Ring *tert*-Butylation of Benzophenones and Benzaldehyde with *tert*-Butyllithium and Thionyl Chloride[1]

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Dedicated to Professor H.J. Bestmann

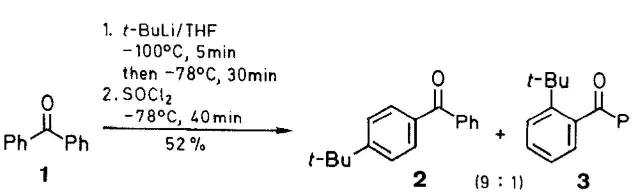
One-flask ring *tert*-butylation of benzophenones and benzaldehyde with *tert*-butyllithium and thionyl chloride is reported. The scope of the reaction and the suggested mechanism are discussed.

The most widely used preparation of *tert*-butylated aromatics involves electrophilic alkylation[2] through carbocationic intermediates resulting in a mixture of isomers.[3]

It has been found that the organolithiums as well as organomagnesiums react with aryl ketones resulting in the formation of 1,2-, 1,4- and 1,6-adducts.[4] The mechanism has been studied and the radical nature of the reaction has been indicated by a variety of techniques.[5] Recently, Yamataka et al. suggested a single electron-transfer mechanism for the addition reaction of organolithium and organomagnesium reagents to various aryl ketones with subsequent formation of aromatic ring substituted adducts.[6] However, the yield of aromatic ring substituted products which were formed upon decomposition of the aromatic ring addition adduct upon usual aqueous workup was unsatisfactory.[7]

We report now the one flask preparation of ring *tert*-butylated benzophenones and benzaldehyde via their butyl substituted lithium enolates, obtained by addition of *tert*-butyllithium, followed by reaction with thionyl chloride.

Reaction of benzophenones (or benzaldehyde) with *tert*-butyllithium followed by oxidation with thionyl chloride gives, via elimination of sulfur monoxide[8] from the vinylsulfuryl chloride intermediates, ring *tert*-butylated products.



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Because of the bulkiness of *tert*-butyllithium, the addition to the aromatic ring shows high regioselectivity[8] with the lithium enolate of the 1,6-adduct predominating over the 1,4-adduct. Subsequent oxidation with thionyl chloride gives the corresponding 4-*tert*-butylbenzophenone **(2)**, in a ratio of 9:1 to 2-*tert*-butylbenzophenone **(3)**.

If the reaction of the benzophenones (or benzaldehyde) with *tert*-butyllithium was carried out with decomposition of the lithium enolate upon usual aqueous workup it gave much lower yields of ring butylated products. The results obtained are summarized in Table 1.

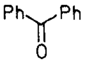
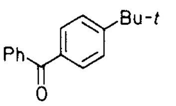
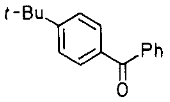
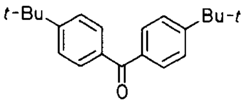
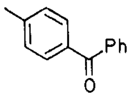
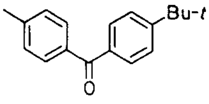
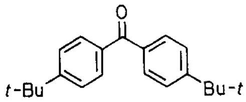
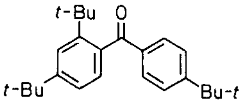
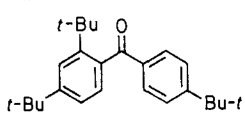
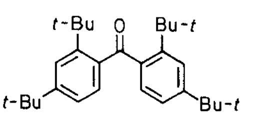
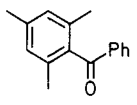
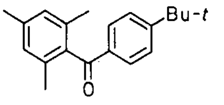
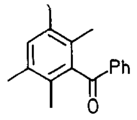
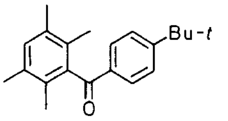
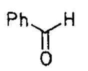
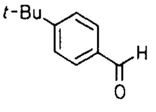
The major competing reaction of aromatic *tert*-butylation with *tert*-butyllithium and thionyl chloride is the formation of 2-methyl-3,3-diphenyl-1-butene.[9]

Further aromatic ring *tert*-butylation of 4-*tert*-butylbenzophenone with *tert*-butyllithium and thionyl chloride gave 4,4′-di-*tert*-butylbenzophenone in 68% yield (a small amount of the 2,4′-isomer is also formed in a ratio 4,4′/2,4′ of > 9:1). Even the reaction of 2,4,4′-tri-*tert*-butylbenzophenone with *tert*-butyllithium and thionyl chloride can be carried out giving 2,2′,4,4′-tetra-*tert*-butylbenzophenone in 71% yield. The regioselectivity of the reaction can again be attributed to steric factors.[10] Some methylated benzophenones and benzaldehyde were also *tert*-butylated by *tert*-butyllithium and thionyl chloride in dry tetrahydrofuran solution at −100°C.

Aromatic *tert*-butylation of benzophenones using *tert*-butylmagnesium halides (chloride or bromide) and thionyl chloride was also studied. Similar results were obtained, however, with lower yields.

It is also significant to note that the solvent used has great influence on the reaction. For example, when the reactions were carried out in non-polar hydrocarbon solvents they gave primarily carbonyl addition. However, in polar solvents at low temperatures aromatic ring *tert*-butylated

Table 1. Aromatic *tert*-Butylation with *tert*-Butyllithium and Thionyl Chloride

Substrate	Product	Yield via (%)[a]	
		Aqueous Workup	$SOCl_2$
	 (4/2 ratio > 9:1)	28	52
	 (4,4'/2,4' ratio > 9:1)	32	49
		34	50
			68
			71
		36	52
		29	46
		20	41

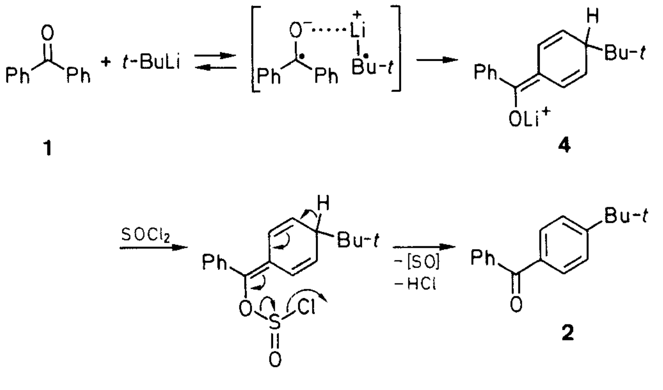
[a] Isolated yield

Table 2. Aromatic *tert*-Butylation of Benzophenone with *tert*-Butyllithium and Thionyl Chloride

Solvent	Yield (%) 2 at Various Temperature (°C)			
	r.t.	0	−78	−100
pentane	trace	2	5	10
hexane	trace	2	5	10
Et_2O	decomposes	trace	40	46
THF	decomposes	trace	41	42

products predominate. The reaction temperature plays an important role in the *tert*-butylation of benzophenone, with low temperatures favoring the formation of ring substituted products (Table 2).

The suggested mechanism of the reaction is shown in the Scheme.



Scheme

The reaction is considered to proceed via initial single-electron transfer (SET) from *tert*-butyllithium to benzophenone.[11] Due to steric hinderence as well as the highly conjugated nature of **4**, *tert*-butyllithium preferentially attacts the aromatic ring. Subsequent reaction with thionyl chloride gives a substituted vinyl sulfuryl chloride. Since elimination of sulfur dioxide would lead to generation of extremely labil vinyl cation intermediate, the reaction proceeds with the elimination of sulfur monoxide and hydrogen chloride[12] to give *tert*-butylated benzophenone, **2**. Holm and Crossland[13] reported previously that aqueous workup decomposes the 1,6-addition adduct giving some *tert*-butylbenzophenone and regenerating benzophenone. Additional work was also carried out by Yamataka et al.[14] but yields of ring butylated product were again low. In contrast as found in present work, when the adduct is reacted with thionyl chloride as oxidizing agent, the yield of ring *tert*-butylated benzophenone **2** is quite satisfactory (46–71%, as contrasted by yields of 20–36% obtained previously).

Attempted ring *tert*-butylation of other phenyl substituted bulky ketones, such as 1-benzoyladamantane and 2,2-dimethylpropiophenone were not successful, presumably, due to the difficulty of forming a highly conjugated lithium enolate, of type **4**. Instead *tert*-butyllithium adds to the oxo groups with formation of lithium alkoxides. The corresponding trisubstituted methyl alcohols were obtained after usual aqueous workup.

tert-Butylation of benzophenones (and benzaldehyde) by their reaction with *tert*-butyllithium followed with thionyl chloride represents a general, effective synthetic method for the easy one-flask preparation of *tert*-butylbenzophenones (and benzaldehyde).

Benzophenone, 4-methylbenzophenone, benzaldehyde, 2-*tert*-butylbenzoic acid, 4-*tert*-butylbenzoic acid and 1-bromo-4-*tert*-butylbenzene were commercially available (Aldrich) and used as such. 2,4,6-Trimethylbenzophenone[15] and 2,3,5,6-tetramethylbenzophenone[16] were prepared according to literature procedures. Authentic samples of 2- and 4-*tert*-butylbenzophenones were prepared by the reaction of PhLi with 2- or 4-*tert*-butylbenzoic acid, respectively. 2,4'-Di-*tert*-butyl and 4,4'-di-*tert*-butylbenzophenone were prepared via the reaction 4-*tert*-butylphenyllithium (prepared in situ from the reaction of BuLi and 1-bromo-4-*tert*-butylbenzene) and 2- or 4-*tert*-butylbenzoic acid. $SOCl_2$ was distilled prior to use. Gas Chromatographic analyses were carried out on a Varian Model 3700 Gas Chromatograph using quartz-silica capillary column coated with DB-1. Mass spectroscopic analyses were performed on Finnigan Incos-50 GC-MS spectrometer. NMR spectra were recorded on a Varian 200, VAX-200 superconducting NMR spectrometer.

2-*tert*-Butylbenzophenone:

To a cold mixture of 2-*tert*-butylbenzoic acid (1.78 g; 10.0 mmol) and dry Et_2O (10.0 mmol) is added during a period of 5 min PhLi (2.0 M in cyclohexane/Et_2O, 10 mL; 20.0 mmol) with good stirring under N_2 at $-78\,°C$ (cooling with dry ice/acetone bath). After the addition of PhLi has been completed, the mixture is maintained stirring for another 30 min. The dry ice/acetone bath is then removed. The mixture is allowed to warm to r.t. and stirring is continued for another 4-6 h, then quenched with ice water and worked up with Et_2O extraction. The combined ethereal layers are dried ($MgSO_4$), filtered and evaporated in vacuo to leave the crude product which could be further purified via column chromatography on silica gel (10% EtOAc/hexane as eluent) to afford pure 2-*tert*-butylbenzophenone (1.01 g, 8.1 mmol; 81% yield from 2-*tert*-butylbenzoic acid) as colorless microcrystals, mp 68-69 °C.

$C_{17}H_{18}O$	calc.	C 85.67	H 7.61
(238.3)	found	86.01	7.32

IR (KBr): ν = 1710 (s) cm^{-1}.

^{13}C-NMR: δ = 196.23 (s), 143.21 (s), 139.09 (s), 138.79 (s), 130.27 (d), 129.02 (d), 128.84 (d), 128.31 (d), 128.19 (d), 127.88 (d), 127.03 (d), 32.12 (s), 26.17 (q).

GC/MS (70 eV): m/z (%) = 238 (M^+; 6.2), 225 (12.9), 105 (100.0), 77 (54.9), 57 (25.6).

4-*tert*-Butylbenzophenone:

Preparation is carried out as in the previous procedure. From the reaction of 4-*tert*-butylbenzoic acid (1.78 g, 10.0 mmol) and PhLi (2.0 M in cyclohexane/Et_2O; 10 mL; 20.0 mmol) is obtained the corresponding 4-*tert*-butylbenzophenone (2.02 g; 8.5 mmol; 85% yield from 4-*tert*-butylbenzoic acid) as colorless microcrystals, mp 67-68 °C.

$C_{17}H_{18}O$	calc.	C 85.67	H 7.61
(238.3)	found	85.95	7.41

IR (KBr): ν = 1700 (s) cm^{-1}.

^{13}C-NMR (50 MHz; $CDCl_3$): δ = 196.27 (s), 144.02 (s), 141.27 (s), 140.04 (s), 131.73 (d), 129.33 (d), 128.46 (d) 128.27 (d), 127.83 (d), 33.10 (s), 27.48 (q).

GC/MS (70 eV): m/z (%) = 238 (10.2), 225 (18.2), 105 (100.0), 77 (37.9), 57 (19.3).

2,4′-Di-*tert*-butylbenzophenone:

To a dry ice/acetone cooled solution of 1-bromo-4-*tert*-butylbenzene (4.26 g; 20.0 mmol) and dry Et_2O (20 mL) is added BuLi (2.0 M in hexane; 10 mL; 20.0 mmol) under N_2 with good stirring over a period of 10 min. After the addition of BuLi has been completed, the mixture is maintained stirring for another 1-2 h, then is dropwise added a solution of 2-*tert*-butylbenzoic acid (1.78 g; 10.0 mmol) in dry Et_2O (10 mL) with good stirring during a period of 10 min. After the addition of 2-*tert*-butylbenzoic acid has beeb completed, the mixture is maintained stirring for another 30 min, then the dry ice/acetone cold bath is removed and the mixture is allowed to warm to r.t. The mixture is maintained stirring for 4-6 h followed by usual aqueous workup with Et_2O extraction. The combined ethereal layers are dried ($MgSO_4$), filtered and evaporated in vacuo to leave crude product which could be further purified via recrystallization from petroleum ether to afford pure 2,4′-di-*tert*-butylbenzophenone (2.41 g; 8.2 mmol; 82% yield from 2-*tert*-butylbenzoic acid) as colorless microcrystals; mp 72-74 °C.

$C_{21}H_{26}O$	calc.	C 85.66	H 8.90
(294.4)	found	85.88	8.62

IR (KBr): ν = 1720 (s) cm^{-1}.

^{13}C-NMR (50 MHz; $CDCl_3$): δ = 196.33 (s), 140.98 (s), 140.37 (s), 139.91 (s), 129.72 (d), 129.41 (d), 129.18 (d), 128.77 (d), 128.20 (d), 127.37 (d), 34.70 (s), 26.83 (q).

GC/MS (70 eV): m/z (%) = 294 (M^+, 7.2), 279 (10.3), 238 (8.4), 161 (100.0), 57 (21.9).

4,4′-Di-*tert*-butylbenzophenone:

The preparation is carried out as previously. From the reaction of 4-*tert*-butylphenyllithium (prepared in situ via the reaction of 1-bromo-4-*tert*-butylbenzene and BuLi; 20.0 mmol) and 4-*tert*-butylbenzoic acid (1.78 g; 10.0 mmol) is obtained the corresponding 4,4′-di-*tert*-butylbenzophenone (2.45 g; 8.5 mmol; 85% yield from 4-*tert*-butylbenzoic acid) as colorless microcrystals, mp 70-71 °C.

$C_{21}H_{26}O$	calc.	C 85.66	H 8.90
(294.4)	found	85.88	8.62

IR (KBr): ν = 1720 (s) cm^{-1}.

^{13}C-NMR (50 MHz; $CDCl_3$): δ = 197.20 (s), 139.47 (s), 138.23 (s), 128.39 (d), 127.36 (d), 32.95 (s), 26.34 (q).

GC/MS (70 eV): m/z (%) = 294 (M^+, 8.9), 279 (12.6), 238 (17.2), 161 (9.2), 57 (10.3).

***tert*-Butylation of Benzophenone:**

To a dry ice/Et_2O cooled ($-100\,°C$) solution of benzophenone (1.82 g; 10.0 mmol) and dry THF (10 mL) is dropwise added *t*-BuLi (1.7 M in pentane; 7 mL; 12.0 mmol) via application fo a syringe under N_2 atmosphere with good stirring during a period of 5 min. After the addition of *t*-BuLi has been completed, the mixture is maintained stirring for another 30 min at $-78\,°C$, then freshly distilled $SOCl_2$ (2.0 g; 16.8 mmol) is added in a period of 10 min. After the addition fo $SOCl_2$ has been completed, the mixture is stirred for another 30 min. The dry ice/Et_2O bath is then removed and the mixture is allowed to warm to r.t. and kept for several hours. Usual aqueous workup is followed by extraction with Et_2O. The combined ethereal layers are dried ($MgSO_4$), filtered and evaporated in vacuo to leave a mixture of isomeric *tert*-butylbenzophenones (1.90 g; 8.0 mmol; 80% yield from benzophenone) which is identified (via comparison with authentic 2- and 4-*tert*-butylbenzophenone prepared previously) as 9 : 1 of 4- and 2-*tert*-butylbenzophenone, respectively. Fractional recrystallization of the product from petroleum ether gave pure 4-*tert*-butylbenzophenone. Spectral and analytical data are consistent with those of the authentic sample.

***tert*-Butylation of 4-*tert*-Butylbenzophenone:**

The reaction of 4-*tert*-butylbenzophenone (2.38 g; 10.0 mmol) and *t*-BuLi (1.7 M; 7 mL; 12.0 mmol), followed by treatment with freshly distilled $SOCl_2$ gave an isomeric mixture of 4,4′- and 2,4′-di-*tert*-butylbenzophenone (2.32 g; 7.9 mmol; 79% yield from 4-*tert*-butylbenzophenone) which is identified (via the comparison with authentic 2,4′- and 4,4′-di-*tert*-butylbenzophenone prepared previously) as 9 : 1 of 4,4′- and 2,4′-di-*tert*-butylbenzophenone, respectively. Fractional recrystallization of the peroduct is carried out from petroleum ether to afford pure 4,4′-di-*tert*-butylbenzophenone. Spectral and analytical data are consistent with those of the authentic sample.

***tert*-Butylation of 4,4′-Di-*tert*-butylbenzophenone:**

The reaction of 4,4′-di-*tert*-butylbenzophenone (2.94 g; 10.0 mmol) and *t*-BuLi (1.7 M; 7 mL; 12.0 mmol) followed by treatment with freshly distilled $SOCl_2$ gave exclusively 2,4,4′-tri-*tert*-butylbenzophenone (238 g; 6.8 mmol; 68% yield from 4,4′-di-*tert*-butylbenzophenone) as a colorless liquid.

$C_{25}H_{34}O$	calc.	C 85.66	H 9.77
(350.5)	found	85.65	9.89

IR (neat): ν = 1720 (s) cm^{-1}.

^{13}C-NMR (50 MHz; $CDCl_3$): δ = 198.32 (s), 144.30 (s), 144.02 (s), 139.39 (s), 139.02 (s), 138.82 (s), 129.82 (d), 129.61 (d), 129.03 (d), 128.30 (d), 128.06 (d), 33.20 (s), 33.09 (s), 32.98 (s), 26.84 (q).

GC/MS (70 eV): m/z = 350 (M^+; 1.2), 335 (6.7), 294 (13.5), 217 (100.0), 161 (97.3), 57 (19.9).

2,2′,4,4′-Tetra-*tert*-butylbenzophenone:

The reaction of 2,4,4′-tri-*tert*-butylbenzophenone (3.50 g; 10.0 mmol) and *t*-BuLi (1.7 M; 7 mL; 12.0 mmol) followed by treatment with freshly distilled $SOCl_2$ gave 2,2′,4,4′-tetra-*tert*-butylbenzophenone (2.88 g; 7.1 mmol; 71 % yield from 2,4,4′-tri-*tert*-butylbenzophenone) as colorless microcrystals.

$C_{29}H_{42}O$	calc.	C 85.66	H 10.41
(406.6)	found	85.82	10.22

IR (neat): $\nu = 1720$ (s) cm^{-1}.

^{13}C-NMR (50 MHz; $CDCl_3$): $\delta = 196.84$ (s), 142.03 (s), 141.56 (s), 141.14 (s), 129.05 (d), 128.30 (d), 128.06 (d), 33.20 (s), 33.01 (s), 26.69 (q). GC/MS (70 eV): m/z (%) = 406 (M^+; 2.1), 391 (5.3), 350 (10.3), 217 (100.0), 57 (13.2).

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