Ligation reactions were run in total volumes of 10 μL of 0.25 M imidazole (Im) buffer, pH 7.7, for 3 days at 0 °C. The concentration of the PNA primer was 8 μM, of the template 12 μM, and of the activated dimer 0.8 mM. When we used a mixture of DD and LL dimers, the concentration of each enantiomer was 0.8 mM. The duplexes between the primer and templates were preformed by preincubation at 20 °C for 2 h in 5 μL of 10 mM sodium phosphate buffer, pH 7.0, containing 100 mM NaCl and 0.1 mM ethylenediaminetetraacetate (EDTA). The dimers were activated in 0.1 M Im buffer at pH 6.0 containing 0.1 M 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide (EDC) by incubating the solution for 3 h at 20 °C and then diluting with an equal volume of 1 M Im buffer at pH 7.7. Aliquots of the resulting solution (5 μL) were added to reaction tubes containing the preformed duplexes. HPLC analyses of the reaction mixtures were performed on an RPC5 column as previously described.[16] Reaction products were eluted with a linear gradient of $NaClO_4$ (pH 12, 0 – 0.06 M over 60 min) and the UV absorption at 254 nm monitored.

Circular dichroism spectra were obtained using equimolar concentrations (10 μM) of the two complementary strands hybridized in 10 mM sodium phosphate at pH 7.0 containing 100 mM NaCl.

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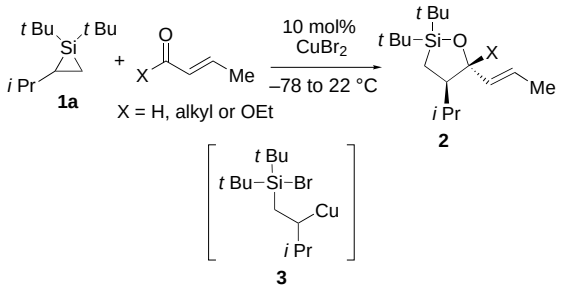
$ZnBr_2$-Catalyzed Insertions of Carbonyl Compounds into Silacyclopropanes: Regiochemical Reversal Dependent on Metal Salt**

Annaliese K. Franz and K. A. Woerpel*

We recently reported that copper salts catalyze the insertion of various carbonyl compounds into the C–Si bond of silacyclopropane **1a** in a stereospecific and highly stereo-, regio-, and chemoselective fashion (see Scheme 1).[1] While formamides, formate esters, and α,β-unsaturated carbonyl compounds inserted under these conditions, saturated aldehydes such as butyraldehyde could not be coaxed to react. Ring-opening of the unsymmetrically substituted silacyclopropane **1a** occurred exclusively with cleavage at the more substituted C–Si bond to afford insertion products such as **2**. The observed regiochemistry and carbonyl reactivity was rationalized by consideration of organometallic species **3** (Scheme 1) which is believed to form upon transmetalation of the more substituted C–Si bond to copper. We have obtained selectively products with this 1,2-regiochemistry for all insertion reactions of silacyclopropanes thus far.[2–4]



Scheme 1. Copper-catalyzed insertions into silacyclopropane **1a** proceed with up to 98:2 diastereoselectivity and > 99:1 regioselectivity.

To complement our previous results, we desired a method to functionalize the less substituted C–Si bond and insert saturated carbonyl compounds. Insertion into the less substituted C–Si bond would provide access to the 1,3-regioisomer **4** which can be oxidized[5] to obtain the 1,3-diol motif **5** (Scheme 2).[6, 7] Herein, we report that metal salts such as $ZnBr_2$ can be employed to access previously unavailable

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Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

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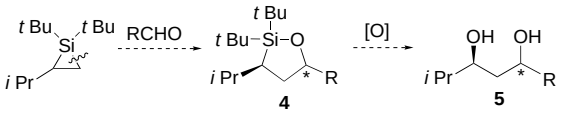


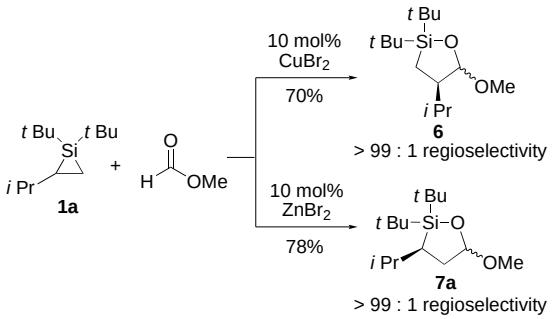
Scheme 2. Stereoselective synthesis of 1,3-diols by an insertion and oxidation sequence.

insertion products with a complete reversal of the regiochemistry compared to that of the copper-catalyzed conditions. By the appropriate choice of metal salt, precise control of the silacyclopropane ring-opening can be achieved to obtain either the 1,2- or the 1,3-regioisomeric insertion product with excellent regioselectivity (>99:1).

While attempting to elucidate the role of the metal salt in the ring-opening of silacyclopropanes, we discovered that zinc and copper salts exhibit complementary regioselectivities for the insertion of formate esters. Methyl formate inserted into the more substituted C–Si bond of silacyclopropane **1a** to afford 1,2-regioisomer **6** (Scheme 3) when copper salts were used, but a complete reversal of regiochemistry to give 1,3-regioisomer **7a** was observed when $ZnBr_2$ was employed.[8, 9] We have shown that oxasilacyclopentane acetals such as **6** and **7a** serve as precursors to oxocarbenium ions that undergo Lewis acid mediated nucleophilic substitution with excellent diastereoselectivities.[10, 11]

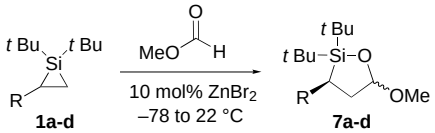
The regiochemical preference of the $ZnBr_2$-catalyzed formate insertion was investigated for a series of monosubstituted silacyclopropanes with increasing steric size (Table 1). Unsymmetrical silacyclopropanes **1a** and **1b** (entries 1 and 2) reacted to afford exclusively 1,3-products **7a** and **7b**, respectively. The presence of an electron-withdrawing group on the β-carbon in silacyclopropane **1c** did not affect the regioselectivity of the insertion (entry 3). When the size of the substituent on the strained ring was increased to *tert*-butyl (**1d**), however, an erosion of regioselectivity (83:17) was observed (entry 4). The selective functionalization of tri-*tert*-butyl substituted **1d** indicates that steric interactions between the substituent on carbon and the *tert*-butyl groups on silicon exert only a minor influence on the regioselectivity of insertion.

Catalysis by $ZnBr_2$ was determined to be general for the insertion of both aliphatic and aromatic aldehydes and ketones to provide oxasilacyclopentanes **8a–j** (Table 2). Employing $ZnBr_2$ as the catalyst allowed the insertion of saturated carbonyl compounds, such as butyraldehyde,



Scheme 3. Catalyst-based regiocontrol of methyl formate insertion to obtain either the 1,2- or 1,3-regioisomeric product.

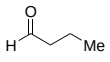
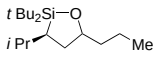
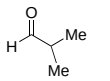
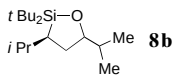
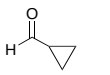
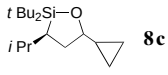
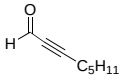
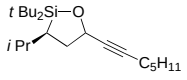
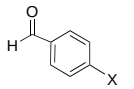
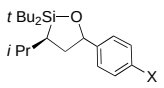
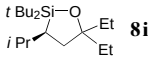
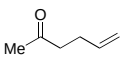
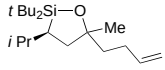
Table 1. Regioselectivity of $ZnBr_2$-catalyzed insertion of methyl formate into silacyclopropanes **1a–d**.



Entry	R	Product	Yield [%]	Regioselectivity[a]
1	*i*Pr	**7a**	78	>99:1
2	*n*Bu	**7b**	79	>99:1
3	-CH_2CH_2OTIPS	**7c**	72[b]	>99:1
4	*t*Bu	**7d**	77	83:17

[a] As determined on the basis of GC analysis. [b] This yield includes the synthesis of silacyclopropane **1c** from tBu_2SiCl_2. TIPS = Triisopropylsilyl.

Table 2. $ZnBr_2$-catalyzed insertion of aliphatic and aromatic aldehydes and ketones into silacyclopropane **1a**.

Entry	Carbonyl compound	Major product	Yield [%][a]	Diastereoselectivity[b]	Regioselectivity[b]
1		 **8a**	70	55:45	>99:1
2		 **8b**	73	57:43	>99:1
3		 **8c**	71	57:43	96:4[c]
4		 **8d**	72	79:21	>99:1
					
5	X = H	**8e**	74	66:34	>99:1
6	X = CF_3	**8f**	63	60:40	>99:1
7	X = CH_3	**8g**	78	93:7	61:39[c]
8	X = OCH_3	**8h**	68	55:45[d]	72:28
9		 **8i**	58	–	>99:1
10		 **8j**	70	66:34	>99:1

[a] Yield of purified materials. [b] As determined on the basis of GC and GC/MS analysis. [c] Reaction was run in the presence of 4-Å activated molecular sieves. [d] When the *p*-anisaldehyde insertion product was resubmitted to reaction conditions, isomerization occurred to afford a 94:6 diastereoselectivity for the 1,3-regioisomer.

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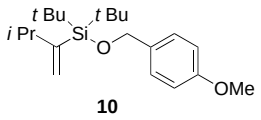
which do not react under any other conditions.[12] The 1,3-regioisomer resulting from cleavage of the less substituted C–Si bond was obtained predominantly ($\geq$96:4) for all substrates, with the exception of the electron-rich aryl aldehydes *p*-tolualdehyde and *p*-anisaldehyde (entries 7 and 8), which afforded **8g** and **8h** with reduced regioselectivities. Products **8a–j** have complementary regioselectivity compared to the insertion of carbonyl compounds under all conditions reported previously.[2–4]

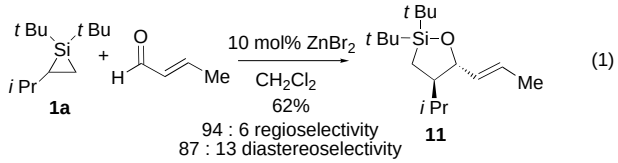
An extensive screening of catalysts demonstrated that $ZnBr_2$ is the optimal catalyst for the insertion of aldehydes into silacyclopropane **1a** with excellent regiocontrol and yield. Metal salts such as $Zn(OTf)_2$ (OTf = trifluoromethanesulfonate), $InCl_3$, $InBr_3$, $MnBr_2$, and $SnBr_2$ were also effective catalysts for the aldehyde insertion pathway. Sources of bromide ion (LiBr, $MgBr_2$, and Bu_4NBr) did not catalyze the insertion of aldehydes into **1a**. Other Lewis acids ($AlCl_3$, $Sc(OTf)_3$, $TiCl_4$, $BF_3 \cdot OEt_2$, $SnBr_4$, and $MgBr_2 \cdot OEt_2$) proved to be too reactive in the presence of the silacyclopropane, affording only products of decomposition.

In an effort to optimize the regioselectivity for insertions of electron-rich aldehydes (Table 2, entries 7 and 8), we evaluated the influence of reaction conditions and reagents on the insertion of *p*-anisaldehyde. None of the factors investigated initially (reaction temperature, catalyst loading, equivalents of aldehyde, concentration, and order of addition) affected the regiochemistry of insertion. When the heterogeneous reaction mixture was treated with a drop of water, however, the unexpected 1,2-regioisomer **9** was observed with >99:1 regioselectivity (entries 1 and 2, Table 3). The hydride transfer product **10** (5%) was also formed under these conditions.[3, 13] When di-*tert*-butylpyridine was added to rule out the possibility of protic acid catalysis, excellent regioselectivity (>99:1) was still observed (entry 3). A control experiment with only di-*tert*-butylpyridine also afforded 1,2-regioisomer **9** with high regioselectivity (93:7; entry 4). Additional experiments indicated that this effect also extends to reagents such as THF and menthol (entries 5 and 6) while treatment with *N*-benzyl-*N*-methylformamide or pyridine leads to recovery of the silacyclopropane starting material (entries 7 and 8).[14] We believe that additives containing a less nucleophilic oxygen or of increased steric size (entries 2–6) serve as ligands to increase the solubility of the $ZnBr_2$ in CH_2Cl_2 and enhance the activity of the catalyst.[15] In the presence of pyridine or formamide, the $ZnBr_2$ most likely forms a stable complex which is catalytically inactive.[16]

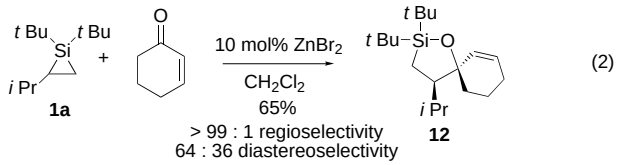


10

An unexpected reversal of regiochemistry was also observed for the insertion of α,β-unsaturated carbonyl compounds relative to their saturated analogues, butyraldehyde and 3-pentanone (Table 2, entries 1 and 9). Under $ZnBr_2$-catalyzed conditions, the insertion of crotonaldehyde and cyclohexenone into silacyclopropane **1a** proceeded with excellent regioselectivity to afford 1,2-regioisomers **11** and **12**, identical products to those obtained under copper-catalyzed conditions [Eq. (1) and (2)].[17] These results



(1)

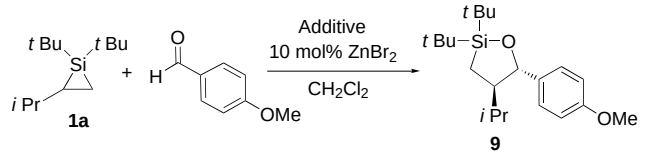


(2)

prompted us to investigate the relative reactivity of saturated and α,β-unsaturated aldehydes under $ZnBr_2$ conditions. When silacyclopropane **1a** was treated with an excess of both crotonaldehyde and butyraldehyde in the presence of $ZnBr_2$, only the crotonaldehyde insertion product was observed with ^1H NMR spectroscopy. Although the effect of the conjugated alkene on reactivity and regiochemistry is unclear, it appears that an alternate reaction pathway is available for α,β-unsaturated aldehydes and ketones.

Three possible roles can be envisioned for $ZnBr_2$ in this insertion pathway: 1) a source of bromide ion that activates the silane, 2) a metal salt that undergoes a direct interaction with the strained σ bond of the silacyclopropane, or 3) a Lewis acid that complexes to the carbonyl compound. It is unlikely that the $ZnBr_2$ in this system is acting solely as a bromide source since alternate bromide sources did not catalyze this reaction. We also do not believe that there is evidence to support a direct interaction between the metal and the strained σ bond[18] of silacyclopropane. In contrast to copper salts, no evidence of an interaction was observed between silacyclopropane **1a** and $ZnBr_2$ in either the ^1H or ^{13}C NMR spectra. In addition, the transmetalation reaction proposed

Table 3. Effect of various additives on the regioselectivity of the $ZnBr_2$-catalyzed insertion of *p*-anisaldehyde into silacyclopropane **1a**.



Entry	Additive[a]	Yield [%]	Diastereoselectivity[b]	Regioselectivity[b]
1	none	68	55:45[c]	28:72
2	H_2O	66	>99:1	>99:1
3	H_2O/di-*tert*-butylpyridine	67	>99:1	>99:1
4	di-*tert*-butylpyridine	72	>99:1	93:7
5	THF	76	>99:1	94:6
6	menthol	39	93:7	90:10
7	*N*-benzyl-*N*-methylformamide	n.r.	–	–
8	pyridine	n.r.	–	–

[a] Two equivalents of each additive were employed with the exception of THF which was employed as the solvent for convenience. All reagents were rigorously purified to exclude H_2O. [b] As determined on the basis of GC analysis. [c] This diastereoselectivity was determined for the 1,3-regioisomer; the 1,2-regioisomer was produced exclusively (>99:1) as one isomer as determined on the basis of GC analysis. n.r. = no reaction.

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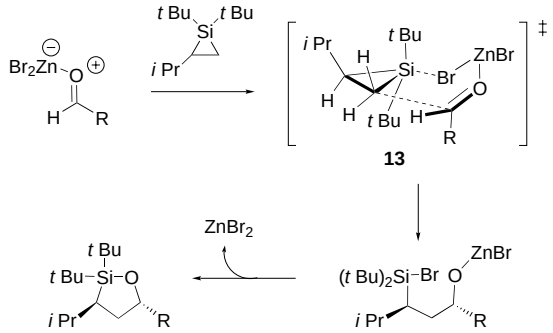
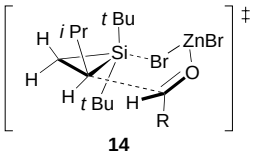
for the related copper-catalyzed insertion into silacyclopropane **1a** exhibits different carbonyl reactivity and affords products of opposite regiochemistry (Scheme 1).[1] A radical pathway has been discounted based on the isolation of cyclopropane-containing products for the insertion of cyclopropane carboxaldehyde (Table 2, entry 3).[19]

The initial results presented herein support our hypothesis that $ZnBr_2$ serves as a Lewis acid to activate the carbonyl moiety through complexation.[20–22] We envision that a ligand on the $ZnBr_2$ catalyst can coordinate to the silicon to form a penta- or hexacoordinate silane,[23] thus enhancing the nucleophilicity of the silacyclopropane.[24, 25] This mechanism is similar to those proposed for the Lewis acid-catalyzed cyanosilation or hydrosilation of aldehydes and ketones (Scheme 4).[26–29] We believe that formation of the 1,3-



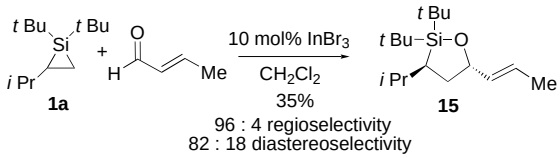
Scheme 4. Proposed mechanism for the $ZnBr_2$-catalyzed insertion of carbonyl compounds into silacyclopropane **1a**.

regioisomer is favored because the substituent on the silacyclopropane encounters less steric interaction with the *tert*-butyl groups on silicon (transition structure **13**; Scheme 4) than with the carbonyl substrate (transition structure **14**). The effect of additives such as H_2O, di-*tert*-butylpyridine, and menthol on the regiochemistry of insertion is unclear. These reagents could either prevent formation of the siliconate intermediate or increase the steric congestion around silicon to provide the 1,2-regioisomer as the major product.



The most intriguing mechanistic question is the divergent regioselectivity and enhanced reactivity of crotonaldehyde as compared to the saturated or alkynal analogues. We believe that a simple coordination between the metal salt and the C–C π bond can be precluded because the α,β-unsaturated alkyne and the unconjugated alkene[30] do not exhibit the same effect on regiochemistry; reactions of these substrates afford solely 1,3-regioisomeric products (Table 2, entries 4 and 10). Based on our investigations with copper-catalyzed insertions into silacyclopropanes, it is possible that the α,β-unsaturated alkene moiety facilitates a silicon to zinc transmetalation that cannot occur for the saturated or alkynal substrates. Further investigations are underway to determine the factors that dictate the regiochemistry of this process.

Preliminary results indicate that the regioisomeric products not observed using $ZnBr_2$- or copper-catalyzed conditions can be obtained by employing other metal salts as catalysts. When silacyclopropane **1a** and crotonaldehyde were treated with 10 mol% $InBr_3$, 1,3-regioisomer **15** was obtained as the major insertion product with 96:4 regioselectivity [Eq. (3)] Conditions will be optimized to increase the efficiency of this insertion reaction.



In conclusion, we have shown that the regiochemistry of silacyclopropane ring-opening is dependent on the choice of metal salt catalyst. Employing $ZnBr_2$ as a catalyst provides a method of complementary regiocontrol for insertion reactions of silacyclopropanes as compared to copper-catalyzed conditions. We have also demonstrated that the regioselectivity of the insertion process is influenced by the electronic nature of the carbonyl substrate and the presence of an α,β-unsaturated alkene moiety. The importance of ligands such as THF, menthol, and di-*tert*-butylpyridine as factors which can affect the regioselectivity and reactivity of this process will be further examined.

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A Linker Scaffold to Present Dimers of Pharmacophores Prepared by Solid-Phase Syntheses**

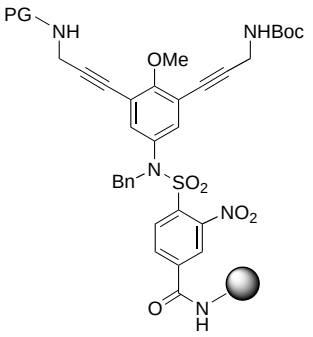
Mookda Pattarawarapan and Kevin Burgess*

Protein–protein interactions generally feature contact points ("hot-spots") situated on discontinuous sites on the protein surfaces.[1] It is therefore difficult to find small monomeric compounds that mimic or disrupt protein–protein interactions. This situation is unfortunate because this type of target is important, and is likely to become even more prevalent as data from The Human Genome Project are processed.

One apparent approach to mimick discontinuous hot-spots is to link potential pharmacophores on a scaffold that holds them apart. An early example of this is the coupling of FK506 ligands to form FK1012 and its analogues.[2] This approach featured rational design rather than high-throughput or combinatorial methods. More recently, NMR techniques have been used to design combinations of small pharmacophores wherein the monomers used are usually found by random screening.[3] Others have designed solution-phase approaches involving mixtures of compounds.[4, 5] However, none of the existing approaches capitalize on the advantages of separating the products from excess reagents in solid-phase syntheses. Moreover, the scaffolds featured in this solution-phase work were relatively flexible ones.

Solid-phase syntheses of combinations of pharmacophores from libraries of monomers can also provide a numerical advantage for the rapid generation of large libraries. A library of n components could, for instance, be attached in a one-compound-per-well format to one arm of a scaffold supported on a solid phase. If the samples of the resin were then distributed appropriately and the monomers coupled to the second arm of the scaffold it would be possible to form $n(n+1)/2$ dimers, one per well. If nonoverlapping libraries of n and m components were used then the number of combinations would be $n \times m$.

Herein we describe the synthesis of new "linker scaffolds" **1** for the solid-phase syntheses of dimeric combinations of pharmacophores. Linker scaffold **1a** has two orthogonally



	PG
1a	Fmoc
1b	Boc

protected reactive groups on scaffold arms that can support pharmacophores at a relatively rigid separation of approximately 10 Å. The scaffold is attached to the resin through a cleavable linker that is stable to the coupling steps and to the acidic conditions typically used to remove side-chain protecting groups (for example, trifluoroacetic acid). Moreover, cleavage of the scaffold from the resin involves a reagent that gives only volatile or innocuous by-products, so the crude materials could be taken directly from the resin-cleavage step into biological assays.

Scheme 1 delineates a synthesis of linker scaffold **1a**. Sequential Sonogashira couplings were used to introduce the two scaffold arms in reactions that are promoted by the electron-withdrawing nitro group. Reduction of that nitro functionality gives an aryl amine **4** for coupling to a known[6]

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