Reagents for Organic Synthesis

VOLUME FOURTEEN

Fieser and Fieser's

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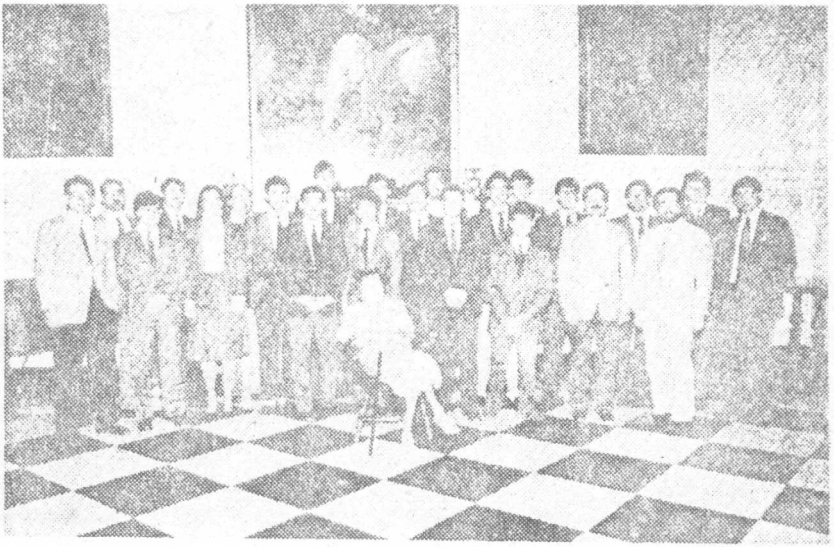
PREFACE

This volume reviews synthetic use of reagents reported for the most part from January, 1986 to August, 1988. The manuscript has benefited markedly from the careful scrutiny of John O. Link and Greg Fu, who caught many errors and suggested many improvements in the presentations. My co-workers provided expert proofreading of both galleys and page proofs. They include Philip A. Carpino, Keith DeVries, James R. Gage, Guy V. Lamoureux, Kristin M. Lundy, John K. Lynch, Seiichi P. T. Matsuda, John A. Porco, Jr., John A. Ragan, Greg Reichard, Soroosh Shambayati, Robert F. Standaert, Edward M. Suh, Scott Virgil, Keith Woerpel.

Greg Fu supervised the proofreading and provided the structural formula based on the x-ray data for the new Sharpless catalytic reagent for osmylation of alkenes. Martita F. Barsotti is the photographer for the picture of some present and former co-workers for Reagents.

MARY FIESER

March 15, 1989

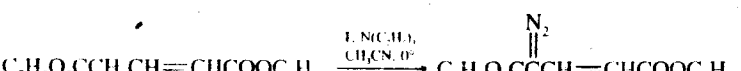


CONTENTS

A

***p*-Acetamidobenzenesulfonyl azide,** *p*-$AcNHC_6H_4SO_2N_3$ (**1**, m. p. 108° dec.). The azide is prepared by reaction of the sulfonyl chloride with NaN_3 in aqueous CH_2Cl_2 in the presence of $(C_4H_9)_4NCl$ as phase-transfer catalyst.

Diazo transfer. This azide is recommended as a relatively safe substitute for tosyl azide for diazo-transfer reactions to reactive methylene groups. Either DBU or $N(C_2H_5)_3$ is a suitable base. It is also suitable for synthesis of vinyl diazo compounds.[1]

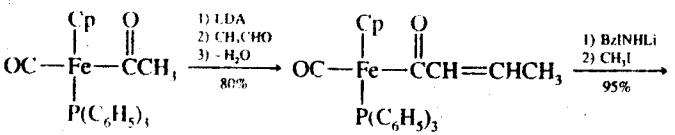


[1] J. S. Baum, D. A. Shook, H. M. L. Davies, and H. D. Smith, *Syn. Comm.*, **17**, 1709 (1987).

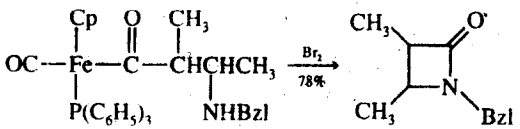
Aceto(carbonyl)cyclopentadienyl(triphenylphosphine)iron (1), **12**, 1–2.

Reactions of this pseudooctahedral complex have been studied in particular detail by the Davies group at Oxford and the Liebeskind group in the United States because of its potential use as a chiral auxiliary for control of the absolute stereochemistry of various reactions of the acyl enolate. Both R-(−)-**1** and S-(+)-**1** are now available commercially (Fluka), but at a prohibitive cost ($125.60 per gram).

α,β-*Unsaturated iron acyls.*[1] The aldols formed by reaction of an aldehyde with the enolate of **1** can be dehydrated via the acetate to (E)-α,β-unsaturated iron acyls (**2**). These products undergo 1,4-addition with RLi or RNHLi, and the intermediate enolate can be alkylated with high diastereoselectivity. Thus addition



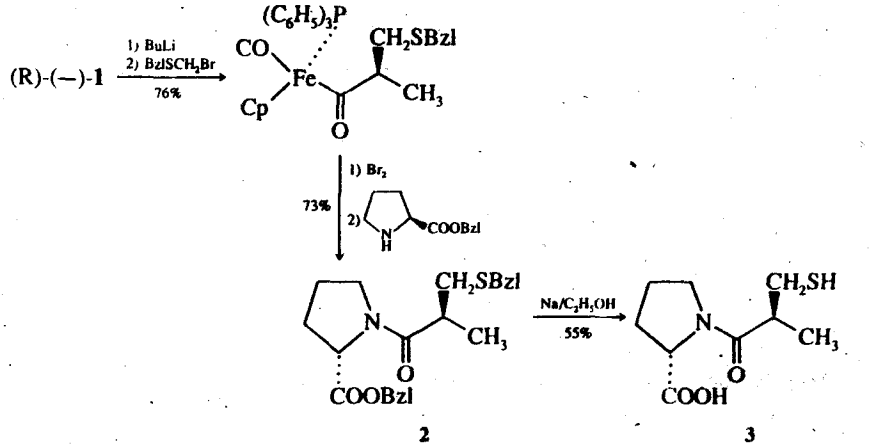
1 (E)-**2**



3 (24:1) *cis*-**4**

of BzlNHLi to **2** followed by alkylation with CH_3I gives **3** (24:1), which on oxidative cleavage provides the *cis*-2,3-disubstituted lactam **4**.

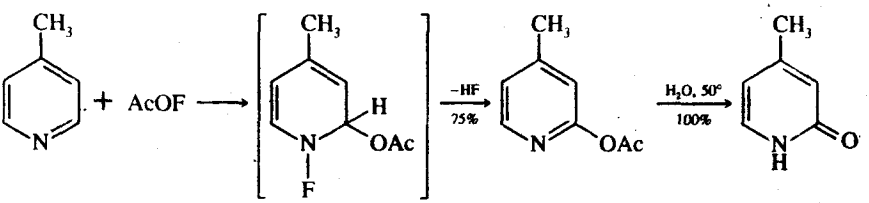
Asymmetric alkylation.[2] Deprotonation of (−)-**1** provides exclusively an (E)-enolate, which is alkylated to provide a single diastereomeric product. Decomplexation by oxidation [Br_2, I_2, Ce(IV)] in the presence of water provides the corresponding acid with the same configuration. This sequence has been used for synthesis of the drug (−)-captopril (**3**). In this case liberation of the acyl group in the presence of the amine provides the amide **2**.



[1] L. S. Liebeskind, M. E. Welker and R. W. Tengl, *Am. Soc.*, **108**, 6328 (1986).
[2] S. G. Davies, *Pure Appl. Chem.*, **60**, 13 (1988).

Acetyl hypofluorite, AcOF **(1)**, **12**, 3–4.

Oxygenation of pyridines.[1] Reaction of the reagent with pyridine or 4-methylpyridine results in a 2-acetoxypyridine in high yield. A similar reaction with 3-

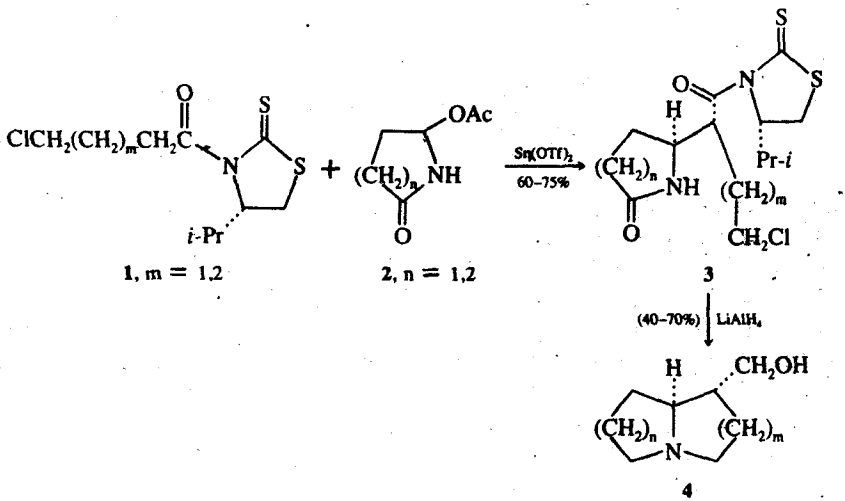


methylpyridine gives a 1:1 mixture of 2- and 5-acetoxy-3-methylpyridine, which is hydrolyzed to the corresponding pyridones. Substitution of chlorine at the α-position prevents this oxidation.

[1] S. Rozen, D. Hebel, and D. Zamir, *Am. Soc.*, **109**, 3789 (1987).

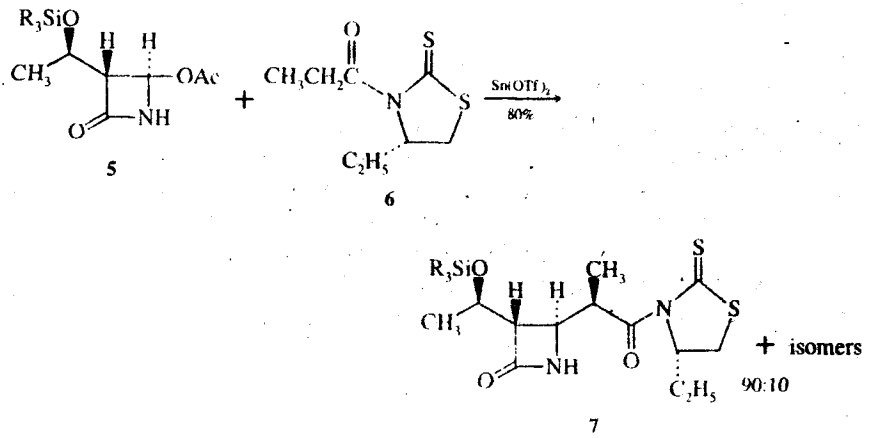
3-Acylthiazolidin-2-thiones, chiral, 11, 518–519; **12**, 4.

Bicyclic alkaloids. Nagao *et al.*[1] have developed a general synthesis of chiral bicyclic alkaloids with a nitrogen atom at the ring juncture, such as pyrrolizidines [5.5], quinolizidines [6.6], and indolizidines [6.5], based on a highly diastereoselective alkylation of 3-ω-chloroacyl-(4S)-isopropyl-1,3-thiazolidine-2-thiones (**1**, m = 1, 2) with 5-acetoxy-2-pyrrolidinone (**2**, n = 1) or 6-acetoxy-2-piperidinone (**2**, n = 2). Thus the tin enolate of **1** (m = 1), prepared with $Sn(OTf)_2$ and *N*-



ethylpiperidine, is alkylated by **2** (n = 1) to give **3** (n = m = 1) in 64% chemical yield and 97% de. Reaction of **3** with lithium aluminum hydride in THF at 0° to reduce the amide linkage and then at reflux to effect reductive annelation provides the [5.5]-bicyclic **4** [(−)-trachelanthamide] in 44% yield and 99% optical purity. The same sequence but with **1** (m = 2) and **2** (n = 2) provides the quinolizidine (−)-epilupinine. The naturally occurring (+)-epilupinine can be synthesized by using the (4R)-isopropyl-1,3-thiazolidine-2-thione.

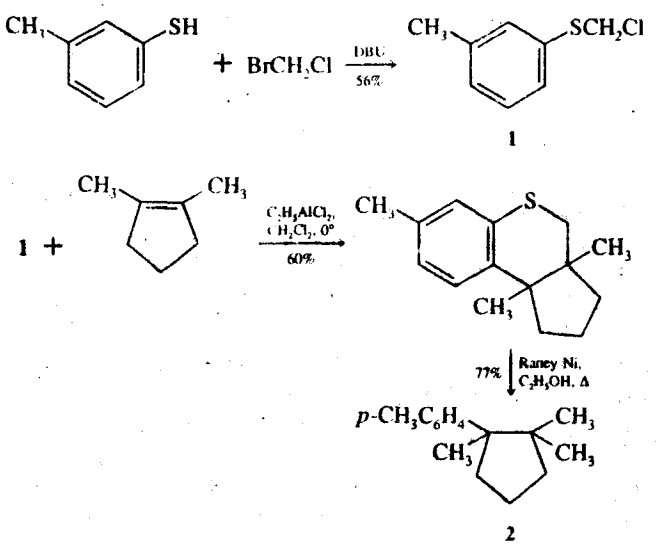
This asymmetric alkylation of cyclic acylimines can provide optically active precursors to carbapenems.[2] Thus reaction of the 4-acetoxy-2-azetidinone **5** with the chiral 3-acyl-(4S)-ethyl-1,3-thiazolidine-2-thione **6** provides the substituted azetidinone **7**, an intermediate in a total synthesis of (−)-1-β-methylcarbapenem.



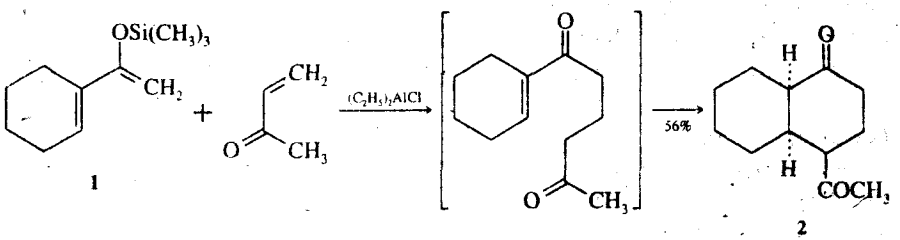
[1] Y. Nagao, W.-M. Dai, M. Ochiai, S. Tsukagoshi, and E. Fujita, *Am. Soc.*, **110**, 289 (1988).
[2] Y. Nagao, T. Kumagai, S. Tamai, T. Abe, Y. Kuramoto, T. Taga, S. Aoyagi, Y. Nagase, M. Ochiai, Y. Inoue, and E. Fujita, *Am. Soc.*, **108**, 4673 (1986).

Alkylaluminum halides.

[4 + 2]-*Dipolar cycloaddition*.[1] Arylthiomethyl chlorides (**1**) in the presence of a Lewis acid can undergo a [4 + 2]cycloaddition to a tetrasubstituted alkene. They can be prepared by reaction of thiophenol with $BrCH_2Cl$ in the presence of DBU in CH_3CN. $C_2H_5AlCl_2$ is preferred over $AlCl_3$, $SnCl_4$, or $TiCl_4$ as the Lewis acid. This reaction provides a short synthesis of cuparene (**2**).



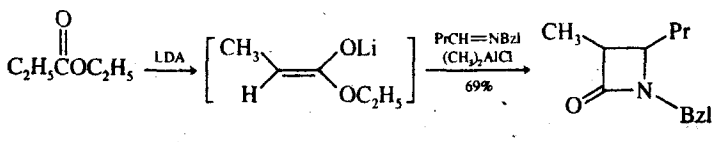
Michael reactions of silyl enol ethers.[2] The silyl enol ether of 1-acetylcyclohexene (**1**) undergoes two consecutive Michael reactions with an α,β-enone or -enal in the presence of this Lewis acid to form 1-decalones.



1 **2**

β-*Lactams.* In the presence of $(CH_3)_2AlCl$, lithium ester enolates react with enolizable aldimines to afford β-lactams in 60–95% yield as a mixture of *cis*- and *trans*-isomers.[3]

Example:

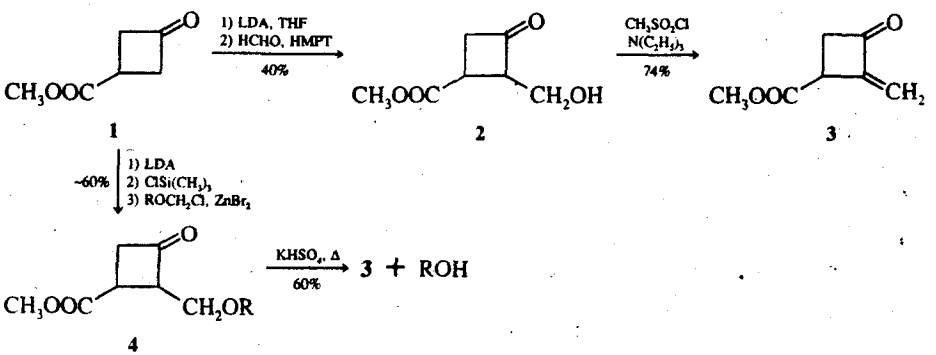


cis/trans = 76:24

[1] H. Ishibashi, T. S. So, H. Nakatani, K. Minami, and M. Ikeda, *Chem. Pharm. Bull.*, **33**, 90 (1985); *J. C. S. Chem. Comm.*, 827 (1988).
[2] H. Hagiwara, A. Okano, T. Akama, and H. Uda, *ibid.*, 1333 (1987).
[3] M. Wada, H. Aiura, and K. Akiba, *Tetrahedron Letters*, **28**, 3377 (1987).

Alkyl chloromethyl ethers.

α-Methylenecyclobutanones.[1] The simplest route to norsarkomycin methyl ester (**3**) involves α-methylenation of the cyclobutanone **1**. However, reaction of the enolate of **1** with monomeric formaldehyde under the best conditions proceeds



in low yield to give the ketol (**2**). A more useful route to α-methylenecyclobutanones involves alkylation of the silyl enol ether of the cyclobutanone with $ROCH_2Cl$ to give an α-(alkoxymethyl)cyclobutanone (**4**), which undergoes elimination of ROH when heated with $KHSO_4$ (**9**, 415). The R group is chosen so that the boiling point of ROH is significantly different from that of the α-methylenecyclobutanone.

[1] J. Vidal and F. Huet, *J. Org.*, **53**, 611 (1988).

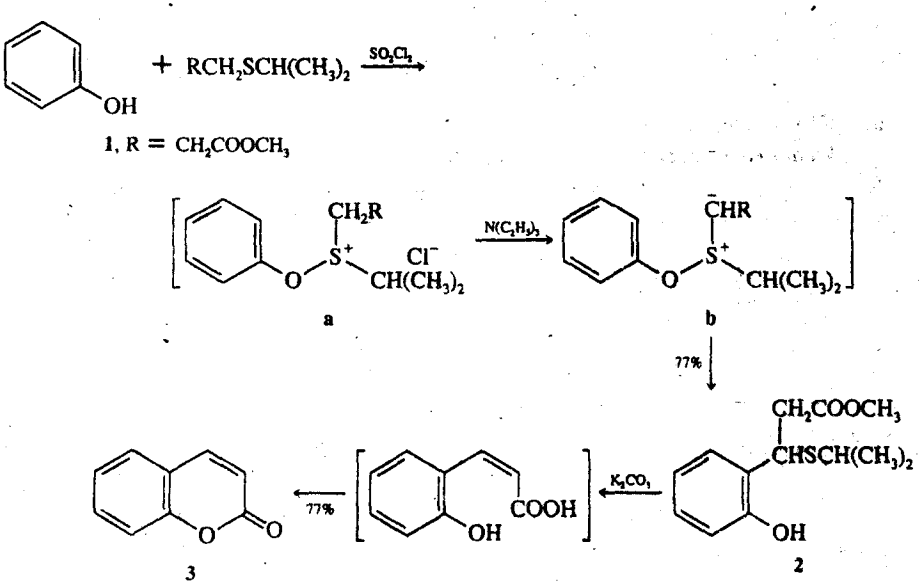
Alkyldimesitylboranes.

Boron–Wittig reaction (**12**, 12–13).[1] The direct reaction of the anion of an alkyldimesitylborane at −78° with an aromatic aldehyde followed by oxidation results in an (E)-alkene in low yield. The intermediate adduct can be isolated in about 80% yield as the silyl ether of a *syn*-1,2-diol by addition of $ClSi(CH_3)_3$ to the reaction, and this product on desilylation (HF, CH_3CN) affords (E)-alkenes with high selectivity. Somewhat lower (E)-selectivity obtains in a one-pot reaction. In contrast, addition of trifluoroacetic anhydride (slight excess) to the reaction at −78° to −110° results in a (Z)-alkene with almost comparable selectivity (Z/E ~ 9:1).

[1] A. Pelter, D. Buss, and E. Colclough, *J. C. S. Chem. Comm.*, 297 (1987).

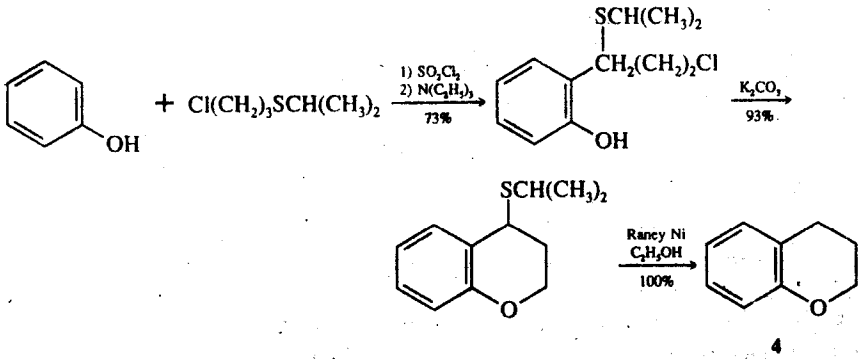
Alkyl isopropyl sulfide–Sulfuryl chloride.

ortho-*Alkylation of phenols* (**5**, 131–132; **12**, 213).[1] This combination of reagents converts phenols into a phenoxysulfonium chloride (**a**), which forms an ylide



(**b**) when treated with triethylamine. This ylide (**b**) rearranges at 25° to an *o*-alkylphenol (**2**), which is a useful precursor to coumarin (**3**).

Chroman (**4**) is prepared by a related process.

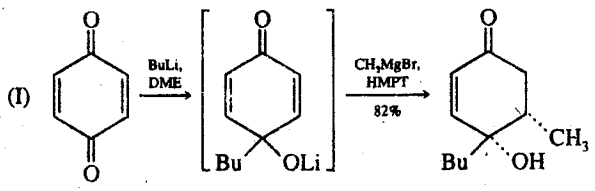


4

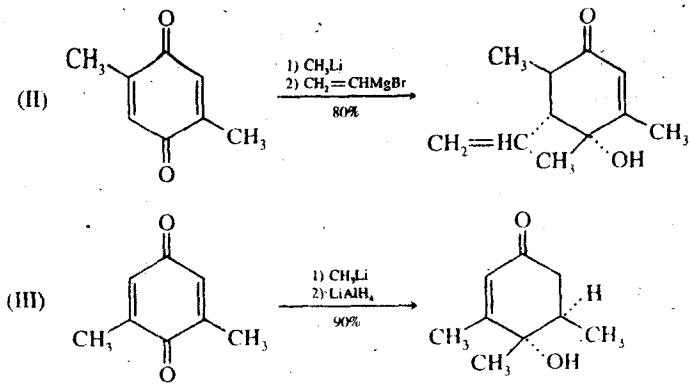
[1] S. Inoue, H. Ikeda, S. Sato, K. Horie, T. Ota, O. Miyamoto, and K. Sato, *J. Org.*, **52**, 5495 (1987).

Alkyllithium reagents.

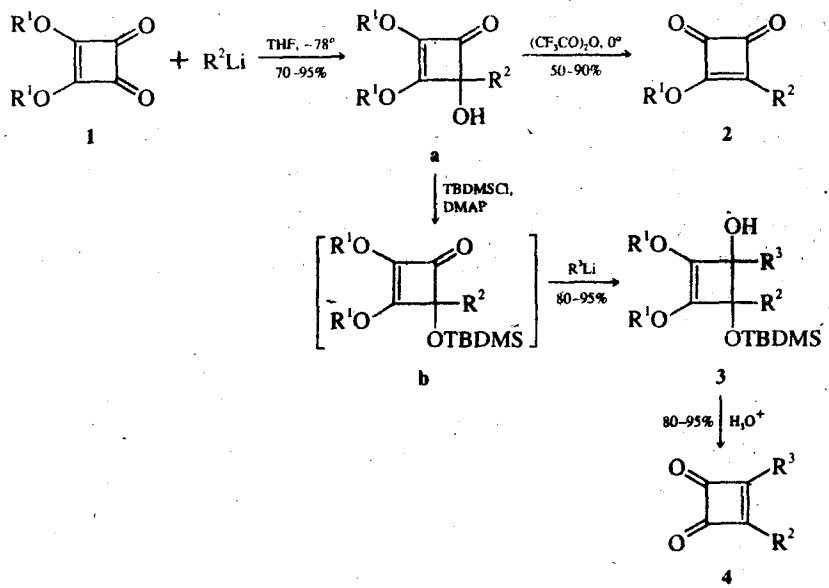
***Tandem* 1,2- *and* 1,4-*additions to quinones*.**[1] The lithium alkoxide formed by 1,2-addition of an alkyllithium to a *p*-benzoquinone can react as a Michael acceptor with some nucleophiles in the presence of HMPT or DMPU (**13**, 122). The process involves lithium–metal exchange followed by intramolecular delivery



of the nucleophile to the β-carbon atom. The reaction shows high regioselectivity, and only a single conjugate adduct is formed (equation II). In addition to delivery of carbon nucleophiles, this process can transfer hydride ion from DIBAL or $LiAlH_4$ (equation III).

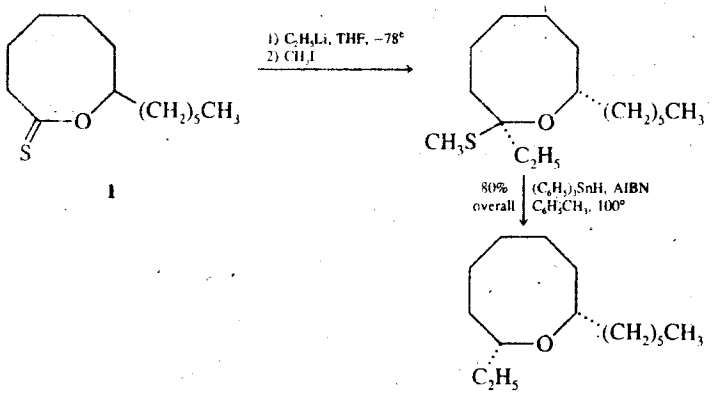


Substituted cyclobutenediones. These useful precursors to quinones (**13**, 209–210) can be prepared from commercially available dialkoxycyclobutenediones (**1**, dialkyl squarates). Thus a wide variety of organolithium reagents add to **1** at −78°, and the adducts (**a**) are hydrolyzed under mild conditions to the cyclobutenediones **2**.[2,3] Protection of **a** as the *t*-butyldimethylsilyl ether (**b**) permits a second addition



of an alkyllithium to provide the diadduct **3**, which is hydrolyzed by acid to dialkylcyclobutenediones (**4**).

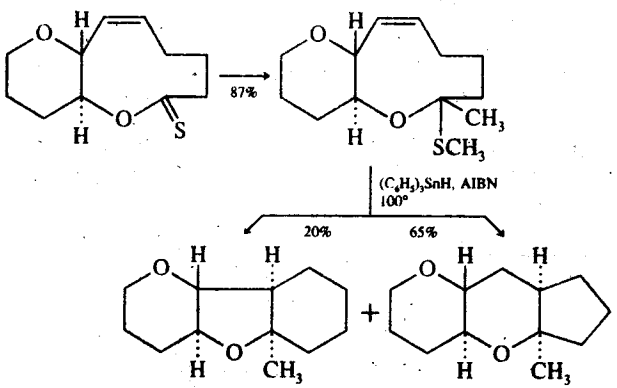
Addition to thionolactones; cyclic ethers.[4] A wide variety of alkyllithium reagents add to the C=S group of thionolactones. The adducts, after reaction with CH_3I, can be isolated in high yield as mixed methyl thioketals. The methylthio group can be removed by reduction with triphenyltin hydride (AIBN) to give cyclic ethers. The reaction is not dependent on the ring size and can be stereoselective, as shown by the synthesis of the ether lauthisan (**2**) from a thionolactone (**1**).



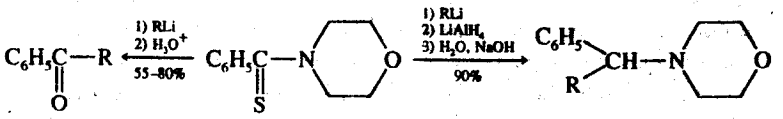
1 2

The radical formed on reduction of the methylthio group can be used to effect intramolecular cyclization of an unsaturated ring.

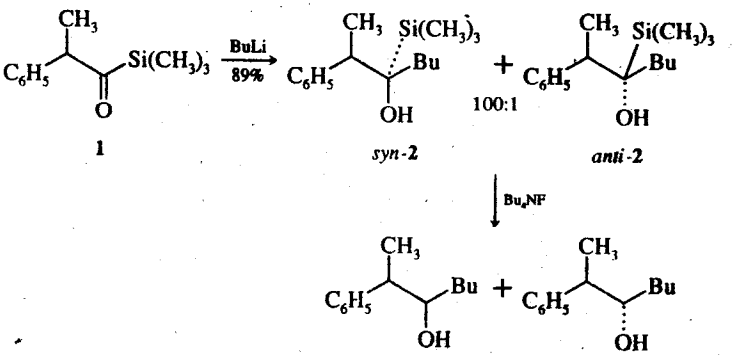
Example:



Addition to thioamides.[5] Alkyl- or aryllithiums add to the carbon–sulfur bond of aromatic thioamides to give adducts that are hydrolyzed to unsymmetrical ketones. Reduction of the adducts with $LiAlH_4$ before hydrolysis provides α-alkylated amines.



Addition to chiral acylsilanes.[6] Addition of alkyllithium or Grignard reagents to α-chiral aldehydes shows only modest (about 5:1) *syn*-selectivity. In contrast, the same reagents add to chiral acylsilanes with high *syn*-selectivity to give, after

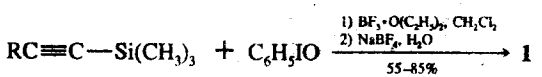


protiodesilylation, the adducts of the nucleophiles to the corresponding aldehydes.

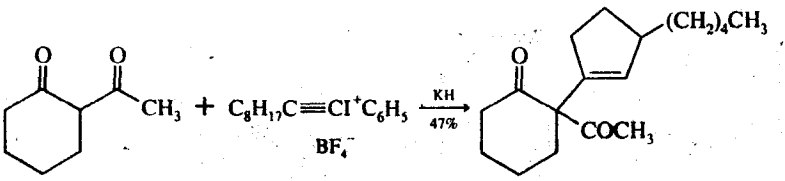
[1] M. Solomon, W. C. L. Jamison, M. McCormick, D. Liotta, D. A. Cherry, J. E. Mills, R. D. Shah, J. D. Rodgers, and C. A. Maryanoff, *Am. Soc.*, **110**, 3702 (1988).
[2] M. W. Reed, D. J. Pollart, S. T. Perri, L. D. Foland, and H. W. Moore, *J. Org.*, **53**, 2477 (1988).
[3] L. S. Liebeskind, R. W. Fengel, K. R. Wirtz, and T. T. Shawe, *ibid.*, **53**, 2482 (1988).
[4] K. C. Nicolaou, D. G. McGarry, P. K. Somers, C. A. Veale, and G. T. Furst, *Am. Soc.*, **109**, 2504 (1987).
[5] Y. Tominaga, S. Kohra, and A. Hosomi, *Tetrahedron Letters*, **28**, 1529 (1987).
[6] M. Nakada, Y. Urano, S. Kobayashi, and M. Ohno, *Am. Soc.*, **110**, 4826 (1988).

Alkynyliodonium tetrafluoroborates, $RC{\equiv}C{-}I^{+}C_6H_5BF_4^{-}$ **(1).**

Preparation[1]:

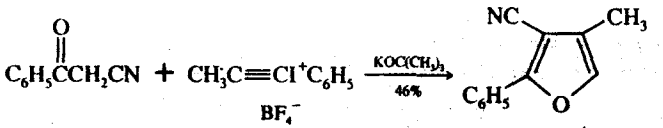


Cyclopentene annelation.[2] The reaction of the anion of a 1,3-dicarbonyl compound with 1-decynyl(phenyl)iodonium tetrafluoroborate results in an annelated 3-pentylcyclopentene in reasonable yield. The product is considered to result fro



Michael addition to the salt to form an alkylidenecarbene, which undergoes intramolecular C—H insertion to form a cyclopentene.

The reaction can also be used for synthesis of furans by a [2 + 3]annelation. Example:

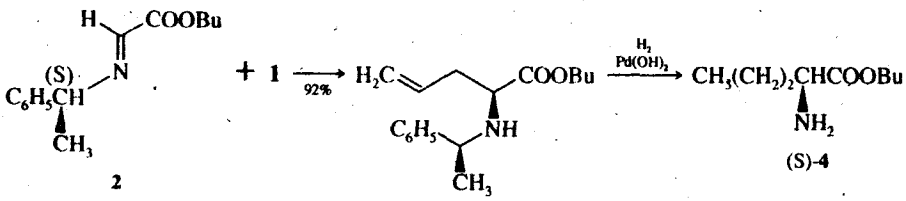


[1] M. Ochiai, M. Kunishima, K. Sumi, Y. Nagao, M. Arimoto, H. Yamaguchi, and E. Fujita, *Tetrahedron Letters*, **26**, 4501 (1985).

[2] M. Ochiai, M. Kunishima, Y. Nagao, K. Fuji, M. Shiro, and E. Fujita, *Am. Soc.*, **108**, 8281 (1986).

B-Allyl-9-borabicyclo[3.3.1]nonane (1).

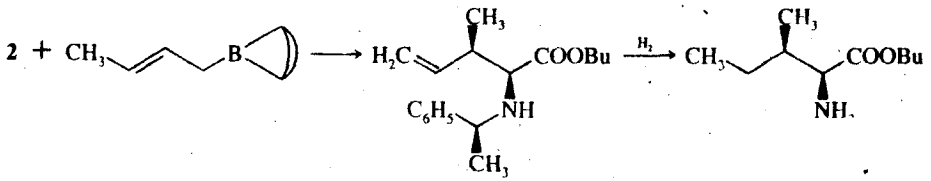
Amino acid synthesis (*cf.* **12**, 15). The reaction of **1** with chiral α-imino esters provides an enantio- and diastereoselective synthesis of amino acid derivatives.[1] The imine (**2**), prepared from (S)-phenethylamine, reacts with **1** to give **3**, which



is hydrogenated to the butyl ester of L norvaline (**4**).

The addition of crotyl-9-BBN to the chiral imino ester **2** provides a *syn*-selective synthesis of optically active amino esters.[1]

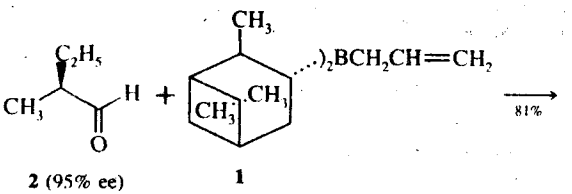
Example:



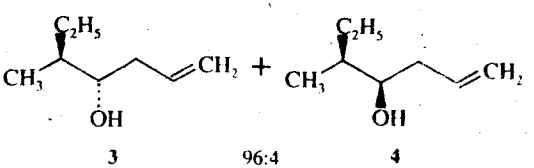
[1] Y. Yamamoto, S. Nishii, K. Maruyama, T. Komatsu, and W. Ito, *Am. Soc.*, **108**, 7778 (1986).

B-Allylisopinocamphenylborane (1).

Allyboration of chiral aldehydes (**12**, 17). The borane **1**, prepared from (+)-α-pinene, reacts with a chiral, α-substituted aldehyde such as **2** with 96:4 diastereofacial selectivity. Reaction of **2** with *ent*-**1**, prepared from (−)-α-pinene, shows reversed facial selectivity (5:95).[1]



2 (95% ee) **1**



3 96:4 **4**

2 + *ent*-**1** ⟶ **4** + **3**

95:5

[1] H. C. Brown, K. S. Bhat, and R. S. Randad, *J. Org.*, **52**, 320 (1987).

Allyl methyl carbonate, $CH_2{=}CHCH_2OCO_2CH_3$ (**1**).

The reagent, b.p. 127–130°, is prepared by reaction of allyl alcohol in ether with methyl chloroformate and pyridine (86% yield).

Dehydrogenation of alcohols.[1] Allylic or secondary alcohols can be oxidized to the ketones by reaction with **1** catalyzed by $RuH_2[P(C_6H_5)_3]_4$ in benzene. The