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Transformation of Alkynes into Chiral Alcohols via TfOH-Catalyzed Hydration and Ru-Catalyzed Tandem Asymmetric Hydrogenation

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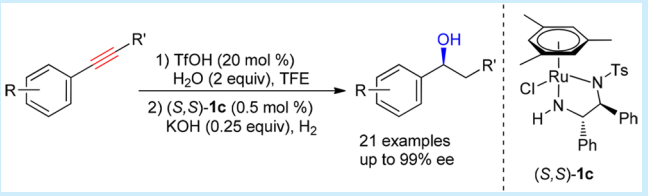
Supporting Information

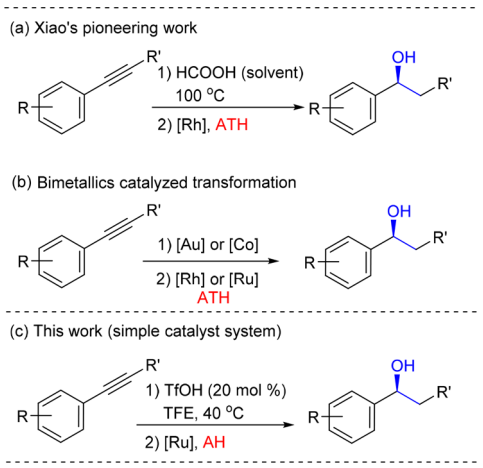
ABSTRACT: A novel full atom-economic process for the transformation of alkynes into chiral alcohols by TfOH-catalyzed hydration coupled with Ru-catalyzed tandem asymmetric hydrogenation in TFE under simple conditions has been developed. A range of chiral alcohols was obtained with broad functional group tolerance, good yields, and excellent stereoselectivities.



The transformation of alkynes is of great importance in organic synthesis, because of the wide availability of alkynyl substrates, as well as the fundamental importance of the functionalized compounds. Much effort has been devoted to the conversion of alkynes into carbonyl compounds through hydration.[1−4] Alkynes can also be converted to alcohols by hydroboration reactions[5] or hydration/reduction processes.[6] However, the one-pot direct transformation of alkynes into alcohols via hydration/reduction is challenging, because of the incompatibility of the catalysts and reaction conditions of the two steps. So far, examples of direct transformation of alkynes into alcohols are very rare.[6−11] In 2013, Xiao and co-workers reported the first enantioselective transformation of alkynes into chiral alcohols by formic acid-mediated hydration coupled with Rh-catalyzed asymmetric transfer hydrogenation (ATH).[7] However, the hydration step needs an excess amount of formic acid as solvent and high temperature (100 °C), and the second ATH reaction must adjust the pH to 7 by adding a large amount of NaOH. Subsequently, several examples about the synthesis of chiral alcohols via one-pot sequential hydration−ATH reactions from alkynes catalyzed by the combination of bimetallic complexes, such as [(IPr)AuX]/Ru-TsDPEN (X = NTf_2 or BF_4),[8] [(IPr)AuCl]/Rh-TsDPEN,[9] Co-Salen/Ru-TsDPEN,[10] and Co-Porphyrin/Rh-TsDPEN[11] have also been reported. Despite these advances, to develop a novel process with a simple catalyst system and mild reaction conditions for the alkyne-to-chiral alcohol transformation is highly desirable, from both a practical standpoint and an environmental point of view.

The chiral η^6-arene/*N*-tosylethylenediamine-Ru(II) chloride complexes were famous catalysts for ATH developed by Noyori.[12] Interestingly, the cationic chiral Ru(II) diamine catalysts, prepared by cleavage of the Ru−Cl bond with base and adding CF_3SO_3H (TfOH), can also be used for asymmetric hydrogenation (AH).[13] The cationic chiral Ru(II) diamine triflate ion pairs have been proved to be ideal AH catalysts for ketones[14] and heteroaromatics.[15] Very recently, Li's group reported a metal-free Markovnikov-type alkyne hydration, using TfOH as the catalyst and 2,2,2-trifluoroethanol (TFE) as the solvent under mild conditions.[4] Notably, the reaction conditions (20 mol % TfOH, 2 equiv H_2O, 1 mL TFE, 25 °C) are not only simple but also compatible with the cationic chiral Ru(II) diamine triflate-catalyzed AH of ketones. In addition, it was reported that the stereoselectivities can be enhanced in asymmetric synthesis using fluorinated solvents.[16] Therefore, we reason that the alkynes could be converted to chiral alcohols via sequential hydration−AH catalyzed by the combination of TfOH and cationic chiral Ru(II) diamine triflate in TFE (see Scheme 1).

Scheme 1. Comparison of Previous Work and This Work



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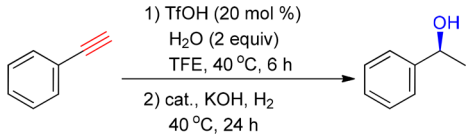
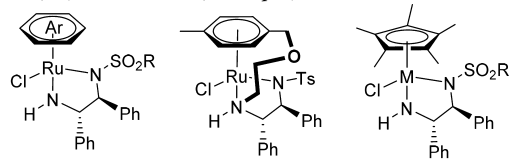
To test our hypothesis, phenylacetylene was selected as the model substrate. The hydration reaction was conducted with 20 mol % TfOH as the catalyst and 1 mL of TFE as the solvent in the presence of 2 equiv of H_2O.[4] It was found that the phenylacetylene could be converted to acetophenone completely at 40 °C for 6 h, as monitored by gas chromatography (GC).[17] Then, 0.5 equiv of KOH and 1 mol % (*S*,*S*)-**1a** were added to the reaction tube, which was put into a stainless steel autoclave. The AH was conducted at 40 °C under 40 atm of hydrogen for 24 h, affording the desired (*S*)-1-phenylethanol in 30% yield and 63% enantiometric excess (ee) (Table 1, entry 1). Then, AH catalysts, such as chiral diamine ruthenium complexes **1a**–**1d**, rhodium complex **1e**, and iridium complex **1f**, were screened. It was found that (*S*,*S*)-**1c** is the best one, giving 97% yield and 98% ee (see entries 2–6 in Table 1). If the amount of KOH was reduced to 0.25 equiv, there is no effect on the results (entry 7 in Table 1). However, the hydrogenation step did not occur when no more than 0.20 equiv of KOH was added (see entries 8 and 9 in Table 1).[18] In addition, the desired alcohol was not detected in the absence of hydrogen gas, indicating that the reductive step is AH rather than ATH (entry 10 in Table 1). The enantioselectivity was insensitive to the H_2 pressure, but the yield decreased apparently with 10 atm of hydrogen (entries 11 and 12 in Table 1). Next, the hexafluoro-2-propanol (HFIP) as the twin of TFE could also give the desired product but in relatively lower yield and ee (entry 13 in Table 1). Finally, high yield and excellent ee remained even if the catalyst loading was reduced to 0.5 mol % (entry 14 in Table 1).

To expand the scope of this novel sequential hydration–AH process, a range of alkynes with different functional groups were investigated, and the results have been summarized in Table 2. All the tested alkynes could be converted to the corresponding chiral alcohols with high yields and excellent ee values. As for the phenylacetylene derivatives bearing electron-withdrawing groups such as F (**2b**–**2d**), Cl (**2e** and **2f**), and Br (**2g** and **2h**), a higher temperature (70 °C) and longer time (12 h) were required for the hydration step. By contrast, in the case of electron-deficient 4-nitrophenylacetylene (**2i**), HFIP was used as a solvent instead of TFE, because of its poor solubility, and the hydration step was conducted at 70 °C for 48 h. The electron-rich phenylacetylene derivatives **2j**–**2m** gave the corresponding alcohols **3j**–**3m** in 82%–87% yield and 97%–99% ee under standard conditions. In addition, 2-ethynylnaphthalene(**2n**) could also be converted to (*S*)-1-naphthylethanol (**3n**) in 90% yield and 93% ee under standard conditions. Notably, this novel procedure was also applicable to internal arylalkynes. For example, the internal arylalkynes **2o**–**2r** were transformed to the corresponding alcohols **3o**–**3r** in

Table 1. Optimization of the Reaction Conditions[a]

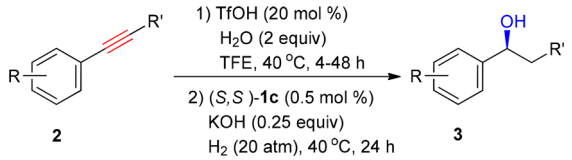


entry	cat.	additive	H_2, atm	yield (%)	ee (%)
1	(*S*,*S*)-**1a**	KOH (0.5 equiv)	40	30	63
2	(*S*,*S*)-**1b**	KOH (0.5 equiv)	40	35	91
3	(*S*,*S*)-**1c**	KOH (0.5 equiv)	40	97	98
4	(*S*,*S*)-**1d**	KOH (0.5 equiv)	40	85	89
5	(*S*,*S*)-**1e**	KOH (0.5 equiv)	40	46	80
6	(*S*,*S*)-**1f**	KOH (0.5 equiv)	40	57	61
7	(*S*,*S*)-**1c**	KOH (0.25 equiv)	40	96	98
8	(*S*,*S*)-**1c**	KOH (0.20 equiv)	40	0	0
9	(*S*,*S*)-**1c**		40	0	0
10[b]	(*S*,*S*)-**1c**	KOH (0.25 equiv)	40	0	0
11	(*S*,*S*)-**1c**	KOH (0.25 equiv)	20	97	99
12	(*S*,*S*)-**1c**	KOH (0.25 equiv)	10	52	99
13[c]	(*S*,*S*)-**1c**	KOH (0.25 equiv)	2	63	90
14[d]	(*S*,*S*)-**1c**	KOH (0.25 equiv)	20	96	99



[a]Reaction conditions: phenylacetylene (0.5 mmol), TfOH (20 mol %), H_2O (2 equiv), TFE (1 mL), 40 °C, 1 mol % catalyst, the yields were determined by GC with an internal standard (mesitylene), the ee values were determined by HPLC analysis. [b]In the absence of hydrogen gas. [c]Hexafluoro-2-propanol (HFIP) was used as a solvent. [d]0.5 mol % (*S*,*S*)-**1c** was used.

Table 2. Substrate Scope for the Transformation of Alkynes into Chiral Alcohols[a]



entry	substrate	product	yield (%)	ee (%)
1	**2a**: R = H, R′ = H	**3a**	96	99
2[b]	**2b**: R = 2-F, R′ = H	**3b**	90	93
3[b]	**2c**: R = 3-F, R′ = H	**3c**	81	99
4[b]	**2d**: R = 4-F, R′ = H	**3d**	96	95
5[b]	**2e**: R = 4-Cl, R′ = H	**3e**	94	91
6[b]	**2f**: R = 2, 5-Cl, R′ = H	**3f**	79	87
7[b]	**2g**: R = 3-Br, R′ = H	**3g**	82	95
8[b]	**2h**: R = 4-Br, R′ = H	**3h**	89	97
9[c]	**2i**: R = 4-NO_2, R′ = H	**3i**	62	81
10	**2j**: R = 4-Me, R′ = H	**3j**	85	99
11	**2k**: R = 4-Et, R′ = H	**3k**	82	99
12	**2l**: R = 4-*n*-Pr, R′ = H	**3l**	83	97
13	**2m**: R = 4-MeO, R′ = H	**3m**	87	97
14	**2n**: 2-ethynylnaphthalene	**3n**	90	93
15[d]	**2o**: R = H, R′ = Me	**3o**	79	99
16[d]	**2p**: R = H, R′ = Et	**3p**	72	93
17[d]	**2q**: R = H, R′ = *n*-Bu	**3q**	75	94
18[d]	**2r**: R = H, R′ = Ph	**3r**	83	97

[a]Standard reaction conditions: alkyne (0.5 mmol), TfOH (20 mol %), H_2O (2 equiv), TFE (1 mL), 40 °C, 6 h, then add 0.5 mol % (*S*,*S*)-**1c**, KOH (0.25 equiv), H_2 (20 atm), 40 °C, 24 h; isolated yield; the ee values were determined by HPLC analysis. Please refer to the Supporting Information for the details of each substrate. [b]Conditions were 70 °C and 12 h for the hydration step. [c]HFIP was used as a solvent. Conditions were 70 °C and 48 h for hydration step. [d]Conditions were 40 °C and 48 h for hydration step.

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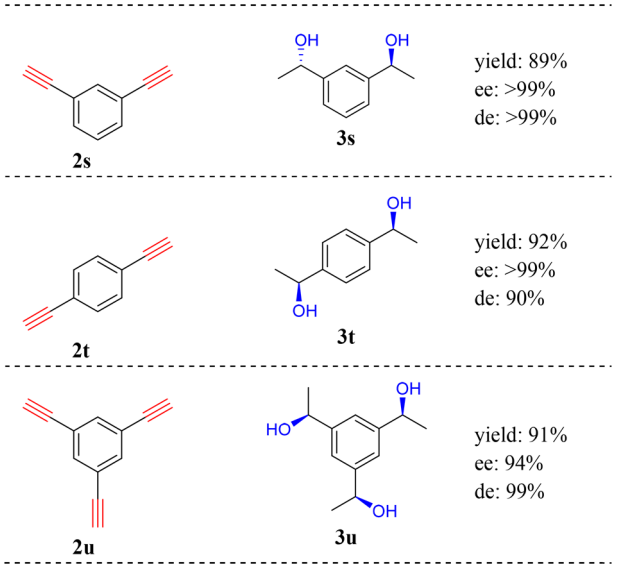
72%−83% yield and 92%−99% ee. Furthermore, other alkynes including 2-ethynylpyridine, 3-ethynylpyridine, methyl propiolate, and propargylic alcohol were also attempted. Unfortunately, this protocol is not applicable to these alkynes.

Most importantly, this novel hydration−AH process was also applicable to multiethynylbenzenes. As shown in Scheme 2, the

Scheme 2. Conversion of Multiethynylbenzenes to Chiral Alcohols[a]

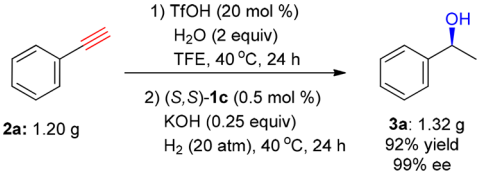


[a]Reaction conditions: alkyne (0.5 mmol), TfOH (40 or 60 mol %), H_2O (4 or 6 equiv), TFE (1 mL), 70 °C, 48 h, 1 mol % (*S*,*S*)-**1c**, KOH (0.45 or 0.65 equiv), H_2 (40 atm), 40 °C, 24 h; isolated yield; the ee values were determined by HPLC analysis.

transformation of 1,3-diethynylbenzene (**2s**), 1,4-diethynylbenzene (**2t**), and 1,3,5-triethynylbenzene (**2u**) into the corresponding chiral diols (**3s**, **3t**) and chiral triols (**3u**) was achieved successfully for the first time with 89%−92% yield, 94%−99% ee, and 90%−99% diastereomeric excess (de).

As shown in Scheme 3, to further examine the potential practical application of this sequential process, a gram-scale

Scheme 3. Gram-Scale Reaction



reaction of phenylacetylene (**2a**, 1.2 g) was conducted. The desired (*S*)-1-phenylethanol (**3a**) was isolated in 92% yield (1.32 g) and 99% ee.

In summary, we have developed a novel process for the direct transformation of alkynes into chiral alcohols via sequential hydration−AH with the combination of TfOH and chiral Ru(II) diamine triflate in TFE under mild conditions. Notably, it was the first time multiethynylbenzenes were directly converted to chiral diols and triols. Moreover, the gram-scale reaction further demonstrates the practical potential of this method.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00034.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(17) Based on Li's procedure in ref 4, the reaction conditions were improved by enhancing the temperature and shortening the time. Please refer to the Supporting Information for the details of each substrate.
(18) According to refs 12−14, the AH of ketones with prepared chiral ruthenium(II) diamine triflate as a catalyst was operated under neutral or slightly acidic conditions. However, in this sequential procedure, 0.2 equiv of base was required to convert TfOH into triflate. In addition, the cleavage of the Ru−Cl bond to prepare cationic chiral Ru(II) diamine catalyst in situ need base. Practically, an excess of base was necessary due to the solubility and dissociation equilibrium of KOH in TFE.

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