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1,2,3-Triazole: Unique Ligand in Promoting Iron-Catalyzed Propargyl Alcohol Dehydration

Wuming Yan, Xiaohan Ye, Novruz G. Akhmedov, Jeffrey L. Petersen, and Xiaodong Shi*

C. Eugene Bennett Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506, United States

xiaodong.shi@mail.wvu.edu

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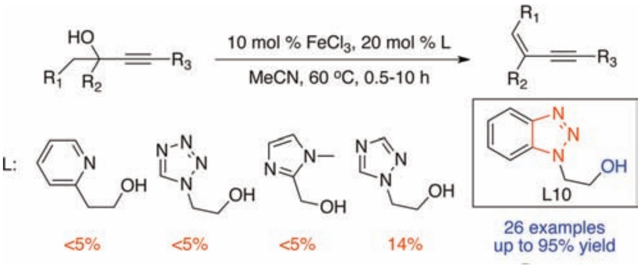
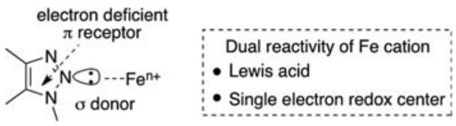
ABSTRACT



A 1,2,3-traizole-promoted iron(III)-catalyzed propargyl alcohol dehydration was developed for the synthesis of conjugated enynes. The desired conjugated enynes were prepared in good to excellent yields (up to 95%) with a large substrate scope and excellent stereoselectivity (only *Z*-isomers).

Ligands play a crucial role in transition-metal catalysis. Besides determining the spatial arrangement (asymmetric synthesis) at the metal center, ligands often influence the electronic environment, thus adjusting metal reactivity.[1] The great successes of alkyne–azide cycloaddition (click chemistry) made 1,2,3-triazole one of the most important heterocycles in chemical,[2] biological,[3] and material research.[4] However, its application in metal complexation remains far less developed.[5] The combination of σ donor (nitrogen lone-pair electrons) and π receptor (highly electron-deficient aromatic ring) makes triazoles potentially unique ligands in altering metal cation reactivity (Scheme 1). Herein, we report the iron-catalyzed propargyl alcohol dehydration for the synthesis of conjugated enyne on gram-scale. In this investigation, 1,2,3-triazoles were revealed as the only ligands effectively promoting this

Scheme 1



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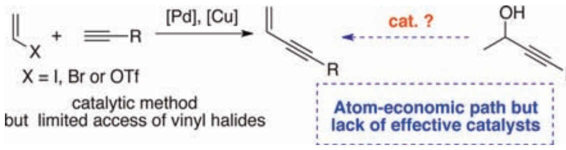
important and challenging transformation (gave up to 95% yields). Other tested N-heterocycles, including the 1,2,4-triazole, tetrazole, and pyridine, all gave poor results (< 15%) even with similar binding patterns, which highlighted the unique role of 1,2,3-triazole ligands in iron catalysis.

Scheme 2. Conjugated Enyne Synthesis: Important but Challenging Process

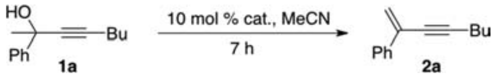


In the past several years, our group has been working on new methods for the preparation of various triazole derivatives[6] and their applications in coordination chemistry to form new catalysts/reagents. These efforts led to the discoveries of triazole–Au[7] and triazole–Rh catalysts[8] and triazole–borane reagent[9] with interesting new reactivities. These encouraging results initiated our interest in evaluating the influence of 1,2,3-triazole ligands in iron-based catalysis.

Homogeneous iron catalysis is becoming more attractive due to the economic benefit (much lower cost compared with noble metals) and low toxicity.[10] Although the iron-containing catalysts (enzyme) have been long known,[11] small organic molecule coordinated iron catalysts are much less developed.[12] One interesting property of iron catalyst is the dual reactivity, where Fe^{n+} could either serve as Lewis acid (electron pair receptors) or as redox center through single electron process. To evaluate how 1,2,3-triazole influences the iron cation reactivity, we studied the propargyl alcohol dehydration for the preparation of conjugated enynes (Scheme 2).

Conjugated enynes and enediynes are basic building blocks in biology,[13] material science,[14] and fine chemical synthesis.[15] However, there are few available methods for effective preparation of this synthon. Although special methods (such as cyclopropane ring-opening) have been reported for specific substrates,[16] the Pd/Cu-catalyzed vinyl halide/alkyne coupling[17] remains the primary available method, which suffered from limited substrate scope and was considered less practical for large-scale enyne preparation. The catalytic propargyl alcohol dehydration should be one atom-economic and practical approach for conjugated enyne synthesis. However, this transformation is challenging and problematic.

Table 1. Direct Propargyl Alcohol Dehydration: A Challenging Transformation[a]



entry	catalyst	temp (°C)	conv[b] (%)	yield[c] (%)
1	TfOH	60	90	30
2	$AlCl_3$	60	10	<5
3	$Bi(OTf)_3$	60	90	21
4	$NiCl_3$	60	22	<5
5	$In(OTf)_3$	60	80	15
6	$CeCl_3$	60	23	<5
7	$LaCl_3$	60	26	<5
8	$RuCl_3$	60	78	22
9	$IrCl_3$	60	75	20
10	$PdCl_2$	60	30	<5
11	$Cu(OAc)_2$	60	52	<5
12	$Co(OAc)_3$	60	26	<5
13	Ti(O*i*-Pr)$_4$	60	71	9
14	$FeCl_2$	60	30	<5
15	$FeCl_3$	60	95	29
16	$Fe(acac)_3$	60	59	12
17	$FeCl_3$	rt	32	11

[a] General reaction conditions: **1a** (0.25 mmol, 1.0 equiv) and Lewis acid catalyst (10 mol %) in MeCN (5 mL). [b] Conversions were determined on the basis of the consumption of propargyl alcohol. [c] NMR yields of **2a** with 1,3,5-trimethoxybenzene as internal standard.

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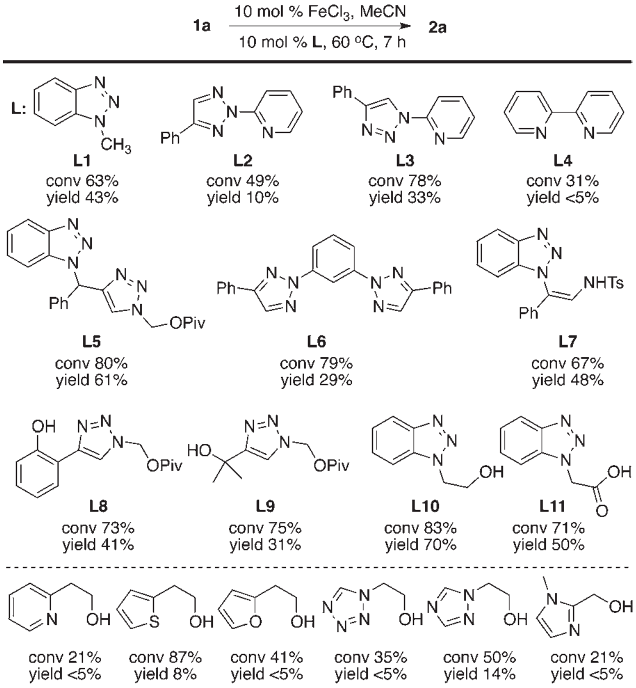
As shown in Table 1, the commonly used Lewis acids gave poor yields of enyne **2a**; even most of the propargyl alcohol **1a** were consumed. Therefore, to fill this "missing methodology", new catalysts need to be developed either by providing proper acidicity (only activating the C–O bond without formation of "pure" carbocation) or by going through an alternative reaction path (such as radical) to avoid the undesired decomposition. On the basis of our recent success in developing new triazole–metal catalysts, we postulated that triazole ligands might provide the needed reactivity for this simple but important transformation.



$FeCl_3$	**L10**	time	temp (°C)	conv	yield
10%	10%	7 h	60	85%	72%
10%	20%	7 h	60	91%	82%
10%	30%	7 h	60	76%	60%
10%	40%	7 h	60	71%	56%
10%	20%	10 h	60	100%	92%

Figure 1. Screening of ligands. (a) General reaction conditions: **1a** (0.25 mmol, 1.0 equiv), ligands (10 mol %), and Lewis acid catalyst (10 mol %) in MeCN (5 mL). (b) Conversions were determined on the basis of the consumption of propargyl alcohol. (c) NMR yields of **2a** with 1,3,5-trimethoxybenzene as internal standard.

To test our hypothesis, various triazole–$FeCl_3$ mixtures were employed as the catalysts to react with **1a**. To ensure consistency, all reactions were conducted under identical conditions, and the reaction mixtures were measured after 7 h (Figure 1). To our surprise, the simple addition of *N*-methylbenzotriazole **L1** to $FeCl_3$ significantly decreased the undesired decomposition of **1a**, giving the desired enyne **2a** in good yields. Screening the triazole ligands revealed even better reactivity of chelating ligands, giving enyne in excellent yields. Interestingly, other heteroaromatic ligands, including pyridine, imidazole, tetrazole, and 1,2,4-triazoles, could not provide this chemoselectivity at all, even with very similar binding patterns, which demonstrates the unique properties of 1,2,3-triazoles as ligands in adjusting iron cation reactivity.

The bidentate ligands gave improved reactivity. Increasing the ligand loading revealed a 2:1 (ligand/Fe) ratio as the optimal condition, which was consistent with the Fe^{3+} octahedral coordination (six coordination sites, requiring open coordination sites for OH binding in the transition state). Solvent screening revealed acetonitrile as the optimal solvent (see details in the Supporting Information). Attempts to obtain the iron–triazole complex crystal structure have been unsuccessful to this point. Nevertheless, addition of readily available 1,2,3-triazole to $FeCl_3$ provided a practical and efficient catalyst system, which gave the critical chemoselectivity for the C–O bond activation. To the best of our knowledge, this is the first catalytic system reported that can effectively promote this transformation.[18] Various functional propargyl alcohols were prepared to investigate the reaction substrate scope. The results are summarized in Figure 2.

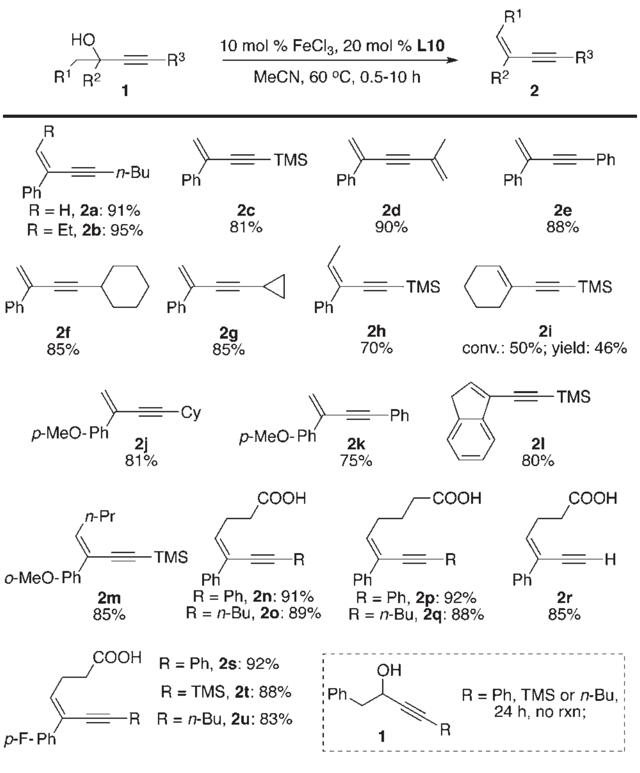


Figure 2. Substrate scope. (a) General reaction conditions: **1a** (0.25 mmol, 1.0 equiv), ligands **L10** (20 mol %) and Lewis acid catalyst (10 mol %) in MeCN (5 mL). (b) Isolated yields.

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As indicated in Figure 2, both terminal alkyne (**2r**) and internal alkyne were suitable for this reaction, giving the desired enynes in excellent isolated yields. The alkyne terminal can tolerate various substituted groups, including alkyl (**2a**, **2b**), aryl (**2e**), TMS (**2c**), cyclopropanyl (**2g**), and even vinyl groups (**2d**). The propargyl position tolerates an aromatic ring with either electron-donating (**2j**, **2k**) or electron-withdrawing (**2s** to **2u**) groups. Elimination to the alkenes showed excellent stereoselectivity, with only one double bond isomer observed, which were unambiguously characterized by X-ray crystal structure (**2n**). The formation cyclohexenyl enyne **2i** indicated a slower reaction rate caused by the lower reactivity of the C–O bond. However, the starting propargyl alcohol could be fully recovered, indicating the excellent chemoselectivity of the 1,2,3-triazole/Fe catalysts. Enynes with 1,2-disubsitututed alkenes could not be formed because of the low reactivity of the C–O bond. Raising the reaction temperature caused the decomposition of propargyl alcohols. However, the highly reactive 1,4-enediynes could be easily synthesized with this method (Figure 3), which highlighted the benefits of the milder reaction condition.[19]

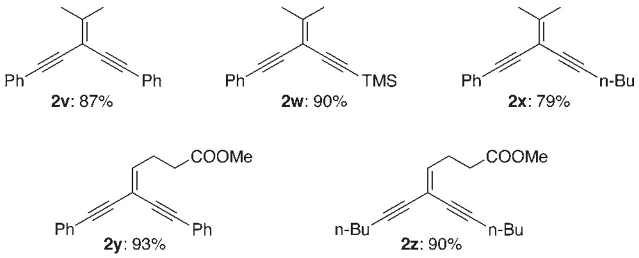

Figure 3. Synthesis of 1,4-enediynes. (a) General reaction conditions: identical as above. (b) Isolated yields.

Substrates **2n**–**u** illustrated good functional group tolerability of this method. The COOH or ester-substituted enyne could be readily prepared through this approach. Treating **2s**, **2t**, and **2u** with NBS resulted in either 6-endo or 5-exo cyclization, giving the bromoallenes or lactone in excellent yields and diastereoselectivity.[20] Notably, large-scale (10 g) reaction has been performed, and **2a** was prepared with 82% isolated yield.

To investigate the reaction mechanism of this triazole-ligand coordinated Fe^{3+} cation catalyst,[21] the cyclopropane-substituted propargyl alcohols (**3a**, **3b**) were prepared and treated with $FeCl_3$ under various conditions.

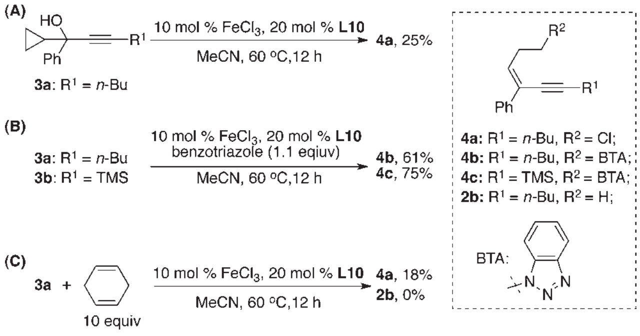

Figure 4. Mechanistic investigations.

Comsidering that both Lewis acid catalyzed cyclopropane opening[22] and radical initiated ring-opening[23] were plausible, mixtures of NH-triazole and radical trapper 1,4-cyclohexyldiene (CHD) were used to investigate the mechanism.

As shown in Figure 4, reaction of **3a** gave the chloro enyne **4a** as the only isolated product (25% yield). With the addition of NH-triazole, enyne **4c** was obtained (75% yield, confirmed by X-ray). Addition of radical trapper CHD did not lead to the formation of H-quenched enyne **2b**. Instead, the chloro enyne **4a** was the only enyne product isolated. These results strongly suggested the carbocation ring-opening pathway instead of radical mechanism, which is consistent with our hypothesis that 1,2,3-triazole ligands provided the required electronic effect in adjusting Lewis acidity of Fe^{3+} to achieve the needed chemoselectivity for this transformation.

In conclusion, 1,2,3-triazoles were identified as unique ligands for iron-mediated catalysis. The challenging catalytic dehydration of propargyl alcohols to conjugated enynes was successfully achieved. The fact that 1,2,3-triazoles were the only heterocycles "working" among the tested ligands illustrated their ability in adjusting iron cation reactivity, thereby providing the foundation for further development of new iron-catalyzed transformations.

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Supporting Information Available. Experimental details, spectrographic data, and X-ray crystal structures and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.