Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 63 (2007) 5103–5122
Tetrahedron

Tetrahedron report number 801

Recent advances in heterolytic nucleofugal leaving groups

Salvatore D. Lepore* and Deboprosad Mondal

Department of Chemistry, Florida Atlantic University, Boca Raton, FL 33431 0991, USA

Received 2 March 2007
Available online 13 March 2007

Contents

---

1. Introduction and scope

Leaving groups have been defined as that part of a substrate that becomes cleaved by the action of a nucleophile.[1] The IUPAC definition specifies a leaving group as a molecular fragment (charged or uncharged) that becomes 'detached from an atom in what is considered to be the residual or

---

Keywords: New leaving groups; Heterolytic leaving groups; Nucleophile assisting leaving groups; NALG; Activation–deactivation leaving groups; Chiral leaving groups; Nucleofugal.

* Corresponding author. Fax: +1 561 297 2759; e-mail: slepore@fau.edu

doi:10.1016/j.tet.2007.03.049

main part of the substrate' in a given reaction.[2] A leaving group that carries away an electron pair is called a nucleofuge.[3] However, these terms are not synonymous since a nucleofuge may be a functional group that simply receives an electron pair during a nucleophilic attack without itself being cleaved away from the substrate.

The term 'leaving group' seems to have entered the chemical literature[4] in the early 1950s although its mechanistic role was certainly understood much earlier. For example, in a 1951 paper detailing the study of nucleophilic displacement reactions of neopentyl tosylates, the term 'leaving group' does not appear anywhere in the abstract or discussion.[5] In this 1951 paper, the leaving group concept was expressed by naming the actual departing group in each example under consideration (such as halide, tosylate, etc.). In the following year and in the same journal, a paper describing a study of solvolysis reactions of norbornyl halide and arylsulfonate systems uses the term 'leaving group' in the paper's abstract. However, in the body of the six-page paper the term is used only once along with 'departing ionizing group'.[6] In a 1953 short communication on the solvolysis of various alkyl halides (<600 words), the term 'leaving group' appears three times.[7] By the following year, the term seems to have gained general acceptance, appearing for the first time in the title of a paper.[8] By the mid 1960s the term 'leaving group' appeared in the titles of over 25 papers and was used in over 125 abstracts. Some undergraduate textbooks of organic chemistry also adopted the term by this time period.[9]

Leaving groups are ubiquitous in organic chemistry, playing a key role in a wide range of reactions, including nucleophilic substitution (aliphatic and aromatic), electrophilic substitution, and elimination reactions. A survey of 135 named organic reactions widely utilized in modern preparative organic chemistry[10] reveals that 38 reactions involve heterolytic nucleofugal leaving groups at some stage of their mechanism. If this selection of named reactions is representative, then it could be inferred that leaving groups play an important role in as many as 25% of all organic reactions.

Despite the wide variety of available leaving groups, there is still a need to improve their performance in terms of selectivity, reaction rates, scalability, environmental compatibility, atom economy, and other parameters. Thus, research on leaving groups continues to be an area of fruitful endeavor. As described in the subsequent pages, variations on traditional leaving group motifs have been the principal means of developing groups with improved performance. This review therefore begins with a discussion of advances in sulfonate and carboxylate-based leaving groups. The use of chiral leaving groups in asymmetric synthesis is not a new area. However, an improved mechanistic understanding of asymmetric induction in a variety of reactions in recent years has inspired the design of new chiral leaving groups that are, in many cases, modifications of traditional groups such as sulfonates and carboxylates. These and other chiral leaving groups will be discussed in some detail. The field of organometallic chemistry has offered powerful new reagents and catalysts for small molecule synthesis over the years. It is then no surprise that new organometallic leaving groups such as carboranes have recently emerged. Heterocyclic leaving groups have long been part of the synthesis chemist's repertoire and new groups arise from this class of compounds with regularity. Many researchers look into biological systems for inspiration in the design of improved reagents. This trend is also seen in the development of nucleophile assisting leaving groups (NALGs), which stabilize a reaction transition state through chelating interaction with the incoming nucleophile. Several recent examples of this relatively new class of leaving group will be described in this review.

To our knowledge, the present article is the first review of heterolytic nucleofugal leaving groups broadly defined. Given the ubiquity of leaving groups in organic chemistry, it would seem nearly impossible to review this topic exhaustively except as an extensive monograph. Indeed, reviews in this area have concentrated on specific leaving group types such as sulfonates,[11] pyridines,[12] 2-thiopyridylcarbonates,[13] and carbanionic[14] to name a few. Thus, the present review will extend to research findings primarily from the last 15 years, although a limited number of leaving group technologies from earlier periods that have not been covered in previous reviews will also be discussed. Also, some leaving groups that have been briefly reviewed as part of a larger work have been revisited here in greater detail. New reactions involving existing leaving groups will not be discussed here. Instead, the focus of this review will be on the mechanisms and performance characteristics of relatively new leaving groups.

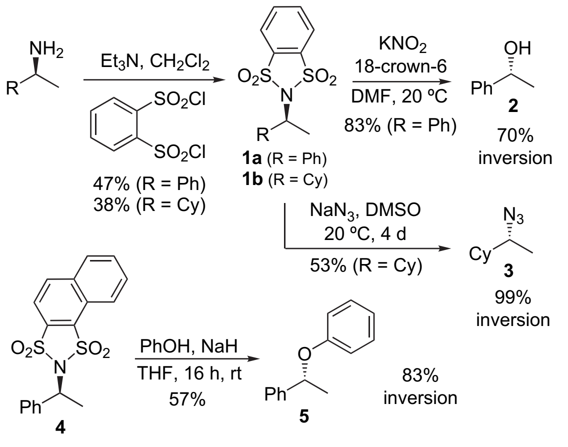
To further reduce the scope of this report to manageable proportions, heterolytic nucleofugal leaving groups involved in the vast field of acyl coupling chemistry has been excluded, especially since this area is reviewed on a routine basis.[15] Also, reports describing the adaptation of existing leaving groups to the solid phase will not be discussed here since this area has been reviewed in extensive surveys of solid phase organic synthesis techniques.[16] Finally, new leaving groups in purely inorganic systems[17] and in biological applications[18] have been omitted here as these are somewhat tangential to the emphasis of this review on new leaving groups that facilitate the synthesis of organic small molecules.

2. Sulfonate and carboxylate leaving groups

Sulfonyl chlorides such as tosyl and mesyl have found widespread use as reagents to convert alcohols into substrates for nucleophilic reactions. Significantly more reactive trifluoromethanesulfonate (triflate) leaving groups were subsequently introduced, which exhibited several orders of magnitude increased reactivity.[19] To gain some perspective, the relative reactivity of the most common leaving groups has been estimated to be substituted benzoates (1)<halides ($\sim10^4$–10^6)<sulfonates ($\sim10^{10}$–10^{12})<perfluoroalkane sulfonates ($\sim10^{15}$–10^{16}).[20] In the past 25 years, sulfonate and carboxylate leaving groups with intermediate reactivity have been prepared, often involving the introduction of electron-withdrawing substituents. In addition, new sulfonate leaving groups have been designed to suppress unwanted sulfur substitution and sulfene formation. Some of these sulfonate leaving group developments have been recently reviewed.[11]

2.1. Benzenedisulfonylimides

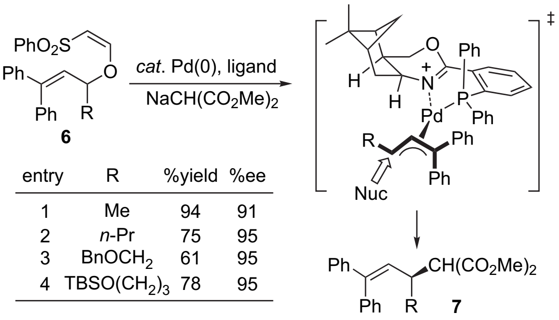
The conversion of alcohols to a sulfonate ester is a well-established strategy to create substrates capable of undergoing nucleophilic substitution whereas the related conversion of amines to sulfonamides does not lead to a similar result. However, the addition of a second sulfonyl group, as in the case of benzenedisulfonylimides, provides a suitable leaving group. Using the bis-sulfonyl technique, amines have been converted to alcohols and azides with inversion of configuration.[21] This conversion has been demonstrated with 1-phenyl and 1-cyclohexyl ethylamine (Scheme 1). The reaction of either primary amine with benzene-1,2-disulfonyl chloride led to the corresponding benzenedisulfonylimide intermediates **1a** and **1b** in somewhat low yields. The reaction of **1a** with KNO_2 led to alcohol **2** in 83% yield and with 70% inversion of configuration. Using NaN_3, azide product **3** was obtained with essentially complete inversion although the yield was fairly modest (53%) even after a reaction time of 4 days (Scheme 1). Earlier studies involving dimesylimides and dinosylimides led to similarly high percent inversions but suffered from lower yields in both the imide formation and subsequent nucleophilic substitution steps.[22] Disulfonylimide leaving group technology has also been used in the synthesis of aryl ethers starting from naphthyl disulfonylimide **4**.[23] The reaction of **4** with sodium phenoxide gave inverted aryl ether product **5** in 53% yield (Scheme 1).



Scheme 1. Conversion of primary amine to alcohols, azides, and aryl ethers via disulfonylimide intermediates.

2.2. Vinylogous sulfonates

Vinylogous sulfonates have been developed to serve as improved leaving groups for a variety of palladium-catalyzed allylic substitution reactions.[24] Using a *cis*-phosphino-1,3-oxazine ligand, a variety of alkyl-substituted β-phenylcinnamyl substrates **6** are converted to malonate products **7** via Pd(II) catalysis. The stereochemical outcome was rationalized using a palladium allyl transition state involving the chiral oxazine ligand (Scheme 2). This allylation reaction exhibits high enantioselectivity (95%) and increased catalyst turnover rates relative to traditional acetate leaving groups (Scheme 2).[25] However, this asymmetric method has only been demonstrated with β-phenylcinnamyl alcohol derivatives **6** with straight chain substituents at the carbinol position.

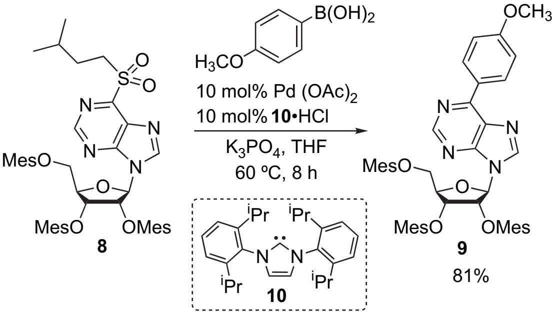


entry	R	%yield	%ee
1	Me	94	91
2	*n*-Pr	75	95
3	$BnOCH_2$	61	95
4	$TBSO(CH_2)_3$	78	95

Scheme 2. Vinylogous sulfonate leaving groups for asymmetric allylic alkylation.

2.3. Alkyl sulfonyls

Using 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene (**10**) as a palladium ligand, sulfonyl purine nucleoside **8** was coupled to a *p*-methoxyphenyl group to give product **9** in 81% yield via a Suzuki reaction (Scheme 3).[26] The sulfonyl purine derivative was obtained by an S_NAr displacement of a halopurine precursor followed by a high-yielding oxidation. This methodology opens a new avenue for modification of purines at the C6 position.

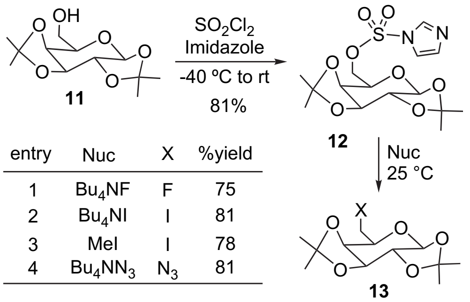


Scheme 3. Alkyl sulfonyl leaving group in Suzuki coupling reaction to give substituted nucleosides.

2.4. Imidazole-1-sulfonates (imidazylates)

Imidazole-1-sulfonates (imidazylates) have been used with success in S_N2 reactions involving mono and oligosaccharide substrates at primary and secondary positions.[27] The imidazole-1-sulfonate can be prepared from an alcohol by reaction with sulfuryl chloride to form the chlorosulfate ester followed by reaction with imidazole or by reaction with N′,N-sulfuryldiimidazole.[28] This leaving group has been applied primarily to the synthesis of mono and oligosaccharides. For example, diisopropylidene galactopyranose (**11**) was converted to derivative **12** with an imidazyl group at the 6-position. Imidazyl **12** was then converted to the corresponding 6-fluoro, iodo, and azido products **13** in good yields (Scheme 4). An imidazylate intermediate has also been methylated (remote activation[29]) at the imidazole nitrogen leading to increased nucleofugacity (entry 3, Scheme 4). The imidazylate leaving group has also been utilized in oligosaccharide derivatization.[30]

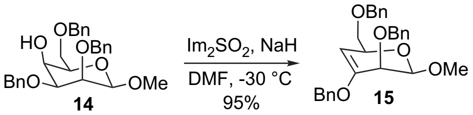
More recently, the reaction of an imidazylate of a 4-deoxy-arabinoside with tetrabutylammonium cyanide (prepared in situ from Bu_4NF and TMSCN) gave the cyanide product



entry	Nuc	X	%yield
1	Bu_4NF	F	75
2	Bu_4NI	I	81
3	MeI	I	78
4	Bu_4NN_3	N_3	81

Scheme 4. Galactopyranose derivatization via imidazylates.

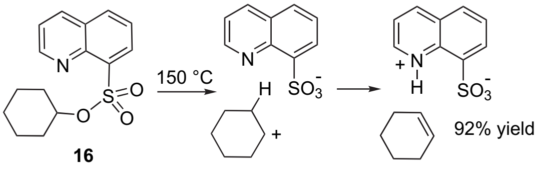
in an exceptionally high yield (81%).[31] Highly regioselective elimination reactions involving imidazylate intermediates have been reported. As a representative example, pyranose **14** was converted to the corresponding imidazylate intermediate, which underwent an elimination reaction in situ to form enopyranoside **15** in 95% yield (Scheme 5).[32]



Scheme 5. Highly regioselective imidazylate elimination to give an enopyranoside.

2.5. Pyridine and quinoline sulfonates

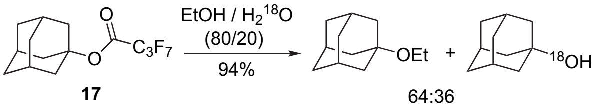
The secondary esters of 2-pyridine and 8-quinoline sulfonic acid decompose cleanly at moderate temperatures to give olefins in high yields (Scheme 6).[33] A variety of substrates were successfully converted to the olefin using this pyrolysis method including cyclohexanol sulfonate ester **16** (Scheme 6), *exo*-norbornol, menthol, neomenthol, and 2-octanol. Negligible differences in product yield were observed between the pyridine and quinoline sulfonate esters. Product studies indicated that the pyrolysis did not proceed via a concerted E2-type mechanism. Instead, an E1 mechanism was invoked in which the reaction was facilitated by the basic nitrogen of the quinoline sulfonate leaving group.



Scheme 6. Pyrolysis of 8-quinoline sulfonate **16** to give cyclohexene.

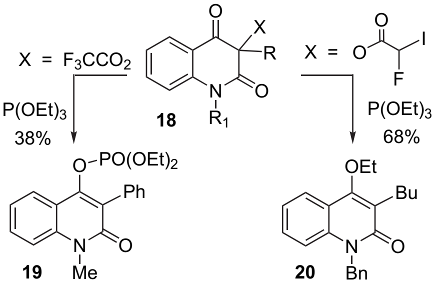
2.6. Fluorocarboxylates

Perfluorobutyrate, conveniently prepared from a precursor perfluoro alcohol, has been shown to possess a reactivity similar to that of halides in solvolysis reactions.[20] A product and isotope distribution study for the reaction of 1-adamantyl perfluorobutyrate (**17**) in 80:20 ethanol/$H_2{}^{18}O$ demonstrated exclusive alkyl–O cleavage to give the ethyl ether and ^{18}O-alcohol products in a 94% combined yield (Scheme 7). The 1- and 3-homoadamantyl perfluorobutyrate analogs of **17** exhibited faster solvolysis rates due to the increased flexibility of the hydrocarbon skeleton.



Scheme 7. Perfluorobutyrate leaving group in solvolysis.

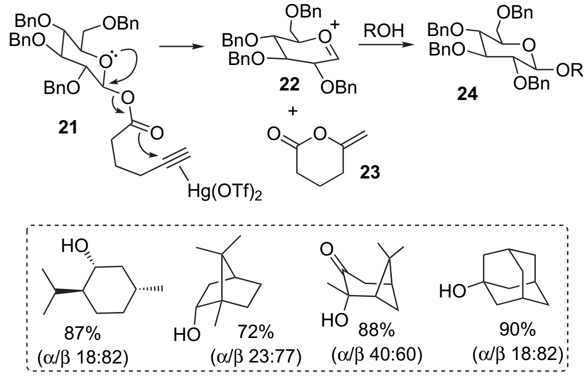
Quinoline-2,4(1*H*,3*H*)-diones give the Perkow reaction product or lead to enol ether depending on the nature of the carboxyl leaving group at the 3-position.[34] The use of the trifluoroacetate leaving group in substrate **18** led to the Perkow enol phosphite product **19** upon treatment with triethyl phosphite (Scheme 8). With the novel fluoroiodoacetyl leaving group, enol ether **20** was obtained in 68% yield.



Scheme 8. Perkow reaction involving fluorocarboxylates.

2.7. Alkynoate

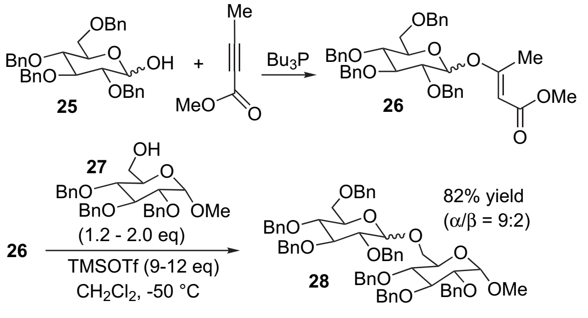
A novel $Hg(OTf)_2$-catalyzed glycosylation procedure has been developed using alkynoic acid residues as the leaving group under mild reaction conditions and efficient catalytic turnover.[35] This leaving group is remotely activated in the presence of Hg(II), which complexes the alkyne moiety such as in **21** (Scheme 9). Intermediate **21** underwent endocyclization with the mercury/alkyne complex leading to oxonium cation **22** and to methylene lactone **23** (regenerating the mercury catalyst). Addition of alcohols to intermediate **22** then gave glycosyl products **24**. This procedure was particularly efficient for the glycosylation of hindered alcohols such as menthol, adamantanol, and fenchol (Scheme 9). Due to its remote activation mechanism, this alkynoate leaving group can also be categorized as an activation–deactivation strategy, which is discussed in Section 6 of this report.



Scheme 9. Alkynoate leaving group for glycosylation.

2.8. Vinylogous carboxylates and carbonates

Glycosylation using vinylogous carboxylates and carbonates (enol ethers) as leaving groups have been described.[36] The reaction of tetra-*O*-benzyl glucopyranose (**25**) with 2 equiv of methyl-2-butynoate in the presence of a catalytic amount of tri-*n*-butylphosphine gave corresponding glycosyl donor **26** (Scheme 10). In this synthesis, glycosyl donor **26** was obtained exclusively in the *E*-configuration due to the steric bulk imposed by the pyranose moiety during the formation of the enol ether. Treatment of donor **26** with alcohol **27** at room temperature gave disaccharide **28** in 82% yield (α/β=9:2). A large excess of TMSOTf (9–12 equiv) was required to obtain an optimal yield and anomeric ratio. With a smaller amount of TMSOTf (1 equiv) at room temperature, the coupling yield to give **28** was reduced to 19%.



Scheme 10. Synthesis of disaccharide **28** using a vinylogous carbonate leaving group.

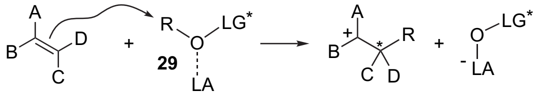
3. Chiral leaving groups

Methods for asymmetric synthesis have been classified into four types, each based either on the chirality of the substrate, auxiliary, added reagent, or catalyst.[37] Although research to develop new and more efficient chiral catalysts currently appears to dominate the field of asymmetric methodology,[38] the development of new chiral auxiliary-based methods continues. The conversion of a prochiral substrate to a chiral center using a chiral leaving group provides an attractive alternative to traditional chiral auxiliary-based methods. Chiral leaving groups such as menthoxy have been used in the highly efficient syntheses of planar chiral binapthyl compounds, an area extensively reviewed.[39] Importantly, chiral leaving groups do not require a removal step, which is a common drawback in many chiral auxiliary methods.

3.1. BINOL derivatives

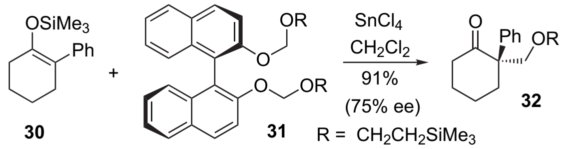
A method for face-selective alkylation of prochiral olefins using BINOL derivatives as chiral leaving groups under acidic conditions has been developed.[40] In this strategy, a Lewis acid-activated C–O bond (as in **29**) is cleaved at the moment of electrophilic addition releasing the BINOL leaving group (Scheme 11). Lewis acid/LG complex **29** can be thought of as a cationic synthon possessing a chiral environment analogous to Lewis acid-assisted chiral Brønsted acid (LBA) used in enantioselective protonation reactions.[41]

Analogous to the LBA method, asymmetric methods for alkoxymethylation of silyl enol ethers using a non-racemic



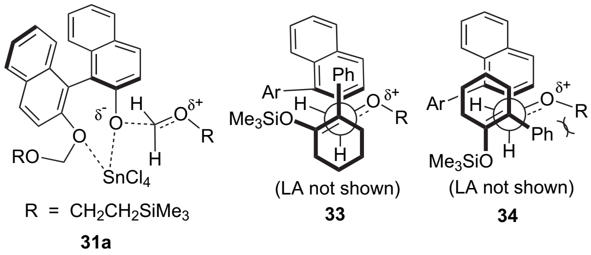
Scheme 11. Lewis acid-activated alkene addition reaction involving chiral leaving group LG*.

BINOL leaving group has been developed. For example, the reaction of trimethylsilyl enol ether **30** with BINOL derivative **31** in the presence of $SnCl_4$ led to product **32** in 91% yield and 75% ee (Scheme 12). This result was an improvement over an earlier reported asymmetric hydroxymethylation reaction.[42]



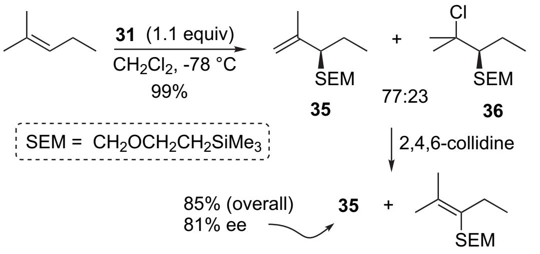
Scheme 12. Enantioselective alkoxymethylation of enol ether **30** with BINOL derivative **31** using $SnCl_4$.

The observed stereochemical outcome of the alkoxymethylation reaction can be explained in terms of an acyclic extended transition state similar to one proposed by Noyori.[43] NMR studies indicate that the BINOL leaving group in **31** coordinates with $SnCl_4$ at the aryl ether oxygens (Scheme 13).[40] The introduction of silyl enol ether **30** is thought to give transition state **33**, which can be represented using a Newman-type diagram (Scheme 13). As indicated in the scheme, transition state **33** is stabilized by a π–π attractive interaction between the phenyl group of **30** and one of the napthyl groups of BINOL **31**. The other possible approach of enol ether **30** to the **31a** complex would give transition state **34** involving a destabilizing steric repulsion between the R and the phenyl group of **30** (Scheme 13).



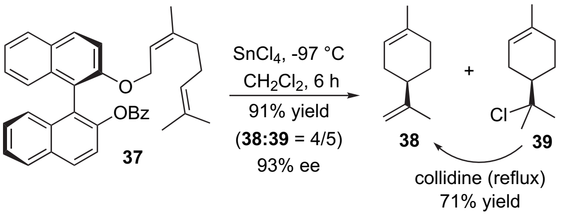
Scheme 13. Proposed extended transition states for enantioselective alkoxymethylation reactions.

The chiral naphthol leaving group of **31** has also been utilized in enantioselective Prins-type reactions with trisubstituted alkenes in the presence of $SnCl_4$. Rapid additions of SEM ($CH_2OCH_2CH_2SiMe_3$) were observed with several alkenes with selectivity for the less substituted carbon of the double bond. Chlorinated side products were also observed. These side products could be converted to the SEM-alkene on treatment with collidine. In the case of 2-methyl-2-pentene, electrophilic SEM addition occurred at the 3-postion giving desired allyl SEM product **35** and chloro product **36** in quantitative yield. Subsequent treatment of the mixture with base gave 85% yield of **35** in 81% ee (Scheme 14).[40]



Scheme 14. Enantioselective Prins-type reaction of 2-methyl-2-pentene with **31**.

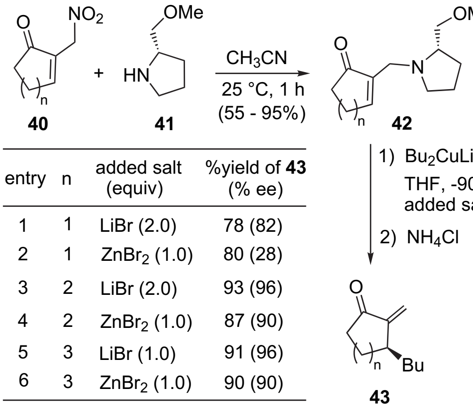
The first biomimetic asymmetric synthesis of (+)-limonene was accomplished in 1983 (up to 77% ee) using (*R*)-BINOL as a leaving group in an intramolecular cyclization of a mononeryl ether with bulky organoaluminium reagents.[44] More recently, improved enantioselectivities have been obtained using BINOL derivatives activated by $SnCl_4$ (Scheme 15). Thus neryl-BINOL derivative **37** was converted to (+)-limonene (**38**) and α-terpinyl chloride (**39**) in 91% yield as a 4:5 mixture.[40] The transformation was highly enantioselective (93% ee) in chlorinated solvents such as CH_2Cl_2 and propyl chloride. Heating the mixture of **38** and **39** in 2,4,6-collidine under reflux conditions converted chloride **39** to limonene in 71% yield (Scheme 15).



Scheme 15. Enantioselective cyclization of BINOL derivative **36** to give limonene **37**.

3.2. Chiral amines

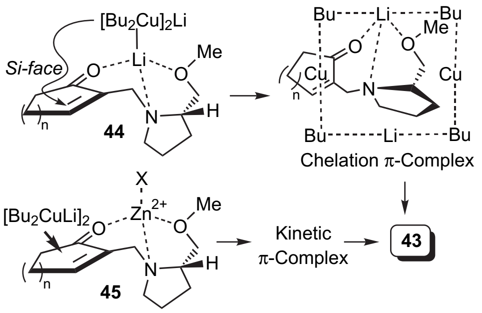
Chiral amine leaving groups derived from proline have been used to direct cuprate additions to cycloalkanones **42**. The treatment of **42** with *n*-$Bu_2CuLi\cdot LiBr$ and added salts (LiBr or $ZnBr_2$) led to non-racemic 3-substituted 2-*exo*-methylenecycloalkanones **43**. In most cases, reaction yields were between 80% and 90% with good enantioselectivities observed (Scheme 16).[45] Enones **42** were conveniently prepared from the reaction of α-(nitromethyl) enones **40** with (*S*)-(+)-(methoxymethyl) pyrrolidine (**41**) in acetonitrile (Scheme 16).[46] The use of $ZnBr_2$ as an additive led to lower enantioselectivities especially in the case of cyclopentanone (Scheme 16, entry 2).



entry	n	added salt (equiv)	%yield of **43** (% ee)
1	1	LiBr (2.0)	78 (82)
2	1	$ZnBr_2$ (1.0)	80 (28)
3	2	LiBr (2.0)	93 (96)
4	2	$ZnBr_2$ (1.0)	87 (90)
5	3	LiBr (1.0)	91 (96)
6	3	$ZnBr_2$ (1.0)	90 (90)

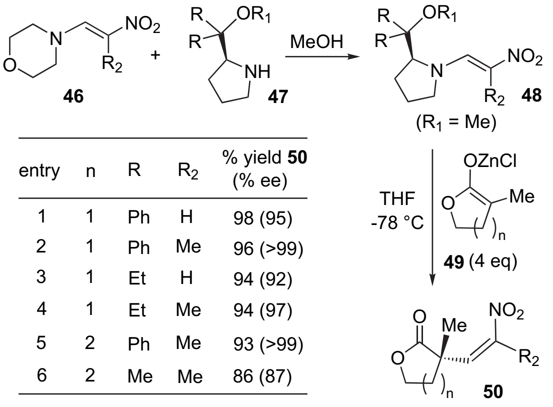
Scheme 16. Synthesis of non-racemic 3-butyl-2-*exo*-methylenealkanones.

A transition state model to explain the enantioselectivity for the selective Bu_2CuLi additions has been proposed (Scheme 17).[45] Chiral enone **42** initially forms weak tridentate chelation complex **44** with Bu_2CuLi by coordination of three heteroatoms to the lithium, followed by additional d–π^* complex formation between the copper atom and the conjugated enone moiety. This chelation d–π^* complexation occurs at the *Si* face, since the *Re* face is shielded by the extruding pyrrolidine ring. Added $ZnBr_2$ gave complex **45**, which led to lower enantioselectivities (Scheme 16, entries 2, 4, and 6) by impeding Li^+-directed chelation π-complexation between Bu_2CuLi and **42** leading to fast 1,4-addition via a kinetic or non-chelated d–π^* complex due to the strong Lewis acidity of $ZnBr_2$.



Scheme 17. Transition state models of Bu_2CuLi addition to **42** with LiBr and $ZnBr_2$ additives.

Proline-derived leaving groups have been used to induce asymmetry in addition–elimination reactions of chiral nitroenamines.[47] A class of compounds with unique reactivity,[48] nitroenamines have been prepared as chiral reagents through an amine exchange reaction between morpholino enamines **46** and amines **47** to give chiral enamines **48** in 90% yields with exclusive *E*-configuration (Scheme 18).[49] Nitroenamines **48** were reacted with zinc enolates of α-methyl substituted lactone **49** in THF at −78 °C to give adduct **50** containing a chiral quaternary carbon in high enantioselectivity and yield (Scheme 18).[50] The zinc countercation was

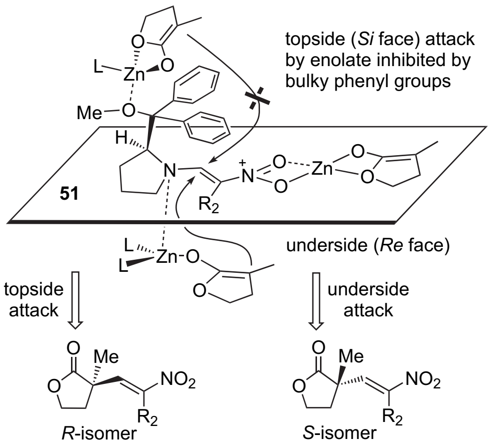


entry	n	R	R_2	% yield **50** (% ee)
1	1	Ph	H	98 (95)
2	1	Ph	Me	96 (>99)
3	1	Et	H	94 (92)
4	1	Et	Me	94 (97)
5	2	Ph	Me	93 (>99)
6	2	Me	Me	86 (87)

Scheme 18. Synthesis of chiral nitroenamines **48** and asymmetric addition of α-methyl substituted lactone enolates **49**.

chosen since initial reports indicated that this metal led to superior enantioselectivities and chemical yields relative to analogous Li^+ and Cu^+ enolates.[51] Extensive optimization indicated that 4 equiv of zinc enolate was essential for high enantioselectivities. The enantioselectivity depended on the bulkiness of R in the chiral nitroenamines, namely, the order was Ph>Et>Me, which indicated that increase in bulk of the chiral auxiliary increased the enantioselectivity of the reaction. The effects of substituents at the 1-position (R_2) were also recently explored using an achiral nitroenamine.[52]

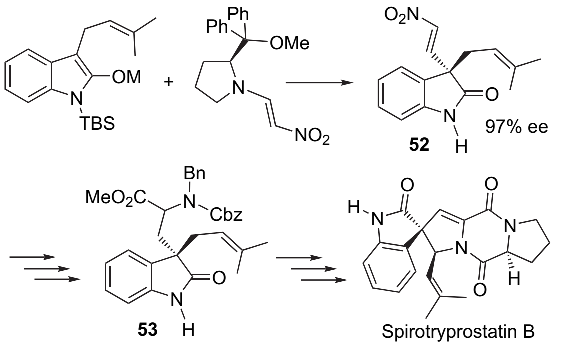
A possible transition state model to explain the enantioselective product outcome and the role of multiple equivalents of zinc enolate has been proposed (Scheme 19). Two equivalents of zinc enolate were consumed to form complex **51** by coordination with nitroenamine. Zinc enolate can then attack **51** from topside or underside. Attack of **51** from the topside requires 2 equiv of zinc enolate. However, the steric bulk of the R groups (phenyl as shown in Scheme 19) inhibits zinc enolate approach from the topside. Although *Re* face attack of complex **51** requires a third zinc enolate, the approach of the nucleophile entails less steric impedance.



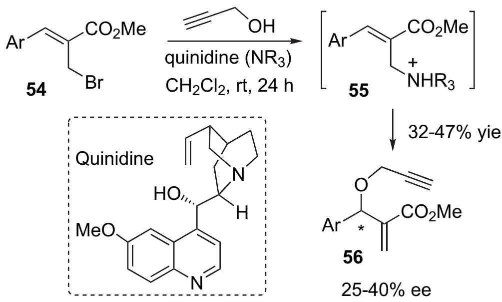
Scheme 19. Transition state model rationalizing enantioselective formation of nitro-olefination product.

Asymmetric nitro-olefinations have been utilized in the efficient synthesis of a variety of indole alkaloid natural products containing quaternary carbon stereocenters. These syntheses have been previously reviewed.[47,53] A recent total synthesis of spirotryprostatin B is illustrative of asymmetric nitro-olefination synthetic approaches (Scheme 20).[54] Nitro-olefination of an indole enolate gave intermediate **52** in 97% ee. Synthetic manipulation of the highly versatile vinyl nitro group gave advanced intermediate **53** after several steps. The remaining key transformations to obtain spirotryprostatin B involved the introduction of proline as a peptidic linkage to **53** followed by heteroatom substitution at the allylic position (Scheme 20).

More recently, a Baylis–Hillman type reaction has been developed to give non-racemic propargyl ethers **56** using stoichiometric quinidine as a chiral leaving group (Scheme 21). Propargyl alcohol was added to bromomethyl enoates **54** via quinidinium intermediates **55** to give adducts **56** in modest enantioselectivities (25–40% ee) and yields (32–47%).[55]



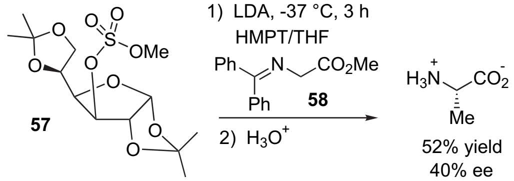
Scheme 20. Application of nitro-olefination in the total synthesis of spirotryprostatin B.



Scheme 21. Enantioselective synthesis of propargyl ethers **56** using quinidine as a chiral amine leaving group.

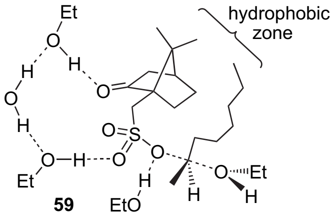
3.3. Chiral sulfonates

The methylester of *N*-diphenylmethylene glycine (**58**) has been lithiated with LDA and treated with non-racemic furanose-derived methylating agent **57** to give alanine in 52% yield and 40% ee after hydrolysis (Scheme 22).[56]



Scheme 22. Enantioselective alkylation of protected glycine using a chiral sulfate leaving group.

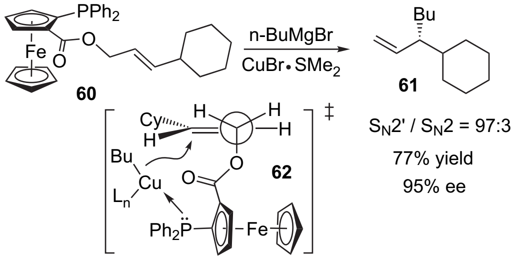
Chiral camphor-10-sulfonate (casylate) leaving groups have been studied in solvolysis reactions.[57] The solvolysis rate of the two diastereomers formed from D-2-octyl L-casylate and from L-2-octyl L-casylate was measured. These studies revealed a difference in the rate arguing for an S_N2-type transition state. The approach of the ethanol nucleophile was thought to be influenced in part due to van der Waals interactions between the chiral leaving group and the octanyl substrate as in proposed transition state **59** (Scheme 23). Reactions proceeding through a solvent-separated ion pair mechanism as in the case of a cholesterol D- and L-casylates gave nearly identical rates of solvolysis in aqueous ethanol.[58] In neither the octyl nor the cholesterol casylate solvolysis reactions was the enantioselectivity measured although it was anticipated to be low.



Scheme 23. Proposed low energy transition state for the ethanolysis of camphor-10-sulfonate of 2-octanol.

3.4. Chiral carboxylates

The use of chiral carbamates as leaving groups in allylic substitution is an area of active investigation and has been recently reviewed.[59] However, analogous reactions with chiral carboxylates have been little explored. Enantioselective copper-mediated S_N2' substitution reactions involving *ortho*-diphenylphosphanylferrocene carboxylate (*o*-DPPF) as chiral leaving groups have been recently reported (Scheme 24).[60] DPPF, which is conveniently prepared,[61] was initially developed as a catalyst-directing group in rhodium-based hydroformulation reactions.[62] The high enantioselectivity of product **61** (95%) observed in the addition of copper catalyst to **60** was rationalized on the basis of a strong phosphine–copper liganding interaction in transition state **62** (Scheme 24). Interestingly, the use of a chiral ferrocene thiol as a copper ligand gave product **61** in only 64% ee when reacted with the precursor allylic acetate.[63] In this case a nearly stoichiometric amount of the ferrocene thiol ligand was required to achieve a reasonable enantioselectivity.



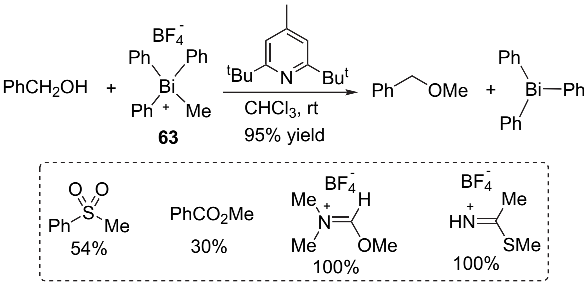
Scheme 24. Enantio- and regioselective addition of *n*-BuMgBr to *o*-DPPF ester **60**.

4. Organometallic leaving groups

Most leaving groups contain a heteroatom or halogen atom at the point of cleavage from the substrate. A general strategy for improving the nucleofugacity of such leaving groups is to incorporate an electron-withdrawing functional group as part of the departing moiety. Organometallic leaving groups offer the possibility of improved nucleofugacity through redox processes not available to second-row heteroatoms typically found in leaving groups. For example, the phenyliodonio leaving group exhibits a nucleofugacity 10^6 times greater than the triflate group allowing for S_N2 substitutions on vinyl substrates.[64] Surveys of nucleophilic reactions involving this leaving group have recently been published.[65]

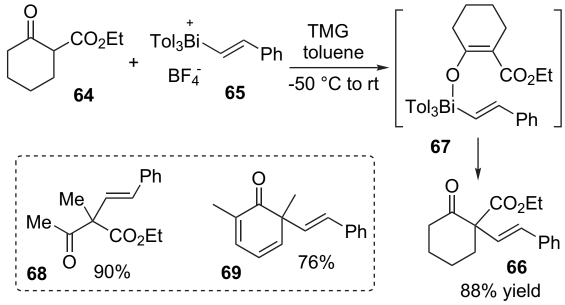
4.1. Triarylbismuth

In the presence of a bulky amine base, methyltriphenylbismuthonium tetrafluoroborate (**63**) reacts with benzyl alcohol to give the corresponding methyl ether in 95% yield (Scheme 25).[66] Kinetic studies of this methylation reaction revealed a twofold rate enhancement relative to the analogous transformation involving methyl triflate, a powerful leaving group. These studies indicate that triphenylbismuth is an exceptionally good leaving group. Other weak nucleophiles have also been successfully methylated with **63** including benzene sulfinate, benzoate, DMF, and thioacetamide (Scheme 25).



Scheme 25. Reaction of bismuthonium **63** with benzyl alcohol and synthesis of other methylation reaction products.

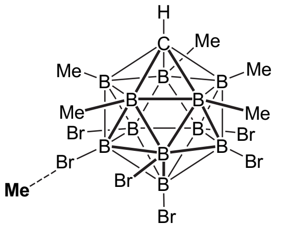
The excellent nucleofugal properties of triarylbismuth have also been utilized in the direct alkenylation of β-dicarbonyl and phenol compounds in the presence of 1,1,3,3-tetramethylguanidine (TMG) (Scheme 26).[67] For example, 2-oxocyclohexanecarboxylate (**64**) reacted with tritolylbismuthonium **65** to give vinylated product **66** in 88% yield. The reaction is thought to proceed via a pentacoordinate bismuth intermediate such as **67**. Under the same conditions, ethyl oxobutanoate and 2,6-dimethyl phenol substrates led to vinylation products **68** and **69**, respectively (Scheme 26). The use of hypervalent bismuth reagents in the α-arylation and vinylation of silyl enol ethers[68] and enones[69] is also known. Related vinylation reactions with alkenyllead triacetates have also been reported.[70]



Scheme 26. Reaction of alkenyltriarylbismuthonium salt **65** with 2-oxocyclohexanecarboxylate (**64**) to give vinylated product **66**.

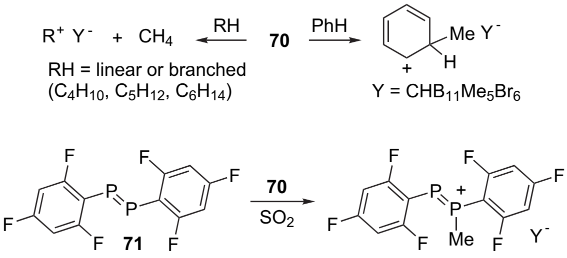
4.2. Carboranes

A new class of potent alkylating agents based on carborane leaving group $(CB_{11}Me_5Br_6)^-$ has been recently developed. Carborane anions are among the least nucleophilic anions presently known. They also offer improved leaving group characteristics over the better-known fluoroantimonates in that they are non-oxidizing and are not a source of fluorides, which may participate in unwanted nucleophilic side reactions. In solution, the carborane reagents exist as equilibrating isomers with the alkyl group at the 7–11 or 12 bromide position of the CB_{11} icosahedral anion (Scheme 27). A crystal structure analysis revealed that the alkyl–carborane bond is covalent.[71]



Scheme 27. 7-Isomer of $Me(CB_{11}Me_5Br_6)$.

In the case of $Me(CHB_5Me_5Br_6)$ (**70**), the high electrophilic reactivity of this reagent has been illustrated in three methylation reactions[71] that do not occur with methyl triflate, a traditional and powerful methylating agent (Scheme 28). Benzene was methylated using stoichiometric amounts of **70** to give the toluenium ion. Remarkably, carborane **70** also reacted with several linear and branched alkanes containing four to six carbons to form tertiary carbocations at or below room temperature via hydride abstraction. Highly electron-deficient phosphorus compounds such as **71** were methylated in the presence of carborane **70** in liquid SO_2 while remaining unreactive toward neat boiling methyl triflate.



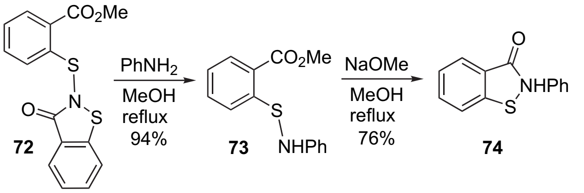
Scheme 28. Methylation reactions involving carborane **70**.

5. Heterocyclic leaving groups

If leaving groups employed in activated ester reactions for amide synthesis are excluded, pyridines are among the most widely used heterocyclic leaving groups in organic synthesis, an area extensively explored and reviewed elsewhere.[12] However, a limited number of other heterocyclic leaving groups have appeared in the intervening years involving more specialized applications.

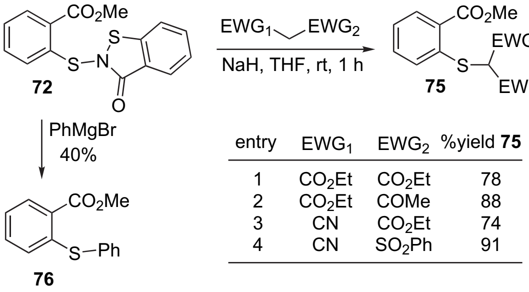
5.1. Benzoisothiazole-3-ones

Mercaptobenzoates containing a 1,2-benzoisothiazole-3-one at the sulfur position are useful substrates for nucleophilic attack of anilines and primary amines to give *N*-substituted sulfenamides. As a representative example, mercaptobenzoate **72** reacted with aniline to give sulfenamide **73** (Scheme 29).[72] Subsequent treatment of **73** with sodium methoxide in methanol led to *N*-substituted 1,2-benzoisothiazole-3-one **74**.



Scheme 29. Representative synthesis of *N*-substituted 1,2-benzoisothiazole-3-ones.

The benzoisothiazole-3-one leaving group also functions well with activated methylene nucleophiles leading to products **75** and, to a lesser extent, with Grignard reagents to give aryl thioether **76** (Scheme 30).[73] A related benzothiazole leaving group has been employed in the stereospecific *syn* conjugate attack of a 2,3-enopyranoside leading to an unsaturated sugar.[74]

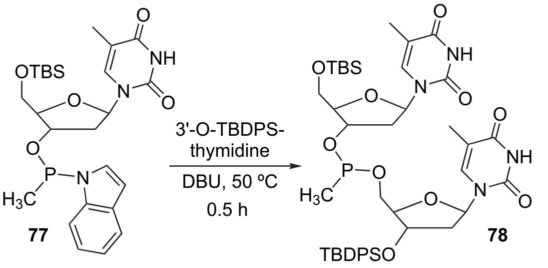


entry	EWG_1	EWG_2	%yield **75**
1	CO_2Et	CO_2Et	78
2	CO_2Et	COMe	88
3	CN	CO_2Et	74
4	CN	SO_2Ph	91

Scheme 30. Reaction of benzoisothiazolin-3-one **72** with activated methylene nucleophiles and Grignard reagent.

5.2. Indole

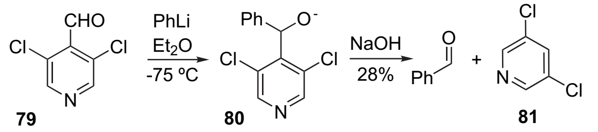
Dinucleoside methylphosphinite **78** has been prepared by the attack of a 5′-hydroxyl of a protected thymidine on substrate **77** containing a tricoordinate phosphorous reagent with an indole leaving group (Scheme 31).[75] Similar but lower yielding coupling reactions involving tetracoordinate phosphorous with *p*-nitrophenol leaving groups have also been described.[76]



Scheme 31. Use of indole as a leaving group in dinucleoside synthesis.

5.3. 3,5-Dichloropyridine

In the presence of organolithium and magnesium reagents, 3,5-dichloro-4-pyridinecarbonitrile behaved primarily as an electrophilic substrate. Thus alkyl or aryl nucleophiles have been reported to produce substitution products with displacement of the cyano group at the 4-position or the chloro group at the 5-position. However, 3,5-dichloro-4-pyridinecarboxaldehyde (**79**) underwent addition with phenyl lithium at the carbonyl carbon to yield anion intermediate **80** (Scheme 32). Aqueous basic workup of this intermediate led to the formation of benzaldehyde in low yields most likely through the expulsion of the 3,5-dichloro-4-pyridyl residue as a carbanionic leaving group leading to 3,5-dichloropyridine (**81**) after protonation.[77]

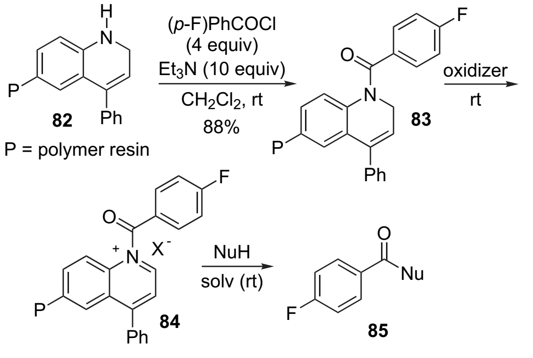


Scheme 32. Use of 3,5-dichloro-4-pyridyl anion as leaving group in aldehyde synthesis.

5.4. Quinolines

Resin-bound 4-phenyl-1,2-dihydroquinoline (DHQ) **82** has been synthesized in high yields using an aza Diels–Alder cycloaddition reaction for applications as a safety catch linker in the synthesis of amides and carboxylic acids.[78] While this solid phase technique has been previously reviewed as a parallel synthesis strategy,[79] it is included in this report since it represents a new type of heterocyclic leaving group.

The use of resin **82** in the synthesis of 4-fluorobenzoyl amide **85** began with the treatment of this resin with 4-fluorobenzoyl chloride to give resin-bound intermediate **83** (Scheme 33). Activation of **83** was achieved with several oxidizing agents to give quinolinium **84**. In the case of DDQ and CPh_3BF_4, resin **83** was treated with 3 equiv of oxidizing agents at room temperature for 10 h and 3 h, respectively, to promote the formation of the quinolinium species. Subsequent addition of benzylamine then cleaved the benzoyl substrate from solid support to give amide product **85**. With the CAN oxidant (entry 4), cleavage was performed in an aqueous acetonitrile solution at room temperature to give 4-fluorobenzoic acid in 62% yield in high purity.



entry	oxidizer	solvent	NuH	% Yield of **85**
1	DDQ	CH_2Cl_2/CH_3CN	$BnNH_2$	34
2	CPh_3BF_4	THF	$BnNH_2$	42
3	CPh_3BF_4	CH_2Cl_2	$BnNH_2$	59 (96[a])
4	CAN	CH_3CN/H_2O	water	62 (98[a])

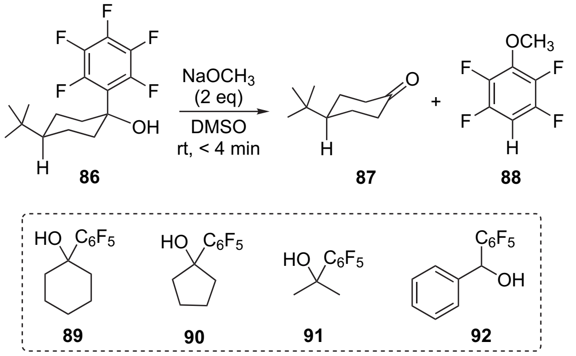
[a]Cumulated yield after two-activation/cleavage sequences

Scheme 33. Use of 4-phenyl-1,2-dihydroquinoline as safety catch linker.

5.5. Pentafluorophenyl

Reactions that result in the cleavage of carbon–carbon bonds are relatively rare. Most of these reactions involve alkoxide fragmenting to give ketones and generally require stabilized carbanion leaving groups.[80] Some common examples include the haloform reaction and the retro-aldol reaction. However, examples involving less stabilized[81] or even non-stabilized carbanions are known, though extreme steric crowding or high temperatures are often required.[82]

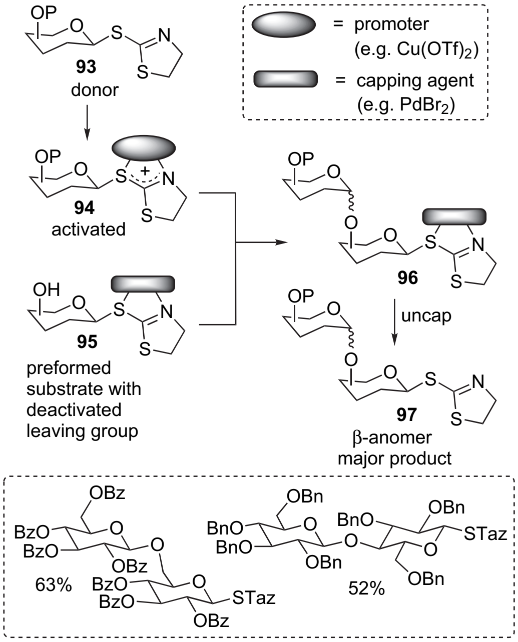
Pentafluorophenyl anion leaving groups have been observed in carbon–carbon bond cleavage reactions of *cis*-1-pentafluorophenyl-4-*tert*-butylcyclohexanol (**86**) to give ketone **87** (Scheme 34).[83] This fragmentation reaction was performed using alkali metal methoxides in DMSO since the alkoxide of **86** was unreactive in ethereal solvents (as in the Grignard reaction used to prepare **86** in the first instance). A nucleophilic aromatic substitution reaction of the pentafluoro leaving group occurred subsequent to the fragmentation of **86** to give observed coproduct **88**. The fragmentation has also been observed with other tertiary alcohols (**89**–**91**) and secondary alcohol **92** (Scheme 34). Although no isolated yields are reported, NMR studies indicate that the conversions are nearly quantitative.



Scheme 34. Pentafluorophenyl anions in the fragmentation of alcohols to give carbonyl products.

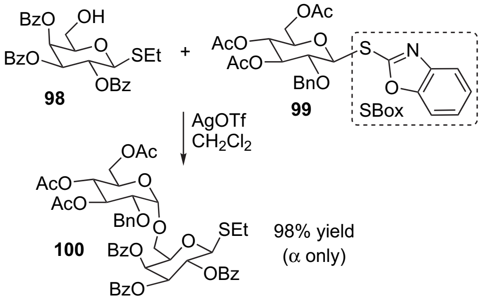
6. Activation–deactivation leaving groups

The synthesis of oligosaccharides through iterative glycosylation reactions of thioglycosides has been applied with success over a number of years due to the stability of the anomeric thio functional group toward a wide range of reaction conditions.[84] The use of leaving groups that are activated at an atom that is not directly attached to the anomeric center of a glycosyl donor has been defined as remote activation (recently reviewed).[85] In recent years, a new glycosylation strategy that allows chemoselective activation of an *S*-thiazolyl (STaz) leaving group of a glycosyl substrate has been developed. This principle can be illustrated with donor glycosyl substrate **93** (Scheme 35). The reaction of **93** with a promoter such as $Cu(OTf)_2$ gave activated substrate **94**. Significantly, this activation can occur in the presence of a glycosyl substrate containing a STaz group (such as **95**) that has been deactivated (capped) by complexation with $PdBr_2$ or other agent.[86] The removal of the Pd(II) cap from intermediate **96** following the coupling step to give product **97** was then accomplished with NaCN. An attractive feature of this strategy is that it does not require protecting group manipulation (armed/disarmed techniques[87]) to control the leaving group ability. Overall yields of disaccharide syntheses using this activation–coupling–deactivation strategy were high regardless of the protecting group choice (Scheme 35).



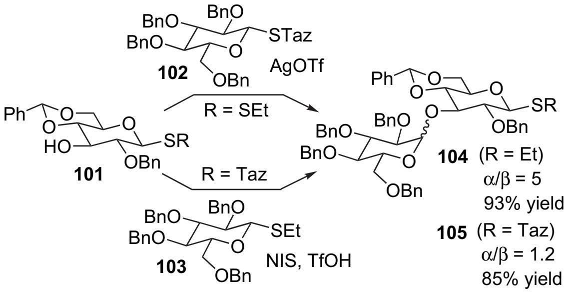
Scheme 35. Schematic of activation–deactivation concept and representative synthesis examples.

The selective activation of an *S*-benzoxazolyl (SBox) leaving group of glycosyl donor **99** in the presence of acceptor **98** containing a thioethyl group at the anomeric center has been reported (Scheme 36).[88] Disaccharide product **100** was obtained as a single diastereomer (α only) in nearly quantitative yield. Importantly, the SBox leaving group is stable toward protecting group manipulations and it is activated for glycosyl coupling under mild conditions using silver triflate. The SBox leaving group in combination with certain saccharide protecting group schemes has been shown to offer a degree of chemoselectivity in coupling reactions not envisioned by the armed–disarmed principle.[89] Hexofuranosyl 1-phosphates have also been efficiently prepared in non-protected form using the SBox leaving group with phosphoric acid activation.[90]



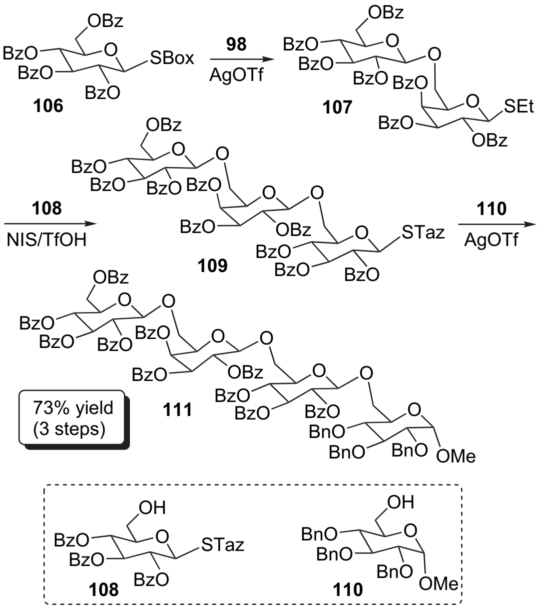
Scheme 36. Selective activation of SBox glycoside in the presence of an anomeric thioethyl group.

A more flexible oligosaccharide synthesis approach involved the selective activation of glycosyl substrate **101**, which contained either a STaz leaving group (R=Taz) or a SEt (R=Et) at the anomeric position (Scheme 37).[91] When **101** contained a thioethane leaving group, it was coupled to monosaccharide **102** to give product **104** in good yield (93%). This coupling was accomplished by the selective activation of the STaz leaving group of **102** using silver triflate in the presence of the thioethane group of substrate **101** (Scheme 37). Alternatively, when **101** contained a STaz leaving group, it was coupled to **103** to give disaccharide **105** in 85%. The selective coupling was accomplished by activation of the thioethane group using *N*-iodosuccinimide (NIS) with catalytic triflic acid. This selective activation strategy has been extensively optimized and its versatility in multistep oligosaccharide synthesis demonstrated.[92]



Scheme 37. Selective activation of STaz over SEt and vice versa in disaccharide synthesis.

Taking advantage of the unique reactivities of the Sbox and STaz leaving groups, a one-pot, three-step, synthesis of tetrasaccharide **111** was achieved in 73% overall yield (Scheme 38).[93] Thus donor **106** was activated in the presence of thioethyl-containing **98** in the presence of AgOTf to give dimer **107**. In the same pot, STaz-containing receptor **108** was added.

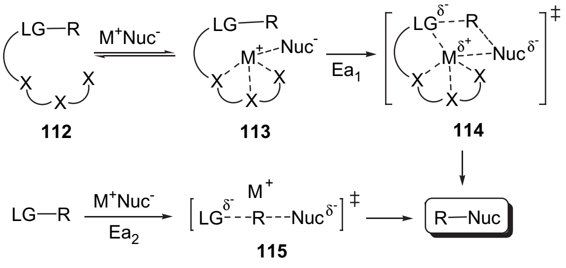


Scheme 38. One-pot synthesis of tetrasaccharide **111** using selective activation of SBox, SEt, and STaz.

In the presence of NIS/TfOH, the thioethyl group of disaccharide **107** was selectively activated leading to coupling product **109**. In a final step, the STaz group of trisaccharide **109** was activated with AgOTf to promote coupling with receptor **110** leading to tetrasaccharide **111** in an overall isolated yield of 73% (Scheme 38). The SBox and STaz leaving group strategies have also been extended to the synthesis of oligosaccharides containing α-sialosides.[94]

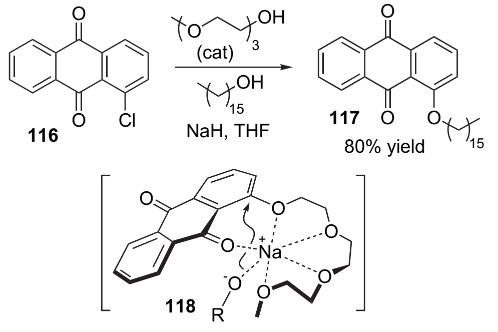
7. Nucleophile assisting leaving groups (NALGs)

Nucleophile assisting leaving groups (NALGs) may be defined as a leaving group that contains a chelating unit capable of stabilizing the transition state of a nucleophilic reaction. The rate enhancement afforded by a NALG is not necessarily due to an increase in the nucleofugacity of the leaving group upon cation chelation as observed in the activation–deactivation method described in the previous section. Instead, a NALG should also interact with nucleophiles in the course of a reaction to lower the transition state energy of the rate-limiting step. For example, in the case of substrate **112**, it is expected that the negative charge imparted to the leaving group moiety (LG) by an incoming nucleophile (Nuc) in transition state **114** should provide a more favorable chelation complex relative to its neutral precursor ligand **113** (Scheme 39). Depending on the specific nucleophilic reaction mechanism, cation chelation in the transition state should reduce the energy of activation (E_{a_1}) of NALG substrates relative to substrates containing traditional leaving groups. Without the added stabilizing effect of nucleophilic salt chelation with a nearby multidentate ligand, the energy of activation (E_{a_2}) for reactions involving traditional leaving groups (leading to a transition state such as **115**) is expected to be higher ($E_{a_2} > E_{a_1}$). As described in the following paragraphs, differential metal ion stabilization of transition states relative to reactants in acetyl transfer reactions has been observed in numerous systems.[95]



Scheme 39. Rationale for rate enhancement observed with nucleophile assisting leaving groups (NALGs).

The reaction of 1-chloroanthraquinone (**116**) with a variety of alkanols in NaH failed to give the desired nucleophilic aromatic substitution product in refluxing THF. However, the addition of catalytic amounts of oligo-ethylene glycols led to successful alkanol substitution products. In the case of n-hexadecanol, substitution product **117** was obtained in 80% yield using a catalytic amount (24%) of triethylene glycol (Scheme 40).[96] Initially acting as nucleophile, triethylene glycol added to **116** produce intermediate **118**, which coordinated the sodium cation as suggested by X-ray crystal structure data. This cation-complexed intermediate most likely played a key role in both coordinating the stoichiometric alkoxide nucleophile (RO$^-$) as well as stabilizing the negative charge forming on the oxygen of the leaving group. In this chloroanthraquinone study, metal chelated oligoglycol oxides were superior nucleophilic agents relative to straight chain alkanoxide anions. However, a separate group demonstrated that phenolate anions containing oligoether units in the ortho position exhibited no improved nucleophilic properties relative to their non-chelating analogs.[97]

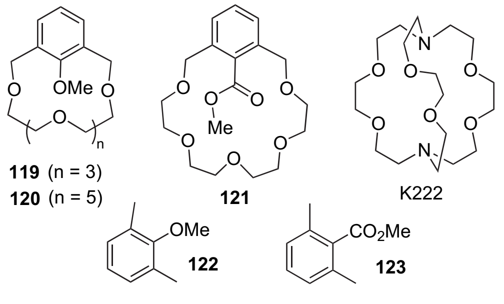


Scheme 40. Podand-catalyzed nucleophilic aromatic substitution reaction of 1-chloroanthroquinone.

This podand-catalyzed method gave optimal results with long chain n-alkanols (C_9 and C_{16}) most likely due to their improved solubility in THF relative to smaller alkanols. Similar experiments involving 15-crown-5 methyl alcohol gave significantly poorer results. Although a more effective sodium cation chelating agent than triethylene glycol, the crown ether analog was thought to draw the sodium cation into its cavity away from the anthraquinone residue.[98] This presumably limited the ability of the cation to stabilize the negative charge building up on the oxygen of the leaving group in the transition state.

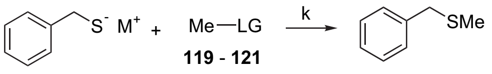
Crown ether-based phenolate and carboxylate nucleophile assisting leaving groups (NALGs) exhibited enhanced nucleofugacity in methylation and acylation reactions. Although this area has been previously reviewed,[99] aspects of this research will be readdressed in the present paper to provide a theoretical basis and backdrop for more recent NALG research.

The rates of nucleophilic displacement of the electrophilic methyl group of substrates **119**, **120**, and **121** (Scheme 41) by benzyl thiolate varied markedly depending on the metal counter ion.[100] With potassium benzyl thiolate, the metal was sequestered using a well-known potassium cation chelating agent 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo-[8.8.8]hexacosane (K222) leading to a loss of rate enhancement. To help assess the relative contribution of the metal countercation, all methylation reactions in the study were compared to experiments involving K222 to give relative rates (k_{rel}).



Scheme 41. Methylating agents containing crown ether leaving groups and structure of K222.

In the case of benzo-18-crown-5 substrate **119**, the peak reactivity occurred with potassium thiolate giving a relative rate of 826 when compared to the potassium sequestered experiment involving K222 (Scheme 42). This effect was far less marked with analogous 27-crown-8 substrate **120** where the maximum relative rate was 53. Presumably, the much larger crown ether system of **120** provided a poor fit for the cations used in the study. However, in both **119** and **120**, the methylation rate was enhanced relative to an electronically similar substrate, 2,6-dimethyl anisole (**122**). Rate studies of **122** showed a slight rate depression relative to the potassium cation sequestration experiment involving K222 (Scheme 42) suggesting a weak association of the alkali metal ions with the thiolate nucleophile.[97]

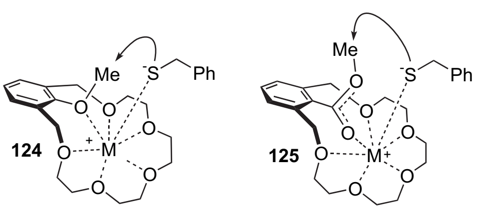


M	k_{rel} (119)	k_{rel} (120)	k_{rel} (121)	k_{rel} (122)	k_{rel} (123)
K•K222	1	1	1	1	1
Li	26	-	1.5	0.25	0.54
Na	565	3	47	0.43	0.57
K	826	53	17	0.43	0.66
Cs	146	50	4.4	0.42	0.43

Scheme 42. Relative methylation reaction rates of **119–121** containing crown ether leaving groups (LG) and control substrates **122** and **123**.

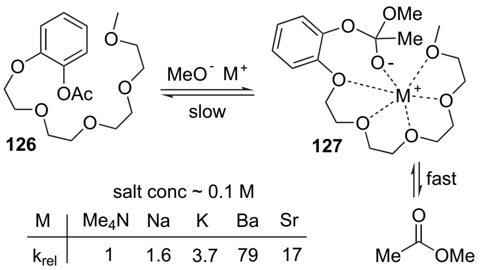
Substrate **121** containing an 18-crown-5 benzoate moiety also showed a methylation rate enhancement in the presence of various metal cations with the optimal relative rate of 47 occurring in the presence of sodium benzyl thiolate (Scheme 42). The preference for sodium cation in the case of **121** has been rationalized in terms of the decreased pore size of the crown ether cavity relative to **119**. Due to the bulkier methoxycarbonyl group, the cavity of **121** was expected to be somewhat smaller than the corresponding cavity of **119** and therefore more suitable to host the smaller sodium cation.

Metal cation effects on the rate of benzyl thiolate methylation were nearly an order of magnitude larger with crown-anisole substrate **119** relative to crown-benzoate **121**. This effect has been explained on the basis of a strong electrostatic interaction between the chelated metal and the aryl ether oxygen in transition state **124** (Scheme 43). With crown-benzoate substrate **121**, the negative charge from the incoming thiolate nucleophile is delocalized over the two oxygens of the carboxylate functional group, as in **125**, and therefore not as effectively stabilized by the chelated metal.



Scheme 43. Transition state of **124** and **125** in the methylation of a benzyl thiolate metal salt.

In the presence of metal methoxide in methanol, an aryl acetate substrate bearing a tetra(oxyethylene) chain in the *ortho* position, compound **126**, exhibited substantially accelerated acetyl transfer reactions (Scheme 44).[101] In general, the mechanism of acyl-transfer reactions is known to proceed by a two-step process, the first of which involves the rate-determining formation of a tetrahedral intermediate. In the case of **126**, the presence of a nearby multidentate ligand was expected to stabilize a metal cation interaction with the methoxide addition product as depicted in transition state **127** (Scheme 44). Acetyl transfer reactions of **126** were carried out in methanol solutions of Me_4NOMe of varying concentrations and the reaction rates were calculated. These rates were then compared to reactions carried out at the same concentration of Me_4NOMe but containing added metal bromide salts. Rate enhancements were observed with several metal bromides (Scheme 44).



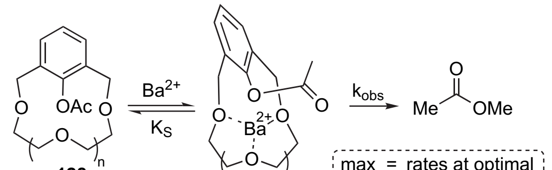
salt conc ~ 0.1 M

M	Me_4N	Na	K	Ba	Sr
k_{rel}	1	1.6	3.7	79	17

Scheme 44. Rate acceleration of acetyl transfer with substrate **126** containing an oligoether NALG.

In the case of added $BaBr_2$ (at 0.1 M), the relative rate was determined to be 79. Under the same conditions, the relative rate of acetyl transfer with phenyl acetate (with no chelating arm) was determined to be 3. Although considered a fairly weak chelating unit, the oligo(oxyethylene) chain of **126** was responsible for a net 25-fold rate enhancement. The improved rate enhancement of the alkaline earth metals Ba^{2+} and Sr^{2+} was attributed to both a larger electrostatic stabilization of the transition state leading to the tetrahedral intermediate as well as to a better utilization of the coordinative interactions with the oligoether unit.[95]

Improved metal-catalyzed rate accelerations of acetyl transfer reactions to methoxide were observed with all of the homologs of crown ether **128** in the presence of barium salts relative to the same reactions using only Me_4NOMe (Scheme 45).[95,102] Interestingly, Ba^{2+} gave the optimal acetyl transfer rates despite the fact that its cation binding affinities for **128** are an order of magnitude lower than the alkali cations. This increased acceleration of Ba^{2+} relative to the



(at optimal conc of $BaBr_2$)

n	2	3	4	5	6
K_S (M^{-1})	<10	<10	50	260	74
k_{rel}	93	760	250	100	160

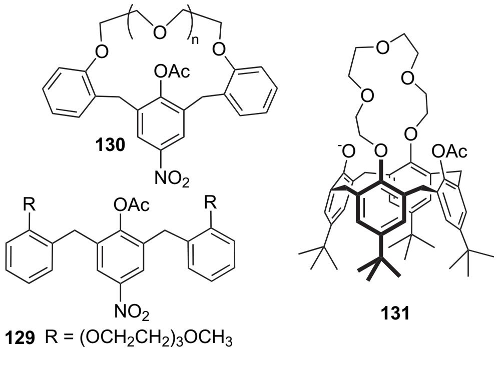
max = rates at optimal $BaBr_2$ conc
k_o = acetylation rate in the absence of added $BaBr_2$
$k_{rel} = \left(\frac{k_{obs}}{k_o}\right)_{max}$

Scheme 45. Barium cation-catalyzed acetylation reactions with crown ether NALG **128**.

alkali cations may be partially explained by improved electrostatic stabilization of divalent over monovalent cations.

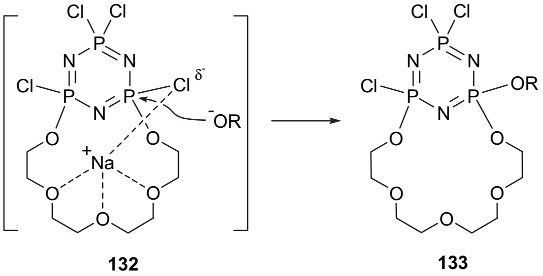
When considering the differences of Ba^{2+} catalysis among crown ether substrates **128**, there is no correlation between binding affinity (as measured by K_S) and relative rate. Indeed, the highest observed rate (k_{rel}=760) occurred with the 18-crown-5 analog of substrate **128** (n=3) where no appreciable binding affinity ($<10\ M^{-1}$) for the barium cation was measured (Scheme 45). While larger ring sizes better accommodate the barium cation (for example K_S=260 M^{-1} when n=5), the improved fit of the cation in the crown ether pore may shift the cation away from the reactive center and diminish its ability to stabilize the forming negative charge in the transition state through electrostatic interaction. Similar rate studies involving acetyl transfer to ethoxide instead of methoxide revealed a more pronounced metal catalysis effect with substrates **128**.[103] Both methoxide and ethoxide studies underscore the concept that effective rate enhancement of acetyl transfer reactions by metal cations does not require strong metal-binding affinity in the reactant state.

The rate enhancement effect in acyclic NALG systems is competitive with more rigid macrocyclic entities (Scheme 46). In rate studies of acetyl transfer reactions to ethoxide in the presence of barium salts, the relative rate of **129** was over 10-fold greater than macrocycle **130** for smaller ring sizes (n=2 and 3). The conformational rigidity of these smaller macrocycles destabilizes interactions with the metal catalyst. Only when macrocycle **130** was of sufficient size (n=4) did the rate enhancement supersede that of acyclic NALG **129**.[104] Further improvement in acetyl transfer was realized with calix[4]arene **131**, which contained a phenoxide anion capable of providing an additional binding interaction with the Ba^{2+} catalyst.[99b]



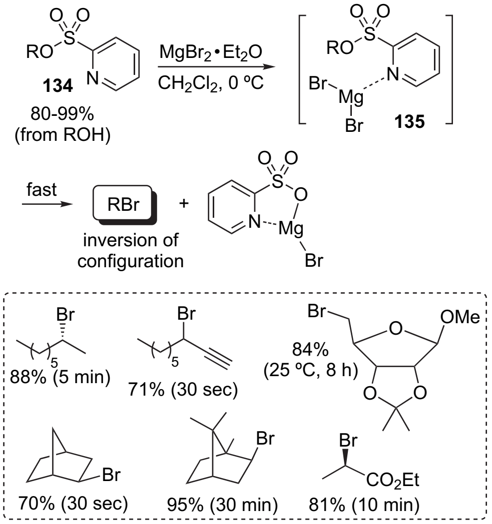
Scheme 46. Other acyclic and macrocyclic acetylating agents accelerated by $BaBr_2$.

There are numerous examples of leaving group stabilization by a metal cation in substrates containing a chelating unit. While these examples involve traditional leaving groups and are therefore outside the scope this review, they further illustrate the concept of cation-mediated electrophilic assistance in nucleophilic reactions. For example, the addition of sodium alkoxide to a chlorocyclophosphazene led to regioselective addition of alkoxide to give product **133** (Scheme 47).[105] These nucleophilic substitution reactions also proceed at enhanced rates. Both the acceleration and regioselectivity were rationalized in terms of transition state **132** involving sodium cation stabilization of the partial negative charge forming on the chloride leaving group.



Scheme 47. Cation assisted addition of sodium alkoxide to a macrocyclic substrate.

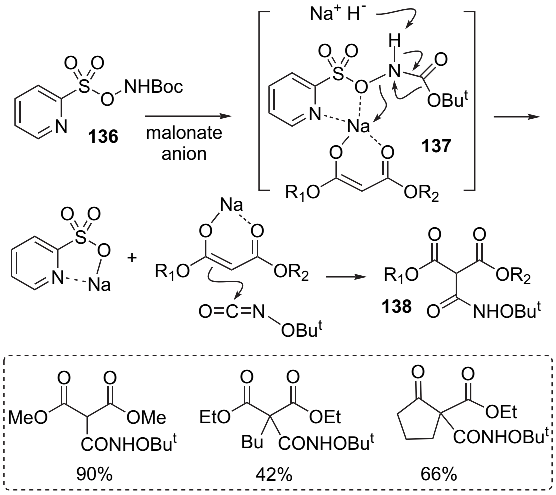
Alkyl bromide products were obtained in good yields and under mild conditions with substrates **134** containing a 2-pyridyl sulfonate leaving group. This leaving group exhibited enhanced reactivity toward magnesium bromide, a divalent metal salt (Scheme 48). Pre-coordination of **134** with the nucleophilic salt leading to complex **135** provided an internal activation effect.[106] The bromination reactions were remarkably fast with unactivated secondary substrates. In the case of two norbornyl substrates, 2-pyridyl sulfonate was displaced by bromide to give complete conversion to the corresponding inverted bromide products in 30 s (Scheme 48). The reaction rates with these norbornyl substrates were significantly higher than the tosylates (70 min) and 8-quinolylsulfonates (120 min).[106] Inversion of configuration was observed for all substrates **134**.



Scheme 48. Transformation of 2-pyridyl sulfonates **134** to alkyl bromides with inversion of configuration.

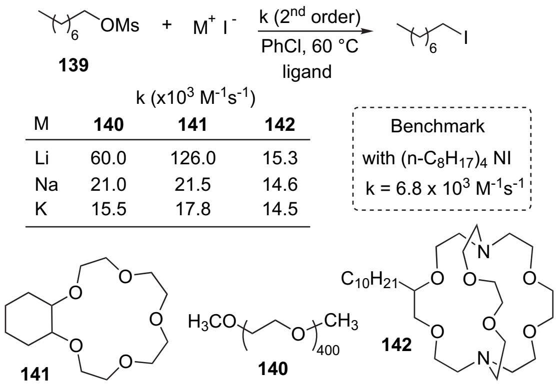
The 2-pyridyl sulfonate leaving group has also been employed in the alkoxyaminocarbonylation of β-dicarbonyl compounds (Scheme 49). Activated amine reagent **136** containing the 2-pyridyl sulfonate leaving group reacted with enolates of β-dicarbonyl compounds following a Lossen-type rearrangement (most likely via intermediate **137**) to give tricarbonyl hydroxamates **138** (Scheme 49).[107]

Studies involving nucleophilic reactions with traditional sulfonate leaving groups revealed a strong rate dependence on



Scheme 49. Alkoxyaminocarbonylation using a 2-pyridyl sulfonate leaving group.

cation identity and coordinative availability. In these studies, nucleophilic reactions of mesylates and tosylates were accelerated by the addition of polyether and macrocyclic ether ligands in low polarity solvents.[108] In the case of *n*-octyl mesylate (**139**), treatment with metal iodide salts in the presence of several chelating reagents led to a rate acceleration relative to the benchmark reaction using tetraoctyl ammonium iodide (Scheme 50). With polyethylene glycol **140** and 15-crown-5 **141**, the acceleration effect was most marked with lithium iodide, which was explained on the basis of the stronger Lewis acid character of Li$^+$ relative to sodium and potassium cations. A similar but less pronounced rate acceleration effect was also observed in this same system with some alkali earth metals.[109] Phosphinic ester substrates also exhibit accelerated rates of alkylation with metal iodides.[110] In the presence of added ligand **142** (a cryptand), the acceleration effect of the addition of metal iodide to octyl mesylate is minimal relative to the benchmark reaction and shows no cation preference (Scheme 50). The strong chelation properties of cryptand **142** were thought to have limited the ability of the cation to provide electrophilic assistance in the transition state of the nucleophilic reaction.



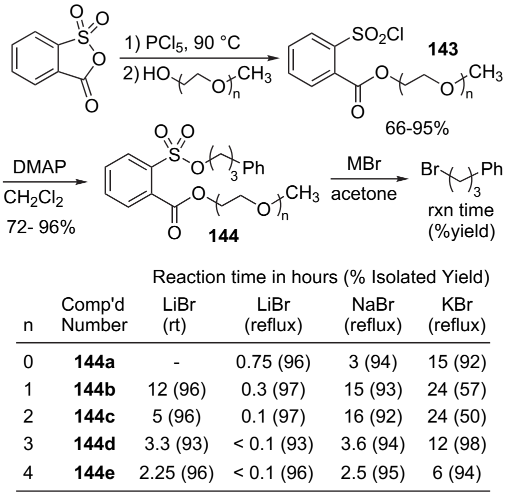
k (x10^3 M^{-1}s^{-1})

M	140	141	142
Li	60.0	126.0	15.3
Na	21.0	21.5	14.6
K	15.5	17.8	14.5

Benchmark
with (n-C_8H_{17})$_4$ NI
k = 6.8 x 10^3 M^{-1}s^{-1}

Scheme 50. Rate acceleration of iodide addition to mesylate **139** with added ligands **140–142**.

Sulfonate leaving groups containing an oligoether metal-chelating moiety have been recently reported.[111] The chelating units were designed to stabilize developing negative charge on the oxygens of the sulfonate leaving group in the transition state analogous to previously described work involving aryloxy and arylcarboxyl leaving groups that contained metal-chelating units (Scheme 41).[99] Sulfonylating agents **143** required for the various NALGs used in the study were prepared from sulfobenzoic acid anhydride by treatment with phosphorous pentachloride followed by the addition of methyl-oligo-ethylene oxides (Scheme 51). Arylsulfonyl chlorides **143** were then reacted with 3-phenylpropanol to give the corresponding sulfonate esters **144** in yields ranging from 72% to 96%. Sulfonate esters **144** (except for n=0) were exceptionally stable to silica gel chromatography. Sulfonate esters **144** were reacted with lithium, sodium, and potassium bromide giving 3-phenyl-1-bromopropane as the substitution product (Scheme 51). Methylester sulfonate **144a** (n=0) served as a baseline to help determine the rate enhancing role of the various oligoether side chains in compounds **144b–144e**.



Reaction time in hours (% Isolated Yield)

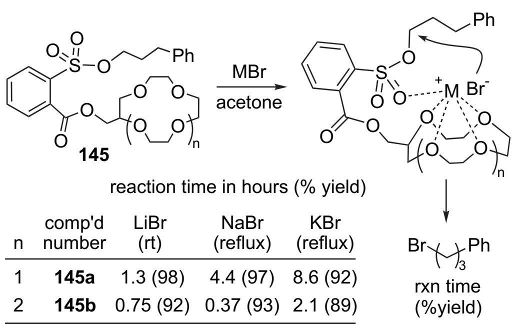
n	Comp'd Number	LiBr (rt)	LiBr (reflux)	NaBr (reflux)	KBr (reflux)
0	**144a**	-	0.75 (96)	3 (94)	15 (92)
1	**144b**	12 (96)	0.3 (97)	15 (93)	24 (57)
2	**144c**	5 (96)	0.1 (97)	16 (92)	24 (50)
3	**144d**	3.3 (93)	< 0.1 (93)	3.6 (94)	12 (98)
4	**144e**	2.25 (96)	< 0.1 (96)	2.5 (95)	6 (94)

Scheme 51. Rates of metal bromide additions to arylsulfonates **144** to give 3-phenyl-1-bromopropane.

The reaction of LiBr with **144a** gives nearly complete conversion to product at four times the rate of NaBr. The increasing number of ethylene oxide units correlates well with a decrease in reaction time required for LiBr to convert substrates **144** to product. In the case of **144e**, which contains a tetraethylene oxide unit, the rate of reaction with LiBr is approximately 15 times faster than with **144a** (n=0). The increased reaction rate of LiBr relative to NaBr and KBr for all NALGs **144** appear to parallel earlier intermolecular studies involving alkylmesylate reactions with various metal iodide salts.[108] The presence of ethylene oxide units increases the relative rate of LiBr versus NaBr additions to 50-fold for **144b** (n=1) and 160-fold for **144c** (n=2). The trend seems to level off with additional ethylene oxide units. Significant rate enhancements toward metal halide addition have also been observed with secondary sulfonate substrates derived from reagent **143**.[111]

Macrocyclic ether-containing sulfonates also exhibited a rate enhancement and salt selectivity effect in metal bromide addition reactions (Scheme 52). The reaction rates of LiBr with substrates **145a** and **145b** were nearly 50 times faster than the baseline methylester sulfonate **144a** (Scheme

51). In terms of selectivity, the 12-crown-4 containing **145a** reacts with LiBr in acetone to form product in 1.3 h at room temperature. However, with sodium or potassium bromide, the displacement reaction required 4 h and 8 h under refluxing conditions, respectively. This corresponds to a selectivity of greater than 200-fold for lithium bromide over sodium and potassium bromide.[111]

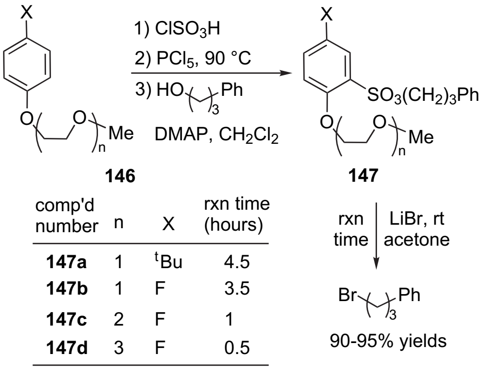


reaction time in hours (% yield)

n	comp'd number	LiBr (rt)	NaBr (reflux)	KBr (reflux)
1	**145a**	1.3 (98)	4.4 (97)	8.6 (92)
2	**145b**	0.75 (92)	0.37 (93)	2.1 (89)

Scheme 52. Rates of metal bromide additions to crown ether-containing sulfonates.

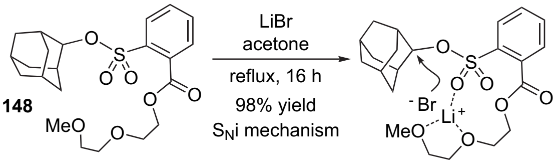
Crystallographic studies of triethylene oxide-containing NALGs derived from **144d** revealed that three of the side arm ether oxygens of the NALG and one of the sulfonyl oxygens are coordinated to metal cation. Interestingly, the ester carbonyl of the NALG was nearly orthogonal and therefore poorly conjugated to the phenyl ring.[111] To avoid this nonideal chelation geometry, a series of NALGs related to **144** but without the carbonyl group have been prepared (Scheme 53).[112] Starting from aryl ethers **146**, chlorosulfonylation followed by the addition of phenylpropyl alcohol led to sulfonates **147**. The reaction of **147** with LiBr in acetone at room temperature to give 3-phenyl-1-bromopropane exhibited enhanced rates (5- to 10-fold) relative to NALGs **144**, which possess an ester group. As in the ester NALG series **144**, increased length of chelating side chain corresponded to heightened reactivity toward a nucleophilic metal salt.



comp'd number	n	X	rxn time (hours)
147a	1	^{t}Bu	4.5
147b	1	F	3.5
147c	2	F	1
147d	3	F	0.5

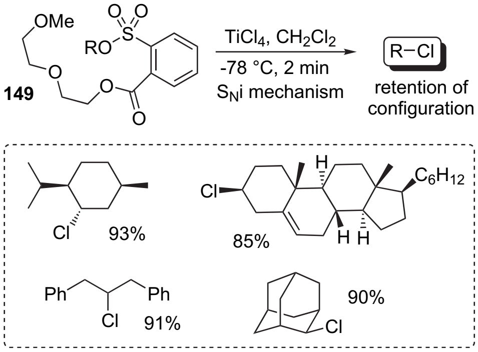
Scheme 53. Rates of metal bromide additions to NALGs **147** containing oligo-ethylene oxide chelating units without a carbonyl group.

Limited studies of NALGs derived from **143** suggest that the nucleophilic displacement reactions may occur (at least in some cases) via an S_Ni-type mechanism. For example, 2-adamantyl NALG substrate **148** was expected to exhibit little or no reactivity toward metal halide salts since backside nucleophilic displacement is essentially precluded due to steric crowding and ionization mechanisms are disfavored due to the constrained ring geometry.[113] However, treatment of this substrate with LiBr in refluxing acetone gave the 2-bromoadamantane product in 98% yield after 16 h (Scheme 54). By contrast, the corresponding 2-adamantyl tosylate gave no reaction even after 70 h in refluxing acetone. The triflate of 2-adamantol also failed to give bromide product when treated with LiBr.



Scheme 54. Evidence in support of an S_Ni-type mechanism with 2-adamantyl NALG substrate **148**.

Arylsulfonates of hindered secondary alcohols derived from reagent **149** were also converted to the corresponding alkyl chlorides very rapidly and in the presence of titanium tetrachloride at low temperatures.[114] These chlorination reactions are thought to proceed via an S_Ni-type mechanism leading to exclusive retention of configuration. Thus the treatment of sulfonate esters **149** with $TiCl_4$ in methylene chloride at −78 °C led to high yields of the corresponding alkyl chlorides (Scheme 55). In each case, the reaction was complete in less than 2 min.



Scheme 55. Reaction of sulfonate esters **149** with $TiCl_4$ leading to alkyl chlorides with retention of configuration.

With NALG **149** derived from 1,3-diphenyl-2-propanol, the respective chloride product was obtained in 91% yield upon treatment with $TiCl_4$. Tosyl esters of this substrate gave nearly exclusive elimination product in the presence of alkali metal chloride agents. NALG sulfonates **149** of cholesterol and menthol were converted to the corresponding chlorides almost instantaneously at −78 °C (Scheme 55). In the 2-adamantyl system, a 90% conversion to the chloride product was observed with no side product arising from rearrangement of the adamantine nucleus.[115] Recently this method has been extended to stereospecific bromination and azidations using $TiBr_4$ and $Ti(N_3)_4$, respectively.[116]

8. Conclusions

In this report, we have provided an overview of recent developments in heterolytic leaving group chemistry. Although leaving groups have been an area of active research since at least the mid 1950s, progress in this field continues at an unabated pace. Indeed, it might be argued that the increasing molecular complexity of modern synthesis targets has spurred the development of leaving groups in recent years. This has certainly been true in the area of oligosaccharide synthesis, which has moved forward in large part due to improved anomeric leaving groups such as activation–deactivation groups. In more established leaving group classes such as sulfonates and carboxylates, we have shown in this report that many useful variations are still being made to improve their performance. Non-traditional leaving groups such as carboranes and chiral ferrocenyl-containing carboxylates can be seen as early offerings from the organometallic field. It is expected that, just as this field has made powerful contributions to the area of organic reaction catalysis, so will new and more useful organometallic leaving groups emerge. Finally, nucleophile assisting leaving groups (NALGs), including those inspired by biological systems, offer impressive degrees of selectivity and rate enhancement. We anticipate that future advances in this area will lead to new classes of 'designer' leaving groups, which will facilitate the synthesis of molecular targets of ever-increasing complexity. Hopefully, this review will stimulate further development in this exciting field.

Acknowledgements

The authors wish to thank the National Institutes of Mental Health (66963-01), General Medical Science (073621-01), and NSF (0311369) for their support of our research in this area.

References and notes

1. Smith, M. B.; March, J. *Advanced Organic Chemistry*, 5th ed.; John Wiley: New York, NY, 2001; p 275.
2. Muller, P. *Pure Appl. Chem.* **1994**, *66*, 1077–1184.
3. Mathieu, J.; Allais, A.; Valls, J. *Angew. Chem.* **1960**, *72*, 71–74.
4. Based on a CAS database search using SciFinder Scholar 2006 searching the term 'leaving group' with the two words closely associated.
5. Bordwell, F. G.; Pitt, B. M.; Knell, M. *J. Am. Chem. Soc.* **1951**, *73*, 5004.
6. Winstein, S.; Morse, B. K.; Grunwald, E.; Jones, H. W.; Corse, J.; Trifan, D.; Marshall, H. *J. Am. Chem. Soc.* **1952**, *74*, 1127–1132.
7. Swain, C. G.; Dittmer, D. C. *J. Am. Chem. Soc.* **1953**, *75*, 4627.
8. Lewis, E. S.; Boozer, C. E. *J. Am. Chem. Soc.* **1954**, *76*, 791–793.
9. Including the popular undergraduate text by Morrison, R. T.; Boyd, R. N. *Organic Chemistry*, 2nd ed.; Allyn and Bacon: Boston, MA, 1966.
10. Laue, T.; Plagens, A. *Named Organic Reactions*, 2nd ed.; John Wiley: New York, NY, 2005; p IX.
11. Netscher, T. *Recent Res. Dev. Org. Chem.* **2003**, *7*, 71–83.
12. (a) Katritzky, A. R. *Tetrahedron* **1980**, *36*, 679–699; (b) Katritzky, A. R.; Musumarra, G. *Chem. Soc. Rev.* **1984**, 4768.
13. Lou, B.; Eckhardt, E.; Hanessian, S. *Preparative Carbohydrate Chemistry*; Dekker: New York, NY, 1997; pp 449–466.
14. Capozzi, M. A. M.; Cardellicchio, C.; Naso, F. *Eur. J. Org. Chem.* **2004**, 1855–1863.
15. For a recent comprehensive review, see: Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827–10852.
16. For a recent comprehensive review, see: Dolle, R. E. *J. Comb. Chem.* **2005**, *7*, 739–798.
17. For representative examples: (a) Bulluss, G. H.; Knott, K. M.; Ma, E. S. F.; Aris, S. M.; Alvarado, E.; Farrell, N. *Inorg. Chem.* **2006**, *45*, 5733–5735; (b) Parsons, S.; Smith, A. A.; Winpenny, R. E. P. *Chem. Commun.* **2000**, 579–580; (c) Pasini, A.; D'Alfonso, G.; Manzotti, C.; Moret, M.; Spinelli, S.; Valsecchi, M. *Inorg. Chem.* **1994**, *33*, 4140–4148.
18. For representative examples: (a) Wood, T. C.; Johnson, K. L.; Naylor, S.; Weinshilboum, R. M. *Drug Metab. Dispos.* **2002**, *30*, 1123–1128; (b) Hlasta, D. J.; Ackerman, J. H.; Court, J. J.; Farrell, R. P.; Johnson, J. A.; Kofron, J. L.; Robinson, D. T.; Talomie, T. G.; Dunlap, R. P.; Franke, C. A. *J. Med. Chem.* **1995**, *38*, 4687–4692; (c) Krantz, A.; Copp, L. J.; Coles, P. J.; Smith, R. A.; Heard, S. B. *Biochemistry* **1991**, *30*, 4678–4687.
19. Crossland, R. K.; Wells, W. E.; Shiner, V. J. *J. Am. Chem. Soc.* **1971**, *93*, 4217–4219.
20. Farcasiu, D.; Jaehme, J.; Ruechardt, C. *J. Am. Chem. Soc.* **1985**, *107*, 5717–5722.
21. Sorbye, K.; Tautermann, C.; Carlsen, P.; Fiksdahl, A. *Tetrahedron: Asymmetry* **1998**, *9*, 681–689.
22. Heggvik, L.; Fiksdahl, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2189–2192.
23. Said, S. A.; Fiksdahl, A. *Tetrahedron: Asymmetry* **1999**, *10*, 2627–2633.
24. Evans, P. A.; Brand, T. A.; Robinson, J. E. *Tetrahedron Lett.* **1999**, *40*, 3105–3108.
25. Evans, P. A.; Brandt, T. A. *Org. Lett.* **1999**, *1*, 1563–1565.
26. Liu, J.; Robins, M. J. *Org. Lett.* **2005**, *7*, 1149–1151.
27. Vatele, J.; Hanessian, S. *Preparative Carbohydrate Chemistry*; Dekker: New York, NY, 1997; pp 127–149.
28. (a) Hanessian, S.; Vatele, J. M. *Tetrahedron Lett.* **1981**, *22*, 3579–3582; (b) Vatele, J. M.; Hanessian, S. *Tetrahedron* **1996**, *52*, 10557–10568.
29. (a) Hanessian, S.; Bacquet, C.; LeHong, N. *Carbohydr. Res.* **1980**, *80*, C17; (b) Hanessian, S. *Preparative Carbohydrate Chemistry*; 1997; pp 381–388.
30. David, S.; Malleron, A.; Dini, C. *Carbohydr. Res.* **1989**, *188*, 193–200.
31. Best, W. M.; MacDonald, J. M.; Skelton, B. W.; Stick, R. V.; Tilbrook, D. M. G.; White, A. H. *Can. J. Chem.* **2002**, *80*, 857–865.
32. Attolino, E.; Catelani, G.; D'Andrea, F. *Tetrahedron Lett.* **2002**, *43*, 1685–1688.
33. Corey, E. J.; Posner, G. H.; Atkinson, R. F.; Wingard, A. K.; Halloran, D. J.; Radzik, D. M.; Nash, J. J. *J. Org. Chem.* **1989**, *54*, 389–393.
34. Paleta, O.; Pomeisl, K.; Kafka, S.; Klasek, A.; Kubelka, V. *Beilstein J. Org. Chem.* **2005**, *1*, 17.
35. Imagawa, H.; Kinoshita, A.; Fukuyama, T.; Yamamoto, H.; Nishizawa, M. *Tetrahedron Lett.* **2006**, *47*, 4729–4731.
36. Osa, Y.; Takeda, K.; Sato, T.; Kaji, E.; Mizuno, Y.; Takayanagi, H. *Tetrahedron Lett.* **1999**, *40*, 1531–1534.
37. (a) Mackie, R. K.; Smith, D. M.; Aitken, R. A. *Guidebook to Organic Synthesis*, 3rd ed.; Longman: UK, 1999; 302–303; (b) Seyden-Penen, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley: New York, NY, 1995.
38. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, NY, 1999; Vol. 3.

39. (a) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384–5427; (b) Wallace, T. W. *Org. Biomol. Chem.* **2006**, *4*, 3197–3210.
40. Nakamura, H.; Ishihara, K.; Yamamoto, H. *J. Org. Chem.* **2002**, *67*, 5124–5137.
41. Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2001**, *123*, 1505–1506 and references cited therein.
42. Fujii, M.; Sato, Y.; Aida, T.; Yoshihara, M. *Chem. Express* **1992**, *7*, 309.
43. Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248–3249.
44. Sakane, S.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 6154–6155.
45. Tamura, R.; Watabe, K.; Ono, N.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 4895–4903.
46. Tamura, R.; Katayama, H.; Watabe, K.; Suzuki, H. *Tetrahedron* **1990**, *46*, 7557–7568.
47. The use of chiral leaving groups in nitro-olefination reactions has been briefly reviewed: Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, *12*, 1877–1894.
48. Rajappa, S. *Tetrahedron* **1999**, *55*, 7065–7114.
49. Faulques, M.; Rene, L.; Royer, R. *Synthesis* **1982**, *4*, 260–261.
50. Yang, X.; Wand, R. *Tetrahedron: Asymmetry* **1997**, *8*, 3275–3281.
51. Fugi, K.; Node, M.; Nagasawa, H.; Naniwa, Y.; Terada, S. *J. Am. Chem. Soc.* **1986**, *8*, 3855–3856.
52. Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E.; Morganti, S.; Rizzato, E.; Spinelli, D.; Dell'Erba, C.; Petrillo, G.; Tavani, C. *Tetrahedron* **2004**, *60*, 11011–11027.
53. Fuji, K. *ACGC Chem. Res. Commun.* **2000**, *11*, 32–37.
54. Bagul, T. D.; Lakshmaiah, G.; Kawabata, T.; Fuji, K. *Org. Lett.* **2002**, *4*, 249–251.
55. Basavaiah, D.; Kumaragurubaran, N.; Sharada, D. S.; Reddy, R. M. *Tetrahedron* **2001**, *57*, 8167–8172.
56. (a) Duhamel, P.; Valnot, J. Y.; Eddine, J. J. *Tetrahedron Lett.* **1982**, *23*, 2863–2866; (b) Duhamel, P.; Ple, G.; Valnot, J. Y. *Heterocycles* **1994**, *37*, 751–757.
57. McManus, S. P.; Roberts, F. E.; Lam, D. H.; Hovanes, B. *J. Org. Chem.* **1982**, *47*, 4386–4388.
58. McManus, S. P.; Safavy, K. K.; Roberts, F. E. *J. Org. Chem.* **1982**, *47*, 4388–4389.
59. (a) Alexakis, A.; Malan, C.; Lea, L.; Tissot-Croset, K.; Polet, D.; Falciola, C. *Chimia* **2006**, *60*, 124–130; (b) Karlström, A. S. E.; Bäckvall, J.-E. Copper-Mediated Enantioselective Substitution Reactions. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: 2002; pp 262–269.
60. Breit, B.; Breuninger, D. *Synthesis* **2005**, 147–157.
61. Breit, B.; Breuninger, D. *Synthesis* **2005**, 2782–2786.
62. Breit, B.; Breuninger, D. *J. Am. Chem. Soc.* **2004**, *126*, 10244–10245.
63. Karlström, A. S. E.; Huerta, F. F.; Meuzelaar, G. J.; Bäckvall, J.-E. *Synlett* **2001**, 923–926.
64. Okuyama, T.; Takino, T.; Sueda, T.; Ochiai, M. *J. Am. Chem. Soc.* **1995**, *117*, 3360–3367.
65. (a) Ochiai, M. *J. Organomet. Chem.* **2000**, *611*, 494–508; (b) Stang, P. J. *J. Org. Chem.* **2003**, *68*, 2997–3008.
66. Matano, Y. *Organometallics* **2000**, *19*, 2258–2263.
67. Matano, Y.; Imahori, H. *J. Org. Chem.* **2004**, *69*, 5505–5508.
68. Ooi, T.; Goto, R.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 10494–10495.
69. Koech, P. K.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 5350–5351.
70. Moloney, M. G.; Pinhey, J. T. *J. Chem. Soc., Chem. Commun.* **1984**, 965–966.
71. Kato, T.; Stoyanov, E.; Geier, J.; Grutzmacher, H.; Reed, C. A. *J. Am. Chem. Soc.* **2004**, *126*, 12451–12457.
72. Shimizu, M.; Sugano, Y.; Konakahara, T.; Gama, Y.; Shibuya, I. *Tetrahedron* **2002**, *58*, 3779–3783.
73. Bao, M.; Shimizu, M.; Shimada, S.; Inoue, J.; Konakahara, T. *Tetrahedron* **2004**, *60*, 11359–11366.
74. Al Neirabeyeh, M.; Rollin, P. *J. Carbohydr. Chem.* **1990**, *9*, 471–478.
75. Wang, J. C.; Just, G. *Tetrahedron Lett.* **1997**, *38*, 2241–2244.
76. Lesnikowski, Z. J.; Jaworska, M.; Stec, W. J. *Tetrahedron Lett.* **1987**, *28*, 5535–5538.
77. Picci, N.; Pocci, M.; Gugliuzza, A.; Puoci, F.; De Munno, A.; Iemma, F.; Bertini, V. *Heterocycles* **2001**, *55*, 2075–2084.
78. Arseniyadis, S.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **2004**, *45*, 2251–2253.
79. (a) See Ref. 16; (b) Fraser, H. L.; Floyd, M. B.; Sosa, A. C. B. *Prog. Heterocycl. Chem.* **2005**, *17*, 261–303.
80. Wietzerbin, K.; Bernadou, J.; Meunier, B. *Eur. J. Inorg. Chem.* **2000**, 1391–1406.
81. Benkeser, R. A.; Siklosi, M. P.; Mozdzen, E. C. *J. Am. Chem. Soc.* **1978**, *100*, 2134–2139.
82. (a) Lomas, J. S.; Dubois, J. E. *J. Org. Chem.* **1984**, *49*, 2067–2069; (b) Arnett, E. M.; Small, L. E.; McLver, R. T.; Miller, J. S. *J. Org. Chem.* **1978**, *43*, 815–817; (c) Zook, H. D.; March, J.; Smith, D. F. *J. Am. Chem. Soc.* **1959**, *81*, 1617–1620.
83. Garner, C. M.; Fischer, H. C. *Tetrahedron Lett.* **2006**, *47*, 7405–7407.
84. Codee, J. D. C.; Litjens, R. E. J. N.; Van den Bos, L. J.; Overkleeft, H. S.; Van der Marel, G. A. *Chem. Soc. Rev.* **2005**, *34*, 769–782.
85. Hanessian, S.; Lou, B. *Chem. Rev.* **2000**, *100*, 4443–4463.
86. Pornsuriyasak, P.; Gangadharmath, U. B.; Rath, N. P.; Demchenko, A. V. *Org. Lett.* **2004**, *6*, 4515–4518.
87. Mootoo, D. R.; Konradsson, P.; Udodong, U. E.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583–5585.
88. Demchenko, A. V.; Malysheva, N. N.; De Meo, C. D. *Org. Lett.* **2003**, *5*, 455–458.
89. Kamat, M. N.; Demchenko, A. V. *Org. Lett.* **2005**, *7*, 3215–3218.
90. Euzen, R.; Ferrieres, V.; Plusquellec, D. *J. Org. Chem.* **2005**, *70*, 847–855.
91. Demchenko, A. V.; Pornsuriyasak, P.; De Meo, C.; Malysheva, N. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 3069–3072.
92. Pornsuriyasak, P.; Demchenko, A. V. *Chem.—Eur. J.* **2006**, *12*, 6630–6646.
93. Pornsuriyasak, P.; Demchenko, A. V. *Tetrahedron: Asymmetry* **2005**, *16*, 433–439.
94. De Meo, C.; Parker, O. *Tetrahedron: Asymmetry* **2005**, *16*, 303–307.
95. Cacciapaglia, R.; Van Doorn, A. R.; Mandolini, L.; Reinhoudt, D. N.; Verboom, W. *J. Am. Chem. Soc.* **1992**, *114*, 2611–2617.
96. Lu, T.; Yoo, H. K.; Zhang, H.; Bott, S.; Atwood, J. L.; Echegoyen, L.; Gokel, G. W. *J. Org. Chem.* **1990**, *55*, 2269–2270.
97. Illuminati, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1983**, *105*, 555–563.
98. Yoo, H. K.; Davis, D. M.; Chen, Z.; Echegoyen, L.; Gokel, G. W. *Tetrahedron Lett.* **1990**, *31*, 55–58.

99. (a) Cacciapaglia, R.; Mandolini, L. *Chem. Soc. Rev.* **1993**, *22*, 221–231; (b) Cacciapaglia, R.; Mandolini, L. *Pure Appl. Chem.* **1993**, *65*, 533–538.
100. Cacciapaglia, R.; Mandolini, L.; Romolo, F. S. *J. Phys. Org. Chem.* **1992**, *5*, 457–460.
101. Ercolani, G.; Mandolini, L. *J. Am. Chem. Soc.* **1990**, *112*, 423–427.
102. Cacciapaglia, R.; Lucente, S.; Mandolini, L.; Van Doorn, A. R.; Reinhoudt, D. N.; Verboom, W. *Tetrahedron* **1989**, *45*, 5293–5304.
103. Cacciapaglia, R.; Mandolini, L.; Reinhoudt, D. N.; Verboom, W. *J. Phys. Org. Chem.* **1992**, *5*, 663–669.
104. Kraft, D.; Cacciapaglia, R.; Boehmer, V.; Abu El-Fadl, A.; Harkema, S.; Mandolini, L.; Reinhoudt, D. N.; Verboom, W.; Vogt, W. *J. Org. Chem.* **1992**, *57*, 826–834.
105. Brandt, K.; Siwy, M.; Porwolik-Czomperlik, I.; Stilberring, J. *J. Org. Chem.* **2001**, *66*, 5701–5712.
106. Hanessian, S.; Kagotani, M.; Komaglou, K. *Heterocycles* **1989**, *28*, 1115–1120.
107. Hanessian, S.; Johnstone, S. *J. Org. Chem.* **1999**, *71*, 3285–3286.
108. Gobbi, A.; Landini, D.; Maia, A.; Secci, D. *J. Org. Chem.* **1995**, *60*, 5954–5957.
109. Gobbi, A.; Landini, D.; Maia, A.; Penso, M. *J. Chem. Soc., Perkin Trans. 2: Phys. Org. Chem.* **1996**, *11*, 2505–2509.
110. Albanese, D.; Landini, D.; Maia, A. *J. Org. Chem.* **2001**, *66*, 3249–3252.
111. Lepore, S. D.; Bhunia, A. K.; Cohn, P. C. *J. Org. Chem.* **2005**, *70*, 8117–8121.
112. Lepore, S. D.; Mondal, D. Unpublished results.
113. Kozikowski, A. P.; Lee, J. *Tetrahedron Lett.* **1988**, *29*, 3053–3056 and references cited therein.
114. Lepore, S. D.; Bhunia, A. K.; Mondal, D.; Cohn, P. C.; Lefkowitz, C. *J. Org. Chem.* **2006**, *71*, 3285–3286.
115. Sinnott, M. L.; Storesund, H. J.; Whiting, M. C. *J. Chem. Soc. D: Chem. Commun.* **1969**, 1000–1001.
116. Lepore, S. D.; Mondal, D.; Li, S. Unpublished results.

Biographical sketch

Salvatore D. Lepore was born in Philadelphia, PA and received his B.S. in Chemical Engineering with honors in 1992 from the University of South Florida. He worked for a year as an engineer for an environmental consulting firm before deciding to pursue graduate studies at Purdue University. Salvatore received his doctoral degree in 1997 under the guidance of Merritt B. Andrus in the area of natural product total synthesis. He then spent three years as a postdoctoral fellow at Eli Lilly in Indianapolis under the direction of Michael R. Wiley. Salvatore's studies at Lilly focused on the development of new solid phase synthesis methods. In 2000, he joined the chemistry faculty at Florida Atlantic University as an Assistant Professor and was promoted to the Associate level in 2006. His current research efforts are in the development of new leaving groups with applications in radiotracer synthesis. He is also developing new asymmetric methods for the preparation of conjugated allenyl carbonyl compounds with applications in natural product total synthesis. Salvatore's research has been funded by a number of agencies including the ACS PFR, NIMH, NIGMS, NSF, and Florida Centers of Excellence program. In 2006, he received his university's Researcher of the Year award.

Deboprosad (Debo) Mondal was born in Diamond Harbour (India) in 1981. He received his B.S. in Chemistry from Calcutta University in 2002 and an M.S. from the Indian Institute of Technology, Kanpur in 2004. He is currently a doctoral student under the guidance of Professor Salvatore D. Lepore in the Department of Chemistry at Florida Atlantic University. Debo's main research involves the design of new leaving groups to solve some critical problems in organic synthesis. He is also developing new titanium IV reagents for stereoselective halogenations and azidations.