyl 1,4-dilithio-1,3- butadienes and $Ba[N(SiMe_3)_2]_2$ *via* formation of Ba-C (sp^2) bonds. Preliminary reaction chemistry of barium dibenzopentalenides **25** has confirmed that synthetically useful applications can be expected. As demonstrated in Scheme 12,[31] dibenzopentalene derivatives, which have attracted considerable attention recently because of their unique planar structures and anti-aromatic character, could be obtained efficiently via further reactions of the isolated barium dibenzopentalenides **25**.

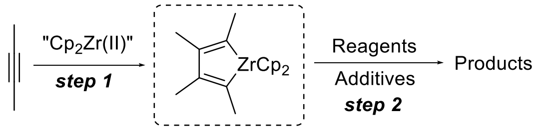
Scheme 12. Synthesis, Characterization and Application of Barium Dibenzopentalenides 25



5. SOME OTHER EXAMPLES INVOLVING STRUCTURALLY CHARATERIZED ORGANOMETALLIC INTERMEDIATES

Other representative examples including transition-metal or rare earth metal-mediated or catalyzed reactions, in which reactive organometallic intermediates are isolated and structurally characterized, are demonstrated in Schemes 13 and 14. The preparation and reaction chemistry of metallacyclic compounds have attracted much attention in recent years. In particular, a number of zirconacycles have been isolated and structurally characterized. One-pot generation of zirconacycles and sequential reactions with various substrates have been applied for organic synthesis (Scheme 13).[32]

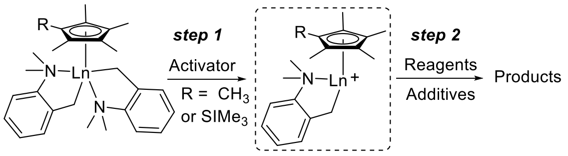
Scheme 13. *in situ* Generation and Synthetic Applications of Zirconacyclopentadiene Derivatives



step 1. *in situ* Generation or Isolation of Zirconacycles
step 2. Synthetic Applications of Zirconacycles
via a Stoichiometric Reaction Manner

Cationic half-sandwich rare earth metal alkyl complexes are of much current interest and regarded as a class of highly reactive intermediates. Well-defined cationic half-sandwich rare earth metal alkyl complexes remain scarce because of facile ligand scrambling and other decomposition reactions. As illustrated in Scheme 14, the reaction of the dialkyl complexes with activators yields the corresponding cationic monoalkyl species. These either *in-situ* generated or isolated cationic monoalkyl species exhibit excellent catalytic activity for organic transformations including polymerization (Scheme 14).[33]

Scheme 14. Synthetic Applications of *in situ* Generated or Isolated Cationic Rare Earth Metal Alkyl Species



step 1. *in situ* Generation or Isolation of Cationic Rare Earth Metal Alkyl Species
step 2. Synthetic Applications of the *in situ* Generated or Isolated Species
via a Catalytic Reaction Manner or Polymerization

6. CONCLUDING REMARKS

In this Perspective, the above-introduced research strategy on organometallic intermediate-based organic synthesis is centered with isolation and structural characterization of reactive organometallic intermediates, which usually require more time and efforts than the discovery of the reaction itself and are considerably more challenging experimentally. The isolation and study of reactive organometallic intermediates not only leads to a better understanding of their reactivity and reaction mechanisms, but can also guide the discovery of new reactions, culminating in the advancement of novel synthetic methods.

We hope this manuscript has demonstrated a useful bridge between organometallic chemistry and synthetic organic chemistry. Filling this gap should benefit both areas and advance the development of synthetic chemistry as a whole. Furthermore, we hope this manuscript will encourage more researchers to have deeper interest in the chemical nature of metal-mediated or catalyzed reactions, and will convince, to a certain extent, funding agencies to better support such fundamental and widely applied research areas.

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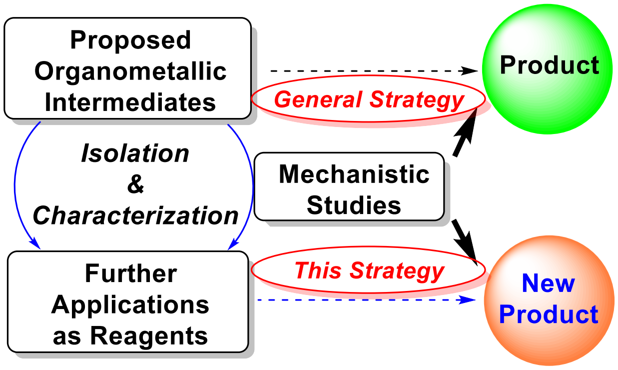
Proposed Organometallic Intermediates
General Strategy
Product
Isolation & Characterization
Mechanistic Studies
Further Applications as Reagents
This Strategy
New Product