

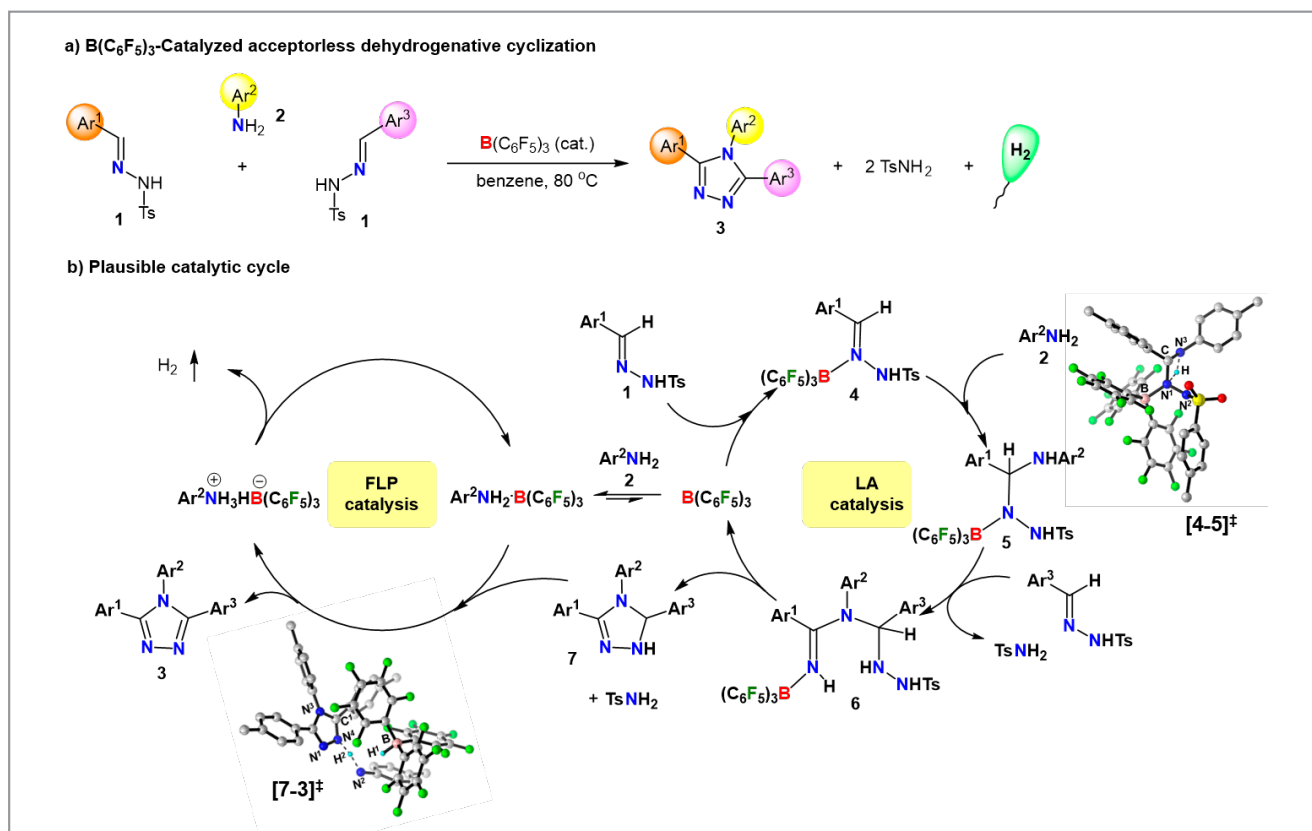
Acceptorless Dehydrogenative Cyclization of *N*-Tosylhydrazones and Anilines: Dual Role of $B(C_6F_5)_3$

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Tris(pentafluorophenyl)borane [$B(C_6F_5)_3$] acts as a powerful Lewis acid catalyst for numerous organic transformations. In combination with a sterically demanding Lewis base, it forms Frustrated Lewis-acid Pairs (FLPs), which have recently been applied for small-molecule activations and metal-free hydrogenation as well as dehydrogenation reactions. Recently, the group of Professor Debasis Koley and Professor Biplab Maji at the Indian Institute of Science Education and Research (Kolkata, India) described the $B(C_6F_5)_3$ -catalyzed cyclization of *N*-tosylhydrazones **1** and anilines **2** to form triaryl-1,2,4-triazoles **3** (Scheme 1a), which are essential heterocyclic scaffolds in pharmaceutical, biological, and materials sciences. Professor Maji explained: “The work utilizes a unique dual mode of

activation of $B(C_6F_5)_3$, which initially acts as a Lewis acid to activate **1** thus triggering its cyclization with **2** (Scheme 1b, right).” He continued: “Later, the FLP generated from $B(C_6F_5)_3$ and **2** acts as a dehydrogenation catalyst to liberate hydrogen from the saturated triazole intermediate **7** without the need of an acceptor. The gain in aromaticity drives the dehydrogenation reaction (Scheme 1b, left). The reaction operates at low loading of catalyst, tolerates several functional groups and can be extended to unsymmetrical 1,2,4-triazoles when utilizing two different *N*-tosylhydrazones.”

Professor Maji remarked that it is highly challenging to design acceptorless dehydrogenative transformations, even with transition-metal catalysts, whereas metal-free protocols are



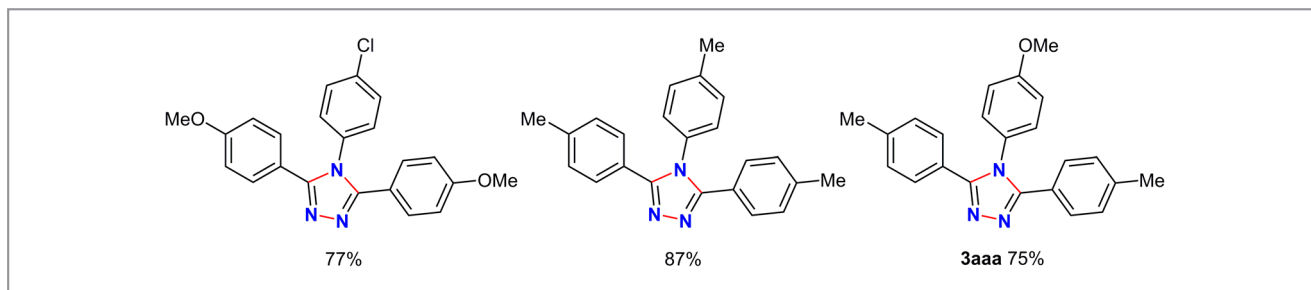


Figure 1 Selected examples for the synthesis of symmetrical 1,2,4-triazoles.

elusive. Using $B(C_6F_5)_3$ as a catalyst, Dr. M. M. Guru – one of the authors – explored the scope of the synthesis of symmetrical triazoles (Figure 1), where *p*-toluene sulfonamide ($TsNH_2$) and hydrogen were obtained as byproducts.

“Expansion of the protocol for the synthesis of unsymmetrical 1,2,4-triazoles using two different *N*-tosylhydrazones was challenging, as the selectivity remained poor after several trials (Scheme 2a),” said Professor Maji. A competitive equilibrium study was performed with two electronically biased *N*-tosylhydrazones (**1a** vs **1c**) with $B(C_6F_5)_3$ which afforded the Lewis acid–base adduct **4a** whereas **1c** remained unreacted (**4a**:**1c** = 1:1) (Scheme 2b). Professor Maji remarked: “Thus, we realized that the electronic difference might be a crucial factor for the selectivity of unsymmetrical 1,2,4-triazole formation. Indeed, we solved the issue by utilizing electronically biased *N*-tosylhydrazones which afforded good to excellent yields of unsymmetrical 1,2,4-triazoles (Scheme 2c).”

He continued: “Moreover, from the Hammett correlation study performed by varying different electronic groups on the aryl ring of **2**, we determined a small $\rho = -1.17$, which plausibly indicates a weak resonance interaction involving a positive charge at the N-center of aniline in the rate-determining step (Scheme 2d).”

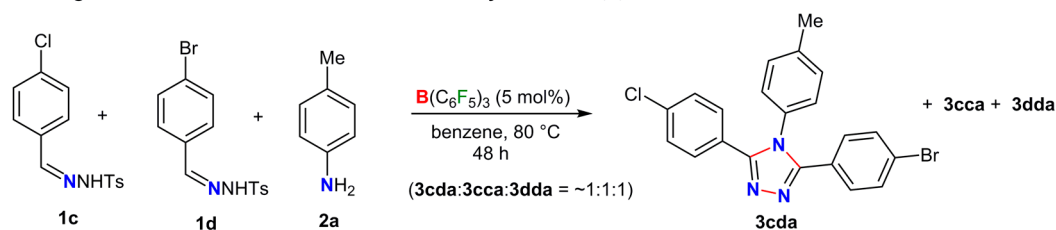
Professor Koley and co-authors Mr. De and Mr. Dutta performed DFT calculations [B3LYP-D3/TZVP(CPCM)//B3LYP/SVP level of theory] to investigate the detailed reaction mechanism, the specific role of $B(C_6F_5)_3$ and the rate-limiting-step in the reaction, and finally the product distribution for the unsymmetrical coupling. Professor Koley said: “As per the experimentally observed equilibrium ratio in Scheme 2b, the formation of **4a** is computed to be more facile than **4c** by ca. 3.0 kcal mol⁻¹ (Figure 2).” He continued: “Eventually, the activation barrier for $B(C_6F_5)_3$ coordination is 3.6 kcal mol⁻¹ more favorable for the OMe substituent ($\Delta\Delta^\ddagger G_L^\ddagger$; Figure 2). What is more interesting is that the overall energy span for the formation of **5** is substantially higher for the Cl than the OMe substituent (42.5 vs. 33.3 kcal mol⁻¹), clearly indicating

the preference for **1a** to undergo $B(C_6F_5)_3$ -assisted intramolecular proton transfer in a facile manner. Therefore, when **5aa** couples with another hydrazone unit, the preferred choice will be the chloro-substituted analogue **1c** as most of **1a** will be available in the adduct form **4a**.”

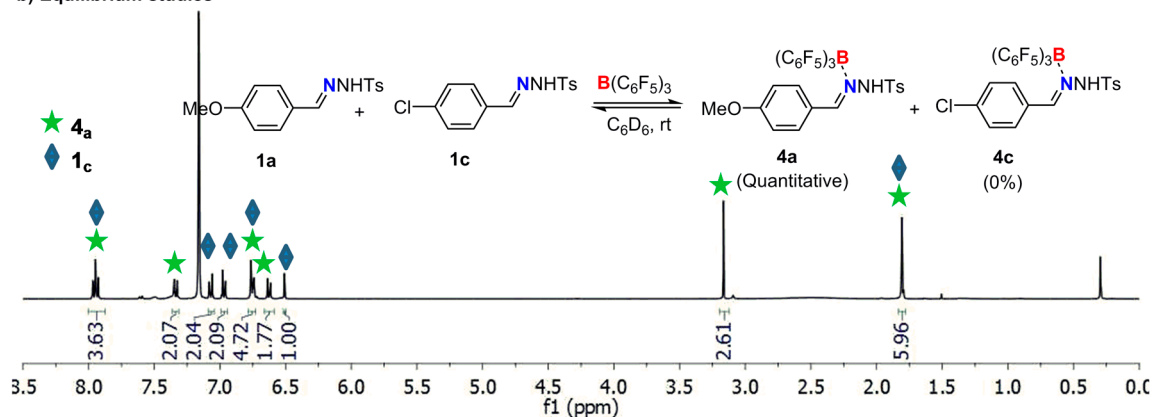
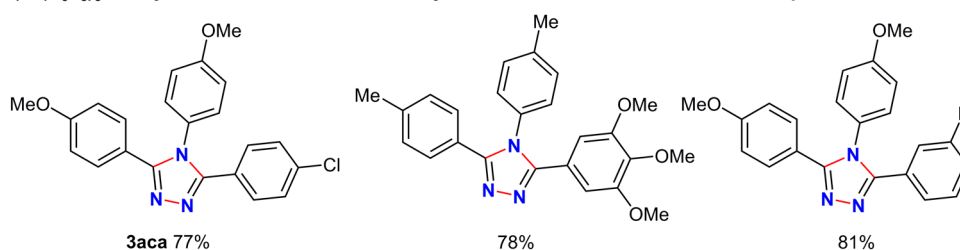
As for the potential applications of the triazole products, the group has recently shown that pyrene-appended triazole-linked dimers could be applied in solution-processable resistive memory devices on a flexible substrate (*Chem. Commun.* **2019**, *55*, 4643).

“In summary, we have developed $B(C_6F_5)_3$ -catalyzed single-pot, acceptorless dehydrogenative cyclization of hydrazones with anilines to access both symmetrical and unsymmetrical 1,2,4-triazoles,” said Professor Maji. He concluded: “Mechanistic experiments and DFT calculations suggest that the boron catalyst plays a dual role, initially acting as a Lewis acid to activate the hydrazone for the nucleophilic attack and later forming an FLP with aniline for acceptorless dehydrogenation. This chemoselective and mild reaction protocol could foster further studies and generate further interest in main-group-catalyzed chemical transformations performed without the use of transition-metal catalysts.”

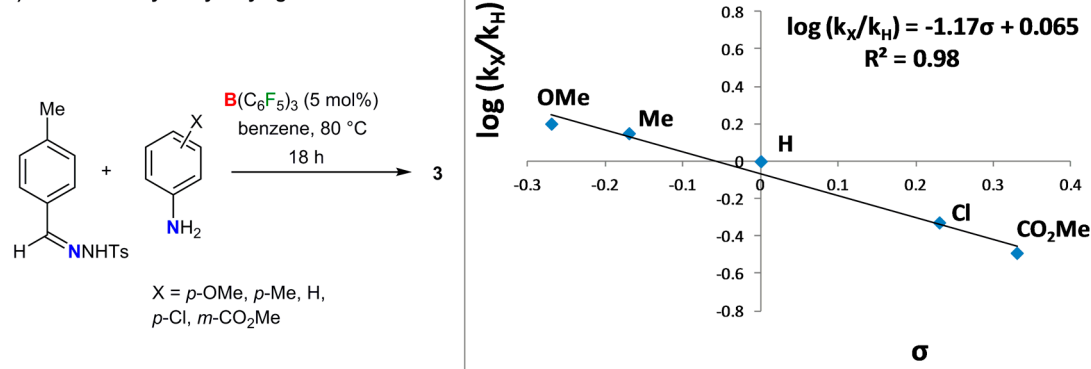
a) Challenges associated with selective formation of unsymmetrical 1,2,4-triazole



b) Equilibrium studies

c) $\text{B(C}_6\text{F}_5)_3$ -Catalyzed selective formation of unsymmetrical 1,2,4-triazole: selected examples

d) Hammett analysis by varying aniline



Scheme 2 a) Challenges for the synthesis of unsymmetrical 1,2,4-triazoles. b) Equilibrium studies with electronically different *N*-tosylhydrazones. c) Selected examples for the synthesis of unsymmetrical 1,2,4-triazoles. d) Hammett analysis.

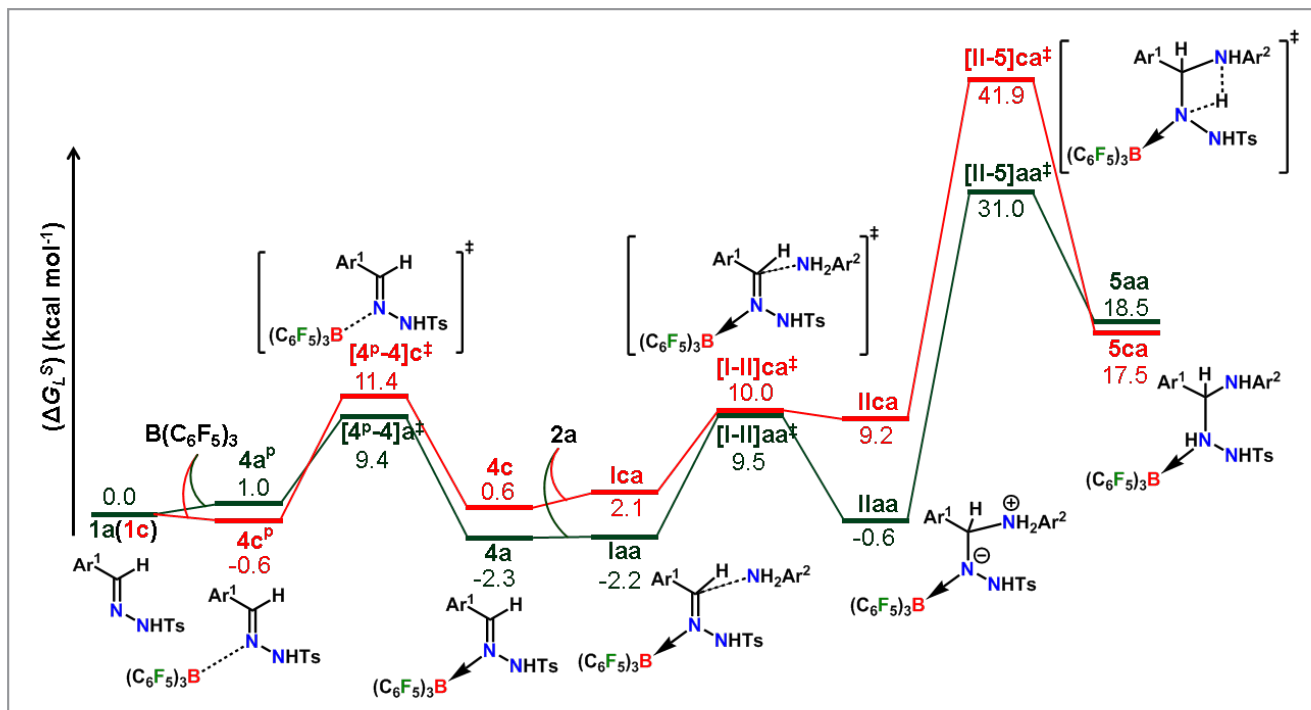


Figure 2 Overlaid energy profiles for the formation of unsymmetrical triazole **3aca** and symmetrical triazole **3aaa** up to the formation of **5**. Energy values are concerning the starting materials [**1a/c** + B(C₆F₅)₃]. For green solid line, Ar¹ = *p*-MeOC₆H₄ and Ar² = *p*-MeC₆H₄ where for red solid line, Ar¹ = *p*-ClC₆H₄ and Ar² = *p*-MeC₆H₄. All the energy values (ΔG_L[‡]) are in kcal mol⁻¹.

Mattias Fank

About the authors



Dr. M. M. Guru

Murali Mohan Guru received his Ph.D. from Indian Institute of Technology Guwahati (India) in 2013 under the supervision of Prof. T. Punniyamurthy. Subsequently, he moved to RIKEN (Japan) as a postdoctoral researcher in the lab of Prof. Zhaomin Hou, working there from 2013–2016. He returned to India in 2017 and joined the group of Dr. Biplab Maji in IISER Kolkata (India) as a SERB-NPDF. Currently, he is working on novel organic transformations using main-group borane catalysts.



S. De

Sriman De was born in Burdwan, West Bengal, India. He completed his B.Sc. at Burdwan University (India) in 2011. In 2013, he completed his study in chemistry with his M.Sc. degree at Visva-Bharati University (India). In 2014, he started as a Ph.D. student under the supervision of Dr. Debasis Koley at IISER Kolkata (India). His research interests are focused on bimetallic complexes in catalysis using computational methods.



S. Dutta

Sayan Dutta received his B.Sc. from Visva-Bharati University (India) in 2011. He obtained his M.Sc. in chemistry from the same university in 2013 before joining Dr. Debasis Koley's research group at IISER Kolkata (India) in 2014 as a Ph.D. student. His current research focuses on mechanistic investigations of main-group- and transition-metal-mediated chemical transformations and theoretical exploration of the bonding scenario in various donor–acceptor complexes.



Prof. D. Koley

Debasis Koley studied chemistry (honors) at Ramakrishna Mission Vidyamandira (India) from 1996 to 1999. In 2001, he completed his M.Sc. in chemistry at Indian Institute of Technology Delhi (India). In 2005, he received his doctoral degree from Heinrich Heine Universität Düsseldorf (Germany), working under the supervision of Professor Walter Thiel at MPI für Kohlenforschung, Mülheim an der Ruhr (Germany). During 2006 to 2008, he was engaged as a postdoctoral researcher at MPI für Biophysikalische Chemie, Göttingen (Germany). Later he moved to IISER Bangalore (India) as a Centenary postdoctoral fellow in the Inorganic and Physical Chemistry Department under the supervision of Professor S. Ramakrishnan. Since 2011, he has been at the Indian Institute of Science Education and Research (IISER) Kolkata (India), currently a professor in the Department of Chemical Sciences. His Computational Chemistry and Molecular Modelling (CCMM) group focuses on structure, bonding and mechanistic interpretations of various chemical systems using state-of-the-art computational techniques.



Prof. B. Maji

Biplab Maji was born in Howrah (India) in 1987. He obtained his B.Sc. in chemistry (Honors) from University of Calcutta (India) in 2004 and M.Sc. in chemistry from the Indian Institute of Technology Kanpur (India) in 2009. Subsequently, he joined the group of Prof. Herbert Mayr at the Ludwig Maximilian Universität Munich (Germany) for his doctoral studies, which he completed in 2012. In 2013, he joined the group of Prof. Hisashi Yamamoto at the Molecular Catalyst Research Center of Chubu University (Japan) as a postdoctoral fellow. In 2015, he moved to the group of Professor Frank Glorius at Westfälische Wilhelms-Universität Münster (Germany) as an Alexander von Humboldt fellow. Since 2016, he has been working as an assistant professor in the Department of Chemical Sciences, IISER Kolkata (India). His research focuses on organic synthesis, catalysis, and mechanistic studies.