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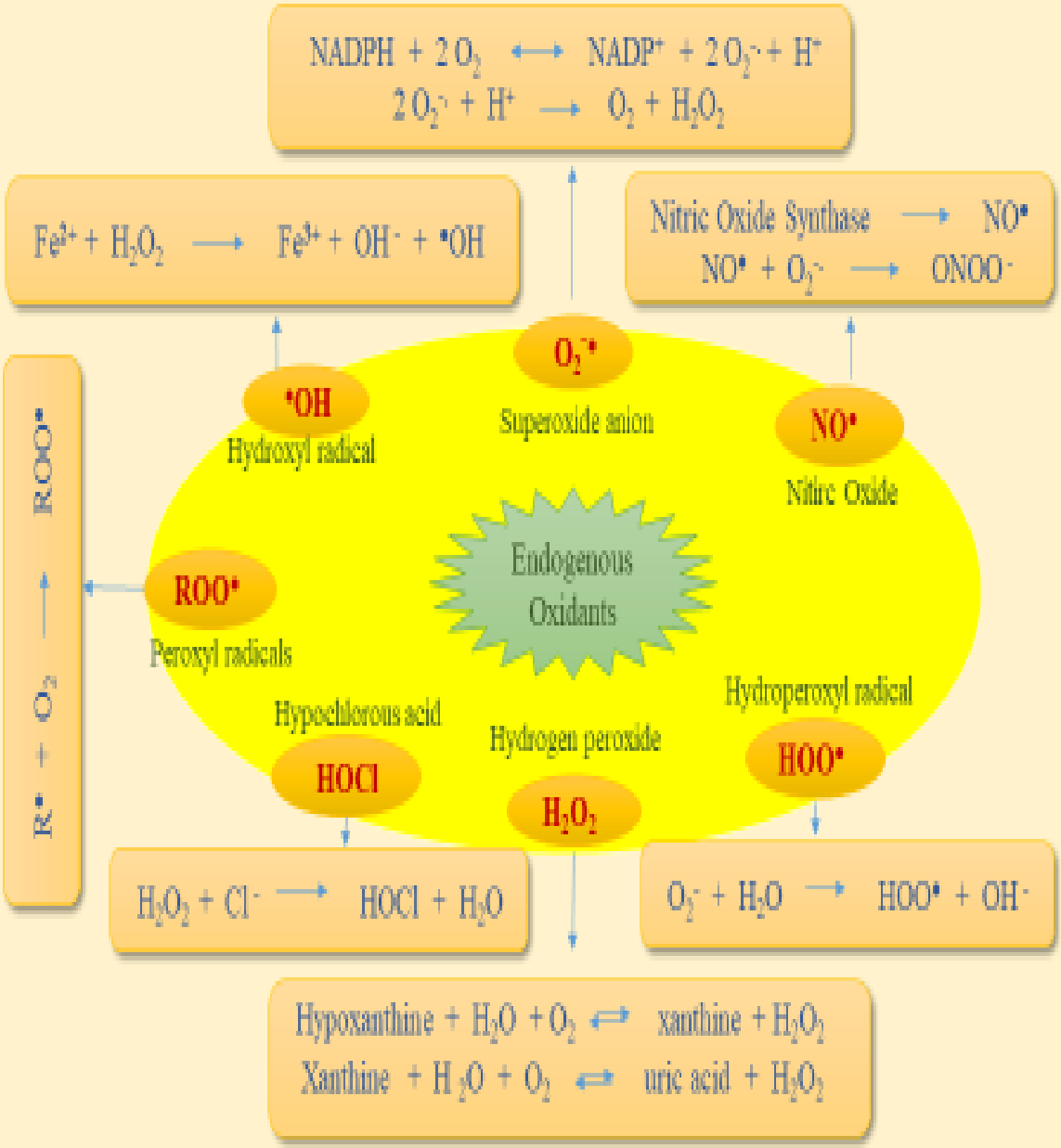

Promoting Neuronal Survival

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

* Expansion of the concept of aromaticity to heavy elements containing π-conjugated system

* Organocatalyst-mediated asymmetric Michael Reaction of a non-activated aldehyde with α-nitro α,β-unsaturated ester

* 3 Å Molecular sieves as an additive-controlled chemoselectivity

* A facile one-pot synthesis of spiro-pyrrolidinyl indeno-quinoxaline derivatives

* Highly chemoselective reduction of tertiary amides

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Promoting Neuronal Survival

Atef S. Iskander

Cerium oxide nanoparticles seems to be a promising novel therapeutic strategy to reduce the deleterious effects of acute overproduction of the reactive oxygen species which, in turn, lead to reduce neuronal cell death and potentially improve neurologic function.

Neuronal cell death has been found to be a major cause of neurodegenerative disease. The most common occurring of neuronal cell death is related to oxidative stress as a result of overproduction of reactive oxygen species.

Oxidative stress

Reactive oxygen species (ROS) are formed by living organisms as a result of normal cellular metabolism and play an important role in many physiological cell process. The most common ROS are those involving oxygen and nitrogen free radicals (Figure 1). The major sources of ROS of physiological significance are including mitochondria, the enzymes nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, cytochrome P450, and other oxide-reductases.

When the production of ROS overwhelms the intrinsic anti-oxidant defenses, a situation of perturbations in the redox balance of the cell occurs and shifts the balance between oxidant/antioxidant status in favor of the oxidants leading to oxidative stress. Cells have adapted to the existence of

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reactive intermediates by the evolution of defense mechanisms that either scavenge these intermediates or repair the damage they cause. High levels of damage can lead to cell death through apoptosis or necrosis depending on various exogenous factors as well as the cell's ability to reduce such stress.[1]

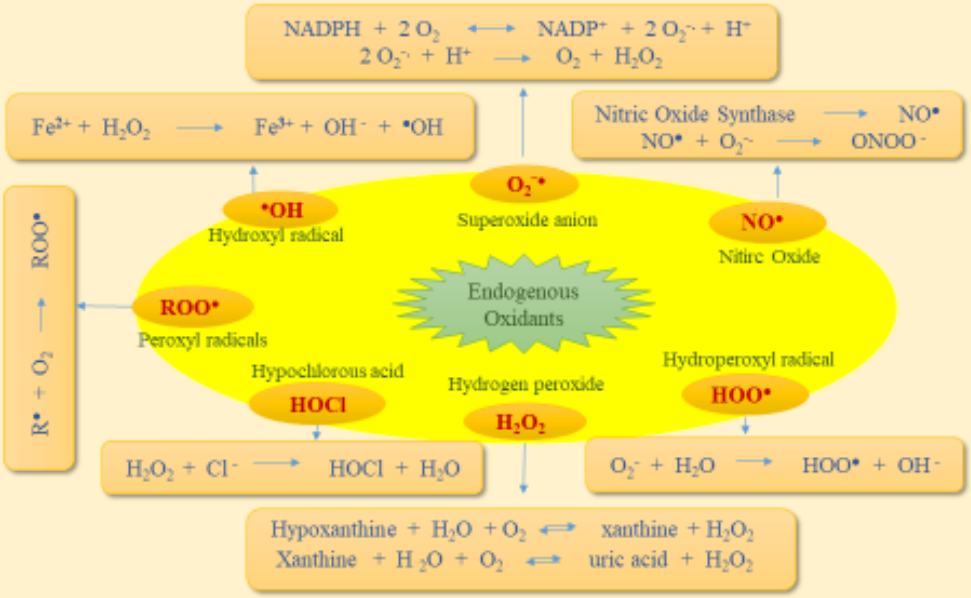

Figure 1. Major Endogenous Oxidants. NADPH, nicotinamide adenine dinucleotide phosphate, $ONOO^-$, peroxynitrite.

In many cases, the initially generated reactive intermediates convert cellular constituents into second-generation reactive intermediates capable of inducing further damage. For instance, evidence indicates that a severe overproduction of ROS is produced after spinal cord injury as a consequence of the inflammatory process leading to secondary injury and concomitant neuronal cell death, focal axonal degeneration, neuropathic pain, and locomotor dysfunction.[2] Indeed, reduction of dramatically increased production of ROS level of cell is made difficult by the fact that as extremely reactive species, they tend not to diffuse far within the cell before participating in a potentially damaging reaction, as well as the limited action of the neutralization of antioxidants. Counteracting oxidative

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stress by powerful antioxidants, such as nanoparticles, might be one of the mechanisms by which these substances exert their neuronal protective effects.

Cerium oxide nanoparticles

Recently, there has been increasing interest in the therapeutic capacity of nanoparticles (NPs). Nanoparticles constitute an important modality for the delivering of therapeutics and imaging agents as they are capable of delivering a highly potent dose to a target site while also preserving the activity of the agent during transit in the blood stream. Promising results have been suggested that cerium oxide nanoparticles (nano-ceria) exhibit antioxidant activity in biological systems.[3] Cerium oxide nanoparticles are nontoxic lanthanide metal oxide that by virtue of the redox potentials of cerium(III) (Ce_2O_3) and cerium(IV) (CeO_2) can exhibit facile cycling between two oxidation states. A unique feature of the ceria nanoparticles is that they have shown the ability to auto-regenerate over time. They are able to return to their original concentration of Ce(III), allowing them to continuously act as ROS scavengers.

Promote functional recovery

Cerium oxide nanoparticles can serve as containers for the targeting of therapeutics to neuronal cell death as they exhibit an effective role in controlling the ROS level of cells. In this context, a study of the therapeutic effect of these nanoparticles in acute injury of spinal cord is highlighted.

Das *et al.* reported that nano-ceria protected adult spinal cord neurons against oxidative stress.[4] Hyun *et al.*[5] demonstrated that cerium oxide nanoparticles have an effective therapeutic role in the treatment of a moderate contusion injury of adult rat spinal cord. They revealed that these antioxidant nanoparticles suppressed the enzyme inducible nitric oxide synthase at moderate doses. This enzyme has been implicated as a critical mediator of inflammation due to the production of the free radical nitric oxide ($NO^{\cdot}$) that can react with superoxide ($O_2^{\cdot -}$) to form a powerful pro-oxidant peroxynitrite ($ONOO^-$). They showed that the treatment of spinal cord contusion by an optimal therapeutic dose rang (500-1000 $\mu g\ mL^{-1}$) of cerium oxide nanoparticles leads to reduce ROS within hours, suppressing inflammation and apoptosis within days, and enhancing neuronal cell growth and axonal regeneration within weeks, and functional recovery in few months.

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Although the unusual properties of the antioxidant behavior of cerium oxide nanoparticles in the treatment of spinal cord injury could prove useful for therapeutic intervention, further studies remain necessary to determine precisely the threshold of doses used and to identify the proper cell type without adverse consequences such as endocytic activity and cellular toxicity.

References

1. G. Serviddio, A. D. Romano, T. Cassano, F. Bellanti, E. Altomare, G. Vendemiale. *Current Pharmaceutical Design,* **2011,** *17,* 2036.
2. L. Portt, G. Norman, C. Clapp, M. Greenwood, M. T. Greenwood, *Biochimica et Biophysica Acta,* **2011,** *1813,* 238.
3. O.C. Farokhzad, R. Langer, *ACS Nano,* **2009**, *3,* 16.
4. S. Das, J.M. Dowding, K.E. Klump, J.F. McGinnis, W. Self, S. Seal, *Nanomedicine* (Lond), **2013,** *8,* 1483.
5. J.W. Kim, C. Mahapatra, J.Y. Hong, M. S. Kim, K. W. Leong, H.W. Kim, and J. K. Hyun, *Adv. Sci.*, **2017**, *4,* 1700034.

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

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Expansion of the Concept of Aromaticity to Heavy Elements Containing π-Conjugated System

Ever since the discovery of benzene by Faraday, the chemistry of aromatic compounds has been developed extensively to such an extent that a considerable volume of the entire encyclopedia of chemical reactions comprised of the chemistry of aromaticity. However, it was almost two centuries later that the field further blossomed to a new class of aromatic compounds bearing the heavier Group 14 elements. These compounds are characterized by the replacement of a carbon atom in the skeleton of an aromatic compound by a heavy element. They have unique electronic structures and properties that are different from those of aromatic hydrocarbons. This family of compounds has now grown to include aromatic compounds bearing silicon and germanium atoms in the skeletons (Figure 1). Recently, M. Saito expended this class of aromatic compounds by synthesizing tin- and lead-containing π-conjugated systems.

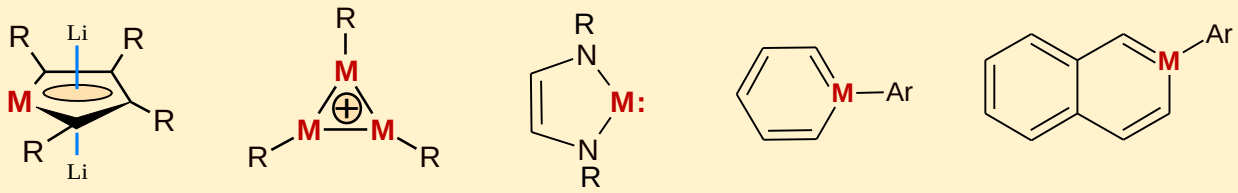

Figure1: aromatic compounds bearing silicon and germanium atoms in the skeletons

Synthesis of dilithiostannole and dilithioplumbole were achieved by reduction of substituted 1,1-di-phenylstannole **1** and hexaphenylplumbole **3** with lithium to provide the corresponding dilithiostannole **2** and dilithioplumbole **4** respectively (Scheme 1). X-ray diffraction analysis showed that the stannole ring of **2a** is almost planar with the sum of the internal angles of 539.9° and the C-C bond distances are about (1.422(6) - 1.446(6) Å). The ^{7}LiNMR resonances of **2** were observed at high-field (-6 to -4 ppm), which are caused by a shielding effect of the diatropic ring current, which reflected the aromatic nature

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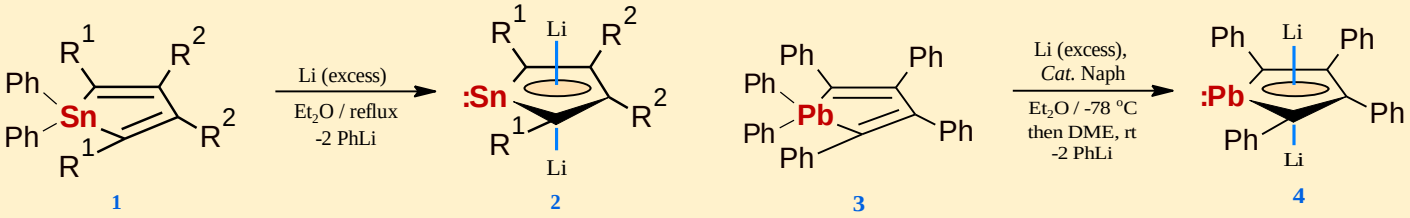
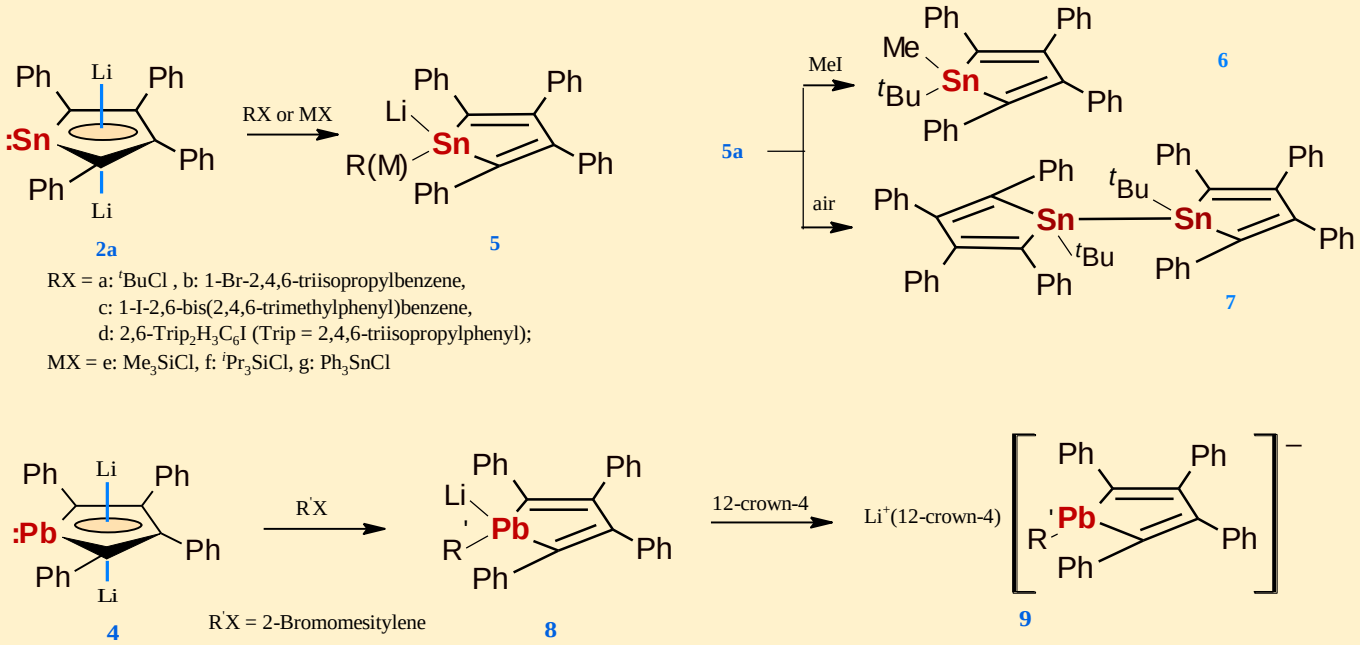
of the compound.



1 2 3 4

Scheme 1: Preparation of dilithiostannoles **2** and dilithioplumbole **4**.

Both dilithio-stannoles and –plumbole reacted with alkyl-, aryl- and metal-halides to afford the corresponding adducts through an electron transfer mechanism (Scheme 2). Further alkylation of the adduct **5a** with iodomethane produced **6**, while its oxidation by air afforded **7**. In the presence of 12-crown-4, they produced the corresponding salts of anion **9**.



Scheme 2: Reaction of dilithio-stannoles and –plumbole with alkyl-, aryl-, metal-halides and crown ether.

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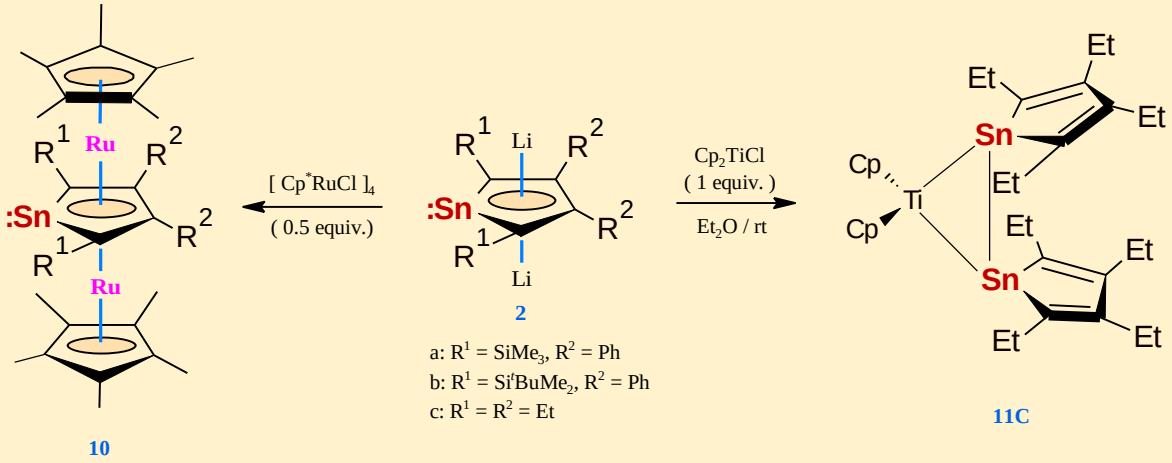
Synthesis of triple-decker sandwich-type complexe **10** was achieved by the reaction of a transition metal $[Cp^*RuCl]_4$ with dilithiometallole **2** as dianionic ligand (Scheme 3), while reaction of **2c** with Cp_2TiCl afforded three-membered ring complex **11c**.



10

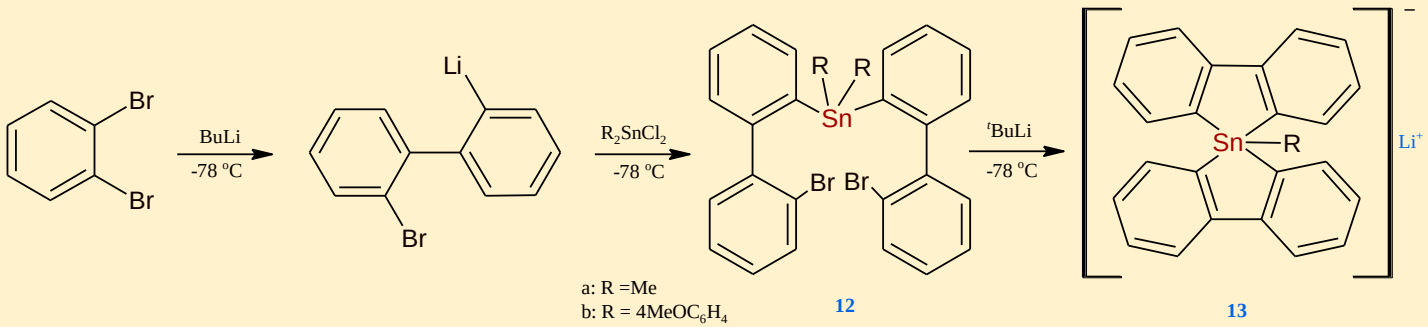
a: $R^1 = SiMe_3$, $R^2 = Ph$
b: $R^1 = Si^tBuMe_2$, $R^2 = Ph$
c: $R^1 = R^2 = Et$

2

11C

Scheme 3: Formation of triple-decker complexes.

Pentaorganostannates bearing five carbon substituents on the tin atoms **13** were serendipitously generated by the reaction of bis(2-bromo-2′-biphenyl)stannanes **12** with ^{t}BuLi at -78 °C (Scheme 4).



a: R =Me
b: R = $4MeOC_6H_4$

12

13

Scheme 4: Formation of pentaorganostannates.

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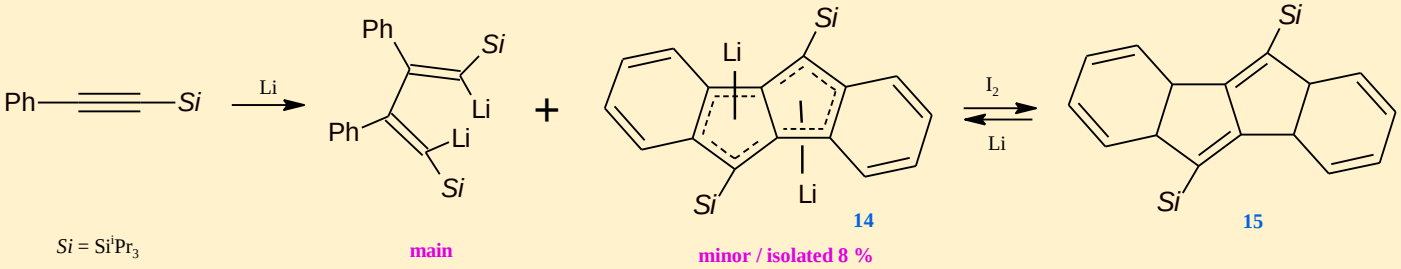
On the other hand, dilithium dibenzopentalenide **14** was prepared by the reaction of a phenylsilyl-acetylene with lithium, which further treated with iodine to yield dibenzopentalene **15** (Scheme 5).



Scheme 5: Formation of dilithium dibenzopentalenide and dibenzopentalene.

Review:

M. Saito, *Bull. Chem. Soc. Jpn.*, **2018**, *91*, 1009–1019.

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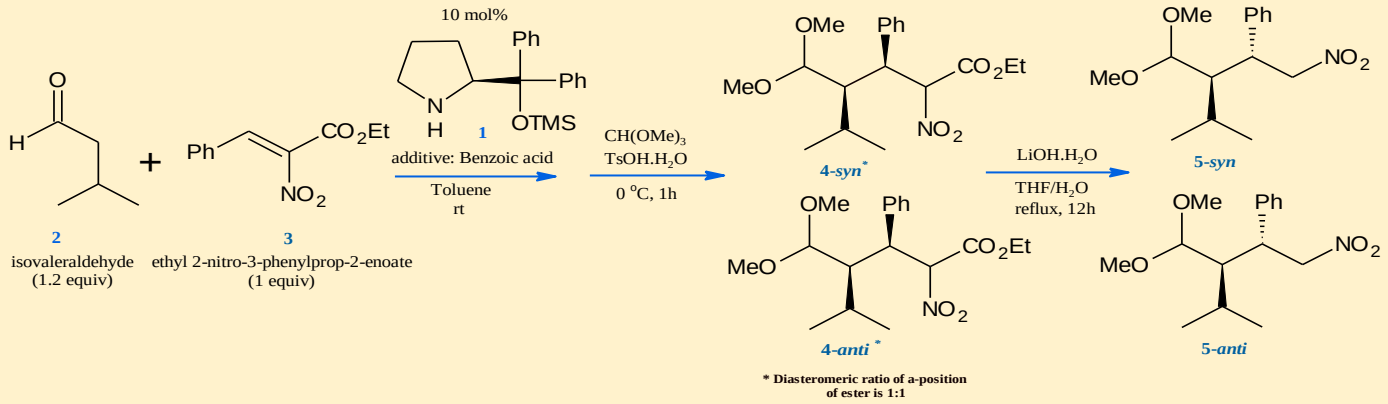
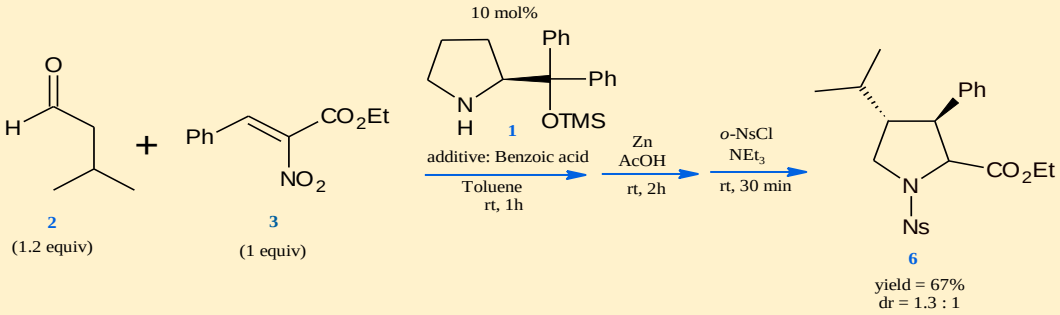
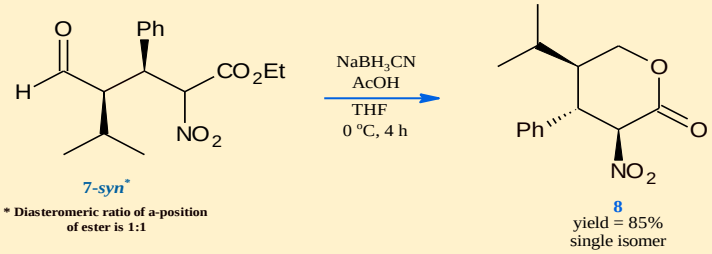
Organocatalyst-Mediated Asymmetric Michael Reaction of a Non-activated Aldehyde with α-Nitro α,β-Unsaturated Ester







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Reported is an organocatalyst, diphenylprolinol silyl ether **1**, catalyzed the asymmetric Michael reactions of aldehyde **2** with ester **3** to afford the corresponding Michael products, in which the chiral enamine is generated from aldehyde and catalyst proline **1**. The nitroalkane **5** was obtained in high yield with good diastereoselectivity (syn:anti > 10:1) and excellent enantioselectivity (99% ee) through a sequential reaction (1 5). The reaction has a wide substrate scope. Different functionalized aldehydes and electron-rich and electron-deficient aromatic, heteroaromatic moieties, and alkyl substituents of the Michael acceptor were employed and they afforded products with excellent diastereo- and enantioselectivities. Screening the reaction conditions showed that using benzoic acid as an additive plays an effective role in forming Michael products in a short time and with high stereoselectivity.

The reported method allows for generation of several functional groups, which have been demonstrated to be useful chiral synthetic intermediates. Reduction of the amino moiety of the resulted product of reaction isovaleraldehyde **2** with ester **3** by Zn/AcOH followed by the addition of *o*-NsCl yielded *N*-protected 3,4-*trans*-proline derivatives **6** in 67% yield**.** While reduction of the formyl group of Michael product **7** furnished lactone **8** as a single isomer.

Review:

D. Sakamoto and Y. Hayashi, *Chem. Lett.*, **2018**, *47*, 833–835.

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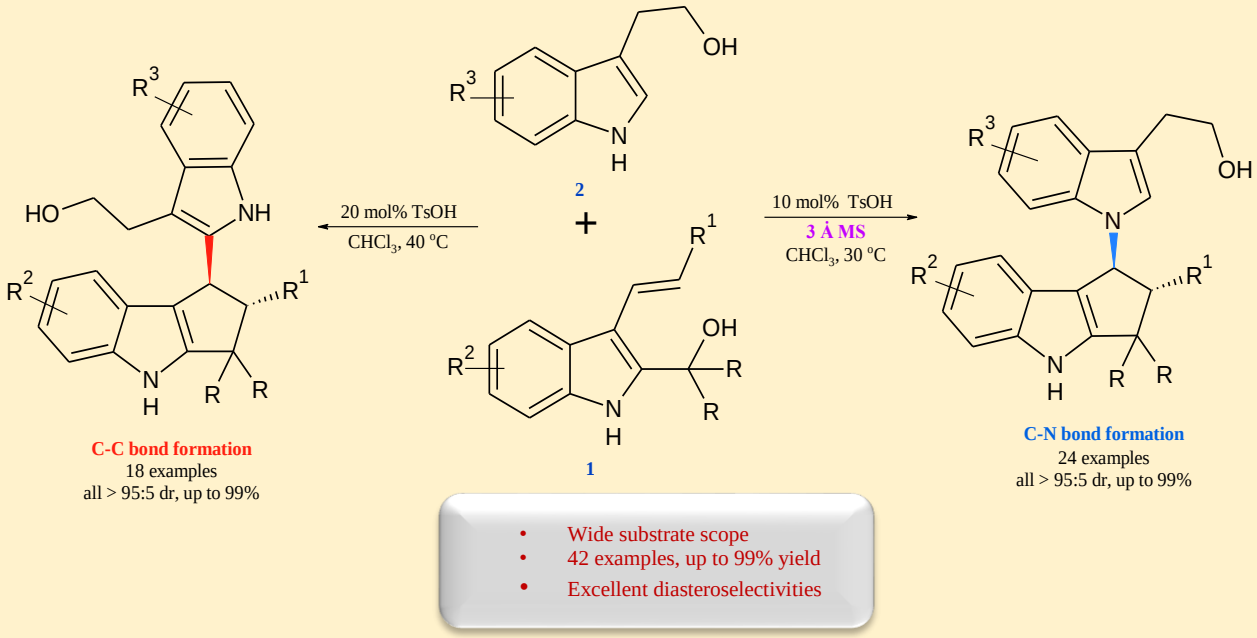
3 Å molecular sieves as an additive-controlled chemoselectivity

Shi and co-workers reported an interrupted Nazarov-type cyclization in the presence of Brønsted acid for the construction of cyclopenta[*b*]indole derivatives from the reaction of 2-indolylmethanols **1** with tryptophols **2** (Scheme). They found that 3 Å molecular sieves could efficiently promote C-N bond over C-C bond formation.



Scheme: Tandem Cyclizations of 2-Indolylmethanols with Tryptophols.

Review:

Jing-Yi Wang, Ping Wu, Jia-Le Wu, Guang-Jian Mei, and Feng Shi, *J. Org. Chem.*, **2018**, *38* (11), 5931-5946.

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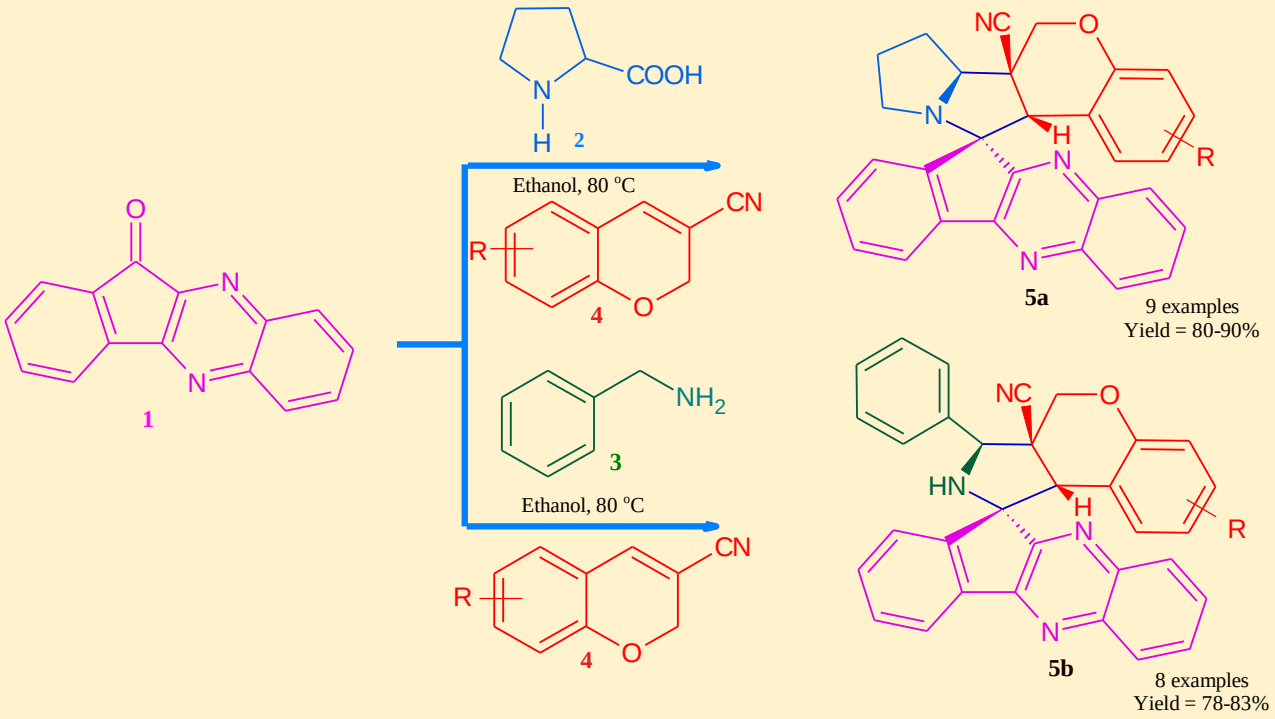
A facile one-pot synthesis of spiropyrrolidinyl indenoquinoxaline derivatives

Reported is a one-pot synthesis of spiropyrrolidinyl indenoquinoxaline derivatives **5a** and **5b** by the reaction of indenoquinoxaline **1** with proline **2**/benzylamine **3** and chromene-3-carbonitrile **4** in ethanol under mild conditions in high yields. The reaction involves 1,3-dipolar cycloaddition process in which azomethine ylides are produced *in situ* by the decaroboxylative condensation of indenoquinoxalone



Scheme: synthesis of spiropyrrolidinyl indenoquinoxaline derivatives.

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with proline/benzyl amine and their selectivity towards the endo cyclic double bonds of chromene-3-carbonitrile (dipolarophile) as the Nayak team explained. The reported method employs an excellent functionalized regio- and diastereoselective synthesis of **5a** and **5b** from readily available substrates.

Review:

P. Pattanaik, S. Nayak , D. R. Mishra, P. Panda, B. P. Raiguru, N. P. Mishra, S. Mohapatra, N. A. Mallampudi, *Tetrahedron Lett.*,**2018**, *59*,2688-2694.

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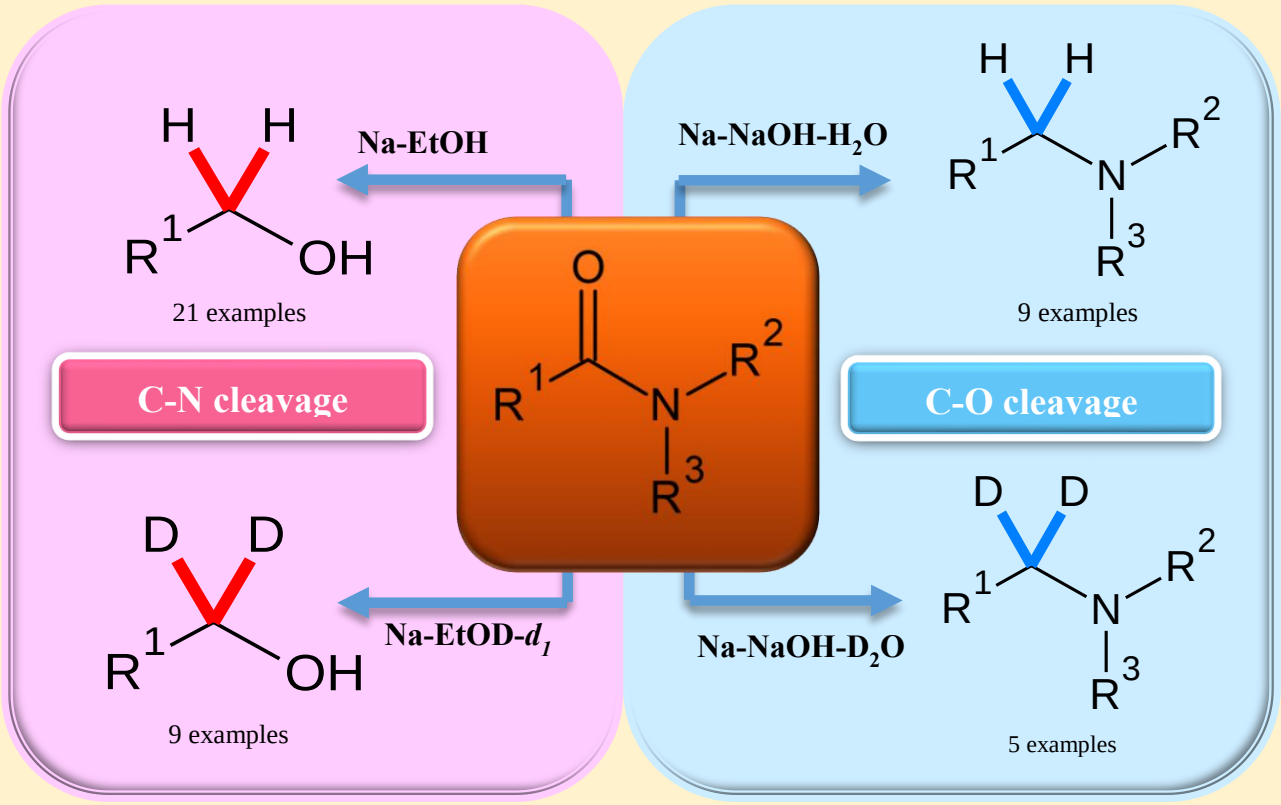
Highly Chemoselective Reduction of Tertiary Amides

The team of An presented a highly chemoselective distinct reduction and reductive deuteration of tertiary amides to alcohols or amines mediated by sodium dispersions in proton donor solvents. They found that the reaction proceeded with C-N bond cleavage by employing sodium dispersions in EtOH or EtOD-d_1 to form the corresponding alcohols rather than C-O bond cleavage which promoted by sodium dispersions in $NaOH/H_2O$ or $NaOH/D_2O$ to generate the corresponding amines in high yields (Scheme)



Scheme: Reduction and reductive deuteration ef teriary amides.

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Review:

Bin Zhang, Hengzhao Li, Yuxuan Ding, Yuhao Yan, and Jie An, *J. Org. Chem.*, **2018**, *38* (11), 6006-6014.