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Desymmetrization of Cyclohexadienones via Asymmetric Michael Reaction Catalyzed by Cinchonine-Derived Urea

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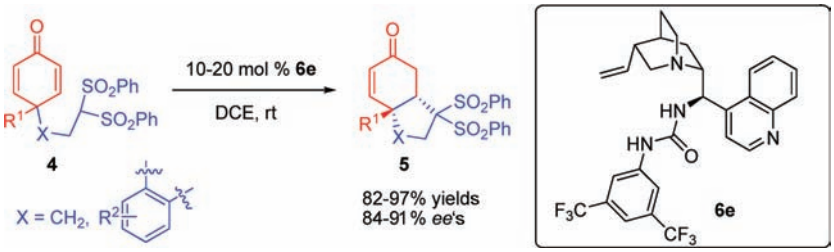
ABSTRACT



Desymmetrization of cyclohexadienones bearing a bisphenylsulfonyl methylene group via asymmetric Michael reaction catalyzed by cinchonine-derived urea was realized to afford a series of highly enantioenriched polycyclic cyclohexenones in high yields and *ee*'s.

Functionalized chiral cyclohexenones[1] are versatile building blocks that have been widely utilized in the total synthesis of natural products and found in numerous compounds that display significant biological activities.[2] For instance, the abietane type diterpenoid **1** is a novel and highly potent inhibitor of nitric oxide (NO) production in mouse macrophages[2d] (Figure 1). It has also been shown to be orally active in a preliminary *in vivo* inflammation model. Compound **2** acts as a pathway-selective or "dissociated" agonist of the glucocorticoid receptor (GR).[2e] Various methodologies have been developed toward the construction of enantioenriched cyclohexenone derivatives. These include the kinetic resolution of racemic substituted cyclohexenones by catalytic asymmetric reactions,[3] organocatalytic cascade reactions[4] and various multistep syntheses.[5] Despite extensive efforts, most of these methods only provide access to simple substituted cyclohexenones. The development of highly efficient synthesis of chiral polycyclic cyclohexenones is still in great demand.

Oxidative dearomatization of arenes offers a facile introduction of ring systems from readily available and cheap

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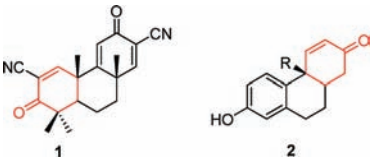

Figure 1. Representative compounds containing chiral cyclohexenones.

aromatics.[6] On the other hand, desymmetrization reaction is a very powerful methods for enantioselective synthesis of chiral molecules.[7] The combination of desymmetrization reaction with the dearomatization process provides a facile construction of optically active cyclic and polycyclic compounds from readily available starting materials. This strategy has been demonstrated successfully in asymmetric desymmetrization of cyclohexadienones providing efficient carbon−carbon bond formation methods.[8−10] For instance, Feringa et al. realized the desymmetrization of cyclohexadienone via intramolecular Heck reaction with excellent enantioselectivity using TADDOL-derived phosphoramidite ligands.[8] For cyclohexadieones bearing an aldehyde side chain, Rovis et al. elegantly developed an highly enantioselective intramolecular-type Stetter reaction with a nucleophilic carbene catalyst generated from an aminoindanol-derived triazolium salt.[9] Hayashi et al. and Gaunt et al. respectively utilized diarylprolinol silyl ether as the catalyst to achieve the intramolecular Michael reaction of cyclohexadieones bearing aldehyde side chain providing highly functionalized enantioenriched polycyclic molecules.[10] In general, the strategy combining oxidative dearomatization of phenol derivatives and subsequent desymmetrization reaction has the following advantages: (1) cheap aromatic compounds are used as starting materials; (2) more than two stereogenic centers are formed in one step; and (3) chiral quaternary carbon center is installed with high enantioselectivity.

Recently, efforts from our group demonstrated that the desymmetrization of cyclohexadienone via a chiral phosphoric acid-catalyzed oxo-Michael reaction[11] and cinchonine-derived thiourea-catalyzed aza-Michael reaction[12] could be realized to provide a series of highly enantioenriched heterocycle-fused cyclohexenone derivatives. We envisioned that carbocycle-fused cyclohexenones could also be obtained utilizing such a dearomatization/desymmetrization process in a highly efficient manner through a Michael addition reaction of active methylene side chain. As part of our ongoing program on asymmetric dearomatization reaction,[13] we recently found that the bisphenylsulfonyl methylene group bearing cyclohexadieones could be synthesized easily via the dearomatization reaction and undergo the asymmetric Michael reaction smoothly. Herein we report such a desymmetrization reaction of cyclohexadieones bearing an active methylene group via a cinchonine-derived urea-catalyzed asymmetric Michael reaction.

We began our studies by synthesizing the cyclohexadienone substrate bearing an active methylene group. The bisphenylsulfonyl methyl group was chosen given its highly enhanced acidity of the methylene proton and the facile removal ability of the phenylsulfonyl group.[14] Therefore, substrate **4a** was obtained from phenol **3a** via a $PhI(OAc)_2$-mediated oxidative dearomatization process. We then tested the intramolecular Michael reaction of **4a** with bifunctional (thio)ureas **6** as the catalysts.[15,16] With 10 mol % of (thio)ureas (**6a**−**h**) in CH_2Cl_2 at room temperature,

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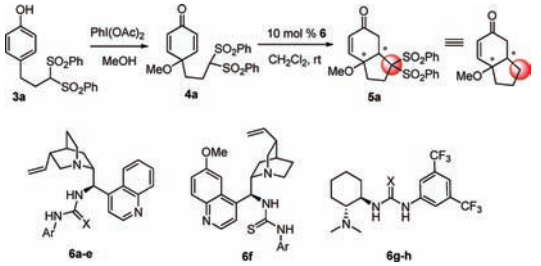
Table 1. Screening of the Catalysts[a]



entry	catalyst (Ar, X)	time (h)	yield (%)[b]	*ee* (%)[c]
1	**6a**(3,5-$(CF_3)_2C_6H_3$, S)	72	90	84
2	**6b** (C_6H_5, S)	72	12	33
3	**6c** (4-FC_6H_4, S)	72	18	58
4	**6d** (4-$CF_3C_6H_4$, S)	72	42	78
5	**6e** (3,5-$(CF_3)_2C_6H_3$, O)	72	88	86
6	**6f** (3,5-$(CF_3)_2C_6H_3$, S)	72	82	−51
7	**6g** (X = S)	72	93	81
8	**6h** (X = O)	72	92	84
9	cinchonine	72	88	35
10	quinine	72	87	−12

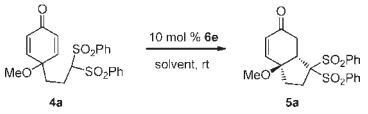
[a] Reaction conditions: 10 mol % of catalyst, 0.1 mol/L **4a** in CH_2Cl_2 at room temperature. [b] Isolated yields. [c] Determined by HPLC analysis (Chiralpak AD-H).

gratifyingly, all reactions proceeded smoothly to give the desired product **5a** with yields ranging from 12 to 93% and *ee* values ranging from 33 to 86% (Table 1, entries 1−8). Urea **6e**[17] derived from cinchonine bearing a 3,5-$(CF_3)_2$-C_6H_3 group proved to be the most efficient catalyst, affording **5a** in 88% yield and 86% *ee*. Notably, Takemoto catalysts[18] also gave the product **5a** in excellent yields and good *ee*'s (Table 1, entries 7, 8). Both cinchonine and quinine alone afforded product in good yields but low *ee*'s (88% yield, 35% *ee* and 87% yield, −12% *ee*, Table 1, entries 9, 10). These results indicate the importance of the double-hydrogen bonding mode of the thio(urea) catalysts.

With 10 mol % of urea **6e** as the catalyst, various solvents were investigated. The results are summarized in Table 2. Various solvents such as $CHCl_3$, CCl_4, toluene, and DCE led to the formation of **5a** in good yields and enantioselectivity (58−98% yields and 84−91% *ee*'s, Table 2, entries 1−6). However, reaction in THF or ether gave only trace amount of product **5a** (entries 7, 8). The addition of 4 Å MS or increasing the catalyst loading to 20 mol % did not give better results (entries 9, 10).

Under the above optimized reaction conditions (10 mol % of **6e**, DCE, rt), different substrates were carried out to test the generality of the current methodology. As summarized in Table 3, regardless of the substituent R^1 in the 4-position of cyclohexadienones, all the asymmetric Michael reaction proceeded smoothly to afford products with good enantioselectivities (85−90% *ee*'s, Table 3, entries 1−6). For substrate **4g**, the desired product was obtained in a slightly decreased yield

Table 2. Screening of Solvents[a]



entry	solvent	time (h)	yield (%)[b]	*ee* (%)[c]
1	CH_2Cl_2	72	88	86
2	$CHCl_3$	48	97	87
3	CCl_4	72	58	84
4	Toluene	48	98	85
5	Benzene	48	98	91
6	DCE	48	97	90
7	Ether	72	trace	n.d.
8	THF	72	trace	n.d.
9[d]	DCE	40	95	79
10[e]	DCE	30	96	90

[a] Reaction conditions: 10 mol % of **6e**, 0.1 mol/L **4a** in solvent at room temperature. [b] Isolated yields. [c] Determined by HPLC analysis (Chiralpak AD-H). [d] 4 Å MS was added. [e] 20 mol % of **6e**.

(68%) but with excellent *ee* (93%) after 14 days under the above reaction conditions. After further optimizing the reaction conditions including catalyst loading and substrate concentration, the Michael adduct **5g** was

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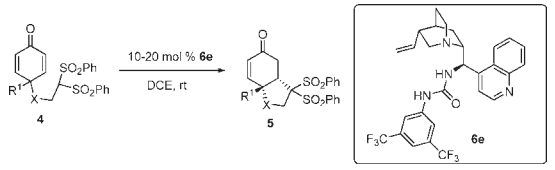
Table 3. Asymmetric Intramolecular Michael Reaction[a]

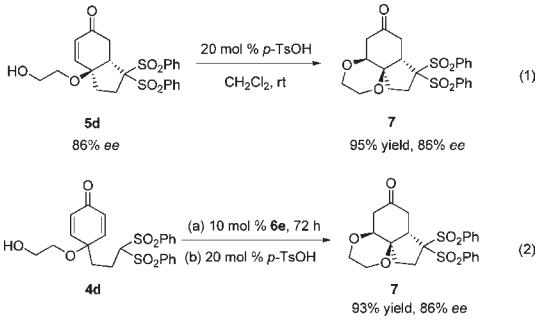


entry	products	R^1, R^2	time (h)	yield (%)[b]	*ee* (%)[c]
1		R^1 = OMe (**5a**)	48	97	90
2		R^1 = OH (**5b**)	48	85	85
3		R^1 = OEt (**5c**)	48	97	90
4	condition A	R^1=O(CH$_2$)$_2$OH (**5d**)	48	92	86
5		R^1=O(CH$_2$)$_3$OH (**5e**)	48	83	87
6		R^1 = OAc (**5f**)	48	94	85
7		R^1 = OMe, R^2 = H (**5g**)	72	95	91
8		R^1 = OH, R^2 = H (**5h**)	48	96	84
9		R^1 = OMe, R^2 = F (**5i**)	96	82	90
10	condition B	R^1 = OMe, R^2 = Cl (**5j**)	48	89	88

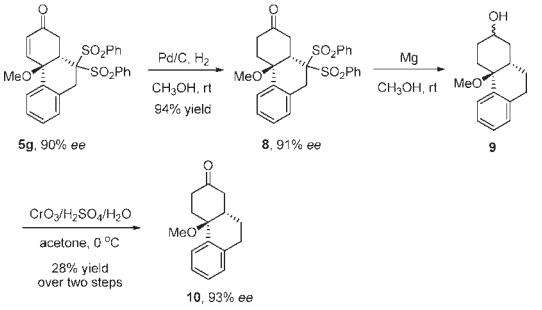
[a] Condition A: 10 mol % of **6e**, 0.1 mol/L **4a**–**f** in DCE, rt; condition B: 20 mol % of **6e**, 0.3 mol/L **4g**–**j** in DCE, rt. [b] Isolated yields. [c] Determined by HPLC analysis (Chiralpak AD-H).

obtained in 95% yield and 91% *ee* in 72 h when the reaction was carried with 20 mol % of **6e** in DCE (0.3 mol/L). These reaction conditions could tolerate various substrates **4** bearing different aromatic groups at 4-position (82–96% yields, 84–91% *ee*'s, entries 7–10). To determine the absolute configuration of the product, the crystal structure of enantiopure **5g** was obtained, and a single crystal X-ray analysis determined its configuration as (4aS,10aS).[19]

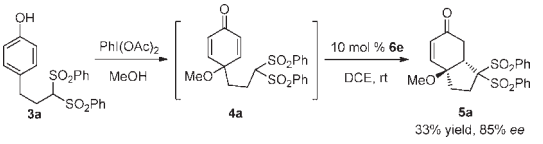
Several transformations of the multifunctionalized products obtained here have been demonstrated. Product **5d** bearing a hydroxyl group could undergo oxo-Michael addition in the presence of catalytic amount of *p*-TsOH affording a spiro-tricyclic compound **7** (eq 1). Interestingly, it could also be obtained in a one-pot process including the Michael and oxo-Michael reaction in 93% yield and 86% *ee* (eq 2). As shown in Scheme 1, hydrogenation of **5g** afforded ketone **8** in 94% yield. Subjecting ketone **8** to activated magnesium in methanol for the reductive removal of the phenylsulfonyl groups, followed by Jones oxidation led to ketone **10** in 28% yield over two steps. In all cases, the products were obtained without loss of the enantiomeric purity. The one-pot dearomatization/desymmetrization process was also explored for the synthesis of **5a**. As shown in Scheme 2, after the dearomatization reaction (PhI(OAc)$_2$ in MeOH), the solvent was removed and then the residue was treated with 10 mol % **6e** in DCE. The product **5a** was obtained in a 33% overall yield and 85% *ee*.



Scheme 1. Transformation of the Michael Adduct



Scheme 2. One-pot Dearomatization/Desymmetrization Process



In summary, we have developed a cinchonine-derived urea-catalyzed desymmetrization of cyclohexadienones bearing active methylene groups via an asymmetric Michael reaction, affording highly enantioenriched cyclohexenone derivatives in good to excellent yields and *ee*'s. The products obtained here could be subjected to versatile transformations.

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Supporting Information Available. Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) CCDC 835391 contains the supplementary crystallographic data for (*S*)-**5g**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.