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Catalytic Cyclopropanation Reactions with α -Silyl-, Germanyl- and Stannyl Carbenes Generated from Cyclopropenes

Darío Coto,^a Iratxe Barbola,^{a,b} and Rubén Vicente*^a

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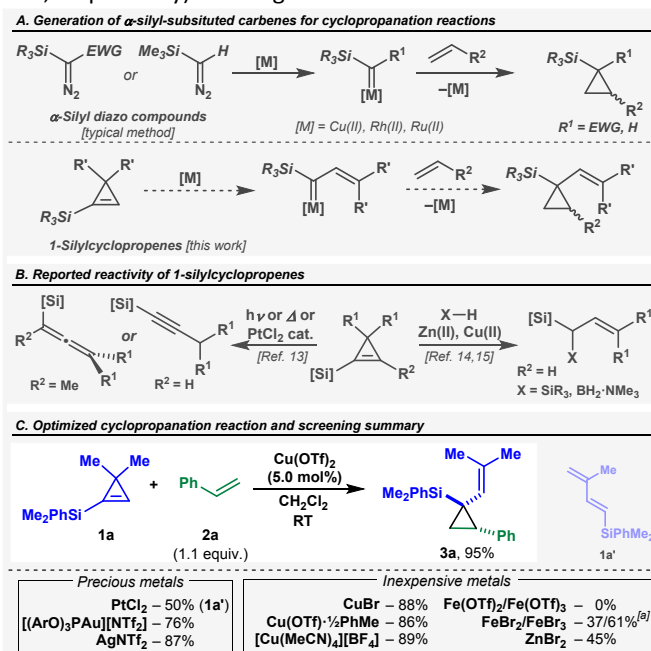
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Silylcyclopropenes are employed as precursors of α -silyl vinyl carbenes and trapped with alkenes. Cyclopropylsilanes were obtained in good yields with ample scope and complete regio- and diastereoselectivity. Stereoretentive protodesilylations enabled access to *cis*-cyclopropanes. Cyclopropylstannanes and –germanes can also be prepared from the corresponding cyclopropenes.

Metal carbenes are valuable synthetic intermediates,¹ yet their unparalleled reactivity contrasts with the limited availability of precursors for catalytic reactions. Indeed, diazo compounds stabilized with electron-withdrawing groups are regularly employed.^{2,3} Cyclopropanation of alkenes is arguably the most characteristic reaction of metal carbenes.⁴ Its relevance is indubitable since this is the preferred synthetic route to cyclopropanes, which are ranked within the Top-10 cyclic scaffolds in drugs.⁵ Cyclopropanations with unsubstituted or α -C-substituted diazo compounds have been well studied.^{2,4} On the contrary, alkene cyclopropanations with α -silyl-substituted *stabilized* diazo compounds have been fairly less explored (Scheme 1A),⁶ although this approach provides a handle for further manipulations.⁷ Indeed, few examples of Rh(II)- and Cu(I)-catalysed cyclopropanation with α -silyl-substituted diazo compounds have been reported.⁸ Noteworthy, Ru(II)-catalysed cyclopropanations with *non-stabilized* α -silyl-substituted diazo compounds have been only reported with TMS-diazomethane.⁹ Besides, cyclopropenes are suitable precursors of vinyl carbenes,¹⁰ which have been fruitfully exploited in metal-catalysed cyclopropanations.¹¹ Indeed, we recently reported intermolecular zinc-catalysed alkene cyclopropanations using 3,3-disubstituted cyclopropenes.¹² Continuing our studies, we wondered if 1-silylcyclopropenes could be used as α -silyl carbene precursors for the cyclopropanation of alkenes

(Scheme 1A) to complement the diazo approach. The intrinsic reactivity of 1-silylcyclopropenes comprises a rearrangement to allenes or alkynes (Scheme 1B).¹³ However, the metal-catalysed generation of the desired carbene was proved by their trapping with silanes and boranes (Scheme 1B) as demonstrated by our group¹⁴ and later by Zhu.¹⁵

To test the feasibility of the metal-catalysed cyclopropanation, 1-silylcyclopropene **1a** and styrene (**2a**) were used as model reagents (Scheme 2C).¹⁶ While, PtCl₂ promoted the isomerization of **1a** to diene **1a'** without merging the alkene,¹⁶ Au(I) and Ag(I) were suitable catalysts. Thus, [(ArO)₃PAu][NTf₂] and AgNTf₂ led to cyclopropylsilane **3a** in good yields (76 and 86%, respectively) as a single diastereoisomer.



Scheme 1. A. Catalytic generation of α -silyl carbenes for cyclopropanation. **B.** Reactivity of 1-silylcyclopropenes. **C.** Synthesis of cyclopropylsilane **3a**: Optimized conditions and screening summary. ^[a] ¹H NMR yield. (Ar = *tris*(2,4-di-*tert*-butylphenyl)phosphite).

^a Departamento de Química Orgánica e Inorgánica and Instituto Universitario de Química Organometálica "Enrique Moles" Universidad de Oviedo C/ Julian Clavería 8, 33006-Oviedo (Spain)

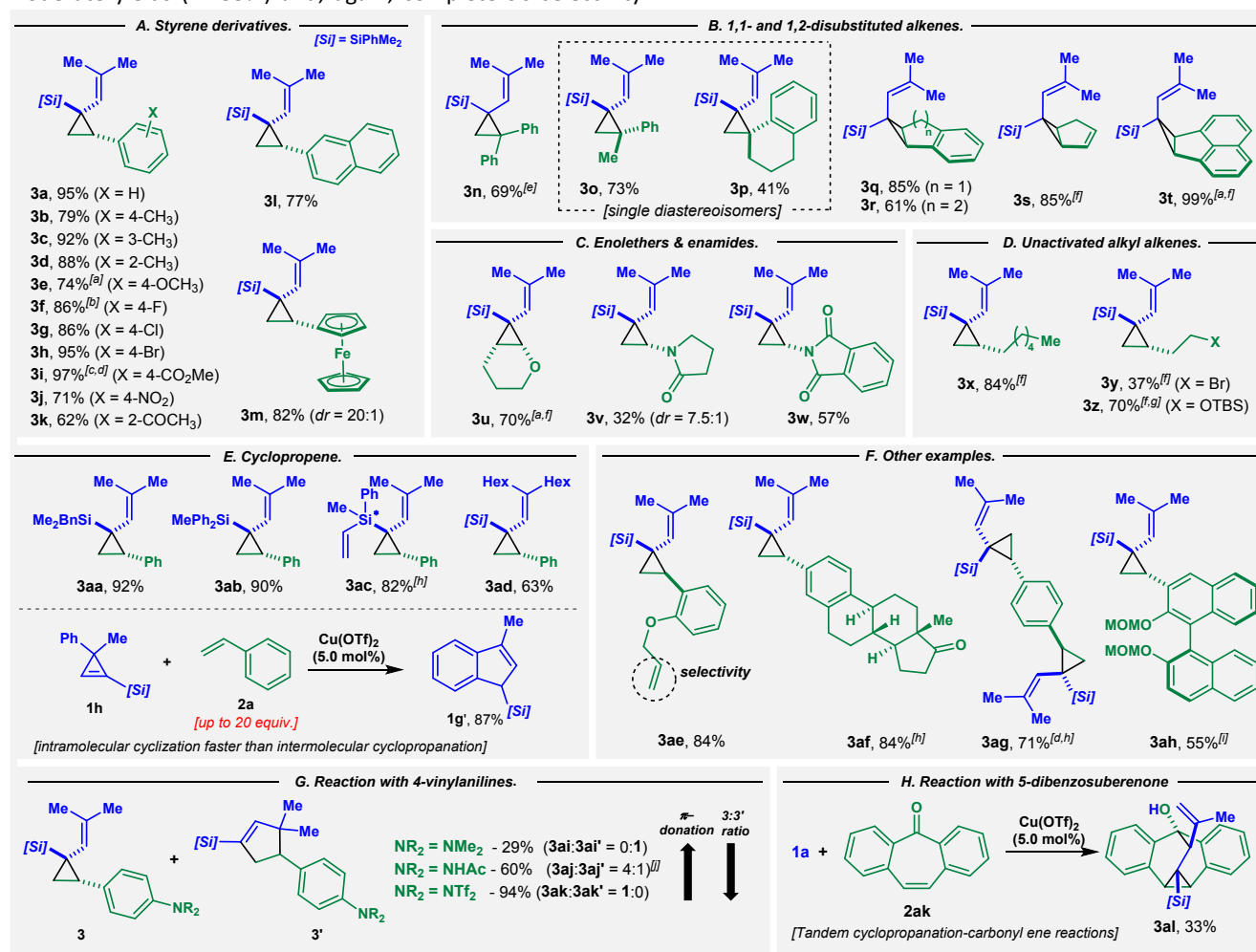
^b Departamento de Química Orgánica e Inorgánica, Universidad del País Vasco, Apto. 644, 48080-Bilbao (Spain)

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Searching for economical catalysts, we found that copper catalysts were the most efficient ones. Above all, $\text{Cu}(\text{OTf})_2$ enabled the preparation of **3a** in near quantitative yield (95%) without needing an excess of styrene (**2a**, 1.1 equiv.) Noteworthy, FeBr_2 and FeBr_3 proved also active catalysts and constitute, to our knowledge, the first examples of Fe-catalysed cyclopropanations using cyclopropenes. In contrast to reactions with α -silyl-substituted diazo compounds which usually lead to mixtures of diastereoisomers, **3a** was consistently obtained as a single diastereoisomer within ^1H NMR limit of detection.

With optimized reaction conditions, we explored the scope of the reaction (Scheme 2). Starting from styrene derivatives (Scheme 2A), we prepared a set of cyclopropylsilanes **3a-m** in good yields (74–97%) and complete diastereoselectivity. Examples included arenes bearing donor and acceptor groups, *ortho*-substituents or ferrocene. 1,1- and 1,2-Disubstituted alkenes could be employed as well (Scheme 2B), yet at least one aryl group is required. Thus, compounds **3n-t** were obtained in moderate yields (41–99%) and, again, complete *cis* selectivity

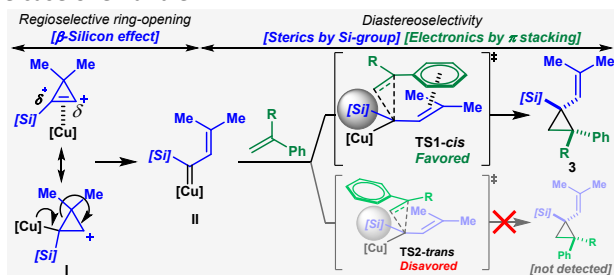
(relative to aryl and vinyl groups). This stereoselectivity is particularly relevant for compounds **3o-p**, since these alkenes typically lead to mixtures of diastereoisomers in reactions with diazo compounds. Within 1,2-disubstituted alkenes, cyclopentadiene and acenaphthylene were converted into cyclopropylsilanes **3s** and **3t**, respectively, in excellent yields. Enoethers and enamides could also be employed as indicated by the synthesis of *O*- and *N*-substituted cyclopropanes **3u-w** in reasonable yields and high diastereoselectivities (Scheme 2C). Challenging unactivated alkyl-substituted alkenes could be employed as well (Scheme 2D). Thus, cyclopropane **3x**, derived from 1-octene was obtained in good yield (84%) as a single diastereoisomer. Moreover, 4-bromo-1-butene or silyl-protected homoallylic alcohol were fruitfully converted into cyclopropanes **3y** and **3z**, respectively. Modifications at cyclopropene were less kind (Scheme 2E). Cyclopropenes decorated with some typical silanes at position 1, could be routinely used in the reaction with styrene to afford cyclopropylsilanes **3aa-3ac** in high efficiency and selectivity.



Scheme 2. Synthesis of cyclopropylsilanes **3**: Scope. Reaction conditions: **1** (0.15–0.25 mmol), **2** (1.1 equiv.), $\text{Cu}(\text{OTf})_2$ (5 mol%) in CH_2Cl_2 (1.0 M) at RT. ^[a] At 0 °C. ^[b] With 1.5 equiv. of alkene. ^[c] With 2.0 equiv. of cyclopropene. ^[d] 85% yield (NMR) with 1.1 equiv. of alkene but inseparable from unreacted alkene. ^[e] With 3.0 equiv. of alkene. ^[f] With 6.0 equiv. of alkene. ^[g] At 40 °C. ^[h] Mixture of diastereoisomers, *dr* = 1:1. ^[i] Mixture of diastereoisomers, *dr* = 5:3:1. ^[j] Inseparable mixture.

The preparation of compound **3ad** indicates that modification of the alkyl groups at position 3 of the cyclopropene should not be problematic. However, the use of 3-phenyl-substituted cyclopropene **1g** inevitably led to indene **1g'**, through a well-known Nazarov-like cyclization,^{12a,17} even though the alkene was used in large excess. Additional examples (Scheme 2F) included compound **3ae** demonstrating complete selectivity for aryl vs alkyl alkenes. An initial approach to structural complexity is depicted with cyclopropylsilanes **3af-ah** derived from estrone, 1,4-divinylbenzene and a BINOL-derived styrene, respectively, which were efficiently prepared.

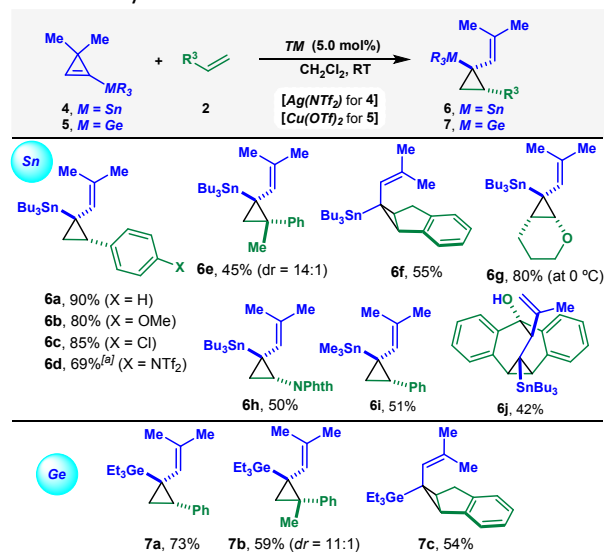
The study of the scope revealed some particularities. For instance, *p*-vinylanilines reacted according to their π -donor ability (Scheme 2G). Strongly donating *N,N*-dimethylaniline led to *cyclopentene* **3ai'**,¹⁶ while (Tf)₂N-derived aniline yielded solely *cyclopropane* **3ak**. In between, 4-vinylacetanilide provided a **3aj/3aj'** mixture. Besides, 5-dibenzosuberone (**2ag**) led to intricate cyclopropane **3al** in moderate yield (33%) (Scheme 2H). This compound likely arises from a tandem cyclopropanation/intramolecular carbonyl-ene reaction.¹⁸ Two features regarding selectivity deserve comment (Scheme 3). The regioselective ring-opening of the cyclopropenes **1** provides only the desired α -silyl copper carbene intermediate **II** (products from other cleavage were not detected). The well-known silicon β -stabilizing effect on species **I** accounts for the regioselective ring-opening.^{14,15} More importantly, the diastereoselectivity could be explained considering both steric and electronic factors. Thus, the bulkiness of the silicon group, along with favourable π -stacking interactions (**TS1**, vinylcarbene-arene) serve to explain all the results observed.¹⁹ The participation of the π -stacking is particularly evident in the formation of compounds **3o-t** or when relating selectivities in the case of **3v** and **3w**.



Scheme 3. Regio- and diastereoselectivity rationale for the formation of cyclopropylsilanes **3**.

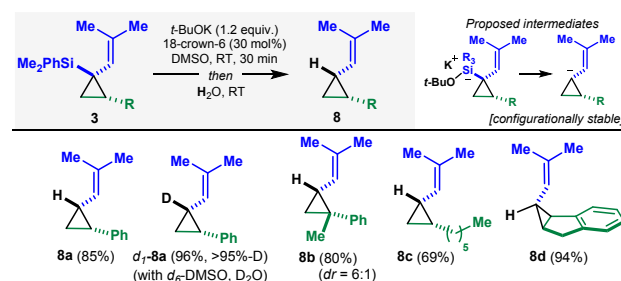
Since β -stabilizing effect could also be exerted by tin and in the wake of relevant recent reports from Fürstner's group dealing with α -stannyl diazoacetates,²⁰ we subsequently explored the reaction with 1-stannylcyclopropenes **4** (Scheme 4). Thus, we found that cyclopropenes **4** reacted with alkenes **2**, being Ag(NTf₂) the most competent catalyst.¹⁶ A set of representative cyclopropylstannanes **6a-j** was prepared in synthetically useful yields and selectivities, pointing out to a scope comparable to the silyl analogues. The interest of organogermanium compounds has increased in the recent years,²¹ consequently, we wondered if the process could be applicable to this metal.

Gratifyingly, preliminary studies with 1-germanylcyclopropene **5** enabled the synthesis of representative cyclopropylgermanes **7a-c** in reasonable yields (Scheme 4). In this case, Cu(OTf)₂ was again the catalyst of choice.



Scheme 4. Synthesis of cyclopropylstannanes and -germanes.

Finally, a protodesilylation reaction of cyclopropylsilanes **3** was attempted. This seemingly simple reaction might actually serve to prepare relevant *cis*-1,2-disubstituted cyclopropanes,²² the synthesis of which is challenging due to their inherent strain.²³ It should be noticed that the control of the stereoselectivity might be challenging since loss of stereochemical information,⁸ retention^{24a-b} and inversion^{24c} in protodesilylations of related cyclopropylsilanes have been reported. Gratifyingly, applying the procedure reported by Gu (Scheme 5),^{24c} treatment of cyclopropylsilanes **3** with *t*-BuOK and 18-crown-6 ether in DMSO, led to the formation of a set of representative *cis*-1,2-disubstituted cyclopropanes **8a-d** in good yields (69–94%).²⁵ It should be noticed that in contrast to the inversion reported by Gu,^{24c} cyclopropanes **8** were formed via stereoretentive reaction with the exception of **8b**, which gave a significant amount of the *trans* isomer.



Scheme 5. Synthesis of *cis*-1,2-disubstituted cyclopropanes **8** by stereoretentive protodesilylation of cyclopropylsilanes **3**.

These results could be explained by the configurational stability of the cyclopropyl anion.²⁶ Additionally, by this method we could also prepare isotopically labelled *d*₁-**8a** (90%, >95%-D by

using *d*₆-DMSO and subsequent quenching with D₂O.²⁷ Regrettably, attempts to perform cross-coupling reactions with cyclopropylsilanes²⁸ or –stannanes²⁰ were futile, although in the latter case closely related derivatives were effectively used.

In summary, we reported herein the use of 1-silylcyclopropenes as precursors of α -silyl carbenes, which can be used for efficient and selective syntheses of valuable cyclopropylsilanes. The transformation showed an enjoyable scope and high selectivities. The reaction was extended to heavier group 14 cyclopropenes enabling the synthesis of the corresponding cyclopropylstannanes and –germanes. Finally, a stereoretentive desilylation was described for the preparation of *cis*-1,2-disubstituted cyclopropanes. We are currently trying to expand the methodology to the use of other substituents at the silicon (tin or germanium) atom to facilitate further functionalizations by cross-coupling chemistry.

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There are no conflicts to declare.

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