SYNTHESIS ALERTS

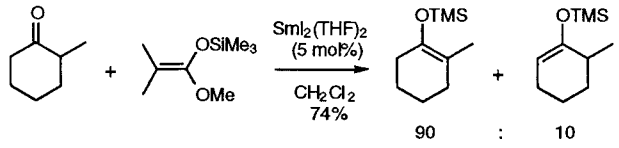
Synthesis Alerts is a new monthly feature to help readers of Synthesis keep abreast of new reagents, catalysts, ligands, chiral auxiliaries, and protecting groups which have appeared in the recent literature. Emphasis is placed on new developments but established reagents, catalysts etc are also covered if they are used in novel and useful reactions. In each abstract, a specific example of a transformation is given in a concise format designed to aid visual retrieval of information.

Synthesis Alerts is a personal selection by Paul Blakemore, Brian Dymock, Philip Hall, Philip Kocienski, J.-Y. Le Brazidec and Alessandro Pontiroli of the University of Glasgow. The journals regularly covered by the abstractors are: Angewandte Chemie International Edition, Bulletin de la Societe Chimie de France, Bulletin of the Chemical Society of Japan, Chemische Berichte, Chemistry Letters, Helvetica Chimica Acta, Journal of Organic Chemistry, Journal of Organometallic Chemistry, Journal of the American Chemical Society, Liebigs Annalen, Tetrahedron Letters.

Samarium (II) Iodide — ***Catalyst***

Ketones and α-substituted aldehydes are converted to trimethylsilyl enol ethers by treatment with the trimethylsilyl ketene acetal of methyl isobutyrate in presence of SmI_2.

SmI_2



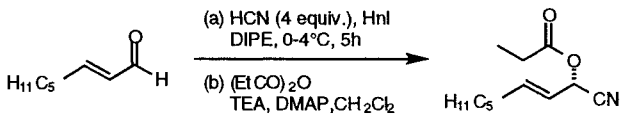
12 examples with ketones and aldehydes are reported with good yields and good to excellent regioselectivities.

J. Hydrio, P. Van de Weghe, J. Collin *Synthesis* **1997**, 68.

(*S*)-Hydroxynitrile Lyase (Hnl) from *Hevea brasiliensis* — ***Catalyst***

The title enzyme, available in large quantities after overexpression in *Pichia pastoris*, transforms(*E*)-octan-2-al into the corresponding cyanohydrin in excellent yield and er.

Hnl



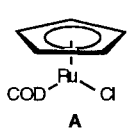
80% overall yield
er >99:1

The synthesis of the natural product coriolic acid has been achieved using this reaction on large scale to introduce chirality.

D. V. Johnson, H. Griengl *Tetrahedron* **1997**, *53*, 617.

(η^5-Cycloocta-1,5-diene)(η^5-cyclopentadienyl)chlororuthenium(II) — ***Catalyst***

Ru-catalyzed three component addition to form 1,5-diketones.



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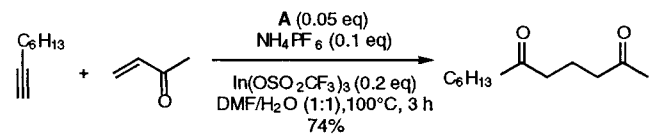
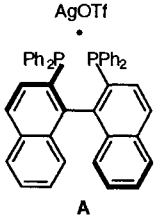


This reaction is limited to monosubstituted enones (16 examples).

B. M. Trost, M. Portnoy, H. Kurihara *J. Am. Chem. Soc.* **1997**, *119*, 836.

(*R*)-(–)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl Silver(I) Trifluoromethanesulfonate — *Catalyst*

The title complex (abbreviation: BINAP•Ag (I)OTf) catalyses the asymmetric addition of crotyltributyltin or methallyltributyltin to aldehydes to give homoallylic alcohols.



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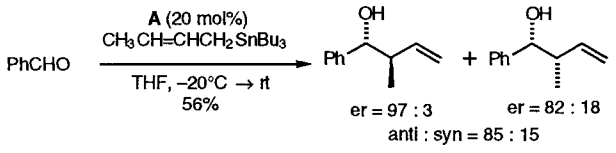


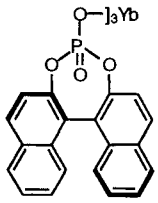
9 other examples using methallyltributyltin

A. Yanagisawa, A. Ishiba, H. Kakashima, H. Yamamoto *Synlett* **1997**, 88.

Ytterbium Tris[(*R*)-(–)-1,1′-binaphthyl-2,2′-diyl] Phosphonate — *Catalyst*

Addition of 1 equivalent of 2,6-lutidine to the title complex facilitates the lanthanide catalysed hetero Diels-Alder reaction of Danishefsky's diene at room temperature.

Abbreviation: Yb[(*R*)-(–)BNP]$_3$



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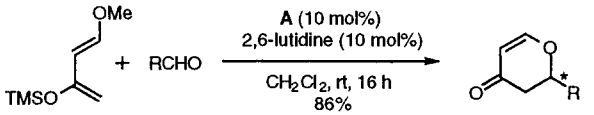


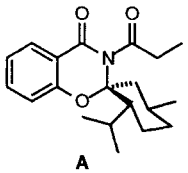
9 examples

er = 97:4
R = *p*-methoxyphenyl

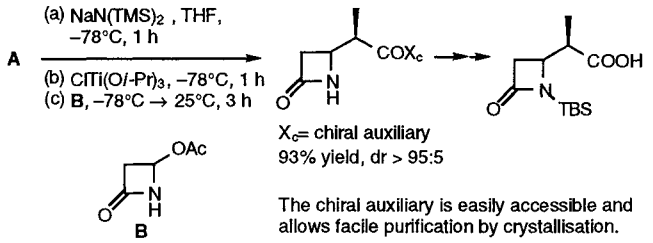
T. Hanamoto, H. Furuno, Y. Sugimoto, J. Inanaga *Synlett* **1997**, 79.

3-Propionyl-*spiro*{2,3-dihydro-4*H*-1,3-benzoxazine-2,1′-[(2′*R*,5′*S*)-2′-isopropyl-5′-methylcyclohexane]}-4-one — *Chiral Auxiliary*

Titanium enolates prepared from the title compound undergo aldol-type reaction with 4-acetoxyazetidin-2-one (**B**) to give a key intermediate of 1-β-methylcarbapenems in high yield and stereoselectivity.



A



B

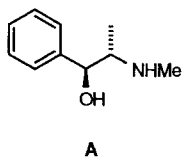
X_c= chiral auxiliary
93% yield, dr > 95:5

The chiral auxiliary is easily accessible and allows facile purification by crystallisation.

M. Seki, T. Miyake, T. Izukawa, H. Ohmizu *Synthesis* **1997**, 47.

(1*S*,2*S*)-2-*N*-Methylamino-1-phenylpropan-1-ol — *Chiral Auxiliary*

Highly practical methodology for the synthesis of D- and L-α-amino acids.



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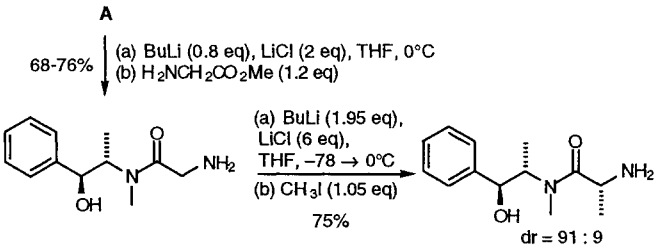
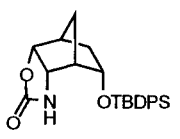


A. G. Myers, J. L. Gleason, T. Yoon, D. W. Kung *J. Am. Chem. Soc.* **1997**, *119*, 656.

(1*S*,2*S*,6*R*,7*S*,9*S*)-5-Oxa-3-aza-9-[(*tert*-butyldiphenylsilyl)oxy]tricyclo[5.2.1.0^{2,6}]decan-4-one — *Chiral Auxiliary*

Powerful chiral auxiliary for asymmetric alkylation, Diels-Alder, and conjugate addition reactions.



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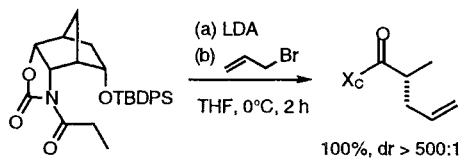


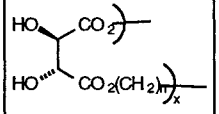
100%, dr > 500:1

3 examples of alkylation, 2 examples of Diels-Alder reactions and 7 of conjugate addition reactions all using imides derived from oxazolidinone **A**. In each case high yields can be obtained (>90%) with very high diastereoselection (dr > 99:1). The auxiliary is easily removed by treatment with $LiBH_4$/MeOH or LiOOH.

T. Nakamura, N. Hashimoto, T. Ishizuka, T. Kunieda *Tetrahedron Lett.* **1997**, *38*, 559.

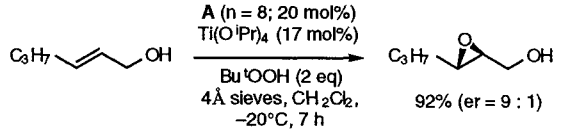
Linear Poly(tartrate ester) Ligands — *Ligand*

Sharpless asymmetric epoxidation on a solid phase can be accomplished with the title ligands.



n = 2, 6, 8, 12

A

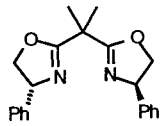


6 different catalysts; yields 22-92%; ee = 8-79%

L. Canali, J. K. Karjalainen, D. C. Sherrington, O. Hormi *Chem. Commun.* **1997**, 123.

2,2-Bis[(*R*)-4-phenyl-1,3-oxazolin-2-yl)]propane — *Ligand*

Enantiotopic differentiation of *pro-R* or *pro-S* chloride in (dichloromethyl)borates by chiral Lewis acid.



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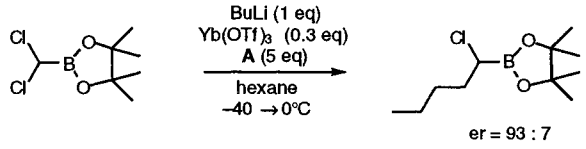
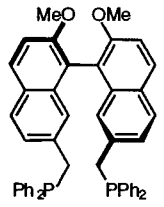


A large excess of ligand **A** is necessary to obtain high enantioselectivity.

P. K. Jadhav, H.-W. Man *J. Am. Chem. Soc.* **1997**, *119*, 846.

(*R*)-7,7′-Bis(diphenylphosphinomethyl)-2,2′-dimethoxy-1,1′-binaphthyl — *Ligand*

The Rh(I) complex derived from the title ligand catalyses the asymmetric conjugate addition of 2-cyanopropionates to methyl vinyl ketone.



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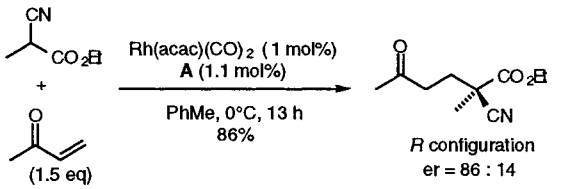
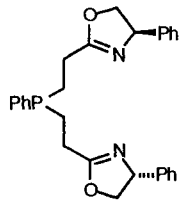


12 examples. The active catalyst is simply prepared by mixing the ligand and rhodium precursor at room temperature.

K. Inagaki, K. Nozaki, H. Takaya *Synlett* **1996**, 119.

Phenyl Bis{2-[(*S*)-4-phenyl-1,3-oxazolin-2-yl]ethyl}phosphine — *Ligand*

A complex derived from the title ligand and [RuCl$_2$(C$_6$H$_6$)]$_2$ catalyses the asymmetric transfer hydrogenation of ketones.



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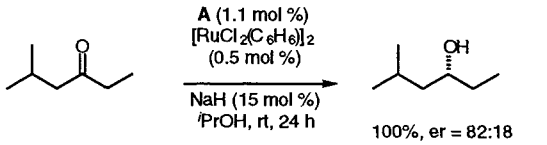
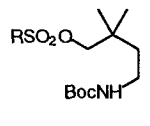


9 examples of simple aliphatic ketones or acetophenone analogues (yields 72-100%, %ee 14,16, 63-92%).

Y. Jiang, Q. Jiang, G. Zhu, X. Zhang *Tetrahedron Lett.* **1997**, *38*, 215.

N-Boc-4-amino-2,2-dimethylbutyl (neoN-B) — *Protecting Group*

Neopentylsulfonate ester formation provides convenient protection for arylsulfonic acids. A variation utilising neoN-B (**A**) provides suitable sulfonic acid protection for solid phase peptide synthesis. Deprotection can be effected under mild conditions at room temperature.



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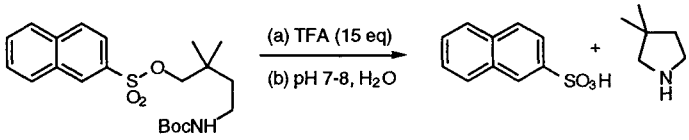


Simple neopentylsulfonate esters provide more robust sulfonic acid protection (*eg* compatible with metallation, halogen-metal exhange), but require harsh deprotection conditions (Me$_4$NCl, DMF, 160°C, 16 h).

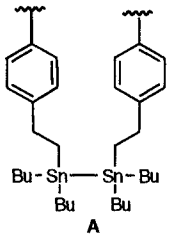
J. C. Roberts, H. Gao, A. Gopalsamy, A. Kongsjahju, R. J. Patch *Tetrahedron Lett.* **1997**, *38*, 355.

Polymer-Supported Distannane

Reagent

The title polymer-supported distannane promotes radical cyclisations of acyclic α-haloesters to γ-butyrolactones providing products almost free of Sn byproducts.

J. Junggebauer, W. P. Neumann *Tetrahedron* **1997**, *53*, 1301.



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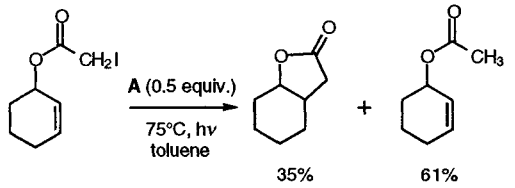


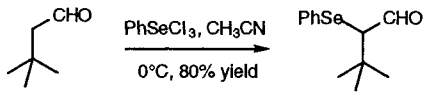
Phenylselenium Trichloride

Reagent

Treatment of aldehydes and ketones with $PhSeCl_3$ in acetonitrile yield α-phenylselenyl carbonyl compounds in good to very good yields.

D. Houllemare, S. Ponthieux, F. Outurquin, C. Paulmier *Synthesis* **1997**, 101.

$PhSeCl_3$



20 examples with aldehydes and ketones are reported.

$Ni(acac)_2$ and Organozinc Reagents

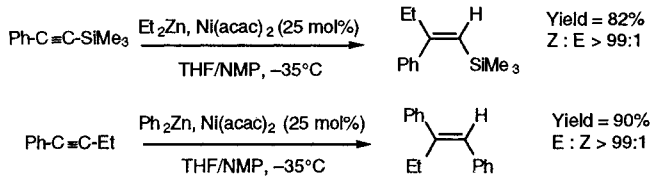
Reagent

Nickel-catalysed carbozincation of internal alkynes is a novel method for the stereoselective synthesis of tri- and tetrasubstituted olefins in good yield.

T. Stüdemann, P. Knochel *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 93.

R_2Zn, $Ni(acac)_2$

R= Me, Et, Ph, $SiMe_3$



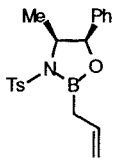
Transmetallation of the intermediate organozinc with CuCN•2LiCl and quenching with electrophiles provides tetrasubstituted olefins or α,β-unsaturated esters.

(4*S*,5 *R*)-*B*-Allyl-4-methyl-5-phenyl-*N*-*p*-toluenesulfonyl-1,3,2-oxazaborolidine

Reagent

The highest selectivity to date (96:4 er) for the enantioselective allylation of imines is obtained using the title *B*-allyloxazaborolidine derived from triallylborane and (–)-norephedrine.

S. Itsuno, K. Watanabe, K. Ito, A. El-Shehawy, A. A. Sarhan *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 109.



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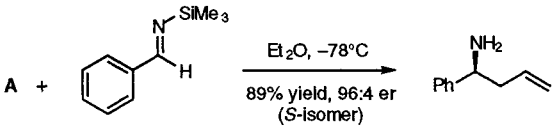


8 other catalysts and 3 substrates were used with comparable yields and inferior stereoselectivity (up to 94.5 : 5.5 er).

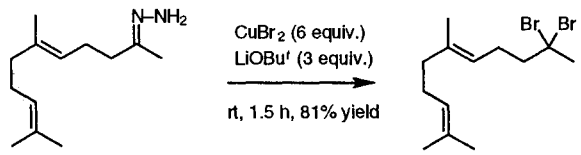
Copper(II) Halides-Lithium *tert*-Butoxide

Reagent

$CuBr_2$ and $CuCl_2$ with lithium *tert*-butoxide effects the transformation of hydrazones from ketones or aldehydes into *gem*-dihalides in good yield.

T. Takeda, R. Sasaki, S. Yamauchi, T. Fujiwara *Tetrahedron*, **1997**, *53*, 557.

$CuBr_2$/ $CuCl_2$
$LiOBu^t$

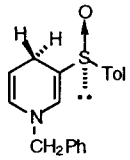


Several other examples reported; $CuBr_2$ and amines such as Et_3N or Bu_3N also effect the reaction.

N-Benzyl-3-*p*-tolysulfinyl-1,4-dihydropyridine — Reagent

The title NADH model compound reduces ketones to alcohols in good yield and very good enantioselectivity.

S. Obika, T. Nishiyama, S. Tatematsu, K. Miyashita, C. Iwata, T. Imanishi *Tetrahedron*, **1997**, *53*, 593.



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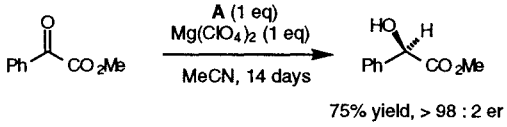


75% yield, > 98 : 2 er

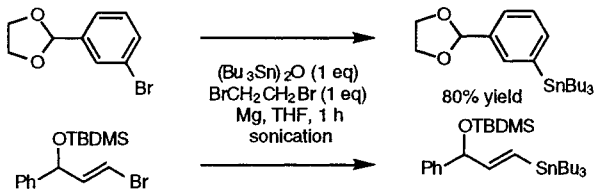
Examples with 4 ketones are reported with lower yield and very good er.

Bis(tributyltin) Oxide — Reagent

Clean and high yielding conversion of aryl, vinyl, allyl and alkyl bromides into the corresponding tributylstannanes is achieved *via* Barbier reaction by sonication of their solution in THF in the presence of Mg powder, 1,2-dibromoethane and bis(tributyltin) oxide.

A. S.-Y. Lee, W.-C. Dai *Tetrahedron* **1997**, *53*, 859.

$(Bu_3Sn)_2O$



80% yield

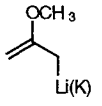
73% yield

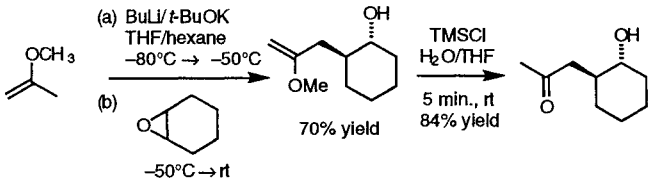
Several other examples with aryl, vinyl, allyl, and alkyl bromides are reported.

2-Methoxyprop-2-enyllithium — Reagent

The title compound and its potassium derivative serve as a substitute for acetone enolate in the reaction with various electrophiles.

F. Taherirasgar, L. Brandsma *Chem. Ber.* **1997**, *130*, 45.





70% yield

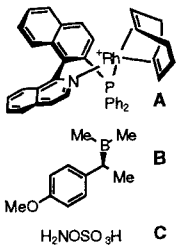
84% yield

13 other electrophiles were employed with yields between 85 and 95%.

Trialkylborane/Rhodium (*S*)-Quinap/Hydroxylamine-*O*-sulfonic Acid — Reagent

The title reagents convert vinyl arenes to chiral primary amines *via* a one-pot hydroboration-amination sequence.

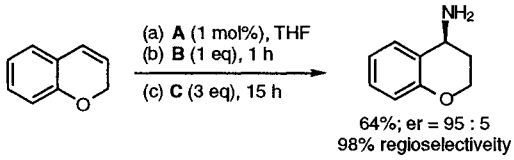
E. Fernandez, M. W. Hooper, F. I. Knight, J. M. Brown *Chem. Commun.* **1997**, 173.



A

B

H_2NOSO_3H C



64%; er = 95 : 5

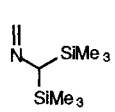
98% regioselectiveity

7 examples; yields 50-64%; ee's 77-98%

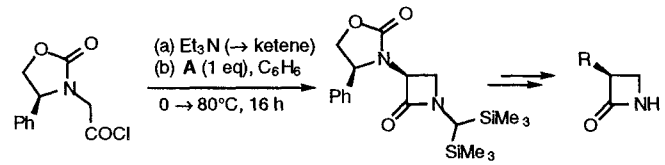
N-Methylidene [Bis(trimethylsilyl)methyl]amine — Reagent

The title compound is the first stable, isolable monomeric methanimine which undergoes thermal [2+2] cycloadditions with ketenes.

C. Palomo, J. M. Aizparua, M. Legido, R. Galarza *Chem. Commun.* **1997**, 233.



A

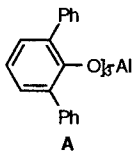


3 examples; yields 62-75%

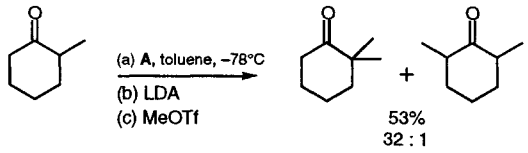
The bis(TMS)methyl protecting group may be removed in a 2 step sequence

Tris(2,6-diphenylphenoxy)aluminium — *Reagent*

The title compound enables highly regioselective alkylation at the more-hindered α-site of unsymmetrical ketones.



A



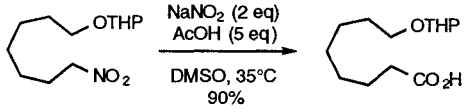
10 examples, yields from 53 to 99%

S. Saito, M. Ito, H. Yamamoto *J. Am. Chem. Soc.* **1997**, *119*, 611.

Sodium Nitrite — *Reagent*

Primary alkyl bromides and nitroalkanes are oxidised to the corresponding carboxylic acid when treated with sodium nitrite and acetic acid.

$NaNO_2$

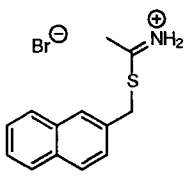


9 examples cited. Yields consistently >85%.

C. Matt, A. Wagner, C. Mioskowski *J. Org. Chem.*, **1997**, *62*, 234.

(*S*)-2-Naphthylmethyl Thioacetimidate Hydrobromide — *Reagent*

An easily prepared, convenient reagent for the synthesis of substituted acetamidines from amines.The 2-naphthylmethyl mercaptan by-product is odorless and easily separated upon work up.



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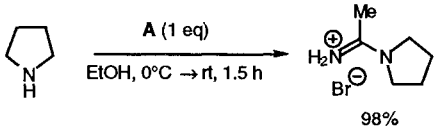


8 simple examples (yields 69, 95-98%).

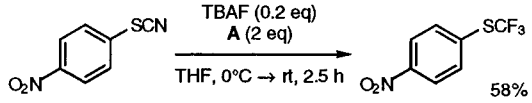
B. G. Shearer, J. A. Oplinger, S. Lee *Tetrahedron Lett.* **1997**, *38*, 179.

Trifluoromethyltrimethylsilane — *Reagent*

Trifluoromethyl sulfides (or selenides) can be easily obtained from the corresponding thiocyanates by reaction with **A** in the presence of a catalytic quantity of TBAF.

Me_3SiCF_3

A



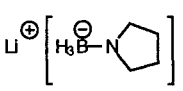
10 examples, including 3 for the preparation of trifluoromethyl selenides (yields 30-87%).

TBAF = tetra-*n*-butylammonium fluoride

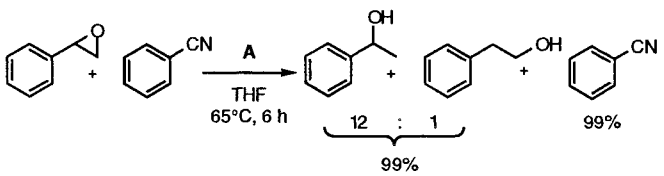
T. Billard, S. Large, B. R. Langlois *Tetrahedron Lett.* **1997**, *38*, 65.

Lithium Pyrrolidinoborohydride — *Reagent*

A powerful non-pyrophoric reagent which can quantitatively reduce aldehydes, ketones, esters and epoxides in the presence of nitriles.



A



7 examples of competitive reduction (yields 84, 93-99%). In each case the added nitrile component is not transformed.

C. J. Collins, G. B. Fisher, A. Reem, C. T. Goralski, B. Singaram *Tetrahedron Lett.* **1997**, *38*, 529.