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Asymmetric dihydroxylation of heteroaromatic acrylates

Zhi-Xiang Feng and Wei-Shan Zhou*

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

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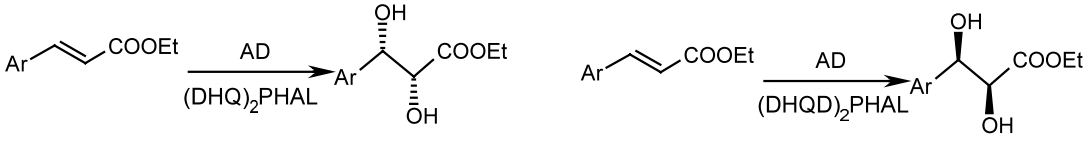
Abstract—*N*- and *O*-Heteroaromatic acrylates were dihydroxylated with high ee's and good yields. While the AD of pyridyl and pyrryl acrylates afforded diverse yields under the present reaction condition, some corresponding *N*-substituted pyridyl and pyrryl acrylates (**1d**, **1e**, **1g**) proved to be appropriate substrates. The diols obtained can be used as chiral building blocks for the synthesis of various biologically active molecules.

The important application of optically active α-hydroxyfuryl and α-hydroxypyrryl derivatives is that they can be converted into the dihydropyranone derivatives via oxidation[1] with *m*CPBA, NBS, TBHP or by kinetic resolution methods.[2] Furthermore, α-hydroxyfuryl compounds can be converted to be α-aminofurfuryls[3] which can be easily transformed into the dihydropyridone derivatives by the similar methods as mentioned above.[4] Both dihydropyranone and dihydropyridone derivatives are very useful for the synthesis of various biologically active compounds such as piperidine alkaloids,[5] polyhydroxy indolizidine alkaloids,[6] styryl lactones[7]and steroids.[8] Meanwhile, pyridyl-substituted diols are a class of potentially valuable versatile building blocks for the synthesis of polyhydroxy indolizidine alkaloids.[9]

Our laboratory has prepared chiral α-hydroxyfuryl[7a] and α-hydroxypyrryl[1d] derivatives using kinetic resolution. However, we have not found in the literature examples of successful asymmetric dihydroxylation (AD) of heteroaromatic acrylates such as furyl, pyrryl and pyridyl acrylates for preparing corresponding chiral diols which can be also regarded as a type of α-hydroxyheteroaromatic derivatives, although recently ADs of other different vinyl furan derivatives[3c,10] and thiophene acrylates have been reported.[11]

Herein we report our first application of AD to the furyl acrylates as well as pyridyl and pyrryl acrylates, to give chiral building blocks (Scheme 1).[12]

The acrylates **1a**–**g** were readily synthesized by Wittig–Horner reactions from the corresponding aldehydes and **1f** can be also prepared by Heck reaction[13] from 2-chloropyridine. Initially, like Bonini's groups results,[11] we found that when all substrates were subjected to the standard AD condition (1 mol% of the ligand), they reacted very slowly at room temperature. So we increased the amount of the ligand from 3 to 10 mol% and found that more ligand accelerates the reaction but different yields under the conditions of 3 and 10 mol% of the ligands were the same after 24 h. Therefore, we chose to perform the AD reaction with 3 mol% of the ligand. The AD of **1a** proceeded smoothly in 73 and 75% yields based on 55 and 60% conversions at 25°C



Ar= furyl, 5-methylfur-2-yl, pyrrol-2-yl, *N*-tosylpyrrol-2-yl, *N*-benzylpyrrol-2-yl, pyridin-2-yl and *N*-oxide of pyridin-2-yl.

Scheme 1.

Keywords: asymmetric dihydroxylation; heteroaromatic acrylates; building blocks.

* Corresonding author. Tel.: 86-21-64163300; fax: 86-21-64166128; e-mail: zhws@pub.sioc.ac.cn

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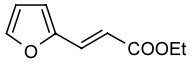
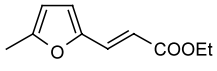
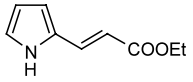
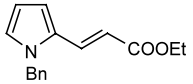
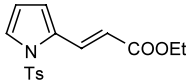
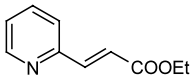
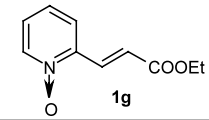
with >99% ee's (entries 1 and 2). However, when increasing the electron density in the furan moiety by inclusion of a methyl substituent, the AD occurred with lower enantioselectivity (entry 4, 90% ee). The reactions of **1a** and **1b** were carried out at room temperature for only 12 h, since after that period, many by-products appeared due to the decomposition of furyl ring. Occasionally, we found that the ee changed slightly if 3 mol% $(DHQD)_2PHAL$ was added to the reaction mixture of **1a** containing 3 mol% $(DHQ)_2PHAL$ after 1 h (entries 1 and 3), which revealed that osmium almost fully coordinated with $(DHQ)_2PHAL$ after 1 h and $(DHQD)_2PHAL$ rarely substituted $(DHQ)_2PHAL$ from the complex. This observation provided the evidence for the mechanism of AD:[14] the second catalytic cycle was inhibited under the reaction conditions, so that high ee's (96.0 and 99.2%) were obtained. Pyrrole derivative **1c** proved to be a problematic substrate (entries 5 and 6), most likely due to the coordination of the nitrogen atom with osmium and the sensitivity of the pyrrole ring to oxidation. The yield from **1c** was very low and the product was unstable. However, unlike their asymmetric aminohydroxylation (AA),[15] *N*-tosyl and *N*-benzyl protected pyrrole acrylates **1d** and **1e** proved to be excellent substrates for the AD and the reaction time could be prolonged to 24 h because of the stability of protected pyrrole ring to oxidation, resulting in full conversion, good yields, and high ee's (entries 7–10, 89–95% isolated yields of diols, >98% ee's).

To explore new concise routes to synthesize biologically active polyhydroxyindolizidine alkaloid lentiginosine[16] and its analogs, we hope to employ the pyridyl-substituted diol derivatives as the key building blocks. Based on this idea, we made efforts to extend the AD to pyridyl acrylate **1f**. Unfortunately, the AD proceeded sluggishly and only 18–20% yields were obtained with substantial recovery of the starting material (entries 11 and 12), a result similar to that of the AA of

Table 1. Asymmetric dihydroxylation of heteroaromatic acrylates[a]

entry	substrate	ligand	t(h)	Yield[c] (%)	ee[d] (%)
1	 **1a**	$(DHQ)_2PHAL$	12	75	99.2
2		$(DHQD)_2PHAL$	12	78	99.9
3		$(DHQ)_2PHAL$+ $(DHQD)_2PHAL$[b]	12	74	96.0
4	 **1b**	$(DHQ)_2PHAL$	12	70	90.1
5	 **1c**	$(DHQ)_2PHAL$	12	15	
6		$(DHQD)_2PHAL$	12	13	
7	 **1d**	$(DHQ)_2PHAL$	24	89	99.0
8		$(DHQD)_2PHAL$	24	93	98.8
9	 **1e**	$(DHQ)_2PHAL$	24	91	99.3
10		$(DHQD)_2PHAL$	24	95	98.9
11	 **1f**	$(DHQ)_2PHAL$	24	20	
12		$(DHQD)_2PHAL$	24	18	
13	 **1g**	$(DHQ)_2PHAL$	24	80	100
14		$(DHQD)_2PHAL$	24	75	99.8

[a]General conditions: 0.4 mol% $K_2[OsO_2(OH)_4]$,3 mol% $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$, 3 equiv. of $K_3[Fe(CN)_6]$, 3 equiv. of K_2CO_3 and 1 equiv. $MeSO_2NH_2$ in $H_2O/^tBuOH$ (1:1). [b]$(DHQD)_2PHAL$ was added after 1h. [c]Based on their conversions of 55%, 60%, 57%, 50%, 53% and 52% for entries 1, 2, 3, 4, 13 and 14 respectively. [d]Determined by HPLC on Chiralcel column, OD for entries 1-4 based on their conversions into the dibenzoates, AD for entries 7-10, OB-H for entries 13 and 14.

2-vinylpyridine reported previously.[17] More ligand proved to be profitable for the AD of electron deficient olefins,[11] but increasing 10 mol% of the ligand did not improve the yield. A reasonable explanation is that the nitrogen atom on the pyridine ring interferes with the catalytic cycle by chelating with osmium. Therefore, we turned to a pyridine derivative in which the nitrogen functionality is blocked in order not to interfere with the catalytic cycle. We chose the *N*-oxide **1g**, which can be easily obtained from **1f** by oxidation with *m*CPBA.[15b] Indeed, this derivative readily underwent AD, giving rise to the *N*-oxide of pyridyl-substituted diols with good yields and excellent enantioselectivities (entries 13 and 14, 75% and 80% yields based on 52 and 53% conversions, >99% ee's). The derivatives obtained were particularly favorable for the synthesis of polyhydroxyindolizidine alkaloid lentiginosine and its analogs, the accompanying paper describes the total synthesis of lentiginosine.[18]

In conclusion, the furyl acrylates as well as the *N*-protected pyridyl and pyrryl acrylates could be asymmetrically dihydroxylated with good yields and high enantioselectivities, but *N*-exposed pyridyl and pyrryl acrylates afforded very low yields in the present reaction conditions. The corresponding chiral diol derivatives give very useful access to the synthesis of various biologically active compounds.

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