# Shared Success— s-Block Cooperativity Toward Triazoles

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Exploration of the synergistic catalytic activities of a bimetallic s-block system unveils new reactivities of these elements. In this issue of Chem Catalysis, Hevia and co-workers report the discovery of s-block bimetallic cooperative catalysis to afford 1,5-disubstituted 1,2,3 triazoles regioselectivity in good-to-excellent yields.

The synthesis of triazoles has gained colossal interest from both academic and industrial settings due to their high medicinal utility[1] and their extensive use as connective linkers.[2] The triazole moiety is a core structural unit in numerous medicinally important compounds that exhibit high biological activities, such as antimicrobial, anti-allergic, analgesic, anti-HIV, anti-inflammatory, anti-cancer, anti-malarial, anti-tuberculosis, local anesthetic, anti-anxiety, anti-depressant, anti-histaminic, anti-oxidant, and anti-Parkinson's agents.[1] The conventional way to synthesize triazoles is through an azide-alkyne Huisgen cycloaddition in which the azide reacts with a terminal or internal alkyne to afford a 1,2,3-triazole.[3] Although the synthesis of 1,4-disubstituted 1,2,3-triazoles using copper catalysts has been extensively investigated,[4] the synthesis of 1,5-disubstituted 1,2,3-triazoles has not received as much attention. Studies by Fokin and co-workers demonstrated the ruthenium-catalyzed, ligand-controlled regioselective synthesis of 1,5-disubstituted 1,2,3-triazoles,[5] but the use of a non-toxic metal catalyst toward the synthesis of 1,5-disubstituted 1,2,3-triazoles is underdeveloped yet highly desirable. A few reports based on the stoichiometric use of s-block[6]/$ZnEt_2$,[7] or catalytic amounts of rare-earth metal amides[8]/$NMe_4OH$/$KO^tBu$,[9] showed promising outcomes for the regioselective synthesis of 1,5-disubstituted triazoles. However, these processes are limited in scope to activated aryl acetylenes or aryl azides to afford the desired product. Recent studies by Hevia and co-workers demonstrated an elegant synthetic route for the regioselective synthesis of 1,5-disubstituted 1,2,3-triazoles.[10]

In this issue of Chem Catalysis, Hevia and co-workers disclose the new cooperative chemical reactivity of an s-block Na/Mg bimetallic system which could be utilized as a powerful tool for the regioselective synthesis of 1,5-disubstituted 1,2,3-triazole compounds. A model reaction between phenylacetylene and benzyl azide was utilized to explore the influence of s-block element catalysts to generate the heterocycle. When monometallic alkali metal compounds $NaCH_2SiMe_3$ or $LiCH_2SiMe_3$ were used as a catalyst, low yields of the triazole were obtained, whereas $KO^tBu$ led to azide decomposition. Catalytic monometallic alkaline earth metal compound $Mg(CH_2SiMe_3)_2$, however, gave quantitative conversion after 6 h of heating. The same result was observed using the bimetallic complex $NaMg(CH_2SiMe_3)_3$. Further tuning of this sodium magnesiate complex demonstrated the true power of the cooperative bimetallic system over the individual monometallic counterparts. $(TMEDA)_2Na_2Mg(CH_2SiMe_3)_4$ (1) was found to be the best pre-catalyst that enabled near-quantitative yield of the desired product in just 45 min.

To explore the synthetic utility and applicability of cooperative s-block bimetallic system catalysis in 1,5-disubstituted 1,2,3-triazole synthesis, 5 mol% of the $(TMEDA)_2Na_2Mg(CH_2SiMe_3)_4$ (1) pre-catalyst was tested for triazole formation with various aromatic/aliphatic azides and alkynes (Scheme 1A). Wide applicability of the reported synthetic methodology was proven through the investigation of a broad substrate scope giving up to 99% yield of the product in as little as 30 min. Of note triazole formation reactions with substrates containing Lewis basic donors such as nitrogen or sulfur, gratifyingly afforded good-to-excellent yields of the corresponding products. This demonstrates the superiority and complementarity of this methodology in relation to the traditional copper-catalyzed cycloaddition reaction in which the copper catalyst can be deactivated in the presence of donor atoms such as nitrogen or sulfur. Other challenging functional groups such as -CN and $-NO_2$ were also tolerated, further illustrating the potential advantage of the catalytic s-block bimetallic reagent. Additional investigations revealed that symmetrical di-triazole derivatives can be synthesized from the 1:2 stoichiometric reaction between 1,4-diethynylphenyl and aryl azides in excellent yields (up to 83%). Alternatively, the sequential addition of different aryl azides could lead to the formation of mixed (unsymmetrical) 1,5-disubstituted 1,2,3-triazoles (Scheme 1B).

A comprehensive mechanistic study was undertaken to account for the regioselective formation of the 1,5-disubstituted 1,2,3-trizole compounds (Scheme 1C). Initially, the pre-catalyst $(TMEDA)_2Na_2Mg(CH_2SiMe_3)_4$ (1) deprotonates four equivalents of the

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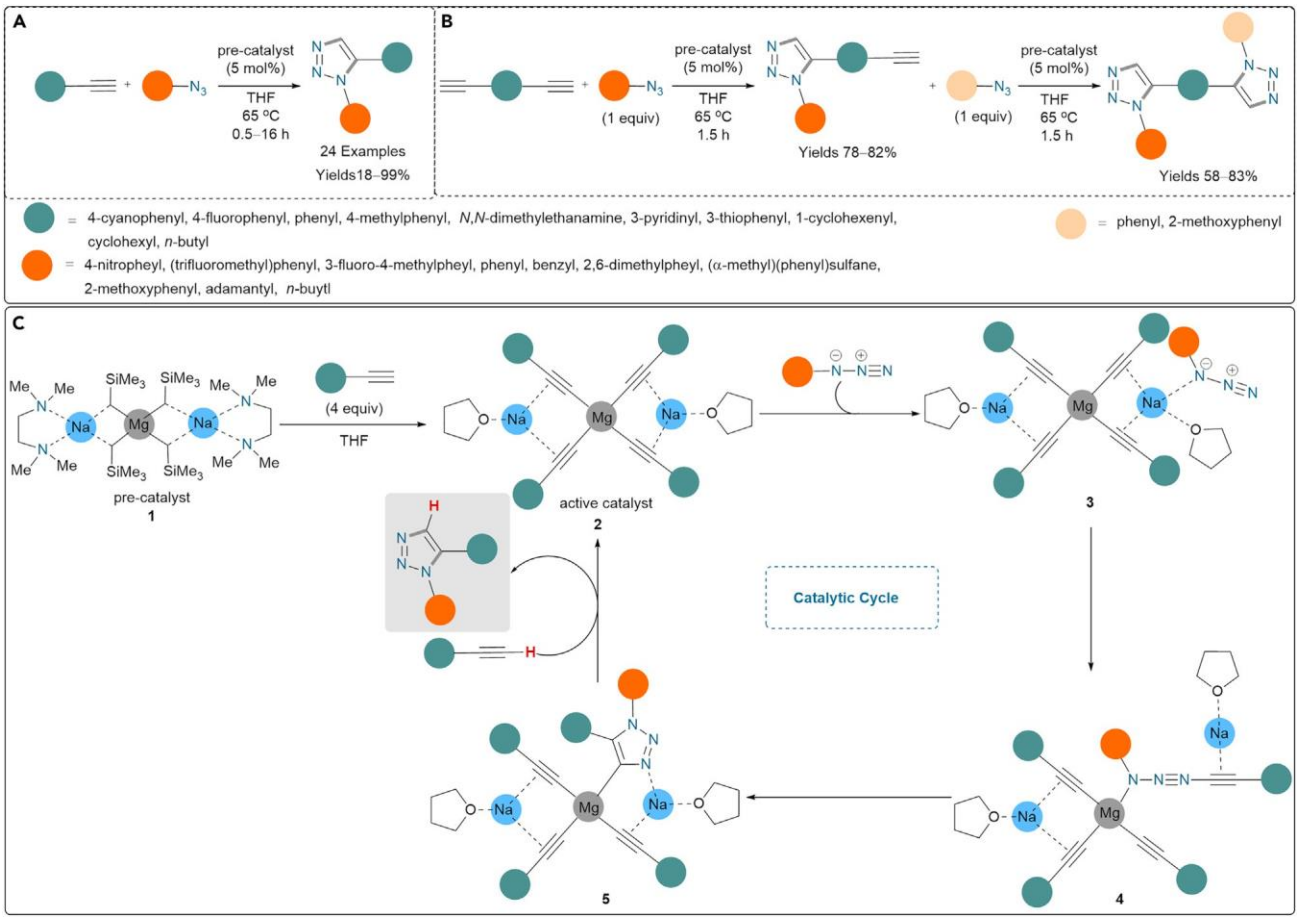


Scheme 1. Cooperative s-block bimetallic catalysis toward triazoles

Shown are the syntheses of (A) 1,5-disubstituted 1,2,3-triazoles, (B) symmetric and unsymmetrical 1,5-disubstituted 1,2,3- di-triazoles using 5 mol% pre-catalyst $(TMEDA)_2Na_2Mg(CH_2SiMe_3)_4$ (1), and (C) the proposed reaction mechanism to account the formation of the 1,5-disubstituted 1,2,3-triazoles.

arylacetylene to afford a tetra-alkynyl sodium magnesite species $(THF)_nNa_2Mg(ChC\text{-}Ar)_4$ (2). 2 was characterized in the solid-state through single crystal X-ray diffraction analysis and in solution through $^1H$ DOSY NMR studies. Independent synthesis of 2 gave comparable times and yields to the pre-catalyst 1, indicating that this species is the active catalyst. Coordination of the azide substrate to the solvated sodium cation was then found to yield 3, which subsequently leads to the insertion of the azide into one of the Mg-$C_{arylacetylene}$ bonds generating intermediate 4. Kinetic studies on the reaction between 1-ethynylcyclohexene and 1-azido-2-methoxybenzene using pre-catalyst $(TMEDA)_2Na_2Mg(CH_2SiMe_3)_4$ (1) revealed that this insertion step is rate determining and that only one alkynyl substituents from the tetra-alkynyl sodium magnesiate (2) is active in the catalytic cycle. Following insertion, rapid intramolecular attack of the magnesium-bound nitrogen atom to the ChC bond leads to the formation of a 1,2,3-triazole ring 5. Here the sodium atom activates the ChC bond through a Na$$$p interaction. In the final step, the complex 5 undergoes rapid protonoylsis with an unreacted terminal acetylene to afford the desired 1,5-disubstituted 1,2,3-triazole and to regenerate the active catalyst (2).

To highlight the importance of both s-block elements in the catalytic cycle, 15-crown-5 was added to the reaction to sequester the sodium cation. This destroyed the efficacy of the catalyst toward triazole formation.

In conclusion, Hevia and co-workers have illustrated new and exciting catalytic reactivities of the s-block elements where two elements, sodium and magnesium, work together to access synthetically valuable 1,5-disubstituted 1,2,3-triazoles. Combining elegant structural, kinetic, and spectroscopic studies, this team has uncovered the mechanism of this reaction, highlighting the important cooperative roles of the two elements. The Lewis acidic sodium atom acts to bind and activate the azide and ChC triple bond, while the anionic magnesiate has greater nucleophilic/basic power than a neutral magnesium complex.

This, combined with the close proximity of the s-block elements, accounts for facile formation of the triazole products. Transition metal-free syntheses of medicinally important compounds are desirable, and the discovery of new or improved methods to prepare such compounds is challenging. These new findings will stimulate considerable interest in the use of the s-block elements in catalysis and the potential of s-block cooperative catalysis.

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## DECLARATION OF INTERESTS

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