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SNAPSHOTS OF SOME TOPICS OF INTEREST OF RECENT NOTABLE ADVANCES IN CHEMISTRY

- A versatile route to heterobimetallic lanthanide-coinage-metal complexes
- Mitochondrial Cl^--selective fluorescent probe
- Copper-catalyzed Goldberg-Ullmann coupling for the synthesis of aryl 2,2,2-trifluoroethyl sulfides
- Thiolate-mediated reductive cyclization

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Snapshots of some topics of interest of recent notable advances in chemistry

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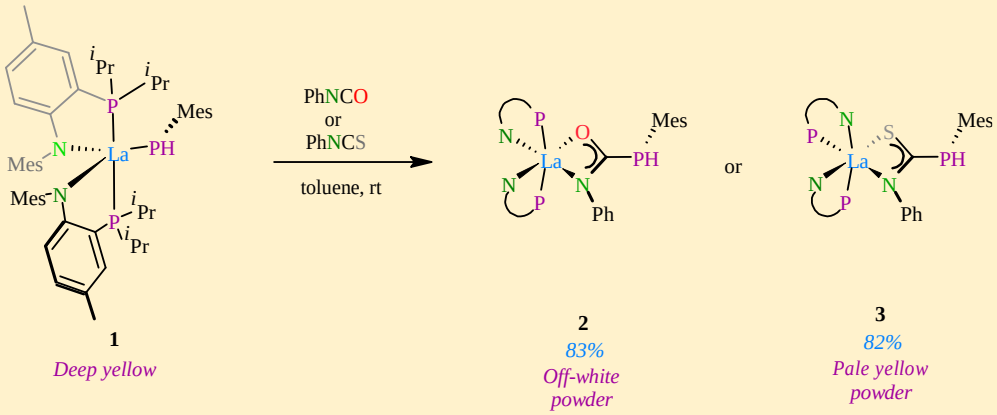
A Versatile Route to Heterobimetallic Lanthanide-Coinage-Metal Complexes

A simple route for the synthesis of a series of novel hetetobimetallic lanthanum-copper(I) and lanthanum-gold(I) complexes containing a phosphaureate bridging ligand with unprecedented $\kappa^2(O,N):\kappa^1(P)$ binding mode is presented.

The lanthanides (Ln) exhibit a range of features in their chemistry: i) they have a very wide range of coordination number; ii) their coordination geometries are determined by ligand steric factors; iii) they form labile ionic complexes that undergo facile exchange of ligand; iv) their spectroscopic and magnetic properties are largely uninfluenced by the ligand; v) they prefer anionic ligands with donor atoms of high electronegativity; vi) they readily form hydrated complexes; and vii) they do not form stable carbonyls and have no chemistry in the 0 oxidation state. Thus, their applications are involved in many fields ranging from molecular magnetism and (bio)analytical sensors to optical communication and catalysis.

Recently, ongoing research in the field has emerged to design more sophisticated lanthanide complexes with the desired chemical, magnetic, or photophysical properties through rational design of heterobimetallic lanthanides-coinage-metal complexes. In this context, Watt *et al.* have adapted a strategy based on selective insertion of organic substrates into the La-P bond of the primary phosphido complex $(PN)_2La(PHMes)$ **1** with retention of the P*H* protons as a tool to obtain further reactivity. Selective deprotonation and subsequent metalation with late-transition-metal complexes thus make it possible to design new types of heterobimetallic lanthanum-copper(I) and lanthanum-gold(I) complexes. This phosphido complex is supported by a bidentate, monoanionic anilidophosphine ligand (*N*-(2-(diisopropylphosphanyl)-4-methylphenyl)-2,4,6-trimethylanilide, abbreviated PN^-).

As shown in Scheme 1, the insertion of either phenyl isocyanate or phenyl isothiocyanate into the La-P phosphide bond of **1** was proceeded quickly at room temperature to yield phospha(thio)ureate complex **2** or **3**.



1
Deep yellow

2
83%
Off-white powder

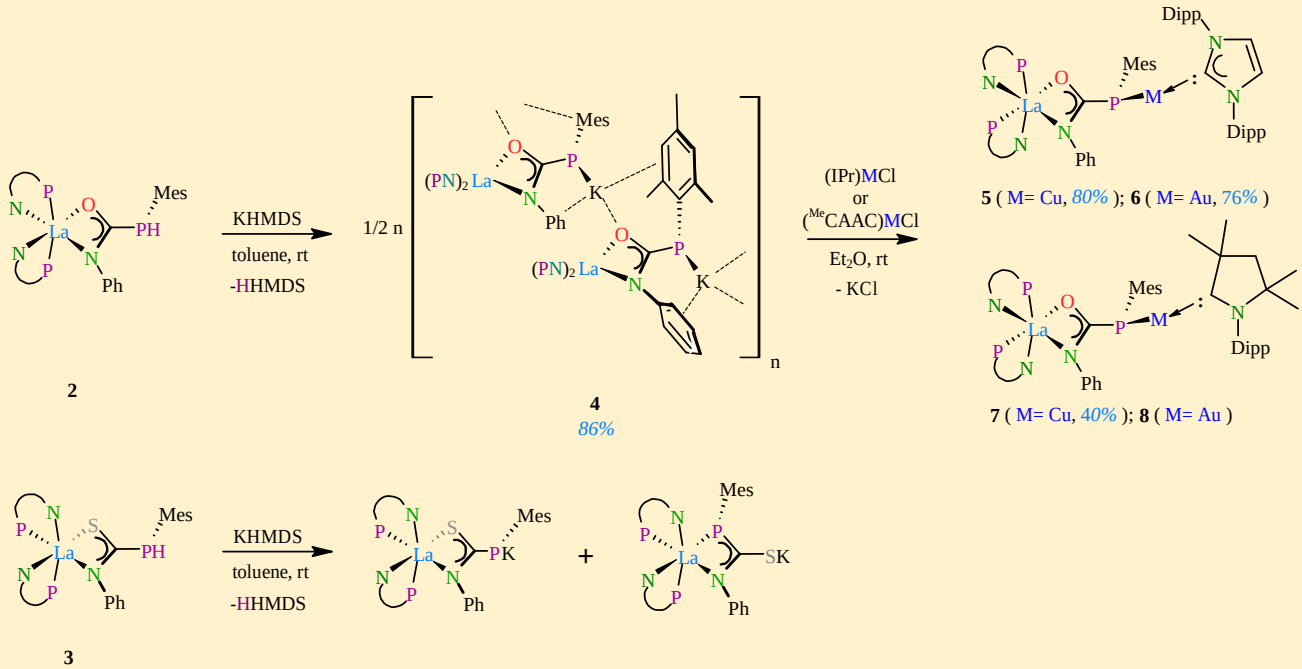
3
82%
Pale yellow powder

Scheme 1. Preparation of phospha(thio)ureate complex **2** or **3**

X-ray diffraction studies revealed that the lanthanum atom is six-coordinate in a strongly distorted octahedral, almost trigonal prismatic fashion by two PN ligands as well as the nitrogen and chalcogenide atoms of the newly formed phospha(thio)ureate ligand. Complex **2** exhibits a *trans* arrangement of the $^{i}Pr_2$-phosphanyl groups, with the inserted PhNCO fragment being roughly perpendicular to it. Whereas, in the case of **3** the phosphanyl groups are *cis* to each other, indicating a high flexibility of the PN ligands for rearrangement around the lanthanum atom. Furthermore, all the structural parameters lie in the expected range for phospha(thio)ureates in the coordination sphere of highly electropositive metal ions.

The deprotonation of the *PH* group in **2** and **3** was accomplished by treating them with 1 equiv. of KHMDS in toluene at room temperature to give a polymeric complex **4** and two different isomers, respectively (Scheme 2). These two different isomers, resulting from the deprotonation of complex **3**, led the authors to hypothesize that the phosphathioureate is not only $\kappa^2(S,N)$-bound to lanthanum (III), but can also rearrange to the $\kappa^2(P,N)$-bound form. The authors targeted the polymeric complex **4** for its salt metathesis reactions to build heterobimetallic complexes using carbene coinage-metal chlorides, namely, 1,3-bis(2,6-diisopropyphenyl)-imidazol-2-ylidene (IPr)- or 1-(2,6-diisopropylphenyl)-3,3,5,5-tetramethylpyrrolidin-2-ylidene (^{Me}CAAC)-supported copper(I) and gold(I) chloride.

A suspension of compound **4** and 1 equiv. of either (IPr)CuCl or (IPr)AuCl were stirred in diethyl ether at room temperature to yield the heterobimetallic complexes **5** and **6** with an IPr supporting ligand at the coinage-metal ion (Scheme 2). While the corresponding ^{Me}CAAC-supported systems **7** and **8**, with (^{Me}CAAC)CuCl or (^{Me}CAAC)AuCl were produced (Scheme2). Alternatively, a one-pot synthesis of heterobimetallic complexes by consecutive addition of KHMDS and (IPr)MCl (M = Cu, Au) to compound **2** in diethyl ether at room temperature was also found to form the desired complexes **5** and **6** without the isolation of the potassium salt **4**.



Scheme 2. Deprotonation of complexes **2** and **3**, and salt metatheses of **4** with a selection of carbene coinage-metal chlorides.

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This straightforward route for the synthesis of novel heterobimetallic lanthanum−copper(I) and lanthanum−gold- (I) complexes containing a phosphaureate bridging ligand should provide access to a wide range of designed heterobimetallic lanthanide(III)−coinage-metal complexes with intriguing properties for photochemistry and catalysis.

Review

F. A. Watt, N. Dickmann, R. Schoch, S. Hohloch, *Inorg. Chem.*, **2020**, *59*, 13621−13631.

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Mitochondrial Cl^--selective Fluorescent Probe

The development of the first mitochondrial Cl^--selective fluorescent probe, Mito-MQAE, and its applications in biological systems are highlighted. The fluorescence resulting from this probe is insensitive to pH over the physiological pH range and is quenched by chloride ions with a Stern-Volmer constant of 201 M^{-1} at pH 7.0. The biological investigation has shown that substances with the ability to disrupt mitochondrial membranes lead to an increase in the mitochondrial chloride ions concentration.

Mitochondria is a double-membrane organelle that play a vital role in energy biogenesis and cellular regulatory processes. Mitochondria membranes contain several cation and anion channels including mitochondrial chloride channels. These chloride channels are involved in the regulation of the mitochondrial volume, maintenance of the mitochondria membrane potential, and apoptosis. The chloride transport activity of these channels is pH dependence, that their activity increases under acidic conditions and decreases at pH > 7.0.

The determination of the levels of chloride ions (Cl^-) in diverse mitochondria-associated biological systems is of great importance due to the fact that it allows to determine the effects of the substances, that impacts the function of mitochondria, on mitochondrial Cl^- concentrations. Due to the lack of appropriate probes to monitor mitochondrial Cl^-, Park *et al.* developed a mitochondrial Cl^--selective fluorescent probe, Mito-MQAE **2**, using MQAE (*N*-(ethoxycarbonylmethyl)-6-methoxyquinolinium bromide **1** as a scaffold for its design (Figure 1A). This developed probe can be used to evaluate the influences of various substances on the level of Cl^- in mitochondria.

The strategy of designing this probe is based on two factors: i) lipophilic quinolinium cation moieties serve as a mitochondria-targeting motif, as do triphenylphosphonium cation moieties; and ii) promoting hydrolytic stability via the replacement of the ester group in MQAE by an amide in order to avoid the formation of zwitterion that may arises from a rapid hydrolysis of the ester group to form carboxylate inside cells. Thus, a rigid isonipecotic acid moiety was introduced as the tether between the quinolinium moiety and the lipophilic benzyl group into the probe to avoid the possible effect of the benzyl group on the fluorescence of a quinolinium group. The synthesis of Mito-MQAE is shown in Figure 1B.

The fluorescence response of Mito-MQAE to pH and Cl^- revealed that its emission intensity at 460 nm (excitation at 350 nm) gradually decreased as the Cl^- concentration increased and that it remained unchanged over a pH range of 3.0−8.0. Furthermore, its fluorescence was quenched by Cl^- in the range of 0−250 mM with a Stern-Volmer constant (quenching sensitivity) of 201 M^{-1} at pH 7.0, but was unaffected by other biologically relevant ions.

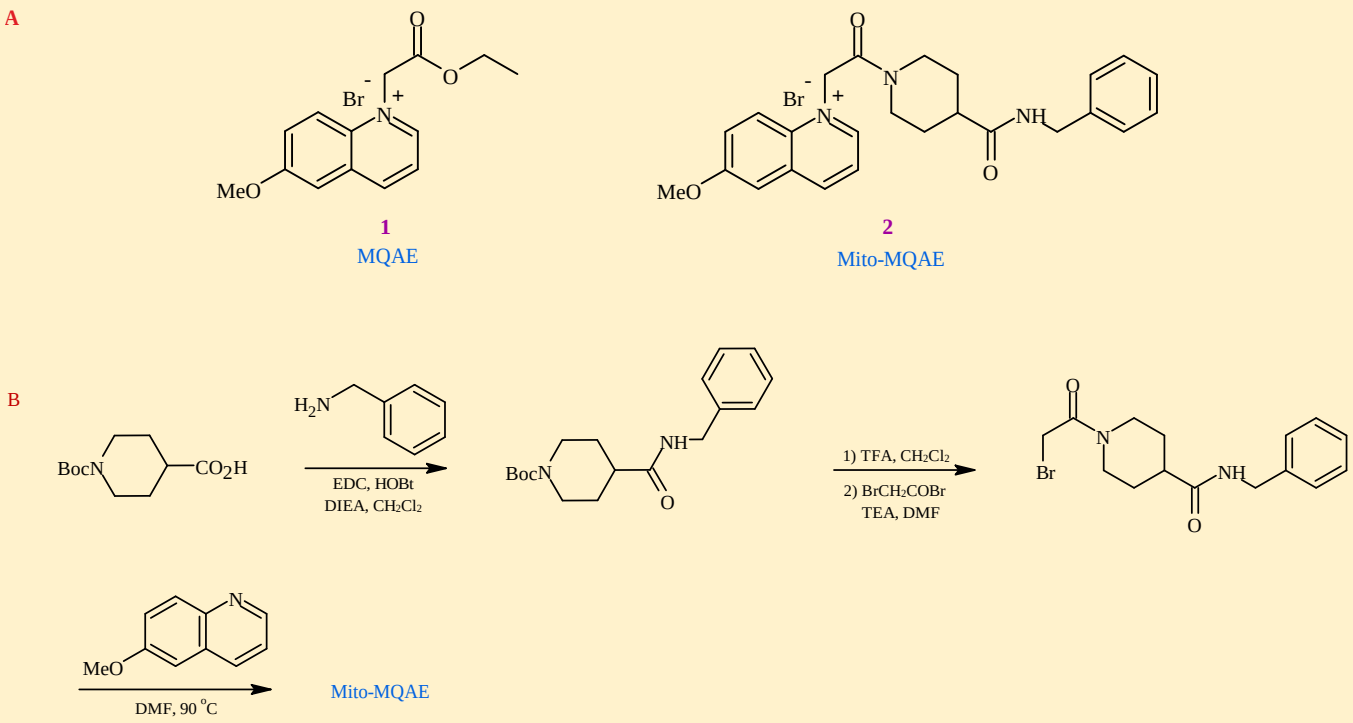

Figure 1. (A) Chemical structures of fluorescent Cl− probes. (B) Preparation of Miro-MQAE.

The results of the efficiency of Mito-MQAE response to mitochondrial Cl^- were shown that the substances with the ability to induce mitochondrial outer membrane permeabilization, leading to apoptosis, have increased mitochondrial Cl^- concentrations, indicating that Cl^- concentration is lower than that in the cytosol in accordance with previous studies.

This study demonstrated that Mito-MQAE has the potential for use as a mitochondrial Cl^--selective fluorescent probe for studies of biological processes associated with mitochondria.

Review

S.-H. Park, I. Shin, Y.-H. Kim, I. Shin, *Anal. Chem.*, **2020**, *92*, 12116−12119.

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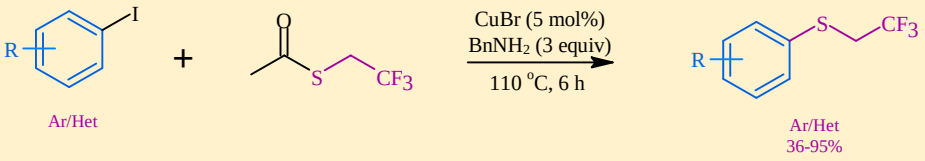
Copper-catalyzed Goldberg-Ullmann Coupling for the Synthesis of Aryl 2,2,2-trifluoroethyl Sulfides

A simple synthetic procedure for the introduction of trifluoroethylthio group into aromatic compounds using copper-mediated aromatic nucleophilic substitution reaction is presented.

There has been a burgeoning interest in recent years in the formation of molecules containing fluoro-alkylthio groups specially in the development of therapeutic agents. In fact, fluoroalkylthio groups are characterized by their biodegradability and enhanced lipophilicity in comparison to their fluoroalkylated counterparts.

In this regard, Menczinger *et al.* have been reported a scalable synthetic route towards an aryl 2,2,2-trifluororethyl sulfides. The synthetic route involves incorporating aryl iodides and 2,2,2-trifluoroethyl thioacetates *via* Goldberg-Ullmann coupling catalyzed by copper(I) halides using benzylamine as a base and solvent (Scheme 1).



Scheme 1. Synthesis of aryl 2,2,2-trifluoroethyl sulfides.

This trifluoroethylthiolation method could easily be adopted for the introduction of trifluoroethylthio group into target molecules of pharmaceutical or agrochemical relevance at multigram scale.

Review

B. Menczinger, A. Nemes, D. Szabó, G. Schlosser, T. Jernei, A. Csámpai, J. Rábai, *J. Flu. Chem.*, **2020**, *231*, 109464.

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Thiolate-mediated Reductive Cyclization

The role of thiolate in the conversion of a singly connected keto-enones into bridged compounds is described. The scope, limitation, and mechanistic insights of the reaction are highlighted.

In the course of their synthetic studies on naphthocyclinones, Ando *et al.* reported the applicability of substrate scope of the thiolate-mediated reductive cyclization of keto-enones. In their study, they adapted three keto-enone substrate models, in which the enone moiety is connected to a cyclohexanone at its γ-position **1**, and at its β-position **2**, whereas the third model is the connection of the enone to a cyclopentanone at its β-position **3** (Figure 1).

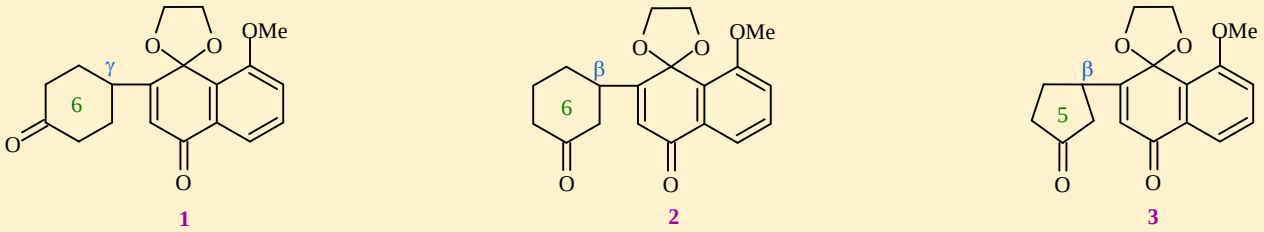
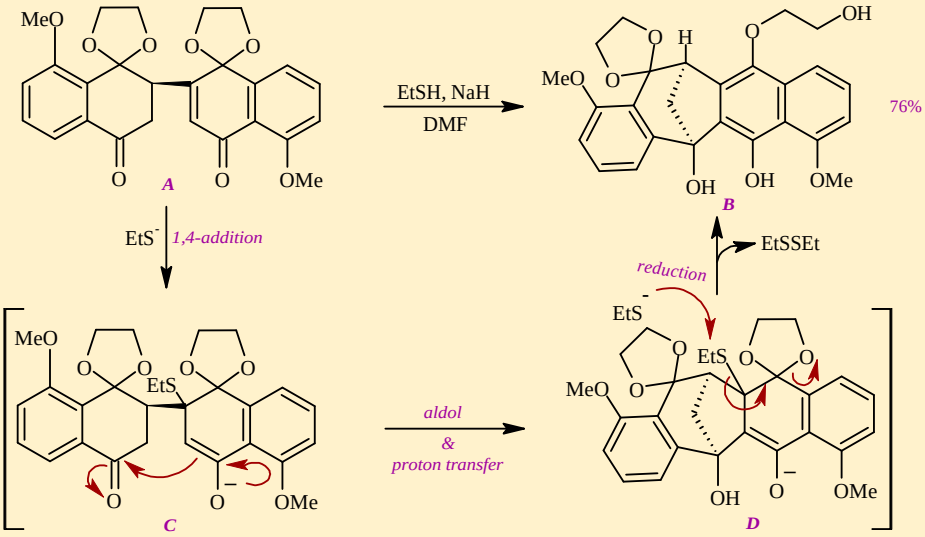


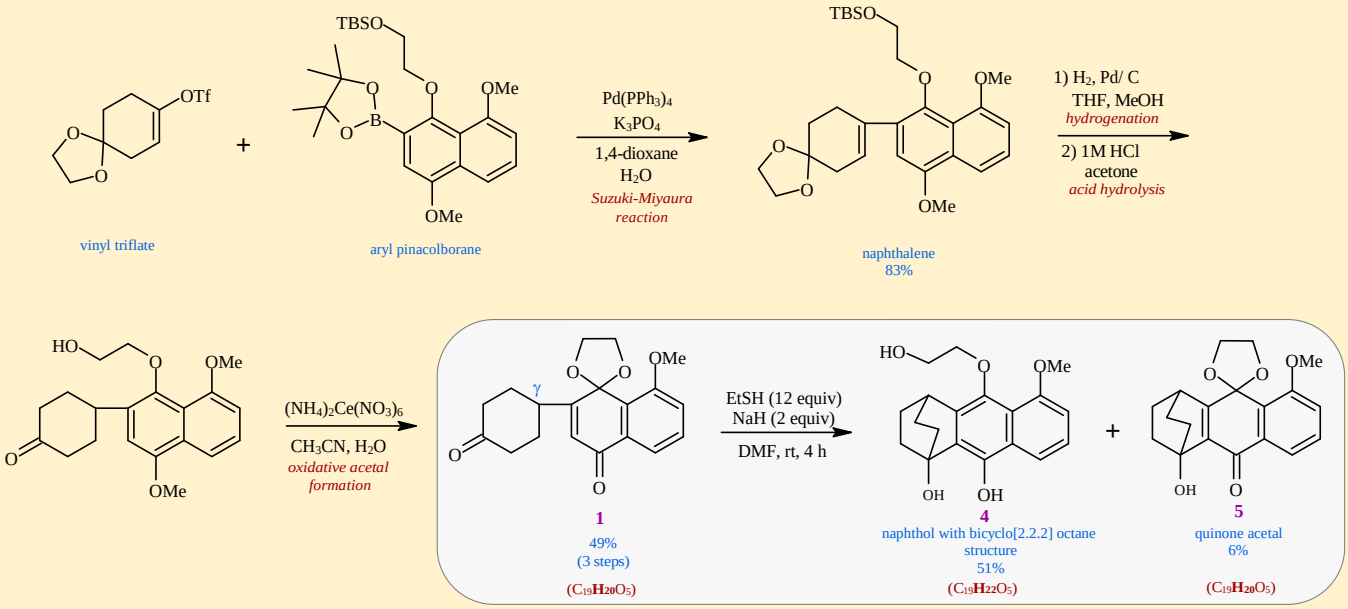
Figure 1. Different keto-enone model substrates.

Generally, the thiolate plays two mechanistically roles: i) generating an enolate intermediate ***C*** through 1,4-addition to the enone moiety ***A*** to induce an intramolecular aldol reaction and a proton transfer to provide bicyclic intermediate ***D***; ii) another thiolate attacks the sulfide ***D*** leading to expulsion of a disulfide to produce a bridged compound ***B*** (Scheme 1).



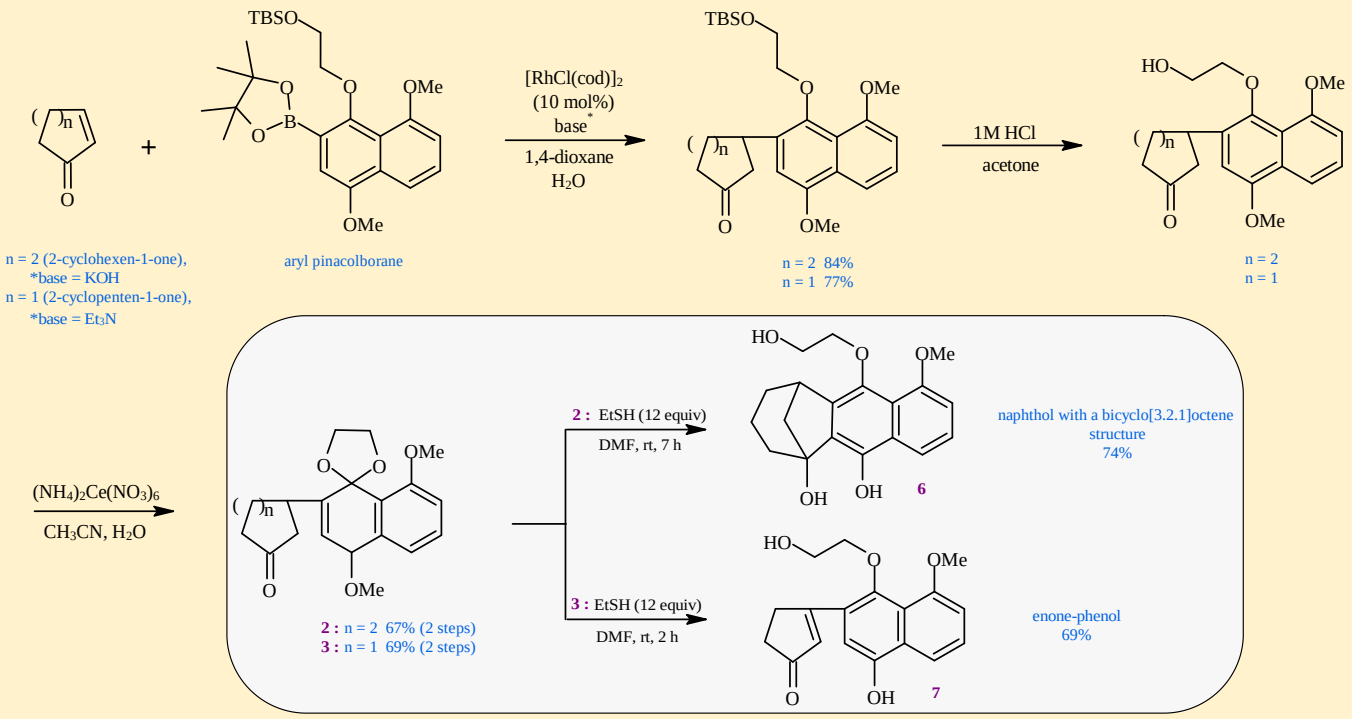
Scheme 1. Thiolate-mediated reductive cyclization.

Scheme 2 shows the synthesis of keto-enone substrate model **1** and the applicability of the reaction to construct a bicyclo[2.2.2]octene system. Observably, the byproduct quinone acetal **5** has the same elemental composition with the starting compound **1**, allowing the authors to hypothesize that the formation of **5** was proceeded *via* Morita-Baylis-Hillman (MBH) reaction as a non-productive, branched cycle, or as a productive process, or both of these two mechanisms.



Scheme 2. Synthesis of keto-enone model **1**, and its reaction.

Scheme 3 describes the preparation of keto-enone models **2** & **3** and their reaction. Under the same reaction conditions, keto-enone **2** gave naphthol **6** with a bicyclo[3.2.1]octene structure unaccompanied by the "MBH product", whereas keto-enone **3** gave a different result, namely, enone-phenol **7**, resulting formally from an internal oxidation-reduction. Therefore, the authors claimed that the limitation of the process to construct a bicyclo[2.2.1]heptene scaffold is related to the molecular strain.



Scheme 3. The preparation and reaction of keto-enone model substrates **2** & **3**.

Such scope and limitation of thiolate-mediated reductive cyclization may pave the way to construct various bridged polycycles or to apply the reaction in other substrates guided by the mentioned mechanistic insights.

Review

Y. Ando, T. Fukazawa, K. Ohmori, K. Suzuki, *Chem. Lett.*, **2020**, *49*, 1103–1106.