Zinc-Catalyzed Functionalization of Si–H Bonds with 2-Furyl Carbenoids via Three Component Coupling

Sergio Mata, Luis A. López,* and Rubén Vicente*

Dedicated to Professor José Barluenga on the occasion of his 75th birthday

Abstract: A three-component coupling of alk-2-ynals, 1,3-dicarbonyls and silanes is reported. $ZnCl_2$ serves as inexpensive and low-toxic catalyst for the overall transformation, which involves Knoevenagel condensation, cyclization and carbene Si–H bond insertion. The process takes place with atom economy in the absence of organic solvents and shows a broad scope. This reaction proves also applicable to the functionalization of oligomeric siloxanes.

Silanes are an important class of compounds in chemistry.[1] With respect to organic chemistry, synthetic applications of organosilanes have been established as routine protocols. Thus, named reactions based on the use of compounds bearing silyl groups such as Hiyama coupling, Sakurai allylation, Peterson olefination or Brook rearrangements, among others, are commonly used synthetic tools.[1c, 2] Moreover, the natural abundancy of silicon, the stability of organosilanes and siloxanes, their low toxicities and macroscopic properties have made silicon-based materials and polymers essential for our society.[3] Considering the significance of silanes, the development of efficient methodologies for their synthesis is a topic of continuous interest. Several methods have been employed to prepare organosilanes, including reactions of organometallics with halosilanes[4] or metal catalyzed cross-couplings[5] and hydrosilylations using hydrosilanes.[6] Moreover, transition-metal-catalyzed insertion of carbenes or carbenoids, generated from stabilized diazocompounds, into Si–H bonds is one of the most efficient tools for the functionalization of silanes.[7, 8] As an alternative to potentially explosive diazocompounds, diiodoalkanes (**A**) and Et_2Zn can be employed to generate Simmons-Smith-type carbenoids capable of inserting into the Si–H bond of simple silanes (**B**) (Scheme 1, top).[9] Unfortunately, *stoichiometric* amounts of *moisture/air sensitive* Et_2Zn are required to accomplish this reaction. We have recently disclosed a methodology to generate zinc carbenoids in a *catalytic* fashion using enynones (**D**) as source of furyl zinc carbene intermediates (**F**), which could be efficiently trapped *in situ* with silanes through a Si–H bond insertion (Scheme 1, middle).[10] This transformation could be accomplished with catalytic amounts of inexpensive and low toxic $ZnCl_2$.

Besides, multicomponent domino reactions constituted the archetype of sustainable processes.[11] Since enynones (**D**) are

prepared by Knoevenagel condensation (between compounds **G** and **H**) and Lewis acids such as $ZnCl_2$ can catalyze this type of condensations,[12] we wondered if a operationally simpler and environmentally more benign three component protocol could be developed (Scheme 1, bottom). According to this hypothesis, $ZnCl_2$ might operate as single catalyst to promote a three step sequence: *(i)* Knoevenagel condensation, *(ii)* 5-*exo-dig* cyclization and, *(iii)* Si–H bond insertion. The overall process could be considered as zinc self-relay catalysis.[13] Herein, we disclose our findings that have allowed us to accomplish a multicomponent reaction with an overall similar efficiency with respect to the standard stepwise approach showing an expanded scope, which includes the functionalization of diversely substituted silanes and oligosiloxanes.
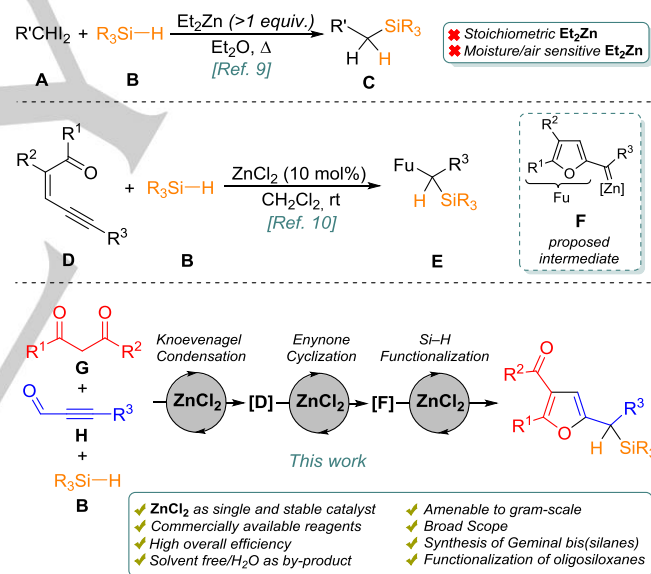

Scheme 1. Zinc-promoted functionalization of Si–H bonds: stoichiometric *vs* catalytic multicomponent approaches.

As benchmark substrates, commercially available reagents 2,4-pentanedione (**1a**), oct-2-ynal (**2a**) and triethylsilane (**3a**) were selected to explore the feasibility of a zinc-catalyzed multicomponent coupling to yield furan derivative **4a**. Temperature, relative ratio of reagents and catalyst loading were screened.[14] Optimal reaction conditions involved the use of a slight excess of the silane **3a** (6 equiv.), 5.0 mol% of $ZnCl_2$ and mild heating at 60 ºC to afford **4a** in 73% yield (Scheme 2).[15] Noteworthy, the use of an organic solvent was not required and H_2O was the only generated by-product, which did not compromise the efficiency of the reaction. This multicomponent protocol yielded **4a** with comparable efficiency to that observed when using previously synthetized enynone (73% and 77%,

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respectively).[10] Moreover, the process could be scaled-up to 50-fold (10 mmol scale) providing **4a** even in a higher yield (88%, 2.83 g).
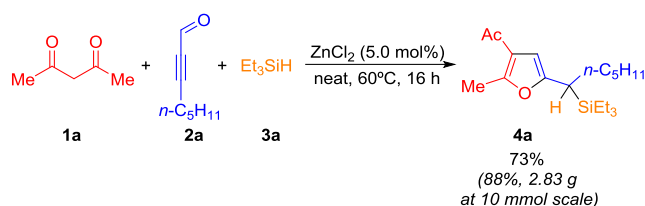
Scheme 2. Zinc-catalyzed three component coupling: Optimized conditions. (**1a** (1.1 equiv.), **2a** (0.2 mmol), **3a** (6.0 equiv.), ZnCl$_2$ (5.0 mol%), 60 ºC, 16 h. (Yields are refereed to isolated products).

The optimized reaction conditions were then applied to study the scope of this multicomponent coupling (Scheme 3). 1,3-Dione **1a** and triethylsilane (**3a**) were combined with a variety of alkyl-substituted alkynals, including primary, secondary,[16] tertiary or remotely functionalized alkyl groups to yield compounds **4a-f** in moderate to good yields. The use of 1-cyclohexenyl-substituted alkynal led to interesting allylsilane **4g** in 61% yield. Aryl-substituted alkynals with different electronic properties proved also suitable substrates providing compounds **4h-j**. Modifications of the 1,3-dione were feasible as showed in compounds **4k-m** and **4o-p**. Noteworthy, when using ketoesters as 1,3-dione component, the reaction took place chemoselectively through the ketone moiety to afford **4l-m** and **4o** in spite of the poor selectivity of the Knoevenagel condensation.[17] Next, we evaluated the scope with respect to silane coupling partner. Trisubstituted silanes bearing alkyl or aryl groups could be employed yielding compounds **4n-q** with similar efficiencies. While triethoxysilane proved unreactive under various reaction conditions tested, inexpensive and readily available in bulk quantities siloxysilanes could also be functionalized with the present procedure to lead to compounds **4r-s** in synthetically useful yields. Other valuable moieties were tolerated in the silane. For instance, alkynylsilane participated in the reaction leading to densely functionalized compounds **4t-u**. 2-Silyl-substituted indole was also a competent coupling partner affording silane **4v**, albeit in lower yield (45%, the two-component procedure led to **4v** in 80% yield). Finally, di- and mono-substituted silanes were studied as well. The corresponding silanes **4w-z** were obtained, albeit in lower yields when compared with the two-component procedure.[18]

The present multicomponent procedure leads to furan derivatives **4** in almost comparable yields to those obtained from two-component approach (except for **4v**, **4x** and **4y**). Aside from its remarkable efficiency, advantages with respect to the operational simplicity, minimization of waste and the scale-up feasibility are noteworthy features of this three-component coupling to consider it as the procedure of choice.
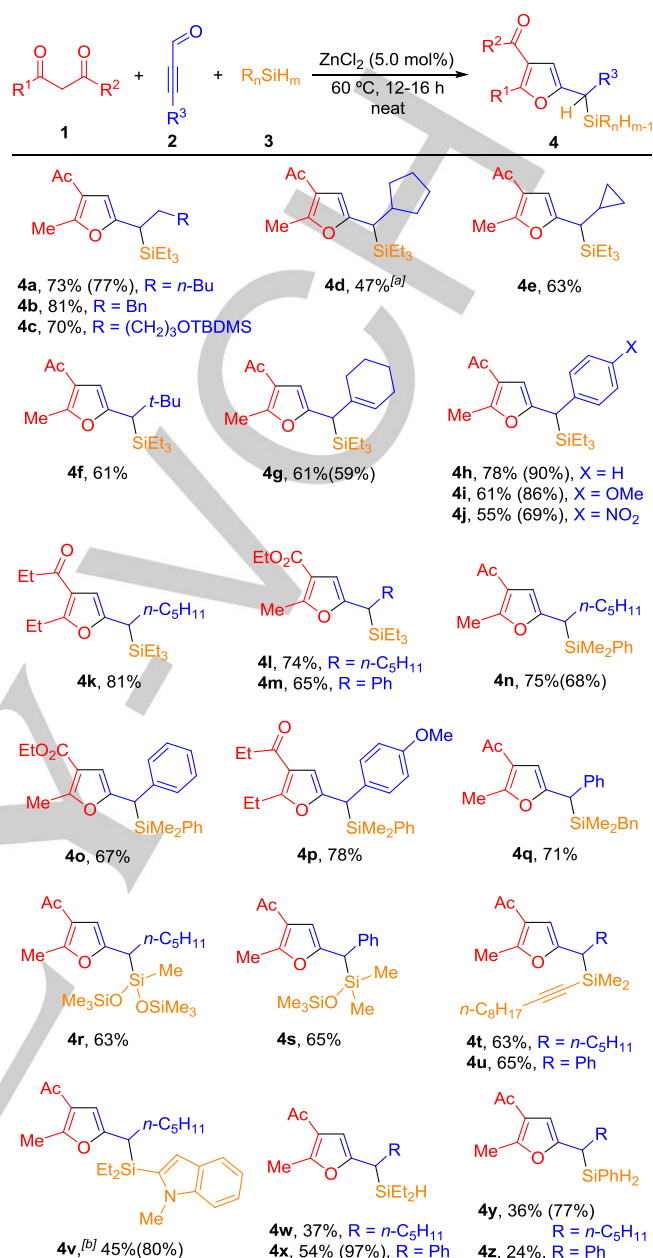
Scheme 3. Scope. (Reaction conditions: **1** (0.3 mmol), **2** (1.1 equiv.), **3** (6.0 equiv.), ZnCl$_2$ (5.0 mol%), 60 ºC, 12-16 h). Yields are refereed to isolated products. The values in parenthesis indicate the yield for the two component reaction using the corresponding enynone and ZnCl$_2$ (10 mol%) at ambient temperature).[a] See Ref. 16. [b] CH$_2$Cl$_2$ (0.5 mL) was used as solvent.
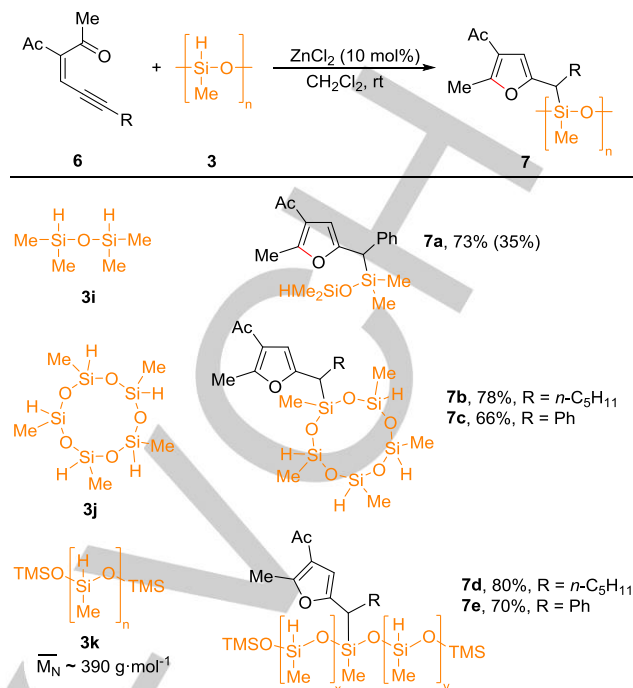
Geminal bis(silanes) represent a special type of organosilanes with potential synthetic applications as coupling reagents due to their bifunctional character given by this particular structure.[19, 20] In view of that, we next explored the feasibility to apply this multicomponent coupling to access orthogonally substituted *geminal bis(silanes)* by means of commercially available 3-(trimethylsilyl)propiolaldehyde (**2k**). Thus, when alkynal **2k** was subjected to optimized reaction conditions using 1,3-dione **1a** and triethylsilane (**3a**), geminal bis(silane) **5a** was obtained in 61% yield (Scheme 4). Subsequent modifications of the 1,3-

dione led to compounds **5b-c** in similar yields. With respect to the silane coupling partner, a dialkylarylsilane, siloxysilanes or a alkynylsilane could be employed for the Si–H bond insertion to afford geminal bis(silanes) **5d-g**.
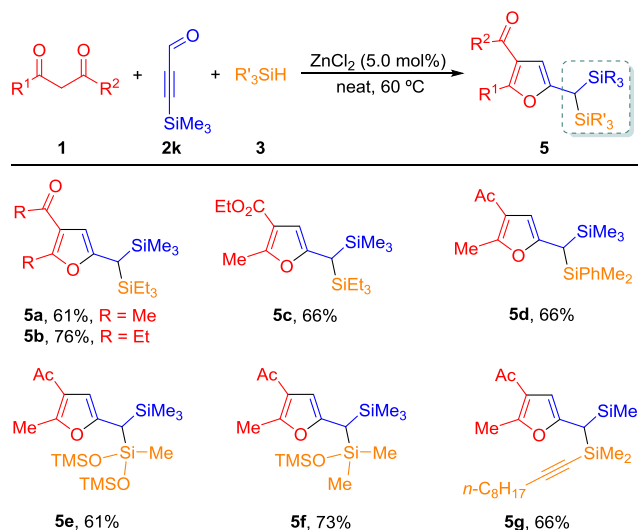
Scheme 4. Zinc-catalyzed synthesis of orthogonally substituted geminal bis(silane) derivatives **5**.

Scheme 5. Zinc-catalyzed functionalization of Si–H bonds in oligosiloxanes. (Values in parenthesis indicate the yield for three-component reaction).

Polysiloxanes and silicones have been considered compounds with marked economic significance for decades.[21] Because of their versatility and unique excellent chemical, physical and electrical properties, polysiloxanes and silicones play a relevant role among advanced materials with widespread applications in products ranging from biomedicine to consumer electronics.[3, 22] As a result of the unquestionable importance of these compounds, methodologies that enable the modification of polysiloxanes to modulate their properties are always on demand. To demonstrate the utility of the methodology developed in this work as a tool with potential applications in materials science, we evaluated the functionalization of Si–H bonds in representative low-molecular weight oligosiloxanes (Scheme 5). Initially, simple 1,1,3,3-tetramethyldisiloxane (**3i**) was selected as a model substrate. Preliminary experiments revealed that the Si–H bond insertion was feasible, albeit two-component reaction proved superior to the multicomponent version (73% vs 35%, respectively). Consequently, we moved to other typical cyclic or linear polysiloxanes (**3j** and **3k**, respectively), which could also be functionalized to obtain the corresponding functionalized oligosiloxanes **7b-e** in good yields, highlighting the potential of this approach.[23]

In summary, we reported the functionalization of Si–H bonds through a zinc-catalyzed multicomponent coupling using 1,3-diones, alk-2-ynals and silanes, through the *in situ* generation of a 2-furyl zinc carbenoid. Inexpensive, low-toxic ZnCl$_2$ was employed as single catalyst promoting a sequence Knoevenagel condensation/enyne cyclization/Si–H bond insertion in a self-relay catalytic process. This transformation proceeds without using organic solvents or harmful residue generation since H$_2$O is the only by-product. The broad scope regarding all coupling partners is remarkable. Thus, the procedure was used for the synthesis of interesting unsymmetrically substituted geminal bis(silanes). Moreover, the functionalization of Si–H bonds in representative oligosiloxanes exemplifies the feasibility to apply this reaction in a relevant field such as polymeric advanced material modifications.

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[13] According to the definition given in: a) N. T. Patil, V. S. Shinde, B. Gajula, *Org. Biomol. Chem.* **2012**, *10*, 211. The transformation can be also defined as an *auto-tandem catalysis*, according to: b) D. E. Fogg, E. N. dos Santos, *Coord. Chem. Rev.* **2004**, *248*, 2365.

[14] For a brief summary of the screening, see the Supporting Information.

[15] The use of smaller amounts of the silane **3a** translated into lower yields along with an increase of the reaction time. Nevertheless, if desired,

most of the unreacted silane could be recovered by simple distillation or flash chromatography.

[16] Along with compound **4d**, the formation of minor amounts (<10%) of 1-(5-(cyclopentylidenemethyl)-2-methylfuran-3-yl)ethan-1-one was also formed. The formation of this 2-vinylfuran derivative would result from a competitive 1,2-C–H insertion in the postulated zinc carbene intermediate.

[17] Reaction of ethyl 3-oxobutanoate with alkynal **2a** under standard Knoevenagel conditions (using catalytic amounts of $Mg(ClO_4)_2$ and $MgSO_4$) led to a 1.2:1 *Z:E*-mixture of the corresponding enynone. In this case, isomerization of the enynone or retro-Knoevenagel condensation could account for the observed yields. On the contrary, attempts to employ unsymmetric 1,3-diones (R^1 = Me; R^2 = *t*-Bu/Ph) failed due to a competitively faster reduction of the alkynal by the silane with respect to the required condensation. Unfortunately, attempts to prepare the corresponding enynones by various condensation procedures failed.

[18] Performing the reactions at lower temperatures did not provide better results. Functionalization of the Si–H bonds in compounds **4w-z** was not observed under the optimized reaction conditions.

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[23] Compounds **7b-e** could be prepared using three-component procedure, although in lower yields. See the Supporting Information for details.

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Broad scope

Geminal Bis(silanes)

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