The Continuing Magic of Benzotriazole: An Overview of Some Recent Advances in Synthetic Methodology

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This lecture describes some of our recent work with benzotriazole. A comprehensive review of work carried out through 1996 has appeared [1], but since then we have published another hundred papers on benzotriazole (for later reviews on individual topics see [2-5]). It is clearly impossible to cover more than a fraction of this work in the present lecture. What I have chosen to do is to try to give the reasons why benzotriazole is such a useful synthetic auxiliary and then to summarize some of its most important applications with emphasis on the more recent work.

Scheme 1 lists some of the advantages of benzotriazole methodology. As shown in Scheme 2, benzotriazole groups can be easily inserted into a molecule by a variety of substitution, addition and three component condensation reactions.

Scheme 1

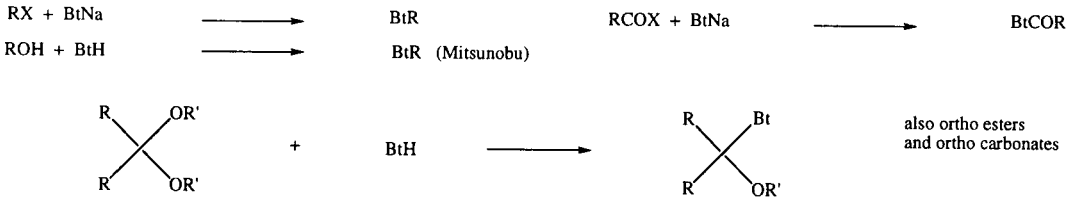
Advantages of Benzotriazole Methodology

1. Benzotriazole is inexpensive and easily introduced into organic molecules.
2. Benzotriazolyl groups convey multiple activating influences on molecule to which it is attached.
3. Benzotriazole is intrinsically unreactive and stable.
4. Benzotriazole exhibits desirable physical and innocuous biological properties.
5. Benzotriazole is readily removed from a molecule and can be easily recovered and recycled.

Scheme 2

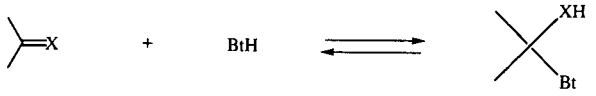
Preparation of Benzotriazole Derivatives

By Substitution

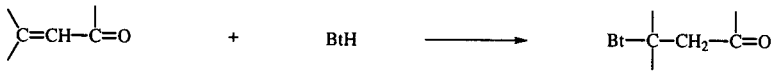


By Addition

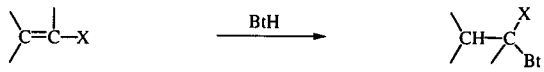
to C-Heteroatom multiple bonds C=O, C=N, C=N$^+$, C=S



to electron deficient C-C multiple bonds by Michael addition



to electron rich C-C multiple bonds (enol ethers, enamines, enamides, vinyl sulfides)

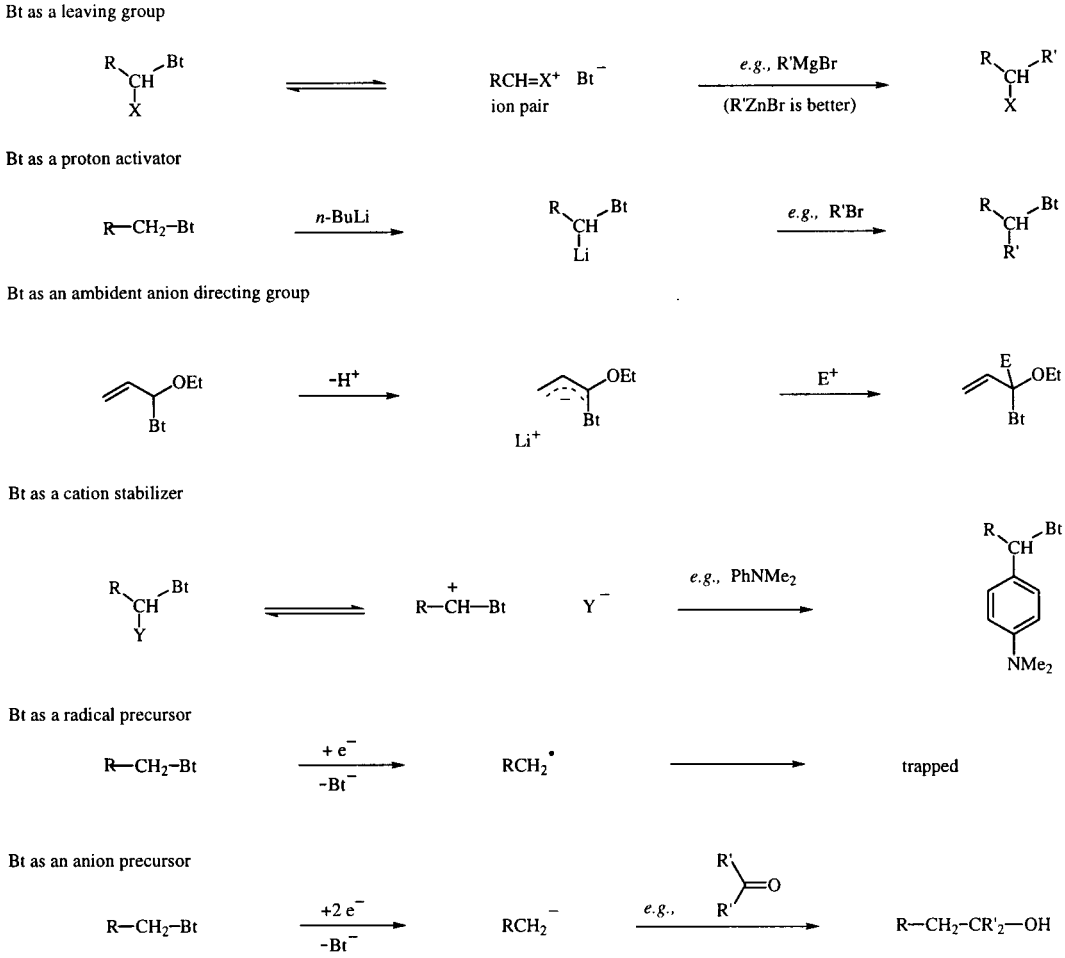


By Three Component Condensation (X = O, N, or S)

A benzotriazole residue conveys multiple activating influences on molecules to which it is attached. As listed in Scheme 3, a benzotriazole residue can act as a leaving group, a proton activator, an ambident anion directing group, a cation stabilizer, and as both a radical and an anion precursor. Moreover, the benzotriazole ring system is itself intrinsically unreactive, stable and exhibits desirable physical and innocuous biological properties as described in Scheme 4. Moreover, benzotriazole is readily removed from molecules and as Scheme 5 documents it can be recycled when used on the large scale and adapted to solid phase synthesis.

Scheme 3

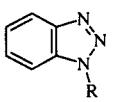
Multiple Activating Influences of a Benzotriazole Residue



Scheme 4

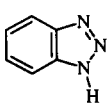
Benzotriazole is Intrinsically Unreactive, Stable and Exhibits Desirable Physical and Innocuous Biological Properties

Chemical Stability of Benzotriazole Ring System



Stable: thermally to 400°,
to hot strong H_2SO_4,
to fused KOH,
to oxidation ($KMnO_4$ oxidizes benzene ring)
to reduction (*e.g.*, $LiAlH_4$; H_2-Pd)

Parent Benzotriazole



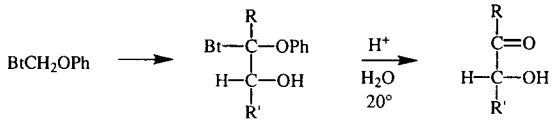
acid pKa 8.2 for proton loss
very weak Bronsted base (pKa < 0 for proton addition)
Lewis base of appreciable strength
non-volatile, crystalline, odorless, nontoxic
almost insoluble in water, soluble in Na_2CO_3 solution
hence easily recovered

Scheme 5

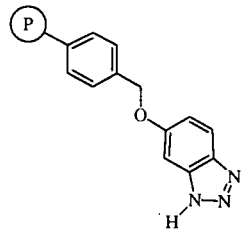
Benzotriazole is Readily Removed from the Molecules and Can be Easily Recycled - Can be Adapted to Solid Phase Synthesis

1. Many examples of activation involve replacement of Bt-residue.
2. Hydrolysis of Bt-acetals, - thioacetals, *etc.* does not require either heavy metals or oxidizing agents.

e.g.,



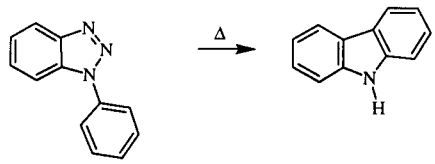
3. Benzotriazole is readily soluble in aqueous Na_2CO_3 but sparingly soluble in H_2O.
4. Resin-linked benzotriazole is available from Novobiochem.



Scheme 6

A Brief History of the Development of Benzotriazole Methodology

1951 M.Sc. thesis work at Oxford on the preparation of indolocarbazoles by the Graebe-Ullmann reaction.



1954 Study of *N*-oxide chemistry commenced.

1956 Started work on rationalization of reactivity of heterocyclic rings and substituents for textbook entitled "Heterocyclic Chemistry" published by Methuen - first edition 1961 (later translated into French, German, Italian, Japanese, Polish, Russian and Spanish). Found that reactivity of *N*-substituents was little studied.

1964 Research started on *N*-imide and *N*-ylid chemistry.

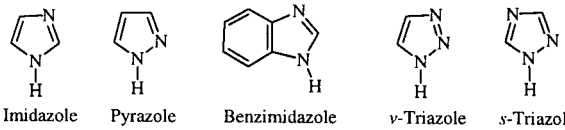
1974 Investigations of *N*-*N*'-linked heterocycles.

1978 Research on the reactions of *N*-substituents in pyridinium salts.

1981 Development of the N-CO_2^- group for protection.

1984 Systematic studies of reactions of *N*-substitued azoles.

Systems investigated:



1987 Major efforts commenced in benzotriazole chemistry.

Scheme 6 offers a brief history of the development of benzotriazole methodology in our group over the last 50 years. I first started research on benzotriazole during my M.Sc. thesis research, though I little realized at the time what an important part this ring system would play in my research in later years. The role of benzotriazole as a synthetic auxiliary was discovered because we carried out in my group a systematic study of the properties and reactions of *N*-substituents in heterocyclic compounds as described in Scheme 6.

Many specific classes of benzotriazoles have been found to be of considerable use and some of the more important ones are listed in Scheme 7. The chief methods of preparation of compounds of the Bt-C-X class are described in Scheme 8. The utility of the class of compounds Bt-C-X where X is a heteroatom is summarized in Scheme 9, which describes their participation in condensations of various types, elimination reactions, double additions and their potential as acyl anion synthons.

Scheme 7

Utility of Specific Classes of Benzotriazoles

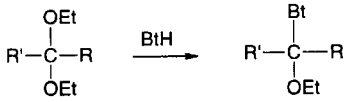
1. Bt-C-X for heteroalkylations, eliminations, double additions, acyl anion synthons
2. Bt-C-C=C for regioselectivity of Bt stabilized conjugated anions, unsaturated acyl anions, in palladium chemistry
3. Bt-C-(hetero)aryl: for introduction of complex substituents and for benzo ring annulation
4. Bt-C-C-X: for carbonyl insertion reactions and preparation of acetylenes and olefins
5. Bt-C-C=O

Scheme 8
Methods for the Preparation of Bt-C-X Compounds
(X = N, O, S or Halogen)

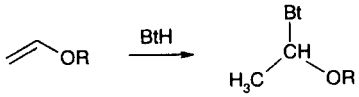
1. From aldehydes by 3-component condensations

easily for amines, readily for amides, less so for alcohols and thiols

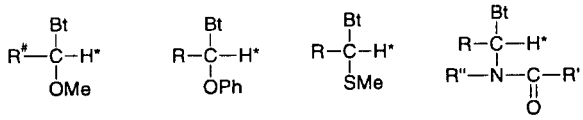
2. From an acetal or mixed acetal



3. By addition to vinyl amine, vinyl ether, *etc.*



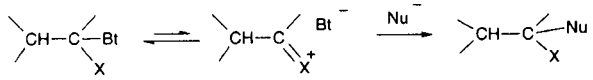
4. By deprotonation and reaction with electrophile



R# = H, aryl, vinyl or ethynyl

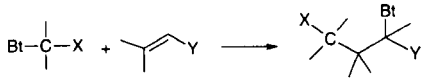
Scheme 9
Utility of Bt-C-X Compounds

1. Aminoalkylation, amidoalkylation, alkoxyalkylation (ether synthesis), acyloxyalkylation (ester synthesis), and alkylthioalkylation (thioether synthesis)

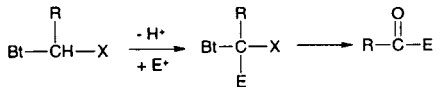


2. Elimination reactions: preparation of enamines, enamides, vinyl ethers, vinyl thioethers

3. Double addition reactions to enamides and vinyl ethers



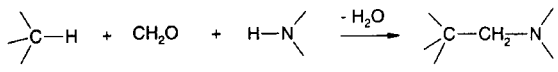
4. Acyl anion synthons



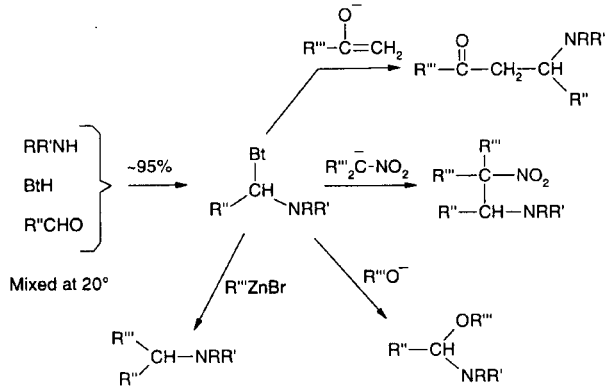
The classical prototype for aminoalkylation is the Mannich reaction which is essentially limited to aminomethylation: as shown in Scheme 10, benzotriazole-mediated aminoalkylation allows extention from the use of formaldehyde in the classical Mannich to all types of aldehydes. Scheme 11 gives an overview of the application of benzotriazole methodology in amidoalkylation reactions, illustrating its wide range of applicability.

Scheme 10
Aminoalkylations Using Bt-C-N-R Derivatives

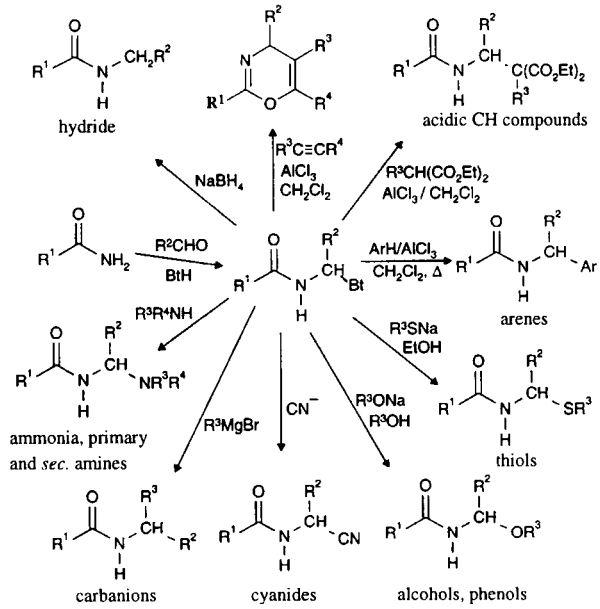
Classical prototype is the Mannich Reactions



Benzotriazole-mediated aminoalkylation allows extention from formaldehyde to all types of aldehydes



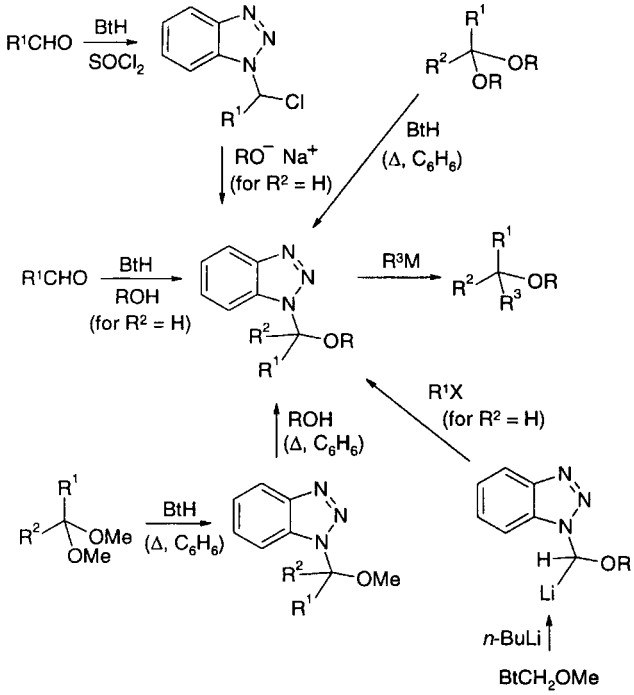
Scheme 11
Overview of Benzotriazole Mediated Amidoalkylation [6]



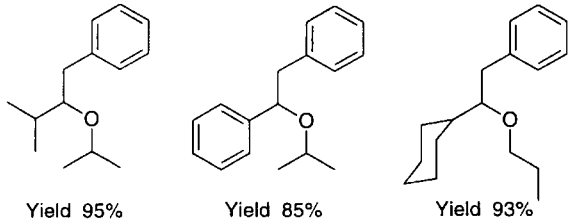
The utility of benzotriazole methodology in alkoxyalkylation is summarized in Scheme 12 where it is applied to the preparation of ethers and is particularly suitable for making hindered ethers. The preparation of enamines, dienamines, enamides, vinyl ethers and vinyl sulfides by the elimination of benzotriazole from easily accessible intermediates is summarized in Scheme 13.

Benzotriazole derivatives of type Bt-C-X undergo double additions to enamines and vinyl ethers. The products formed still possess activated Bt groups and can undergo *e.g.* subsequent cyclization. Such reaction sequences are illustrated in Scheme 14 which documents the preparations of tetrahydroquinolines.

Scheme 12
Alkoxyalkylation. Preparation of Ethers Using Benzotriazole Methodology [7]

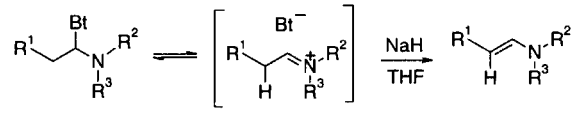


Examples of ethers prepared:



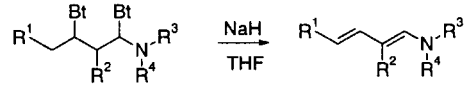
Scheme 13
Preparation of Heterosubstituted Olefins by Elimination of Benzotriazole

1. Preparation of Enamines



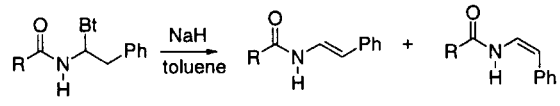
R^1 = H, alkyl; R^2, R^3 = alkyl, aryl [8]

2. Preparation of Dienamines



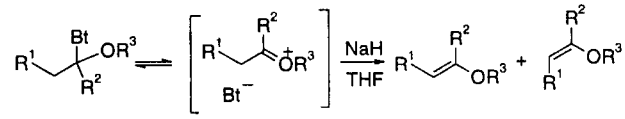
R^1, R^2 = H, Me, Et; R^3, R^4 = alkyl, aryl [9]

3. Preparation of Enamides



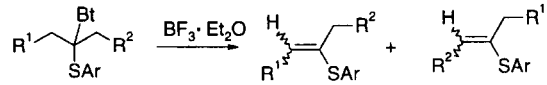
R = alkyl, aryl, heteroaryl [10]

4. Preparation of Vinyl Ethers



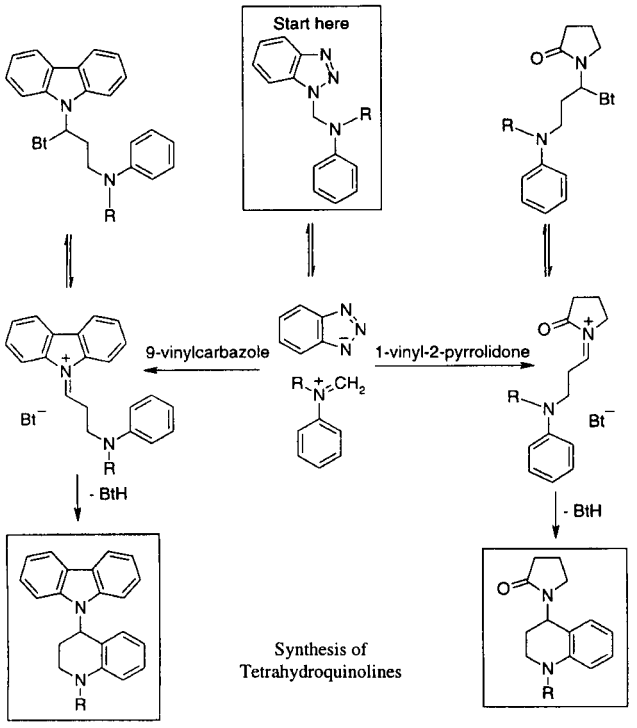
R^1 = H, alkyl; R^2 = alkyl, aryl; R^3 = alkyl [11]

5. Preparation of Vinyl Sulfides



[12]

Scheme 14
An Example of the Double Addition of Bt-C-N to Enamines with Subsequent Cyclization [13]

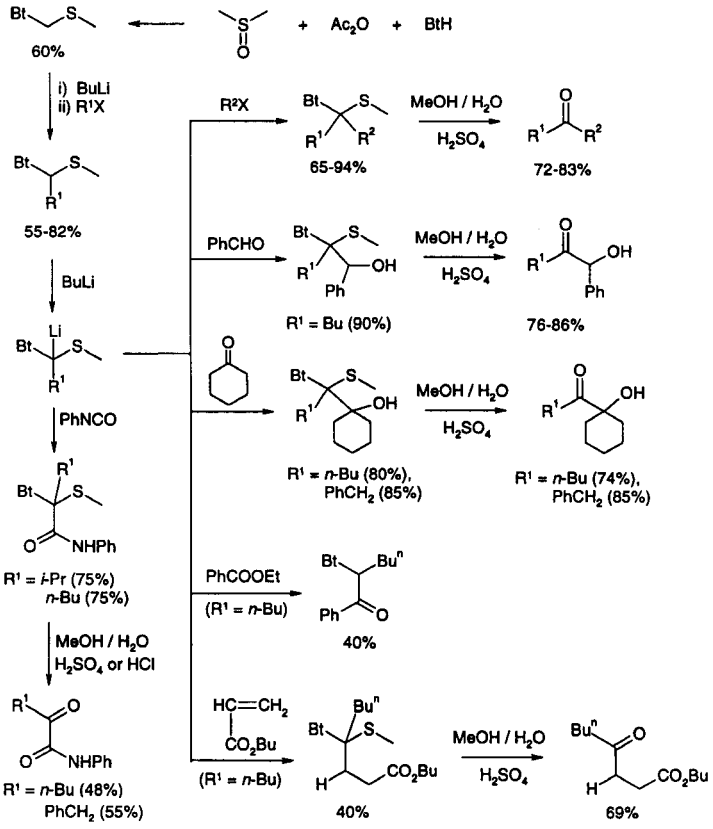


Benzotriazole derivatives provide many versatile acyl anion equivalents. One such application is given in Scheme 15 for the synthesis of simple and functionalized ketones: conditions for the final hydrolysis are mild and require no heavy metal or oxidizing agent.

The rather simple preparation of *N*-allylbenzotriazoles is overviewed in Scheme 16, their utility rests on the α-directive power of the Bt-group in reactions of the corresponding deprotonated anions. The applications of such benzotriazole derived propenoyl anion synthons in the preparation of a variety of polyfunctional vinyl ketones is illustrated in Scheme 17. Further applications of these propenal acetals are given in Scheme 18: advantage is taken of reversible allylic rearrangements and the steric situation to move the Bt-group from one end of a molecule to the other and back. The regiospecificity of the reactions of the derived anions with electrophiles and the susceptibility of the derivatives to S_N2' substitution with Grignards now allows the development of five synthons (boxed in Scheme 18).

Analogous applications of benzotriazole stabilized propargylic anions are considered in Scheme 19 which illustrates the wide variety of functionalized acetylenic ketones that can be prepared using them: the regiospecificity and the mild hydrolysis conditions combine to render these the methods of choice for such compounds.

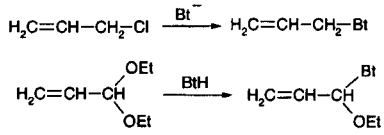
Scheme 15
Benzotriazole-Derived Acyl Anion Equivalents. Syntheses of Dialkyl and Functionalized Ketones [14]



Scheme 16

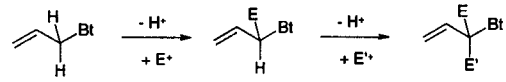
Preparation and Utility of Bt-C-C=C Type Compounds

Preparation - by Substitution from Halide or Acetal

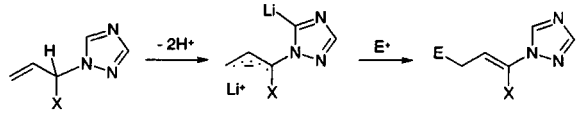


Utility

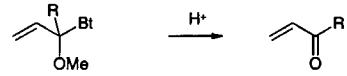
1. Regioselective Reactions of Bt-stabilized Allyl Anions



2. Inverted Regioselectivity Using Triazole Analogues of Bt Compounds

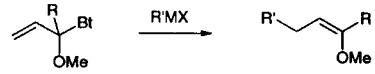


3. Unsaturated Acyl Anion Equivalent

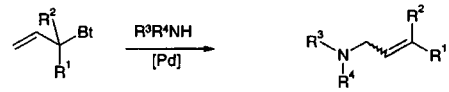


4. S_N2' Replacement Reactions

(i) with Grignard or Organozinc Reagent

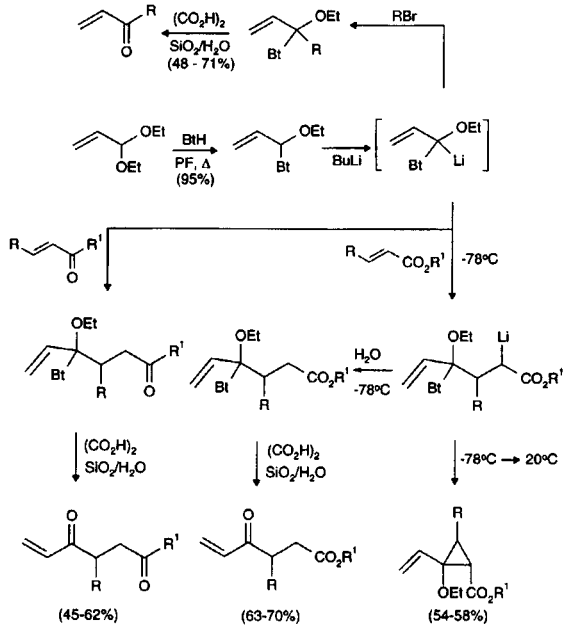


(ii) Palladium Chemistry for the Preparation of Amines

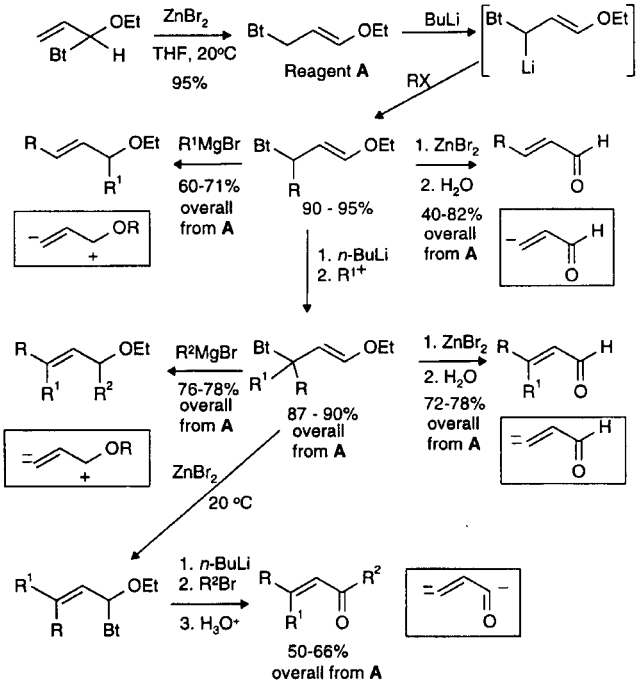


Scheme 17

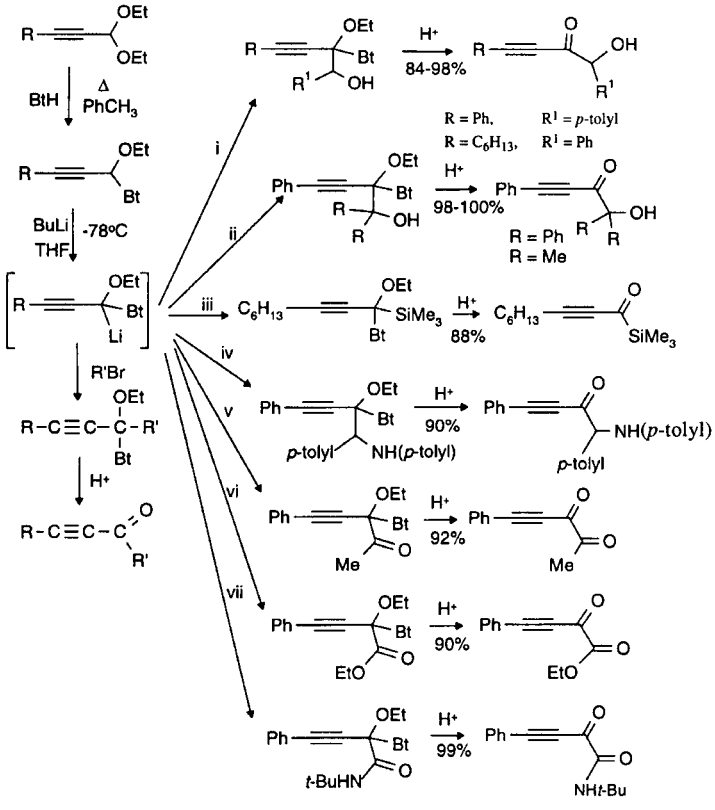
Regioselective Propenoyl Anion Synthon Routes to Vinyl Ketones, Vinyl Diketones, Vinyl Keto Esters and Cyclopropanes [15]



Scheme 18
More Synthetic Applications of Propenal Acetals [16]



Scheme 19
Regiospecific Reactions of Bt-Stabilized Propargylic Anions [17]



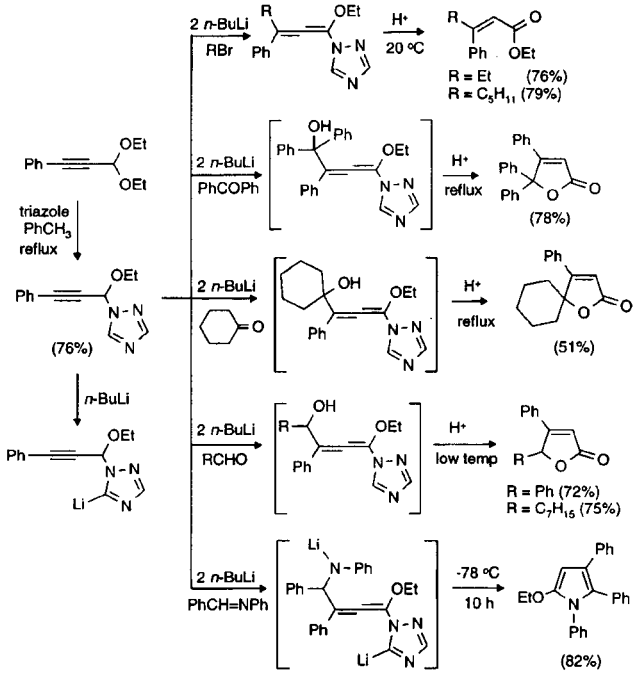
(i) R^1CHO, 73-75%;
(ii) RC(O)R, 66-77%;
(iii) Me_3SiCl, 78%;
(iv) *p*-Tol-CH=N(*p*-Tol), 85%;
(v) EtOAc, 65%;
(vi) EtOCOOEt, 35%;
(vii) *t*-BuNCO, 54%

By using 1,2,4-triazole analogs of the benzotriazole derivatives just discussed, inverted regioselectivity can be achieved as illustrated in Scheme 20 for the acetylenic derivatives: this initially suprising result is connected with the fact that the first deprotonation now occurs at the triazole ring and two moles of BuLi are required for the synthesis of the unsaturated lactones, *etc.*

Compounds in which a Bt group is attached to an aromatic or heteroaromatic ring by a single carbon atom are of considerable synthetic importance. The various methods for the preparation of such Ar-C-Bt compounds are summarized in Scheme 21. The utility of such compounds in (i) the construction of elaborated substituents and (ii) in benzannulation is covered in Scheme 22.

Scheme 20

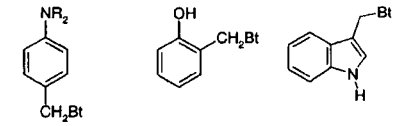
Inverted Regiospecificity of 1,2,4-Triazole Stabilized Allenic Anions [18]



Scheme 21

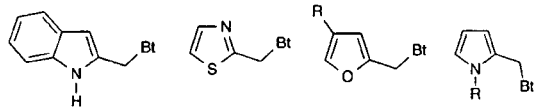
Preparation of Bt-C-(Hetero)aryl Compounds

1. By Electrophilic Substitution ($BtCH_2OH$ + AcOH)



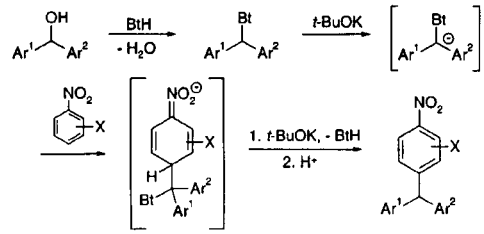
(R = H, alkyl) [19] [20] [21]

2. By Ring Synthesis



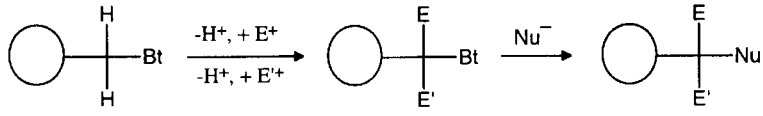
[22] [23] [24] [25]

3. By Vicarious Nucleophilic Substitution [26]



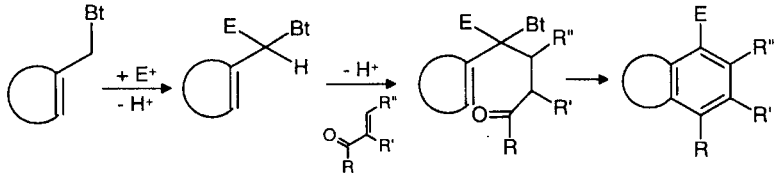
Scheme 22
Utility of Bt-C(hetero)aryl Compounds

1. Construction of elaborated substituents



para-Substituted anilines [19]
ortho-Substituted phenols [20]
2-Substituted indoles [22]
2-Substituted thiazoles [23]
3-Substituted indoles [21]

2. Benzannulation chemistry



Benzenes → naphthalenes [27]
Furans → benzofurans [28]
Benzofurans → dibenzofurans [28]
Pyrroles → indoles [25]
Thiophenes → benzothiophenes [29]

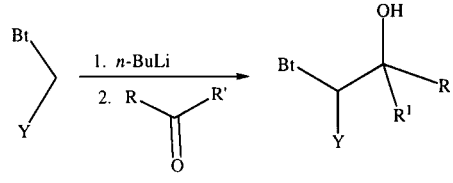
Compounds in which a Bt-group is separated by two carbons from the heteroatom are quite easily prepared (Scheme 23). They possess diverse synthetic importance in enabling insertion reactions and for the preparation of olefins as shown in Scheme 24.

The scope of the Bt mediated insertion reactions is given in Scheme 25, which includes examples of aliphatic and aromatic aldehydes and ketones and indicates that C-1 unit inserted can carry with it a large variety of C-, O-, S-, and N-linked substituents. The *trans*-stereo selective syn-

Scheme 23
Preparation of Bt-C-C-X Compounds

1. X = Oxygen by Bt-C$^-$ + C=O

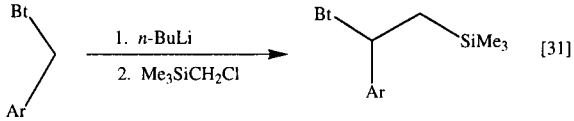
e.g.,



Y = Me, R^2-Z-CH=CH-(Z = CH_2, NR^3, O), R^2-C≡C [30]

2. X = Silicon by Bt-C$^-$ + Me_3SiCH_2Cl

e.g.,

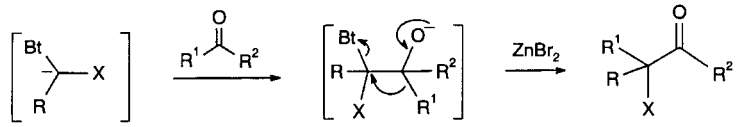


[31]

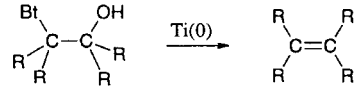
Scheme 24

Utility of Bt-C-C-X Compounds

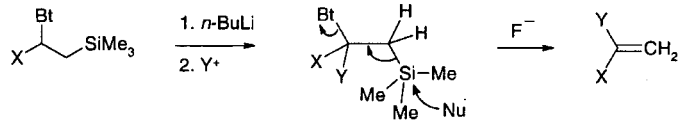
1. For benzotriazole-mediated insertion reactions



2. Preparation of *trans*-olefins



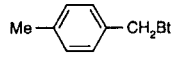
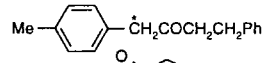
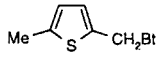
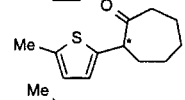
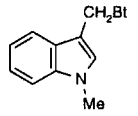
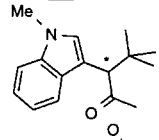
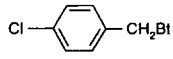
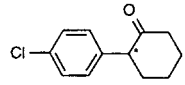
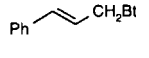
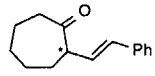
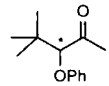
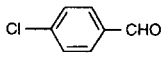
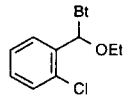
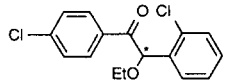
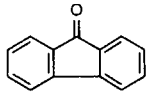
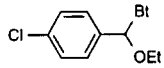
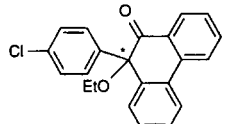
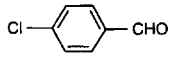
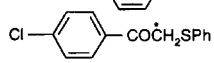
3. Preparation of 1,1-disubstituted ethylenes



Yields 74-96% for X = various Aryl, OPh, SPh, $SiMe_3$

Scheme 25

Benzotriazole-Mediated Insertion of a C-1 Unit Alpha to a Carbonyl Group in Aldehydes and Ketones [32]

Entry	Carbonyl Compound	Bt-Reagent	Temperature, °C/Time, Hours/Solvent	Product (*Indicates C-Inserted)	Yield (%)
1	$PhCH_2CH_2CHO$		210 / 0.5 / neat		65
2			110 / 10 / $ClCH_2CHCl_2$		67
3			65 / 3 / THF		87
4			170 / 12 / neat		85
5			110 / 12 / toluene		60
6	$PhCH_2CH_2CHO$	$BtCH_2OMe$	140 / 1 / $CHCl_2CHCl_2$	$PhCH_2CH_2\dot{C}HCH_2OMe$	50
7		$BtCH_2OPh$	140 / 1 / $CHCl_2CHCl_2$		47
8			65 / 6 / THF		91
9			66 / 24 / THF		51
10		$BtCH_2SPh$	140 / 1 / $CHCl_2CHCl_2$		86
11	PhCOMe	$BtCH_2SPh$	140 / 6 / $CHCl_2CHCl_2$	$PhC\dot{H}(SPh)COMe$	65

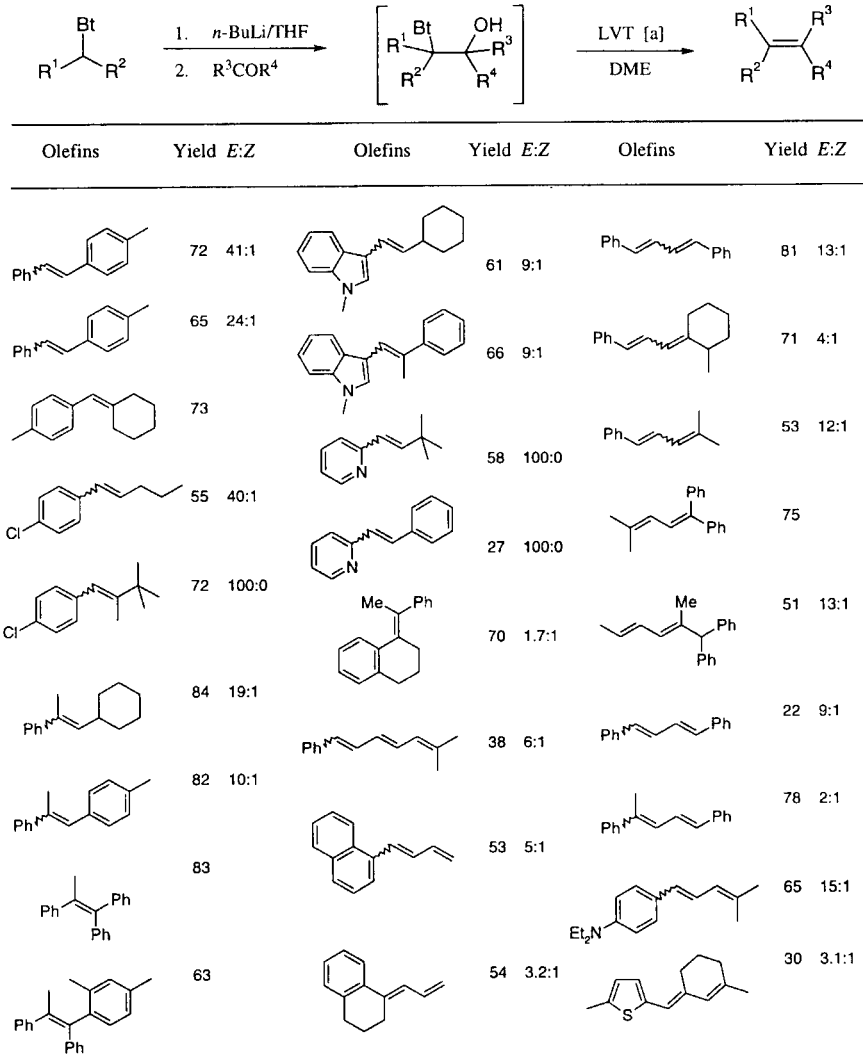
thesis of 27 aryl-conjugated olefins, and dienes and trienes is covered in Scheme 26: it was shown that each of the diastereoisomers formed in the first step gives the same *E*:*Z* ratio, (presumely *via* a common intermediate on the surface of the titanium metal), thus obviating any need for the separation of the intermediates. Our reaction thus has some potential in just those cases where the *E*:*Z* selectivity can be a problem in the Wittig and Julia reactions.

deprotonation alpha to the Bt-group and the anions react readily with a range of electrophiles. Subsequent treatment with fluoride anion causes the elimination of both Me_3Si and Bt-groups and leads to the preparation of a wide variety of olefins, some of which are shown in Scheme 27.

Compounds in which a Bt ring is separated from a carbonyl group by a single carbon atom can be prepared by

Scheme 26

Benzotriazole-Mediated Preparation of Aryl-conjugated Olefins and of Dienes and Trienes [33]



Olefins	Yield	*E*:*Z*	Olefins	Yield	*E*:*Z*	Olefins	Yield	*E*:*Z*
Ph	72	41:1		61	9:1	Ph Ph	81	13:1
Ph	65	24:1		66	9:1	Ph	71	4:1
	73			58	100:0	Ph	53	12:1
Cl	55	40:1		27	100:0	Ph Ph	75	
Cl	72	100:0	Me Ph	70	1.7:1	Me Ph Ph	51	13:1
Ph	84	19:1	Ph	38	6:1	Ph Ph	22	9:1
Ph	82	10:1		53	5:1	Ph Ph	78	2:1
Ph Ph Ph	83			54	3.2:1	Et_2N	65	15:1
Ph Ph	63					S	30	3.1:1

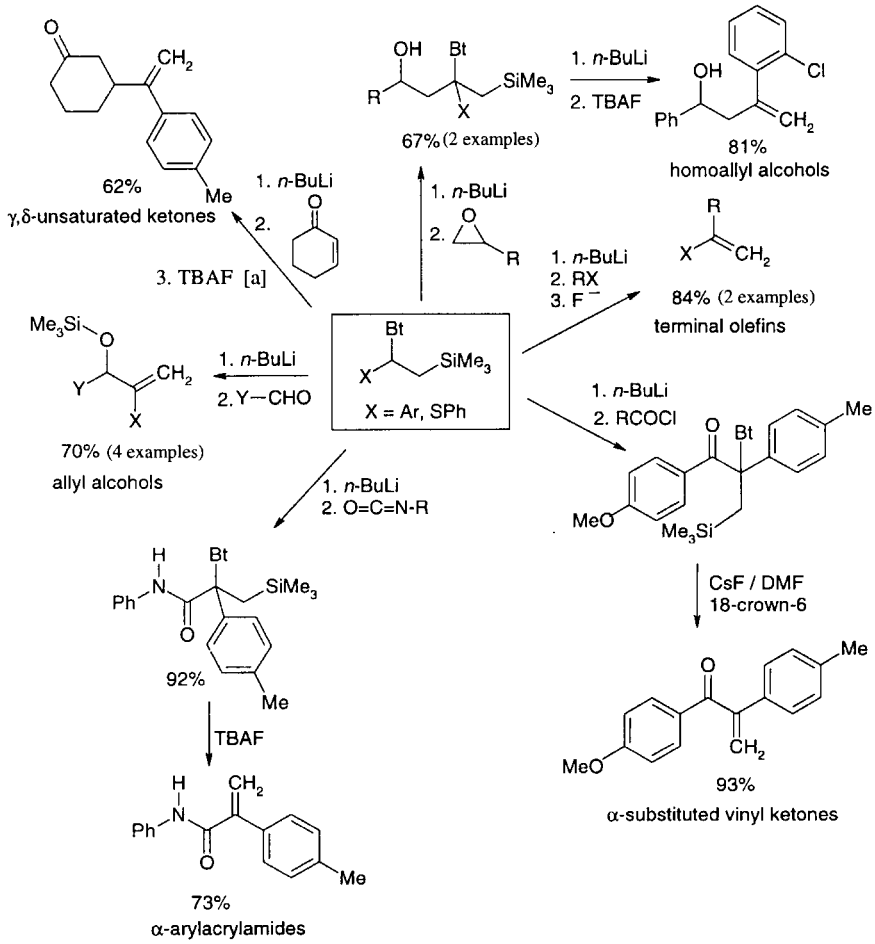
[a] LVT: Low-Valent Titanium.

Scheme 27 overviews the benzotriazole-mediated preparation of monosubstituted and *gem*-disubstituted ethylenes. The starting materials (boxed in Scheme 27) are prepared as per Scheme 23. They undergo ready

various routes as shown in Scheme 28. The utility of compounds of type Bt-C-C=O for the preparation of acetylenes, phenols, ketones, and heterocycles is summarized in Scheme 29.

Scheme 27

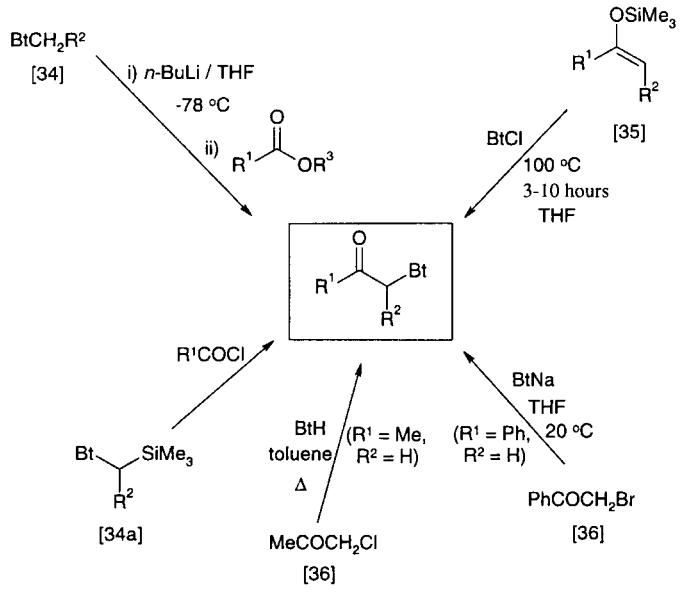
Benzotriazole-Mediated Preparation of Functionalized 1-Mono- and 1,1-Disubstituted Ethylenes [31]



[a] TBAF: Tetrabutylammonium Fluoride.

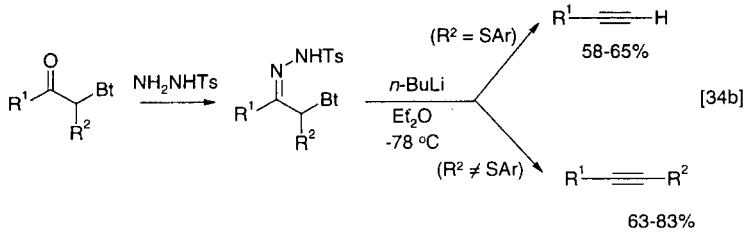
Scheme 28

Preparation of Compounds of the Bt-C-C=O Class



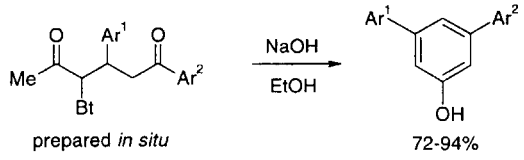
Scheme 29
Preparative Utility of Bt-C-C=O

1. Preparation of Acetylenes



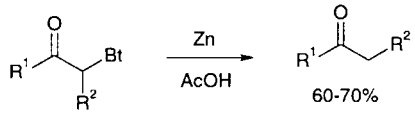
[34b]

2. Preparation of 3,5-Diarylphenols



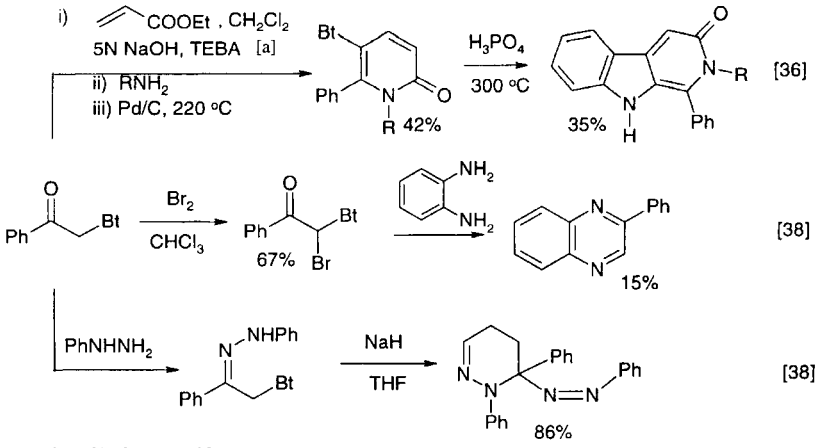
[37]

3. Preparation of Alkyl Aryl Ketones



[34a]

4. Preparation of Heterocyclic Compounds



[36]

[38]

[38]

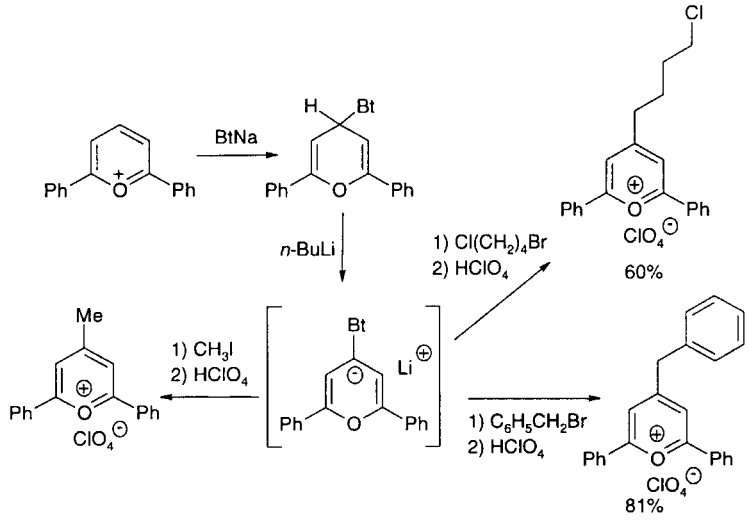
[a] TEBA: Tetrabutylammonium Hydrogensulfate.

A benzotriazole group can mediate umpolung. Such umpolung enables, for example, the use of electrophiles to introduce substitution into the highly electron-deficient 4-position of pyrylium cation as shown in Scheme 30.

Recently we have applied benzotriazole methodology to asymmetric synthesis. The case of piperidines is covered in Scheme 31, yields and *ee* values are high and the methodology is convenient. Examples of further applications to asymmetric synthesis are given in Scheme 32.

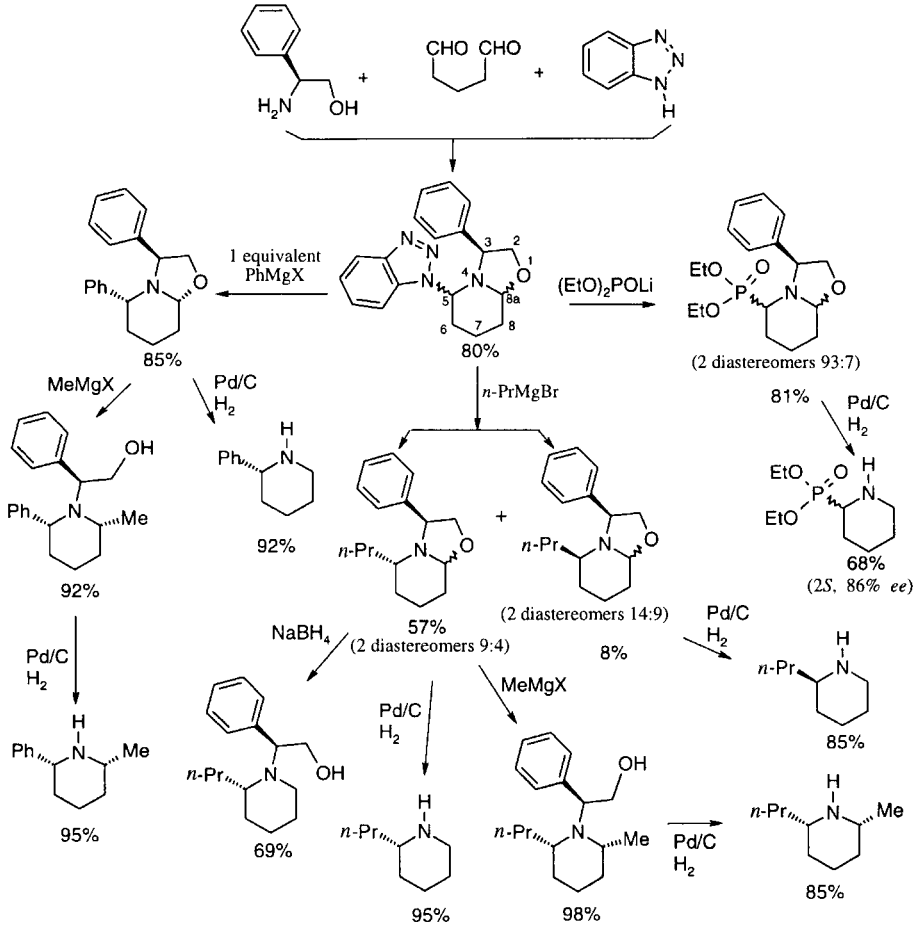
Scheme 30

Electrophilic Introduction of Substituents into the 4-Position of Pyrylium Cations by Benzotriazole-Mediated Umpolung [39]

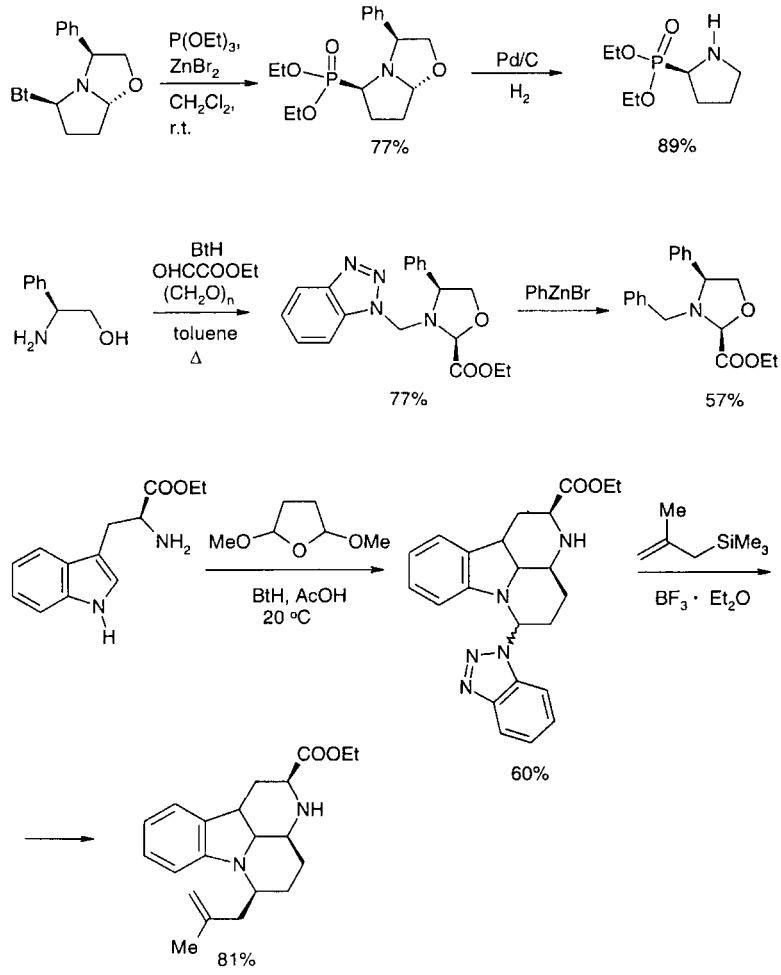


Scheme 31

Benzotriazole-Mediated Asymmetric Synthesis of Piperidines [40]



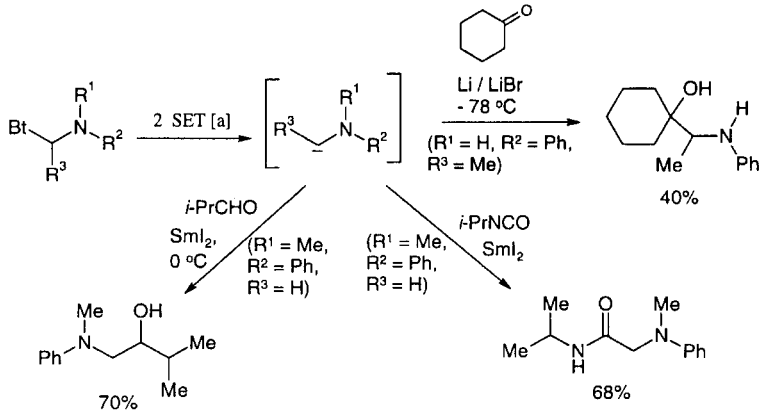
Scheme 32
Further Examples of Benzotriazole-Mediated Asymmetric Syntheses [41,42]



In recent years, we have demonstrated that benzotriazole derivatives can be precursors of both carbanions and of radicals by electron-induced loss of the Bt-group. Scheme 33 illustrates how non-stabilized α-aminocarbanions can be generated and trapped using benzotriazole methodology. The use of Bt precursors for radical-induced cyclization is dealt with in Scheme 34.

Scheme 33

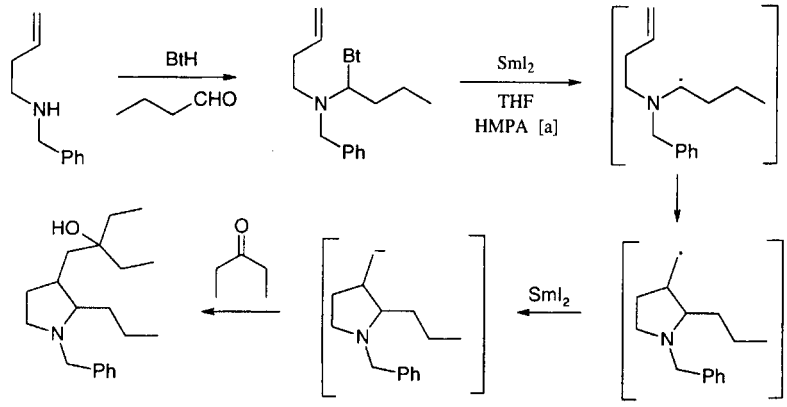
Trapping of Non-Stabilized α-Aminocarbanions Generated from Benzotriazoles [4]



[a] SET: Single-Electron Transfer.

Scheme 34

Benzotriazole-Mediated Radical Induced Cyclization [43]

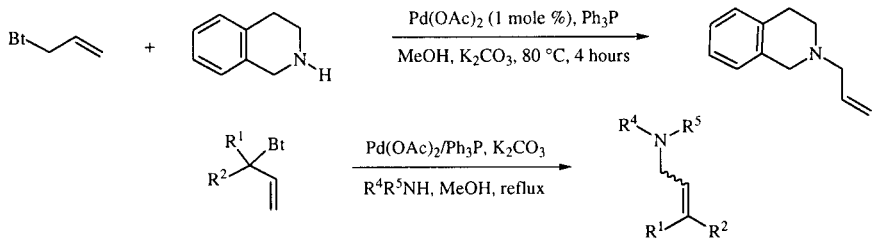


[a] HMPA: Hexamethylphosphoramide.

Another recent development has been the combination of Bt and palladium chemistry as shown in Scheme 35: whereas the preparation of 2-allyl-1,2,3,4-tetrohydroisoquinoline is not of synthetic significance, the fact that diverse substituents can be regiospecifically introduced into the Bt-reagent allows easy access to a variety of substituted allyl anions. Some further results of the combination of Bt- and Pd-methodology are shown in Scheme 36.

Scheme 35

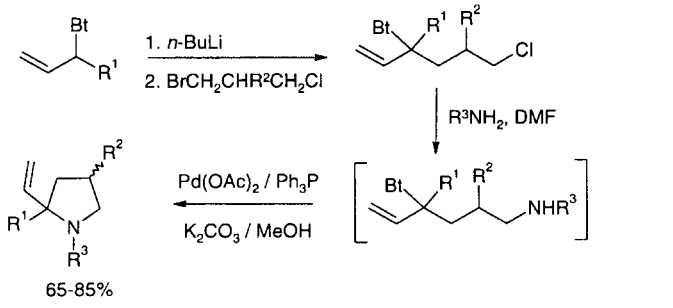
Pd-Catalyzed Preparation of Allylamines from Allylbenzotriazoles [44]



R^1	R^2	R^4	R^5	Yield (%)
H	H	$C_6H_5CH_2$	$C_6H_5CH_2$	80
H	H	n-C_8H_{17}	n-C_8H_{17}	87
CH_3	H	o-$CH_2C_6H_4CH_2$-CH_2-		85
C_2H_5	H	n-C_8H_{17}	CH_3	80
n-C_4H_9	H	$C_6H_5CH_2$	$C_6H_5CH_2$	70
$C_6H_5CH_2$	H	C_2H_5	C_2H_5	70
n-C_4H_9	n-C_4H_9	-$(CH_2)_4$-		75

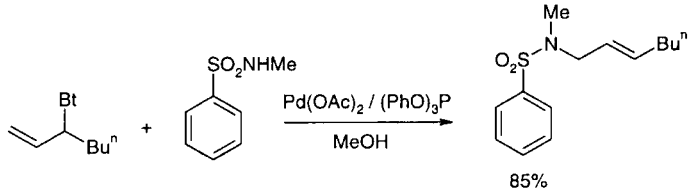
Scheme 36

Further Synthetic Preparations by a Combination of Bt-Methodology with Pd-Chemistry [45]



65-85%

R^1 = H, Me, $PhCH_2$; R^2 = H, Me; R^3 = alkyl, $PhCH_2$

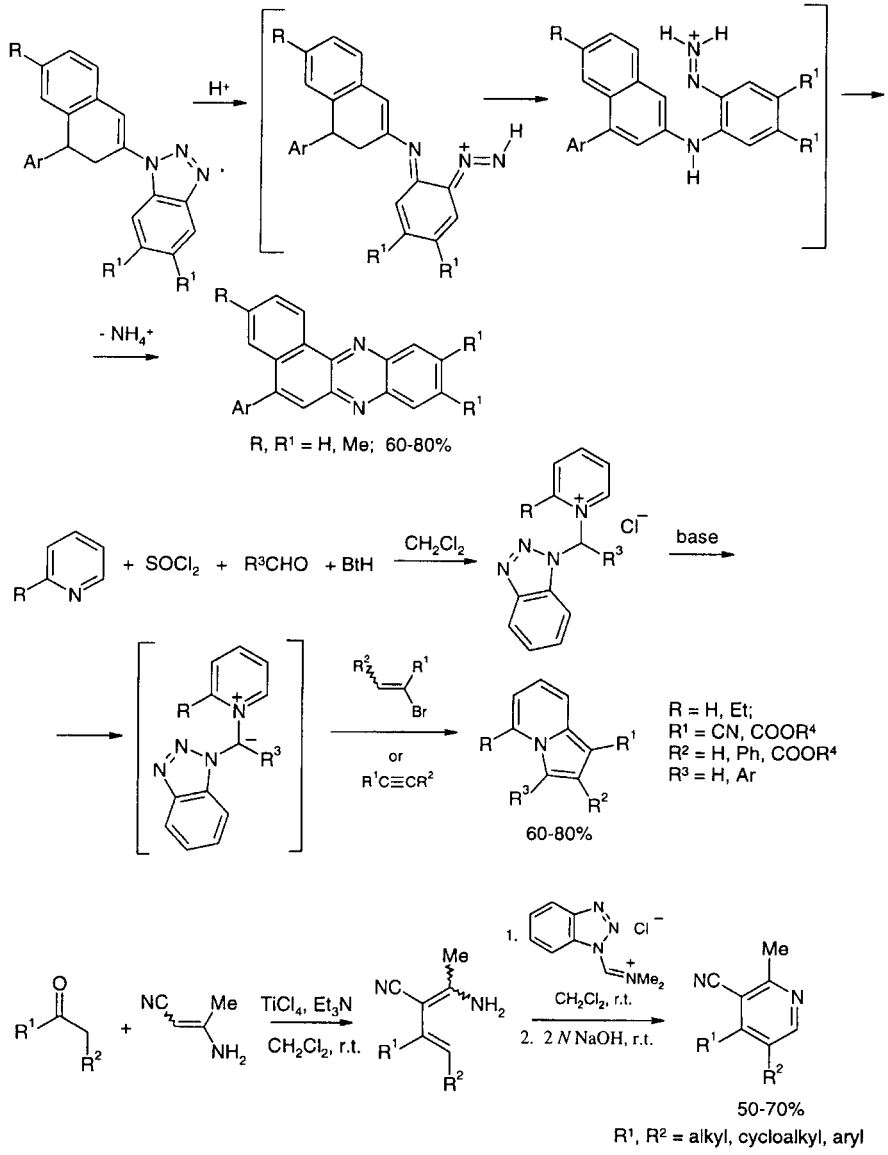


85%

Benzotriazole chemistry is still in the phase of active expansion and Scheme 37 lists some of the areas now under active development in our group.

This lecture has been made possible only by the participation of a large number of dedicated co-workers, whose names are given in Scheme 38. I have only been able to describe a fraction of their work but I would like to thank all of them for the excellent efforts.

Scheme 37
Some Future Prospects of Benzotriazole Chemistry [46]



Scheme 38

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Fu Bao Ji
Jinlong Jiang
Xiangfu Lan
Hengyuan Lang
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Qiu-He Long
Ping Lue
Zhushou Luo
Rexiat Maimait
Ming Qi
Guofang Qiu
Huimin Song
Jin Wang
Junquan Wang
Xiaojin Wang
Zuoquan Wang
Hong Wu
Jiaxiang Wu
Jing Wu
Linghong Xie
Baozhen Yang
Zhijun Yang
Guo-Wei Yao
Jiangchao Yao
Gui-Fen Zhang
Yongmin Zhang
Zhongxing Zhang
Xiaohong Zhao
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J.-J. Vanden Eynde

Columbia
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Egypt
Saad El-Zemity
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Muhammad Latif

Romania
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Ion Ghiviriga
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Scheme 40 summarizes once again some aspects of benzotriazole as a synthetic auxiliary. I very much hope that many of you will consider the use of benzotriazole methods in your own work, and emphasize that we at the University of Florida are delighted when other groups enter into this area of chemistry. Many benzotriazoles are also now available commercially.

Finally, I would like to suggest that benzotriazole can perhaps teach us something as humans and not just as chemists. The "Benzotriazole Code of Ethics" (Scheme 41) can perhaps help us in our daily lives.

Scheme 39
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Arcadia, Denmark
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Athena, South San Francisco, CA
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Geo-Centers, Lake Hopatcong, NJ
Lancaster, UK and Gainesville, FL
Merck, Rahway, NJ
Monsanto, Nutrasweet Division, Chicago, IL
New technology Division, Chicago, IL
Nippon Soda, Japan
NSF, Washington, DC
Organon, Netherlands
Parke-Davis, MI
Pfizer, CT
Pharmos, Alachua, FL
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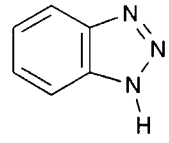
Reilly Industries, Indianapolis, IN
Rhone-Poulenc, Research Triangle Park, NC
Rohm and Haas, Spring House, PA
RW Johnson Research, NJ
Sandoz, Charlotte, NC
Schering-Plough, NJ
SDS Biotech, Tokyo, Japan
Sigma-Aldrich, WI
Solutia, St. Louis, MO
SPECS, Holland
Sterling Winthrop Inc., Malvern, PA
Trega, San Diego, CA
Tularik, San Francisco, CA
Upjohn Corporation, Kalamazoo, MI
Warner-Lambert, Ann Arbor, MI
Zenneca, UK

Scheme 40
Characteristics of Benzotriazole as a Synthetic Auxillary



1. Readily available
2. *N*-Substituted derivatives easy to prepare
3. Bt-Residue can be cleaved by a variety of procedures
4. Acid of pK_a *ca.* 8 enables easy separation and recovery
5. Ring can donate or accept electrons
6. Interesting reactivity patterns

Scheme 41
The Benzotriazole Code of Ethics

1. Readily available and inexpensive
   Be there when your friends need you

2. Bt ring both an electron donor and acceptor
   Remember it is blessed to give as well as receive

3. Bt group endows desirable reactivity patterns
   Motivate the community to do better

4. Bt residue easily cleaved
   Do not outstay your welcome

5. Easily separated and recovered for repeated use
   Forgive, and come back when you are needed again

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