Asymmetric Catalysis

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Catalytic Asymmetric Dihydroxylation of Enamides and Application to the Total Synthesis of (+)-Tanikolide**

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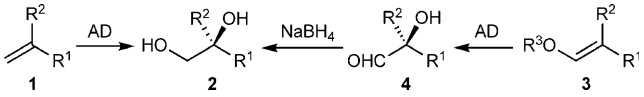
Asymmetric transformations of 1,1-disubstituted alkenes provide important building blocks for chemical synthesis, but are often plagued with low stereoselectivities because it can be difficult for a chiral reagent or catalyst to discriminate between the enantiotopic faces of these substrates.[1] Among the available methods, asymmetric dihydroxylation (AD) stands out as one of the more successful, and can provide high enantioselectivities in certain cases (Scheme 1, **1**→**2**).[2,3] However, low enantioselectivities are usually observed when the two alkene substituents are of similar steric demand.[4,5]

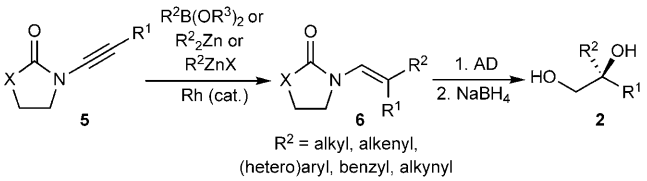


Scheme 1. Asymmetric dihydroxylation (AD) routes to tertiary-alcohol-containing terminal 1,2-diols **2**.

A possible solution to this problem is to employ β,β′-disubstituted enol derivatives **3** as the substrates, where discrimination of the enantiotopic faces is expected to be more straightforward (Scheme 1, **3**→**2**). An additional benefit of this approach is that asymmetric dihydroxylation results in chiral α-hydroxyaldehydes **4**, which are themselves valuable compounds, and which can be reduced to 1,2-diols **2** if required. To ensure high enantioselectivity in the dihydroxylation event, the substrate **3** must be obtained in high stereoisomeric purity.[6] Unfortunately, existing methods to prepare these compounds typically proceed with poor *E*/*Z* stereoselectivity,[7–9] and the resulting geometric isomers can be difficult to separate.

Partial solutions to these problems have been described recently.[10] Ready and co-workers have developed stereocontrolled syntheses of β,β′-disubstituted enol esters and enol silanes involving carbocupration[10a] or carboalumination[10b] of terminal alkynes, oxidation of the resulting alkenylmetal species using a metal *tert*-butyl peroxide, and trapping of the resulting enolate with an acylating or silylating agent.[10] Furthermore, asymmetric dihydroxylation of enol benzoates containing methyl substitution on the alkene was demonstrated.[10b] Nevertheless, improvements with these approaches can be envisaged. In the carbocupration procedure,[10a,11] the organocopper reagents are generated from organolithium or Grignard reagents, which pose restrictions on the functional groups that may be present in the organometallic reagent. Although functionalized organocopper reagents may be obtained from the corresponding organozinc halides, these reagents are poorly reactive towards unactivated terminal alkynes.[12] In addition, because only alkylcopper reagents exhibit sufficient reactivity in alkyne carbocupration, the introduction of important groups such as (hetero)aryl substituents is usually not possible. In the carboalumination procedure,[10b,13] only methyl groups can be transferred. Therefore, full exploration of asymmetric dihydroxylation of enol derivatives **3** to access chiral α-hydroxyaldehydes **4** and diols **2** is compromised by these limitations.

Our research group has recently developed rhodium-catalyzed carbometalation reactions that offer solutions to many of these drawbacks.[14] Instead of providing enol derivatives **3**, these reactions furnish β,β′-disubstituted enamides **6**[15] from the corresponding ynamides **5**[16] (Scheme 2). Collectively, these processes enable the introduction of alkyl,



Scheme 2. Asymmetric dihydroxylation of enamides prepared by rhodium-catalyzed carbometalation of ynamides.

alkenyl, aryl, heteroaryl, benzyl, and alkynyl groups, and the presence of sensitive functional groups such as esters[14a–c] and ketones[14c] on the organometallic reagent is permitted. Accordingly, asymmetric dihydroxylation of enamides **6** should provide access to a much wider range of chiral products than is possible using comparable methods.[10b] To our knowledge, there are only limited reports of Sharpless asymmetric dihydroxylation of enamides, where cyclic substrates were oxidized with modest ($\leq$77% *ee*) enantioselectivities.[17] Herein, we report highly enantioselective dihy-

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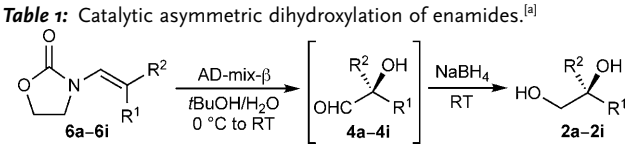
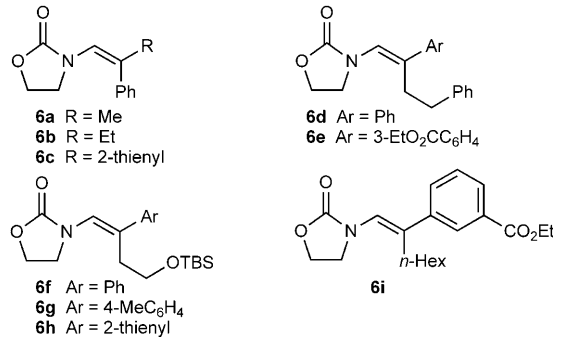
droxylations of β,β′-disubstituted enamides, and the application of this method in the total synthesis of (+)-tanikolide.[18]

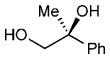
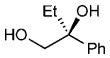
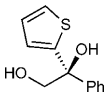
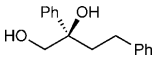
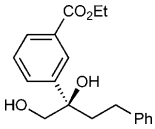
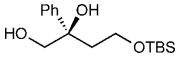
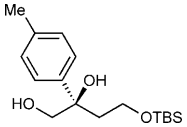
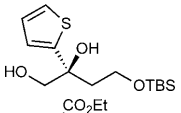
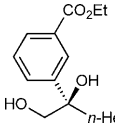
The enamide employed in the initial part of this study are shown in Table 1, and were prepared according to one of the rhodium-catalyzed ynamide carbometalation procedures we have described recently.[14] The enamides **6a**, **6b**, and **6d**–**6g** have been reported previously,[14] whereas enamides **6c**, **6h**, and **6i** are new compounds.[19] Highly enantioselective dihydroxylation of these substrates was readily accomplished using commercially available AD-mix-β without the addition of $MeSO_2NH_2$.[3] After dihydroxylation was complete, addition of $NaBH_4$ to the reaction mixture resulted in formation of the 1,2-diols **2**. The sense of enantiofacial selectivity by AD-mix-β in these reactions is consistent with the Sharpless mnemonic.[3] Enamides **6a**–**6c** containing a phenyl substituent at the R^1 position were effective substrates, with a 2-thienyl group at R^2 (entry 3) providing a higher enantioselectivity than a methyl (entry 1) or an ethyl group (entry 2). Enamides **6d**–**6i** containing aliphatic groups (simple alkyl, oxygenated alkyl) at R^1 and (hetero)aryl groups (phenyl, *p*-tolyl, 3-carboethoxyphenyl, 2-thienyl) at R^2 proved to be especially competent substrates, providing products in generally good yields with uniformly high enantioselectivities (entries 4–9). Comparison of the present method with asymmetric dihydroxylation of 1,1-disubstituted alkenes is informative. While diol **2a** was obtained from enamide **6a** with slightly lower enantioselectivity (90% *ee*; entry 1) and as the opposite enantiomer compared with asymmetric dihydroxylation of α-methylstyrene under comparable reaction conditions (−94% *ee*),[2c] the present method afforded diol **2b** with improved selectivity (87% *ee*; entry 2) compared with that obtained from the corresponding 1,1-disubstituted alkene (−78% *ee*).[2c] Interestingly, diol **2d** was obtained favoring the *R* enantiomer from both enamide **6d** and alkene **1d**, but the enantioselectivity was far superior in the case of the enamide (95% *ee*; entry 4) compared with the alkene [41% *ee*; Eq. (1)].

Table 1: Catalytic asymmetric dihydroxylation of enamides.[a]

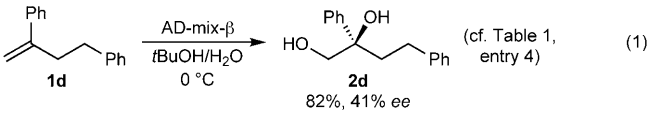


Enamides



Entry	Enamide	Product		Yield [%][b]	*ee* [%][c]
1	**6a**		**2a**	72	90 (−94)[d]
2	**6b**		**2b**	84	87 (−78)[d]
3	**6c**		**2c**	61	94
4	**6d**		**2d**	68	95
5	**6e**		**2e**	70	97
6	**6f**		**2f**	83	97
7	**6g**		**2g**	82	97
8	**6h**		**2h**	86	94
9	**6i**		**2i**	68	96

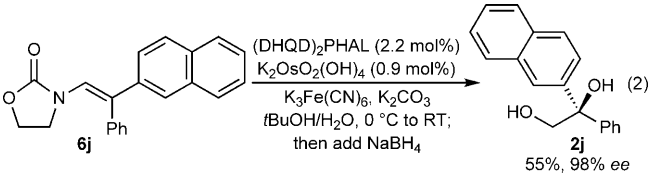
[a] Reactions were conducted using **6a**–**6i** (0.20 mmol) and AD-mix-β (280 mg; 0.4 mol% of Os and 1 mol% of $(DHQD)_2PHAL$) in *t*BuOH (2 mL) and H_2O (1 mL) for 7–24 hours, and subsequent addition of $NaBH_4$ (6 equiv) and stirring for an additional 1 hour. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Values in parentheses refer to *ee* values obtained from asymmetric dihydroxylation of the corresponding 1,1-disubstituted alkene using the same chiral ligand $(DHQD)_2PHAL$ that is present in AD-mix-β, see Ref. [2c]. TBS = *tert*-butyldimethylsilyl.



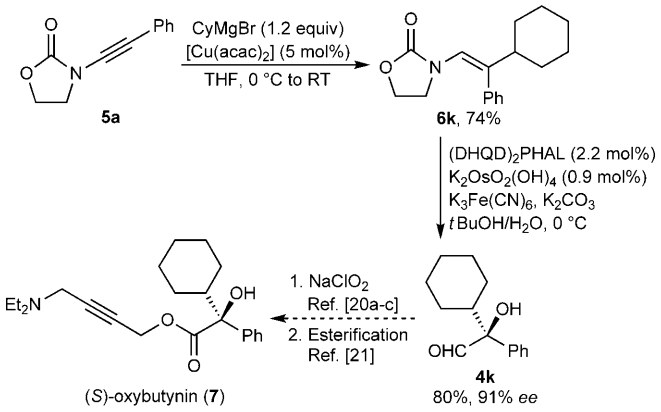
(1)

The reaction of β,β′-diarylenamide **6j**[19] with AD-mix-β was sluggish and did not proceed to completion, but dihydroxylation using increased loadings of $K_2OsO_2(OH)_4$ and the chiral ligand $(DHQD)_2PHAL$ (hydroquinidine 1,4-phthalazinediyl diether), which is present in AD-mix-β, gave improved results and afforded diol **2j** in 98% *ee* [Eq. (2)].

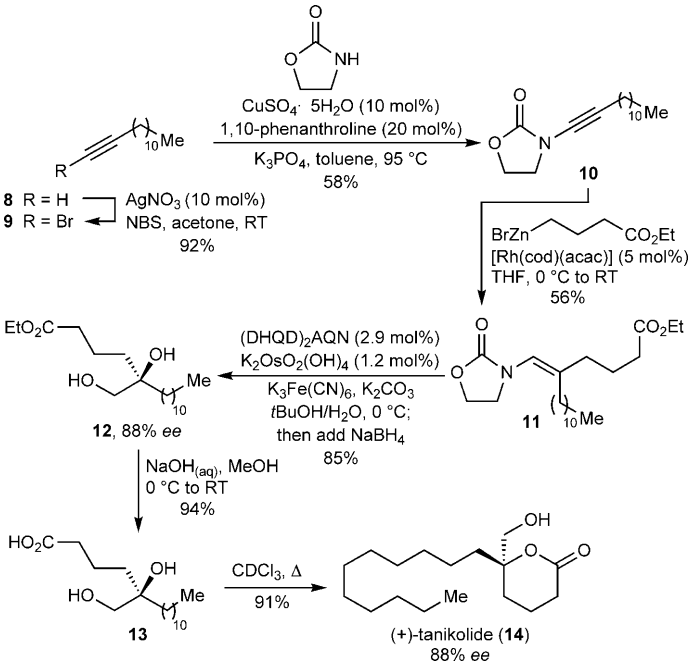
Scheme 3 illustrates application of this method to the concise preparation of α-hydroxyaldehyde **4k**, a known intermediate in the synthesis of (*S*)-oxybutynin (**7**),[20,21] which is widely used in the treatment for urinary problems.[22] In this case, rhodium-catalyzed carbozincation of ynamide **5a**



(2)



Scheme 3. Synthesis of α-hydroxyaldehyde **4k**, a precursor to (*S*)-oxybutynin (**7**). THF = tetrahydrofuran.



Scheme 4. Total synthesis of (+)-tanikolide (**14**). cod = cycloocta-l,5-diene, NBS = *N*-bromosuccinimide.

with Cy_2Zn (prepared from CyMgBr and $ZnCl_2$; Cy = cyclohexyl) according to our reported method[14a,b] did provide enamide **6k**, but in low yield owing to the formation of (*Z*)-3-(2-styryl)oxazolidin-2-one as a major side product resulting from undesired hydrozincation.[14b] However, improved results were obtained from copper-catalyzed carbomagnesiation of **5a** using CyMgBr and [Cu(acac)$_2$] (acac = acetylacetonate), which provided **6k** in 74% yield.[23] In similar fashion to **6j** [Eq. (2)], asymmetric dihydroxylation of **6k** with AD-mix-β was sluggish, but dihydroxylation using increased loadings of $K_2OsO_2(OH)_4$ and $(DHQD)_2PHAL$ afforded α-hydroxyaldehyde **4k** in 80% yield and 91% *ee*. It should be noted that dihydroxylation of α-cyclohexylstyrene using $(DHQD)_2PHAL$ provides the corresponding diol as the opposite *R* enantiomer in only 57% *ee*[2c,24]—once again illustrating that use of β,β′-disubstituted enamides in place of 1,1-disubstituted alkenes can prove advantageous in asymmetric dihydroxylation reactions.

As a further exemplification of asymmetric enamide dihydroxylation, we applied this method to a concise total synthesis of the antifungal natural product (+)-tanikolide (**14**).[18,25] First, bromoalkyne **9** was prepared from commercially available tridecyne **8** using NBS/$AgNO_3$ (Scheme 4).[26] By using the method of Hsung and co-workers,[27] copper-catalyzed coupling of **9** with oxazolidin-2-one then afforded ynamide **10**. Rhodium-catalyzed carbozincation of **10** using commercially available 4-ethoxy-4-oxobutylzinc bromide[14a,b] proceeded smoothly and provided enamide **11** in 56% yield. Unfortunately, dihydroxylation of **11** using AD-mix-β was poorly selective, and after reduction of the initially formed aldehyde with $NaBH_4$, diol **12** was produced in 58% *ee*. However, use of $(DHQD)_2AQN$ (hydroquinidine anthraquinone-1,4-diyl diether)[28] as the chiral ligand in place of $(DHQD)_2PHAL$ led to **12** being obtained in a much improved 88% *ee*.[29] Basic hydrolysis of **12**, and subsequently heating the resulting acid **13** in $CDCl_3$ at reflux led to smooth lactonization and provided (+)-tanikolide (**14**). Overall, the route to (+)-tanikolide (**14**) presented in Scheme 4 is competitive with previous syntheses.[25]

In summary, the asymmetric dihydroxylation of β,β′-disubstituted enamides has been described. By drawing upon the diversity of β,β′-disubstituted enamide derivatives available using recently reported rhodium-catalyzed ynamide carbometalation protocols,[14] and offering often superior enantioselectivity compared with asymmetric dihydroxylation of the corresponding 1,1-disubstituted alkenes, this strategy serves as a versatile method for the preparation of important 1,2-dioxygenated compounds. Many of these tertiary-alcohol-containing building blocks **2** and **4** would be difficult to access efficiently using alternative methods. Application of this process to the concise syntheses of the natural product (+)-tanikolide (**14**) and α-hydroxyaldehyde **4k**, an intermediate en route to (*S*)-oxybutynin (**7**), has been demonstrated.

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Keywords: asymmetric catalysis · dihydroxylation · enamides · total synthesis · ynamides

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