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Research Article

Regio- and Stereoselective Synthesis of Diverse 3,4-Dihydro-2-quinolones through Catalytic Hydrative Cyclization of Imine- and Carbonyl-Ynamides with Water

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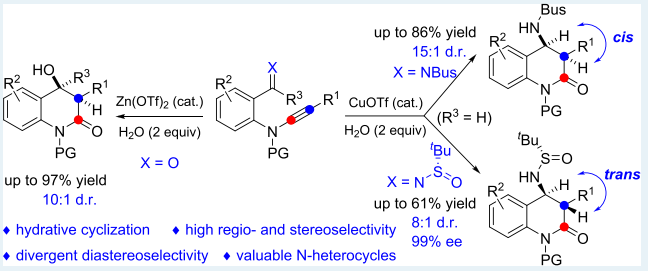
ABSTRACT: Transition-metal-catalyzed alkyne hydration reaction has attracted considerable interest in the past decades because this approach would lead to the facile and efficient formation of synthetically useful carbonyls. However, transition-metal-catalyzed alkyne hydration-initiated tandem reactions have seldom been explored because their metal enolate intermediates generally undergo facile protodemetallation rather than further trapped by other types of electrophiles. Described herein is an efficient copper-catalyzed tandem alkyne hydration/intramolecular Mannich reaction of imine-ynamides with water. This method allows efficient and diastereodivergent synthesis of valuable 3,4-dihydro-2-quinolones with high regio-, diastereo-, and enantioselectivity. Moreover, this hydrative cyclization can also be applicable to the hydrative aldol reaction of carbonyl-ynamides with water to form 3,4-dihydro-2-quinolones regio- and diastereoselectively by employing zinc as the catalyst.



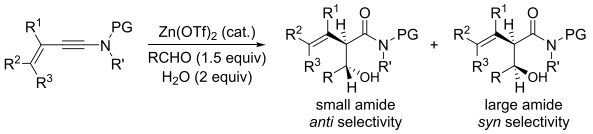
KEYWORDS: *cyclization, cascade, heterocycles, alkynes, stereoselectivity*

INTRODUCTION

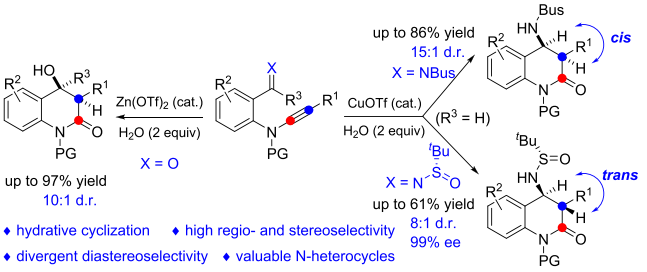
Transition-metal-catalyzed alkyne hydration reaction (M = Au, Pt, Pd, Ag, Zn, and Hg) has attracted considerable interest in the past decades because this approach would lead to the facile and efficient formation of synthetically useful carbonyl derivatives from the readily available alkynyl substrates.[1,2] In particular, a high turnover frequency (TOF) has been achieved in the gold-catalyzed reaction system,[3] as elegantly established by Hayashi et al.,[3a] Nolan et al.,[3b] Zhang et al.,[3c] and Zuccaccia et al.[3d] Despite these significant achievements, transition-metal-catalyzed alkyne hydration-initiated tandem reactions have seldom been explored due to the fact that their metal enolate intermediates generally undergo facile protodemetallation rather than further trapped by other types of electrophiles such as carbonyls and imines.[4−6] A major breakthrough was the zinc-catalyzed hydrative aldol reaction of 3-en-1-ynamides with aldehydes and water developed by Liu and co-workers in 2015 (Scheme 1a).[5a] Subsequently, the relevant gold-catalyzed tandem imination/Mannich reaction of enynamide with anilines and aldehydes was realized by the same group.[5b] Notable is that the conjugated enynes are generally required for these reactions, and the poor diastereoselectivity was obtained in the case of typical internal ynamides. Very recently, Shi et al. disclosed an elegant formal tandem alkyne hydration/aldol addition via Au−Fe dual catalysis, but this protocol relies on the carbonyl-group neighboring-group participation.[6a]

Scheme 1. (a, b) Transition-Metal-Catalyzed Hydrative Aldol and Mannich Reactions of Alkynes

a) Zinc-catalyzed tandem alkyne hydration/intermolecular aldol reactions (Liu's work)



b) Catalytic tandem alkyne hydration/intramolecular Mannich and aldol reactions (this work)



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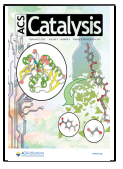

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Therefore, the development of novel alkyne hydration-initiated tandem reactions, especially those with high flexibility, efficiency, and stereoselectivity, is highly desirable.

Inspired by the above achievements and by our recent work on developing ynamide chemistry for N-heterocycle synthesis,[7,8] we envisioned that the catalytic intramolecular hydrative Mannich reaction of imine-ynamides with water might be feasible, thus leading to the formation of the corresponding 3,4-dihydro-2-quinolones (Scheme 1b), which exist in a range of bioactive molecules and natural products (Figure 1).[9] However, realizing this hydrative cyclization, especially with high regio- and stereoselectivity, is highly challenging. First, the generated metal enolates may suffer from the ready protodemetallation process. Second, the imine moiety may undergo facile hydration before or after the alkyne hydration to form the carbonyl moiety. Herein, we describe the realization of such a copper-catalyzed hydrative Mannich reaction of imine-ynamides with water, which represents the first catalytic hydrative Mannich reaction. This method allows efficient, practical, and diastereodivergent synthesis of valuable 3,4-dihydro-2-quinolones with high regio-, diastereo-, and enantioselectivity. Furthermore, this hydrative cyclization can also be applicable to the hydrative aldol reaction of carbonyl-ynamides with water to form 3,4-dihydro-2-quinolones regio- and diastereoselectively by employing zinc as the catalyst. In this article, we report the results of our detailed investigations on this type of catalytic hydrative Mannich and aldol reactions, including substrate scopes, synthetic applications, and mechanistic studies.

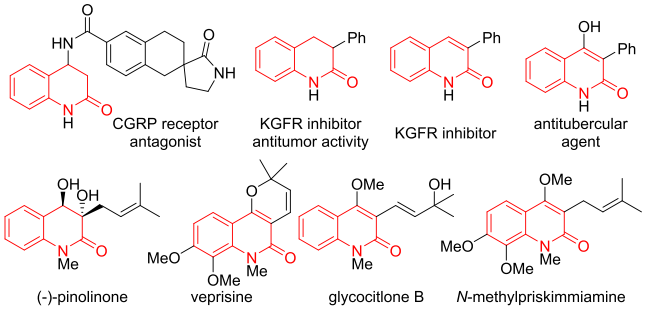
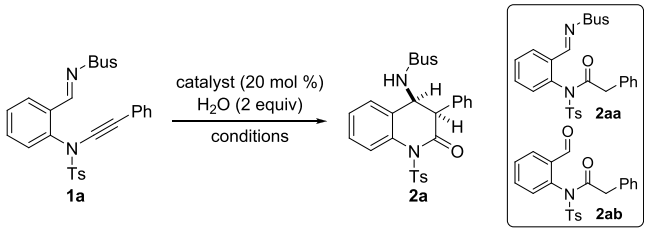


Figure 1. 2-Quinolones in bioactive molecules and natural products.

RESULTS AND DISCUSSION

At the outset, the *tert*-butylsulfonyl (Bus)-substituted imine-ynamide **1a**[10] was chosen as the model substrate due to the facile removal of the Bus group of the formed products.[11] Table 1 shows the realization of the hydrative cyclization reaction of imine-ynamide **1a** with water in the presence of various transition-metal catalysts.[12] The reaction was first performed under Liu's group previously developed conditions,[5a] and the desired hydrative cyclization product **2a** could be obtained in 45% yield together with significant formation of hydration product **2ab** (entry 1). Further screening of other Lewis acids such as $Sc(OTf)_3$ and $Y(OTf)_3$ only led to the decomposition of substrate **1a** (entries 2−5). To our delight, product **2a** was formed in 60% yield in the presence of CuOTf albeit still with significant amounts of hydration product **2aa** (entry 6). In addition, the use of other copper catalysts such as $Cu(OTf)_2$ and $Cu(CH_3CN)_4PF_6$ failed to improve the reaction (entries 7 and 8, respectively). Gratifyingly, subsequent investigations on the reaction concentration demonstrated that low concentrations were necessary to circumvent the competing hydration reaction and other side reactions (entries 9 and 10). The reaction proceeded smoothly under the concentration of 0.0125 M, affording the desired 3,4-dihydro-2-quinolone **2a** in 88% yield with high diastereoselectivity (12:1, entry 10). Of note, the reaction could produce the desired **2a** in the presence of gold catalysts such as $Ph_3PAuNTf_2$ and $IPrAuNTf_2$ and Brønsted acids such as MsOH and $HNTf_2$ but with low efficiency (<40%).[12] In the absence of the catalyst, the reaction failed to give even a trace of **2a**.

Table 1. Optimization of Reaction Conditions[a]



entry	metal catalyst	conditions	d.r.	yield (%) 2a	2aa	2ab
1	$Zn(OTf)_2$	CH_3CN, 80 °C, 2 h	8:1	45	<3	16
2	$Sc(OTf)_3$	CH_3CN, 80 °C, 2 h		<3	<3	<3
3	$Y(OTf)_3$	CH_3CN, 80 °C, 2 h		<3	<3	<3
4	$Fe(OTf)_3$	CH_3CN, 80 °C, 2 h		<3	<3	<3
5	$Fe(OTf)_2$	CH_3CN, 80 °C, 2 h		<3	<3	<3
6	CuOTf	CH_3CN, 80 °C, 2 h	10:1	60	11	<3
7	$Cu(OTf)_2$	CH_3CN, 80 °C, 2 h		16	<5	<5
8	$Cu(CH_3CN)_4PF_6$	CH_3CN, 80 °C, 2 h	6:1	38	7	<3
9	CuOTf	CH_3CN (0.025 M), 80 °C, 10 h	12:1	81	9	<3
10	CuOTf	CH_3CN (0.0125 M), 80 °C, 12 h	12:1	88	<5	<3

[a]Reaction conditions: **1a** (0.1 mmol), catalyst (0.02 mmol), H_2O (0.2 mmol), CH_3CN (2 mL), 80 °C, 2−12 h, and in Schlenk tubes; yields are measured by ^1H NMR using diethyl phthalate as the internal standard; and d.r. values are determined by crude ^1H NMR. Bus = *tert*-butylsulfonyl.

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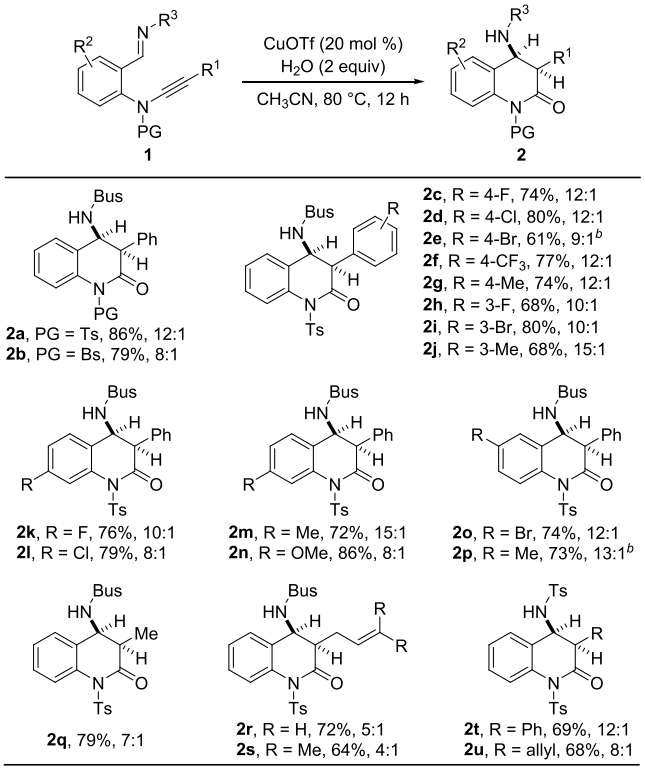
Having the optimum reaction conditions in hand (Table 1, entry 10), the reaction scope of the copper-catalyzed hydrative cyclization of Bus-substituted imine-ynamides with water was then explored. As shown in Table 2, the reaction proceeded

Table 2. Reaction Scope for the Hydrative Cyclization of Imine-Ynamides 1[a]



[a]Reactions run in vials; **1** (0.2 mmol), CuOTf (0.04 mmol), H_2O (0.4 mmol), CH_3CN (16 mL), 80 °C, 12 h, and in Schlenk tubes; yields are those for the isolated products; and d.r. values are determined by crude ^1H NMR. [b]Using 20 mol % $Cu(CH_3CN)_4PF_6$ as the catalyst. PG = protecting group. Bs = 4-bromobenzenesulfonyl.

smoothly with a range of aryl-tethered imine-ynamides **1**, and the corresponding 3,4-dihydro-2-quinolones **2** were obtained in generally high yields. In addition to the Ts group, ynamide containing a Bs group was also a suitable substrate for this hydrative cyclization to furnish the desired benzo-fused δ-lactam **2b** in 79% yield. In addition, the reaction occurred efficiently for various aryl-substituted ynamides (R^1 = Ar) and ynamides bearing both electron-withdrawing and electron-donating groups, producing the corresponding δ-lactams **2c**–**2p** in mostly good yields. This chemistry could also be extended to alkyl- and allyl-substituted ynamides to afford the desired products **2q**–**2s** in 64–79% yields. Interestingly, substrates with the Ts-substituted imine moiety could also be readily converted into the expected 3,4-dihydro-2-quinolones **2t** and **2u** in good yields. Attempts to synthesize the *gem*-disubstituted imine-ynamides and alkyl-tethered imine-ynamides failed probably due to the fact that these imine-ynamides are extremely unstable. Finally, it is notable that the unique regioselectivity here is distinctively different from the related copper-catalyzed arylative cyclization of imine-ynamides with arylboronic acids,[10] where regioselective nucleophilic addition on the β-position of ynamides was observed. Importantly, high diastereoselectivity was achieved in all cases. The relative configuration of **2m** was confirmed by X-ray diffraction analysis (Figure 2).[13] Thereby, this protocol

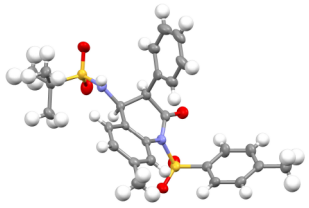
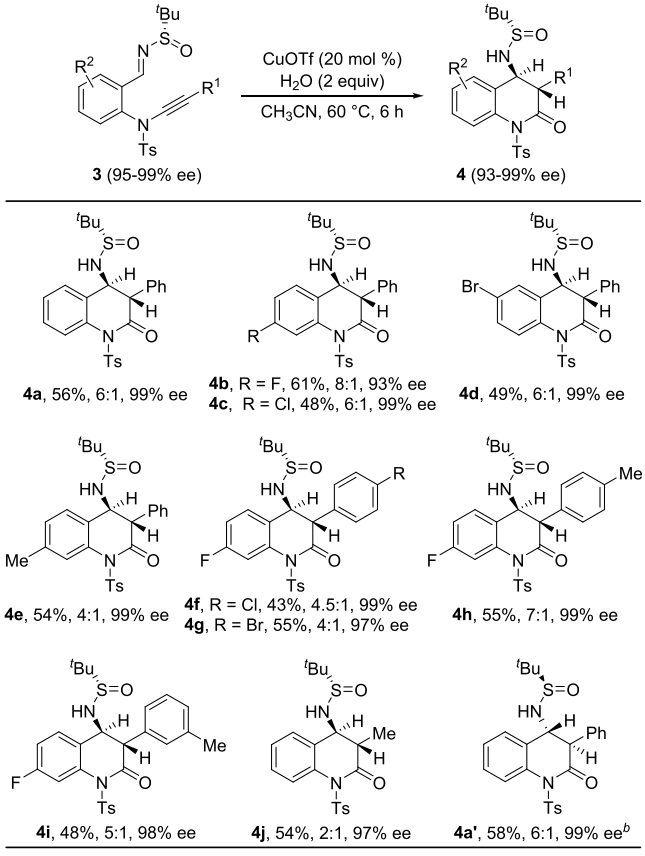


Figure 2. Structure of compound **2m** in its crystal.

not only represents the first catalytic hydrative Mannich reaction but also provides a highly efficient and practical route to prepare valuable structurally diverse 3,4-dihydro-2-quinolones.[14]

Although our attempts to employ various chiral ligands such as bisoxazoline (BOX) ligands and biphosphine ligands to realize this asymmetric catalysis failed, the asymmetric hydrative Mannich reaction could be achieved by combination of chiral *tert*-butylsulfinimine chemistry.[15] As depicted in Table 3, the treatment of (*S*)-*tert*-butylsulfinimine-substituted imine-ynamides **3** with 2 equiv of H_2O in the presence of CuOTf allowed the enantioselective synthesis of the corresponding

Table 3. Reaction Scope for the Hydrative Cyclization of Chiral Imine-Ynamides 3[a]



[a]Reactions run in vials; **3** (0.2 mmol), CuOTf (0.04 mmol), H_2O (0.4 mmol), CH_3CN (32 mL), 60 °C, 6 h, and in Schlenk tubes; yields are those for the isolated products; d.r. values are determined by crude ^1H NMR; and ee values are determined by HPLC analysis. [b](*R*)-*tert*-Butylsulfinamide-derived **3a′** was used as the substrate.

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chiral 3,4-dihydro-2-quinolones **4a**−**4j** in respectable yields. Of note, the reaction of alkyl-substituted imine-ynamide could also afford the desired product **4j** in 54% yield albeit with poor diastereoselectivity. In addition, the (*R*)-(+)-*tert*-butylsulfinamide-derived **3a′** also underwent smooth cyclization to specifically produce the other enantiomer **4a′** in 58% yield. To our surprise, divergent diastereoselectivity (trans-cyclization) was observed in this protocol. Importantly, unique regioselectivity, generally high diastereoselectivity, and excellent enantioselectivity were achieved in these cases. The absolute configurations of **4g** and **4a′** were established based on X-ray crystallographic analysis (Figure 3).[13]

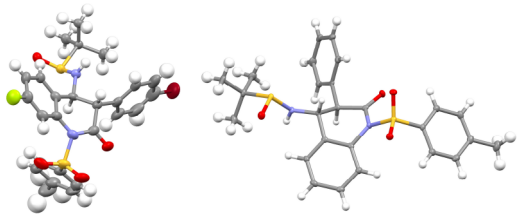
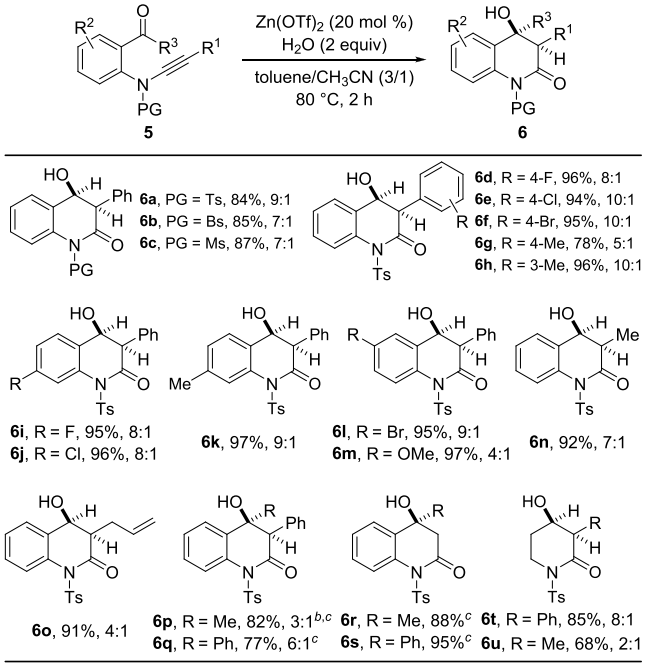


Figure 3. Structures of compounds **4g** and **4a′** in their crystals.

In addition, this hydrative cyclization is applicable to carbonyl-ynamides **5** catalyzed by zinc,[12] affording the corresponding 3,4-dihydro-2-quinolones **6** in generally good to excellent yields with unique regioselectivity and generally high diastereoselectivity (Table 4). Ynamides with different N-protecting groups were first investigated, and it was found that Ts-, Bs-, and Ms-substituted ynamides were all suitable

Table 4. Reaction Scope for the Hydrative Cyclization of Carbonyl-Ynamides 5[a]



[a]Reaction conditions: **5** (0.2 mmol), $Zn(OTf)_2$ (0.04 mmol), H_2O (0.4 mmol), toluene/CH_3CN (3 mL/1 mL), 80 °C, 2 h, and in Schlenk tubes; yields are those for the isolated products; and d.r. values are determined by crude ^1H NMR. [b]Using 20 mol % $Y(OTf)_3$ as the catalyst. [c]Using CH_3CN as the solvent, 60 °C, and 5 h.

substrates for this reaction, leading to the corresponding benzo-*δ*-lactams **6a**−**6c** in 84−87% yields with high diastereoselectivity, respectively. The reaction occurred smoothly with different aryl-substituted ynamides (R^1 = Ar), delivering the desired *δ*-lactams **6d**−**6h** in good to excellent yields. The method also proceeded efficiently for various aryl-tethered ynamides bearing both electron-withdrawing and electron-donating groups, and the expected products **6i**−**6m** were formed in 95−97% yields. Additionally, alkyl-substituted ynamides were also feasible for this hydrative cyclization to afford the desired **6n**−**6o** in 91−92% yields. In addition to aldehyde-ynamides, ketone-ynamides **5p**−**5s** also reacted smoothly to produce the corresponding 3,4-dihydro-2-quinolones **6p**−**6s** in 77−95% yields, respectively.[16] Interestingly, the reaction could be extended to terminal ynamides to deliver the desired **6r** and **6s** efficiently. Finally, it is worth noting that the use of the alkyl-tethered aldehyde-ynamides also led to the expected *δ*-lactams **6t** and **6u** in good yields, but low diastereoselectivity was obtained in the case of the alkyl-substituted ynamide (R^1 = alkyl). Thus, the hydrative aldol reaction exhibits a broader substrate scope in comparison with the above hydrative Mannich reaction. The relative configuration of **6l** was confirmed by X-ray diffraction analysis (Figure 4).[13]

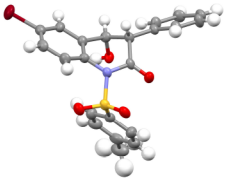
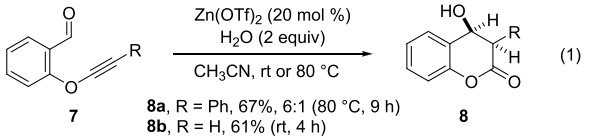


Figure 4. Structure of compound **6l** in its crystal.

In addition to ynamides, this zinc-catalyzed cascade cyclization also occurred efficiently with alkynyl ethers **7**, thus affording the desired dihydrocoumarins **8a** and **8b** in good yields (eq 1).[17] Of note, this heterocyclic moiety can also be found in a variety of bioactive natural and non-natural products.[9a,18]



Further synthetic applications of the as-synthesized 3,4-dihydro-2-quinolones were then explored. For example, the Bus group in **2a**, obtained on a gram scale in 85% yield by employing 10 mol % CuOTf as the catalyst, was smoothly removed upon treatment with $AlCl_3$ (Scheme 2a).[19] The free amine was capped with a Cbz or Boc group to facilitate isolation of the product. The preparative-scale reaction of **3a** was also performed in the presence of 5 mol % CuOTf as the catalyst, affording **4a** in 58% yield and 99% ee. **4a** could undergo subsequent *m*-CPBA oxidation and replacement of the Bus group with the Cbz group, leading to **4ab** in 38% yield (three steps) with well-maintained enantioselectivity (Scheme 2b). Of note, attempts to remove the sulfoxide group of **4a** under various conditions only resulted in the formation of 2-quinolone **6aa** via *β*-elimination. Moreover, the formal synthesis of natural product (±)-martinellic acid was achieved

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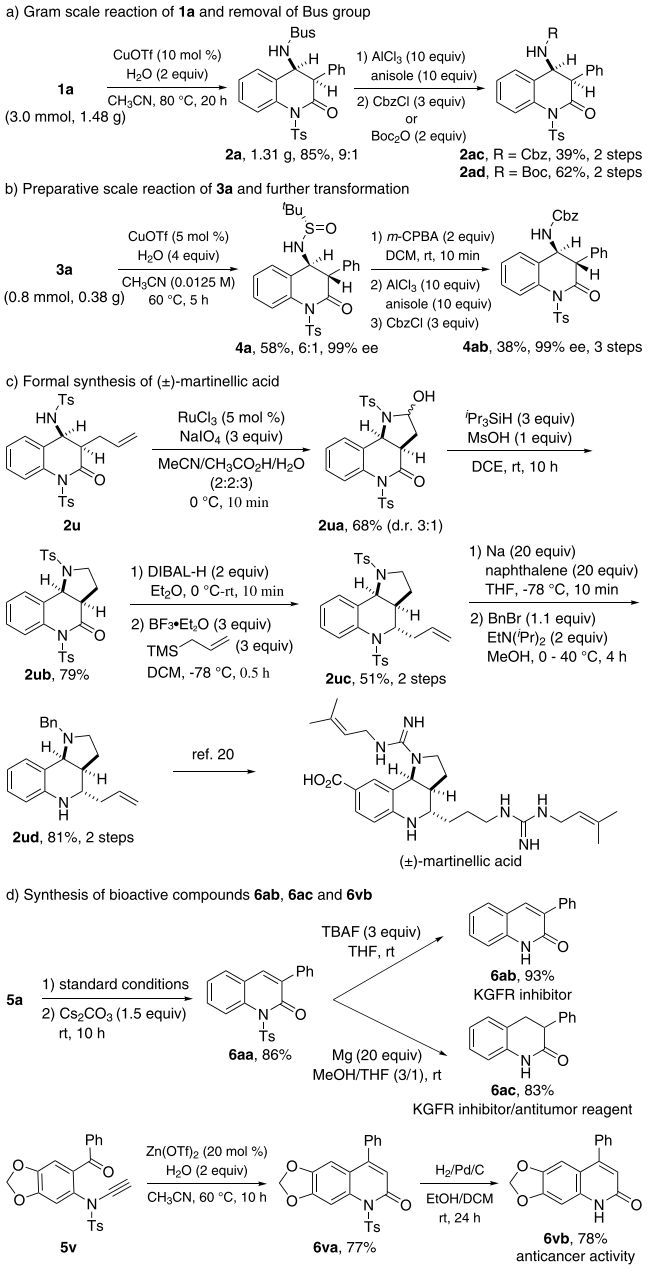
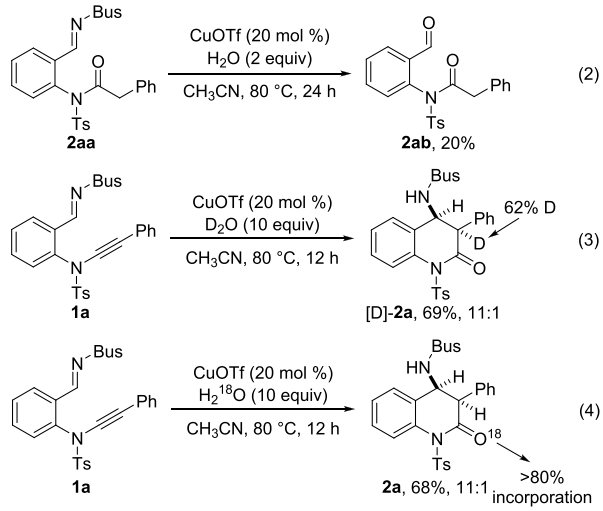
Scheme 2. (a–d) Gram- or Preparative-Scale Reactions and Synthetic Applications



by this method (Scheme 2c). Oxidation of the alkenyl group of **2u** with $RuCl_3$ and $NaIO_4$ led to the formation of aza-hemiacetal **2ua** in 68% yield, which was further transformed into the desired **2uc** in 40% yield (three steps) upon selective reduction of the hydroxyl group by silane and reduction of the amide group by DIBAL-H followed by allylation. Subsequent deprotection of both tosyl groups and selective *N*-Bn protection of the pyrrolidine moiety allowed the formation of the final product **2ud**, which has been previously converted into natural product (±)-martinellic acid.[20] In addition, **6aa**, obtained in 86% yield through the standard hydrative cyclization and dehydration in a one-pot process, could be further converted into **6ab** as a KGFR inhibitor[9f] and **6ac** as a KGFR inhibitor[9f] and an antitumor agent[9h] via deprotection of the tosyl group[8g] and simultaneous deprotection of the tosyl group and reduction of the double bond, respectively (Scheme 2d). Interestingly, the synthesis of the anticancer agent **6vb**[9e] could also be achieved by starting from the corresponding ynamide **5v** through tandem hydrative cyclization/dehydration by simply extending the reaction time and subsequent deprotection (Scheme 2d).

To probe the reaction mechanism, we first subjected **2aa** to the optimal reaction conditions and found that the reaction only afforded the corresponding **2ab** in 20% yield (75% **2aa** recovered) and the formation of **2a** was not observed, thus ruling out **2aa** as an intermediate for the formation of **2a** (eq 2). In addition, when the reaction was run in the presence of



10 equiv of D_2O, 62% deuterium incorporation at the α-position of amide was detected (eq 3). As shown in eq 4, we also performed the reaction in the presence of 10 equiv of $H_2{}^{18}O$ and found that an oxygen atom was incorporated into the product (^{18}O incorporation: >80%). These results suggest that the oxygen of the newly formed carbonyl group of product **2a** originates from the water.

On the basis of the above experimental observations, density functional theory (DFT) calculations, and previous works,[5,6] plausible reaction mechanisms for stereoselective synthesis of 3,4-dihydro-2-quinolones **2a**, **4a**, and **6a** were proposed, as shown in Scheme 3. The reaction presumably involves the formation of *Z*/*E*-configured metal enolate intermediates followed by intramolecular cyclization by the Mannich reaction and aldol reaction, respectively, via preferred chair-like transition states. Through the DFT calculations, it is found that the activation barriers of *cis*-**2a** and *cis*-**6a** are lower than *trans*-**2a** and *trans*-**6a** by 15.1 and 9.5 kcal/mol, respectively. In the case of sulfoxide ynamide **3a**, the positive charge can be located on the low-valent sulfur atom with the proton linked with the oxygen atom of the sulfoxide moiety. According to this catalytic model, the barrier of *trans*-**4a** is 1.5 kcal/mol lower than *cis*-**4a**. Thus, the sulfoxide moiety of **3a** not only dominates the observed high enantioselectivity but also leads to the divergent diastereoselectivity. Moreover, the free energies of *cis*-**2a**, *cis*-**6a**, and *trans*-**4a** are more stable than *trans*-**2a**, *trans*-**6a**, and *cis*-**4a** by 3.7, 1.2, and 3.0 kcal/mol, respectively.[12,21] Hence, these computational results are consistent with the experimental observations in the cyclization reactions.

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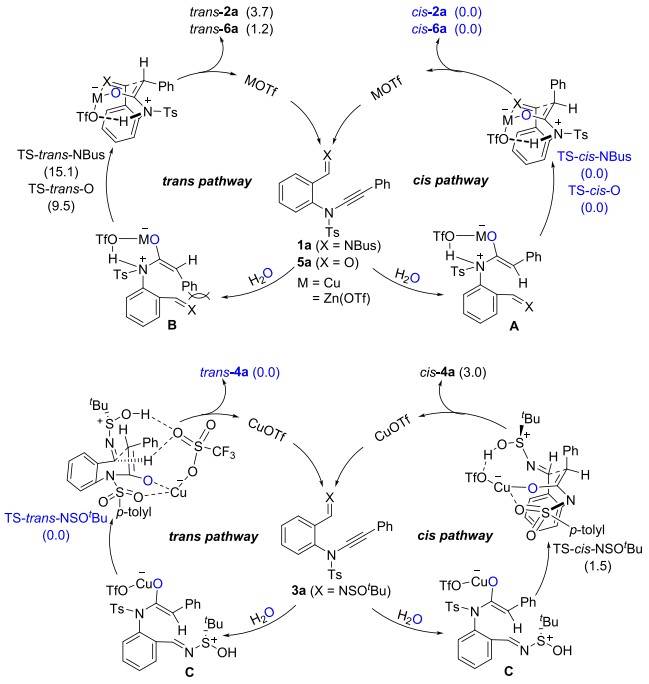
Scheme 3. Plausible Reaction Mechanism and Theoretical Studies on the Key Transition States for the cis and trans Selectivity in the Hydrative Cyclization of Ynamides 1a, 3a, and 5a. The Relative Free Energies Are Given in kcal/mol



CONCLUSIONS

In summary, we have developed the challenging tandem alkyne hydration/intramolecular Mannich reaction of imine-ynamides with water by copper catalysis, which represents the first example of the catalytic hydrative Mannich reaction. Moreover, such an asymmetric hydrative cyclization has been achieved with divergent diastereoselectivity and high enantioselectivities (up to 99% ee) by combination of chiral *tert*-butylsulfinimine chemistry. In addition, this cascade cyclization can also be applicable to the zinc-catalyzed hydrative aldol reaction of carbonyl-ynamides with water. These cascade cyclizations deliver structurally diverse 3,4-dihydro-2-quinolones with unique regioselectivity and high stereoselectivity. The synthetic utility of this chemistry is indicated by the practical and efficient synthesis of two bioactive compounds and formal synthesis of natural product (±)-martinellic acid. Thus, this method opens novel and concise routes to valuable 3,4-dihydro-2-quinolone derivatives. Theoretical calculations are also performed to clarify the origins of diastereoselectivity and enantioselectivity. Owing to these advantages, we believe that this chemistry will be welcomed by academic and industrial researchers. Further direction will focus on the development of the asymmetric version of this protocol by chiral Lewis acid catalysis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c04786.

Experimental procedures, compound characterization data, computational details, and NMR and HPLC spectra (PDF)
Crystallographic data of **2m** (CIF)
Crystallographic data of **4g** (CIF)
Crystallographic data of **4a′** (CIF)
Crystallographic data of **6l** (CIF)

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Notes

The authors declare no competing financial interest.

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