

Gold-Catalyzed Intermolecular C–S Bond Formation: Efficient Synthesis of α -Substituted Vinyl Sulfones

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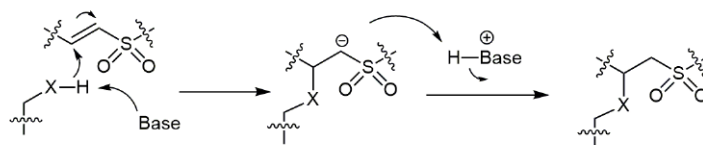
The last decade has witnessed an explosive development of homogeneous gold catalysis. However, a universal drawback of gold as a catalyst is its vulnerability under reaction conditions, especially at high temperatures. In 2009, the laboratory of Professor Xiaodong Shi at the West Virginia University (USA) introduced a new class of gold complexes: 1,2,3-triazole-gold(I) (TA-Au) as catalysts with improved thermal stability. Later it was demonstrated that with 1,2,3-triazole used

as a special ‘X-factor’ [the ligand coordinated to (L-Au)⁺], this class of catalysts possessed unique chemoselectivity in Hashmi phenol synthesis and in a series of transformations related to propargyl ester rearrangements (for a detailed bibliography see Ref. 15 of the original manuscript).

Improved stability certainly costs in terms of reactivity. For this reason, recent efforts by Professor Shi’s group were aimed at developing a novel catalytic system with restored

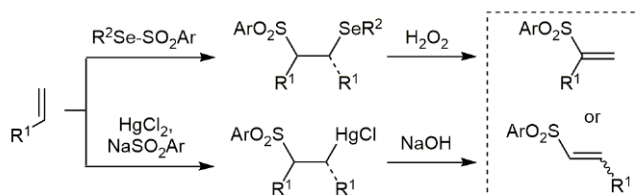
1) Vinyl sulfone in biological research: covalent trapping of nucleophiles

X = O, NR, S



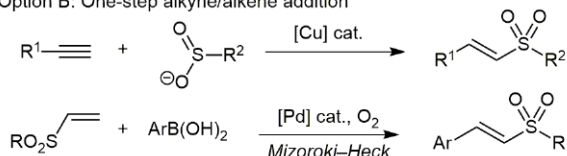
2) Current strategies for vinyl sulfone synthesis

Option A: Two-step alkene addition–elimination



Drawbacks:
toxic materials
stoichiometric reagents
less atom-economy
regioselectivity

Option B: One-step alkyne/alkene addition



Stereochemical outcome:
anti-Markovnikov

3) **This work:** first Markovnikov addition to alkynes with triazole-gold catalyst



α -vinyl sulfone
more reactive Michael acceptor with
less hindered β -carbon

Scheme 1 General design

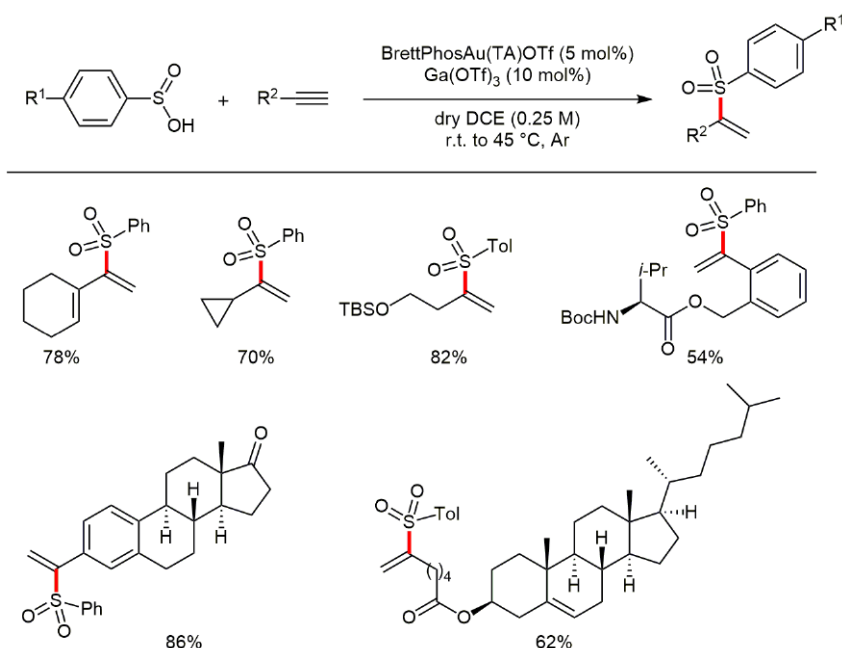
catalytic efficiency while maintaining a reasonable level of stability. Professor Shi said: “Lewis acid was devised as the activator for the TA-Au catalyst to reversibly remove the triazole off the gold center, which is a thermodynamically and kinetically favored process. Gallium triflate turned out to be a good candidate.”

Professor Shi continued: “Vinyl sulfone, a valuable building block in synthesis and a functional unit in biology, has been an interesting target. Typical sulfinic acid addition to an alkyne gives the anti-Markovnikov products through radical processes. It is envisioned that the gold catalyst will preferentially promote Markovnikov addition to alkynes and using sulfinic acid would yield α -substituted vinyl sulfones, which typical methods cannot easily access. Even more importantly, in principle, α -substituted vinyl sulfones, with a much less hindered β -carbon atom, should react faster in Michael additions and should therefore be more suitable substrates. Replacing the β -substituted vinyl sulfone units with α -substituted vinyl sulfones should lead to significant improvements in terms of Michael reactivity.”

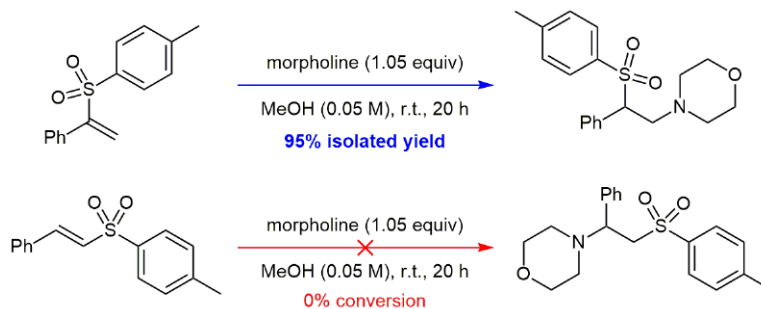
In order to achieve high yield and efficiency, various gold catalysts were screened by Professor Shi’s co-workers. It was found that the ligand used had a strong influence on the reaction performance. Remarkably, the combination of 5 mol% BrettPhosAu(TA)OTf and 10 mol% Ga(OTf)₃ gave the best

result (91% yield) while the Au/Ag system generally performed worse (highest yield obtained with 5 mol% BrettPhosAuCl and 5 mol% AgSbF₆, 76%). Employing only 5 mol% BrettPhosAu(TA)OTf or 10 mol% Ga(OTf)₃ alone resulted in a slower reaction, or no reaction at all. The optimized reaction was then applied to various terminal alkynes for the synthesis of the corresponding α -substituted vinyl sulfones. Professor Shi remarked: “Generally, the yields were good with both aromatic and aliphatic alkynes. More importantly, this method could also be applied to complex molecules, such as amino acids, estrone and cholesterol derivatives.”

The rapid access to α -substituted vinyl sulfones enabled by this methodology provides an opportunity for further derivatization, as demonstrated by the Diels–Alder reaction of *N*-maleic anhydride with 1,3-dienyl sulfone. Professor Shi said: “Furthermore, this method may also find potentially wide applications in biology for the synthesis of covalent enzymatic inhibitors, as highlighted by the strikingly different reactivity of Michael additions involving either α - or β -substituted vinyl sulfones using the secondary amine morpholine as nucleophile. In fact, the α -substituted vinyl sulfone gave the Michael adduct in almost quantitative yield at room temperature, while the β -substituted vinyl sulfone gave no conversion at all under the same set of conditions. Considering the mild



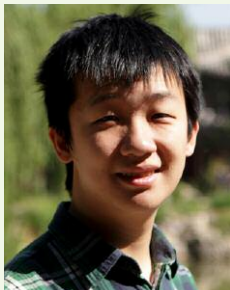
Scheme 2 Reaction scope



Scheme 3 Improved Michael receptor

conditions and high efficiency, one may envision the potential application of this method to vinyl sulfone introduction through addition to alkyne-containing biologically interesting targets.” Overall, the combination of a TA-Au catalyst and $\text{Ga}(\text{OTf})_3$ enables a general synthesis of α -substituted vinyl sulfones from simple terminal alkynes and sulfinic acids. “This success opens up intriguing opportunities to perform other challenging transformations with this novel system,” said Professor Shi, who concluded: “Furthermore, a comparison of the reactivity of α - and β -substituted vinyl sulfones towards Michael addition highlights the potential application of the former compounds in biological and pharmaceutical sciences.”

Matteo Zanda

About the authors

Y. Xi

Yumeng Xi was born in Wuhan (P. R. of China) in 1990. He received his BS degree in chemistry from Peking University (P. R. of China) working in Professor Zhen Yang's laboratory. He recently obtained a Master's degree in Professor Xiaodong Michael Shi's group at the West Virginia University and will move to the University of California, Berkeley (USA) as a PhD student.



Prof. X. M. Shi

Xiaodong Michael Shi was born in Tianjing (P. R. of China). He went to Nankai University (P. R. of China) in 1990 and received his BS and MS degrees in 1994 and 1997, respectively. He then moved to the USA and earned his PhD in 2002 from University of Maryland, College Park, under the guidance of Professor Jeffery T. Davis, with research focused on self-assembled nucleosides. After finishing graduate school, Dr. Shi moved to the

Chemistry Department at the University of California Berkeley and joined Professor Paul A. Bartlett's group as a postdoctoral research associate. In July 2003, he joined Professor F. Dean Toste's group and studied transition-metal catalysis. Professor Shi started his independent research in the fall of 2005 at the Chemistry Department of West Virginia University and was promoted to Associate Professor in 2011.