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First controlled asymmetric dihydroxylation of thiophene acrylates

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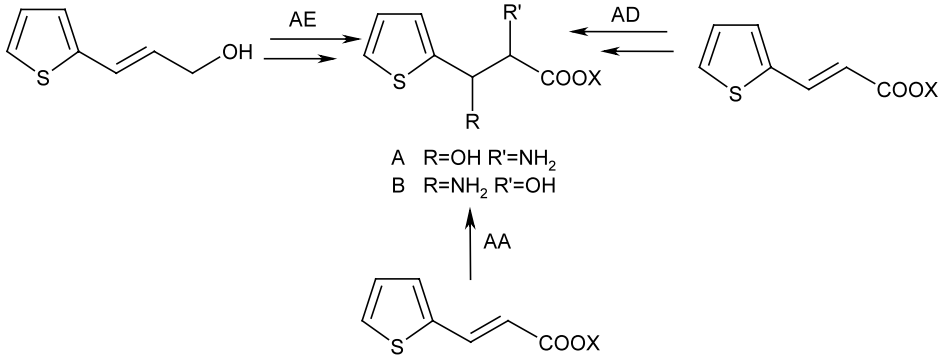
Abstract—The AD of thiophene acrylates afforded the corresponding diols with high ees and good overall yields. The low reactivity of the olefins has been enhanced with the use of a modified AD-mix formulation, by adding up to 2 mol% of the chiral catalyst, without effect on the reactive thiophene ring.

We have been recently involved in the preparation of different amino dihydroxyethylene dipeptide isostere subunits[1,2] which are present in many biologically active compounds and in synthetic new HIV-protease inhibitors.[3] Since it is well known that the thiophene ring mimics the phenyl ring of phenylalanine very well,[4] and none of the drugs in use as HIV-protease inhibitors possess any group different from benzyl derived from phenylalanine, we have started a project to synthesizing different isosteres in new peptidomimetic structures, having thiophene key residues of type A and B (see Scheme 1).

These key synthons A and B could be prepared using the Sharpless asymmetric oxidative methodologies of the appropriate olefins: (1) the direct asymmetric aminohydroxylation (AA),[5] which has been already employed[6] affording mainly type B synthon with excellent ee but varying overall yields after 24 h. (2) The asymmetric dihydroxylation (AD)[7] followed by known manipulation of the chiral diols to both A and B. (3) The asymmetric epoxidation of allylic alcohol (AE)[8] followed by appropriate epoxide ring opening.[8b]

Oxidative methodologies on olefins conjugated with a thiophene ring are rarely employed because of the lower reactivity of electron deficient olefins and of the fact that the thiophene ring is prone to react in the usual reaction conditions. Therefore, not unexpectedly, we have not found in the literature examples of successful olefin asymmetric epoxidation and dihydroxylation of thiophene derivatives, although recently AD of different vinyl furan derivatives has been successfully performed[9] as the AA of different heterocycles derivatives.[6]

Therefore we were intrigued by the possibility to first perform the AD and the AE on suitable thiophene



Scheme 1.

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acrylates, for the preparation of useful synthetic compounds.

The standard thiophene acrylates **1**, **2** and **3** (see Table 1) were chosen as differently substituted olefins to be tested for our experiments.

All three substrates, when subjected to the standard AD mix-α reaction conditions[7b] reacted very slowly, affording only traces of diol after 24 h at 0°C, with substantial recovery of the starting material. Also, increasing the reaction temperature only accelerates decomposition of the aromatic ring for compounds **1** and **2**, while compound **3** remains unaffected.

The low reactivity of the substrates in the standard AD conditions appeared in contrast to the fair reactivity of thiophene acrylates under the standard reaction conditions of the related AA.[6] This low reactivity could be surpassed either by enhancing the olefin electron density or by promoting a ligand acceleration effect on the reaction conditions.

Since, as demonstrated in the AA of thiophene acrylates,[6] the presence of an electron donating group on the aromatic ring led to the decomposition of the substrate, we choose to add more ligand to the reaction, that was already demonstrated to be beneficial for electron deficient olefins.[10] It is noteworthy that, in our case (see Table 1), we only increased the ligand twofold (up to 2 mol%), instead of the fivefold increase of both ligand and oxidant reported in other cases.[10]

As shown in Table 1, this modification was crucial to obtaining substantial encouraging results.

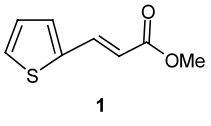
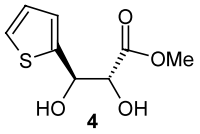
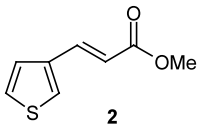
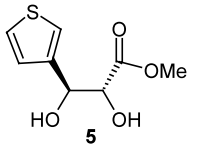
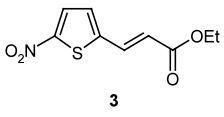
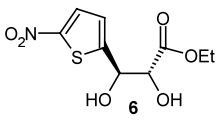
In fact all the substrates **1**–**3** exhibited a superior reactivity compared not only to the previously performed AD on compounds **1**–**3**, but also in comparison with the AA of related thiophene acrylates.[6] On the basis of the results shown in Table 1, the following remarks can be made. Compound **1** was the most reactive, although the reaction has been carried out at 0°C and for only 6 h, since after that considerable by-products appeared due to the decomposition of the thiophene ring; however, the isolated yield (49%) and the ee (>99%) of the final diol **4** represent a major achievement on this unprecedented substrate **1**.

Also, the other two substrates **2** and **3** were found quite reactive under the AD reaction conditions, although they required a longer reaction time to afford the corresponding diols in excellent ees (>99%) and even superior overall isolated yields (59% for diol **5** and 60% for diol **6**). The longer reaction time for both **2** and **3** revealed, however, a lower reactivity of the thiophene ring to the oxidative procedure. Interestingly, the olefin electron poor compound **3** is still an excellent substrate for the AD and the reaction could be prolonged because of the low reactivity of the thiophene ring due to the presence of stabilising nitro group.

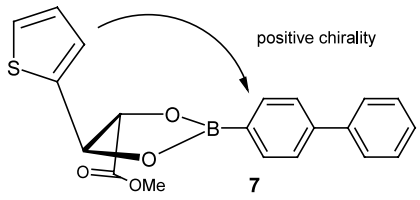
The mnemonic device protocol easily predicts the absolute configuration of the obtained diols, as depicted in Table 1. However, we applied a newly developed methodology[11] for the assignment of 1,2-diol absolute configuration of compound **4**.

To this end the biphenylboronic derivative **7** (Fig. 1), easily obtained from **4**, was studied in UV and circular dichroism in THF (see Fig. 2).

Table 1. Asymmetric dihydroxylation of thiophene acrylates[a]

Substrates	Temp (°C)	Time (h)	Diols (2*R*,3*R*)	Yield[b] (%)	Ee[c] (%)
 **1**	0	6	 **4**	49	99
 **2**	20	18	 **5**	59	99
 **3**	20	48	 **6**	60	99

[a] AD reagent: $K_3Fe(CN)_6$, K_2CO_3, $K_2OsOs_2(OH)_4$ (0.2 mol%), BuOH–H_2O (1:1), $(DHQ)_2$-PHAL (2 mol%).
[b] Yields are referred to the isolated compounds after column chromatography.
[c] Ee determined by HPLC on Chiralcel column, OJ for **4** and **5**, OB for compound **6**.



7

Figure 1. 4-Biphenylboronate **7** derived from methyl-3(2-thiophen), 2,3-diol propionate with 2*R*,3*R* absolute configuration.

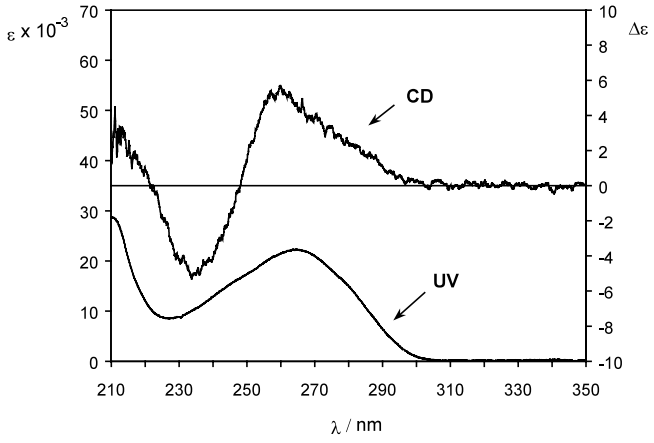


Figure 2. Absorption (UV) and circular dichroism (CD spectra) of compound **7** in THF in the 210–350 nm range.

The positive Cotton effect and the negative curve clearly account for an (*R*,*R*) absolute configuration, in accordance with the empirical rule derived by the AD mnemonic device.

In conclusion, apparently fair substrates for the AD reaction, as thiophene acrylates, were allowed to react under mild conditions with the use of a modified AD-mix formulation (up to 2 mol% of chiral catalyst), thus affording useful pure chiral synthons. The utilization of these synthons for successive elaboration to naturally and synthetic biologically active compounds is currently under investigation.

Acknowledgements

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