

Zn(II)-Catalyzed Intermolecular Hydrative Aldol Reactions of 3-En-1-ynamides with Aldehydes and Water to Form Branched Aldol Products Regio- and Stereoselectively

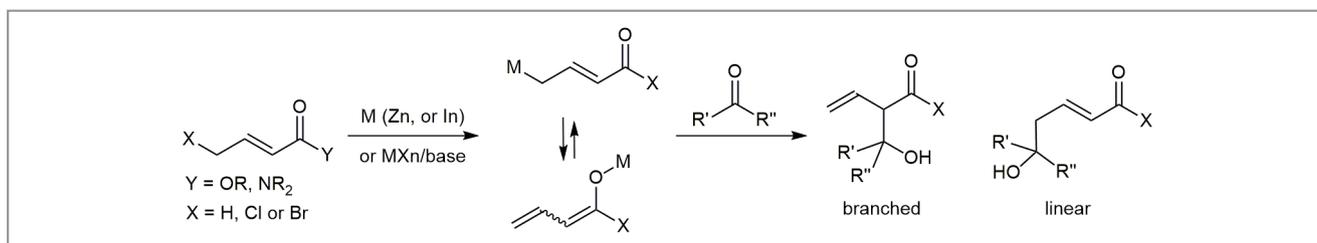
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The aldol reaction occupies a prominent position in organic synthesis and remains one of the most used methodologies for producing chiral compounds in non-racemic form. Metal dienolates are versatile carbanions that can react with carbonyl electrophiles to afford linear or branched products. The stereo- and regioselectivities of the aldol reaction have been extensively examined for various metal salts including Zn(II), Si(IV), Sn(IV), Li(I), B(III) or In(III) because their linear and branched aldol products are useful building blocks for accessing natural products. One major drawback in current methods is the use of metal reagents in stoichiometric proportions (>1.0 equiv, Scheme 1). The development of their catalytic surrogates is highly desirable, but only an Ir-catalyzed enantioselective synthesis of linear aldol products, by Krische et al. (*Angew. Chem. Int. Ed.* **2011**, *50*, 3493), has been achieved.

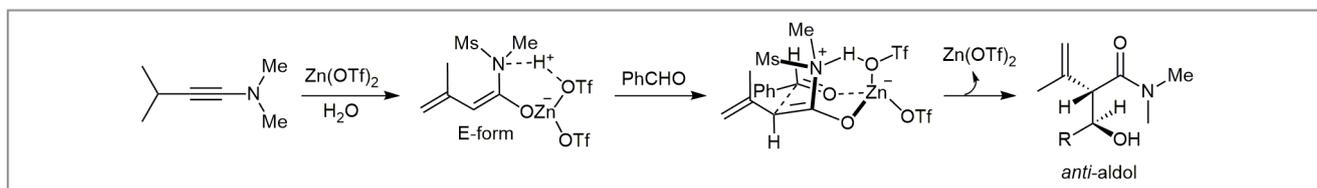
Recently, the laboratory of Professor Rai-Shung Liu at the National Tsing-Hua University (Taiwan) developed a Zn(II)-catalyzed hydrative aldol reaction to generate stable O-bound Zn(II)-dienolates that can react with aldehydes to afford branched aldol products stereoselectively. “Although metal-catalyzed hydrations of alkynes are well known for many

transition metals,” said Professor Liu, “their resulting enolates have not been elaborated for any C–C bond formation due to rapid proto-demetalation reactions. In this work, 3-en-1-ynamides replace unsaturated esters as reagents together with water and Zn(OTf)₂ (5 mol%) as other partners.” With Zn(OTf)₂ as catalyst and a 3-en-1-ynamide, Professor Liu’s group observed the formation of a kinetically stable *E*-configured Zn(II)-dienolate that complexes with a HOTf molecule to impede an undesired proto-demetalation reaction. Professor Liu postulated: “This trapped ‘HOTf’ can enhance the Zn(II) acidity of this dienolate to enable an aldol reaction in water via a chair-like transition state (Scheme 2), yielding anti-configured aldol products stereoselectively. This hydrative aldol reaction represents a successful model of ‘Lewis acid activated by Brønsted acid’.”

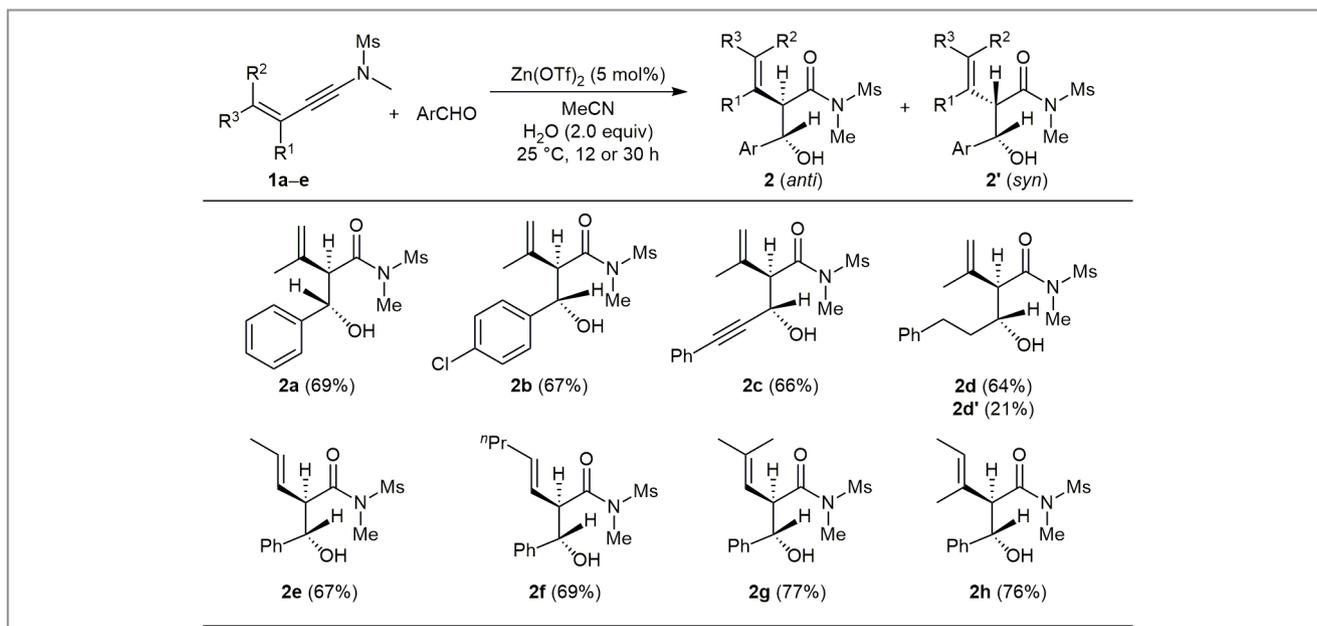
Scheme 3 outlines the reaction scope of this hydrative aldol reaction with various substituted 3-en-1-ynamides and aldehydes. These reactions provide *anti*-configured branched aldol products as sole diastereomers in most instances (*dr* > 20:1), whereas a mixture of *anti/syn* diastereomers were obtained for aliphatic aldehydes (**2d/2d'**). “Applicable alde-



Scheme 1 Aldol reactions involving metal dienolates



Scheme 2 O-bound Zn(II)-dienolates from alkyne hydration



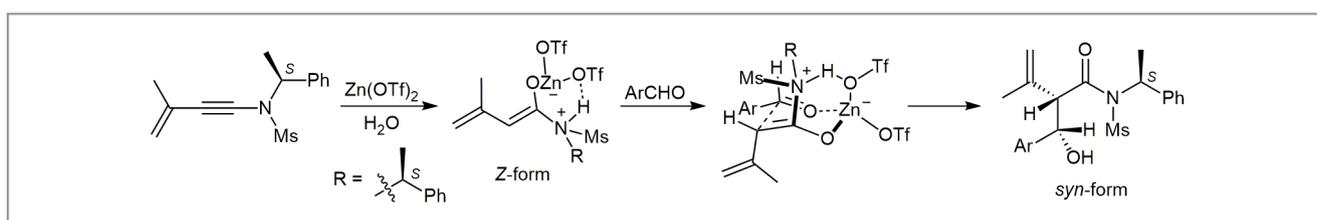
Scheme 3 Branched aldol products with anti-selectivity

hydrides include benzaldehyde, alkynyl-, alkenyl- and 3-phenylpropyl aldehyde, whereas operable 3-en-1-ynamides can comprise 1,1- and 1,2-disubstituted as well as 1,1,2- and 1,2,2-trisubstituted alkenyl moieties,” explained Professor Liu. “X-ray diffraction studies have been performed to confirm the *syn* configuration of several representative aldol products.”

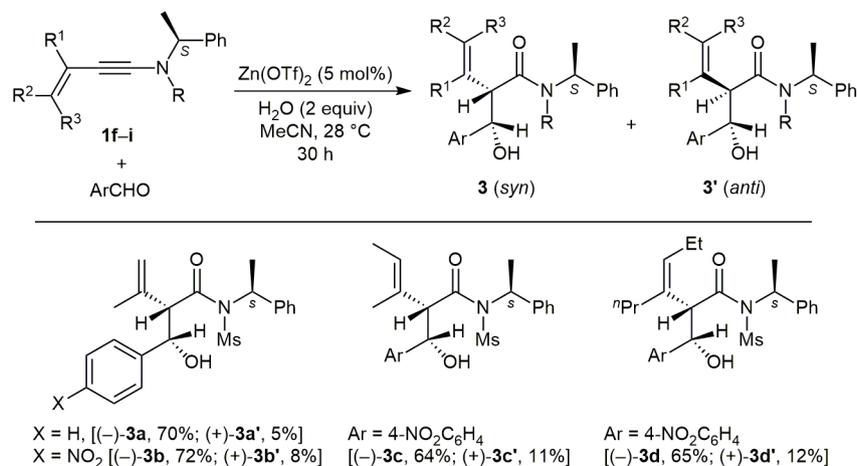
The laboratory of Professor Liu has made successful attempts to modulate the *syn* selectivity using 3-en-1-ynamides bearing a large sulfonamide. “The alteration of stereoselectivity is attributed to preferable formation of *Z*-configured O-bound dienolates in which a large sulfonamide is preferably in a *cis* position relative to a small hydrogen,” explained Professor Liu. Scheme 5 shows several examples for obtaining enantiopure branched aldol products using 3-en-1-ynamides bearing a cheap chiral sulfonamide (R = (*S*)- α -methylbenzyl, EWG = Ms). Professor Liu said: “The reactions preferably afforded *syn*-aldol products as major products. Their *syn* geo-

metries and absolute configurations were confirmed by X-ray diffraction of one representative product. Unfortunately, this large sulfonamide decreases the reactivity of aldol reactions so that only benzaldehyde and their reactive analogues are applicable substrates.”

Professor Liu also commented: “The success of such hydrative aldol reactions is attributed to the use of a sulfonamide to trap a released HOTf, thus impeding competitive protodemetalations of Zn(II) dienolates. Importantly, *E*- and *Z*-configured dienolates can be generated selectively by the sizes of sulfonamides.” He concluded: “This work might inspire research interest on catalytic alkyne hydrations, including the following aspects: (1) new electrophilic reactions of O-bound Zn dienolates, (2) asymmetric hydrative aldol reactions using chiral Zn(II) catalysts and (3) the use of Zn(II)-enolates as reaction partners for Negishi coupling reactions.”



Scheme 4 The use of a bulky sulfonamide to alter stereoselectivity

Scheme 5 Enantiopure aldol products with *syn*-selectivity

Anastas Feneck

About the authors



Prof. R.-S. Liu

Rai-Shung Liu received his BS degree in chemistry (1976) from National Tsing-Hua University (Taiwan), and his PhD in chemistry in 1981 from Columbia University (USA). He then carried out postdoctoral work at Texas A&M University (USA) from 1981 to 1982. In 1982, he started his academic career as an Associate Professor at National Tsing-Hua University. In 1987, he was promoted to Full Professor and he is currently the Dean of the College of Science.



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Appaso M. Jadhav was born in Sangli, MS (India) in 1982. He obtained his BSc from Willingdon College, Sangli (India) and MSc in 2006 from University of Pune (India). From 2006–2008, he worked as research associate in Jubilant Chemistry Ltd. and Ranbaxy Laboratories Ltd. (India). In 2009, he joined the group of Professor Liu to pursue his PhD degree, and completed it in 2013. His doctoral research focused on the development of new organic reactions using gold catalysts. Subsequently, he worked as a postdoctoral researcher in same group for nearly two years. Currently, he is pursuing his second postdoctoral experience at Ohio State University, Columbus (USA).



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Deepak B. Huple was born in Kuntegaon (India) in 1981. He received his BSc (2003) and MSc from Swami Ramanand Teerth Marathwada University Nanded (India) in 2005. He worked as a senior research chemist from 2006–2008 in reputed pharmaceutical companies in India. In 2008, he joined the research group of Professor Liu and received his PhD in 2013. Currently, he is working as a postdoctoral fellow in Professor Liu's group.

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Vinayak Vishnu Pagar was born in Nasik, Maharashtra (India) in 1983. He obtained his BSc and MSc degrees in chemistry from the University of Pune (India) in 2004 and 2006, respectively. From 2006–2010, he worked as research associate in pharmaceutical companies like Jubilant Chemsys Ltd. and Ranbaxy Laboratories Ltd. (India). In 2010, he joined the group of Professor Liu and completed his PhD in 2014. His doctoral research

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