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Synthesis of cyclic allyl vinyl ethers using Pt(II)-catalyzed isomerization of oxo-alkynes

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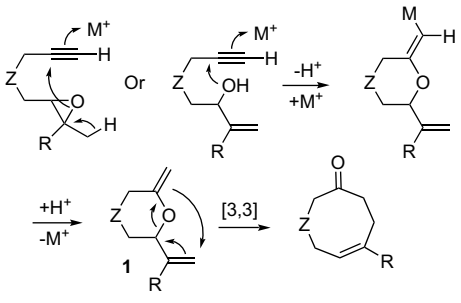
ABSTRACT

Several alkynyl epoxides and one alkynyl allyl alcohol were isomerized to cyclic allyl vinyl ethers (3,4-dihydro-2*H*-1,4-oxazines) using $PtCl_2$ as the catalyst. Three of these allyl vinyl ethers were converted to 2-hydroxymorpholine derivatives by hydrolysis and two were converted to piperidine derivatives by thermal Claisen rearrangement.

1. Introduction

Allyl vinyl ethers are stable compounds, but under thermal conditions, they undergo [3,3] sigmatropic shifts (Claisen rearrangements) to form carbon–carbon bonds in the absence of any catalysts and reagents. Due to these features, in organic synthesis they are valuable intermediates for the construction of highly functionalized molecules.[1] Allyl vinyl ethers are usually synthesized via oxygen alkylation of enolates by an allyl electrophile such as allyl tosylates. Because enolate alkylations are performed under strongly basic conditions, they sometimes limit the application of Claisen rearrangements.

In recent years, some late transition metal salts such as Au(I), Pd(II), and Pt(II) halides have been found capable of acting as soft Lewis acids to activate alkynes toward nucleophilic attack.[2] The nucleophiles can be alkenes, azides, amines, alcohols, carbonyls, furans, arenes, and stabilized carbonanions. When the nucleophile is an alcohol, the product is a vinyl ether.[3] Because such reactions are usually performed under acidic conditions, we envisioned that they could be used to form allyl vinyl ethers under conditions complementary to the widely used basic conditions. Specifically, when the nucleophile is an epoxide, the vinyl carbocation formed by the alkyne and a soft Lewis acid would coordinate with the lone pair of the oxygen and open the epoxide to form a more stable cationic intermediate, which eliminates a proton to form the allyl vinyl ether **1** (Scheme 1). Alternatively, an allyl alcohol can be used as the nucleophile, which attacks the vinyl cation and forms the same type of products (**1**). The resulting allyl vinyl ethers were expected to undergo [3,3] shift to form eight-membered cyclic products. In this paper, we wish to report our results on the investigation of $PtCl_2$-catalyzed isomerization of alkynyl epoxides and an alkynyl allyl alcohol, and the [3,3] sigmatropic shift of the resulting cyclic allyl vinyl ethers.



Z = NTs, O, $C(CO_2Et)_2$, $C(SO_2Ph)_2$

Scheme 1. Proposed methods for allyl vinyl ether formation and their [3,3] sigmatropic shift.

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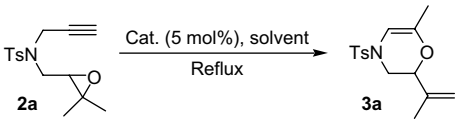
Table 1
Optimization of reaction conditions for Pt(II)-catalyzed isomerization of alkynyl epoxides[a]



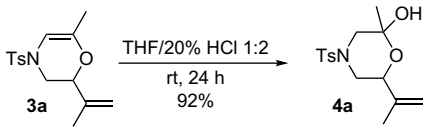
Entry	Catalyst	Solvent	Time	Yield[b]
1	Ph_3PAuCl[c]	$ClCH_2CH_2Cl$	24 h	50%
2	$PtCl_2$	$ClCH_2CH_2Cl$	24 h	40%
3	$PtCl_2$	PhMe	24 h	62%
4	$PtCl_2$	PhH	12 h	60%
5	$PtCl_4$	PhMe	24 h	62%
6	$PtCl_2$	1,4-Dioxane	24 h	30%

[a] Reactions were performed under nitrogen using distilled solvents.
[b] Isolated yields.
[c] $AgSbF_6$ (5 mol %) was added.

2. Results and discussion

2.1. Isomerization of alkynyl epoxides

To probe the feasibility of this approach for allyl vinyl ether formation, we prepared the alkynyl epoxide **2a** by oxidation of the corresponding enyne (see Supplementary data for details).[4] Compound **2a** was subjected to various isomerization conditions. When AuCl, Ph_3PAuCl (with $AgSbF_6$), and $PtCl_2$ were used as catalyst, at rt in solvents such as benzene, toluene, and CH_2Cl_2, the starting material remained unchanged even after a long reaction time. We then performed the reactions at a higher temperature. As shown in Table 1, when $Ph_3PAuCl/AgSbF_6$ was used as the catalyst, in 1,2-dichloroethane at reflux, **2a** was consumed in 24 h. However, TLC indicated that a complex mixture was formed. With careful purification by repeated flash column chromatography, one pure compound was obtained in 50% yield (entry 1). Its structure was proposed to be **3a** through 1D and 2D NMR analysis. Attempts to characterize other compounds in the mixture were unsuccessful. We then used $PtCl_2$ as the catalyst; in the same solvent, after 24 h at reflux, **3a** was obtained in 40% yield (entry 2). Although the yield was lower, the reaction was much cleaner than when $Ph_3PAuCl/AgSbF_6$ was used. In order to reduce the reaction time and to increase the yield, we changed the solvent to toluene, which has a higher boiling point than DCE. Under similar conditions, the reaction was complete in 24 h and **3a** was obtained in 62% yield (entry 3). Changing the solvent to benzene and changing the catalyst to $PtCl_4$ gave similar results (entries 4 and 5). When the more coordinating 1,4-dioxane was used as the solvent, the yield was lowered significantly (30%, entry 6). Other coordinating solvents such as THF and CH_3CN gave yields of **3a** lower than 10%. The non-coordinating solvent CH_2Cl_2 also gave unsatisfactory results; no conversion was observed in 24 h probably due to its low boiling point (not shown in Table 1). We also tested the reaction in the presence of additives such as Et_3N, $(F_3CC{=}O)_2O$, and F_3CSO_3H; when $PtCl_2$ was used as the catalyst and benzene as the solvent, at reflux temperature, complex mixtures were formed. It was reported that 1,5-hexadiene could break apart the polymer formed by $PtCl_2$ and increase its catalytic activity;[5] however, we found little effect of the diene on this isomerization reaction.



Scheme 2. Hydrolysis of **3a**.

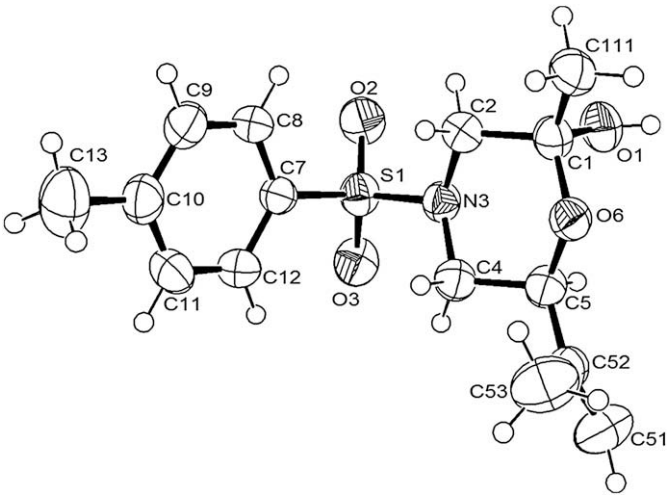


Figure 1. X-ray determined single crystal structure of **4a**.

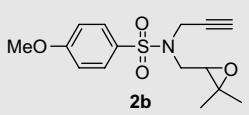
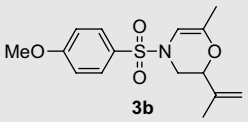
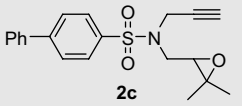
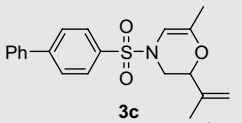
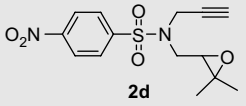
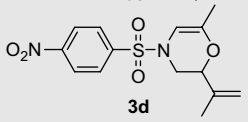
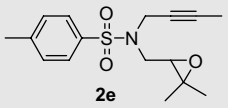
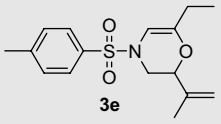
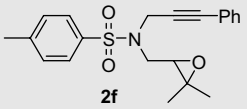
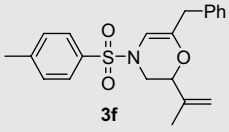
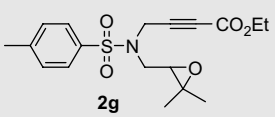
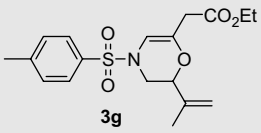
The structure of allyl vinyl ether **3a** differed from the expected **1**. In order to confirm the structure by X-ray analysis, we obtained crystals as colorless thick long needles by slow evaporating of acetone from its solution in a mixture of acetone and hexane. Unfortunately, the crystal melted under X-ray diffraction conditions. Compound **3a** was then converted to the cyclic hemiacetal **4a** by hydrolysis (Scheme 2). The structure of **4a** was proposed by NMR studies and confirmed by single crystal X-ray diffraction analysis (Fig. 1).

Although the isomerization gave an unexpected product, the reaction was interesting and a different allyl vinyl ether was formed, which could still undergo a [3,3] shift.[6] In addition, the new compound contains a 1,4-morpholin core, which is found in many bioactive compounds.[7] Furthermore, the products from hydrolysis and [3,3] shift of **3a** are highly functionalized and may also find biomedical applications.[8] Based on these considerations, we decided to investigate the scope of the reaction.

Among the reaction conditions studied (Table 1) and considering the ease of product purification and yield, the one shown in entry 3 was chosen for substrate scope study. When the methyl group of the tolyl moiety of the substrate was changed to a methoxy group (**2b**), a similar yield of the allyl vinyl ether (**3b**) was obtained (Table 2, entry 1). With phenyl (**2c**) and nitro groups (**2d**), the yields were lowered to 47% (**3c**) and 36% (**3d**) (entries 2 and 3), respectively. We next studied the effect of substitutions on the alkyne. Substrate **2e** with a methyl group on the alkyne was therefore subjected to isomerization. The reaction gave a more complex mixture but product **3e** could be obtained in 39% yield (entry 4). When **2f**, which has a phenyl group on the alkyne, was used, product **3f** was obtained in 22% yield (entry 5). However, with an electron withdrawing ester group on the alkyne, **2g** was isomerized to **3g** in a significantly higher yield (53%, entry 6). This result was consistent with the observation made by Furstner and co-workers; in their studies, they also found that electron deficient alkynes were easier to be activated by soft Lewis acids toward nucleophilic attack.[9]

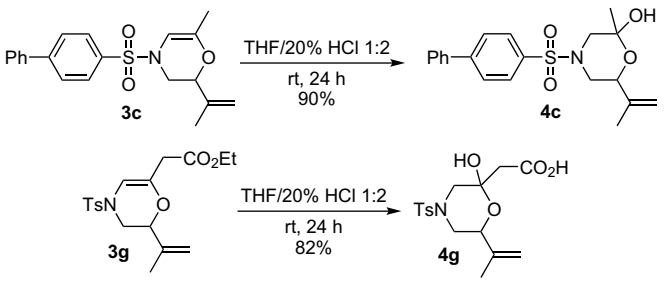
Two reaction pathways are possible for the formation of allyl vinyl ethers **3** from alkynyl epoxides **2**. Mechanism A is similar to that shown in Scheme 1; it does not involve the assistance of the sulfonamide group (Scheme 3). The epoxide attacks the vinyl cation generated from the alkyne and Pt(II) to form a more stable tertiary cation, which loses a proton to form intermediates **5**. Protonation of

Table 2
Substrate scope study of Pt(II)-catalyzed isomerization of alkynyl epoxides[a]

Entry	Substrate	Product	Yield[b]
1	 **2b**	 **3b**	53%
2	 **2c**	 **3c**	47%
3	 **2d**	 **3d**	36%
4	 **2e**	 **3e**	39%
5	 **2f**	 **3f**	22%
6	 **2g**	 **3g**	53%

[a] Reaction conditions: substrate, $PtCl_2$ 5 mol %, toluene, reflux, 24 h.
[b] Isolated yields.

the platinated carbon atom followed by isomerization of the exocyclic double bond into an endocyclic one under acidic conditions gave the allyl vinyl ether products **3**. However, because substrates **2f** and **2g** consistently form products **3f** and **3g**, which would require isomerization of a conjugated double bond to an isolated one, we believe that this is less likely. Mechanism B involves the assistance of the sulfonamide group. Pt(II) coordinates with the alknye and the sulfonamide, and isomerizes the alkyne to allene **7**. The epoxide attacks the Pt(II)-activated allene followed by elimination of a proton to give **6**, which converts to **3**. Because substrates without the sulfonamide function such as those containing an oxygen and a carbon linker between the alkyne and epoxide could not be isomerized under similar conditions, mechanism B is more likely than mechanism A.



Scheme 4. Hydrolysis of **3c** and **3g**.

2.2. Hydrolysis of allyl vinyl ether products

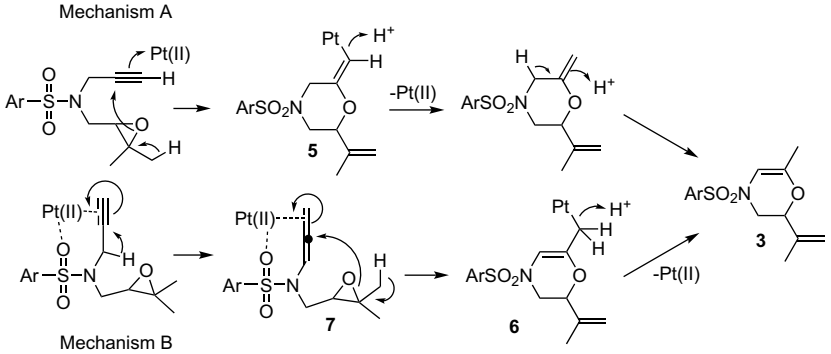
Because some bioactive compounds contain the 2-hydroxymorpholine core of the hydrolysis products of **3**,[8] we were interested to demonstrate that other cycloisomerization products besides **3a** could also be hydrolyzed. Compounds **3c** and **3g** were chosen as examples. Under the same conditions for hydrolysis of **3a**, these two compounds were converted to **4c** and **4g** in 90% and 82% isolated yields, respectively (Scheme 4).

2.3. Claisen rearrangement of allyl vinyl ether products

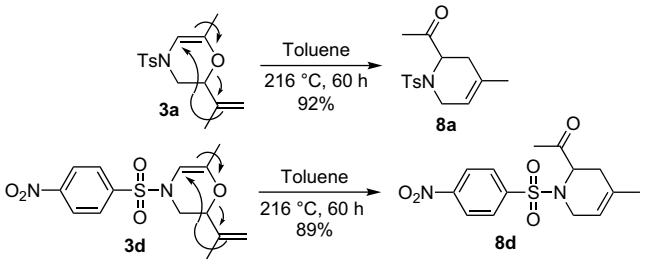
In order to demonstrate the capability of the allyl vinyl ethers to undergo [3,3] shifts, **3a** and **3d** in toluene were stirred at 216 °C in sealed tubes for 60 h; products **8a** and **8d** were formed in 92% and 89% yields, respectively (Scheme 5). The harsh conditions required for the reaction are a result of the highly constrained transition state.[6] The structures of the products were proposed by NMR studies and that of **8d** was confirmed by a single crystal X-ray diffraction analysis (Fig. 2). Interestingly, the crystal of **8d** was enantiopure as evidenced by the fact that it crystallized in the space group 19, $P2_12_12_1$.

2.4. Isomerization of an alkynyl allyl alcohol

Because the yields of the isomerization of alkynyl epoxides were not ideal in some cases, we were interested to know if an alkynyl allyl alcohol could be isomerized to the same type of products with higher efficiency. For this purpose, compound **9** was subjected to various conditions (Table 3). When distilled solvents were used, the yields were generally low (entries 1–4). The only exception was CH_2Cl_2, in which case 56% yield of **10** was obtained, but the reaction took 72 h to complete (entry 4). However, when un-distilled 1,2-dichloroethane was used, the yield was higher (compare entry 5 with 3). With water saturated 1,2-dichloroethane as the solvent, the



Scheme 3. Potential mechanisms for the formation of allyl vinyl ether from alkynyl epoxide.



Scheme 5. [3,3] Sigmatropic shift of **3a** and **3d**.

yield was improved to 71%, which represented the highest yield for preparing allyl vinyl ether using Pt(II)-catalyzed isomerization of oxo-alkynes (entry 6). Thus, it was reasonable to test if wet solvents could also improve the yields of isomerization of alkynyl epoxides. However, it has already been shown that with water such reactions gave different products[4] and therefore this was not pursued.

3. Conclusions

We have developed a method for the preparation of cyclic allyl vinyl ethers under acidic conditions. These conditions are complementary to the normally used strongly basic conditions. The resulting allyl vinyl ether products could be hydrolyzed to cyclic hemiacetals and could undergo a [3,3] sigmatropic shift to give piperidines. Studies on extending the scope of the reaction to substrates with linkers between the alkyne and the oxo function other than sulfonamide and preparing higher order allyl vinyl ethers to form medium-sized cycles are underway.

4. Experimental section

4.1. General

All reactions were performed in oven-dried glassware under a nitrogen atmosphere using standard Schlenk techniques. Reagents and solvents available from commercial sources were used as received unless otherwise noted. Toluene, benzene, and THF were distilled from Na/benzophenone ketyl. 1,2-Dichloroethane, 1,4-dioxane, CH_2Cl_2, and pyridine were distilled over CaH_2. Thin layer chromatography (TLC) was performed using Sigma–Aldrich TLC plates, silica gel 60F-254 over glass support, 0.25 μm thickness. Flash column chromatography was performed using Selecto Scientific silica gel, particle size 32–63 μm. ^1H and ^{13}C NMR spectra were measured on a Varian UNITY *INOVA* spectrometer at 400 MHz and 100 MHz, respectively; chemical shifts (δ) were reported in reference to solvent peaks (residue $CHCl_3$ at δ 7.24 ppm for ^1H and $CDCl_3$ at δ 77.00 ppm for ^{13}C; residue $CD_2HC(O)CD_3$ at δ 2.05 ppm for ^1H and $CD_3C(O)CD_3$ at δ 24.80 ppm for ^{13}C).

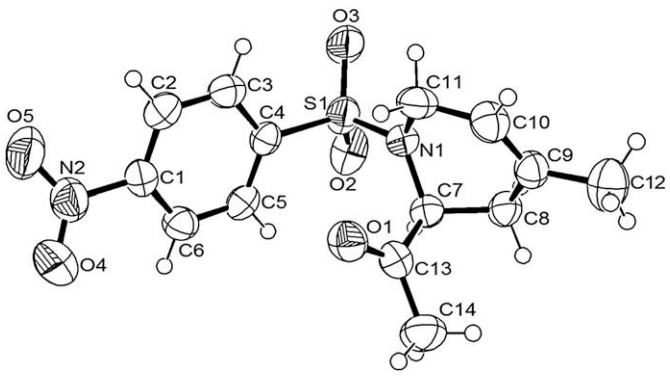
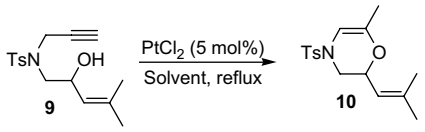


Figure 2. X-ray determined single crystal structure of **8d**.

Table 3
Optimization of reaction conditions for Pt (II)-catalyzed isomerization of alkynyl epoxides



Entry	Solvent	Time	Yield[a]
1	PhMe (distilled)	12 h	32%
2	THF (distilled)	12 h	30%
3	$ClCH_2CH_2Cl$ (distilled)	12 h	18%
4	CH_2Cl_2 (distilled)	72 h	56%
5	$ClCH_2CH_2Cl$ (un-distilled)	12 h	39%
6	$ClCH_2CH_2Cl$ (H_2O saturated)	12 h	71%

[a] Isolated yields.

4.2. 6-Methyl-2-(1-methylethenyl)-4-[(4-methylphenyl)-sulfonyl]-3,4-dihydro-2*H*-1,4-oxazine (3a)

To a round-bottomed flask charged with **2a** (1.0 g, 3.41 mmol) and $PtCl_2$ (45 mg, 0.17 mmol) was added toluene (25 ml) via syringe. The reaction mixture was heated to reflux for 24 h. Solvents were removed under reduced pressure. The residue was partitioned between water and CH_2Cl_2. The organic phase was dried over anhydrous Na_2SO_4, filtered, and solvents were removed under reduced pressure. Purification by flash column chromatography (hexanes/ether 4:1, SiO_2) gave **3a** as a white solid (615 mg, 62%): R_f=0.18 (hexanes/ether 4:1, SiO_2); mp 62–63 °C; ^1H NMR ($CDCl_3$) δ 7.63 (d, J=8.2 Hz, 2H), 7.30 (d, J=8.1 Hz, 2H), 5.82 (s, 1H), 4.90 (s, 1H), 4.85 (s, 1H), 3.79 (d, J=13.6 Hz, 1H), 3.32 (d, J=9.5 Hz, 1H), 2.80 (dd, J=13.6, 9.2 Hz, 1H), 2.40 (s, 3H), 1.74 (s, 3H), 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 143.9, 140.6, 140.5, 133.7, 129.7, 127.5, 113.3, 99.5, 74.5, 46.4, 21.5, 18.4, 17.7; HRMS (FAB) m/z calcd for $C_{15}H_{19}NO_3S$ $[M]^+$ 293.1086, found 293.1087. The compound was crystallized as colorless needles by slow evaporation of acetone from its solution in a mixture of acetone and hexane. X-ray diffraction studies at rt failed due to the low melting point of the crystal. As shown in Table 1, other conditions were also used to convert **2a** to **3a**. The procedures were the same as described above. The only differences were using different catalysts, solvents, and reaction times.

4.3. 6-Methyl-2-(1-methylethenyl)-4-[(4-methoxylphenyl)-sulfonyl]-3,4-dihydro-2*H*-1,4-oxazine (3b)

Following the procedure for the synthesis of **3a**, **2b** (1.5 g, 4.85 mmol) and $PtCl_2$ (64.6 mg, 0.24 mmol) gave **3b** as a colorless oil (796.4 mg, 53%): R_f=0.27 (hexanes/ether 3:1, SiO_2); ^1H NMR ($CDCl_3$) δ 7.68 (d, J=9.0 Hz, 2H), 6.97 (d, J=9.0 Hz, 2H), 5.81 (s, 1H), 4.88 (d, J=15.8 Hz, 2H), 3.84 (s, 3H), 3.76 (d, J=13.4 Hz, 1H), 3.35 (d, J=9.3 Hz, 1H), 2.80 (dd, J=13.7, 9.4 Hz, 1H), 1.75 (s, 3H), 1.62 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.2, 140.7, 140.6, 129.7, 129.6, 128.3, 114.3, 113.3, 99.6, 74.5, 55.6, 46.5, 18.4, 17.7; HRMS (FAB) m/z calcd for $C_{15}H_{19}NO_4S$ $[M]^+$ 309.1035, found 309.1033.

4.4. 6-Methyl-2-(1-methylethenyl)-4-[(4-phenylphenyl)-sulfonyl]-3,4-dihydro-2*H*-1,4-oxazine (3c)

Following the procedure for the synthesis of **3a**, compound **3c** was prepared using **2c** (1.5 g, 4.23 mmol) and $PtCl_2$ (56.2 mg, 0.21 mmol). Purification by flash column chromatography (hexanes/ether 3:1, SiO_2) gave **3c** as a light yellow oil (698.4 mg, 47%):

R_f=0.28 (hexanes/ether 3:1, SiO_2); ^{1}H NMR ($CDCl_3$) δ 7.84 (d, J=9.1 Hz, 2H), 7.73 (d, J=8.4 Hz, 2H), 7.59 (d, J=7.5 Hz, 2H), 7.46 (t, J=7.2 Hz, 2H), 7.41 (t, J=7.2 Hz, 1H), 5.90 (br s, 1H), 4.91 (br s, 1H), 4.88 (br s, 1H), 3.86 (d, J=13.7 Hz, 1H), 3.43 (d, J=9.5 Hz, 1H), 2.88 (dd, J=13.8, 9.5 Hz, 1H), 1.79 (s, 3H), 1.64 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.8, 140.7, 140.4, 138.9, 135.1, 129.0, 128.5, 127.9, 127.6, 127.2, 113.4, 99.4, 74.5, 46.4, 18.3, 17.7; HRMS (FAB) m/z calcd for $C_{20}H_{21}NO_3S$ $[M]^+$ 355.1242, found 355.1244.

4.5. 6-Methyl-2-(1-methylethenyl)-4-[(4-nitrophenyl)-sulfonyl]-3,4-dihydro-2*H*-1,4-oxazine (3d)

Following the procedure for the synthesis of **3a**, compound **3d** was prepared using **2d** (2.4 g, 7.45 mmol) and $PtCl_2$ (99.2 mg, 0.37 mmol). Purification by flash column chromatography (hexanes/ether 4:1, SiO_2) gave **3d** as a light yellow oil (864.0 mg, 36%): R_f=0.17 (hexanes/ether 4:1, SiO_2); ^{1}H NMR ($CDCl_3$) δ 8.36 (d, J=8.8 Hz, 2H), 7.93 (d, J=8.9 Hz, 2H), 5.83 (s, 1H), 4.92 (br s, 1H), 4.86 (br s, 1H), 3.82 (d, J=13.5 Hz, 1H), 3.49 (d, J=8.8 Hz, 1H), 2.88 (dd, J=13.4, 9.3 Hz, 1H), 1.75 (s, 3H), 1.63 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 150.2, 142.5, 141.5, 139.9, 128.5, 124.4, 113.8, 98.6, 74.9, 46.3, 18.3, 17.7; HRMS (FAB) m/z calcd for $C_{14}H_{16}N_2O_5S$ $[M]^+$ 324.0780, found 324.0778.

4.6. 6-Ethyl-2-(1-methylethenyl)-4-[(4-methylphenyl)sulfonyl]-3,4-dihydro-2*H*-1,4-oxazine (3e)

Following the procedure for the synthesis of **3a**, compound **3e** was prepared using **2e** (1.8 g, 5.90 mmol) and $PtCl_2$ (78.0 mg, 0.30 mmol). Purification by flash column chromatography (hexanes/ether 4:1, SiO_2) gave **3e** as a light yellow oil (670.0 mg, 39%): R_f=0.23 (hexanes/ether 4:1, SiO_2); ^{1}H NMR ($CDCl_3$) δ 7.59 (d, J=7.9 Hz, 2H), 7.26 (d, J=7.9 Hz, 2H), 5.79 (s, 1H), 4.84 (s, 1H), 4.80 (s, 1H), 3.75 (d, J=13.7 Hz, 1H), 3.25 (d, J=9.3 Hz, 1H), 2.75 (dd, J=13.6, 8.9 Hz, 1H), 2.35 (s, 3H), 2.00 (q, J=7.5 Hz, 2H), 1.57 (s, 3H), 0.96 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 145.6, 143.8, 140.5, 133.5, 129.6, 127.3, 113.0, 98.6, 74.2, 46.5, 25.1, 21.4, 18.3, 11.4; HRMS (FAB) m/z calcd for $C_{16}H_{21}NO_3S$ $[M]^+$ 307.1242, found 307.1244.

4.7. 6-Benzyl-2-(1-methylethenyl)-4-[(4-methylphenyl)-sulfonyl]-3,4-dihydro-2*H*-1,4-oxazine (3f)

Following the procedure for the synthesis of **3a**, compound **3f** was prepared using **2f** (956.0 mg, 2.60 mmol) and $PtCl_2$ (34.5 mg, 0.13 mmol). Purification by flash column chromatography (hexanes/ether 4:1, SiO_2) gave **3f** as a light yellow oil (211.3 mg, 22%): R_f=0.19 (hexanes/ether 4:1, SiO_2); ^{1}H NMR ($CDCl_3$) δ 7.62 (d, J=8.6 Hz, 2H), 7.32–7.20 (m, 5H), 7.16 (d, J=8.3 Hz, 2H), 5.90 (s, 1H), 4.87 (s, 1H), 4.80 (s, 1H), 3.82 (d, J=13.3 Hz, 1H), 3.34 (s, 2H), 3.32 (d, J=9.3 Hz, 1H), 2.81 (dd, J=13.1, 9.6 Hz, 1H), 2.42 (s, 3H), 1.58 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 144.0, 143.3, 140.4, 137.5, 133.6, 129.7, 128.6, 128.3, 127.6, 126.5, 113.2, 101.2, 74.5, 46.6, 38.4, 21.5, 18.4; HRMS (ESI) m/z calcd for $C_{21}H_{24}NO_3S$ $[M+H]^+$ 370.1477, found 370.1473.

4.8. Ethyl [2-(1-methylethenyl)-4-[(4-methylphenyl)-sulfonyl]-3,4-dihydro-2*H*-1,4-oxazine-6-yl]acetate (3g)

Following the procedure for the synthesis of **3a**, compound **3g** was prepared using **2g** (2.6 g, 7.0 mmol) and $PtCl_2$ (93.5 mg, 0.35 mmol). Purification by flash column chromatography (hexanes/ether 4:1, SiO_2) gave **3g** as a light yellow oil (1.4 g, 53%): R_f=0.18 (hexanes/ether 4:1, SiO_2); ^{1}H NMR ($CDCl_3$) δ 7.64 (d, J=8.2 Hz, 2H), 7.30 (d, J=8.2 Hz, 2H), 6.02 (s, 1H), 4.88 (s, 1H), 4.83 (s, 1H), 4.09 (q, J=7.2 Hz, 2H), 3.77 (d, J=13.5 Hz, 1H), 3.34 (d, J=9.1 Hz, 1H), 3.02 (s, 2H), 2.83 (dd, J=13.5, 9.3 Hz, 1H), 2.39 (s, 3H), 1.58 (s, 3H), 1.18 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.4, 144.1, 140.1, 137.3, 133.6, 129.8, 127.6, 113.5, 103.0, 74.8, 60.8, 46.4, 38.0, 21.5, 18.3, 14.1; HRMS (FAB) m/z calcd for $C_{18}H_{23}NO_5S$ $[M]^+$ 365.1297, found 365.1300.

4.9. 2-Hydroxyl-2-methyl-6-(1-methylethenyl)-4-[(4-methylphenyl)sulfonyl]-morpholine (4a)

A solution of **3a** (246 mg, 0.84 mmol) in THF (5.0 ml) and 20% HCl (10.0 ml) was stirred vigorously. After 24 h, TLC indicated that the reaction was complete. The reaction mixture was extracted by CH_2Cl_2 for three times, the organic layers were combined, and dried over anhydrous Na_2SO_4. After filtration, solvents were evaporated under reduced pressure. Purification by flash column chromatography (hexanes/acetone 4:1, SiO_2) gave **4a** as a white solid (242 mg, 92%): R_f=0.34 (hexanes/ether 1:1, SiO_2); mp 112–113 °C; ^{1}H NMR ($CDCl_3$) δ 7.61 (d, J=8.6 Hz, 2H), 7.32 (d, J=8.6 Hz, 2H), 4.97 (s, 1H), 4.88 (s, 1H), 4.43 (d, J=10.4 Hz, 1H), 3.69 (d, J=11.5 Hz, 1H), 3.58 (dd, J=11.5, 1.8 Hz, 1H), 2.41 (s, 3H), 2.23 (d, J=11.3 Hz, 1H), 2.05 (t, J=11.3 Hz, 1H), 1.68 (s, 3H), 1.38 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 144.2, 141.6, 132.2, 129.9, 127.8, 112.9, 93.3, 71.1, 53.4, 48.9, 26.0, 21.5, 19.0; HRMS (FAB) m/z calcd for $C_{15}H_{22}NO_4S$ $[M+H]^+$ 312.1270, found 312.1271. To confirm the structure of **4a**, crystals were obtained as colorless needles by slow evaporation of hexanes into the solution of **4a** in a mixture of hexanes and acetone at rt. The structure of **4a** was then unambiguously determined by X-ray diffraction analysis (Fig. 1). The crystallographic data (excluding structure factors; CCDC no. 714713) have been deposited to the Cambridge Crystallographic Data Center. Copies of these data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033 or via e-mail: deposit@ccdc.cam.uk or via www.ccdc.cam.ac.uk/conts/retrieving.html.

4.10. 2-Hydroxyl-2-methyl-6-(1-methylethenyl)-4-[(4-phenylphenyl)sulfonyl]-morpholine (4c)

Following the procedure for the synthesis of **4a**, **3c** (202.0 mg, 0.57 mmol) was hydrolyzed in THF (5.0 ml) and 20% HCl (10.0 ml). Product **4c** was obtained as a white solid after purification by flash column chromatography (hexanes/acetone 4:1, SiO_2; 191.2 mg, 90%): R_f=0.13 (hexanes/acetone 4:1, SiO_2); mp 138–139 °C; ^{1}H NMR ($CDCl_3$) δ 7.81 (d, J=8.8 Hz, 2H), 7.74 (d, J=8.4 Hz, 2H), 7.59 (d, J=7.2 Hz, 2H), 7.46 (t, J=7.2 Hz, 2H), 7.40 (t, J=6.8 Hz, 1H), 5.00 (s, 1H), 4.90 (s, 1H), 4.49 (d, J=10.4 Hz, 1H), 3.78–3.66 (m, 3H), 2.33 (d, J=11.2 Hz, 1H), 2.15 (t, J=11.2 Hz, 1H), 1.70 (s, 3H), 1.42 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 146.1, 141.6, 138.9, 133.7, 129.0, 128.6, 128.2, 127.8, 127.2, 112.9, 93.3, 71.0, 53.3, 48.8, 26.1, 18.9; HRMS (FAB) m/z calcd for $C_{20}H_{24}NO_4S$ $[M+H]^+$ 374.1426, found 374.1428.

4.11. [2-Hydroxyl-6-(1-methylethenyl)-4-[(4-methylphenyl)-sulfonyl]-morpholine-2-yl]acetic acid (4g)

Following the procedure for the synthesis of **4a**, **3g** (326.5 mg, 0.89 mmol) was hydrolyzed in THF (5.0 ml) and 20% HCl (10.0 ml). Product **4g** was obtained as a white solid by precipitation by adding hexanes into its solution in acetone dropwise (258.9 mg, 82%): R_f=0.06 (EtOAc, SiO_2); mp 137–138 °C; ^{1}H NMR ($CD_3C(O)CD_3$) δ 7.67 (d, J=8.2 Hz, 2H), 7.44 (d, J=8.2 Hz, 2H), 4.97 (s, 1H), 4.86 (s, 1H), 4.56 (d, J=10.4 Hz, 1H), 3.82 (dd, J=11.4, 1.8 Hz, 1H), 3.67 (d, J=11.4 Hz, 1H), 2.72 (d, J=11.2 Hz, 1H), 2.66 (d, J=11.2 Hz, 1H), 2.47 (d, J=11.4 Hz, 1H), 2.43 (s, 3H), 2.11 (t, J=10.9 Hz, 1H), 1.67 (s, 3H); ^{13}C NMR ($CD_3C(O)CD_3$) δ 171.8, 144.7, 143.3, 134.0, 130.8, 128.7, 112.6, 94.2, 71.8, 52.4, 49.6, 44.0, 21.4, 18.9; HRMS (FAB) m/z calcd for $C_{16}H_{22}NSO_6$ $[M+H]^+$ 356.1168, found 356.1170.

4.12. 1-(1,2,3,6-Tetrahydro-4-methyl-1-(4-methylphenyl)-sulfonyl-2-pyridinyl)-ethanone (8a)

A solution of **3a** (160 mg, 0.6 mmol) in toluene under a nitrogen atmosphere in a sealed tube was heated to 216 °C in an oil bath for 60 h. After cooling to rt, the solvent was removed under reduced pressure. Purification of the residue by flash column chromatography (hexanes/ether 3:1, SiO_2) gave **4a** as a white solid (146 mg, 92%): R_f=0.29 (hexanes/ether 1:1, SiO_2); mp 99–101 °C; ^{1}H NMR ($CDCl_3$) δ 7.64 (d, J=8.3 Hz, 2H), 7.24 (d, J=8.1 Hz, 2H), 5.18 (br s, 1H), 4.62 (d, J=7.0 Hz, 1H), 4.05 (br d, J=16.9 Hz, 1H), 3.67 (br d, J=18.0 Hz, 1H), 2.38 (s, 3H), 2.33 (d, J=17.4 Hz, 1H), 2.19 (s, 3H), 1.98 (br d, J=20.1 Hz, 1H), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 205.8, 143.4, 136.7, 131.0, 129.5, 127.0, 116.2, 59.9, 42.3, 28.4, 26.6, 23.1, 21.4; HRMS (ESI) m/z calcd for $C_{15}H_{20}NO_3S$ $[M+H]^+$ 294.1164, found 294.1169.

4.13. 1-(1,2,3,6-Tetrahydro-4-methyl-1-(4-nitrophenyl)sulfonyl-2-pyridinyl)-ethanone (8d)

Following the procedure for the synthesis of **8a**, **8d** was prepared from **3d** (268.1 mg, 0.83 mmol). The crude product was purified by flash column chromatography (hexanes/ether 4:1, SiO_2) giving **8d** (237.9 mg, 89%) as a light yellow solid: R_f=0.16 (hexanes/ether 4:1, SiO_2); mp 152–153 °C; ^{1}H NMR ($CDCl_3$) δ 8.32 (d, J=9.0 Hz, 2H), 7.95 (d, J=8.9 Hz, 2H), 5.27 (s, 1H), 4.72 (d, J=6.9 Hz, 1H), 4.08 (d, J=17.4 Hz, 1H), 3.71 (d, J=17.1 Hz, 1H), 2.42 (d, J=17.4 Hz, 1H), 2.25 (d, J=34.2 Hz, 1H), 2.15 (s, 3H), 1.63 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 204.4, 150.0, 145.3, 130.7, 128.3, 124.2, 116.5, 60.4, 42.5, 29.8, 26.6, 23.2; HRMS (ESI) m/z calcd for $C_{14}H_{16}N_2O_5S$ $[M]^+$ 324.0780, found: 324.0776. To confirm the structure of **8d**, crystals were obtained as light yellow thick needles by slow evaporation of acetone from the solution of **8d** in a mixture of hexanes and acetone at rt. The structure of **8d** was then unambiguously determined by X-ray diffraction analysis (Fig. 2). The crystallographic data (excluding structure factors; CCDC no. 714714) have been deposited to the Cambridge Crystallographic Data Center.

4.14. 6-Methyl-2-(2-methyl-1-propen-1-yl)-4-[(4-methylphenyl)-sulfonyl]-3,4-dihydro-2*H*-1,4-oxazine (10)

Compound **9** (38 mg, 0.124 mmol), $PtCl_2$ (1.6 mg, 0.006 mmol), and CH_2ClCH_2Cl (saturated with water, 25 ml) were combined and heated to reflux for 12 h. After cooling to rt, the reaction mixture was partitioned between CH_2Cl_2 and water. The aqueous phase was extracted with CH_2Cl_2. The organic phases were combined, dried over anhydrous Na_2SO_4, filtered, and solvents were removed under reduced pressure. Purification by flash column chromatography (hexanes/ether 9:1, SiO_2) gave **10** as a light yellow oil (27 mg, 71%): R_f=0.57 (hexanes/ether 1:1, SiO_2); ^{1}H NMR ($CDCl_3$) δ 7.65 (d, J=8.4 Hz, 2H), 7.30 (d, J=8.4 Hz, 2H), 5.82 (s, 1H), 4.96 (dt, J=8.8, 1.2 Hz, 1H), 3.76 (dt, J=9.2, 2.0 Hz, 1H), 3.61 (dt, J=13.6, 1.6 Hz, 1H), 2.81 (dd, J=13.6, 9.2 Hz, 1H), 2.41 (s, 3H), 1.73 (s, 3H), 1.68 (d, J=1.2 Hz, 3H), 1.42 (d, J=1.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 144.0, 140.6, 139.5, 134.2, 130.0, 127.8, 120.4, 99.6, 69.5, 46.9, 26.0, 21.7, 18.4, 18.1. HRMS (ESI) m/z calcd for $C_{16}H_{22}NO_3S$ $[M+H]^+$ 308.1320, found 308.1325. As shown in Table 3, other conditions were also used to convert **9** to **10**. The procedures were the same as described above. The only differences were using different solvents and reaction times.

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Supplementary data

Synthesis and characterization of substrates, and ^{1}H and ^{13}C NMR spectra of all new compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.01.065.

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