Abbas Hassan

PhD

Assistant Professor (IPFP)
Department of Chemistry
Quaid-i-Azam University
Islamabad, 45320, Pakistan
Phone Office +92 51 90642135
Email: ahassan@qau.edu.pk

Education

The University of Texas at Austin (Fall 2006 – December 2011).
PhD with Prof. Michael J. Krische
"Development of New Transition Metal Catalyzed C-C Bond Forming Reactions and their Application toward Natural Product Synthesis"

HEJ Research Institute of Chemistry, University of Karachi (2005 – 2006)
Research fellow with Prof. Khalid M. Khan
"Studies towards Synthesis of Biologically Important Heterocycles"

University of Peshawar, Pakistan (2001 to September 2004)
MSc Chemistry with Prof. Mohammad Arfan
"Synthesis and Biological activities of Quinaoxazoline Derivatives"

Research Experience

- Development of new catalytic C-C bond forming reaction and their application towards natural product synthesis, 2006-2011.
- Total synthesis of (+)-Roxaticin *via* C-C bond forming transfer hydrogenation, 2008-2010.
- Synthesis of Azaheterocyclic Compounds from Methyl Anthranilate, 2004-05, one year Research experience in Organic Synthetic laboratory, University of Peshawar.

Honors and Scholarships

- **Professional Development Award** to present poster at 42nd National Organic Symposium, Princeton University, June 5-9, 2011, awarded by University of Texas at Austin.
- Rh catalytic complexes named as, **Abbasphos I-IV** that catalyze enantio- and diastereoselective Aldol reaction (*J. Am. Chem. Soc.* **2008**, *130*, 2746).
- Higher Education Commission (Pakistan) **Scholarship for Ph. D. studies.**
- Merit Scholarship awarded for PhD studies by HEJ Research Institute of Chemistry, University of Karachi, Pakistan.
- 1st position among the Biological Sciences in the Govt. Post Graduate College, Mardan, Bachelor of Science.

Scientific Publications

1. "Enantioselective Conversion of Primary Alcohols to α-Methylene γ-Butyrolactones via Iridium Catalyzed C-C Bond Forming Transfer Hydrogenation: 2-(Alkoxycarbonyl)allylation,"
   Montgomery, T. P.; **Hassan, A.;** Park, B. Y.; Krische, M. J. *J. Am. Chem. Soc.* **2012** *ASAP*, **DOI:** 10.1021/ja303839h

2. "Consecutive Iridium Catalyzed C-C and C-H Bond Forming Hydrogenations for the Diastereo- and Enantioselective Synthesis of *syn*-3-Fluoro-1-Alcohols: C-H (2-Fluoro)allylation of Primary Alcohols,"
   Hassan, A.; Montgomery, T. P.; Krische, M. J. *Chem. Commun.*, **2012**, *47*, 4692.
   .
3. "Unlocking Hydrogenation for C-C Bond Formation: A Brief Overview of Enantioselective Methods"
   Hassan, A.; Krische, M. J. *Org. Process Res. Dev*. **2011,** *15*, 1236.

4. "Catalytic Enantioselective Grignard Nozaki-Hiyama Methallylation from the Alcohol Oxidation Level: Chloride Compensates for π-Complex Instability"
   Hassan, A.; Townsend, I. A.; Krische, M. J. *Chem. Commun.* **2011,** *47*, 10028.

   Highlighted in *Synfacts* **2011**, 1206.

5. "Enantioselective Vinylogous Aldol-Reformatsky Addition from the Alcohol or Aldehyde Oxidation Level *via* Iridium Catalyzed Transfer Hydrogenation: Linear Regioselectivity by Way of *C*-Bound Iridium Enolates"
   Hassan, A.; Zbieg, J. R.; Krische, M. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 3493.

   Highlighted in *Synfacts* **2011**, 741.

6. "Total Synthesis of (+)-Roxaticin: A Departure from Stoichiometric Chiral Reagents, Auxiliaries and Premetallated Nucleophiles in Polyketide Construction"
   Han, S. B.; **Hassan, A.**; Kim, I.-S.; Krische, M. J. *J. Am. Chem. Soc.* **2010,** *132*, 15559.

   Highlighted in *Synfacts* **2011**, 121.

7. "Elongation of 1,3-Polyols via Iterative Catalyst-Directed Carbonyl Allylation from the Alcohol Oxidation Level"
   Hassan, A.; Lu, Y.; Krische, M. J. *Org. Lett.* **2009**, *11*, 3112.

8. "1,n-Glycols as Dialdehyde Equivalent in Iridium Catalyzed Enantioselective Carbonyl Allylation form the Alcohol Oxidation Level and Iterative Two-Directional Assembly of 1,3-Polyols"
   Lu, Y.; Kim, I.-S.; **Hassan, A.**; Del Valle, D. J.; Krische, M. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 5018.

   Highlighted in *Synfacts* **2009**, 997.

9. "Diastereo- and Enantioselective Reductive Aldol Addition of Vinyl Ketones via Catalytic Hydrogenation"
   Han, S. B.; **Hassan, A.**; Krische, M. J. *Synthesis* **2008**, 2669.

10. "Diastereo- and Enantioselective Hydrogenative Aldol Coupling of Vinyl Ketones: Design of an Effective Monodentate TADDOL-Like Phosphonite Ligand"
    Bee C.; Han, S. B.; **Hassan, A.**; Iida, H.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 2746.

    Highlighted in *Synfacts* **2008**, 596.

Conferences Attended

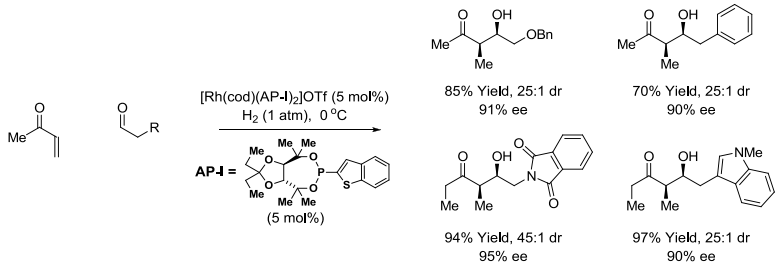
- 42nd National Organic Symposium Princeton University (June, 2011), New Jersey, USA. (Poster presented "Development of New Transition Metal Catalyzed Hydrogenative C-C Bond Forming Reactions and Their Application toward Total Synthesis of (+)-Roxaticin").
- "2008 Chemistry & Biochemistry Spring Symposium, (April, 2008) University of Texas at Austin, USA. (Poster presented "Diastereo- and Enantioselective Reductive Aldol Coupling of Vinyl Ketones via Catalytic Hydrogenation).
- 1st Meeting of Nobel Laureates with Pakistani Graduate Students/Young Scholars (March, 2006), Islamabad, Pakistan.
- 9th International Symposium on Natural Product Chemistry (Jan. 2004), held at Pearl Continental Hotel Karachi, Pakistan.

Detailed Research Summary
Development of New Transition Metal Catalyzed C-C Bond Forming Reactions and their Application toward Natural Product Synthesis

In the Krische group we are developing new transition metal catalyzed carbon carbon (C-C) forming reactions focusing on atom economy and byproduct free, environmental friendly approaches. We have developed a broad family of C-C bond forming hydrogenations with relative and absolute stereocontrol which provide an alternative to stoichiometric organometallic reagents in certain carbonyl and imine additions. Inspired by the group work my goal was to develop new reactions, extend the scope of our group chemistry and their application towards synthesis of biologically active natural products. The following is a summary of interesting studies I have been a part of in the Krische group.

Diastereo- and Enantioselective Hydrogenative Aldol Coupling of Vinyl Ketones: Design of Effective Monodentate TADDOL-Like Phosphonite Ligands

Bee, C.; Han, S. B.; **Hassan, A.**; Iida, H.; Krische, M. J., *J. Am. Chem. Soc.*, **2008**, *130*, 2746.



In this study we report the first distereo and enantioselective reductive aldol couplings of commercially available methyl vinyl ketones (MVK) and ethyl vinyl ketone (EVK), This was achieved through the design of a novel monodentate TADDOL-like phosphonite ligand. Reaction of aldehydes with

methyl vinyl ketone using cationic rhodium catalysts modified by chiral TADDOL-like phosphonite ligands produces aldol adducts with excellent control of relative and absolute stereochemistry. In the course of designing the novel monodentade TADDOL-like phosphonite ligand (**abbasphos, AP**) a structure reactivity relationship of the ligand with respect to absolute stereocontrol was shown. These ligands enabled us to couple aliphatic, aromatic and heteroaromaatic aldehyde in very high enantiocontrol and high yields. We have also shown development of second generation abbasphos ligands with higher selectivity.

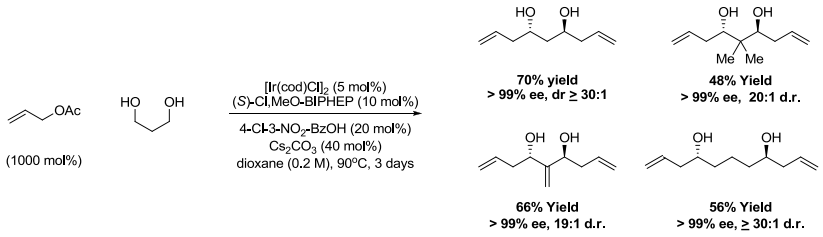
Elongation of 1,3-Polyols via Iterative Catalyst-Directed Carbonyl Allylation from the Alcohol Oxidation Level

Hassan, A.; Lu, Y.; Krische, M. J., *Org. Lett.* **2009**, *11*, 3112.

and

1,*n*-Glycols as Dialdehyde Equivalents in Iridium-Catalyzed Enantioselective Carbonyl Allylation and Iterative Two-Directional Assembly of 1,3-Polyols,

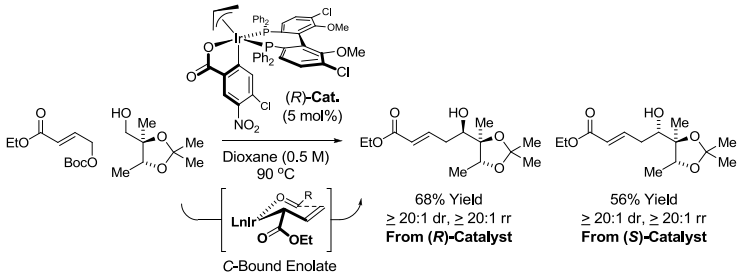
Lu, Y.; Kim, I. S.; **Hassan, A.;** Del Valle, D. J.; Krische, M. J., *Angew. Chem. Int. Ed.* **2009,** *48,* 5018.



We have found that iridium catalyzed transfer hydrogenation of allylic acetates in the presence of aldehydes or alcohols results in highly enantioselective carbonyl allylation under the conditions of transfer hydrogenation. In this study we extended the scope of this reaction to illustrate its application to 1,3-Polyol subunits. We were able to show that under the conditions of transfer hydrogenative carbonyl allylation, the stereochemical bias of enantiomeric iridium catalysts is found to override the intrinsic diastereofacial bias of transient β-chiral aldehydes. Based on this finding, a concise enantio- and diastereoselective synthesis of 1,3-polyols was achieved via iterative chain elongation. Furthermore, iterative asymmetric allylation employing 1,3-propanediol enables the rapid assembly of protected 1,3-polyol substructures with exceptional levels of stereocontrol. The utility of this approach stems from the ability to avoid the use of chirally modified allylmetal reagents, which require multistep preparation, and the ability to perform chain elongation directly from the alcohol oxidation level.

Enantioselective Vinylogous Aldol-Reformatsky Addition from the Alcohol or Aldehyde Oxidation Level via Iridium Catalyzed Transfer Hydrogenation: Linear Regioselectivity by Way of C-Bound Iridium Enolates,

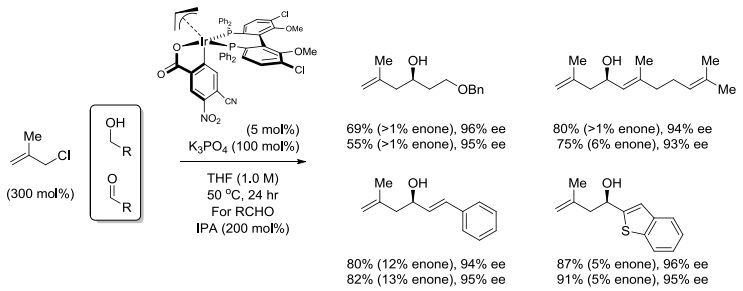
Hassan, A.; Zbieg, J. R.; Krische, M. J., *Angew. Chem. Int. Ed.* **2011**, *50*, 3493.



In this study we report a catalytic method for enantioselective vinylogous Reformatsky- type aldol addition in which asymmetric carbonyl addition occurs with equal facility from the alcohol or aldehyde oxidation level. Good to excellent levels of regioselectivity and uniformly high levels of enantioselectivity were observed across a range of alcohols and aldehydes. Additionally, exceptional levels of catalyst-directed diastereoselectivity may be achieved. Insight into the structural-interactional features of the catalytic system *via* partitioning of linear and branched adducts suggests a Curtin-Hammett scenario, wherein carbonyl addition occurs selectively from an equilibrating mixture of primary and secondary σ-allyl haptomers. The collective data are consistent with carbonyl addition from the secondary α-*C*-bound iridium enolate to form the less substituted C-C bond due to the absence of gauche interactions in the transition state. Notably, in reactions conducted from the alcohol oxidation level, the only stoichiometric byproducts formed are carbon dioxide and *tert*-butanol.

Catalytic Enantioselective Grignard Nozaki-Hiyama Methallylation from the Alcohol Oxidation Level: Chloride Compensates for π-Complex Instability

Hassan, A.; Townsend, I. A.; Krische, M. J. *Chem. Commun.* **2011,** *47*, 10028.

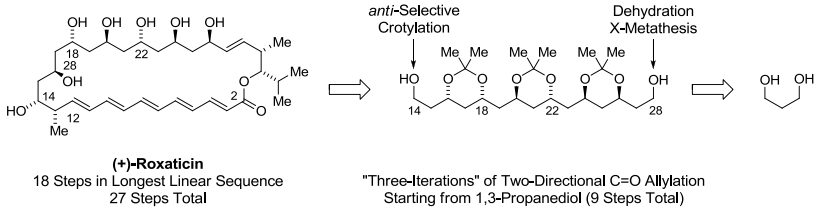


Through the use of a more reactive leaving group in methallyl chloride, the ionization to form the π-allyliridium complex is more rapid, hence compensating for the shorter lifetime of the more highly substituted olefin π-complex. Based on this insight into the requirements of the catalytic process, highly enantioselective Grignard Nozaki-Hiyama methallylation is achieved from the alcohol or aldehyde oxidation levels in the absence of stoichiometric metallic reagents or reductants. Further, double

enantioselective methallylation of 1,3-propanediol was carried out in good yield to obtain C_2-symmetric bis-methallylation product as a single enantiomer, as the minor enantiomer of the mono-adduct is transformed to the *meso*-stereoisomer of the product.

Total Synthesis of (+)-Roxaticin via C−C Bond Forming Transfer Hydrogenation: A Departure from Stoichiometric Chiral Reagents, Auxiliaries, and Premetalated Nucleophiles in Polyketide Construction,

Han, S. B.; **Hassan, A.;** Kim, I. S.; Krische, M. J., *J. Am. Chem. Soc.* **2010,** *132*, 15559.



Our approach to the total synthesis of (+)-roxaticin which takes advantage of carbonyl allylation, crotylation and iterative two-directional carbonyl allylation of 1,3-diols (previous study). Iterative bisallylation was used to construct the C_2-symmetric 1,3-polyol substructure C14−C28 unit of roxaticin. This fragment was elaborated to roxaticin employing transformation that resulted in functional groups that were directly compatible with the next transformation, e.g. alcohols were directly reacted under iridium catalyzed crotylation reaction and alkenes were subjected to cross metathesis. (+)-Roxaticin is prepared from 1,3-propane diol in 20 longest linear steps and a total number of 29 manipulations. This approach bypasses the redox manipulations and use of any chiral auxiliary.

Academic References

Michael J. Krische
Robert A. Welch Chair in Science
Environmental Science Institute
Director, Center for Green Chemistry & Catalysis
Robert A. Welch Chair in Science
Email: mkrische@mail.utexas.edu

Eric V. Anslyn
Norman Hackerman Professor of Chemistry
The University of Texas at Austin
Department of Chemistry and Biochemistry
1 University Station, A5300,
Austin, TX. 78712
Email: anslyn@austin.utexas.edu