Encyclopedia of Reagents for Organic Synthesis

Editor-in-Chief
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Volume 2

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Editorial Board

Preface

The extent to which organic synthetic methodology has developed and flourished during the past several decades has placed unusually heavy demands on the broad range of scientists who utilize chemical reagents. There exists the vital need to know which reagent will perform a specific transformation. Since a number of reagents are often amenable to similar objectives, a researcher's ability to access readily a comparative summary of those features that distinguish one reagent from another can result in a considerable economy of time. The purpose of the *Encyclopedia of Reagents for Organic Synthesis* is to incorporate into a single work a genuinely authoritative and systematic description of the utility of all reagents used in organic chemistry. Its comprehensiveness is further served by an unrivaled ease to locate any specific entry or topic.

These objectives have been met by inviting practicing chemists from throughout the world to provide specific contributions in their area of expertise. Furthermore, the masthead for each of the 3000 reagents provides valuable information concerning physical data, solubility, form supplied in, purification, and, where relevant, preparative methods. The CAS registry number, handling/storing information, and precautions will further serve potential users. The first literature reference in each entry provides reviews, if available, dealing with the subject reagent. The critical coverage of all relevant literature is extensive.

The goal of the *Encyclopedia of Reagents for Organic Synthesis* is to serve as a reference work where the retrievability of useful information concerning any specific reagent is made facile. For this reason there is a detailed subject index and, in addition, a formula index of all the reagents, and also two further indexes that list the reagents by structural class and by function.

In any undertaking of this type, it is important that the term 'reagent' be clearly defined. The guideline that has dominated the thinking of the members of the Editorial Board is that a reagent be an agent or a combination of agents which with some generality effects the transformation of a substrate into a product. In addition, many useful building blocks have been included. As a consequence, we anticipate that a work has been produced that will serve biochemists, material scientists, pharmacologists, and chemical engineers, in addition to chemists from all disciplines, in that manner most conducive to accelerating progress in their respective fields of research.

The entries highlight the various uses characteristic of each reagent, with specific examples illustrative of these chemical reactions. The contributions are organized alphabetically and the cross-referencing to other reagents is liberal. Thus, a concerted effort has been made to bring together in one place a detailed compilation of the uses of those reagents that will serve both the beginning and experienced investigator. The wealth of facts contained within the *Encyclopedia of Reagents for Organic Synthesis* has been assimilated in a manner which will cause all scientists to want this source of information kept in close proximity to their laboratory.

A work of this magnitude could not have been brought to realization without the input of a great deal of time, effort, and dedication on the part of a large number of highly responsible individuals. I am especially indebted to the editors – Steven Burke, Robert Coates, Rick Danheiser, Scott Denmark, David Hart, Lanny Liebeskind, Dennis Liotta, Anthony Pearson, Hans Reich, James Rigby, and William Roush – for their tremendously valuable enthusiasm, intensive work, and unstinting persistence. A most critical role has been played by Colin Drayton, not only in conceiving the project but also as a consequence of his range of knowledge of the publishing business in steering us continually in the proper direction and in overseeing the massive editing operation. James Edwards and Mark Volmer are also to be thanked for their central role as assistant section editors. The body of this encyclopedia was composed by over 1000 authors from 40 countries around the world. The knowledge and expertise contributed by these experienced investigators in the form of authoritative treatises dealing with reagents with which they are thoroughly familiar constitutes the scientific underpinning of the entire undertaking. The enlightening end product of their contributions will have a major impact on the conduct of research in organic chemistry and I thank each of these individuals for their insightful entries.

The large contingent of organic chemists alluded to above, directly and indirectly, expects the *Encyclopedia of Reagents for Organic Synthesis* to play a vital role in stimulating creative research in organic chemistry in the years immediately ahead. All of us hope that you will share in this excitement by perusing its many pages and creatively adapting the valuable information contained therein.

Leo A. Paquette
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Foreword

This Encyclopedia covers comprehensively over 3000 reagents, alphabetically arranged using IUPAC nomenclature. The articles are self-contained but ***Bold Italics*** are used within each article to indicate other reagents that have their own entries in the Encyclopedia. A list of related reagents is given at the end of articles.

Although most articles are devoted to a single reagent, in some cases closely related reagents are covered under one heading, e.g. Methyl Trimethylsilylacetate is discussed in the article on Ethyl Trimethylsilylacetate, and Lithium Trimethoxyaluminum Hydride in the article on Lithium Tri-*t*-butoxyaluminum Hydride.

A particular reagent can be found either directly, by going to the appropriate place in the Encyclopedia, or from the Subject Index in Volume 8. Numerous other topics, such as types of reaction, named reactions, named reagents, general substrates or products, and specific substrates or products, are included in this index.

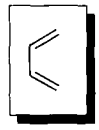
Volume 8 also contains a Formula Index, listing all reagents covered in the Encyclopedia.

In addition, there are two further compilations of all the reagents in Volume 8, a Reagent Structural Class Index and a Reagent Function Index. The former groups the reagents under headings such as Dienes, Hydrides, and Titanium Reagents, while the latter has headings such as Alkylating Agents, Desilylation Reagents, and Ring Expansion Agents.

The abbreviations used for journals in the references are on the front endpapers of all volumes, while the back endpapers list other abbreviations used throughout the Encyclopedia.

But

1,3-Butadiene



[106-99-0] C_4H_6 (MW 54.09)

(co-monomer in synthetic elastomers and polymers, polybutadiene rubber, chloroprene, and nylon intermediate;[1] 4π partner in Diels–Alder reactions[2])

Alternate Names: butadiene; α,γ-butadiene; bivinyl; divinyl; vinylethylene; biethylene.

Physical Data: bp –4.5 °C/760 mmHg; mp –109 °C; fp <–7 °C; ρ_4^{-6} 0.650.

Solubility: sol common organic solvents.

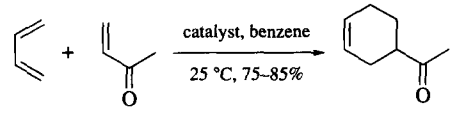
Form Supplied in: widely available in compressed liquid phase. Supplied in several grades ranging from 99.0–99.8% purity. Sizes available range incrementally from lecture bottles (100 g) to large gas cylinders (61 kg).

Preparative Methods: butadiene sulfone (2,5-dihydrothiophene 1,1-dioxide), a crystalline, nonhygroscopic, commercially available solid, can be used to generate 1,3-butadiene in situ: heating the sulfone at 100–130 °C induces loss of SO_2.[3b,3c]

Handling, Storage, and Precautions: extremely flammable liquid and gas. Avoid polymerization initiators. Relatively nontoxic. Suspected chronic carcinogen. Acutely irritating to respiratory tract. 1,3-Butadiene (**1**) is used in the laboratory by condensing the gas directly into a reaction vessel, or by forming a saturated solution of the gas in the reaction solvent. For reactions run below rt (e.g. Lewis acid-catalyzed reactions), normal reaction flasks can be used. For higher temperature reactions, sealed tubes are required to prevent escape of (**1**). A particularly convenient, reusable apparatus is available from Ace Glass, Inc., and consists of a heavy-walled glass tube sealed on one end and threaded on the other. The threaded end can be sealed with a heavy Teflon plug fitted with an O-ring.

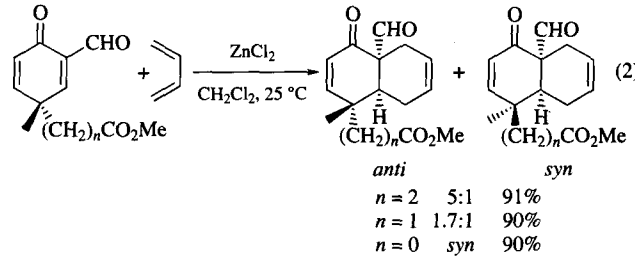
Reactivity. 1,3-Butadiene (**1**) participates as the 4π partner in $[{}_\pi4_s + {}_\pi2_s]$ cycloaddition reactions with a variety of dienophiles. The majority of these cycloadditions are normal Diels–Alder reactions ($HOMO_{diene}$–$LUMO_{dienophile}$ controlled).[2,3a] Theoretical predictions on the mechanism of Diels–Alder reactions of butadiene have pointed towards a synchronous concerted mechanism.[4] 1,3-Butadiene (**1**) is typically less reactive than substituted butadienes, except when steric factors prevent the diene from attaining the reactive *s-cis* conformation. For example ***Tetracyanoethylene*** reacts more slowly with (**1**) than with (*E*)-1-methyl-1,3-butadiene (103×), 2-phenyl-1,3-butadiene (191×), or (*E*)-1-methoxy-1,3-butadiene (50 934×).

Lewis Acid-Catalyzed Cycloadditions. Friedel–Crafts type catalysts are reported to facilitate the cycloaddition reactions of (**1**) with α,β-unsaturated carbonyl compounds.[5] With methyl vinyl ketone (eq 1), cycloaddition was effected in the presence of less than 1 molar equivalent of ***Aluminum Chloride***, ***Tin(IV) Chloride***, ***Boron Trifluoride***, ***Iron(III) Chloride***, or ***Titanium(IV) Chloride*** for 1 h at 25 °C. For comparison, the uncatalyzed reaction required 8–10 h at 140 °C in a sealed tube (75%). ***Acrolein***, ***Methyl Vinyl Ketone***, and ***Acrylic Acid*** all underwent effective catalyzed Diels–Alder reactions with (**1**) in good yields. The principal limitation of this reaction is polymerization of the 1,3-diene. For example, 2,3-dimethylbutadiene and cyclopentadiene underwent polymerization and dimerization, respectively, under these conditions.



(1)

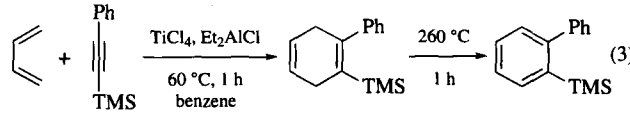
In the cycloaddition of (**1**) with 2,5-cyclohexadienones in an approach to *cis*-clerodanes, the facial selectivity depended on the length of the carboxylate side-chain (eq 2).[6] When the carboxylate was a significant distance from the ring (n = 2), cycloaddition occurred *syn* to the less bulky methyl group to afford the *anti* cycloadduct. Facial selectivity eroded with n = 1, and was reversed when the carboxylate was directly attached to the ring, to afford exclusively the *syn* diastereomer.



(2)

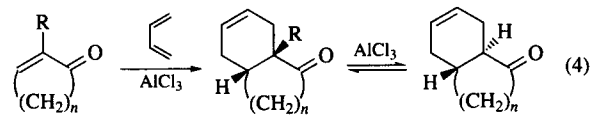
	anti	*syn*
n = 2	5:1	91%
n = 1	1.7:1	90%
n = 0	*syn*	90%

Lewis acids have also been used to catalyze the cycloaddition of (**1**) with alkynes (eq 3).[7] A mixture of $TiCl_4$ and ***Diethylaluminum Chloride*** promoted the [4 + 2] cycloaddition of phenyl(trimethylsilyl)acetylene and (**1**) to afford the dihydrobenzene adduct in 84% yield, which could be aromatized thermally to afford the *ortho*-disubstituted benzene in 92% yield. Cycloaddition of cycloalkenones with butadiene in the presence of $AlCl_3$ affords the expected *cis*-fused systems for n = 2, 3, 4 (eq 4).[8] Partial or total isomerization of the *cis* adduct to the more stable *trans* isomer was observed with R = H.



(3)

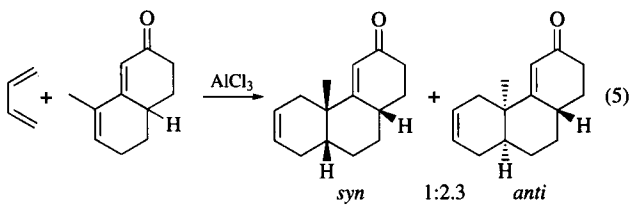
A highly regioselective and moderately stereoselective cycloaddition of (**1**) with the γ,δ-double bond of a dienone was ef-



(4)

R = H, Me

fected by $AlCl_3$ catalysis in 37% yield (eq 5).[9] The cycloadduct formally arising from approach of butadiene *syn* to the enone ring predominated initially, and was shown to isomerize to the more stable *anti* product under the reaction conditions. Contrasteric facial selectivity was observed in the Lewis acid-catalyzed cycloaddition of (**1**) with γ-alkoxycycloalkenones (eq 6).[10] When $n = 1$, cycloaddition at rt in the presence of catalytic $AlCl_3$ afforded predominately the *syn* cycloadduct (76%; 13:1 *syn/anti*). Under similar reaction conditions with $n = 2$, the *syn* cycloadduct was also the major product (10:1 *syn/anti*). The divergence of these results with those obtained with γ-alkylcycloalkenones was discussed, and a tentative theoretical model was proposed to account for the *syn* selectivity.



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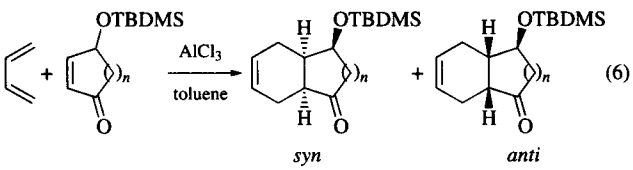
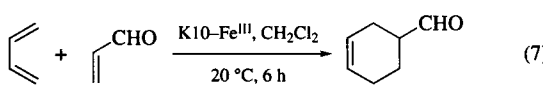


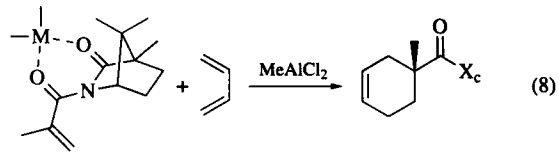
(6)

Montmorillonite K10 exchanged with Fe^{III} has been reported to catalyze the Diels–Alder reaction of butadiene with acrolein (eq 7).[11] Cycloaddition occurs at rt in high yield in the presence of 1.8 g catalyst per 15 mmol cycloaddition partners. Other dienes reacted with equal facility with acrolein under these conditions.



(7)

Asymmetric Diels–Alder Reactions. Cycloaddition of (**1**) with a methacrylate dienophile using a camphor lactam imide in the presence of Lewis acid affords the cyclohexenecarboxylate cycloadduct in 61% yield with 85:15 π-facial selectivity.[12] Presumably the steric bulky of the coordinated metal forces the methacrylate to adopt an *s-trans* conformation as shown (eq 8), and cycloaddition occurs from the less crowded bottom face of the complex. A pyrrolidin-2-one auxiliary containing the bulky 5-(trityloxymethyl) group was effective at asymmetric induction in the Lewis acid-catalyzed cycloaddition of (**1**) with a fumarate dienophile (eq 9).[13] The cyclohexenedicarboxylate was obtained in 52% yield and 96% de. Other dienophiles and Lewis acids were examined and found to be equally effective, giving high *endo* selectivity (≥97:3) and excellent diastereoselectivity (≥94% de).



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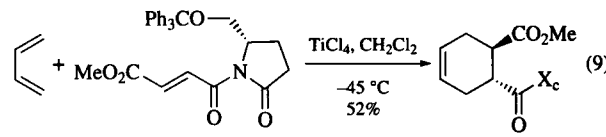
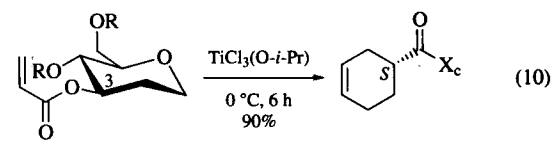


(9)

Carbohydrate-based chiral auxiliaries have proven effective in cycloadditions with (**1**).[14] The auxiliary derived from 3-*O*-acryloyldihydro-D-glucal (eq 10; R = pivaloyl) afforded the (*S*)-cyclohexenecarboxylate (8:92 *R/S*), whereas the pseudoenantiomeric system, 3-*O*-acryloyldihydro-L-rhamnal (eq 11; R = pivaloyl), afforded the (*R*)-cycloadduct (95:5 *R/S*). Complexation of the titanium catalyst to each of the ester carbonyl oxygens was postulated to rigidify the acryloyl group, locking it in the conformation depicted. In both cases, cycloaddition presumably occurs to the less hindered face of the acrylate away from the bulky 4-*O*-pivaloyl group.



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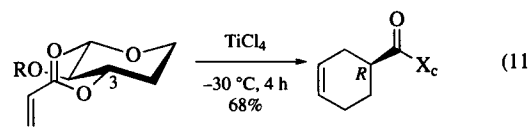
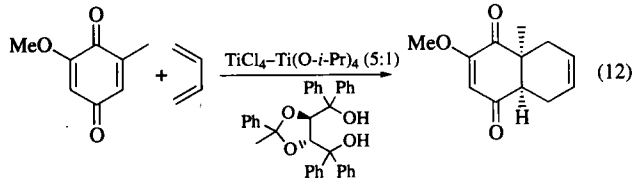


(11)

Chiral titanium-based catalysts have been used in asymmetric Diels–Alder reactions of (**1**). A mixture of $TiCl_4$ and ***Titanium Tetraisopropoxide*** was used with a tartrate-derived auxiliary in the cycloaddition of (**1**) with a quinone (eq 12) to afford the expected bicyclic system in 88% yield and 63% ee.[15] Other dienes underwent stereoselective cycloadditions with better asymmetric induction. A similar catalyst system was used in the cycloaddition of (**1**) with fumarate[16] and acrylate[17] derivatives. The catalyst was prepared by alkoxy exchange with the tartrate-derived auxiliary and ***Dichlorotitanium Diisopropoxide***, and was treated with the cycloaddition partners at rt for 24 h to afford the cyclohexenecarboxylate in 81% yield and in 93% optical purity (eq 13). Other dienes underwent asymmetric cycloaddition with equal success. A model was proposed for the catalyst–dienophile complex.

The C_2-symmetric hydrobenzoin complexed with $TiCl_4$ promoted the cycloaddition of (**1**) with ***Dimethyl Fumarate*** to afford the cyclohexenedicarboxylate in 78% yield with a modest 60% ee (eq 14).[18] Carboxylic ester dienophiles have typically participated ineffectively in asymmetric Diels–Alder reactions.



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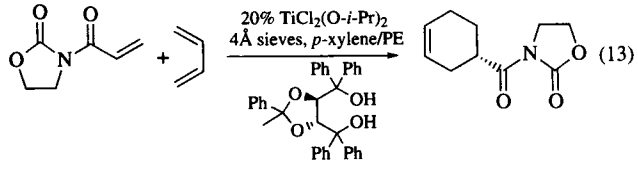

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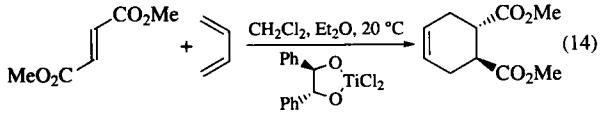
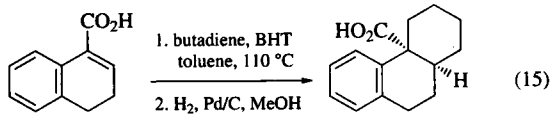


(14)

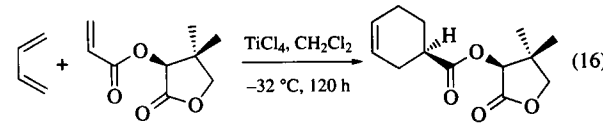
Applications in Synthesis. Butadiene is a widely used reagent in organic synthesis. It is primarily used as the 4π participant in the Diels–Alder construction of carbocyclic and heterocyclic six-membered rings,[2] although numerous other uses have been recorded.

Butadiene cycloaddition was a key step in the synthesis of constrained phenanthrenamine derivatives that are active as noncompetitive NMDA antagonists.[19] Reaction of dihydronaphthalenecarboxylic acid with (**1**) in toluene at 110 °C in the presence of polymerization inhibitor afforded the tricyclic adduct in 60% yield (eq 15). Hydrogenation of the resulting double bond afforded the hydrophenanthrenecarboxylic acid, which was converted to a variety of tetracyclic structures where the carboxylate was converted to an amine by modified Curtius rearrangement.



(15)

Three reports have described the use of butadiene in the asymmetric construction of the C-28–C-34 fragment of the immunosuppressant FK-506.[20–22] In the first report (eq 16), the acrylate ester of (*S*)-(+)-pantolactone was reacted with (**1**) in the presence of $TiCl_4$ to afford the cyclohexenecarboxylate in excellent yield and in 91% de.[20] In the second report, the same Diels–Alder reaction was performed with a chiral sultam auxiliary under $EtAlCl_2$ catalysis to give the cyclohexenecarboxylate in 86% yield in 93% ee (eq 17).[21] In the third report, an acryloyl-(*S*)-2-hydroxysuccinimide underwent cycloaddition with (**1**) under catalysis by $TiCl_4$ to afford the cyclohexenecarboxylate in 85% yield in 98% ee (eq 18).[22] The double bond of all three cycloadducts was subsequently converted to the *anti*-diol of FK-506. A cycloaddition reaction identical to that shown in eq 16 was used as a key step in the asymmetric synthesis of the cyclohexane ring of (+)-phyllanthocin.[23] In this instance the cycloaddition proceeded in 70% yield and in 97% ee.



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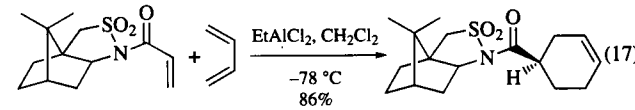

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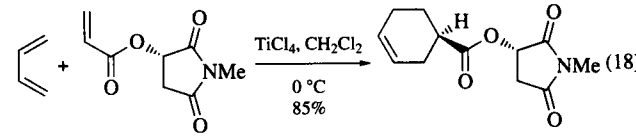
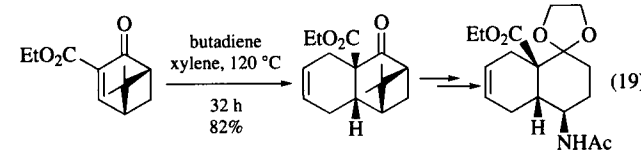


(18)

A β-pinene-derived dienophile was used as the 2π cycloaddition partner with (**1**) in an approach to the morphine skeleton (eq 19).[24] Thermal cycloaddition occurred stereoselectively from the face opposite the substituted bridge to afford the adduct in 82% yield. Cycloaddition was also effected in lower yield under Lewis acid-catalyzed conditions ($Cu(BF_4)_2$, CH_2Cl_2, 25 °C, 12 h, 34%). Further elaboration of the cycloadduct afforded the *cis*-Δ^6-1-octalone acetal possessing the required absolute configuration at three contiguous stereogenic centers for conversion to morphine-related compounds. In a synthetic approach to analogs of the potassium channel activator aprikalim, butadiene was used in a hetero Diels–Alder reaction for the construction of a thiopyran ring (eq 20).[25] Thus reaction of the thiocarbonyl group of an α-thioketo ester (generated in situ) with (**1**) afforded the desired thiopyran in 65% yield.



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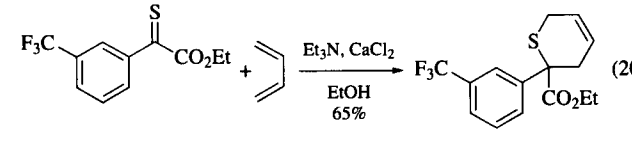
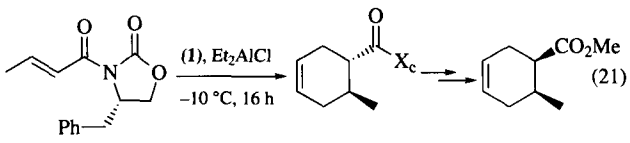


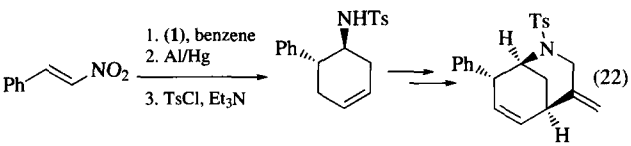
(20)

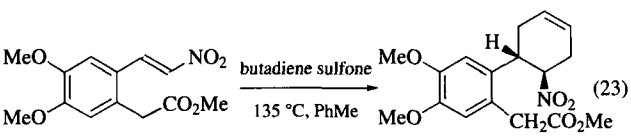
An asymmetric Diels–Alder reaction of (**1**) with a phenylalaninol-derived auxiliary was used to construct the B-ring of (+)-compactin and (+)-mevinolin (eq 21).[26] Cycloaddition of the (*E*)-crotonic acid derivative with butadiene in the presence of catalytic Et_2AlCl afforded the desired cycloadduct in 56% yield and greater than 95% de. The auxiliary was removed and the desired *cis*-isomer of the 2-methyl-4-cyclohexenecarboxylate was obtained by base-promoted epimerization of the *trans*-isomer (65:35 *cis/trans* equilibrium mixture). Use of the corresponding (*Z*)-crotonoyl auxiliary was not examined as the (*Z*) configuration of the alkene is not preserved under the reaction conditions.[27]

A rapid and stereospecific construction of the 2-azabicyclo[3.3.1]nonane ring system characteristic of *Strychnos* alkaloids was initiated with a Diels–Alder reaction of β-nitrostyrene and (**1**) (eq 22).[28] After reduction of the nitro group and

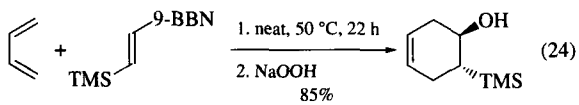


N-acylation, the desired aminocyclohexene was obtained in 63% overall yield. Subsequent elaboration to the 2-azabicyclo[3.3.1]nonane system involved a high-yielding stereoselective Heck reaction. Butadiene sulfone was used for in situ generation of (**1**) in an approach to cephalotaxine analogs. In a key step, a β-nitrostyrene dienophile was treated with butadiene sulfone at 135 °C to afford the butadiene cycloadduct in 74% yield (eq 23).[29]

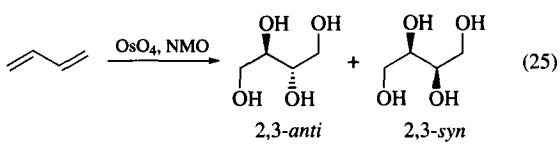




Miscellaneous Reactions. The novel dienophile 2-trimethylsilylvinyl-9-BBN was shown to undergo facile Diels–Alder reaction with butadiene to afford the 2-trimethylsilylcyclohexenol in 85% yield after oxidation of the intermediate trialkylborane (eq 24).[30] The cycloadduct was shown to be a precursor to 5-trimethylsilyl-1,3-cyclohexadiene and -1,4-cyclohexadiene, thus making the dienophile an acetylene equivalent.



Catalytic osmylation was used to convert 1,3-butadiene to a polyol with good control of relative stereochemistry (eq 25).[31] Under standard osmylation conditions, (**1**) was converted to the 2,3-*anti*-tetraol in 80% yield in a 5:1 *anti/syn* ratio. The stereoselectivity of this reaction is consistent with previous findings on the osmylation of allylic alcohols and ethers.



1. Stevens, M. P. *Polymer Chemistry*; Oxford University Press: New York, 1990.
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23. Trost, B. M.; Kondo, Y. *TL* **1991**, *32*, 1613.
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31. Park, C. Y.; Kim, B. M.; Sharpless, K. B. *TL* **1991**, *32*, 1003.

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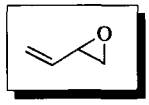
1,3-Butadiene Monoxide



[930-22-3] C_4H_6O (MW 70.09)

(ambident electrophile)

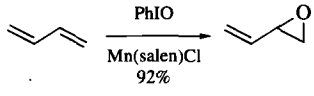
Alternate Names: 3,4-epoxy-1-butene; butadiene epoxide; vinyl epoxide; vinyloxirane.

Physical Data: bp 70 °C; *d* 0.9006 g cm^{-3}.

Solubility: sol most organic solvents.

Form Supplied in: clear liquid.

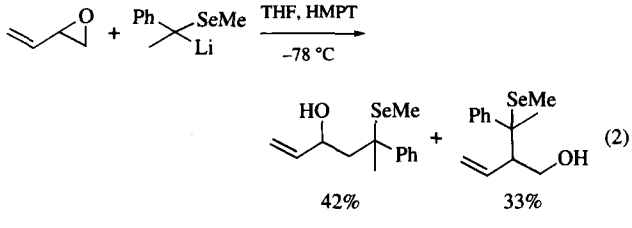
Preparative Method: few attempts have been reported to epoxidize conjugated dienes. Recently, a manganese catalyst was employed in a method developed to epoxidize butadiene selectively in one step (eq 1).[1]



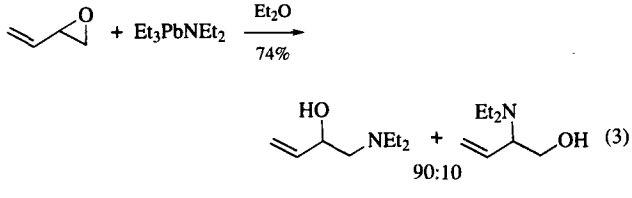
(1)

Handling, Storage, and Precautions: the flammable liquid, flash point −50 °C, is a possible carcinogen and should be used in a fume hood.

Nucleophilic Opening at C(1). Butadiene monoxide is a versatile four-carbon synthon in organic synthesis.[2] With the careful choice of reagents one can selectively react nucleophiles at three sites on the carbon backbone. α-Selenobenzyllithiums react at the C(1) position and the resulting intermediates have been transformed into cyclopropanes (eq 2).[3] Aminolead reagents displayed even greater selectivity for attack at the C(1) position (eq 3).[4]

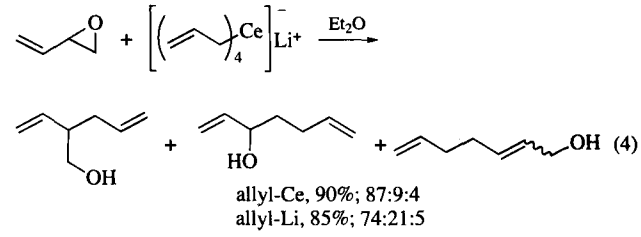


(2)

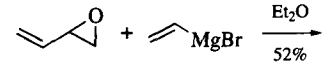


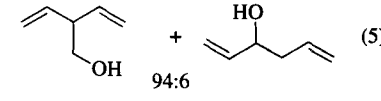
(3)

Nucleophilic Opening at C(2). In Et_2O, allylcerium reagents were found to be more regioselective in additions to the 2-position of butadiene monoxide than allyllithium reagents (eq 4).[5] In THF the yields and product ratios were comparable. ***Vinylmagnesium Bromide*** also adds selectively at the 2-position provided 2–3 equiv of the Grignard reagent are employed (eq 5).[6]



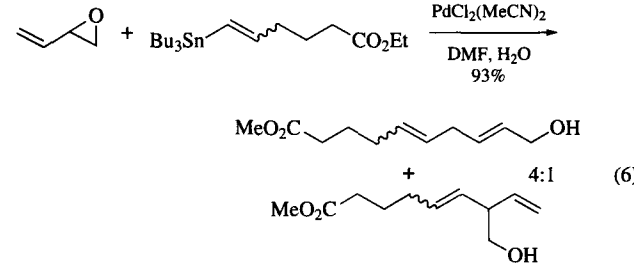
(4)



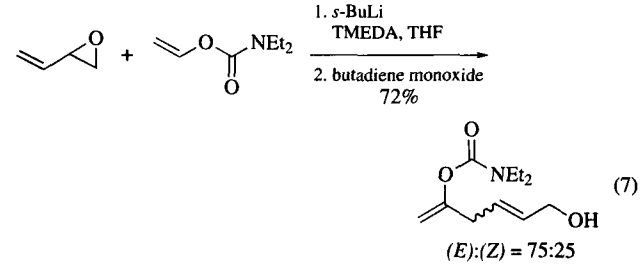


(5)

Nucleophilic Opening at C(4). The S_N2' reaction of organocopper reagents with vinyloxiranes has recently been reviewed.[7] A number of S_N2' reactions with butadiene monoxide have been facilitated by a palladium catalyst.[8] A recent example is found in the synthesis of a linear diene alcohol that was further converted into a cyclopropane-containing eicosanoid of marine origin (eq 6).[9] Under standard metalation conditions enol carbamates are readily lithiated, and these acyl anion equivalents also react selectively at the C(4) position without a catalyst (eq 7).[10]

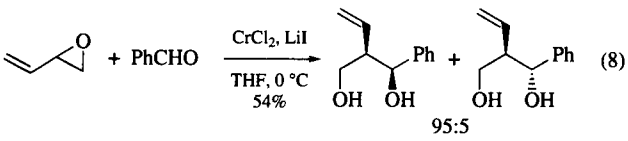


(6)



(7)

Functionalization at C(2). The proton at the 2-position of butadiene monoxide can be selectively deprotonated with ***t-Butyllithium–N,N,N′,N′-Tetramethylethylenediamine*** and silylated with ***Chlorotrimethylsilane***.[11] A similar and perhaps more useful reaction involves the reductive metalation of epoxides by various metals.[12] Employing ***Chromium(II) Chloride***, the 2-position of butadiene monoxide can be functionalized with reasonable selectivity (eq 8).[12a]



Related Reagents. Ethylene Oxide; Isoprene Epoxide; Propylene Oxide.

1. Thomsen, D. S.; Schiott, B.; Jorgensen, K. A. *CC* **1992**, 1072.
2. (a) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989; p 520. (b) Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *T* **1983**, *39*, 2323.
3. (a) Krief, A.; Hobe, M. *SL* **1992**, 317. (b) Williams, K.; Thompson, C. M. *SC* **1992**, *22*, 239. (c) Oppolzer, W.; Gaudin, J.-M.; Bedoya-Zurita, M.; Hueso-Rodriguez, J.; Raynham, T. M.; Robyr, C. *TL* **1988**, *29*, 4709.
4. Yamada, J.; Yumoto, M.; Yamamoto, Y. *TL* **1989**, *30*, 4255.
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6. Yamaguchi, R., Hamasaki, T.; Sasaki, T.; Ohta, T.; Utimoto, K.; Kozima, S.; Takaya, H. *JOC* **1993**, *58*, 1136.
7. Marshall, J. A. *CRV* **1989**, *89*, 1503.
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9. White, J. D.; Jensen, M. S. *JACS* **1993**, *115*, 2970.
10. Sengupta, S.; Snieckus, V. J. *JOC* **1990**, *55*, 5680.
11. Eisch, J. J.; Galle, J. E. *JOC* **1990**, *55*, 4835.
12. (a) Fujimura, O.; Takai, K.; Utimoto, K. *JOC* **1990**, *55*, 1705. (b) Cohen, T.; Jeong, I-H.; Mudryk, B.; Bhupathy, M.; Awad, M. M. A. *JOC* **1990**, *55*, 1528.

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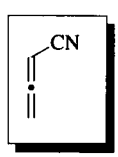
2,3-Butadienenitrile

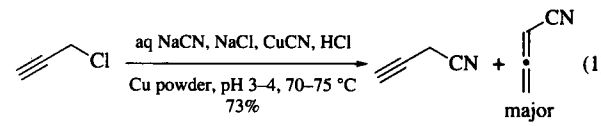


[1001-56-5] C_4H_3N (MW 65.07)

(reactive in transformations involving nucleophilic conjugate addition,[1] radical addition,[2] and dipolar addition, especially with nitrones[3])

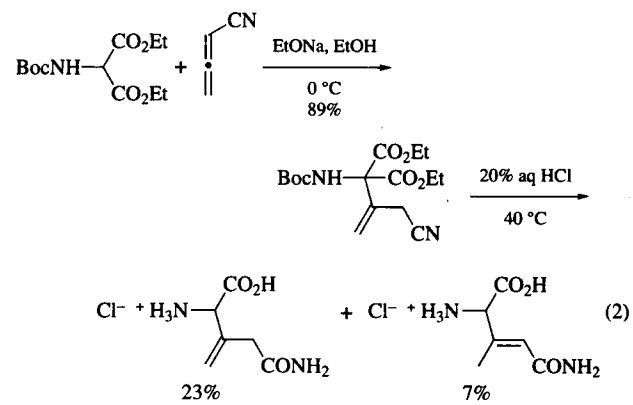
Alternate Names: allenecarbonitrile; cyanoallene; cyanopropadiene.
Physical Data: bp 50–51.5 °C/50 mmHg.
Solubility: sol EtOH, THF, toluene, chloroform, benzene.
Analysis of Reagent Purity: IR 1970, 2230 cm^{-1}.

Preparative Methods: this reagent is not commercially available, but at least two preparative methods have been reported. One proceeds through a Wittig reaction between cyanomethylidenetriphenylphosphorane and ketene.[4] However, the procedure to be recommended involves the formation of 3-butynenitrile and its isomerization in situ to 2,3-butadienenitrile (eq 1).[5] The indicated product mixture can be produced on a scale near 100 g, and its fractional distillation affords pure 2,3-butadienenitrile.

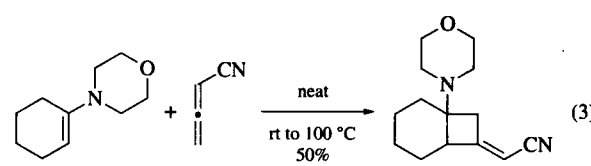


Purification: vacuum distillation.
Handling, Storage, and Precautions: this reagent has been reported[6] to cause severe allergic reactions in some individuals. Handling with double, heavy-duty rubber gloves is recommended. This reagent should only be handled in a fume hood.

Procedures Involving Nucleophilic Conjugate Addition to 2,3-Butadienenitrile. Transformations in which this reagent behaves as a conjugate addition electrophile are well known. For example, eq 2[1] shows an unsaturated amino acid synthesis based on this concept.

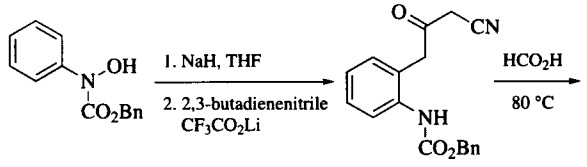


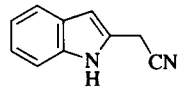
A similar process underlies the [2 + 2] cycloaddition between 2,3-butadienenitrile and cyclohexanone morpholine enamine (eq 3).[7]



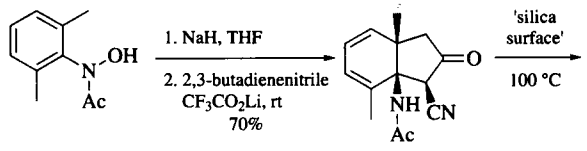
A more sophisticated exploitation of this chemistry is incorporated in the procedure[8] for alkylation *ortho* to aromatic amino nitrogen (eq 4). This protocol delivers an intermediate cyano ketone through nucleophilic addition of the hydroxamate anion to 2,3-butadienenitrile and subsequent [3,3]-sigmatropic rearrangement and tautomerization. ***Formic Acid*** treatment of the cyano

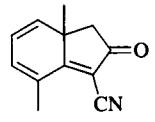
ketone then produces the 2-substituted indole. Likewise, a mechanistically related sequence carried out on a substrate incapable of tautomerization and rearomatization delivers carbocyclic products (eq 5).[9]




(4)

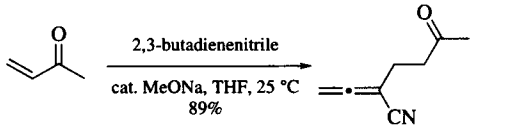
65% overall




(5)

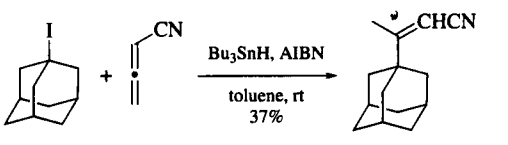
quantitative

2,3-Butadienenitrile can also function in a formal sense as the nucleophilic component in the conjugate addition to ***Methyl Vinyl Ketone*** depicted in eq 6.[10] However, this transformation also occurs by way of conjugate addition of methoxide to this reagent, followed by reaction of the derived allylic nitrile anion with methyl vinyl ketone and base-induced ejection of methoxide to deliver the observed product.



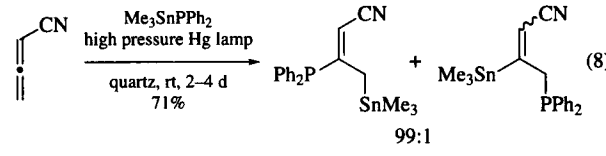
(6)

Transformations Involving Radical Addition to 2,3-Butadienenitrile. Several transformations in which radicals add to 2,3-butadienenitrile have been reported. For example, 1-adamantyl engages the central carbon in the reagent to provide a modest yield of the corresponding 2-substituted 2-butenenitrile (eq 7).[2] Related reactions are shown in eqs 8[11] and eq 9.[6]

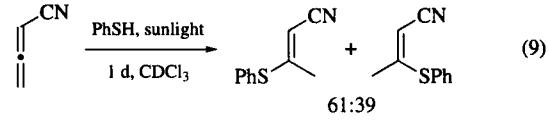


(7)

Dipolar Additions of Nitrones to 2,3-Butadienenitrile. Eq 3 formally constitutes a cycloadditive process involving this reagent. However, among cycloadditions involving 2,3-

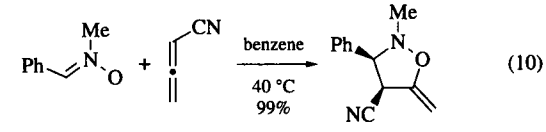


(8)

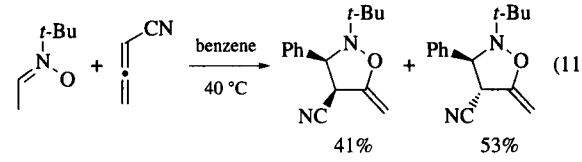


(9)

butadienenitrile, dipolar additions of nitrones are the most commonly encountered (eqs 10 and 11).[3] When the nitrone carries a sterically demanding group on the nitrogen, *cis* stereoselectivity is eroded (eq 11).

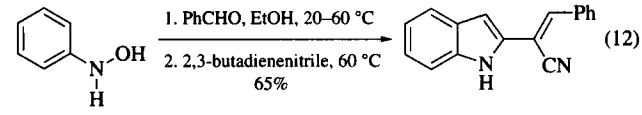


(10)



(11)

A transformation reminiscent of eq 4 is illustrated in eq 12.[12] Formation of the nitrone occurs in situ, and initiates a sequence involving dipolar addition, [3,3]-sigmatropic rearrangement, and further transformation into the 2-vinylindole indicated through a one-pot procedure.



(12)

Related Reagents. Allene; Propynenitrile.

1. Paik, Y. H.; Dowd, P. *JOC* **1986**, *51*, 2910.
2. Ohno, M.; Ishizaki, K.; Eguchi, S. *JOC* **1988**, *53*, 1285.
3. Padwa, A.; Kline, D. N.; Koehler, K. F.; Matzinger, M.; Venkatramanan, M. K. *JOC* **1987**, *52*, 3909.
4. Hamlet, Z.; Barker, W. D. *S* **1970**, 543.
5. Kurtz, P.; Gold, H.; Disselnkötter, H. *LA* **1959**, *624*, 1.
6. Pasto, D. J.; L'Hermine, G. *JOC* **1990**, *55*, 685.
7. (a) Baldwin, J. E.; Fleming, R. H.; Simmons, D. M. *JOC* **1972**, *37*, 3963. (b) For an experimental procedure but an incorrect assignment of the product structure, see: Reid, W.; Käppeler, W. *LA* **1965**, *687*, 183.
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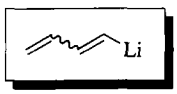
1,3-Butadienyl-1-lithium



[4843-71-4] C_4H_5Li (MW 60.02)
(E)
[91892-10-3]

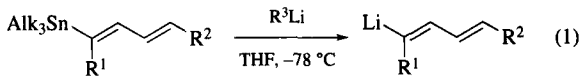
(reagent for single-step introduction of the 1,3-butadienyl group)

Solubility: sol THF and ether.

Preparative Method: (*E*)-1,3-butadienyl-1-lithium was generated from (*E*)-butadienyltributylstannane and BuLi in hexane at –78 °C for 15 min.[1] Concentration of the reagent solution can be determined by titration.[2]

Handling, Storage, and Precautions: the reagent is moisture- and air-sensitive. All solvents must be dried before use.

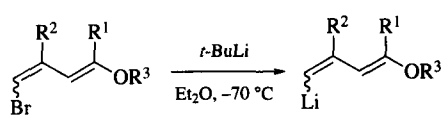
1,3-Butadienyl-1-lithium Reagents. A common approach for the preparation of the 1,3-butadienyl-1-lithium reagents is transmetalation of butadienyltrialkylstannanes with ***Methyllithium***[3] or ***n-Butyllithium***.[1,3–7] Rapid transmetalation proceeds with complete retention of diene configuration (eq 1). The butadienylstannanes are commonly prepared by hydrostannylation of alkynes,[3–5] or addition of (phenylthio)(trimethylstannyl)cuprate to alkynes.[3]



(1)

$R^1 = R^2 = H$; $R^1 = Me$, $R^2 = H$; $R^1 = H$, $R^2 = OEt$; $R^3 = Me$, Bu

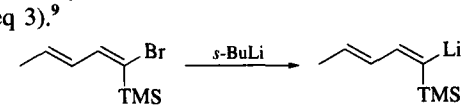
A convenient method for the preparation of 4-alkoxy-[8a] and 4-silyloxy-1,3-butadienyl-1-lithium[8] derivatives is bromine–lithium exchange with ***t-Butyllithium*** (eq 2).



(2)

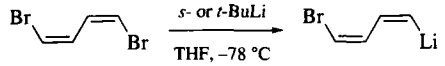
R^1 = H, Me; R^2 = H, Me; R^3 = Et, $SiMe_3$

Metal–halogen exchange between equimolar quantities of (*E,E*)-1-bromo-1-(trimethylsilyl)penta-1,3-diene and ***s-Butyllithium*** (THF–cyclohexane, –78 °C, 30 min) affords lithiated species (eq 3).[9]



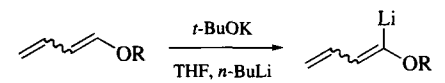
(3)

Exchange of one bromine atom in unstable 1,4-dibromobutadiene occurs with *s*-BuLi (1 equiv) or *t*-BuLi (2 equiv) (eq 4), whereas the use of *n*-BuLi favors polymer formation.[10] Both bromine atoms are exchanged with an excess of *t*-BuLi (4 equiv).

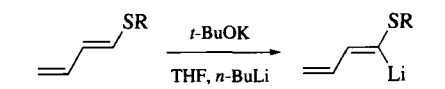


(4)

1,3-Dienyl ethers are readily lithiated at C-1 using *t*-BuLi (R = Me),[11a] *s*-BuLi (R = MOM),[11b] or *n*-BuLi and ***Potassium t-Butoxide*** in THF (R = Me, Ph; diene:*t*-BuOK:*n*-BuLi ratio is 1:1.04:1.10).[11c] The butadienyl-1-potassium formed first is subsequently transmetalated. The metalation of ethers and (*E*)-dienylic sulfides occurs with retention of configuration (eqs 5 and 6), while in the case of (*Z*)-dienylic sulfides the structure of the products depends on both reaction conditions and the *S*-alkyl substituent: higher temperatures and more bulky thioalkyl groups promote inversion of configuration (eq 7).[11c]

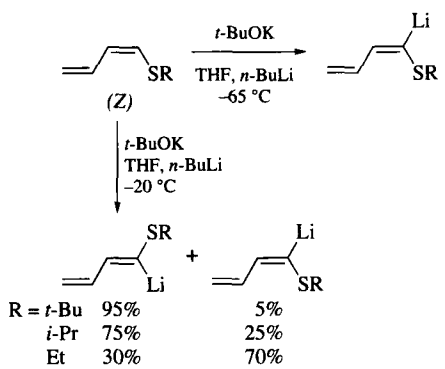


(5)



(6)

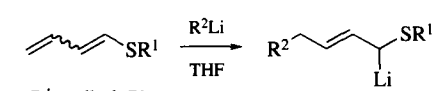
R = alkyl, Ph



(7)

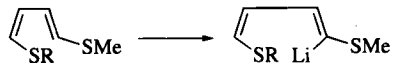
R = *t*-Bu	95%	5%
i-Pr	75%	25%
Et	30%	70%

Higher temperatures also promote side reactions (1,4-addition of BuLi) and tar production. Treatment of butadienyl monosulfides with alkyllithium (*n*-, *s*- or *t*-Bu) reagents in THF in the absence of *t*-BuOK gives insignificant metalation even in the presence of TMEDA (***N,N,N',N'-Tetramethylethylenediamine***). The main reaction is 1,4-addition of R^2Li to the conjugated diene (eq 8). On the other hand, 1,4-bis(methylthio)buta-1,3-dienes are monolithiated with *n*-BuLi in THF–TMEDA mixtures at low temperature.[12] When (1*Z*,3*E*)-bis-sulfides are used, lithium is introduced exclusively at the (*E*) double bond (eq 9).



(8)

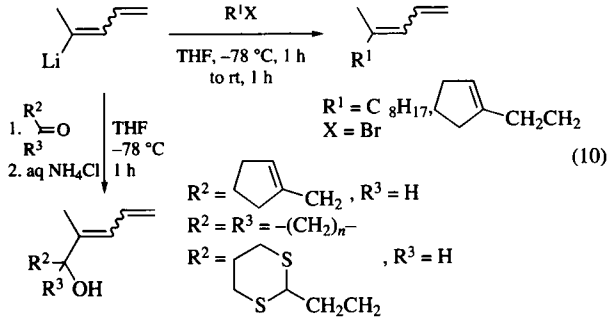
R^1 = alkyl, Ph



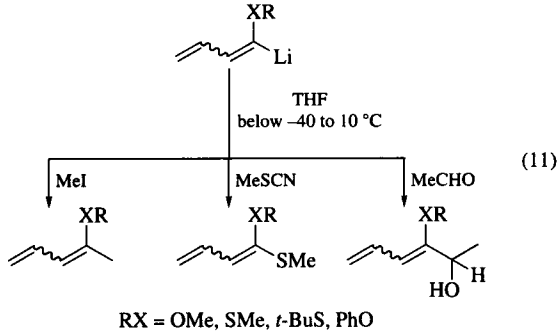
(9)

R = alkyl, Ph

Reactions of 1,3-Butadienyl-1-lithium Reagents. The 1,3-butadienyl-1-lithium reagents (4-lithio-1,3-pentadiene,[3,13] 1-alkoxy-,[11] and 1-alkylthio-1,3-butadienyl-1-lithium[11c]) react smoothly with a variety of electrophiles (halides, methyl thiocyanate, aldehydes, and ketones) and produce the corresponding substituted dienes (eqs 10 and 11).



(10)

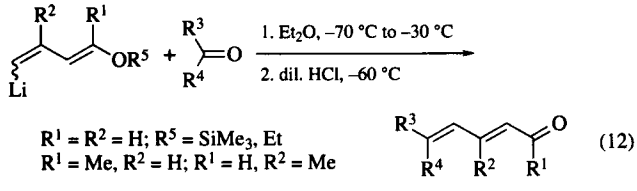


(11)

RX = OMe, SMe, *t*-BuS, PhO

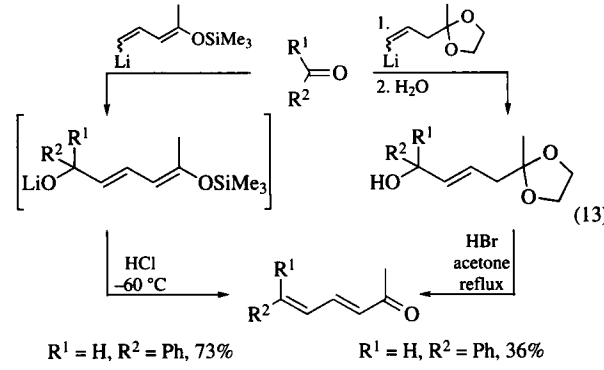
Electrophilic substitution at the lithiated carbon proceeds with retention of configuration. Yields of the substituted dienes are as high as 90% for methylation and 60–75% for alkylation with higher alkyl halides and carbonyl compounds.

Lithiobutadienyl alkyl and silyl ethers are suitable intermediates in the synthesis of polyethylenic aldehydes and ketones (eq 12). These are important building blocks in natural product synthesis (polyene and macrolide antibiotics and terpenes). Starting from (*E*)-lithiated ethers and aldehydes or ketones, exclusively (*E*)-isomers are obtained.[7,8] An exception is benzophenone, which gives some loss of stereochemistry.[8b] Yields of the dienols (dieno ketones) are 70–90%.



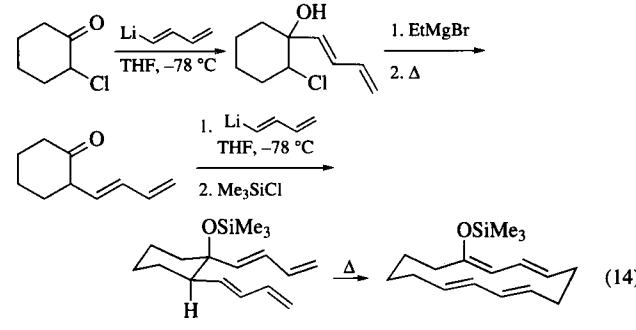
(12)

The condensation of lithiated dienol ethers with conjugated carbonyl compounds and the hydrolysis of the intermediate adduct leads in one pot to polyconjugated ketones. Use of the lithiated dienol ether is recommended over that of the lithiodioxolane (eq 13).[8a]



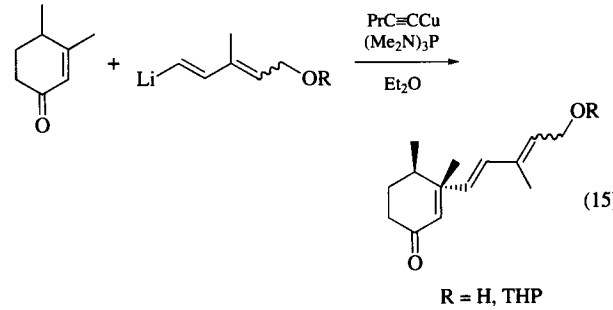
(13)

Reaction of 1,3-butadienyl-1-lithium with chloro ketones is used for the sequential introduction of two neighboring 1,3-butadienyl groups on a cyclohexane ring (eq 14).[4,6] The silylated product undergoes thermal [5,5]-sigmatropic rearrangement to form a macrocyclic enol ether, giving cyclotetradecatrienone after hydrolysis.[1]



(14)

A mixed cuprate derived from a lithiodiene and *n*-PrC≡CCu in ether–$(Me_2N)_3P$ reacted with an unsaturated ketone to yield the 1,4-addition product (eq 15).[5]

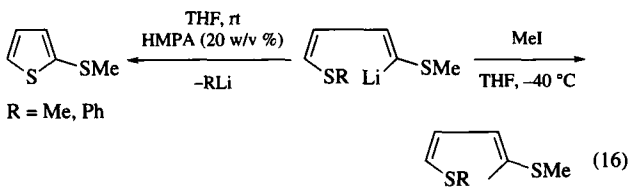


(15)

R = H, THP

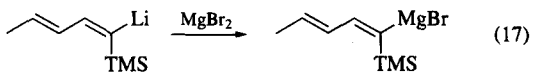
Lithiated 1,3-butadienyl 1,4-disulfides can be alkylated or cyclized to form thiophenes, depending on reaction conditions (eq 16).[12]

1,3-Butadienyllithium derivatives are suitable intermediates for transmetalation reactions (eqs 17 and 18). The 1-trimethylsilyl-1,3-pentadienyl-1-lithium is transmetalated to the corresponding magnesium derivative by interaction with freshly prepared ***Magnesium Bromide*** (obtained from the reaction of

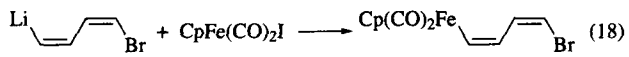


(16)

Mg with $BrCH_2CH_2Br$ in 3:1 ether–benzene solvent).[9] The reaction of cyclopentadienyldicarbonyliron iodide with 4-bromobutadienyl-1-lithium proceeds with the retention of configuration.[10]



(17)



(18)

Related Reagents. 1,3-Butadienyl-2-lithium; 1,3-Butadienyl-2-magnesium Chloride; 1,3-Butadienyl-1-magnesium Chloride.

1. Angoh, A. G.; Clive, D. L. *CC* **1984**, 534.
2. Watson, S. C.; Eastham, J. F. *JOM* **1967**, *9*, 165.
3. Piers, E.; Morton, H. E. *JOC* **1980**, *45*, 4263.
4. Wender, P. A.; Sieburth, S. McN.; Petraitis, J. J.; Singh, S. K. *T* **1981**, *37*, 3967.
5. Mori, K.; Fujioka, T. *TL* **1982**, *23*, 5443.
6. Wender, P. A.; Sieburth, S. McN. *TL* **1981**, *22*, 2471.
7. Wollenberg, R. H. *TL* **1978**, 717.
8. (a) Duhamel, L.; Ancel, J.-E. *T* **1992**, *48*, 9237. (b) Contreras, B.; Duhamel, L.; Ple, G. *SC* **1990**, *20*, 2983.
9. Wrobel, J. E.; Ganem, B. *JOC* **1983**, *48*, 3761.
10. Ferede, R.; Noble, M.; Cordes, A. W.; Allison, N. T.; Lay, J., Jr. *JOM* **1988**, *339*, 1.
11. (a) Soderquist, J. A.; Hassner, A. *JACS* **1980**, *102*, 1577. (b) McDougal, P. G.; Rico, J. G. *JOC* **1987**, *52*, 4817. (c) Everhardus, R. H.; Gräfing, R.; Brandsma, L. *RTC* **1978**, *97*, 69.
12. Everhardus, R. H.; Eeuwhorst, H. G.; Brandsma, L. *CC* **1977**, 801.
13. Burke, S. D.; Powner, T. H.; Kageyama, M. *TL* **1983**, *24*, 4529.

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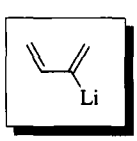
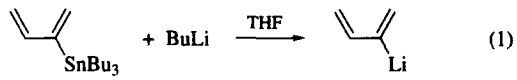
1,3-Butadienyl-2-lithium



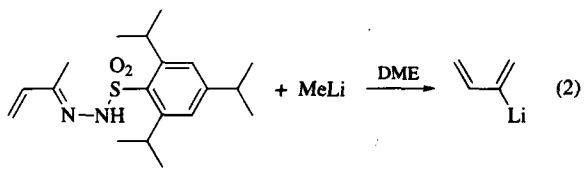
[84531-04-4] C_4H_5Li (MW 60.02)

(reagent for carbon–carbon bond forming reactions with carbonyls[1,2] and α,β-alkenyl esters[3,4])

Preparative Methods: 1,3-butadienyl-2-lithium is synthesized by transmetalation of 1,2-butadienyl-2-tributyltin (eq 1)[1] or by the Shapiro reaction of 2,4,6-$(i\text{-}Pr)_3C_6H_2SO_2NHN{=}CMeCH{=}CH_2$ with ***Methyllithium*** (eq 2).[2] 3-Methyl-1,3-butadienyl-2-lithium has been prepared by lithium–bromine exchange.[5].



(1)

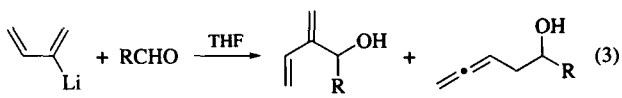


(2)

Analysis of Reagent Purity: 1,3-butadienyl-2-lithium is synthesized and used direclty without further isolation or purification.

Handling, Storage, and Precautions: use in a fume hood.

Reaction with Aldehydes and Ketones. 1,3-Butadienyl-2-lithium reacts with aldehydes and ketones. Dienyl carbinols are generally obtained as major products, along with small amounts of allenyl carbinols (eq 3). Compared with ***1,3-Butadienyl-2-magnesium Chloride***, a stronger preference for dienyl products is observed (Table 1).[1]



(3)

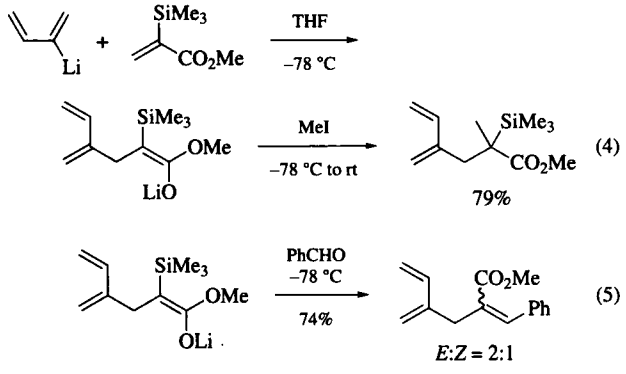
Table 1 Reaction of 1,3-Butadienyl-2-lithium with Carbonyl Compounds

Carbonyl compound	Yield and selectivity (%) (diene/allene)	Selectivity by 1,3-butadienyl-2-magnesium chloride (diene/allene)
PhCHO	80 (91:9)	39:61
$Me(CH_2)_5CHO$	61 (100:0)	–
PhCH=CHCHO	76 (19:1)	7:9
PhCOMe	70 (9:1)	19:81
PhCOPh	73 (1:1)	0:100

1,3-Butadienyl-2-lithium undergoes Michael addition to α,β-alkenyl esters. The reaction with methyl 2-(trimethylsilyl)propenoate affords the corresponding lithium enolate, which upon alkylation yields a series of α-silyl esters (eq 4).[3]

Treatment of the Michael adduct with an aldehyde followed by Peterson alkenation furnishes the dienyl α,β-alkenyl ester (eq 5).[4] Stereoselectivities of the products vary with the substrate (*E*/*Z* = ca. 3:1 to *Z* only).[4]

Substituted 2-lithiobutadienes which have been prepared include 3-methyl-,[5] 3-trimethylstannyl-,[6] 3-trimethylsilyl-,[6] 3-hexyl-,[6] and 4-methoxy-1,3-butadienes.[7]



Related Reagents. 1,3-Butadienyl-1-lithium; 1,3-Butadienyl-1-magnesium Chloride; 1,3-Butadienyl-2-magnesium Chloride.

1. Wada, E.; Kanemasa, S.; Fujiwara, I.; Tsuge, O. *BCJ* **1985**, *58*, 1942.
2. (a) Brown, P. A.; Jenkins, P. R. *TL* **1982**, *23*, 3733. (b) *JCS(P1)* **1986**, 1129.
3. Tanaka, J.; Kanemasa, S.; Ninomiya, Y.; Tsuge, O. *BCJ* **1990**, *63*, 476.
4. (a) Tsuge, O.; Kanemasa, S.; Ninomiya, Y. *CL* **1984**, 1993. (b) Tanaka, J.; Kanemasa, S.; Ninomiya, Y.; Tsug, O. *BCJ* **1990**, *63*, 466.
5. Shea, K. J.; Sakata, S. T. *TL* **1992**, *33*, 4261.
6. Reich, H. J.; Reich, I. L.; Yelm, K. E.; Holladay, J. E.; Gschneidner, D. *JACS* **1993**, *115*, 6625.
7. Schreiber, S. L.; Kiessling, L. L. *JACS* **1988**, *110*, 631.

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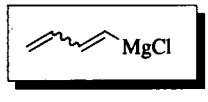
Toyama National College of Technology, Japan

1,3-Butadienyl-1-magnesium Chloride



[114073-55-1] C_4H_5ClMg (MW 112.84)
(E)
[112564-81-5]
(Z)
[112564-82-6]

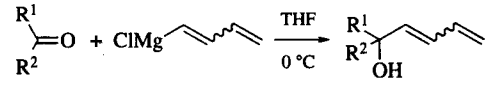
(reagent for single-step introduction of the terminal 1,3-butadienyl group to various organic skeletons)

Solubility: sol THF, dioxane, DMF, 1,2-diethoxyethane, diethylene glycol dimethyl or diethyl ether, as well as in combinations of these solvents with aliphatic (*n*-hexane, *n*-octane) or aromatic (benzene, xylene) hydrocarbons.[1]

Preparative Method:[2,3] a mixture of ***Magnesium*** (24 g, 1.0 mol) and zinc chloride (6.8 g, 0.05 mol) was dried at 130 °C for 2 h under vacuum. Dried THF (30 mL) and ***1,2-Dibromoethane*** (2.0 mL) were added and the mixture was stirred vigorously under an argon atmosphere. After the exothermic reaction had subsided, the reaction mixture was diluted by additional THF (350 mL), and then a solution of 1-chloro-1,3-butadiene (44 g, 0.5 mol) and 1,2-dibromoethane (4 mL) in THF (70 mL) was added dropwise over 1 h and the mixture was heated under reflux for 2 h. The concentration of the reagent solution is determined[4] by titration using 1,10-phenanthroline as indicator. The average yield of 1,3-butadienyl-1-magnesium chloride was about 70%.

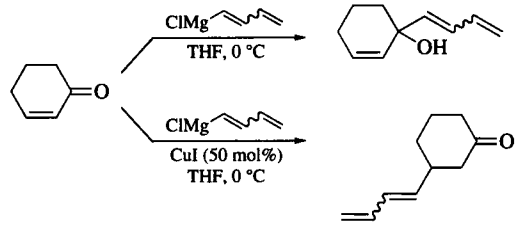
Handling, Storage, and Precautions: the reagent is moisture sensitive. Solvents must be carefully dried before use, and the preparation and reactions should be carried out under nitrogen or argon atmosphere.

Addition to Carbonyl Compounds. Treatment of ketones or aldehydes with 1,3-butadienyl-1-magnesium chloride after hydrolytic work-up gave excellent yields of alcohols containing the 1,3-butadienyl group: 80–98% for aldehydes and aliphatic and alicyclic ketones, and approximately 70% for aromatic ketones and enones (eq 1).[1–3] In these reactions the initial stereochemical (*E*)/(*Z*) ratio, of the 1,3-butadienyl group of the Grignard reagent was found to be retained in the reaction products.



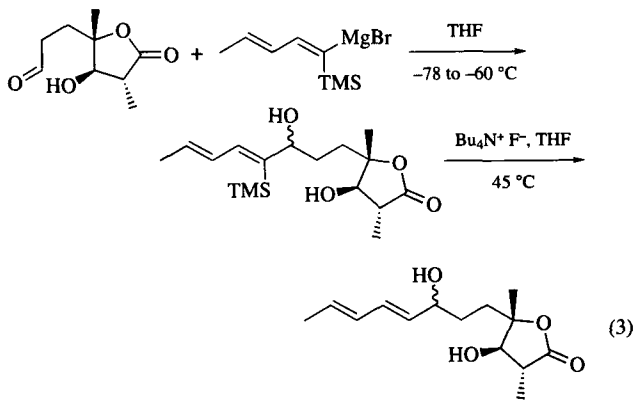
R^1 = H; R^2 = *n*-Hept, *i*-Pr, MeCH=CH–
R^1 = Me; R^2 = Et, Ph, Me
R^1, R^2 = $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_3-CH=CH-$

Butadienylmagnesium chloride usually reacts at the carbonyl group of conjugated ketones, whereas in the presence of ***Copper(I) Iodide*** (addition of 50 mol % CuI forms the butadienylmagnesium Cu^I complex), 1,4-addition is observed (eq 2).



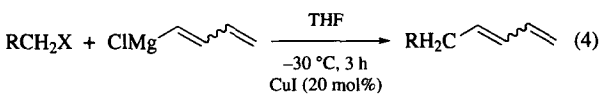
Grignard analogs of higher 1,3-dienes (penta-, hepta-, octa-)[1] or their silylated derivatives (e.g. (*E,E*)-1 bromo-1-(trimethylsilyl)penta-1,3-diene)[5] react with carbonyl compounds in a similar manner (eq 3).

For the introduction of the butadienyl moiety, Grignard reagents are preferred to the lithium derivatives due to the lower basicity of the former. The silylated pentadienyl Grignard reagent in eq 3 was superior to both the precursor lithium reagent and pentadienyllithium itself.[5]



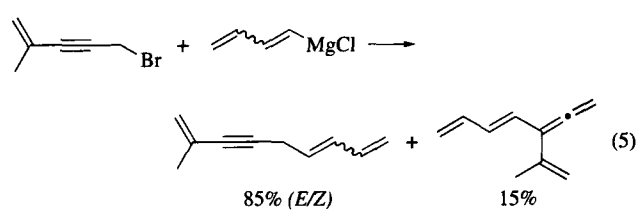
(3)

Coupling with Alkyl Halides. The coupling of 1,3-butadienyl-1-magnesium chloride with alkyl bromides or iodides is catalyzed by CuI and proceeds under mild conditions (eq 4).[3] The stereochemistry of the dienyl moiety is retained in the reaction product. The coupling reaction with 5-bromo-2-methyl-1-penten-3-yne was accompanied by allene formation (eq 5).[6]



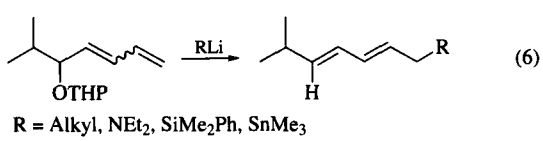
(4)

X = Br, I
R = $Me(CH_2)_4$, $R^1O(CH_2)_7$, Ph; R^1 = THP, Et



(5)

The configuration of the introduced butadienyl group corresponds to the configuration of the starting chlorobutadiene (for purification and isomerization of (*Z*)- and (*E*)-1-chlorobuta-1,3-dienes, see Onishchenko[7]). A mixture of (*Z*)- and (*E*)-isomers of the butadienyl derivatives obtained after reaction of butadienylmagnesium chloride with ketones and aldehydes could be transformed by the action of alkyllithium reagents, ***Dimethylphenylsilyllithium***, ***Trimethylstannyllithium***, or ***Lithium Diethylamide***, into the pure (*E*)-diene with simultaneous lengthening of the chain (eq 6).[2]



(6)

R = Alkyl, NEt_2, $SiMe_2Ph$, $SnMe_3$

4-Substituted-(*Z*,*Z*)-butadienyl cuprates can be prepared by addition of cuprates to alkynes. These form 1,4-disubstituted (*Z*,*Z*)-butadienes with typical electrophiles (alkyl halides, enones, CO_2) (eq 7).[8]

(7)

Related Reagents. 1,3-Butadienyl-2-lithium; 1,3-Butadienyl-1-lithium; 1,3-Butadienyl-2-magnesium Chloride.

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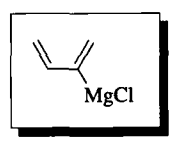
1,3-Butadienyl-2-magnesium Chloride



[32657-89-9] C_4H_5ClMg (MW 112.84)

(reagent for a variety of carbon–carbon bond forming reactions with carbonyls, epoxides, and alkyl and aryl halides; precursor of organotin and organosilicon compounds via transmetalation reactions)

Analysis of Reagent Purity: the IR spectrum of a THF solution of 1,3-butadienyl-2-magnesium chloride showed a strong absorption of a conjugated diene at 1600 cm^{-1}. A butadienyl, rather than allenyl, structure is also indicated by the ^1H NMR spectrum.[1] The concentration of 1,3-butadienyl-2-magnesium chloride is determined by titration with 1 M HCl.

Preparative Method: 1,3-butadienyl-2-magnesium chloride is synthesized by Grignard reaction of 4-chloro-1,2-butadiene with ***Magnesium*** in ether (eq 1)[1] or 2-chloro-1,3-butadiene (chloroprene) with magnesium in the presence of ***1,2-Dibromoethane*** and a catalytic amount of ***Zinc Chloride*** in THF (eq 2).[2] The experimental procedure is as follows: to a flask equipped with a mechanical stirrer under nitrogen were charged magnesium turnings, well activated by scratching (0.15 mol), 0.5 mL of 1,2-dibromoethane, and 5 mL of THF. On cooling, $ZnCl_2$ (3 mol%) was added. To this mixture was added a small amount of freshly distilled chloroprene (ca. 1