Dr. Adeem Mahmood

Ph.D (Synthetic Organic Chemistry) Bristol, UK.
Postdoc (Synthetic Organic Chemistry) Nottingham, UK.

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Glance

Sep, 2014-till date	*Assistant Professor*	Chemistry Dept, King Saud University, Riyadh, KSA
Feb, *2012- Aug, 2014* (*Assistant Professor*)		Chemistry Dept, CIIT, Abbottabad Campus, Pakistan
Jan 2011- Jan 2012	*PDRA*	School of Chemistry, University of Nottingham, UK
Oct 2006-Mar 2011	*Ph.D*	School of Chemistry, University of Bristol, UK
2006	*GRE* (Chemistry)	ETS (USA) 680 score (Reg. No: 7644-204)
2004 -2006	*Research Fellow* (M.Phil)	HEJ (ICCBS), Karachi, Pakistan
2001-2004	*Q.C. Chemist*	Hamaz Pharmaceuticals Pvt. Ltd. Multan, Pakistan
1998-2000	*M.Sc.* (Chemistry) with thesis	Bahauddin Zakariya University Multan, Pakistan 1st Div.
1995-1998	*B.Sc.* (Science)	Bahauddin Zakariya University Multan, Pakistan 1st Div.
1993-1995	*F.Sc.* (Pre-Medical)	Govt. Science College Multan, Pakistan 1st Div.
1992	*SSC* (Science)	Govt. Model High School Multan, Pakistan 1st Div.

Key skills

Scientific Organic synthesis, Catalysis, Heterocycles and Organometallics synthesis, Asymmetric synthesis, Green Synthesis, Natural product Chemistry
Analytical (NMR, GC (chiral), HPLC (chiral), GCMS, UV, IR,), Purification techniques (flash chromatography, preparative HPLC), Microwave synthesis

Computer Scientific database (Beilstein/Reaxys, SciFinder)
Scientific softwares (Chemoffice, Isis Base, Endnote, NMRview, ACD, MestRec…)
MS Office, Visual Basic 5.0, Design Expert 7.0.3 (Statease)

Professional experiences (Research & Teaching)

Sep 22, 2014- till date — Department of Chemistry, King Saud University, Riyadh, KSA.
Assistant Professor – Synthetic Organic Chemistry, Natural Product Chemistry
Main Duties: Conducting Research & Teaching (Synthetic & Natural Product Chemistry)

Feb 27, 2012- Sep 20, 2014 — Department of Chemistry, COMSATS I. I. T, Abbottabad, Pakistan.
Assistant Professor – Synthetic Organic Chemistry
Main Duties: Conducting Research & Teaching (Organic Synthesis)
Research: 3 MS students -Research Supervision on different synthetic projects
Teaching: BS, MS and PhD courses

Jan 04, 2011- Jan 04, 2012 — School of Chemistry, University of Nottingham, UK.
Postdoctoral Research Associate – Synthetic Organic Chemistry
Research Projects:
- ✓ Towards The Synthesis of *Nakadomarin* A.
- ✓ Multicomponent Synthesis of Chiral Sulfinimines.
- ✓ Redical Cyclization of Sulfinamines.

Mentor – Prof. Rob Stockman

Oct 01, 2006- Nov 30, 2010 — School of Chemistry, University of Bristol, UK.
Ph.D Research Scholar – Synthetic Organic Chemistry

Degree Awarded **Thesis** – Asymmetric Lithiation//Borylation of Primary Carbamates and
On Mar 09, 2011 their Applications Towards the Allylation of Aldehydes and the Prins Cyclisation.
Mentor – Prof. Varinder K. Aggarwal FRS

Apr 24, 2003- HEJ (ICCBS), University of Karachi, Pakistan.
Aug 01, 2006 ***Research Fellow*** (M.Phil leading to Ph.D) – Organic Chemistry (Natural Product Chem.)
Project – Isolation/Characterization of Bioactive *Sec*. Metabolites from *E. parvifolia*.
Mentor – Prof. M. Iqbal Chaudhary (*N.I., S.I., T.I.)*

Jan 15, 2001- Hamaz Pharmaceuticals Pvt. Ltd. Multan, Pakistan
Mar 08, 2004 ***Q.C Chemist*** – Drug Stability Control, Chemical Analysis and Research Findings.

Nov, 1998- Bahauddin Zakariya University Multan, Pakistan
Dec, 2000 ***Graduate Research Student*** – Organic Chemistry with research thesis (AAS Analysis)
Mentor – Prof. Humayun Pervaiz

Academic Awards/Achievements

- Awarded Faculty Position (Assist. Professor) in Chemistry (King Saud University, KSA, 2014)
- EPSRC Research Postdoctoral Fellowship (University of Nottingham, UK. 2011-2012)
- HEC Approved Supervisor (Pakistan, 2012)
- Split Scholarship for PhD to study in advanced countries (HEC, Pakistan. 2006-2009)
- HEJ Research Fellowship (HEJ Karachi, Pakistan. 2003-2006)
- Associate Member of the Royal Society of Chemistry (London, UK, 2006)
- Member of the Pakistan Chemical Society (2012)
- Start up Research Funding (HEC, Pakistan, 2013)
- Awarded KACST-NPRST Research Funding 2m SAR (KSU, Saudi Arabia, 2015)
- *Through out 1st-Class Academic Record*

Scientific Contribution (I.F – 55.20, Citation – 220)

Publications

1. Lithiated Carbamates: Chiral Carbenoids for Iterative Homologation of Boranes and Boronic Esters; Jake L. Stymiest, Guillaume Dutheuil, **Adeem Mahmood** and Varinder K. Aggarwal; *Angew. Chem. Int. Ed.,* **2007,** *46*, 7491–7494; *Angew. Chem.* **2007,** *102*, 1455–1456. (Article selected as a **VIP**. Paper also selected for front issue cover) (I.F. 11.455, Citations: 120).
2. Application of the Lithiation-Borylation Reaction to the Preparation of Enantioenriched Allylic Boron Reagents and Subsequent in situ Conversion into 1,2,4-Trisubstituted Homoallylic Alcohols with Complete Control over all Elements of Stereochemistry; Martin Althaus, **Adeem Mahmood**, José R. Suárez, Stephen P. Thomas and Varinder K. Aggarwal*; J. Am. Chem. Soc.,* **2010,** *132*, 4025–4028. (I.F. 12.80, Citations: 68)
3. Blood Zinc and Iron Levels in Children of Out Patient Department at Tertiary Care Hospital of Multan; Tariq M. Ansari, Humayun Pervez, **Adeem Mahmood**, Zulifqar A. Khan, Imran Iqbal and Muhammad I. K. Sherwani; *Medical Forum* (Monthly), 21(4), 35-37 (**2010**) (I.F. 2.01).
4. One-pot synthesis of 2,3,4,5,6-pentasubstituted tetrahydropyrans using lithiation-borylation, allylation and Prins cyclisation reactions; **Adeem Mahmood**, Jose Ramón Suárez, Stephen P. Thomas and Varinder K. Aggarwal; *Tet.Lett.,* **2013** , *54*, 49-51. (I.F. 2.801, Citation: 20)
5. Synthesis and biological evaluation of novel oxadiazole derivatives: A new class of thymidine phosphorylase inhibitors as potential anti-tumor agents; Sohail A. Shahzad, Muhammad Yar, Marek Badja and **Adeem Mahmood**, *Bioorganic & Medicinal Chemistry* , **2014**, *22*, 1008-1015. (I.F. 3.0, Citation: 15).
6. Aromaticities of azines relative to benzene; a theoretical approach through the dimethyl-dihydropyrene probe; Khurshid Ayub and **Adeem Mahmood**, *J. Phys. Org. Chem*, **2014**, *27*, 860-866. (I.F. 2.08, Citation: 9).
7. Pharmacological Applications of Quercetin and its Derivatives: A Short Review; **Adeem Mahmood**, *Trop J Pharm Res,* **2014***, 13, 1561-1566.* (I.F. 1.80, Citation. 6)
8. Chelation-Assisted Substrate-Controlled Asymmetric Lithiation-Allylboration of Chiral Acetonide Carbamate (1,2,4-Butanetriol Acetonide); **Adeem Mahmood** *et. al*., *Molecules,* **2015,** *20*, 9890-9905. (I.F. 2.1)

9. Characterization of Leaves and Flowers Volatile Constituents of *Lantana camara* Growing in Central Region of Saudi Arabia; **Adeem Mahmood** *et. al., Arabian Journal of Chemistry,* **2016,** *9*, 764-774. (I.F. 3.2, Citation. 30)
10. The Steering pathway: Ketene-Claisen Rearrangements (KCR)-1978-2016 (Review Article); **Adeem Mahmood**, *Tetrahedron* , **2017,** *73,* 2173-2190. (I.F. 2.6)
11. Identification of Essential oils, Isolation, Structure Elucidation and Evaluation of Bioactivity of Secondary Metabolites from Centaurea Pseudosinaica; **Adeem Mahmood** *et. al., Arabian Journal of Chemistry*, **2017** (Submitted) (I.F. 3.2)
12. Comparative Study on the Essential Oil and Extracts of *Artemisia judaica* and *Artemisia heba alba* from Saudi Arabia: **Adeem Mahmood** et. al. *Pharmazie* , **2017** (Submitted) (I.F. 1.8).
13. A Study on the Essential Oils of *Calendula tripterocarpa* and *Achillea fragrantissima* and Isolation of non-Volatile Constituents and Bio-assays of *Tripleurospermum auriculatum* and *Koelpinia linearis*; **Adeem Mahmood** et. al. *Pharmazie* , **2017** (Submitted) (I.F. 1.8).

Conference/WorkShop Contributions

- Faculty Development Training Program, KSU, Riyadh, KSA, 5-6 Dec, 2016
- 1st International Conference on Applied Chemistry (ICAC-2015), Jeddah, KSA, 18-19 Nov, 2015
- 2 Days Workshop on Structural Chemistry, CIIT, Abbottabad, Pakistan, Apr. 17-18th , 2014
- Faculty Development Workshop, CIIT, Abbottabad-22060, Pakistan, Feb. 25 – Mar 01, 2013
- RSC Heterocyclic and Synthesis Symposium, Grasmere, UK - May 5-9th 2011
- New Horizons in Natural Product Chemistry, Nottingham, UK - November 3rd 2010
- Loughborough International Chemistry Conference, Loughborough, UK – Jul, 2011
- Bristol Synthetic Meeting, University of Bristol, UK – Apr, 2011
- Bristol Synthetic Meeting, University of Bristol, UK – Mar, 2010
- New horizons in Natural Products Chemistry, University of Nottingham, UK – Nov, 2009
- Organic Chemistry Regional Meeting, University of Southampton, UK - 2009
- Gordon Stone Lecture and Symposium, Bristol, UK-Professor Robert Grubbs, Caltech – Oct, 2008
- Metals in synthesis, University of Bath, UK – Oct, 2008
- Bristol–St Andrews Catalysis Meeting, Bristol, UK – Sep, 2008
- Organic Chemistry Regional Meeting, University of Oxford, UK - 2008
- Bristol Synthesis Meeting, University of Bristol, UK – Apr, 2008
- Bristol Synthesis Meeting, University of Bristol, UK – Apr, 2007
- 9th International Symposium on Natural Product Chemistry, Karachi. Pakistan Jan.10-13, 2004
- 7th Eurasia Conference on Chemical Sciences, Karachi, Pakistan, Mar. 9-12, 2004

Invited Lectures/Session Lectures and Poster Presentation

1. 6th International Chemistry Conference, College of Science, King Saud University, Riyadh, KSA. 8-10 November, 2016. Session Lecture
2. 14th Asian Symposium on Medicinal Plants, Spices and Other Natural Products (ASOMPS-XIV), ICCBS (HEJ), Karachi University, Pakistan, 9-12 December, 2013. Session Lecture
3. Drug Development (Natural & Synthetic) in 5th International Conference ESDEV, CIIT, Abbottabad, Pakistan, 25-27 Aug, 2013. Invited Lecture
4. Allylboration (*C-C* Coupling): Stereoselective Synthesis of 1,2,4-Trisubstituted Homoallylic Alcohols and Tetrahydropyranes; **Adeem Mahmood** & Varinder K. Aggarwal, *Symposium on New horizons in Natural Products Chemistry*, University of Nottingham, UK, Nov 2009. *Poster*
5. Lithiated Carbamates: Chiral Carbenoids for Iterative Homologation of Boranes and Boronic Esters and Stereoselective Synthesis of Homoallylic Alcohols; **Adeem Mahmood** and Varinder Aggarwal, School of Chemistry, University of Bristol, UK. May, 29, 2009. *PhD Talk*
6. Lithiated Carbamates: Chiral Carbenoids for Iterative Homologation of Boranes and Boronic Esters; **Adeem Mahmood** and Varinder K. Aggarwal, University of Bristol, UK, April 2009. *Pfizer Oral Talks Competition*

7. Lithiated Carbamates: Chiral Carbenoids for Iterative Homologation of Boranes and Boronic Esters; **Adeem Mahmood**, Jake L. Stymiest, Guillaume Dutheuil and Varinder K. Aggarwal, , University of Bristol, UK, April 2009. *Pfizer poster competition*
8. Chiral Carbenoids: Asymmetric synthesis of *α*-substituted allylboranes and boronic esters; **Adeem Mahmood** and Varinder K. Aggarwal, *Symposium on Metals in synthesis*, University of Bath, UK, Oct 2008. *Poster*
9. Allylboration of Aldehydes with α-Chiral Allylboron Reagents; **Adeem Mahmood** & Varinder K. Aggarwal, *Organic Chemistry Regional Meeting*, University of Southampton, UK, 2009. *Poster*
10. Chiral Carbenoids: Lithiation Adjacent to Oxygen; **Adeem Mahmood**, School of Chemistry, University of Bristol, UK, May, 21, 2007. *Review Talk*

Personal

Date of Birth	1st March. 1977, Multan, Pakistan
Father Name	Malik Mahmood Baksh
Marital Status	Married to Dr. Saima Parvez (MBBS)
Children	2 (Hafsa Adeem & Muhammad Hadi Adeem)
Nationality	Pakistani (Currently in KSA)
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Selected Publications: (Front Page)

Angewandte Chemie

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Asymmetric Synthesis

Lithiated Carbamates: Chiral Carbenoids for Iterative Homologation of Boranes and Boronic Esters**

*Jake L. Stymiest, Guillaume Dutheuil, Adeem Mahmood, and Varinder K. Aggarwal**

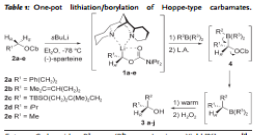
Dedicated to Professor Miguel Yus on the occasion of his 60th birthday

The homologation of chiral boronic esters by Matteson and co-workers represents a landmark contribution in the field of asymmetric synthesis.[1] However, despite achieving exceptionally high enantioselectivities with simple, readily accessible reagents, the methodology has not been widely adopted. One possible factor may be that additional steps are required to control stereochemistry during iterative homologation as a consequence of employing substrate control.[2a,3] Since the stereogenic center created during homologation is dictated by the substrate diol of the boronic ester, if the opposite stereoisomer is required, a three-step sequence is needed to invert (by exchange) the diol stereochemistry.[2f] A potentially more powerful and efficient strategy is to employ reagent control in the homologation process. This approach requires a chiral carbenoid that shows high configurational and chemical stability but sufficient reactivity to effect homologation of boronic esters. We have shown that chiral sulfur ylides fulfil some of these criteria and can be used effectively in the homologation of a range of boranes with very high enantioselectivity.[2f] However, these ylides do not react with boronic esters and only give low enantioselectivity with boronic esters.[2c] Very recently, Blakemore and co-workers described the application of Hoffmann's α-chloro Grignard reagents[4] (although they found that the lithium derivatives worked better) to effect iterative homologation of boronic esters.[2c,e] The chlorosulfoxide precursors were prepared in two steps, but some degree of racemization occurred during the homologation process.[4] Hoppe-type lithiated carbamates, **1a–e**[5] (from lithiation of **2a–e** with *s*BuLi in the presence of (−)-sparteine; see Table 1, where the carbamate moiety is abbreviated OCb) represent another class of chiral carbenoids, which is more readily obtained, and seemed to us to fulfil the requirements for boronic ester homologation. Indeed, Hoppe and co-workers have described the trapping of lithiated carbamates with borates and the subsequent (separate) treatment of the α-carbamoyl alkylboronate with a Grignard reagent to effect 1,2-metalate rearrangement with expulsion of the carbamate moiety. Oxidation of the resultant boronic esters affords the corresponding alcohols with high enantiomeric excesses.[5i] However, the direct reaction of lithiated carbamates, such as **1a–e**, with boranes or boronates and further iterative homologations had not been described.[5i]

We found that lithiated carbamates **1a–e** reacted directly with boranes or boronic esters, thus furnishing secondary alcohols **3a–j** in good yield and with high enantioselectivity (Table 1). A number of points are worthy of note:

1) Reactions with 9-BBN (9-BBN = 9-borabicyclo-[3.3.1]nonane) derivatives resulted in clean migration of the boron substituent in **4** rather than the boracyle in all

Table 1: One-pot lithiation/borylation of Hoppe-type carbamates.



2a R¹ = Ph(CH₂)₃
2b R¹ = Me₂C=CH(CH₂)₂
2c R¹ = TBSO(CH₂)₄C(Me)₂CH₂
2d R¹ = *i*Pr
2e R¹ = Me

Entry	Carbenoid precursor	R²	$(R^B)_2$	Lewis acid	Yield [%] (product)	e.r.[a]
1	2a	Et	Et	–	91 (3a)	98:2
2		*n*Hex	9-BBN	–	90 (3b)	98:2
3		*i*Pr	9-BBN	–	81 (3c)	98:2
4		Ph	9-BBN	–	85 (3d)	88:12
5		Ph	9-BBN	$MgBr_2$	94 (3d)	97:3
6		Et	pinacol	$MgBr_2$	90 (3a)	98:2
7	2b	Et	Et	–	90 (3e)	97:3[b]
8		Ph	9-BBN	$MgBr_2$	71 (3f)	95:5
9		Et	pinacol	$MgBr_2$	75 (3e)	97:3
10		Ph	pinacol	$MgBr_2$	73 (3f)	98:2
11	2c	Et	Et	–	67 (3g)	95:5[b]
12		Ph	9-BBN	$MgBr_2$	65 (3h)	97:3
13		Ph	pinacol	$MgBr_2$	64 (3h)	98:2
14	2d	Ph	9-BBN	$MgBr_2$	68 (3i)	96:4
15		Ph	pinacol	$MgBr_2$	70 (3i)	98:2
16	2e	Ph	pinacol	$MgBr_2$	70 (3j)	97:3

[a] Unless otherwise stated all enantiomeric ratios (e.r.) were calculated using chiral HPLC (Chiracel OD column). [b] The e.r. was determined using ^{1}H NMR of (*S*)-(+)-α-methoxy-α-trifluoromethylphenyl acetic acid ester.[5k] [c] The e.r. was determined using chiral GC on a Supelco Alpha-Dex column.

[*] Dr. J. L. Stymiest, Dr. G. Dutheuil, A. Mahmood, Prof. V. K. Aggarwal
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J|A|C|S ARTICLES

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Application of the Lithiation−Borylation Reaction to the Preparation of Enantioenriched Allylic Boron Reagents and Subsequent In Situ Conversion into 1,2,4-Trisubstituted Homoallylic Alcohols with Complete Control over All Elements of Stereochemistry

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Abstract: The reactions of Hoppe's lithiated carbamates with vinylboranes and boronic esters give allylic boranes/boronic esters, and subsequent addition of aldehydes provides a new route to enantioenriched homoallylic alcohols with high enantiomeric ratios and diastereomeric ratios. Specifically, reactions of sparteine-complexed lithiated carbamates with *trans*-alkenyl-9-BBN derivatives followed by addition of aldehydes gave (*Z*)-*anti*-homoallylic alcohols in greater than 95:5 er and 99:1 dr. However, in the special case of the methyl-substituted lithiated carbamate, diamine-free conditions were required to achieve high selectivity. Reactions of sparteine-complexed lithiated carbamates with (*Z*)-alkenyl pinacol boronic esters and (*E*)-alkenyl neopentyl boronic esters gave (*E*)-*syn*- and (*E*)-*anti*-homoallylic alcohols, respectively, in greater than 96:4 er and 98:2 dr. In these reactions, a Lewis acid ($MgBr_2$ or $BF_3{\cdot}OEt_2$) was required to promote both the 1,2-metalate rearrangement and the addition of the intermediate allylic boronic ester to the aldehyde. This methodology provides a general route to each of the three classes of homoallylic alcohols with high selectivity.

Introduction

The asymmetric allylboration of aldehydes is one of the most reliable and useful methods for making carbon−carbon bonds with control over relative and absolute stereochemistry.[1] In particular, Hoffmann's realization that relative stereochemistry could be controlled by the double bond geometry of crotylboronates[2] and Brown's discovery of highly enantioselective allylborations using pinane-derived reagents[3] provided the foundations to this important reaction which continues to evolve to this date.[4] The most notable recent developments include Hall's discovery that Lewis acids promote reactions of allylic boronic esters,[4a,b,5] Roush's use of bisallylboron reagents for the stereocontrolled synthesis of 1,5-diols,[4c,d,6] and the development of a new chiral allylborane by Soderquist which gives high enantioselectivity even with ketones.[7]

However, generally, these powerful transformations are limited to simple allyl or crotylboron reagents, which ultimately lead to terminal alkenes; substitution in the α-position is considerably less common.[8] We recognized that if we could prepare such reagents with control over enantioselectivity, then, by judicious choice of the *achiral* groups on boron and the initial double bond geometry we had the potential to control all of the

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(2) (a) Hoffmann, R. W.; Zeiss, H.-J. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 306. (b) Hoffmann, R. W.; Zeiss, H.-J. *J. Org. Chem.* **1981**, *46*, 1309. (c) Hoffmann, R. W. *Pure Appl. Chem.* **1988**, *60*, 123. (d) Hoffmann, R. W.; Niel, G.; Schlapbach, A. *Pure Appl. Chem.* **1990**, *62*, 1993.
(3) (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (b) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293. (c) Ramachandran, P. V. *Aldrichimica Acta* **2002**, *35*, 23.

(4) For selected examples published in 2009, see: (a) Rauniyar, V.; Hall, D. G. *J. Org. Chem.* **2009**, *74*, 4236. (b) Penner, M.; Rauniyar, V.; Kaspar, L. T.; Hall, D. G. *J. Am. Chem. Soc.* **2009**, *131*, 14216. (c) Chen, M.; Handa, M.; Roush, W. R. *J. Am. Chem. Soc.* **2009**, *131*, 14602. (d) Kister, J.; DeBaillie, A. C.; Lira, R.; Roush, W. R. *J. Am. Chem. Soc.* **2009**, *131*, 14174.
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(8) The 2008 comprehensive review of allylation reaction using allylboron reagents by Hall[4b] cites 49 pages of tabulated individual reactions using an α-substituted allylboron reagent compared to 419 pages of reactions using allylboron reagents without α-substitution.

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One-pot synthesis of 2,3,4,5,6-pentasubstituted tetrahydropyrans using lithiation–borylation, allylation and Prins cyclisation reactions

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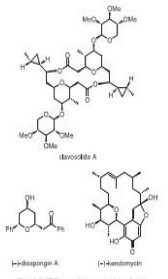
ABSTRACT

2,3,4,5,6-Pentasubstituted tetrahydropyrans have been prepared in good yield (42–57%) with excellent dr (>95:5) and er (>95:5) using a one-pot lithiation–borylation, allylation and Prins cyclisation reaction.

Substituted tetrahydropyrans (THPs) are ubiquitous in Nature.[1] They show great diversity in structure and complexity, from the relatively simple tri-substituted THP, (−)-diospongin A[2] to the highly complex polyketide marine metabolites clavosolide A[3] and (−)-kendomycin[4] with penta-substituted THP cores (Fig. 1). One of the most efficient strategies for their construction involves the Prins cyclisation,[5] as demonstrated by numerous research groups.[5a,b] Indeed, the acid-catalysed Prins cyclisation of an in situ generated oxocarbenium ion has been extensively used for the stereoselective synthesis of diversely functionalised THPs.[5] Although allyltin[6] and allylsilyl[6] reagents have been used in this context, to the best of our knowledge, there is only a single report of allylboron reagents being used for the stereoselective synthesis of racemic THPs via a tandem allylation and Prins cyclisation.[6b]

We recently reported the enantioselective synthesis of α-substituted allylic boron reagents which could be reacted with aldehydes to give homoallylic alcohols with control of all elements of stereochemistry (*syn*/*anti*; *E*/*Z*).[11] We recognised that if these products could be used in a subsequent Lewis acid-catalysed Prins cyclisation we would have the ability to form highly substituted THPs with excellent diastereoselectivity and enantioselectivity.[12]

We postulated that if the allylation products, **6** or **7** formed via an initial allylation with the first equivalent of aldehyde, could be trapped by a second aldehyde in the presence of a Lewis acid, a Prins cyclisation should ensue (**8** → **10** or **9** → **11**) to give highly substituted THPs (Fig. 2). The enantioselectivity would be set in the lithiation–borylation reaction (>98:2 *er*) and the diastereoselectivity would be set in the allylation reaction (>95:5 *dr*), and subsequent Prins cyclisation.



clavosolide A

(−)-diospongin A (−)-kendomycin

Figure 1. THP-containing natural products.

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Synthesis and biological evaluation of novel oxadiazole derivatives: A new class of thymidine phosphorylase inhibitors as potential anti-tumor agents

Sohail Anjum Shahzad [a,*], Muhammad Yar [b,*], Marek Bajda [c,d], Bushra Jadoon [a], Zulfiqar Ali Khan [a], Syed Ali Raza Naqvi [e], Ahson Jabbar Shaikh [a], Khizar Hayat [a], Adeem Mahmmod [a], Nasir Mahmood [f], Sławomir Filipek [c]

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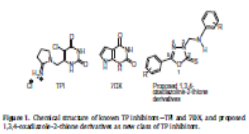
ABSTRACT

Based on the fact that the thymidine phosphorylase inhibitors are considered potential anti-tumor agents, a range of novel oxadiazole derivatives **3a–3u** was designed and synthesized by a simple and facile synthetic route. The biological assay revealed that majority of compounds displayed modest inhibitory activity against thymidine phosphorylase at low micromolar concentrations (IC_{50} 173.23 ± 3.04 to 1440.1 ± 245 μM). In the current study the most active compounds were **3h** and **3q** with IC_{50} values 1440.1 ± 245 and 1750.1 ± 107 μM, respectively. Molecular docking studies were performed on the most active compounds (**3h**, **3k**, **3o–3q**) to show their binding mode.

1. Introduction

Angiogenesis is the formation of new blood vessels from pre-existing vessels and it is essential for organ growth and repair. However, it is well known that this is a vital step in the process of cancer growth.[1,2] Thus, angiogenesis inhibitors are believed to be potential candidates for blocking cancer growth. In particular, thymidine phosphorylase (TP) is a pro-α-angiogenic factor which catalyzes the reversible phosphorolysis of thymidine into thymine and 2-deoxy-α-ribose 1-phosphate.[3–5] The 2-deoxy-α-ribose 1-phosphate undergoes further dephosphorylation to produce 2-deoxy-α-ribose which stimulates the secretion of vascular endothelial growth factor (VEGF). VEGF activates a number of processes including endothelial cells for secretion of matrix metalloproteinases, proliferation, and migration of endothelial cells to tumor tissue. These actions result in fast generation of new blood vessels and cancer metastasis.[6]

TP inhibitors affect the production of 2′-deoxy-α-ribose and in turn suppress tumor growth.[5,6] Therefore, there is an urgent need to develop new and potent thymidine phosphorylase inhibitors which have the ability to suppress the formation of new blood vessels and stop tumor growth. A number of efforts have been reported on the development of TP inhibitors.[3,7–15] The pyrimidine derivative 5-chloro-6-[1-(2-iminopyrrolidinyl)methyl] uracil



TPI TDX Proposed 1,3,4-oxadiazole-2-thione derivatives

Figure 1. Chemical structure of known TP inhibitors—TPI and TDX, and proposed 1,3,4-oxadiazole-2-thione derivatives as new class of TP inhibitors.

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Research Article

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Aromaticities of azines relative to benzene; a theoretical approach through the dimethyldihydropyrene probe

Maria[a], Riffat U. Nisa[a], Muhammad Hanif[a], Adeem Mahmood[a†] and Khurshid Ayub[a,b]*

The aromaticities of azines relative to benzene have been estimated by fusion with 15,16-dimethyldihydropyrene. Chemical shift data for the azine-fused dihydropyrenes (calculated at GIAO HF/6-31G*//B3LYP/6-31 + G*) were used to estimate the reduction in the dihydropyrene nucleus aromaticity. Choice of the saturated reference model was quite crucial in reliable estimation of aromaticity. Reference models with partial unsaturation at azine (2,1,2,3,2S–32) gave better estimate of aromaticity than the parent dimethyldihydropyrene. Aromaticities of azines through chemical shift data and geometric parameter analysis were found to be 90–100% to that of benzene, highly consistent with the aromaticity estimation by nucleus independent chemical shift$_{(0)exo}$ calculations. Copyright © 2014 John Wiley & Sons, Ltd.

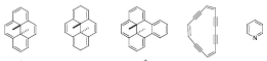
Keywords: Aromaticity quantification; Azines; Density functional theory; Dimethyldihydropyrene probe; Magnetic and geometric criteria

INTRODUCTION

Aromaticity is a general, commonly used, but quite controversial concept in organic chemistry. Qualitative description of a compound as aromatic, non-aromatic or anti aromatic is generally less contentious; however, quantitative estimation of aromaticity is not trivial and generally leads to controversies, primarily due to the quantification methods applied.[1] The aromaticity of a compound may vary considerably depending on the method used for quantitative analysis. Three major categories to quantify aromaticity are energetic, structural and magnetic, essentially all theoretical

Dewar resonance energy,[2–5] Huckel resonance energy,[6–8] Hess-Schaad resonance energy,[9–14] Schleyer isomerization stabilization energies[13,1] and topological resonace energies[15,16–18] are a few important energetic criteria. The Harmonic Oscillator Model of Aromaticity (HOMA),[19–21] Julg aromaticity index,[22] Bird's aromaticity index[23–27] and Fringuelli structural index[28,29] are the most important structure-based methods for the quantification of aromaticity.

The most common magnetic criteria include magnetic susceptibility exaltation,[30–41] nuclear magnetic resonance (NMR)[34,42–46] and nucleus independent chemical shifts (NICS).[40] NMR-based methods are generally more diverse and include chemical shift analysis of ^{3}He and ^{7}Li nuclei placed above the aromatic nucleus,[34,42–46] ^{1}H chemical shift[30,31] analysis of probe protons usually in the center of the nucleus under consideration and coupling constants[32,33] analysis in H-NMR (Gunther Q-values). However, NMR-based methods generally require that a suitable model or probe is chosen. NMR-based methods may even provide experimental scale of aromaticity for theoretical NICS values.[34] A probe of high accuracy based on ^{1}H NMR chemical shift is 15,16-dimethyldihydropyrene **1**.



1 **2** **3** **4** **5**

The internal methyl protons in 15,16-dimethyldihydropyrene **1** appear at δ −4.25 and its comparison with the non-conjugated model **2** δ 0.97 indicates large shielding of ~5.2 ppm due to a strong ring current.[30] When an aromatic ring is [a]- or [e]- fused to the dimethyldihydropyrene, the ring current in the latter is reduced. The internal protons of [e]- fused benzodihydropyrene[30] **3** appear at −1.85 ppm which means that the internal methyl protons in **3** are shielded by 2.82 ppm, and this leads to an experimental estimate of the aromaticity for **3** relative to **1** to be 52%. The greater the aromaticity of the fused ring, the greater is the reduction in the ring current of the dihydropyrene (DHP), and this concept can be used to compare the relative aromaticities of any two molecules provided the following two conditions are met: (i) the effect of fusion on the geometry of the probe

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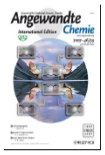
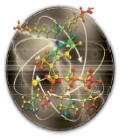
Cover Picture

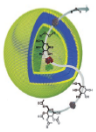
Jake L. Stymiest, Guillaume Dutheuil, Adeem Mahmood, and Varinder K. Aggarwal*



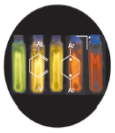
Secondary boranes and boronic esters can be prepared by homologation of boranes and boronic esters using Hoppe-type lithiated carbamates. As described by V. K. Aggarwal and co-workers on pp. 7491 ff., iterative use of this new, broad-ranging methodology allows either enantiomer of either diastereomer to be easily accessed, as depicted in the cover picture. The background photograph "Dusk on Upper Geraldine Lake" was taken in Jasper, Alberta, Canada by Barry Parisien (www.barryparisien.com).



Chiral Cyclopropenes
Chiral cyclopropenes are highly reactive and versatile reagents in organic synthesis. In their Review on page 7364 ff., I. Marek et al. summarize current investigations and how a revival in this area has led to the development of asymmetric syntheses of cyclopropenes and their conversion into complex chiral compounds.



Nanoreactors
In their Communication on page 7378 ff., A. E. Rowan, J. C. M. van Hest, and co-workers describe how the controlled positioning of glucose oxidase and horseradish peroxidase within polymersomes allows the construction of nanoreactors.



Diradical Intermediates
H. Ikeda et al. describe in their Communication on page 7396 ff. how annealing a γ-irradiated glassy matrix containing a 2,5-diaryl-1,5-hexadiene gives rise to an intense thermoluminescence that can be assigned to the singlet excited state of the corresponding cyclohexane-1,4-diyl.

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Review Article

Pharmacological Applications of Quercetin and its Derivatives: A Short Review

Aneela Maalik[1]*, Farhan A. Khan[1], Amara Mumtaz[1], Adeem Mehmood[1], Saira Azhar[2], Muhammad Atif[1], Sabiha Karim[3], Yasir Altaf[1] and Imran Tariq[3]
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Abstract

Quercetin (3,3',4',5,7-pentahydroxyl-flavone) is a flavonol, and it belongs to a class of plant secondary metabolites known as flavonoids. It is present in man's daily diet and is known for biological activities such as antioxidant, antiviral, anticancer, antimicrobial, anti-inflammatory and many more. Quercetin has been reported for its antioxidant and antiviral applications, hence, it is not only used as such but also its various derivatized forms have potentials for development into drugs for the treatment of diseases caused by oxidative stress and lethal viruses.

Keywords: Quercetin, Antioxidant, Pharmacological, Anticancer, Antimicrobial, Antiviral, Hepatoprotective

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INTRODUCTION

Quercetin is a plant pigment, abundantly occurs in many ethnic plants, especially onion and tea, therefore, a sufficient amount may be consumed daily [1]. Quercetin has importance in terms of ethnopharmacology such as its use as antioxidant, anticancer and neuroprotective [2]. It has been reported as an efficient free radical scavenger (antioxidant) [3]. In clinical trials (phase-I), quercetin has been reported to exhibit inhibitory effect on tyrosine kinase which suggests that it has antitumor therapeutic potentials [4].

The review has been prepared using databases such as ISI Web of Knowledge, Science Direct, and Google Scholar, and covers the literature from the last decade. This article includes only original research articles published in English language; articles published in other languages are excluded.

PHARMACOLOGICAL IMPORTANCE OF QUERCETIN

Quercetin is a versatile molecule (Figure 1) with many pharmacological properties including antioxidant, neurological, antiviral, anticancer, cardiovascular, antimicrobial, anti-inflammatory, hepatoprotective, protective of the reproductive system and anti-obesity agent. The literature available on these properties has been summarized here in this review (Table 1).

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Article

Chelation-Assisted Substrate-Controlled Asymmetric Lithiation-Allylboration of Chiral Carbamate 1,2,4-Butanetriol Acetonide

Adeem Mahmood [1,2,*], Hamad Z. Alkhathlan [3,*], Saima Parvez [3], Merajuddin Khan [1] and Sohail A. Shahzad [2]

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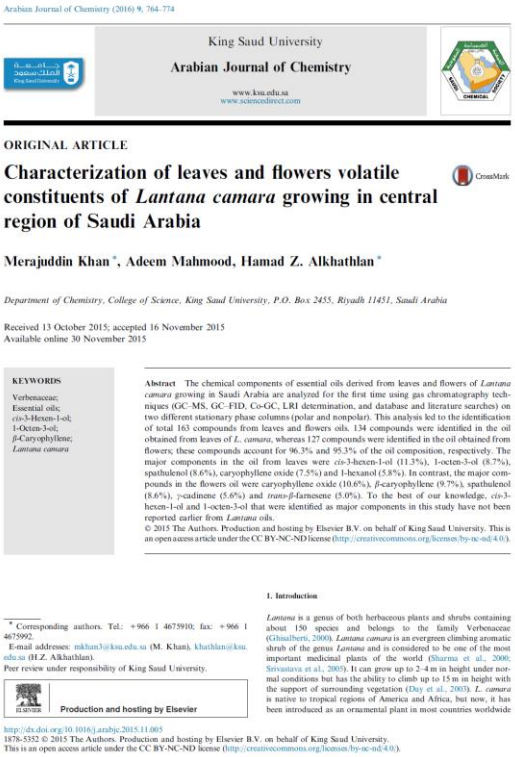
Abstract: The lithiation of 2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl diisopropylcarbamate (**1**) is achieved freely by *sec*-butyllithium in diethylether with high *lk*-diastereoselectivity: the bicyclic chelate complexes **3a** and **3b** are reacted with electrophiles to form optically active precursors **4a** and **4b** with >95% diastereoselectivity. In addition, tertiary diamines can undergo an external complexation in contest with the internal oxygen ligand, leading to improved stereoselectivities. The further reactions of lithiated carbamates with trans alkenyl-9-BBN derivatives after 1,2 metallate rearrangements, gave the key intermediate α-substituted allylic boranes **7**. Subsequent allylboration of aldehydes gave (*Z*)-*anti*-homoallylic alcohols **8** in good yield and excellent *d.r.*

Keywords: lithiation; borylation; allylation; chelation



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ORIGINAL ARTICLE

Characterization of leaves and flowers volatile constituents of *Lantana camara* growing in central region of Saudi Arabia

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Verbenaceae;
Essential oils;
cis-3-Hexen-1-ol;
1-Octen-3-ol;
β-Caryophyllene;
Lantana camara

Abstract The chemical components of essential oils derived from leaves and flowers of *Lantana camara* growing in Saudi Arabia are analyzed for the first time using gas chromatography techniques (GC–MS, GC–FID, Co-GC, LRI determination, and database and literature searches) on two different stationary phase columns (polar and nonpolar). This analysis led to the identification of total 163 compounds from leaves and flowers oils. 134 compounds were identified in the oil obtained from leaves of *L. camara*, whereas 127 compounds were identified in the oil obtained from flowers; these compounds account for 96.3% and 95.3% of the oil composition, respectively. The major components in the oil from leaves were *cis*-3-hexen-1-ol (11.3%), 1-octen-3-ol (8.7%), spathulenol (8.6%), caryophyllene oxide (7.5%) and 1-hexanol (5.8%). In contrast, the major compounds in the flowers oil were caryophyllene oxide (10.6%), *β*-caryophyllene (9.7%), spathulenol (8.6%), *γ*-cadinene (5.6%) and *trans*-*β*-farnesene (5.0%). To the best of our knowledge, *cis*-3-hexen-1-ol and 1-octen-3-ol that were identified as major components in this study have not been reported earlier from *Lantana* oils.

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1. Introduction

Lantana is a genus of both herbaceous plants and shrubs containing about 150 species and belongs to the family Verbenaceae (Ghisalberti, 2000). *Lantana camara* is an evergreen climbing aromatic shrub of the genus *Lantana* and is considered to be one of the most important medicinal plants of the world (Sharma et al., 2000; Srivastava et al., 2005). It can grow up to 2–4 m in height under normal conditions but has the ability to climb up to 15 m in height with the support of surrounding vegetation (Day et al., 2003). *L. camara* is native to tropical regions of America and Africa, but now, it has been introduced as an ornamental plant in most countries worldwide

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The steering pathway: Ketene-Claisen rearrangement (KCR)-1978–2016

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Aza-ketene (allylic amines)
Zwitterion-aza-ketene

ABSTRACT

From what began as a casual discovery of the ketene-Claisen rearrangement (the Malherbe-Bellus rearrangement) over 3 decades ago has flourished a reaction of substantial significance. The noticeable qualities of the ketene-Claisen rearrangement is accomplished in terms of experimental simplicity, forming new C–C bonds, high levels of chemo- and stereocontrol, ring enlargements and constructing new stereocenters. This survey of the ketene-Claisen rearrangement with some applications in organic synthesis will not only recapitulate the prospective of this reaction so far but also illustrate the achievable future significant prospective.

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1.3.4. Diversity in ketene-Claisen reaction 2186
Acknowledgements 2189
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1. Introduction

Ludwig Claisen[1] reported in 1912, the Claisen rearrangement, which involved the [3,3]-sigmatropic rearrangement of an allyl-vinyl ether to give a *γ,δ*-unsaturated carbonyl scaffold (Scheme 1). Simply the Claisen rearrangement to construct a C–C *σ*-bond can be considered as the intramolecular nucleophilic substitution addition of a carbonyl enol (Claisen rearrangement), thiocarbonyl enol (thia-Claisen rearrangement) or enamine (aza-Claisen rearrangement) to an allylic ether, sulfide or amine, respectively. The process involves *π*-bond migration and falls under the classification [3,3]-sigmatropic shift.[2]

In addition, the esteemed growth of this reaction can be seen from different variants such as the Carroll (1940),[7] Eschenmoser (1964),[8] Saucy-Marbet (1967),[9] Johnson (1970),[6] Ireland (1972),[7] Reformatsky-Claisen rearrangement (1973),[8] Malherbe and Bellus (1978)[9] and Denmark (1982).[10]

The ketene-Claisen reaction (the Malherbe-Bellus rearrangement or ketene-[3,3]-sigmatropic rearrangement) was first described by Bellus and Malherbe in 1978.[9] Treatment of allylic ethers with *in situ* prepared dichloroketene (a solo subunit) afford

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Blood zinc and iron levels in children of out patient department at tertiary care hospital of Multan

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