Synthesis of Silylated Cyclobutanone and Cyclobutene Derivatives Involving 1,4-Addition of Zinc-Based Silicon Nucleophiles

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Abstract: A copper-catalyzed conjugate silylation of various cyclobutene derivatives with Me₂PhSiZnCl·2LiCl or (Me₂PhSi)₂Zn·xLiCl (x ≤ 4) to generate β-silylated cyclobutanones is reported. Trapping the intermediate enolate with CIP(O)(OPh), affords silylated enol phosphates that can be further engaged in Kumada cross-coupling reactions to yield silylated cyclobutene derivatives.

Conjugate addition of silicon nucleophiles to α,β-unsaturated carbonyl compounds is one of the standard processes for the formation of C(sp²)–Si bonds. The resulting β-silylated carbonyl compounds can be converted into the corresponding aldols by oxidative degradation of that C(sp²)–Si bond. As to cyclic acceptors, the vast majority of protocols are for cyclopentenone and -hexenone derivatives. Murakami and co-workers reported the 1,4-addition to cyclobutenone derivatives using Fleming’s (Me₂PhSi)₄CuLi·LiCN[a,b] to access functionalized 1,3-dienes after trapping of the enolate intermediate and electrocyclic ring-opening (Scheme 1, top). Aside from this isolated example, there are no further methods known, neither stoichiometric nor catalytic in copper.

Almost 20 years ago, our laboratory introduced copper-catalyzed and even copper-free protocols for conjugate silylation employing bis(triorganosilyl)zinc and tris(triorganosilyl)zincate reagents.[7–9] We also found copper salts to accelerate these reactions and to be essential for hindered and β,β-disubstituted acceptors, respectively.[8] Zinc-based silicon nucleophiles such as (Me₂PhSi)₂Zn·4LiCl and also Me₂PhSiZnCl·2LiCl are in fact highly useful. Their functional-group tolerance is substantially improved over that of the corresponding more reactive lithium compounds from which the zinc reagents are typically prepared by transmetalation. To date, none of these protocols have been applied to cyclobutenones. Moreover, the synthesis of cyclobuty-substituted silanes is limited to a few examples. In 2010, Ito and co-workers reported a copper-catalyzed borylation of silyl-substituted homoallylic sulfonates, and cyclobutylsilane derivatives were obtained by insertion of the C–C double bond into an in situ formed Cu–B bond followed by an intramolecular $\beta_2\gamma$–S$_2$ reaction.[10] The Fu group[11] and our group[12] reported single examples of the synthesis of cyclobutylosilanes by metal-catalyzed radical cross-coupling of a tertiary and a secondary cyclobutyl bromide with zinc- and magnesium-based silicon reagents, respectively. In this work, we describe copper-catalyzed conjugate silylations of highly substituted cyclobutene derivatives with zinc-based silicon reagents (Scheme 1, bottom). The intermediate metal enolates can either be hydrolyzed to afford 3-silyl-substituted cyclobutanones or captured with CIP(O)(OPh), as an electrophile to furnish cyclobutylbenzy phosphates. Subsequent Kumada cross-coupling yields silicon-containing cyclobutene derivatives.

Our study commenced with the conjugate silylation of cyclobutene 1a with 2.0 equiv. of Me₂PhSiZnCl·2LiCl in THF[13] (Table 1). Using Cu(CH₃CN)₂PF₆ as the catalyst in THF at room temperature, β-silylated β-phenylcyclobutanone 2a was obtained in 95% yield after hydrolysis (entry 1). Yields were slightly lower with less silicon nucleophile, for example 91% yield with 1.5 equiv. of Me₂PhSiZnCl·2LiCl. Given the possibility of a copper-free 1,4-addition,[10] we compared different β-

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substituted and α,β-disubstituted cyclobutenones in reactions with and without the copper catalyst. The silylation of 1a in the absence of Cu(CH3CN)PF6 did lead to 2a yet with a substantial decrease in yield (entry 1). Other cyclobutenones such as β-butylyl-substituted 1g and α,β-disubstituted 1o and 1p were tested, and the low yields of the copper-free protocol confirmed the importance of a copper catalyst (entries 2–4).

We further tested the substrate scope of this conjugate silylation (Scheme 2). β-Aryl-substituted cyclobutenones were generally suitable substrates, affording the corresponding β-silylated cyclobutanones in good to excellent yields (1a–f – 2a–f). Electron-donating groups at the aryl ring such as methyl and methoxy led to higher yields than halogenated derivatives. Likewise, cyclobutenones bearing a primary alkyl substituent in the β-position furnished the corresponding products in equally high yields (1g–k – 2g–k); the yield was lowest for 1k containing a C(sp3)–Cl bond. With sterically more demanding secondary alkyl groups such as cyclopropyl and cyclohexyl, yields were still good (1l–m – 2l–m). A silyl group in the β-position was also compatible (1n – 2n). The reactions of α,β-disubstituted cyclobutenones 1o and 1p proceeded equally well. Product 2o was obtained with high diastereoselectivity while 2p formed with a poor diastereomeric ratio. We believe that the diastereoselectivity is mainly controlled by steric factors in the protolysis of the enolate intermediate.

Next, we tried to capture the enolate intermediate as an enol phosphate,[14] that is cyclobutenyl phosphates 3, to allow for subsequent cross-coupling reactions.[15] The brief survey outlined in Table 2 shows that copper-catalyzed 1,4-addition of either Me3SiZnCl·2LiCl or (Me3Si)2Zn·xLiCl (x ≤ 4) to 1a followed by enolate trapping with CIP(O)(OPh)2 furnishes the enol phosphate 3a in moderate yields (entries 1 and 2). Relevant to an enantioselective variant, no uncatalyzed background reaction was seen with an almost salt-free stock solution of (Me3Si)2Zn·xLiCl in Et2O[16] (entry 2). In the light of our recent work about an enantioselective conjugate silylation with a zinc-based silicon nucleophile,[17] we decided to investigate the asymmetric version. The yield increased in the presence of the chiral phosphoramidite ligand (S,R,R)-L1 but enantiominduction was low, even at −78°C (entries 3 and 4).

### Table 1. Comparison of copper-catalyzed and copper-free protocols with Me3SiZnCl·2LiCl[1a]

| Entry | Acceptor | Product | Yield of 2 [%][b] | Yield of 2 [%][b] |
|-------|----------|---------|------------------|------------------|
|       |          |         | w/ Cu(CH3CN)PF6 | w/o Cu(CH3CN)PF6 |
| 1     | 1a       | 2a      | 95               | 71               |
| 2     | 1g       | 2g      | 95               | 71               |
| 3     | 1o       | 2o      | 95               | 30               |
| 4     | 1p       | 2p      | 95               | 0                |

[a] All reactions were performed on a 0.2 mmol scale for 2 h. [b] Isolated yield after flash chromatography on silica gel. [c] Determined by 1H NMR spectroscopy by using CH3Br2 as the internal standard.

### Scheme 2. Synthesis of β-silylated cyclobutanones by conjugate addition of Me3SiZnCl·2LiCl. Unless otherwise noted, all reactions were performed on a 0.2 mmol scale for 2 h. Yields are of analytically pure product obtained after flash chromatography on silica gel. The relative configuration was assigned by 1H NMR spectroscopic analysis prior to purification (see the Supporting Information for details). [a] Value in parentheses for the reaction on a 1.0 mmol scale.

### Table 2. Comparison of copper-catalyzed and copper-free protocols with enolate trapping.[18]

| Entry | Zinc-based silicon nucleophile | Yield of 3a [%][b] | Yield of 3a [%][b] |
|-------|--------------------------------|--------------------|--------------------|
|       | w/o Cu(CH3CN)PF6               | w/ Cu(CH3CN)PF6    | then CIP(O)(OPh)2 (2.0 equiv.) |
| 1     | Me3SiZnCl·2LiCl (2.0 equiv.)   | 56                 | 18                 |
| 2     | (Me3Si)2Zn·xLiCl (1.2 equiv.) | 36                 | 0                  |
| 3     | (Me3Si)2Zn·xLiCl (1.2 equiv.) | 53 (6% ee)[d]      | -                  |
| 4     | (Me3Si)2Zn·xLiCl (1.2 equiv.) | 55 (15% ee)[d]     | -                  |

[a] All reactions were performed on a 0.2 mmol scale for 2 h. [b] Determined by 1H NMR spectroscopy by using CH3Br2 as the internal standard. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The 1,4-addition was conducted at −78°C for 16 h prior to the addition of CIP(O)(OPh)2.
systematic screening of various chiral ligands was completely unsuccessful (see the Supporting Information for the details). However, the yield could be improved to 76% with no enantioselectivity with \((R,R,R)-L_2\) (see Scheme 3), and we continued using this ligand for the reaction scope (a racemic ligand such as rac-binap afforded significantly lower yields; 19% yield). For completion, the corresponding 1,4-addition of Me_2PhSiZnCl · 2LiCl in the presence of \((S,R,R)-L_1\) proceeded with no enantioinduction.

The optimized reaction conditions are 5.0 mol% of Cu-(CH_3CN)_4PF_6 and 6.0 mol% of L_2 in THF with 1.2 equiv. of (Me_2PhSi)Zn · xLiCl as the silicon source and CIP(O)(OPh), as the electrophilic trapping reagent (Scheme 3). The reaction scope was done with the same set of cyclobutenones 1a–p (cf. Scheme 2). Yields were good throughout with \(\beta\)-aryl-substituted cyclobutenones (1a–f→3a–f). Conversely, the \(\beta\)-alkyl-substituted derivatives were less reactive, and moderate yields were obtained (1g–m→3g–m). Again, a silyl group as in 1n was tolerated to give 3n in 52% yield. Both \(\alpha,\beta\)-disubstituted substrates 1o and 1p did react in acceptable yields, affording fully substituted enol phosphates 3o and 3p, respectively.

Enol phosphates can serve as electrophiles in cross-coupling reactions,[16] and we tested several of the above cyclobutenyl phosphates in Kumada coupling reactions (3→4, Scheme 4). These representative reactions proceeded in moderate yields in the presence of catalytic amounts of (dppe)NiCl_2.[18] Arylation with PhMgBr reliably gave the corresponding silylated cyclobutenes. In turn, alkylation with the primary alkyl Grignard reagent n-HexMgBr was low yielding but an acceptable yield was restored with secondary CyMgBr.

To summarize, we reported here a copper-catalyzed conjugate addition of zinc-based silicon reagents to highly substituted cyclobutenones, providing a general and efficient method to access various \(\beta\)-silylated cyclobutanones. Moreover, the enolate intermediate can be trapped with a phosphorus electrophile to arrive at silylated enol phosphates, and these can be converted into the corresponding cyclobutenes by Kumada cross-coupling.

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**Conflict of Interest**

The authors declare no conflict of interest.

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