Synthetic Methods

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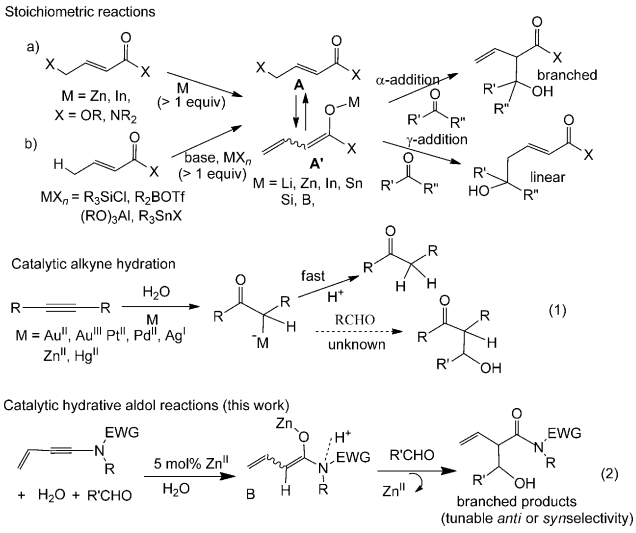
Zinc(II)-Catalyzed Intermolecular Hydrative Aldol Reactions of 2-En-1-ynamides with Aldehydes and Water to form Branched Aldol Products Regio- and Stereoselectively**

*Appaso Mahadev Jadhav, Vinayak Vishnu Pagar, Deepak B. Huple, and Rai-Shung Liu**

Abstract: *This work describes zinc(II)-catalyzed hydrative aldol reactions of 2-en-1-ynamides with aldehydes and water to afford branched aldol products regio- and stereoselectively. The anti and syn selectivity can be modulated by the sizes of sulfonamides to yield E- and Z-configured zinc(II) dienolates selectively. This new reaction leads to enantiopure aldol products by using a cheap chiral sulfonamide. The mechanistic analysis reveals that the sulfonamide amides of the substrates can trap a released proton to generate dual acidic sites to activate a carbonyl allylation reaction.*

Metal dienolates (**A** or **A′**) are versatile carboanions which react with carbonyl electrophiles to access linear or branched aldol products (Scheme 1).[1–7] Although various dienolates (M = Zn,[3,7] Si,[4,6] Sn,[4] Li,[5] B,[6] In,[6] Li[6]) were developed to achieve satisfactory regio- or stereoselectivity of the γ-[3–5] and α-allylations,[6,7] the inevitable use of metal reagents (M or MX_n) and bases in excess (> 1.0 equiv; Scheme 1 a,b) remains a serious concern. The development of their catalytic surrogates is significant and highly desirable, but only iridium-catalyzed enantioselective synthesis of linear aldol products was recently achieved by Krische el al.[8a]



Scheme 1. Aldol reactions of metal dienolates. Advantages of this work: 1) catalytic dienolate reactions, 2) high regioselectivity and tunable *anti* and *syn* selectivity, 3) accessible to enantiopure products, and 4) bifunctional acid property. EWG = electron-withdrawing group, Tf = trifluoromethanesulfonyl.

The well-known catalytic hydrations of alkynes[9,10] emerge as appealing surrogates using readily available alkynes, water, and carbonyl species. This task, however, is difficult because their metal enolate intermediates typically undergo facile protometalations rather than an aldol reaction or other electrophilic additions [Eq. (1)].[11] Ynamides have been widely used in many organic reactions because of their ready availability and easy degradation.[12] We planned to employ 2-en-1-ynamides bearing a sulfonamide such that their resulting zinc enolates (**B**) could trap a released proton, thus generating acid sites to activate a carbonyl group [Eq. (2)]. To describe the success of this new strategy, we report herein the zinc-catalyzed hydrative aldol reactions of 2-en-1-ynamides to yield branched aldol products with tunable *anti* or *syn* selectivity [Eq. (2)]. Importantly, this zinc-catalyzed reaction leads to enantiopure aldol products using a cheap chiral sulfonamide. In Reformatsky reactions (Scheme 1 a), zinc(II) in THF mainly afforded linear aldol products,[3] but the regioselectivity varied for both Zn/graphite and Zn/Cu in diethyl ether, thus giving mainly branched regioisomers[7] albeit in poor and moderate diastereoselectivity.

Table 1 shows the result of optimization of the intermolecular hydrative aldol reactions of the 2-en-1-ynamide **1a** with suitable Lewis acids and solvents. In a typical operation, **1a** was treated with the catalyst (5 mol%), water (2 equiv), and benzaldehyde (1.5 equiv) in a pre-dried solvent at 25 °C for 20–30 hours before workup. Initial tests with various gold(I), silver(I), and copper(II) catalysts in wet CH_3CN (28 °C, 30 h) led predominantly to the hydration product **3a**, albeit in moderate yields (42–57%; these data are provided in Scheme S1 in the Supporting Information). To our delight, $Zn(OTf)_2$ lead to formation of the β-hydroxyamide **2a** in 69% yield, whereas **3a** was present in trace amounts (entry 1). ZnF_2 gave the undesired **3a** (45%), and $ZnCl_2$ afforded **2a** and **3a** in 42% and 22% yields, respectively (entries 2 and 3). $Sc(OTf)_3$ and $In(OTf)_3$ gave disappointing results, thus yielding **2a** and **3a** in 12–14% and 45–48% yields, respectively (entries 4 and 5). Other solvents like THF, 1,2-dichloroethane, and nitromethane were not appropriate solvents for $Zn(OTf)_2$, thus giving **2a** and **3a** in comparable portions (entries 6–8). HOTf (5 mol%) alone led to complete hydration to give **3a** in 87% yield (entry 9). For $ZnCl_2$, $In(OTf)_3$,

[*] Dr. A. M. Jadhav, Dr. V. V. Pagar, Dr. D. B. Huple, Prof. Dr. R.-S. Liu
Department of Chemistry, National Tsing-Hua University
Hsinchu, 30043, Taiwan (ROC)
E-mail: rsliu@mx.nthu.edu.tw

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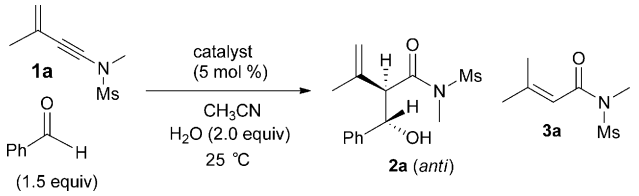
Table 1: Catalyst screening using various Lewis acids.



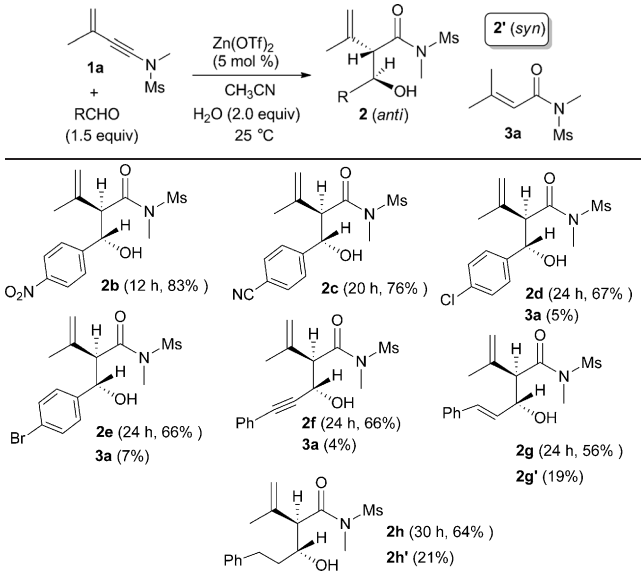
Entry	Catalyst[a]	Solvent	*t* [h]	Products (yield [%])[b]		
				1a	**2a**	**3a**
1	$Zn(OTf)_2$	CH_3CN	30	–	69	trace
2	ZnF_2	CH_3CN	30	40	–	45
3	$ZnCl_2$	CH_3CN	24	–	42	22
4	$Sn(OTf)_2$	CH_3CN	24	–	12	45
5	$In(OTf)_2$	CH_3CN	24	–	14	48
6	$Zn(OTf)_2$	THF	24	–	48	34
7	$Zn(OTf)_2$	DCE	24	–	38	54
8	$Zn(OTf)_2$	$MeNO_2$	24	–	34	48
9	HOTf	CH_3CN	4	–	–	87

[a] [**1a**] = 0.2 M. [b] Product yields are for products isolated after purification using a silica column. DCE = 1,2-dichloroethane, Ms = methanesulfonyl, THF = tetrahydrofuran.

and $Zn(OTf)_2$, the product **2a** was produced with only an *anti* configuration (d.r. > 20:1) according to X-ray diffraction of its 4-nitrobenzaldehyde derivative (**2b**; Table 2). A separate experiment verifies that **3a** and PhCHO are do not lead to **2a** in the presence of $Zn(OTf)_2$ in wet CH_3CN (25 °C, 30 h).

We tested the reactions of **1a** with various aldehydes to assess the substrate scope. The results are summarized in Table 2, in which the major product **2** was determined to be the *anti* isomer because the two methine protons have coupling constants of $J = 8$–9 Hz (for *syn* isomers $J = 3$–4 Hz). Such hydrative aldol reactions were compatible with various benzaldehydes bearing *para* substituents such as

Table 2: Hydrative aldol reactions with aldehydes.

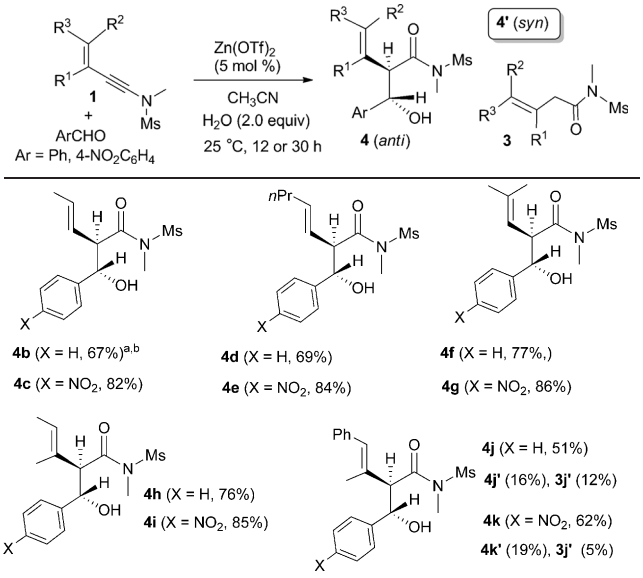


[a] [**1a**] = 0.2 M. [b] Product yields are for products isolated after purification using a silica column.

nitro, cyano, chloro, and bromo groups, and the resulting β-hydroxyamides **2b–d** were obtained in 66–83% yields with d.r. values of greater than 20:1. Herein, **3a** was obtained in 5–7% yield for the chloro and bromo derivatives. This new reaction was extended to an alkynyl aldehyde to give the desired **2f** in 66% with a d.r. value of greater than 20:1. For an alkenyl aldehyde, the resulting β-hydroxyamide was isolated as both *syn* and *anti* isomers, that is, **2g** (56%) and **2g′** (19%), and they were separated on a silica column. This reaction worked well for an aliphatic aldehyde, thus giving **2h** (64%) and **2h′** (21%) as a mixture of *anti* and *syn* products.

These hydrative aldol reactions were applicable to the 2-en-1-ynamides **1b–f** bearing various alkenyl groups (Table 3). The *anti*-configured aldol products (d.r. > 20:1) were

Table 3: Hydrative aldol reactions of 2-en-1-ynamides.

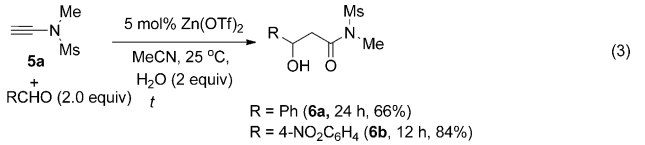


[a] [**1**] = 0.2 M. [b] Product yields are for products isolated after purification using a silica column.

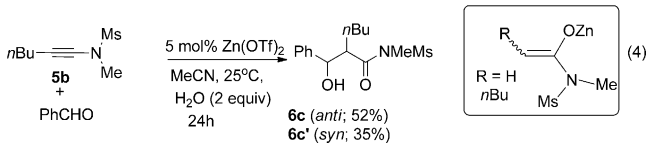
obtained exclusively in most instances except for the substrates **1j** and **1k** for which the *syn* isomers **4j′** and **4k′** and hydration products **3j′** and **3k′** were formed in minor proportions. The reactions worked well for the substrates **1b** and **1c** bearing 1,2-alkenyl groups, and they reacted with benzaldehyde and 4-nitrobenzaldehyde to give the *anti*-configured aldol products **4b–e** in 67–84% yields. The same reactions were also applicable to their gem-dimethylvinyl analogue **1d** to afford desired the *anti*-configured compounds **4f** and **4g** in 77–86% yields. This zinc(II)-catalyzed reaction was extended to the 2-en-1-ynamide **1e** bearing a vicinal dimethylvinyl moiety, thus giving the aldol products **4h** and **4i** (76–85%) with high *anti* selectivity. For the bulky and trisubstituted alkene substrate **1f** its hydrative aldol reactions gave both *anti*- (**4j** and **4k**) and *syn*-aldol products (**4j′** and **4k′**) in 51–62% and 16–19% yields respectively.

These aldol reactions are also applicable to terminal (**5a**) and internal (**5b**) ynamides as depicted in Equations (3) and (4), respectively. The former gave the hydrative aldol

products **6a** and **6b** in 66% and 84% yields, respectively, whereas the latter gave the aldol products **6c** (52%) and **6c′** (35%) as a mixture of *anti* and *syn* isomers. The generation of O-bound zinc enolates is thus ascertained herein.



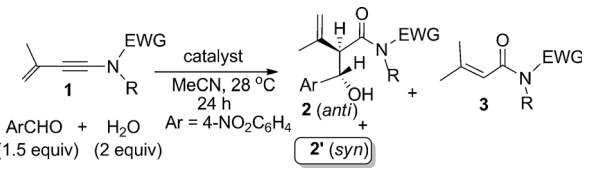
(3)



(4)

We prepared the 2-en-1-ynamides **1g–i** bearing various sulfonamide groups (Table 4). For **1g** (R = *n*-butyl, EWG = Ms), the *anti*-isomer **2i** was obtained exclusively in 74% yield (entry 1). Notably, a switch to **1h** (R = *i*Pr, EWG = Ms) and **1i** (R = Me, EWG = Ts), bearing bulky sulfonamides, gave *anti*/*syn* mixtures (**2j**/**2j′** and **2k**/**2k′**) in comparable portions (entries 2 and 3). Following this trend, we managed to achieve the *syn* selectivity using **1j** bearing an increased size of sulfonamide (entry 4). The details of the resulting products (*anti*/*syn* = 1:9) are presented in Table 5.

Table 4: Effects of sulfonamides on *anti*/*syn* selectivity.

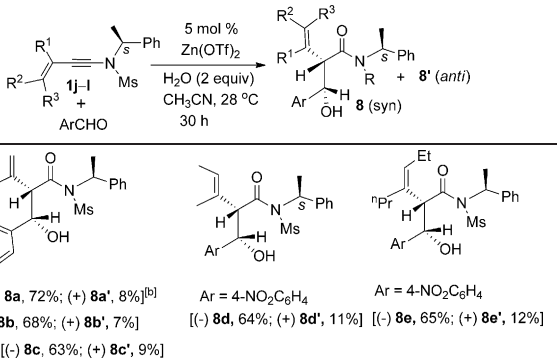


Entry	2-En-1-ynamide[a] R	EWG	Products (yield)[b] **2**/**2′** (*anti*/*syn*)	**3**
1	*n*Bu	Ms (**1g**)	**2i** (74%)	–
2	*i*Pr	Ms (**1h**)	**2j**/**2j′** = 1.1:1 (68%)	3%
3	Me	Ts (**1i**)	**2k**/**2k′** = 1.2:1 (80%)	–
4	(*S*)-α-methyl-benzyl	Ms (**1j**)	*anti*/*syn* = 1:9	–

[a] [**1**] = 0.20 M. [b] Product yields are reported after purification from a silica column.

Inspired by our preliminary success with *syn* selectivity, we developed catalytic asymmetric reactions of the 3-en-1-ynamides **1j–l** containing a cheap chiral sulfonamide appended to (*S*)-α-methylbenzyl (Table 5). These substrates (**1j–l**) were designed to bear 3-substituted alkenyl moieties ($R^1 \neq H$) to elude three or four isomeric products. Only two diastereomeric products were produced from **1j–l** with high stereoselectivity (**8**/**8′** = 5.8–9.0) and good yields. The major *syn* isomers **8a–e** have coupling constants of $J = 4.7$–5.0 Hz, whereas the minor *anti* isomers **8a′–e′** coupling constants of $J = 6.8$–7.0 Hz. We performed X-ray diffraction studies on **8e** and an acyl derivative of the compound **8a** to confirm their *syn* geometries and absolute configurations.

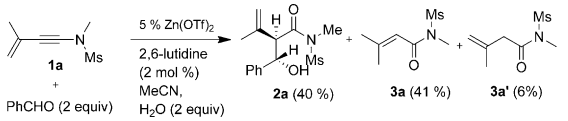
Table 5: Hydrative aldol reactions with *syn* selectivity.



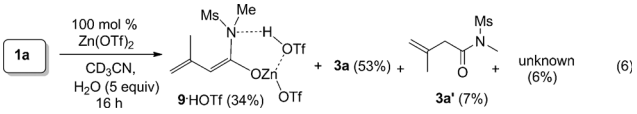
[a] [**1j–1l**] = 0.20 M. [b] Product yields are for products isolated after purification using a silica column. [c] The compounds **8b′** and **8e′** were not isolated in pure form.

As shown in Equation (5), we added 2,6-lutidine (2 mol%) to **1a** to trap a released proton, but the reaction became much less selective, thus giving the aldol product **2a** (40%) together with the hydration products **3a** and **3a′** in 41% and 6% yield, respectively. To characterize the zinc dienolate generated in MeCN/water, **1a** was treated with $Zn(OTf)_2$ (1 equiv) and H_2O (5 equiv) in CD_3CN (28 °C, 16 h), and the ^1H NMR spectra clearly showed the presence of the zinc dienolate **9** (34%), presumably in an *E* configuration because the =CH proton did not show an NOE effect on its sulfonamide group [Eq. (6)]. The species **9** has three olefin protons which appear at $\delta = 6.23$, 5.05, and 5.03 ppm (see Figure S1 in the Supporting Information). In the DEPT ^{13}C NMR spectra, the =CH− and $=CH_2$ signals appear at $\delta =$ 124.8 ppm and 118.5 ppm, respectively. We also observed a minor (6%) unknown species, but its structural assignment was hampered because the signals for two carbon atoms were not observable, probably because they were masked by the MeCN signal. This unknown species was absent when [D_6]acetone was used as the solvent. Interestingly, we observed a slightly broad peak at $\delta = 7.78$ ppm, and it is not due to either free HOTf or $Zn(OTf)_2(H_2O)_n$ ($n = 1$ or 2) in MeCN. This signal is postulated to be associated with the zinc dienolate **9**. The LC-MS(ESI) of this mixture showed a peak of 403.95(^{64}Zn), which was assigned to the parent peak ($M+$ 1) of **9**. Accordingly, we postulate a structure for **9**, as shown in [Eq. (6)], which forms a complex with HOTf.

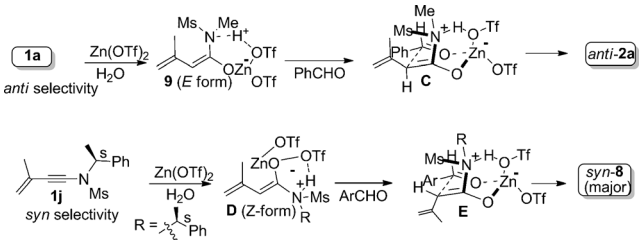
Scheme 2 shows a proposed mechanism to rationalize the *anti* and *syn* selectivity of the branched aldol products. The



(5)



(6)



Scheme 2. Rationale for the *anti* and *syn* selectivity.

size effects of sulfonamides provide mechanistic insight. For **1a** bearing a small sulfonamide like NMe(Ms), its initial alkyne hydrations generate the *E*-configured zinc dienolate **9** predominantly. As suggested by our NMR and ESI-MS characterization [Eq. (6)], this O-bound dienolate reacts with benzaldehyde to form a chairlike transition state (**C**) to give *anti* selectivity.[13] This reaction model **E** reveals the function of a Brønsted acid, tightly bound with the nitrogen atom to enhance the acidity of Zn^{II}.[14] This dual acidic property facilitates an aldol reaction. For **1j** bearing a large sulfonamide, the *E*-configured zinc dienolate suffers an increasing interaction between its methyl and bulky sulfonamide. Accordingly, only the *Z*-configured dienolate **D** is generated to react with an aldehyde in a chairlike transition state (**E**) to yield the *syn*-products **8**. We do not exclude an open transition state which can govern the *syn* selectivity without chelation.[15]

Before this work, the enolates generated in the alkyne hydration had not been elaborated for catalytic C–C bond formations.[16] Herein, we report the success in the zinc-catalyzed hydrative aldol reactions of 2-en-1-ynamides to afford branched aldol products with high stereoselectivity. Our strategy employs 2-en-1-ynamides bearing a sulfonamides to enable the resulting zinc dienolate to complex with HOTf. In one instance, we were able to characterize the zinc dienolate **9** by NMR spectroscopy and ESI-MS. This newly generated Brønsted acid increases the acidity of the zinc to facilitate an aldol reaction. Importantly, the *anti* and *syn* selectivity can be modulated by the size of the sulfonamide through selective formation of *E*- or *Z*-configured zinc dienolates. This zinc-catalyzed reaction leads to enantiomerically pure products using a cheap chiral sulfonamide. We believe that this reaction will lead to the design of new tandem reactions involving alkyne hydrations as the initial step.

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[16] CCDC 1030151 (**2a**), 1030152 (**8a** an acyl derivative), and 1030153 (**8e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

