

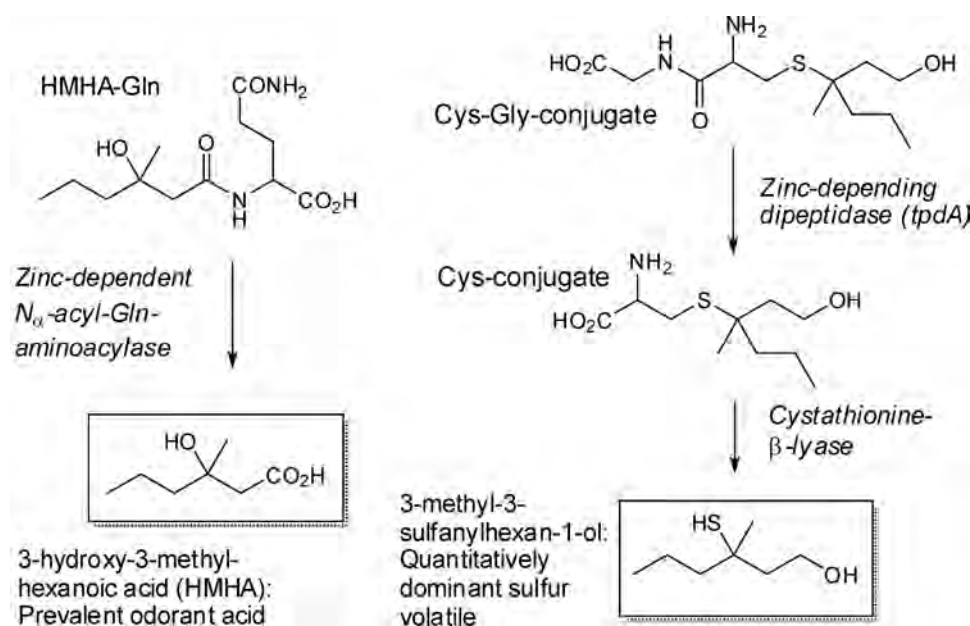
Supplementa to Issue 7-8/2014

SCS Fall Meeting 2014 Oral Presentation Abstracts Session of Organic Chemistry

September 11, 2014
University of Zurich, Irchel Campus
<http://scg.ch/fallmeeting2014>

KGF-SCS Industrial Investigator Award 2014: The human scent: Chemicals, enzymes and genes and our 'olfactive self'Andreas Natsch¹¹Givaudan Schweiz AG

We identified in axilla secretions a number of odorant branched acids and sulfanylalkanols. They are secreted as precursors: The acids as glutamine-conjugates [1] and the sulfanylalkanols mainly linked to the dipeptide Cys-Gly [2]. The cleavage of the Gln-conjugates is catalyzed by an aminoacylase cloned from the skin bacterium *Corynebacterium striatum* [1], and the Cys-Gly-conjugates are cleaved by the sequential action of a dipeptidase [3] and a β -lyase isolated from the same skin bacterium.



The genetic influence on the pattern of odor precursor secretion was investigated: Monozygotic human twins share a common and stable pattern of precursors of odorant acids [4], but no link to the HLA-locus (a key component of the immune system) is apparent from our data, different from data in mice. In a study combining genetic typing and chemical analysis we could link absence of body odor in large part of the population in the Far East to the lack of odor precursor secretion by individuals carrying a mutation in the ABCC11 transport protein on both chromosomes. Finally, this detailed biochemical understanding opened the door for rational design and synthesis of deodorant actives directly targeting the odor releasing enzymes. Design, synthesis and activity studies on these novel actives will be discussed.

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Sterol C(14)-demethylase inhibitors as fungicides for use in crop protection

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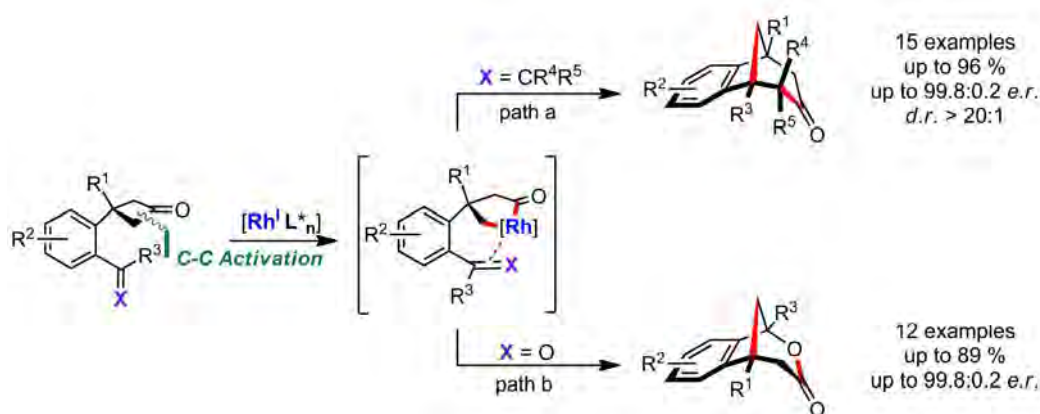
Fungicides play an important role in controlling diseases in crops. A particular important class of fungicides are the sterol C(14) demethylase inhibitors, which inhibit the oxidative demethylation of C(14) during the fungal biosynthesis of ergosterol. This talk will discuss design and synthesis of molecules acting as inhibitors of the involved cytochrome P450 'CYP51'.

Highly Enantioselective Rh(I)-Catalyzed Activation of Cyclobutanones Enantiotopic C-C Bond.

Laetitia Souillart¹, Nicolai Cramer¹ *

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Small rings play an important role for C-C bond activation as their inherent ring strain facilitates metal insertion. Our group reported enantioselective β -carbon eliminations from *tert*-cyclobutanols giving rise to a diverse set of products *via* different downstream reaction pathways.^[1] Strained ketones have proven as well to be highly versatile for reactions involving oxidative addition of transition-metals as C-C cleavage mechanism. We reported the first examples of enantiotopic C-C bond activation of cyclobutanones in which the C-C cleavage step is the enantiodetermining step.^[2] This rhodium(I)-catalyzed process allows for an efficient access to the valuable bicycloheptanone scaffold (path a)^[2a] or tricyclic lactones (path b)^[2b] in exceptionally high enantioselectivities.



[1] a) for a recent example: L. Souillart, N. Cramer, *Chem. Sci.* **2014**, 5, 837-840; b) for a review: T. Seiser, N. Cramer, *Chimia* **2010**, 64, 153-156.

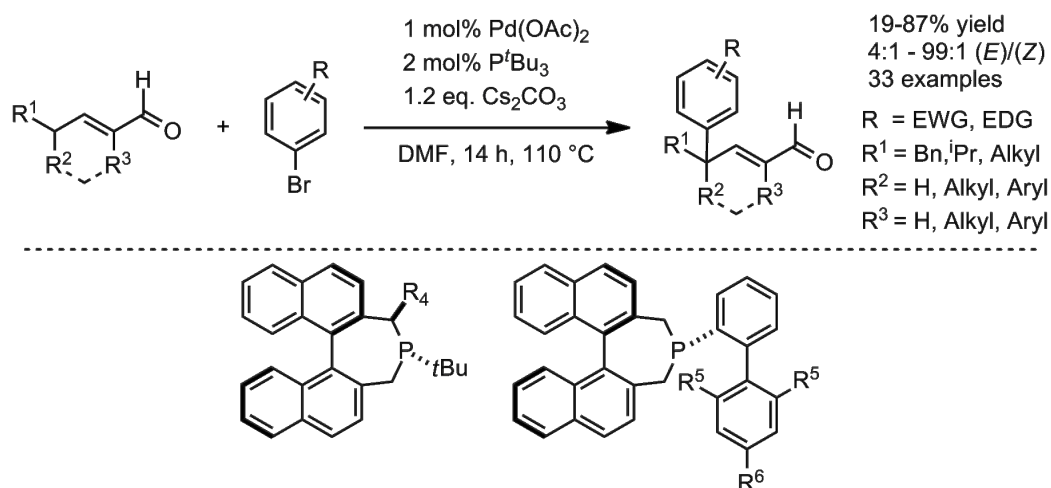
[2] a) L. Souillart, E. Parker, N. Cramer, *Angew. Chem. Int. Ed.* **2014**, 53, 3001-3005; b) L. Souillart, N. Cramer, *manuscript submitted*.

Pd-catalyzed selective arylations of aldehydes

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In the last two decades, the α -arylation of enolizable carbonyl compounds has advanced with significant strides.¹ In this context, aldehydes have revealed particularly challenging substrates.² Our group has recently reported an enantioselective intramolecular α -arylation of α -branched aldehydes using novel chiral (P,N) ligands.³ In a direct continuation of this work, and based on the vinylogous analogy,⁴ we developed a perfectly regio- and stereoselective intermolecular γ -arylation of γ -branched α,β -unsaturated aldehydes using commercial ligands and palladium precursors.⁵ In addition to the γ quaternary center, the products of this remote coupling bear substantial synthetic potential as derivatizations are possible both at the olefinic position and the aldehyde functionality.

We next set out to develop an enantioselective version of this reaction. We present herein our results in this direction. This includes the design and the stereoselective synthesis of a novel class of monodentate chiral phosphine ligands as well as their evaluation in this challenging cross-coupling reactions.⁶



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New Synthetic Applications of Nitrous Oxide

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Despite its high chemical energy, nitrous oxide (N₂O, 'laughing gas') is rarely used in organic synthesis due to its highly inert nature. Although many transition metal complexes react with N₂O under mild conditions,[1] catalytic turnover is difficult to achieve. So far, only few examples are known and the catalytic efficiency of these systems is typically poor (TON ≤ 100).

We present a novel procedure for oxidative homo- and cross coupling of Grignard reagents in which nitrous oxide serves as an oxidant.[2] Oxidation reactions with N₂O are environmentally friendly, because an ozone-depleting greenhouse gas is destroyed and dinitrogen is released. Whereas catalytic oxidation reactions with N₂O reported so far demand harsh conditions and give low turnover numbers, the coupling reactions presented herein proceed at room temperature, atmospheric pressure of nitrous oxide with simple first row transition metal salts as catalysts and turnover numbers of up to 9.4 x 10³. It is demonstrated that N₂O displays distinct advantages over alternative oxidants such as dioxygen.

Furthermore, we describe novel methods to use N₂O as a building block for more complex, organic molecules.[3] So far, very few examples of such procedures are known in the literature.



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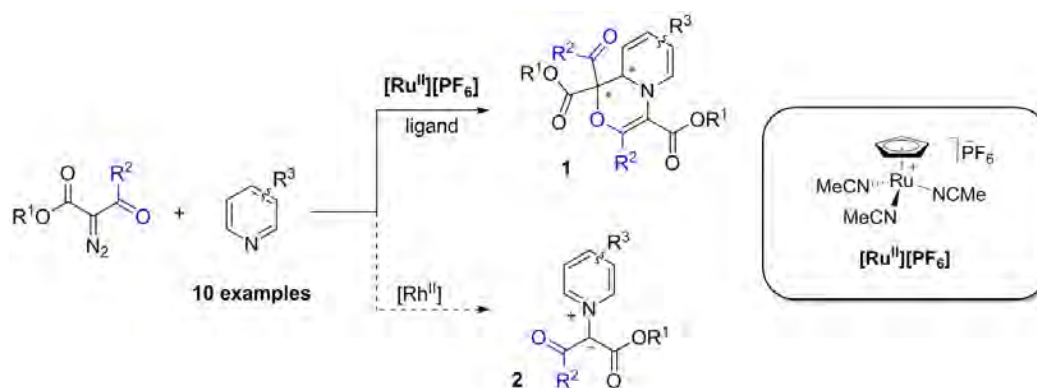
Pyridine Dearomatization Through Double Ru-Metal Carbene Insertions

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¹University of Geneva

CpRu complexes are interesting alternatives to copper and dirhodium species for the catalyzed decomposition of diazo compounds.[1] Our group has shown that combinations of [CpRu(CH₃CN)₃][PF₆] and diimine ligands catalyze the decomposition of α -diazo- β -ketoesters and allow further condensation, O-H and 1,3-C-H insertion reactions.[2] Recently, using the same catalytic combination, a synthesis of original dioxene motifs has been demonstrated with reactions between acceptor/acceptor carbenes and epoxides.[3]

In a new development, that uses electron-poor pyridines as substrates, the direct formation of unique oxazine species (**1**) is described, via a dearomatization process of the pyridine moieties. The process is only possible through ruthenium cyclopentadienyle catalysis as, under Rh(II)-mediated reactions, pyridinium ylides **2** are the side products.[4] Good yields but low global diastereoselectivity are observed. Solutions to this selectivity issue and extension of the reactivity to electron-rich pyridines will be detailed.



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[3] T. Achard, C. Tortoreto, A. I. Poblador-Bahamonde, L. Guénée, T. Bürgi, J. Lacour, *Angew. Chem. Int. Ed.* **2014**, in press.

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Difunctionalization of Activated Alkenes via Radical Addition/Desulfonylation/1,4-Aryl Migration Cascade Reaction

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Difunctionalization of alkenes is a class of significant synthetic reactions that allow for the buildup of molecular complexity in a single procedure.¹ However, the carbo- and heterofunctionalization of alkenes involving the incorporation of arenes across C=C π system in a catalytic, regio- and stereocontrolled manner is still a distinct challenge.

Our group recently has developed a novel and unique Cu-catalyzed 1-pot trifluoromethylation of conjugated tosyl amides to generate α -aryl- β -trifluoromethyl amides bearing an α -quaternary stereocenter or trifluoromethylated oxindoles in a regioselective fashion.²

A successful realization of this concept with the introduction of azido and phosphonyl radicals for the flexible synthesis of α -aryl- β -heterofunctionalized amides has also been discovered. Furthermore phosphorylated oxindoles and spirobicycles could also be obtained in a completely regioselective manner.³



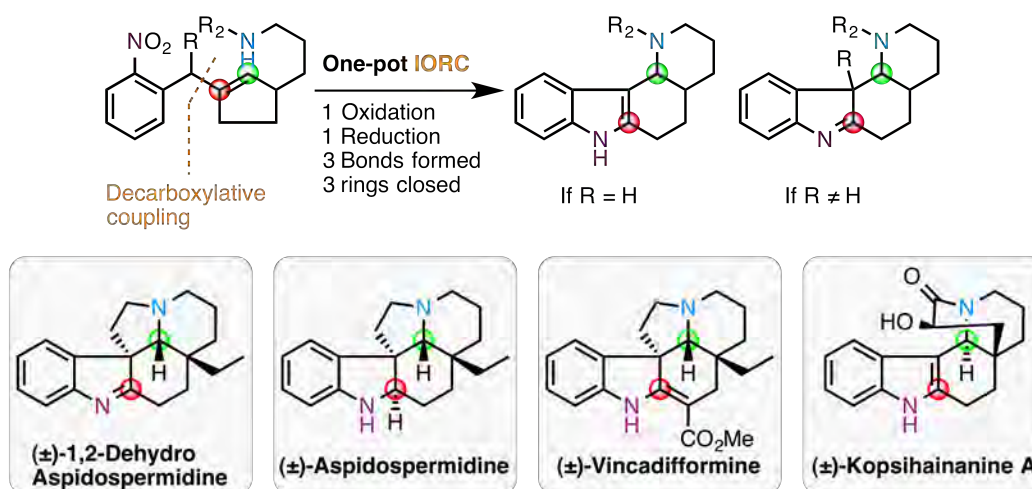
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Total Synthesis of *Aspidosperma* Family Monoterpene Indole AlkaloidsOlivier Wagnières¹, Zhengren Xu¹, Qian Wang¹, Jieping Zhu¹ *¹EPFL Lausanne

By virtue of their potent biological activities, indole alkaloids have been privileged synthetic targets that attracted much attention from the synthetic community over the past decades. The development of divergent synthesis strategies giving efficient access to structurally diverse natural products is a highly demanding endeavour. We are working on a unified strategy towards the synthesis of *Aspidosperma* family monoterpene indole alkaloids featuring two key steps: Pd-catalyzed cross coupling and Integrated Oxidation/Reduction/Cyclization (IORC) sequence (Scheme 1).^[1] Presented herein are our recent results dealing with the synthesis of (±)-1,2-dihydroaspidospermidine, (±)-aspidospermidine, (±)-vincadifformine and (±)-kopsihanainanine A.^[2]



[1] Z. Xu, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2013**, 52, 3272-3276

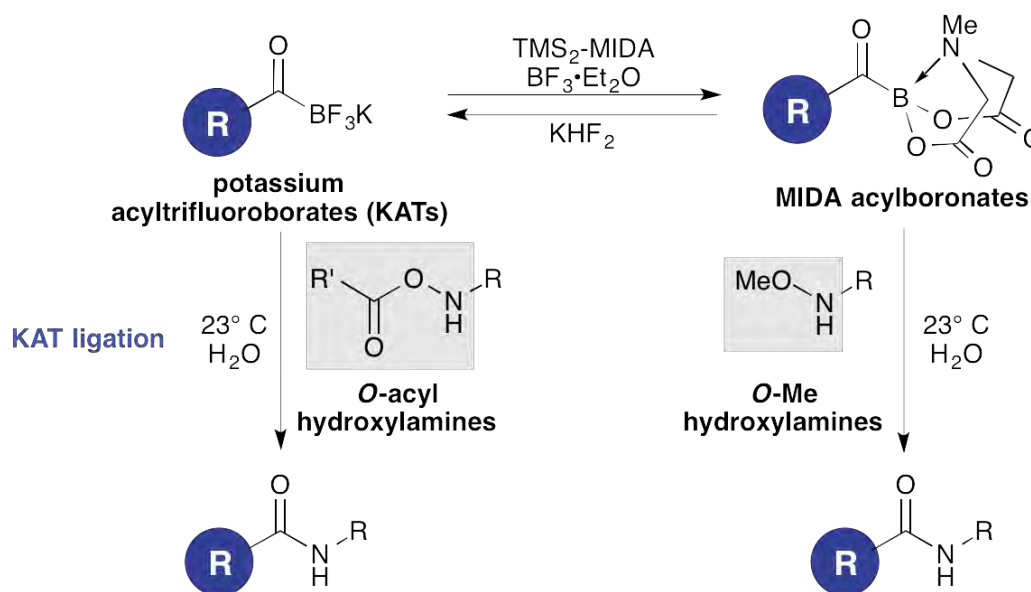
[2] Unpublished work

Syntheses and Applications of Acylboronates in Chemoselective Amide Formations

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Acylboron compounds have rarely been utilized in synthetic organic chemistry, particularly in comparison with their widely used non-acyl variants, partly because of a general assumption of their instability and a lack of practical synthetic route to them. We recently identified potassium acyltrifluoroborates (KATs) as bench stable solids and they undergo extremely rapid amide-forming ligations with *O*-acylhydroxylamines in water.^{1,2} Our group also devised convenient accesses to KATs from either aldehydes³ or aryl lithium species.⁴ Given the interest in this unique functional group, we envisioned synthesizing other acylboronates and evaluating their property and reactivity. In this presentation, we report that a variety of bench stable acylboronates were prepared from their corresponding KATs in one step. These new acylboronates were also easily converted back to KATs. Among them, *N*-methyliminodiacetyl (MIDA) acylboronates were found to possess higher reactivity than KATs towards hydroxylamines. MIDA acylboronates undergo chemoselective amide formations with *O*-Me hydroxylamines in water, including unprotected peptide substrate.⁵ Preliminary mechanistic study and origins of their higher reactivity will also be discussed.



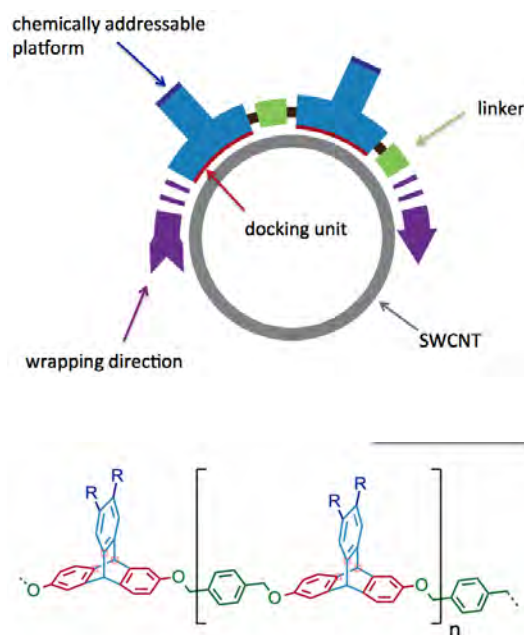
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Setting the Hook for Specific Single Walled Carbon Nanotubes (SWCNT)

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The desire to selectively address SWCNT with well-defined characteristics such as diameter, n,m -indices and even chirality, is an ongoing challenge in today's research as the electronic properties of SWCNT depend strongly on these characteristics.^{[1][2][3]} Here, we propose a strategy to achieve a controlled and selective separation of SWCNT depending on their size or possibly even their chirality. The main idea consists on synthesizing an enantiomerically pure building block with a concave π -system using Diels-Alder reactions as key step. Polymerization with interlinking building blocks leads to a chiral ribbon, which is envisaged to coat selectively one type of SWCNT and disperse it. The driving force for the coating process is mainly the interaction of the SWCNT with the concave π -moiety and the size exclusion is essentially directed by the interlinking molecules and the structure of the polymer. Variation of the linkage allows altering of the properties of the polymer at a late stage in the assembly and ultimately defines the dispersion capability of the polymer. Finally, as an easy release of the coated SWCNT is highly desirable, we also propose a *retro*Diels-Alder-based release strategy.



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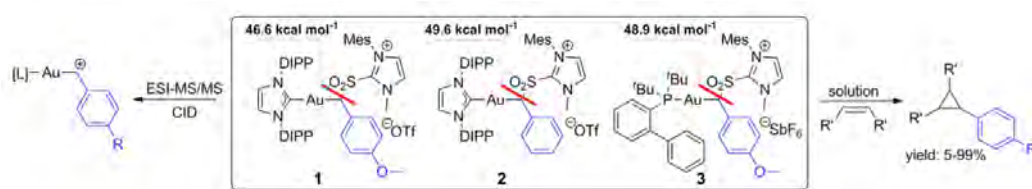
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Rational Design of a Gold Carbene Precursor Complex for a Catalytic Cyclopropanation Reaction

David Ringger¹, Peter Chen¹ *

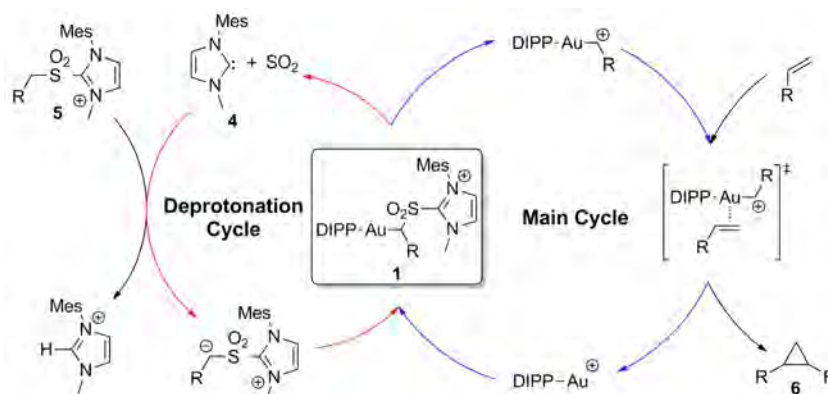
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Many reported gold-promoted cyclopropanation reactions involve as a key intermediate an Au^I carbene. Many of these reactions work well, but the scope is often less broad than would be desired. A more thorough understanding of the intermediates can help in the pursuit of an alternative route to the synthesis of positively charged Au^I carbenes. The rational design of isolable Au^I carbene precursor complexes **1–3**, active in stoichiometric and complex **1** in catalytic cyclopropanation reactions, was accomplished using an electrospray tandem mass spectrometer (ESI-MS/MS) as a screening tool. The measured gas phase bond-dissociation energies (BDE) were found to be dependent on the ligand *trans* to the carbene and on the *p*-methoxy benzyl substituent. These results gave an indication of the likelihood that the desired C-S bond breakage would occur competitively under thermal conditions, if one factors in observed trends in solvation.



The most electron rich and reactive complex **1** was used in a catalytic cyclopropanation reaction, giving the desired cyclopropane **6** with up to 4.3 turnovers. The SO₂–imidazolium moiety acts as a leaving group, which can dissociate to give SO₂ and imidazolylidene **4**. The latter, produced in situ, serves as a base to deprotonate another molecule of imidazolium sulfone salt **5** in the putative catalytic cycle.^[1]

These results support chemical intuition, which suggests that electron donating groups on gold will stabilize the electrophilic carbene. The measured BDEs are useful for benchmarking future endeavors in the search of Au^I carbenes, active in cyclopropanation.^[2]



[1] Ringger, D. H.; Chen P. *Angew. Chem. Int. Ed.* **2013**, 52, 4686.

[2] Manuscript in preparation.