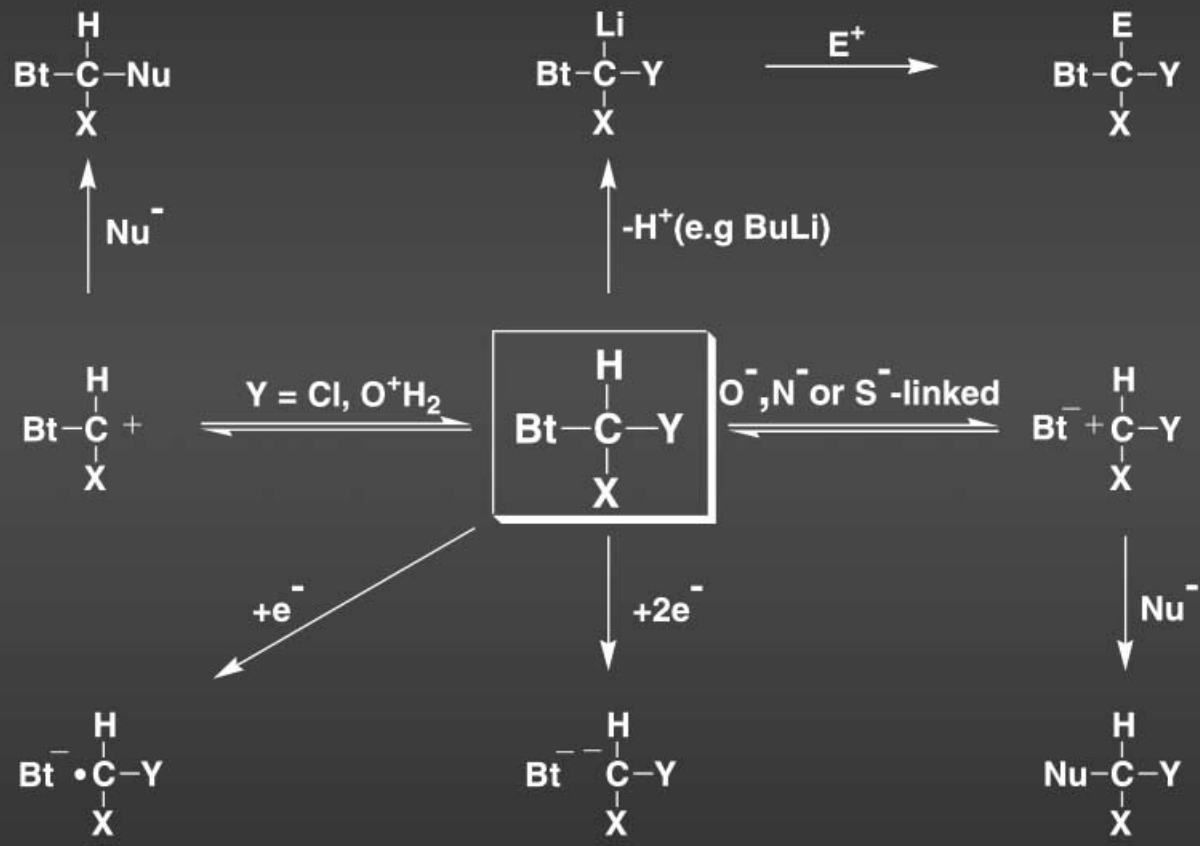
1. Examples of the Preparation of Benzotriazole-Containing Reagents

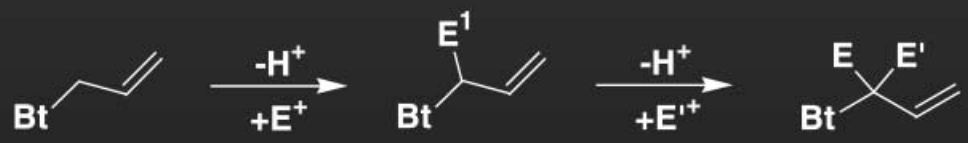
$$RCHO + R^1XH + BtH \longrightarrow RCH(XR^1)Bt$$

$$R^1R^2C(OMe)_2 + BtH \longrightarrow R^1R^2C(OMe)\,Bt$$

2. Transformations demonstrating stability of carbocation and carbanion, and leaving ability of cation, anion and radical species



3. Ambident anion direction ability



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Benzotriazole: An Ideal Synthetic Auxiliary**

Alan R. Katritzky* and Boris V. Rogovoy[a]

Abstract: Benzotriazole is a synthetic auxiliary that offers many advantages. It is inexpensive, odorless, and stable. A benzotriazole group is easily introduced, activates molecules towards numerous transformations, and can be removed easily at the end of the reaction sequence. This Concept provides some recent examples of the synthetic application of benzotriazole methodology and is intended to draw attention to the versatile applications of benzotriazole in organic chemistry.

Keywords: benzotriazole · deprotonation · heterocyclic synthesis · nucleophilic substitution · regioselectivity

Introduction

A benzotriazole group variously activates the carbon atom to which it is attached: 1) by behaving as a leaving group, 2) by enabling deprotonation, 3) by acting as a electron donor, and 4) by being capable of reductive elimination to provide a radical or carbanion. Moreover, in allylic systems, the benzotriazolyl moiety behaves as an ambident anion-directing group. In combination, these properties facilitate a vast array of synthetic transformations.

Because of its benign biological (nontoxic, odorless) and physical (crystalline, nonvolatile, soluble in Na_2CO_3/H_2O, sparingly soluble in H_2O) properties, and its ready availability, benzotriazole is an ideal synthetic auxiliary.

Benzotriazole chemistry is usually simple and easy to understand. Its advantage frequently lies in enabling rather common transformations to be formed efficiently, quickly, and inexpensively. As exemplified in the illustration at the start of this Concept, benzotriazole derivatives are easy to prepare and are capable of a plethora of transformations.

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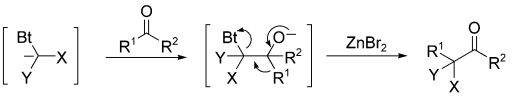
[**] Based on the Cope Senior Scholar Award Lecture presented by Alan R. Katritzky in August 2002.

Discussion

Insertion reactions: The classical insertion of a CH_2 group next to a carbonyl group by using diazomethane is of little synthetic use. The insertion of $-C(X)(Y)-$ groups can now be effected efficiently using $BtC(X)(Y)Li$ (Bt = benzotriazole) reagents[1] (Scheme 1). The diversity of the reaction is

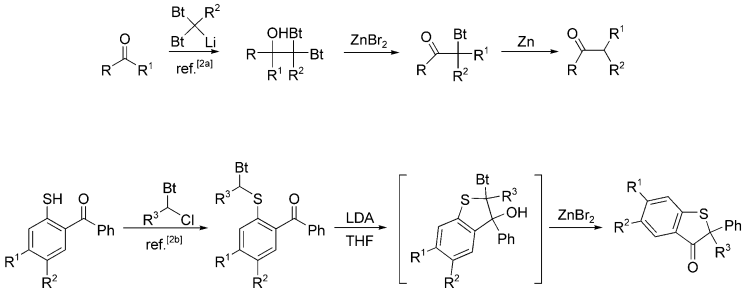


X = OR, SR, N-Carbazolyl
Y = vinyl, aryl, thienyl, indolyl, H
R^1, R^2 = H, alkyl, aryl

Regioselectivity
R^1, R^2 – The moving group is the one, which can best stabilize electron deficiency

Scheme 1. Benzotriazolyl-mediated insertion reactions.

illustrated in Table 1; many more examples are available.[1b,c] More recent work, exemplified in Scheme 2, extends the method to purely alkyl substituents[2a] and to intramolecular examples.[2b]

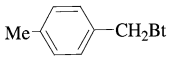
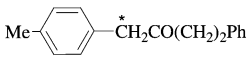
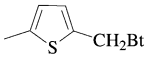
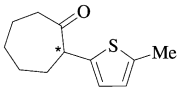
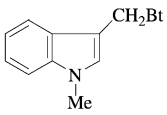
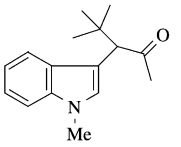
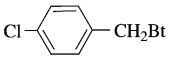
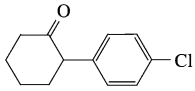
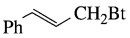
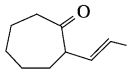
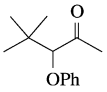
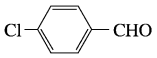
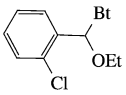
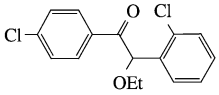
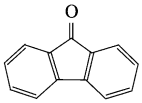
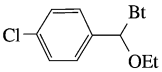
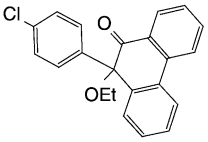
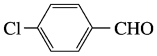
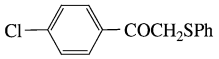


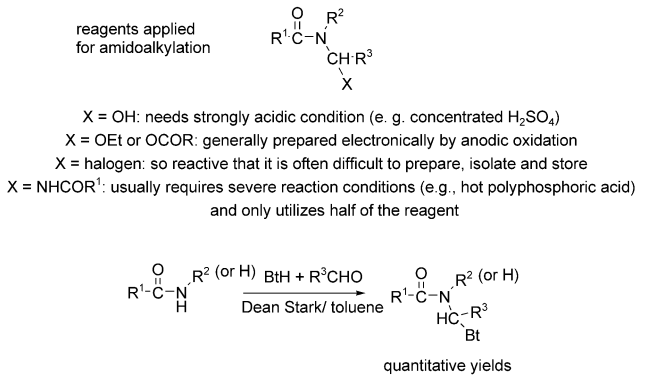
Scheme 2. Insertion reactions: future potential.[2]

Amidoalkylation: The incorporation of a group $-CHR^3N(R^2)COR^1$ into a molecule is a classical reaction, and many amidoalkylating agents have been proposed and applied (Scheme 3).

 DOI: 10.1002/chem.200304990

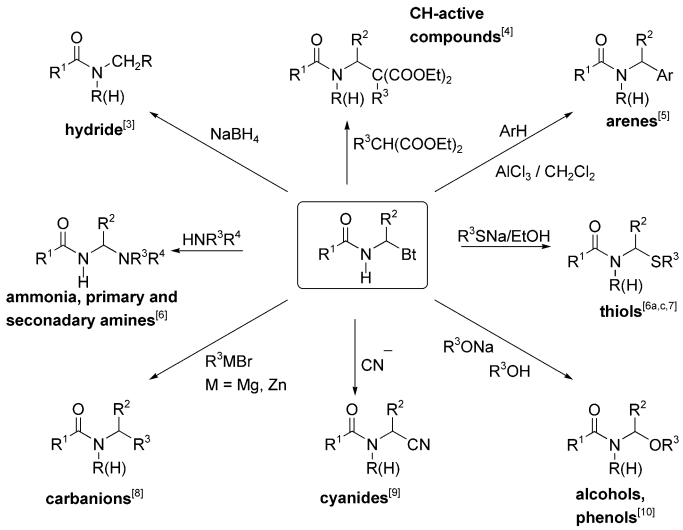
Table 1. Carbon insertion into aldehydes and ketones.[1a]

	Carbonyl compound	Bt reagent	T [°C]	t [h]	Solvent	Product	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	neat		60
6	$PhCH_2CH_2CHO$	$BtCH_2OMe$	140	1	$Cl_2CHCHCl_2$	$PhCH_2CH_2COCH_2OMe$	50
7		$BtCH_2OPh$	140	1	$Cl_2CHCHCl_2$		47
8			65	6	THF		91
9			65	24	THF		51
10		$BtCH_2SPh$	140	1	$Cl_2CHCHCl_2$		86
11	PhCOMe	$BtCH_2SPh$	140	6	$Cl_2CHCHCl_2$	PhCH(SPh)COMe	65



Scheme 3. Background for amidoalkylation.

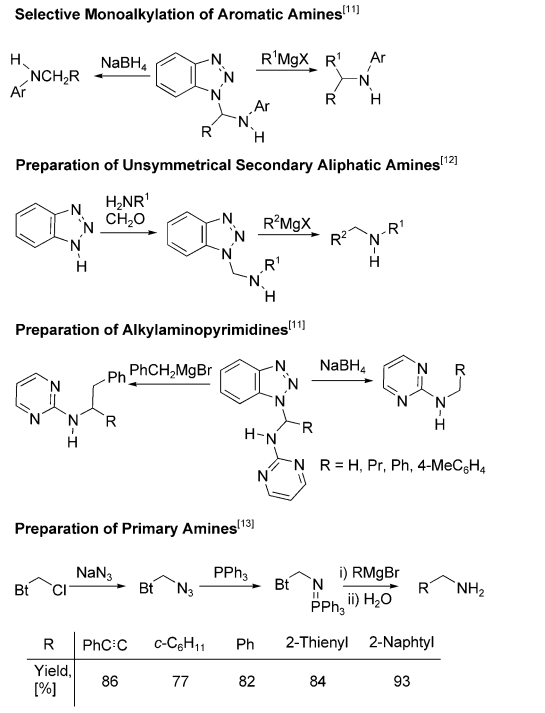
The applicability of benzotriazole amidoalkylating reagents $R^1CONRCHR^2Bt$ is far more general than that of previously suggested alternatives and enables a wide range of amidoalkylations[3–10] (Scheme 4).



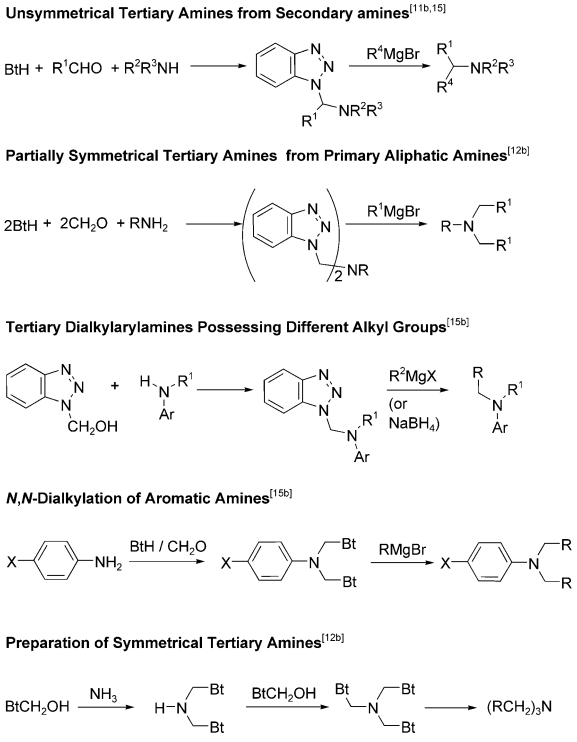
Scheme 4. Benzotriazole-mediated amidoalkylation.

Preparation of amines and aminoalkylation: Benzotriazole methodology is ideally suited to the preparation of amines; Schemes 5 and 6 illustrate how primary, secondary, and tertiary aliphatic amines as well as secondary and tertiary aromatic amines can all be constructed efficiently. A particular plus is the easy alkylation of heteroaromatic amino groups without complications from attack at the ring nitrogen atom.

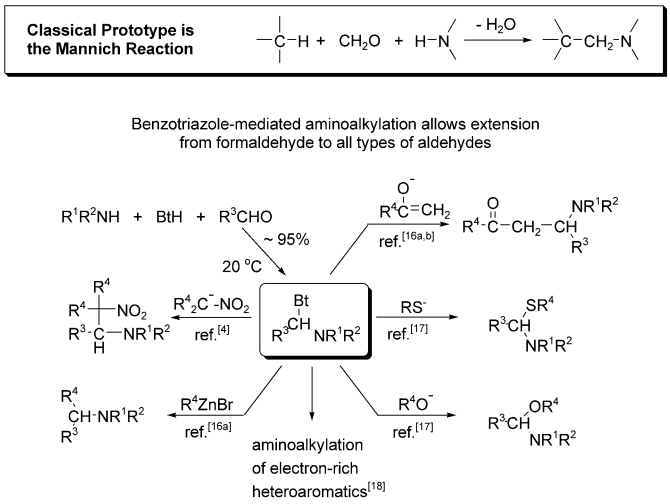
Aminoalkylation, essentially restricted in the classical Mannich reaction to formaldehyde, is easily generalized and its application extended to aliphatic, aromatic, and heteroaromatic aldehydes[4, 16–18] by means of benzotriazole methodology (see Scheme 7).



Scheme 5. Examples of syntheses of primary and secondary amines.



Scheme 6. Examples of the preparation of tertiary amines.

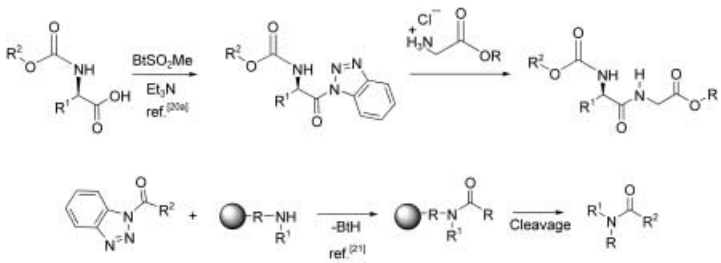


Scheme 7. Bt-C-N-R systems for aminoalkylation.

N- and C-acylation by *N*-acylbenzotriazoles: Staab pioneered the use of acylazoles for acylation many years ago.[19] Acylbenzotriazoles are easy to make directly from acids[20] by the reaction given in Equation (1):

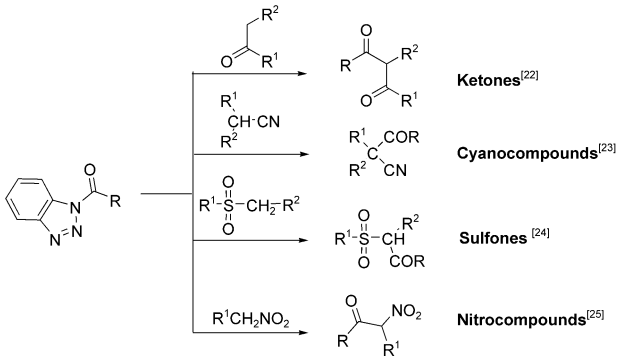
$$RCO_2^- + BtSO_2Ph(\text{or } CH_3) \rightarrow RCOBt + Ph(\text{or } CH_3)SO_3^- \quad (1)$$

They form stable crystalline, chiral reagents[20a] and are especially suitable for N-acylation in combinatorial chemistry[21] (Scheme 8). Their applications to C-acylation[22–25] are illustrated in Scheme 9: a major advantage in regioselective C over O acylation.



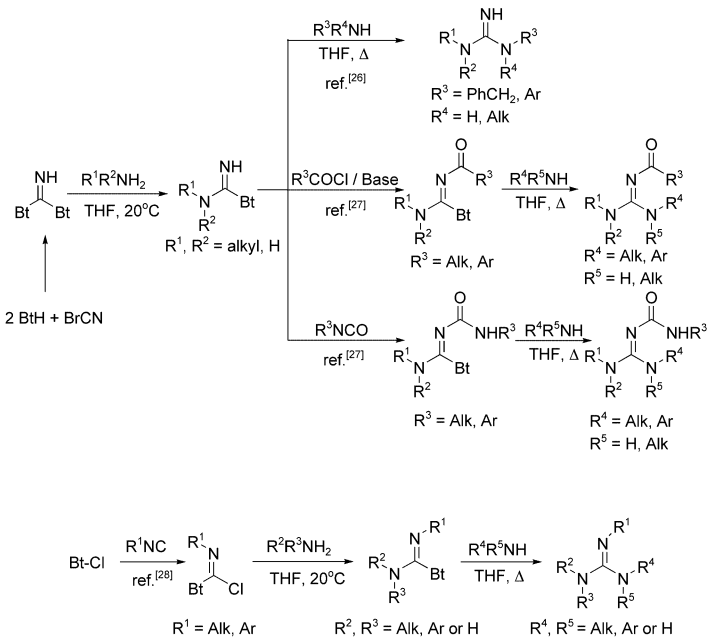
Scheme 8. Stable, crystalline chiral *N*-(aminoacyl)benzotriazoles for peptide and combinatorial chemistry.

Imidoylation reactions: Recently, two new guanylating agents have been developed. Di(benzotriazolyl)methanimine, readily



Scheme 9. Regioselective carbon acylations by *N*-acylbenzotriazoles.

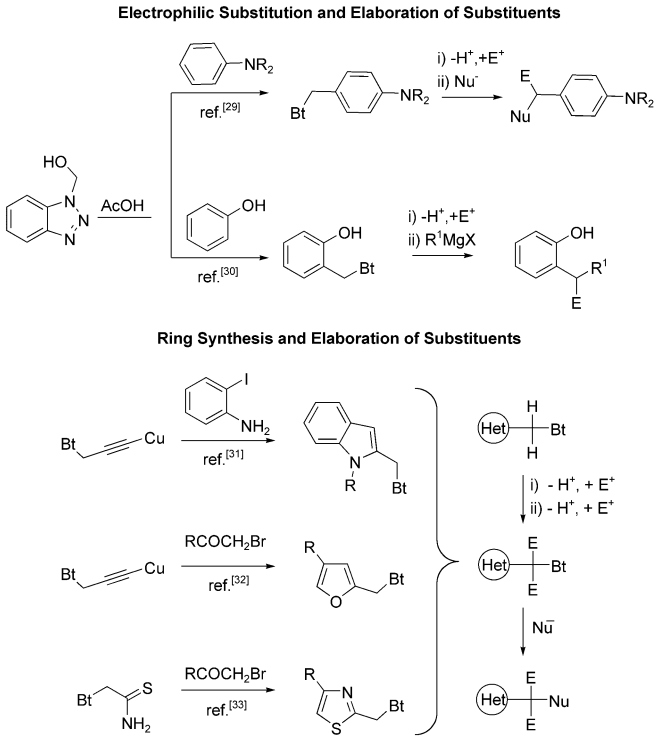
available from benzotriazole and cyanogen bromide shows differential reactivity of the two Bt groups and is an efficient reagent for the preparation of tri- and tetra-substituted guanidines,[26] polysubstituted *N*-acylguanidines, and guanylureas.[27] Benzotriazolylcarboximidoyl chlorides (stable, odorless, and convenient to handle) allow the preparation of unsymmetrical guanidines;[28] the synthesis of unsymmetrical guanidines from isocyanide dichlorides is limited to acyl and sulfonyl derivatives (Scheme 10).



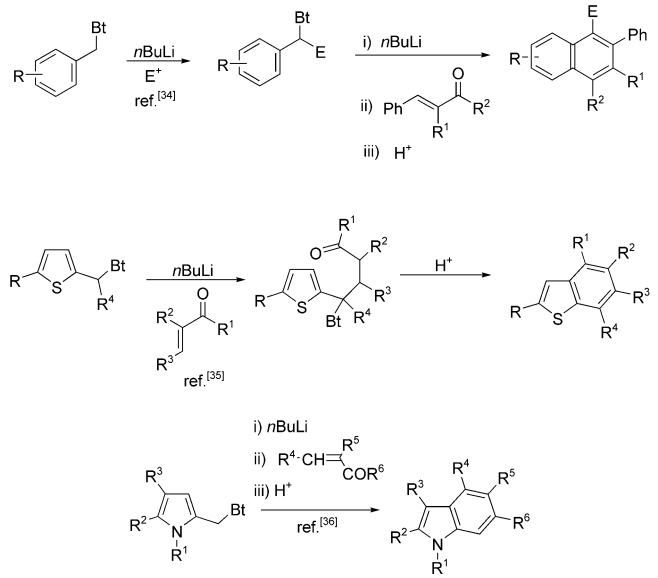
Scheme 10. Imidoylation reactions: guanidine synthesis.

Utility of Bt-C-(aryl or heteroaryl) derivatives: Easily available compounds $ArCH_2Bt$ enable the construction of elaborate substitutents in aromatic systems. Successive deprotonation allows the replacement of the hydrogen atoms by electrophiles, and the Bt group is susceptible to nucleophilic displacement[29–33] (Scheme 11).

A further application of $ArCH_2Bt$ is in benzannulation, that is, the construction of an additional benzene ring onto an existing benzenoid[34] or heteroaromatic[35, 36] ring (Scheme 12).



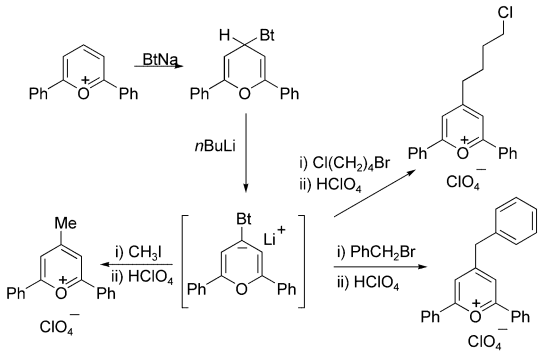
Scheme 11. Preparation and utility of Bt-C-(Hetero)aryl compounds.



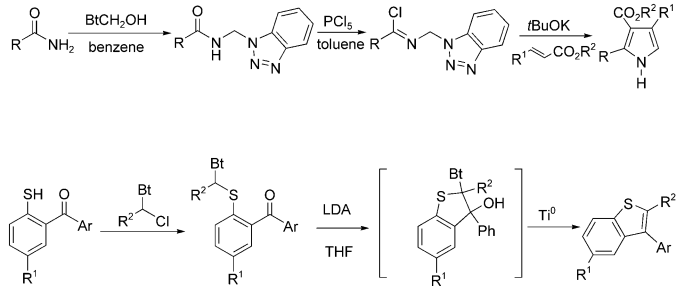
Scheme 12. Benzotriazole-mediated benzannulation.

Umpolung: Scheme 13 provides examples of the utility of benzotriazole in the umpolung of pyrylium cations by enabling the introduction of alkyl groups from electrophilic reagents.[37] The technique has been applied to other electron-deficient heteroaromatic systems.

Application in heterocyclic synthesis: Selected from numerous published examples, Scheme 14 shows novel routes to the heteroaromatic systems of pyrroles[39] and benzothiophenes.[39]

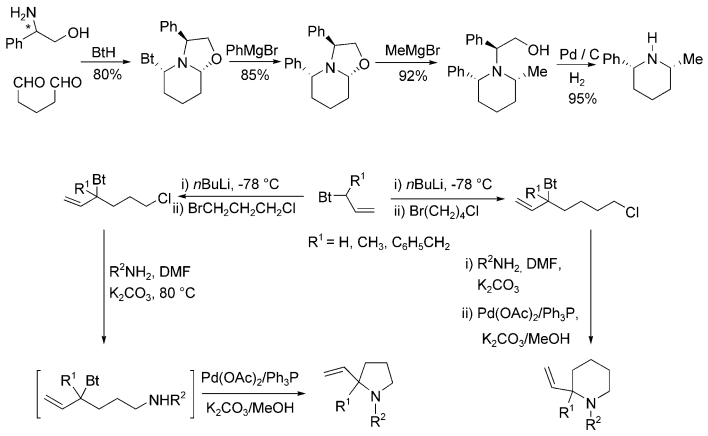


Scheme 13. Benzotriazole-mediated umpolung.



Scheme 14. Examples of the benzotriazole-mediated syntheses of heteroaromatic systems.

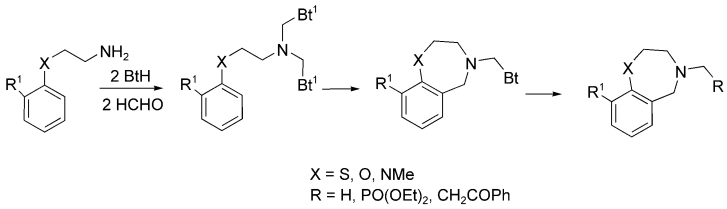
To illustrate the utility of the Bt methodology in heteroaliphatic ring formation, Scheme 15 documents 1) the synthesis of chiral 2,6-disubstituted piperidines[40] and 2) palladium-assisted benzotriazole substitution leading to 2-vinylpyrrolidines and -piperidines.[41]



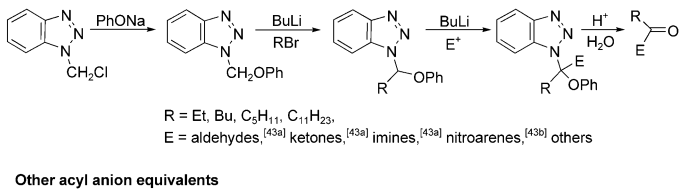
Scheme 15. Examples of the benzotriazole-mediated saturated heterocyclic ring systems.

The Bt methodology is equally applicable to large rings as exemplified by Scheme 16, which shows examples of the synthesis of seven-membered rings.[42]

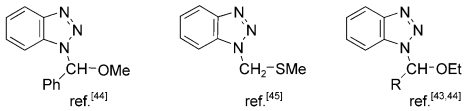
Benzotriazole-derived acyl anion equivalents: Benzotriazole-derived acyl anion equivalents[43–45] (Scheme 17) offer many



Scheme 16. Synthesis of 2,3,4,5-tetrahydro-1,4-thiazepines, -diazepines and -oxazepines.

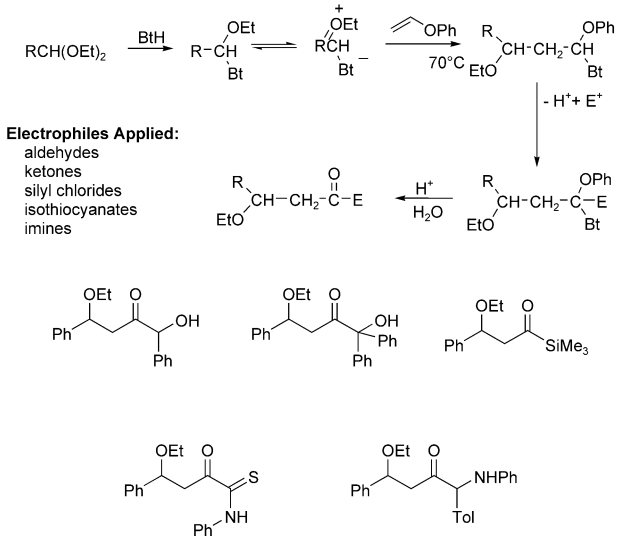


Other acyl anion equivalents



Scheme 17. Benzotriazole containing acyl anion equivalents.

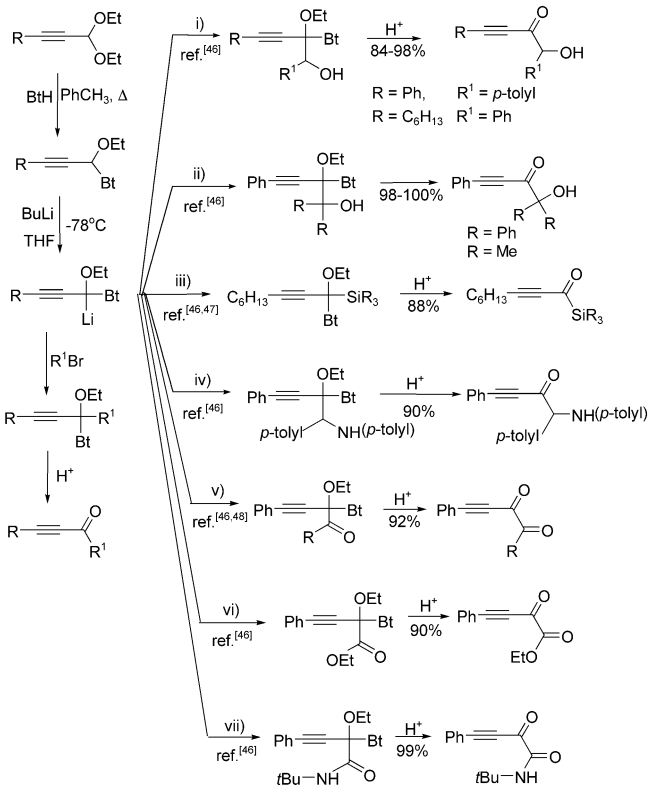
advantages over classical acyl anion equivalents such as 1,3-dithianes. A simple example is given in Scheme 18, whereby addition to phenyl vinyl ether provides intermediates capable of manifold transformations.[43a]



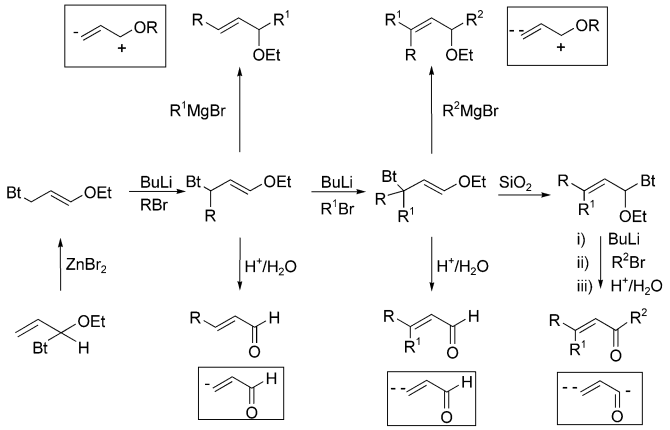
Scheme 18. Double addition to enol ethers.[43a]

Applications to acetylenic chemistry[46–48] are detailed in Scheme 19; the ambident anion-directing power of the Bt group enables the efficient synthesis of polyfunctional acetylenic ketones.

Somewhat analogous work with propenoyl anions is documented in Scheme 20.[49] Note the very mild conditions for hydrolysis (no heavy metal, no oxidizing agents!). The reversible ionization and consequent possibility of isomer-

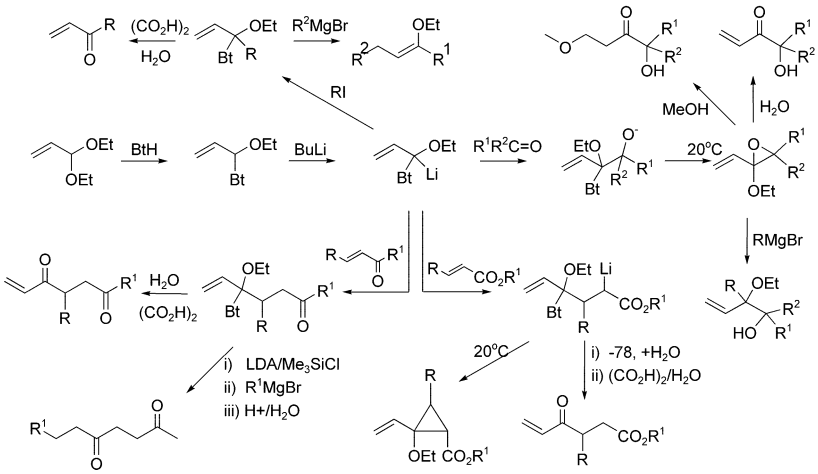


Scheme 19. Regeoselective reactions of Bt-stabilized propargylic anions.



Scheme 21. Further diverse applications of propenal acetal derived Bt reagent.

tions in this area in the past dozen years. The well shows no sign of running dry. Many Bt reagents are now available commercially. More detailed sources of benzotriazole work are available in the literature[51] and on our homepage at http://ark.chem.efl.edu. A database of benzotriazole reactions has been constructed and is available for free access and can be downloaded from our homepage. We invite all chemists to avail themselves of Bt methodology in their own chemistry and to help expand its areas of utility.



Scheme 20. Application of propenoyl anion synthon methodology.

ization of allylbenzotriazoles is utilized in Scheme 21 to provide, in this scheme alone, the five synthons shown in boxes.[50]

Conclusion

In this "Concept" it has been possible to describe briefly only a fraction of the synthetic potential of benzotraizole methodology from our group. Many other applications have appeared from other laboratories and in all approaching 500 publica-

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