

An Enolate-Mediated Organocatalytic Azide–Aldehyde [3+2]-Cycloaddition Reaction: General Method for the High-Yielding Regioselective Synthesis of 1,4-Disubstituted 1,2,3-Triazoles

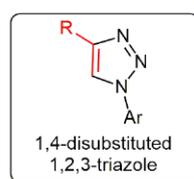
Angew. Chem. Int. Ed. **2014**, *53*, 10420–10424

Functionalized 1,2,3-triazoles have an important role in a large number of medicinally and materially useful compounds (Scheme 1, eq. 1). Furthermore, the substituted 1,2,3-triazole function is at the core of the most used bioconjugation technology based on the so-called ‘click chemistry’, so it is incorporated in a number of bioactive conjugates. Straightforward access to this important class of compounds has been feasible since the inception of versatile copper-catalyzed azide–alkyne [3+2]-cycloaddition (CuAAC), ruthenium-catalyzed azide–alkyne [3+2]-cycloaddition (RuAAC) and iridium-catalyzed azide–alkyne [3+2]-cycloaddition (IrAAC) reactions, and thanks to the pioneering contributions of Meldal, Sharpless, Fokin and other research groups (*Chem. Rev.* **2013**, *113*, 4905). In the meantime, other strategies such as Bertozzi’s strain-promoted [3+2]-cycloaddition reactions and the Ramachary–Bressy–Wang enamine-mediated organocatalytic [3+2] cycloaddition of carbonyls (enones, β -keto esters, ketones and enals) with azides have also contributed significantly to the development of this area (Scheme 1, eq. 2) (for references, see the original paper).

Existing strategies often make use of either costly alkynes or less reactive carbonyl compounds, other than the simple aldehydes, as the starting materials along with aryl azides. Also, the alkynes used in CuAAC, RuAAC or IrAAC click reactions are costlier compared to the corresponding aldehydes. For example, the price of phenylacetylene is \$76 for 100 mL whereas phenylacetaldehyde costs only \$33 for the same amount. These limitations inspired Professor Dhevalapally Ramachary at the University of Hyderabad (India) to develop a novel green protocol for the high-yielding regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles based upon enolate-mediated organocatalytic azide–aldehyde [3+2]-cycloaddition (OrgAAC) reaction from commercially available enolizable aldehydes, aryl azides and catalytic amounts of DBU (Scheme 1, eq. 3).

In continuation of their earlier studies of the organocatalytic synthesis of highly functionalized NH-1,2,3-triazoles (*Chem. Eur. J.* **2008**, *14*, 9143) and functionalized benzotriazoles (*Chem. Eur. J.* **2013**, *19*, 13175) via push–pull

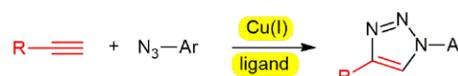
1) Potential applications based on the 1,2,3-triazoles



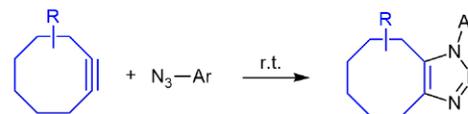
- HIV protease inhibitors
- anticancer drugs
- anti-tuberculosis drugs
- antifungal agents
- antibacterial drugs
- histone deacetylase inhibitors
- bioorthogonal probes

2) Current strategies for the synthesis of 1,2,3-triazoles

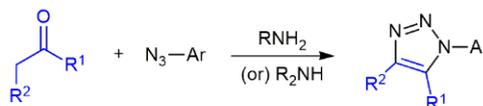
a) Copper-acetylide mediated click reaction: Meldal, Sharpless, and Fokin



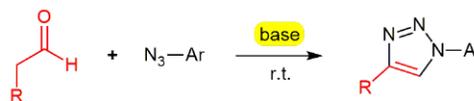
b) A strain-promoted click reaction: Bertozzi



c) Enamine-mediated click reaction: Ramachary, Pons-Bressy, and Wang



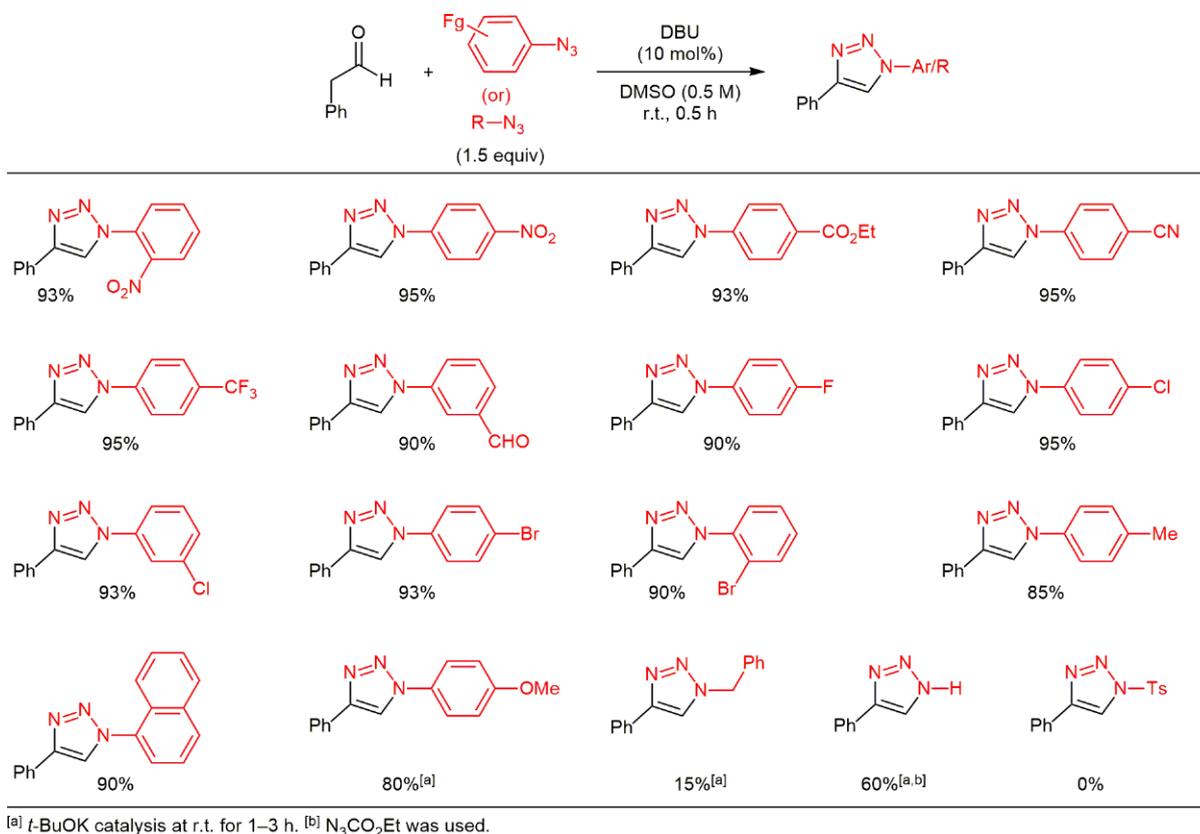
3) This work: First amine-catalyzed enolate-mediated [3+2]-cycloaddition reaction



Scheme 1 General design for the [3+2]-cycloaddition reaction



Scheme 2 First DBU-catalyzed enolate-mediated click reaction



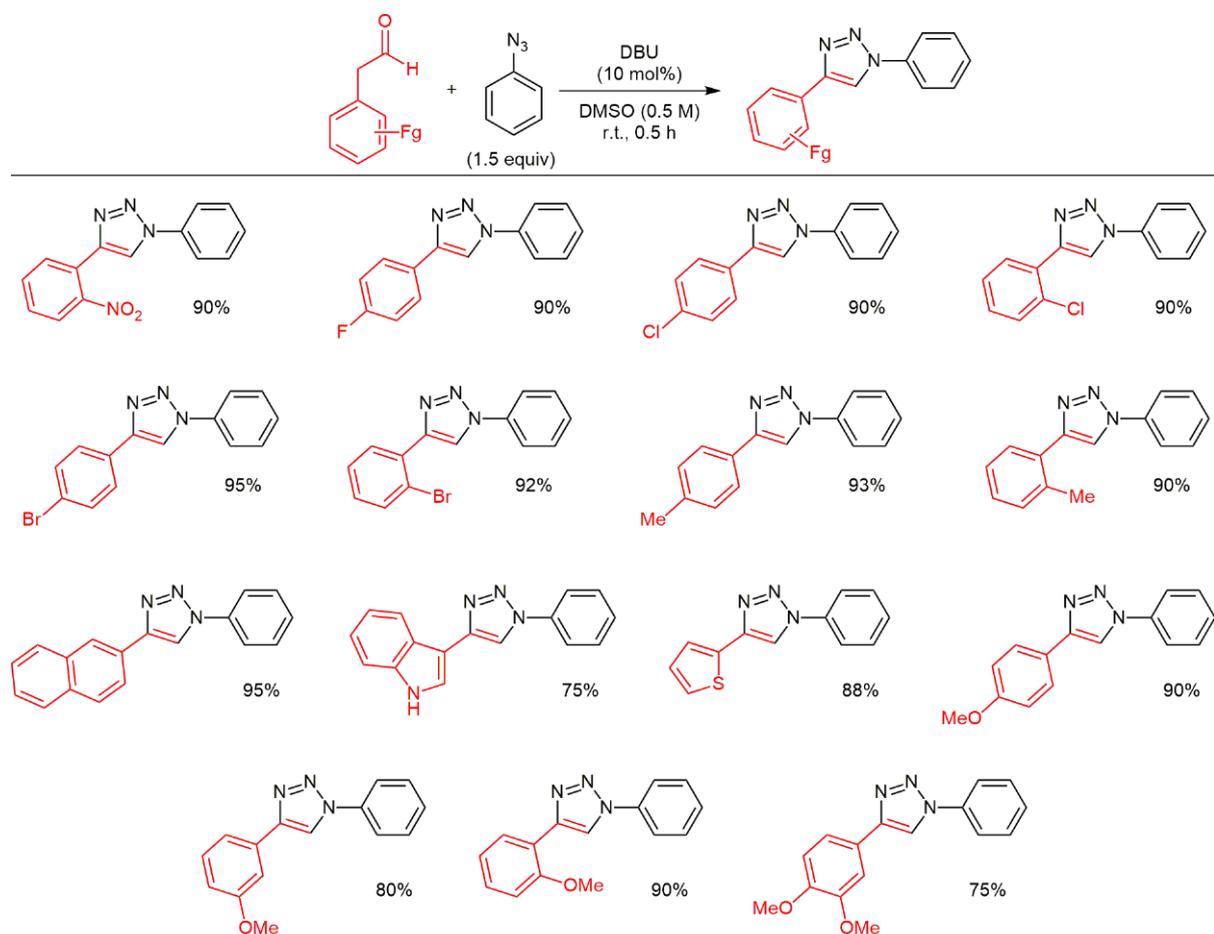
Scheme 3 Reaction scope with different azides

dienamines, Professor Ramachary and co-workers described for the first time an efficient high-yielding enolate-mediated OrgAAC reaction of phenylacetaldehyde with phenyl azide at room temperature for just 30 minutes under the DBU catalysis (Scheme 2). Professor Ramachary said: “An attractive feature of this OrgAAC reaction is that it provides an alternative method for accessing the library of 1,4-disubstituted 1,2,3-triazoles where metal-catalyzed or enamine-mediated click reactions either fail or are low-yielding (Scheme 3). This diversity-oriented approach displays a high degree of flexibility with different azides and the nature of base and solvent is crucial for obtaining the best results (Scheme 3).”

After getting a clear understanding of the electronic factors of ArN_3/RN_3 in the OrgAAC reaction, Professor Ramachary investigated the reaction scope with different 2-arylacetaldehydes in the OrgAAC reaction with PhN_3 (Scheme 4). “In this reaction, 2-arylacetaldehydes containing different functional groups, such as nitro, halo, alkyl, heteroaryl and methoxy, were used as substrates for the organocatalytic synthesis of

the single isomer of 1,2,3-triazoles in good to excellent yields within 30 minutes,” explained Professor Ramachary, continuing: “The results in Scheme 4 demonstrate the broad scope of this novel methodology, covering a structurally diverse groups of 2-arylacetaldehydes and phenyl azide. Many of the OrgAAC products were obtained in good yields compared to other routes.”

In order to further understand the importance of the acidic nature of enolizable aldehydes in the OrgAAC reaction, Professor Ramachary’s group chose simple aliphatic aldehydes, which have a less acidic α -methylene compared to 2-arylacetaldehydes (Scheme 5). Professor Ramachary said: “Surprisingly, the reaction of simple aliphatic aldehydes with different aryl azides under the DBU or *t*-BuOK catalysis at 25 °C for 30 minutes furnished the expected 1,2,3-triazoles in good yields.” With industrial applications in mind, Professor Ramachary and co-workers investigated the gram-scale synthesis of 1,4-diphenyl-1*H*-1,2,3-triazole and 3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)benzaldehyde from the DBU-promoted



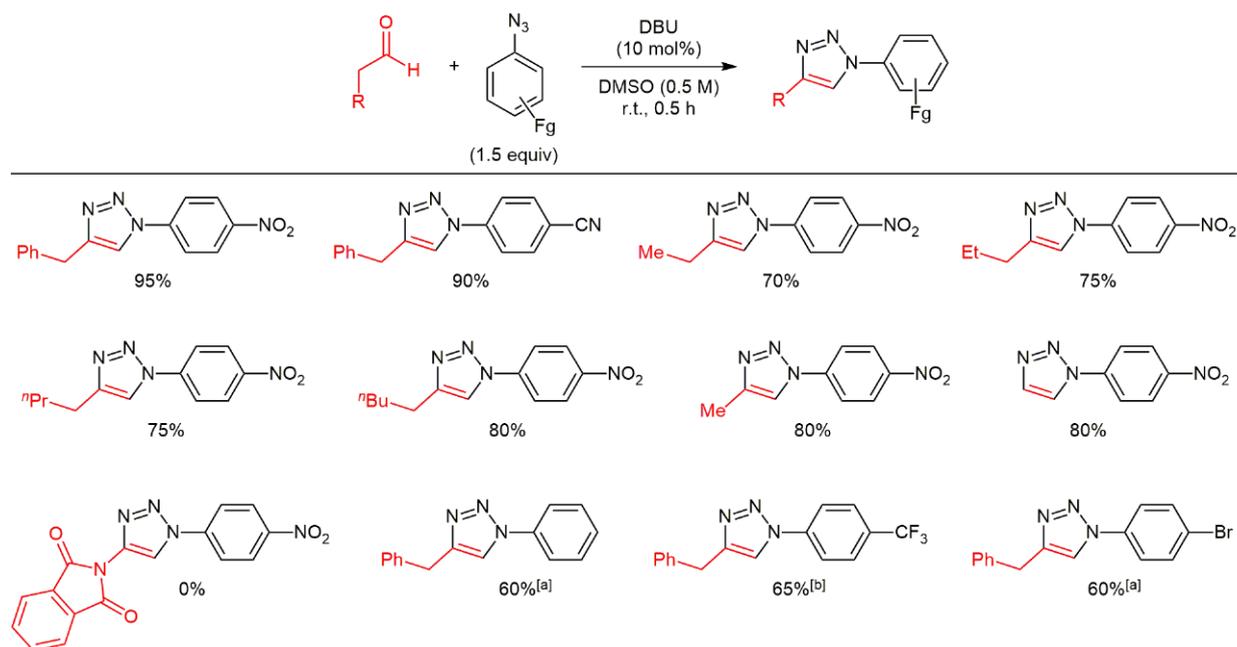
Scheme 4 Reaction scope with different 2-arylacetaldehydes

reaction of 1.00 g of phenylacetaldehyde with 1.19 g of phenyl azide or 1.47 g of 3-azidobenzaldehyde in 17 mL of DMSO at 25 °C without compromising the reaction rate, yield or purity.

Professor Ramachary remarked: “Recent developments in the metal-free synthesis of 1,2,3-triazoles are impressive, and the development of more sustainable variants is highly warranted since the click reaction has already found significant applications in pharmaceuticals and materials. However, the discovery of room-temperature reactions under the ‘friendly’ catalysts, namely simple molecules without extra ligands, environmentally friendly, cost-effective and that can be prepared in few synthetic steps, and employing reduced azide loading could be of immense interest in industrial applications. In this scenario, the aforementioned method provides rapid access to 1,4-disubstituted 1,2,3-triazoles in both academic and industrial research.”

Professor Ramachary concluded: “This novel and more practical metal-free DBU-catalyzed [3+2]-cycloaddition reaction has a broad substrate scope, good functional-group tolerance, simple operation, and high reaction rate and efficiency, thus providing easy access to various 1,4-disubstituted 1,2,3-triazoles. This reaction opens up new prospects in synthesis, materials and pharmaceutical chemistry for further exploiting the synthetic power of the amine-catalyzed enolate-mediated click reaction.”

Matteo Zanda



^[a] *t*-BuOK catalysis at r.t. for 1 h. ^[b] DBU catalysis at r.t. for 0.5 h and 60 °C for 1 h.

Scheme 5 Reaction scope with other aldehydes

About the authors



Prof. D. B. Ramachary

D. B. Ramachary was born in Thatikal, Nalgonda district of AP state (India) in 1973. He obtained his BSc in 1994 and his MSc in 1996. After PhD work in natural product synthesis with Professor A. Srikrishna at the Indian Institute of Science, Bangalore (India), he completed postdoctoral studies as a Skaggs Postdoctoral Fellow in the laboratories of Professor Carlos F. Barbas III at The Scripps Research Institute (La Jolla, USA)

working with small molecular catalysts. In January 2005, he joined the faculty of the School of Chemistry, University of Hyderabad (India) as an Assistant Professor and became Full Professor in March 2013. He was awarded the INSA Young Scientist Medal in 2006, and became a Member of The National Academy of Sciences, India in 2009 and Associate Fellow of the Andhra Pradesh Academy of Sciences in 2010. He was awarded the Anil Kumar Bose Memorial Award of the INSA in 2010, the B. M. Birla Science Prize of Chemical Sciences in 2011, and The Chancellor Award in 2014. In 2013, he joined the Editorial Board of *Organic & Biomolecular Chemistry*. His research focuses on the design and implementation of biomimetic sequential one-pot strategies for the synthesis of biologically important drugs and drug-like molecules, in addition to the development of new synthetic methods including asymmetric catalysis and multi-catalysis cascade (MCC) processes.



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Adluri B. Shashank was born in India in 1987. After his initial schooling in Thorrur (India), he obtained his BSc degree from A. P. R. Degree College, Nagarjuna Sagar (India) in 2007. For his Master's thesis he developed strategies for enamine-mediated amination/isoaromatization (EA/IA) reactions with Professor D. B. Ramachary at the University of Hyderabad. In 2009, he received his Master of Science degree from the

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