Cyclopropane Reagents

Formal [3+2] Addition of Acceptor-Substituted Cyclopropylmethylsilanes with Aryl Acetylenes**

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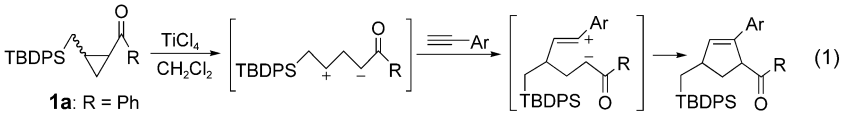
Dedicated to Dr. Sukh Dev on the occasion of his 80th birthday

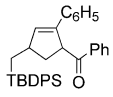
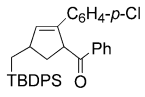
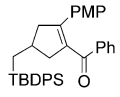
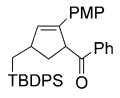
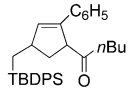
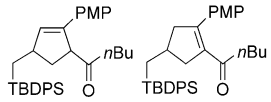
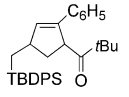
Cyclopentene-based skeletons are frequently encountered in biologically important natural products. For example, carbovir, a cyclopentenoid carbocyclic nucleoside,[1] is a promising drug candidate because of its significant anti-HIV activity.[2] Consequently, many methods have been developed for the assembly of cyclopentene skeletons.[3] During our investigations into the synthetic potential of cyclopropylmethylsilanes,[4] we have discovered that cyclopropyl phenyl ketones with a vicinal *tert*-butyldiphenylsilylmethyl substituent serve as excellent synthetic equivalents of 1,3-dipolar compounds under Lewis acid mediated conditions. We report herein the application of these donor–acceptor-substituted cyclopropane reagents in formal [3+2] addition reactions with aryl acetylenes as dipolarophiles in the presence of Lewis acids to generate substituted cyclopentenes in excellent yields in a single step. All previously reported addition reactions of acetylenic dipolarophiles have been carried out with hetero-1,3-dipolar compounds to construct heterocycles.[5]

The special feature of a donor–acceptor-substituted cyclopropane of type **1** is its dual reactivity: Either it can react first with a nucleophile at the silicon-stabilized positive end of the dipole, or the enolate equivalent, that is, the negative end of the dipole, can first be captured by an electrophile.[6] The reaction outlined in Equation (1) (TBDPS = *tert*-butyldiphenylsilyl) entails initial attack of a terminal acetylenic carbon center at the positive end of the cyclopropane dipole. The enolate intermediate then intercepts the resulting vinyl cation, and a cyclopentene ring is formed. Our past experience led us to use $TiCl_4$ as the Lewis acid with substrates **1a–c**.[4]



1a: R = Ph
1b: R = *n*Bu
1c: R = *t*Bu

Table 1: Formal [3+2] addition of **1a–c** with aryl acetylenes.

Entry	Silane	Acetylene	Product	Yield [%]	*cis*/*trans*
1 2[a]	**1a** (*cis*) **1a** (*trans*)	C_6H_5	 **2**	75	85:15
3	**1a** (*cis*/*trans*)	C_6H_4-*p*-Cl	 **3**	55	85:15
4[b]	**1a** (*cis*/*trans*)	PMP	 **4**	85	
5[c]	**1a** (*cis*/*trans*)	PMP	 **5**	60	75:25
6	**1b** (*cis*/*trans*)	C_6H_5	 **6**	70	75:25
7	**1b** (*cis*/*trans*)	PMP	 **7** **8**	**7**: 55 **8**: 20	57:43
8 9[d]	**1c** (*cis*) **1c** (*trans*)	C_6H_5	 **9**	80	95:5

[a] Yield and product ratio were the same as in entry 1. [b] PMP = *p*-methoxyphenyl. [c] Reaction was conducted in the presence of suspended anhydrous K_2CO_3. [d] Yield and product ratio were the same as in entry 8.

All substrates **1a–c** underwent smooth ring opening at −78 °C in CH_2Cl_2 and subsequent reaction with aryl acetylenes (Table 1). Aryl acetylenes with electron-donating substituents reacted better than those substituted with electron-withdrawing groups (see Table 1, entries 3 and 4). A *p*-methoxy substituent caused extensive migration of the double bond under the reaction conditions (Table 1, entries 4 and 7). This double-bond migration appeared to be catalyzed by acid, as it could be completely prevented by conducting the

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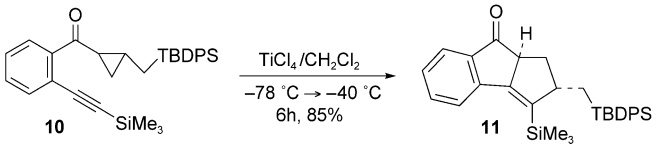
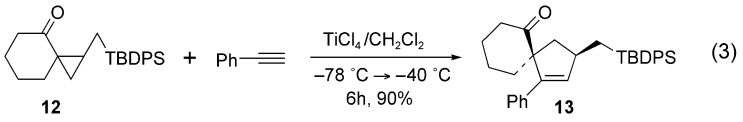
reaction in the presence of suspended K_2CO_3 (Table 1, entry 5). Simple alkyl acetylenes, such as 1-decyne and benzyl propargyl ether, did not react. The *cis* or *trans* orientation of the *tert*-butyldiphenylsilylmethyl and carbonyl substituents in the adducts was ascertained by NOE measurements.

The intramolecular variant of the above [3+2] addition also proceeded very well. For example, the reaction of *trans*-**10** furnished **11** in 85% yield [Eq. (2)]. The hydrogen at the ring junction was determined to be *cis* to the silylmethyl substituent based on NOE measurements.



(2)

Spiro ring systems, which are present in a large number of natural products, often constitute challenging synthetic targets.[7,8] The [5,6] spiro skeleton could be constructed readily in high yield by our method. Both *trans*-**12** and *cis*-**12** (formed as a 3:1 mixture) reacted smoothly under the standard conditions to generate **13** as the sole product in 90% yield [Eq. (3)]. The stereochemical assignment of **13** was possible through comparison of its ^{1}H NMR spectroscopic data with those of similar species, in combination with NOE measurements.



(3)

The high regio- and stereoselectivities of the above addition reactions are remarkable and deserve comment. The predominant *cis* selectivity can be understood by considering the possible transition-state structures for the addition. Based on our previous studies on the ring-opening of similar cyclopropyl ketones, the Ti enolate exists predominantly in the *Z* configuration, and of the ketones studied, the concentration of the titanium enolate was highest for the *tert*-butyl ketone and lowest for the *n*-butyl ketone.[9]

Four possible transition-state structures, **TS-I** to **TS-IV** (Figure 1), can be constructed for the species generated by attack of the aryl alkyne at the positive end of the cyclopropane dipole and formation of a new C–C bond. For the *Z* enolates of the *tert*-butyl and phenyl ketones, the possible transition structures are **TS-I** and **TS-II**. Likewise, the possible transition structures for the *E* enolate of the *n*-butyl ketone are **TS-III** and **TS-IV**. **TS-I** and **TS-III**, which lead to the *trans* product, are of higher energy than **TS-II** and **TS-IV**, respectively, because of the pseudo-diaxial interactions indicated. Therefore, the *cis* product will be generated predominantly, via **TS-II** and **TS-IV**. However, the pseudo-diaxial interactions will not be as significant in **TS-III** (from the reaction with the *n*-butyl ketone) as in **TS-I** (from the reaction with the phenyl or *tert*-butyl ketones) because of the small size of the *n*-butyl group. For this reason **TS-III** can also participate appreciably, thus leading to a decrease in the observed *cis* selectivity. The exclusive formation of the *cis* isomer **13** from both *trans*-**12** and *cis*-**12**, in which cases only the *Z* enolate is formed, supports the above transition-state analysis.[10]

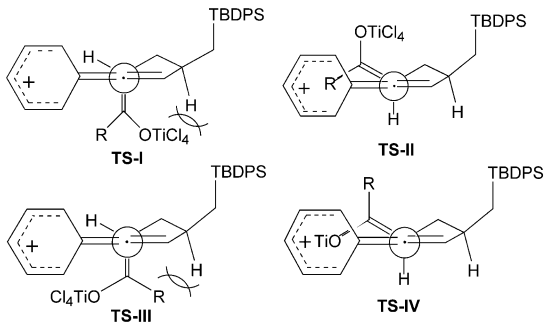


Figure 1. Possible transition states for ring closure.

In summary, *tert*-butyldiphenylsilylmethyl-substituted cyclopropyl phenyl/alkyl ketones reacted efficiently with aryl acetylenes in the presence of $TiCl_4$ to form cyclopentene derivatives with high regio- and stereoselectivity. The scope of this methodology for ring construction, including its application to the synthesis of carbocyclic nucleosides and spirocyclic natural products, is being explored further.

Experimental Section

Typical procedure: A solution of $TiCl_4$ (61 mg, 0.326 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added slowly under a nitrogen atmosphere to a stirred solution of **1a** (100 mg, 0.251 mmol) and phenylacetylene (33 mg, 0.326 mmol) in anhydrous CH_2Cl_2 (0.8 mL) at −78 °C. The resulting deep red mixture was stirred for 3 h at −78 °C, then warmed slowly over 1 h to −40 °C and stirred for a further 2 h at −40 °C. The reaction mixture was then taken up in Et_2O (20 mL) and washed with saturated aqueous NH_4Cl (2 × 7 mL), then with water (1 × 7 mL). The combined aqueous washings were extracted with Et_2O (2 × 7 mL), and the combined organic extracts were washed with brine, dried, and concentrated. Purification of the crude residue by column chromatography on silica gel (EtOAc/hexanes) gave **2** (*cis*/*trans* 85:15) in 75% yield as a viscous liquid. The *cis* and *trans* isomers were separated by radial chromatography over silica gel.

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[10] B3LYP6-31G* calculations of bond lengths and NBO charges of phenylpropenyl cation show that it exists predominantly in the cumulene form. However, this may not necessarily be the discrete reactive intermediate.

