A New and Selective Metal-Catalyzed Baeyer-Villiger Oxidation Procedure

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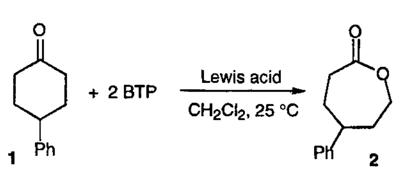
Abstract: A new, highly selective and high yielding procedure is described for the Baeyer-Villiger oxidation, using a tin-catalyst and bis(trimethylsilyl) peroxide (BTP).

The Baeyer-Villiger reaction is an important tool in organic synthesis which is frequently employed.[1] However, when performing this reaction one faces problems of regio- as well as chemoselectivity, especially in the presence of carbon-carbon double bonds. To overcome these problems we were eager to develop new reaction conditions that allow highly selective Baeyer-Villiger oxidations. Furthermore we wanted to develop a Lewis acid catalyzed reaction that would allow us - in the long term - to perform enantioselective Baeyer-Villiger reactions by employing appropriate ligands. In this article we report our first results towards these goals. To enable us to work under water-free, aprotic conditions, we chose the easily available bis(trimethylsilyl) peroxide (BTP) as oxidant,[2] a reagent used in Baeyer-Villiger reactions before.[3]

At first we tested various Lewis acids for the Baeyer-Villiger oxidation using BTP. To avoid problems of regioselectivity at this early stage we chose 4-phenylcyclohexanone **1** as a substrate.

Gallium(III)-chloride and tin(IV)-chloride[3b] proved to be the most suitable Lewis acids.[4] However, even though a complete consumption of the ketone was observed using these Lewis acids, only low to moderate amounts of lactone **2** could be isolated. Furthermore, an increased reaction time led to reduced yields of lactone. Obviously under these conditions lactone opening and other side reactions occurred.[5] This is comparable to previous reports in which the reaction-time and -temperature needed to be adjusted carefully for different substrates.[3] We figured that reducing the amount of Lewis acid and adding donor ligands would reduce the Lewis acidity of the reaction mixture and thereby prevent such reactions. This proved to be true as can be seen from the results given in Table 1.

Table 1. Influence of ligands on the Lewis acid promoted Baeyer-Villiger reaction



entry No.	Lewis acid	mol %	ligand 1 equiv. to Lewis acid	time (h)	yield (%)
1	$GaCl_3$	50	without ligand	3	58
2	$GaCl_3$	50	TEA	18	55
3	$GaCl_3$	50	diisopropylamine	18	53
4	$GaCl_3$	50	2-propanol	8	trace
5	$GaCl_3$	25	2-propanol + TEA	8	24
6	$SnCl_4$	25	without ligand	2	trace
7	$SnCl_4$	25	TEA	3	60
8	$SnCl_4$	25	1-phenylethylamine	8	82
9	$SnCl_4$	5	1-phenylethylamine	48	62
10	$SnCl_4$	1	1-phenylethylamine	144	36
11	$SnCl_4$	25	2-propanol	3	34
12	$SnCl_4$	25	2-propanol + TEA	3	69

(TEA = triethylamine)

As the yields obtained with $SnCl_4$[3b] were superior to the $GaCl_3$ systems and $SnCl_4$ is the cheaper reagent, we focused our attention on tin-based catalysts. Up to 82% of lactones were obtained using amines as ligands and we were very pleased to find, that even upon employing 10 or 5 mol % of $SnCl_4$, moderate to good yields of lactone were obtained. Major side products in all these reactions are ketone-peroxides[6] as reported earlier.[3] We found that upon addition of molecular sieves,[7] the formation of these could be minimized[8] and the yield of lactone **2** increased in general, whilst molecular sieves without any addition of Lewis acid provided no product. With these new reaction conditions we next intended to look for the best ligand. Amines, sulfonamides and alcohols proved to be good ligands, however only with amines and pyridines did no reaction of alkenes occur.[9,10] Therefore we concentrated our attention on nitrogen containing ligands. Of the various amines tried *trans*-1,2-(diamino)cyclohexane (DA) gave the best result and was therefore chosen as a suitable ligand. Varying the amount of this ligand reduced the reaction rate and/or gave lower yields, therefore a 1 : 1 ratio of $SnCl_4$: DA produces the best Lewis acid to catalyze the Baeyer-Villiger oxidation (25 °C, 5 h, 91% yield).

Although to date we have obtained no evidence, the reaction might proceed via the mechanism outlined in Fig. 1.[11]

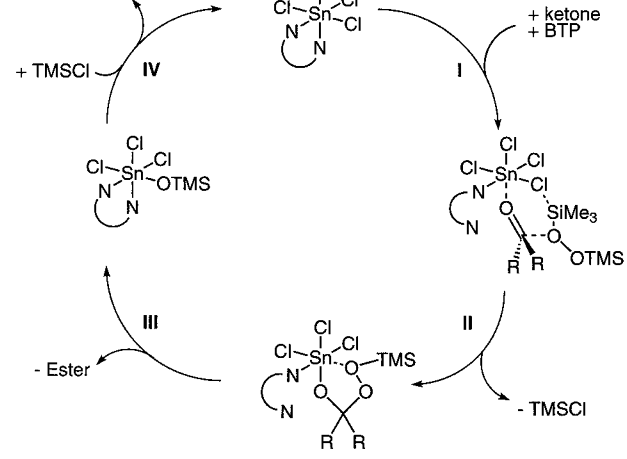


Figure 1

This mechanism offers an explanation for the different yields obtained upon using different diamines. In the initial step (**I**) one of the two amino-functions dissociates from the tin to create a vacant coordination site for the ketone. In this step flexible diamines should be advantageous, therefore 1,2-diaminobenzene did not produce very high yields.[9] In the rearrangement step (**III**), which is normally rate-determining in Baeyer-Villiger reactions, the pending amino-group coordinates again to the tin and thereby increases the electron density on the metal center, facilitating the rearrangement and the release of the product. In this step diamines which are somewhat more rigid and keep the second amino-function in close proximity for binding should accelerate the reaction. Therefore *trans*-1,2-(diamino)cyclohexane gives better yields than the different open chain diamines employed.

This is the first time that catalytic amounts of a tin(IV) Lewis acid are reported to efficiently promote the Baeyer-Villiger oxidation with BTP. Therefore we were eager to see whether this reaction can be performed with lower amounts of Lewis acid too.

Unfortunately upon reducing the amount of catalyst to 10 mol % only 42 % of lactone was isolated and a complete consumption of ketone **1** could not be achieved. This is strikingly different to the results obtained without addition of molecular sieves (see Table 1). We suppose that this is due to a deactivation of the tin-chloride catalyst by hexamethyldisiloxane as outlined in Fig. 2 (see also step **IV** in Fig. 1). However, by slowly adding TMS-chloride during the reaction this equilibrium could be shifted to the left and a complete conversion was obtained after 3.5 hours.

In a second experiment TMS-chloride was used without any additional Lewis acid. Only 24% lactone, as well as unreacted starting material, were isolated from this reaction after 24 hours. Therefore the reaction is mainly promoted by a tin-complex and not by TMS-chloride.

$$\underbrace{\text{"Sn"—Cl}}_{\text{active catalyst}} + \text{TMSOTMS} \rightleftharpoons \underbrace{\text{"Sn"—OTMS}}_{\text{inactive catalyst}} + \text{TMSCl}$$

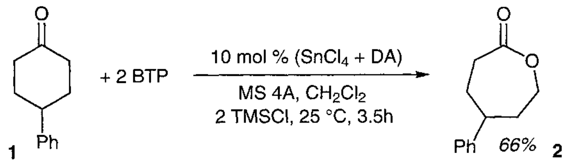


Figure 2

However, due to the low price of $SnCl_4$ we did not try to optimize these conditions, but continued our investigations using 25 mol % of the catalyst.

To prove the generality and to check the regioselectivity of this high yielding Baeyer-Villiger oxidation we performed the reaction using different substrates (Table 2).[12]

Good yields and regioselectivities were obtained in most cases and even an aldehyde could be reacted (Table 2, entry 9). In the cases where a comparison with previous results using BTP as the oxidant is possible the yields are now higher, proving the advantage of this new procedure. Furthermore, carbon-carbon double bonds are not attacked under these conditions, and unsaturated ketones can be converted to unsaturated esters in good yield (Table 2 , entries 3, 4, 6 and 8), thereby proving the high chemoselectivity of this new procedure.

However, with aliphatic open-chain ketones there is no turnover of the catalyst. Ketone and ester were obtained in a 3:1 ratio (Table 2, entry 10). Using 1 equivalent of Lewis acid led to a complete conversion and the isolation of 74% of the ester (in the case of dibutyl ketone as the substrate).

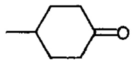
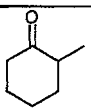
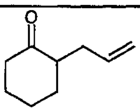
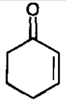
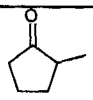
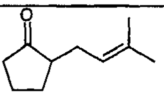
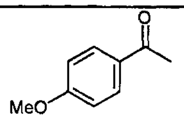
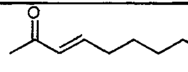
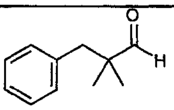
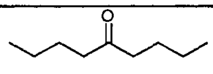
We figured that an increase in the catalyst's Lewis acidity could lead to turnovers. This proved to be correct, dibutyl ketone reacted completely when the *N,N'*-disulfonamide of DA was used instead of DA (Table 2. entry 10). The rather modest yield obtained in this experiment is probably due to the low boiling point of the product.

In summary we developed a new, high yielding procedure for the Baeyer-Villiger reaction in which for the first time catalytic amounts of a tin(IV)-Lewis acid are used together with BTP to achieve this transformation.

This new procedure leads not only to high regioselectivities, but carbon-carbon double bonds are not attacked, thereby making these reaction conditions superior to others.[1]

Furthermore the reaction can be easily optimized for a certain substrate by varying the ligand(s). Therefore this procedure should be useful especially for the synthesis of complex molecules in which a triggering of the reactivity is often desirable.

Table 2: Baeyer-Villiger reactions of various carbonyls:[a]

entry No.	substrate	time (h)	regio-selectivity[b,c]	yield (%)[13]	previous result using BTP
1		2		90	
2		2	31 : 1	91	
3		24	17 : 1	78	40[3a]
4		2	only one isomer detected	61	
5		2	only one isomer detected	86	73[3b]
6		3	only one isomer detected	80	44[3b]
7		3	only one isomer detected	97	
8		4	only one isomer detected	68	
9		24	only one isomer detected	45[14]	
10		30		21 (74)[d] (78)[e]	

a) Using 2 equiv. of BTP, MS 4A and 25 mol % of a 1:1 mixture of $SnCl_4$ and DA.
b) The preferred regioisomers are the ones expected for Baeyer-Villiger reactions, with sp2-centers and higher substituted carbons rearranging preferentially.
c) The regioisomeric ratio was determined by proton-NMR.
d) When using 1 equiv. of Lewis acid.
e) This yield was obtained using the *N,N'*-bis-tosylate of DA as a ligand (see text).

With this reliable procedure for a catalytic Baeyer-Villiger oxidation being developed, we are now turning our attention towards developing an asymmetric version of this reaction.[15]

Acknowledgment:

We thank the Japan Society for the Promotion of Science (JSPS) for supporting these studies. R. G. is grateful for a postdoctoral scholarship from JSPS.

References and Notes

(1) For reviews on the Baeyer-Villiger reaction see: Hassall, C. *Org. React.* **1957**, *9*, 73. Krow, G. R. *Org. React.* **1993**, *43*, 3.
(2) Jackson. W. P. *Synlett* **1990**. 536.
(3) a) Suzuki, M.; Takada, H.; Noyori, R. *J. Org. Chem.* **1982**, *47*, 902. b) Matsubara, S.; Takai, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2029.
(4) Without the addition of any Lewis acid no reaction occurred.

(5) One of these might be an attack of the aromatic ring, which is known for BTP and Lewis acids. Apatu, J. O.; Chapman, D. C.; Heaney, H. *J. Chem. Soc. Chem. Commun.* **1981**, 1079.

(6) a) Criegee, R.; Schnorrenberg, W.; Becke, J. Justus *Liebigs Ann. Chem.* **1949**, *565*, 7. b) Story, P.R.; Lee, B.; Bishop, C. E.; Denson, D. D.; Busch, P. *J. Org. Chem.* **1970**, *35*, 3059. c) Jefford, C. W.; Boukouvalas, A. J. J. *Synthesis* **1988**, 391.

(7) Dry molecular sieves 4A was used and added to the reaction vessel prior to any other compound.

(8) Molecular sieves removes trace amounts of HCl[9] (which might be formed by the reaction of tin(IV)-chloride with traces of water) and is thereby inhibiting a silicon-proton exchange reaction of the peroxide and HCl. We suppose that the addition of a hydroperoxide to the ketone is faster than the addition of the silylperoxide. This is in agreement with the observation of an overall reduced reaction rate upon addition of molecular sieves.

The intermediate **3** (see below) can add to a second ketone to form ketone peroxides or rearrange to the Baeyer-Villiger product. Whilst the second addition is slowed down in the absence of HCl, the rearrangement is not affected, resulting in an overall increased lactone: ketone-peroxide ratio. For removal of HCl by molecular sieves, see: Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, K. *Chem. Commun.* **1997**, 281.

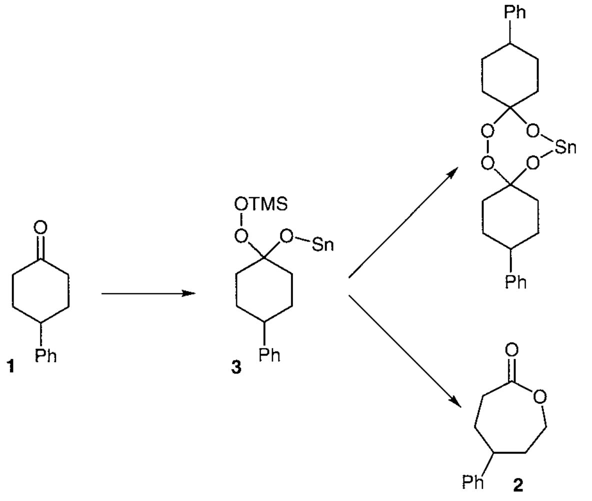


Figure 3

(9) Other ligands gave following results (25 mol % $SnCl_4$, 25 °C, in the presence of MS 4A in CH_2Cl_2): 2-propanol (2.5 h); 56% yield, *p*-toluenesulfonamide (13 h); 83%, (±)-*trans*-1,2-bis(tosylamido)-cyclohexane (18 h); 61%, pyridine (2 h); 83%, 2-aminopyridine (13 h); 59%, 2-(2-aminoethyl)pyridine (13 h); 81%, (±)-1-phenylethylamine (27 h); 71%, 3-aminopropanol (18 h); 66%, ethylenediamine (4 h); 48%, 1,3-diaminopropane (2 h); 32%, 1,2-diaminobenzene (13 h); 72%.

(10) This was checked by adding cyclohexene instead of ketone **1** to the oxidation system. In the case of alcohols and sulfonamides as ligands chlorohydrins were formed, whilst in the case of amine ligands no reaction occurred.

(11) An octahedral complex is proposed, a geometry very common for tin(IV)-complexes. Nevertheless, some examples of 7- and 8-coordination exist for tin(IV) too. See: Harrisin, P. G. *Chemistry of Tin*; Blackie: Glasgow, 1989.

(12) A standard procedure is the following: (Only dry solvents were used, the flask was heat-vacuum dried prior to use and the reaction was carried out under argon).

To a mixture consisting of molecular sieves (4A, approx. 0.2 g) and 0.25 ml of a 1.0 molar solution of *trans*-1,2-(diamino)cyclohexane (in THF) in 7 ml dichloromethane tin(IV)-chloride was added (0.25 ml of a 1.0 molar solution in dichloromethane). The resulting suspension was cooled with an ice-bath and 2.0 ml of bis(trimethylsilyl) peroxide (1.0 molar solution in dichloromethane) was added. The mixture was stirred for 5-10 minutes and then the ketone (1.0 mmol) was added. The ice-bath was removed and the reaction was stirred at room temperature until all ketone was consumed (TLC-control). Solid sodium sulfite was added (0.3 g) and the suspension stirred for 3 h at room temperature. Then the mixture was filtered over 2 cm of silica and washed with 30 ml of ethyl acetate. The solvent was evaporated and the crude product was purified by flash-chromatography.

(13) The proton- and carbon-NMR spectra were identical with published data.

(14) Whilst 2-methyl-1-phenylpropan-2-ol formate is a known compound, no NMR-data has been published.

^{1}H-NMR (in $CDCl_3$, 270 MHz): 8.02 (s, 1H); 7.3 (m, 5H); 3.10 (s, 2H); 1.52 (s, 6H).

^{13}C-NMR (in $CDCl_3$, 67.5 MHz): 160.6; 136.6; 130.6; 128.0; 126.6; 83.3; 46.8; 26.1.

The compound could not be obtained in an analytical pure form and was identified by conversion to the free alcohol via LAH-reduction.

(15) For previous examples of enantioselective Baeyer-Villiger oxidations see: a) Bolm, C.; Schlingloff, G.; Weickhardt, K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1848. b) Gusso, A.; Baccin, C.; Pinna, F.; Strukul, G.; *Organometallics* **1994**, *13*, 3442. c) Lopp, M.; Paju, A.; Kanger, T.; Pehk, T. *Tetrahedron Lett.* **1996**, *37*, 7583.