Cycloadditions

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Thermally Induced and Silver-Salt-Catalyzed [2+2] Cycloadditions of Imines to (Alkoxymethylene)cyclopropanes**

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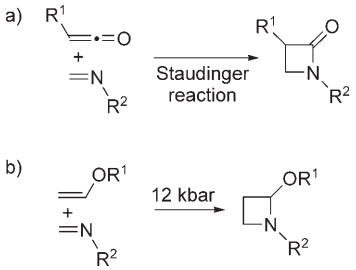
[2+2] Cycloadditions of imines to carbon–carbon multiple bonds have been widely applied in organic synthesis, as they produce highly useful azetidine derivatives in a single step.[1] [2+2] Cycloadditions of imines to ketenes, originally discovered by Staudinger,[2] provide azetidin-2-ones (β-lactams) (Scheme 1, type a). Recently, allenes[3] and enones[4] were



Scheme 1. [2+2] Cycloadditions of imines to a) ketenes[2] and b) enol ethers.[5]

utilized as substrates for [2+2] cycloadditions with imines. However, cycloadditions of imines to enol ethers (Scheme 1, type b) have rarely been employed; Scheeren and co-workers reported that [2+2] cycloadditions of imines to enol ethers require high pressure (12 kbar).[5] Owing to their ring strain, (alkoxymethylene)cyclopropanes, which are easily accessible and stable at room temperature, ought to be particularly favorable substrates for various cycloadditions;[6] de Meijere et al. reported high-pressure-promoted [4+2] cycloadditions of (alkoxymethylene)cyclopropanes to β,γ-unsaturated α-

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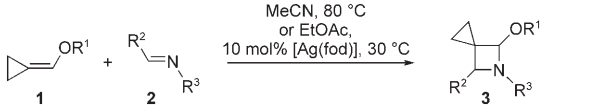
ketoesters.[7] Herein we report our first results concerning [2+2] cycloadditions of imines to (alkoxymethylene)cyclopropanes **1** at ambient pressure.

When (benzyloxymethylene)cyclopropane (**1a**; 1.5 equiv) was heated with *N*-tosylbenzaldimine (**2c**; 1.0 equiv) in acetonitrile at 80 °C for 40 h, the [2+2] cycloadduct 4-benzyloxy-6-phenyl-5-tosyl-5-azaspiro[2.3]hexane (**3ac**) was isolated in 97 % yield, predominantly as the *cis* diastereomer (51:1) (Table 1). The same reaction, but with 1 equivalent of

Table 1: Thermal [2+2] cycloadditions of **2** to (alkoxymethylene)cyclopropanes **1**.



1[a]	R^1	**2**	R^2	R^3	*t* [h]	**3**	Yield [%][b]	*cis*/*trans*[c]
1a	Bn	**2c**	Ph	Ts	40	**3ac**	97[d]	51:1
1a	Bn	**2d**	*p*-$MeOC_6H_4$	Ts	46	**3ad**	82	24:1
1a	Bn	**2e**	*p*-$CF_3C_6H_4$	Ts	6	**3ae**	91	18:1
1a	Bn	**2f**	*t*Bu	Ts	61	**3af**	80	29:1
1a	Bn	**2g**	Ph	Ns	4	**3ag**	92	28:1
1a	Bn	**2h**	Ph	SO_2Ph	32	**3ah**	71	28:1
1b	*n*Bu	**2c**	Ph	Ts	24	**3bc**	80	8:1

[a] In general, **1** (0.3 mmol) was treated with **2** (0.2 mmol). [b] Yields of isolated products. [c] The diastereomeric ratio was determined by ^{1}H NMR spectroscopy. [d] Scale: **1a** (3.0 mmol), **2c** (2.0 mmol); product **3ac** obtained in 68 % yield. Ns = nosyl = *p*-nitrobenzenesulfonyl; Ts = *p*-toluenesulfonic acid.

1a, gave **3ac** in 65 % yield along with recovered **2c** (14 %). The reaction of **1a** with other *N*-tosylarylaldimines **2d** and **2e** produced **3ad** and **3ae** in 82 and 91 % yield, respectively. The *N*-tosylimine of pivaldehyde **2f** also reacted with **1a** to give the corresponding [2+2] cycloadduct **3af** in 80 % yield. With *N*-nosylbenzaldimine (**2g**) and *N*-benzenesulfonylbenzaldimine (**2h**), the corresponding *N*-nosylazetidine **3ag** and *N*-benzenesulfonylazetidine **3ah** were obtained in 92 and 71 % yield, respectively. (*n*-Butoxymethylene)cyclopropane (**1b**) reacted with **2c** smoothly to give **3bc**. The constitutions of the spirocyclopropanated azetidines **3** were confirmed by spectroscopic methods. Furthermore, the structures of both the *cis* and the *trans* isomers of **3ac** were established unambiguously by X-ray crystallographic analyses (Figure 1).[8]

To test the possibility of performing this cycloaddition more efficiently and at lower temperature, several Lewis acidic transition-metal compounds were screened. Among the Lewis acids tested ($AuBr_3$, [Cu(acac)], $Pd(OAc)_2$, $Zn(OTf)_2$, $Sc(OTf)_3$, $Yb(OTf)_3$, AgOTf, [Ag(acac)]), only [Ag(fod)] (fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) exhibited the desired catalytic activity. Thus, the reaction of **1a** (1 equiv) with **2c** (1 equiv) in the presence of [Ag(fod)] (10 mol %) in ethyl acetate at 30 °C proceeded smoothly to give **3ac** in 94 % yield (Table 2, entry 1). At 30 °C in the absence of the silver catalyst, no reaction was observed, and only the starting materials were recovered quantitatively. The choice of solvent turned out to be very important; the reaction proceeded almost equally well in acetone, THF, and CH_2Cl_2, but sluggishly in acetonitrile, toluene, and hexane.

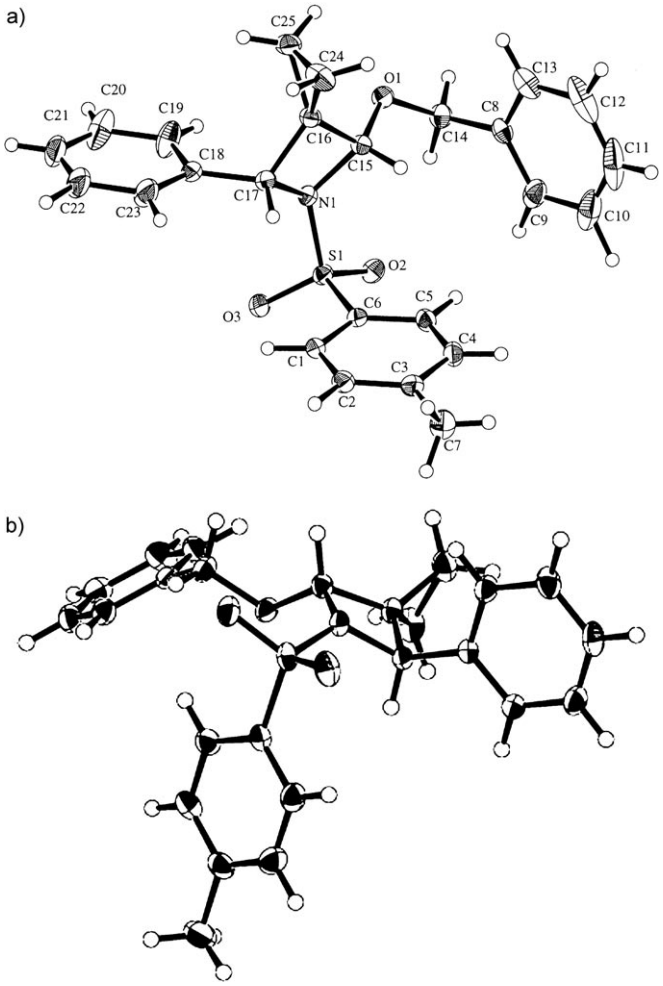


Figure 1. Crystal structures of a) *cis*-**3ac** and b) *trans*-**3ac**. ORTEP representations with thermal ellipsoids set at 50 % probability.[8]

Table 2: Catalyzed versus thermally induced [2+2] cycloadditions of **2** to **1a**.

Entry	**2**	R^2	R^3	**3**	Catalytic[a]		Thermal[b]	
					Yield [%][c]	*cis*/*trans*[d]	Yield [%][c]	*cis*/*trans*[d]
1	**2c**	Ph	Ts	**3ac**	94	135:1	97	51:1
2	**2i**	CO_2Et	Ts	**3ai**	45	35:1	57[e]	1.2:1
3	**2j**	Ph	Ms	**3aj**	77	46:1	93	5:1
4	**2k**	4-$CF_3C_6H_4$	Ms	**3ak**	76	48:1	84	4:1

[a] The reaction of **1** (0.3 mmol) and **2** (0.3 mmol) was carried out in the presence of [Ag(fod)] (10 mol %) in ethyl acetate (0.3 mL) at 30 °C. [b] The reaction of **1** (0.3 mmol) and **2** (0.2 mmol) was carried out in acetonitrile (0.1 mL) at 80 °C. [c] Yields of isolated products. [d] The diastereomeric ratio was determined by ^{1}H NMR spectroscopy. [e] The reaction was carried out at 30 °C. Ms = methanesulfonyl.

The catalyzed reaction of the *N*-tosylimine **2i** derived from ethyl glyoxylate produced **3ai** with higher *cis* selectivity than that of the thermal reaction (Table 2, entry 2). The reaction of *N*-mesylbenzaldimines **2j** and **2k** also proceeded with higher *cis* selectivity under the catalytic conditions (Table 2, entries 3 and 4).[9]

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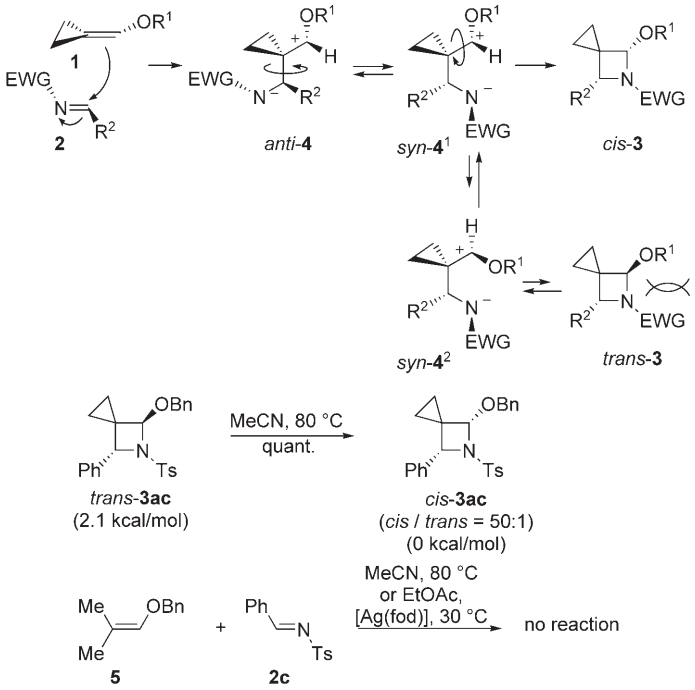
This [2+2] cycloaddition is proposed to proceed in two steps via the well-stabilized 1,4-zwitterion **4**. Initially, nucleophilic attack of the carbon–carbon double bond in **1** on the electrophilic center in the imine **2** would most probably lead to the *anti*-oriented zwitterion *anti*-**4**, which after internal rotation cyclizes to the azetidine *cis*-**3** or *trans*-**3** (Scheme 2).

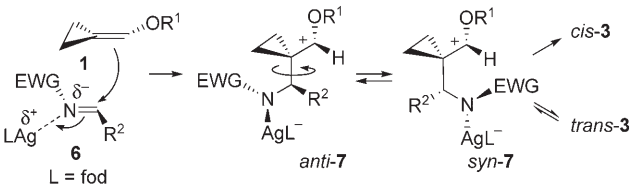


Scheme 2. Mechanism of the thermally induced [2+2] cycloaddition of **1** + **2**. EWG = electron-withdrawing group.

Apparently, this ring closure is reversible, and *cis*-**3** is the thermodynamically more stable isomer, as isolated *trans*-**3ac**, when heated in acetonitrile at 80 °C for 16 h, isomerized virtually completely to *cis*-**3ac**. Under the same conditions, *cis*-**3ac** remained unchanged. The greater stability of *cis*-**3ac** most likely stems from a smaller repulsion between the toluenesulfonyl and the benzyloxy group in the *cis* isomer (see Figure 1). According to DFT calculations at the B3LYP/6-311G level of theory, *cis*-**3ac** is 2.1 kcal mol^{-1} more stable than *trans*-**3ac**. The stabilization of the zwitterionic intermediate **4** by the cyclopropyl group adjacent to the cationic center is essential, as the enol ether **5**, which does not contain a cyclopropane ring, did not react with the *N*-tosylimine **2c**, neither under purely thermal nor under catalytic conditions.[10]

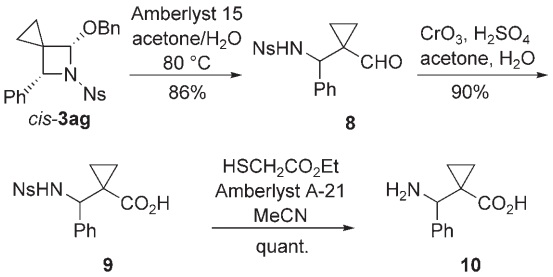
The silver complex certainly acts as a Lewis acid and enhances the electrophilicity of the imine as in **6** (Scheme 3), and C–N bond formation would occur through the silver amide intermediate *syn*-**7**, leading predominantly to the *cis*-**3** isomer.

One of the potential applications of these newly accessible spirocyclopropanated azetidines was demonstrated by the facile three-step conversion of the [2+2] cycloadduct *cis*-**3ag** into the β-phenylalanine analogue **10**. Hydrolysis of *cis*-**3ag** afforded the aldehyde **8** in 90% yield. Jones oxidation of **8**



Scheme 3. Mechanism of the silver-catalyzed [2+2] cycloaddition of **1** + **2**.

and subsequent removal of the nosyl group of **9** gave **10** (Scheme 4).



Scheme 4. Synthesis of α-cyclopropane-modified β-phenylalanine **9**.

Several catalyzed cycloadditions of methylenecyclopropanes to imines have been reported in recent years; [3+2] cycloadditions occur upon palladium-catalyzed reactions of alkylidenecyclopropanes with sulfonylimines[11] and upon Lewis acid catalyzed reactions of arylidenecyclopropanes with tosylimines.[12] Under scandium catalysis, arylidenecyclopropanes react with *N*-phenylimines in a [4+2] cycloaddition.[13] The reactions presented herein are the first examples of [2+2] cycloadditions of imines to methylenecyclopropane derivatives. The readily available 2-alkoxyazetidines offer themselves as versatile building blocks for the synthesis of various other compounds. One such application is preparation of α-cyclopropanated β-amino acids such as **10**, some of which are found in biologically active compounds.[14] It has also been shown that oligopeptides derived from α-cyclopropanated β-amino acids may have interesting secondary structures.[15]

Experimental Section

General procedure: a) Thermal conditions: Substrate **1** (0.3 mmol) was added to a solution of the imine **2** (0.2 mmol) in acetonitrile (0.1 mL) under argon in a Wheaton microreactor. The mixture was stirred at 80 °C for 4–61 h, and the product **3** was purified by column chromatography through silica gel (Fuji Silysia) with hexane/EtOAc/Et_3N (20:1:2) as eluent. b) Catalytic conditions: Substrate **1** (0.3 mmol) was added to a mixture of [Ag(fod)] (12.1 mg, 0.030 mmol) and the imine **2** (0.3 mmol) in ethyl acetate (0.3 mL) under argon in a Wheaton microreactor. The mixture was stirred for 37–42 h and then filtered through a short silica gel (Fuji Silysia) column with EtOAc/Et_3N (10:1) eluent. Purification of the crude product by chromatography through silica gel (Fuji Silysia) with hexane/EtOAc/Et_3N (20:1:2) afforded **3**.

3ac: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05–0.08 (m, 1H), 0.55–0.60 (m, 2H), 0.78–0.82 (m, 1H), 2.39 (s, 3H), 4.84 (dd, J = 84, 12.4 Hz, 2H), 4.85 (s, 1H), 5.50 (s, 1H), 7.20–7.37 (m, 12H), 7.65 ppm

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(d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 4.4$, 8.3, 21.6, 29.7, 65.4, 70.6, 92.3, 127.4, 127.6, 127.7, 127.7, 127.9, 128.2, 128.3, 129.4, 135.2, 137.3, 137.7, 143.6 ppm; IR (neat): $\tilde{\nu} = 3062$–2953, 2902, 1596, 1338, 1250, 1115 cm^{-1}; elemental analysis: calcd for $C_{25}H_{25}NO_3S$ (419.54): C 71.57, H 6.01, N 3.34, S 7.64; found: C 71.40, H 6.14, N 3.34, S 7.56; HRMS(EI): m/z calcd for $C_{25}H_{25}NO_3S$: 419.1555; found: 419.1550.

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