

Professor Keith Smith

A Tribute

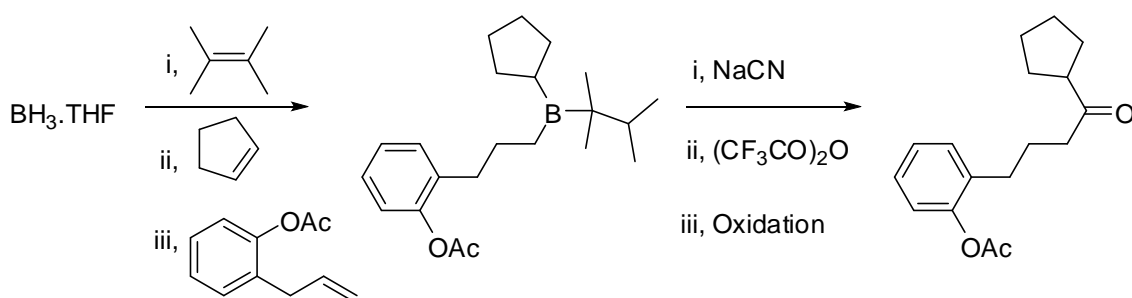


A male child born in Walsall, England, on January 15 1947 to a family in difficult circumstances was adopted by a miner and his wife from North Staffordshire and his name became Keith Smith. As a result, Keith grew up in the rural village of Brown Edge, close to the pottery city of Stoke-on-Trent. Following the death of his mother when he was five years old, his father re-married and Keith acquired two older step-siblings. He attended the local primary school in Brown Edge, but as one of the fortunate few from the village to pass the “eleven-plus” examination his secondary education was at Leek High School, necessitating a 7 mile each way daily bus trip to Leek. It was during his time at Leek High School that he met his future wife, Lynn, who attended the neighboring high school for girls. It was also there that his interest in science, and in chemistry in particular, was stimulated. When he left Leek High in 1965 he was awarded the Mathematics, Chemistry and University Entrance Prizes.

He then attended Manchester University, where he studied Chemistry. He was awarded the A F Edwards Memorial Prize at the end of his first year and went on to achieve a BSc with First Class Honors in 1968. Following his graduation, two of the most significant events that would influence his future life occurred. In August he married Lynn and in October he began research studies under the supervision of Dr Andrew Pelter, then a young member of staff in the Chemistry Department at Manchester University.

His initial research project involved continuation of recent work of the Pelter group, which depended upon reactions of acyloxyboron compounds. This was successful and his first paper, on synthesis of thioesters, was submitted just a few months after he started his studies.¹ However, around that time H C Brown’s seminal work into the hydroboration reaction had demonstrated that many different organoboron compounds could be easily synthesised and the first useful synthetic reactions of such compounds were beginning to emerge. With

encouragement from his supervisor, Keith proposed a new reaction type, involving formation of a trialkylcyanoborate and its subsequent reaction with an electrophile. Together Pelter and Smith investigated a variety of electrophiles, most of which induced rearrangements, but the use of trifluoroacetic anhydride was particularly effective and led to a new method for the synthesis of ketones.² The method could be applied to unsymmetrical thexyldialkylboranes and allowed simple and convenient one-pot syntheses of unsymmetrical, cyclic and functionally substituted ketones (*e.g.* Scheme 1).³



Scheme 1 An example of ketone formation *via* trifluoroacetylation of a trialkylcyanoborate

The ketone-forming reaction involved migration of two alkyl groups from boron to carbon, but the third alkyl group could also be caused to migrate by warming with excess trifluoroacetic anhydride; oxidation then provided tertiary alcohols.⁴ The migratory aptitudes of the alkyl groups were in the order primary > secondary > tertiary.⁵ The method attracted much attention and was widely used in syntheses of a variety of target compounds, but perhaps the greater significance of the work was that it established a new kind of useful organoboron reaction - the reaction of four-coordinate borate salts with electrophiles to induce migrations. Many other reactions of this general type were subsequently studied by several groups around the world.

Meanwhile, Keith received an MSc in 1969 and a PhD in 1971 for his work in this area and was awarded a Royal Society European Exchange Fellowship to take up a postdoctoral research position with Professor Albert Eschenmoser at the ETH in Zürich, Switzerland, where he contributed to a project on chlorophyll derivatives.⁶ While Keith was in Switzerland, Andrew Pelter moved to Swansea University to take up a position as Professor of Organic Chemistry and a lectureship became available there. Keith was appointed to the position from October 1972 and rejoined his collaboration with Pelter on organoboron chemistry. Among other reactions, they introduced methods for syntheses of unsymmetrical conjugated diynes from the corresponding dialkyldialkynylborates,⁷ of secondary and tertiary alcohols from reactions of trialkylboranes with bis(phenylthio)alkyllithiums⁸ or 2-lithio-2-alkylbenzodithioles,⁹ of *N*-substituted sulfonamides,¹⁰ and of dialkylbromoboranes.¹¹

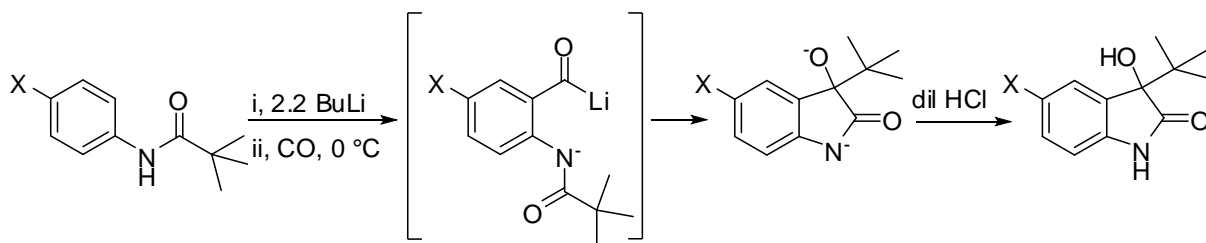
During this period Keith was initiating his independent research career, some part of which also involved boron chemistry. For example, he re-examined claims relating to preparation of an acyldialkylborane, showing them to be ill-founded,¹² and he identified a new type of boron compound from the reaction of diphenylbromoborane with di-isopropylcarbonyllithium.¹³ He became well known internationally within the boron community and was invited by H C Brown to spend a sabbatical year (1978-79) collaborating with him at Purdue University in the USA, where he worked to understand some difficulties

associated with hydride-induced carbonylation of organoboranes.¹⁴ He was delighted and honored to be asked to accompany Brown to Stockholm in December 1979, when Brown shared the Nobel Prize for Chemistry with G Wittig.

In view of Keith's strong reputation in organoboron chemistry, it is not surprising that he received many invitations to contribute to review articles (*Chemical Society Reviews*, *Annual Reports of the Chemical Society*, *Specialist Periodical Reports*) and to major reference works, such as *Comprehensive Organic Chemistry*,¹⁵ *Kirk-Othmer Encyclopedia of Chemical Technology*,¹⁶ and the *Dictionary of Organometallic Compounds*, for which he was editor of the boron section for the main volume and the first four supplements.¹⁷ He also co-authored a book on boron chemistry with Pelter and Brown¹⁸ and contributed the boron section to M Schlosser's manual on organometallics in synthesis.¹⁹

Keith's interests in boron chemistry were enduring and he continued intermittently to publish in the area.²⁰ Indeed, even at the present time he continues to contribute to the field.²¹ However, even before he went to Purdue there were signs that his interests were broadening and that lithium reagents, heterocyclic compounds and the need for more sustainable chemical methods were becoming important to him. For example, in the lithium area he generated di-isopropylcarbamoyllithium directly by deprotonation of di-isopropylformamide,²² in the heterocyclic field he developed new syntheses of various tricyclic systems,²³ and his interest in sustainable chemistry was demonstrated by his study of the possibility of using seaweed as a source of chemicals.²⁴ However, these topics assumed greater significance in his researches in the decade and a half following his return from the USA, during which time he was promoted to Senior Lecturer (1980), Reader (1985) and Professor (1988), and also became Head of the Chemistry Department (1990-93).

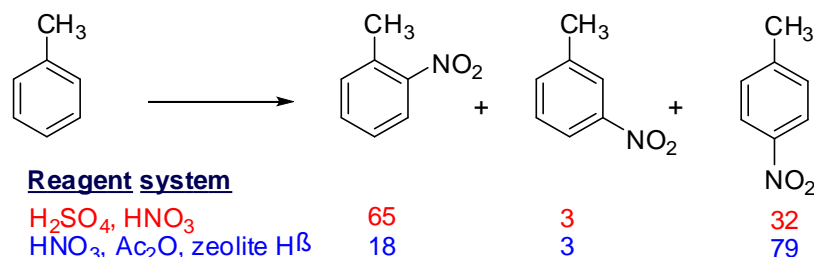
In the lithiation field during that time, *inter alia*, he developed new carboxyl carbanion equivalents,²⁵ demonstrated how arenethiols could be directly *ortho*-lithiated,²⁶ showed that certain types of substituted organolithium reagents could usefully react with carbon monoxide to give heterocyclic products (*e.g.* Scheme 2),²⁷ used directed metallation to generate thiazolo[5,4-*c*]pyridines²⁸ and thiazolo[4,5-*b*]pyridines,²⁹ developed a superior approach to formation of substituted benzyllithiums from the corresponding benzyl chlorides,³⁰ and introduced a new synthesis of sulfonic acids *via* reactions of organolithiums with a sulfur trioxide complex.³¹



Scheme 2 An example of heterocycle formation *via* carbonylation of an organolithium

It was also during this period that Keith began to look at the use of solids to control chemical reactions. His interest started from a chance observation during chromatographic purification of chloroalkane products from organoborane reactions with dichloramine-T.³² Traces of new products generated during chromatography encouraged examination of

combinations of silica with various chloro compounds, which proved to be effective electrophilic chlorinating agents for substitution of toluene and other aromatic compounds.³³ Use of a zeolite instead of silica allowed control of the regiochemistry of the reaction, so that greater *para*-selectivity could be achieved.³⁴ Keith also examined *N*-bromosuccinimide in the presence of silica, which turned out to be an excellent selective reagent for bromination of heterocyclic compounds such as indoles, benzimidazoles, carbazoles, β -carbolines and iminodibenzyls.³⁵ Again, use of a zeolite instead of silica, together with an appropriate brominating agent, allowed highly *para*-selective bromination of toluene and other aromatic compounds.³⁶ In view of the selectivity that had been achieved with zeolites in halogenation reactions, Keith explored a range of other electrophilic aromatic substitution reactions to see if similar benefits could be achieved and was able to develop highly selective procedures for allylation,³⁷ acylation,³⁸ methanesulfonylation,³⁹ and nitration (*e.g.* Scheme 3)⁴⁰ of substituted benzenes. It was mainly for his work on such reactions that he was awarded the inaugural (2001) Royal Society of Chemistry Industrially Sponsored Award in Green Chemistry. He also edited a book on the use of solid supports and catalysts⁴¹ and produced several reviews.



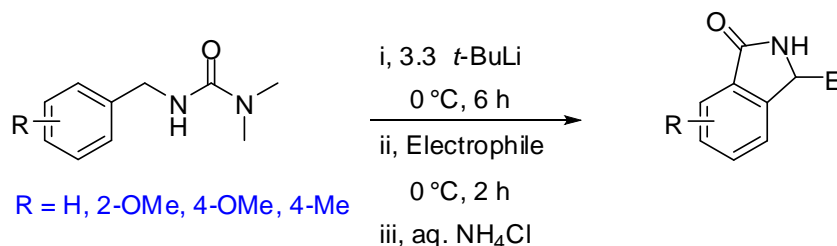
Scheme 3 Proportions of products by traditional and zeolite-enhanced nitrations of toluene

Within the decade and a half of his return from the USA Keith was also developing his interests in synthesis of heterocyclic compounds. Some of the lithiation and solid-mediated reactions illustrated above were aimed at heterocycles synthesis, but he was also developing methods that did not involve such approaches. These included 3-hydroxypyridine-2-thione,⁴² phenoxathiins and related compounds,⁴³ substituted 1,2,4-triazoles,⁴⁴ and tetrathiafulvalenes.⁴⁵

I first joined Keith's research group in 1993 while enrolled for a PhD in Egypt. I was awarded a scholarship to allow me to spend two years in the UK to take advantage of the availability of advanced facilities. Keith and I decided to apply some of the techniques used in lithiation chemistry to quinazalinones, which I had already been studying in Egypt. We were able to elaborate various quinazolinones into more complex derivatives⁴⁶ and this formed the basis of my PhD thesis when I returned to Egypt to resume my job as a lecturer. As soon as my university would permit it, Keith invited me back to the UK as a postdoctoral researcher and found support funding. He did the same on two more occasions and the latter has been continuous for the last 11 years, including a move to Cardiff University when Keith transferred to there in 2007. During these periods I have formed a very close working relationship with Keith's group and we have collaborated extensively. Together we have over 50 joint publications, including ones in all major areas in which Keith's group is involved.

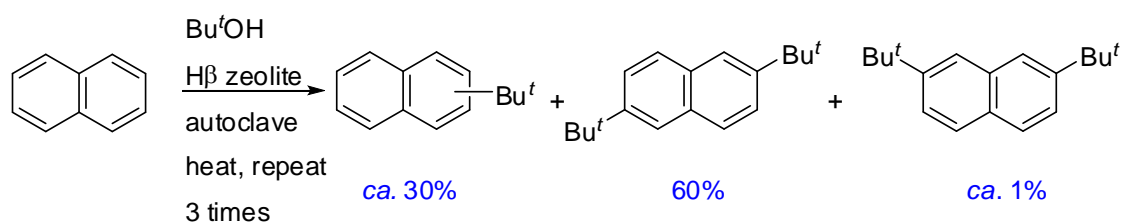
Among the many contributions made by Keith's group in the last decade or so are many examples of lithiation as a means to elaborate organic structures, including formation of

substituted trifluoroacetanilides,⁴⁷ several cases of selective substitution of aromatic and heteroaromatic substances,⁴⁸ and a one-pot synthesis of isoindolinones (Scheme 4).⁴⁹



Scheme 4 A one-pot method for synthesis of substituted isoindolinones *via* lithiation

In the field of use of solids to mediate reactions there are several notable achievements, including preparation of a singly-bound, polymer-supported Katsuki catalyst that gives high levels of asymmetric induction,⁵⁰ development of a completely different nitration system based on dinitrogen tetroxide and air over a zeolite catalyst,⁵¹ achievement of substantial selectivity in nitration of deactivated disubstituted aromatic compounds⁵² and significantly increased proportions of *para*-substituted products from nitration of deactivated monosubstituted aromatic systems,⁵³ and rearrangement of epoxides over solids to give either carbonyl compounds or allylic alcohols.⁵⁴ However, the most remarkable selectivity has been demonstrated in dialkylation of naphthalene to give almost exclusively the 2,6-isomer. Considering that the α -position is more reactive than the β -position in naphthalene, and that introduction of alkyl groups encourages polyalkylation, the production of 2,6-di-*tert*-butylnaphthalene in 60% yield (Scheme 5)⁵⁵ with no more than 2% of any other isomeric di-*tert*-butylnaphthalenes, is surprising. We have recently provided an overview of the work of Keith's group on the use of zeolites to control regioselectivity in aromatic substitution.⁵⁶



Scheme 5 Highly regioselective 2,6-di-*tert*-butylation of naphthalene

Although some work was conducted earlier on the development of chemiluminescent biological probes based on acridinium esters,⁵⁷ Keith's group has become increasingly involved with such developments recently. In particular, the group has developed acridinium derivatives that can be used to label oligonucleotides in conjunction with a quencher in such a way that the so-called HICS probes can be used to detect nucleic acid markers (including simultaneous dual analyte analysis) with high sensitivity, making amplification unnecessary.⁵⁸

As is clear from the above discussion, Keith's researches have covered a broad spectrum. When books, chapters, reference works, review articles, patents and conference proceedings are included he has well over 300 publications. He has collaborated extensively with scientists

in the USA (*e.g.* D J Faulkner,⁵⁹ G E Martin, C A Brown), France (G Bram), Japan (*e.g.* M Wada),⁶⁰ and elsewhere, as well as with scientists in various industrial concerns. He and I have set up a company and Keith is the Managing Director. He has previously been President of the National Conference of University Professors and is currently a member of the Council of the Royal Society of Chemistry and a Trustee of the Sir Richard Stapley Educational Trust. He was elected to Fellowship of the newly established Learned Society of Wales in 2011.

Keith has two children, Gareth (born 1973) and Tonya (1976), and a granddaughter, Alys (2006). Outside of his professional roles, he likes to spend time with his granddaughter and other family members, to complete puzzles such as Sudoku, and to watch Formula 1 Grand Prix. In his younger days he played soccer and table tennis and ran a marathon in 3h 5 min.

Keith has taken over 80 research students (mostly PhDs) through to completion of their degrees and remains in touch with many of them. On January 15 2012 he celebrates his 65th birthday and in September 2012 reaches normal retirement age. On behalf of his friends and colleagues I wish him well and congratulate him on his contributions to chemistry and the wider community, which fully warrant the recognition afforded by this special issue.

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