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Organocatalyzed Asymmetric 1,6-Conjugate Addition of *para*-Quinone Methides with Dicyanoolefins

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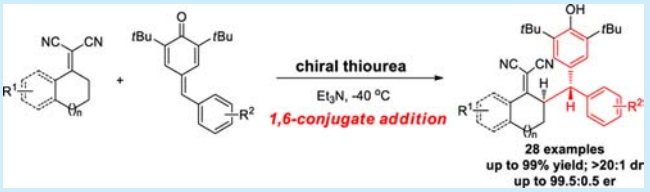
Supporting Information

ABSTRACT: A chiral thiourea catalyzed asymmetric 1,6-conjugate addition of *para*-quinone methides with dicyanoolefins has been developed. The reaction provided an efficient approach to the synthesis of chiral diarylmethine skeletons in good yields (up to 99% yield) with high diastereo- and enantioselectivity (>20:1 dr and up to 99.5:0.5 er), also on a gram scale. The preliminary mechanistic study showed that the remote stereocontrol was achieved through intermolecular hydrogen-bond interaction between the chiral thiourea catalyst and the *para*-quinone methides directly for the first time.



Diarylmethine stereogenic centers are important substructures found in pharmaceuticals and natural products,[1] such as (*R*)-tolterodine,[1a] COP-840,[1b] (−)-*Schisandra* lignan,[1c] and (−)-kadangustin J[1c] (Figure 1). The development of promising strategies for enantioselective synthesis of compounds with a diarylmethine stereogenic center from simple starting materials has attracted considerable attention in the past decades.[2] The asymmetric 1,6-conjugate addition of *para*-quinone methides (*p*-QMs)[3] provided an effective way to achieve the skeleton. In 2013, Fan's group reported chiral quaternary ammonium salt-catalyzed asymmetric 1,6-conjugate addition of *p*-QMs with malonates (Scheme 1a).[4] In 2014, Jørgensen's group realized chiral secondary amine catalyzed asymmetric 1,6-conjugate addition of *p*-QMs with aldehydes through enamine catalytic mode (Scheme 1b).[5] In 2015, Liao's group reported a copper-catalyzed 1,6-conjugate addition of *p*-QMs with $B_2(pin)_2$, achieving chiral dibenzylic boronates (Scheme 1c).[6] In aforementioned works, the selectivity was obtained from catalytically generated chiral nucleophiles rather than the activation of the *p*-QMs directly. The stereoselectivity induced by the activation of *p*-QMs directly is challenging,

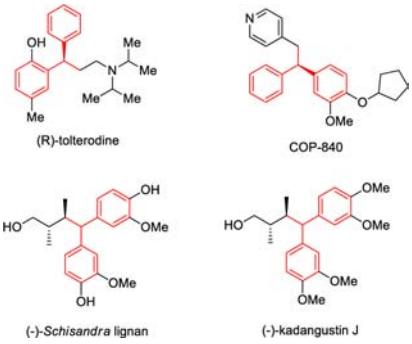
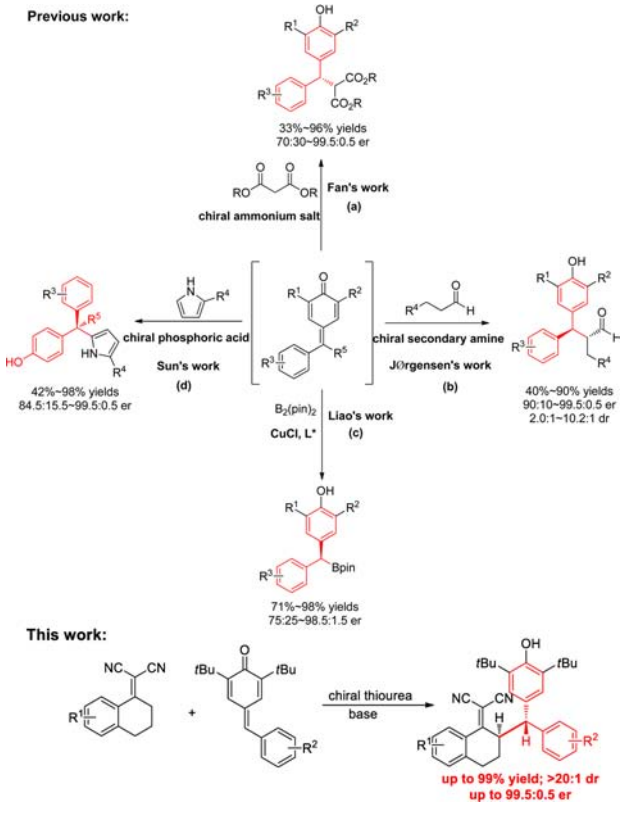


Figure 1. Selected bioactive compounds containing a chiral diarylmethine stereogenic center.

Scheme 1. Asymmetric 1,6-Conjugate Addition of *p*-QMs



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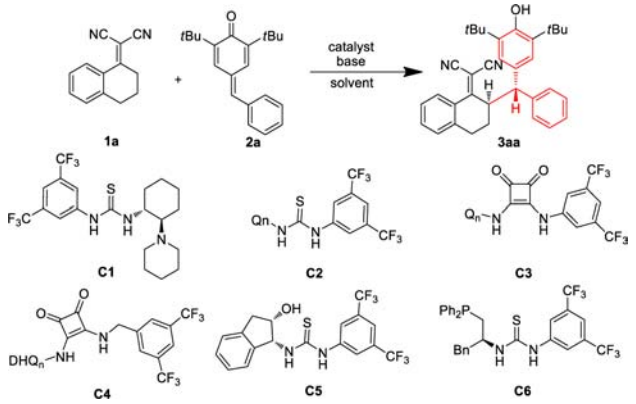
because of the increased distance between the catalyst activation site of *p*-QMs (carbonyl) and the reaction center. In 2015, Sun's group reported chiral phosphoric acid catalyzed 1,6-conjugate addition of *in situ* generated *p*-QMs with 2-methylpyrroles, realizing the first remote stereocontrol by activating the *p*-QMs and nucleophiles simultaneously (Scheme 1d).[7] In conjunction with our ongoing interest in *p*-QMs[8] and to explore a new asymmetric activation mode of *p*-QMs, herein, we describe our results on the chiral thiourea catalyzed[9] 1,6-conjugate addition of *p*-QMs with dicyanoolefins,[10] affording the diarylmethine stereogenic centers in good yields with good to excellent enantioselectivity (up to 99.5:0.5 er) and high diastereoselectivity (>20:1 dr). The preliminary mechanistic study showed that the chiral thiourea catalyst catalyzed the *p*-QMs directly through intermolecular hydrogen-bond interaction between the thiourea portion and the carbonyl of *p*-QMs, thus leading to the remote stereocontrol.

We started our investigation with the reaction between dicyanoolefin (**1a**) and *p*-QM (**2a**). Compound **1a** reacted with **2a**, affording the desired product **3aa** in 61% yield with 20:1 dr as a racemic product under the catalysis of **C1** in CH_2Cl_2 at room temperature (Table 1, entry 1). To improve the enantioselectivity, various catalysts were then evaluated (Table 1, entries 2–6). The assessment of catalysts led to the identification of **C6**[11] as the best catalyst, which furnished **3aa** with an enantiomeric ratio of 64:36. When the reaction was performed at −40 °C, the enantiomeric ratio of **3aa** was increased to 92:8 (Table 1, entry 7). After solvents were screened, we found that toluene was better than others in terms of yield, while from an er value standpoint the Et_2O was the best choice.

Table 1. Optimization of Reaction Conditions[a,b]

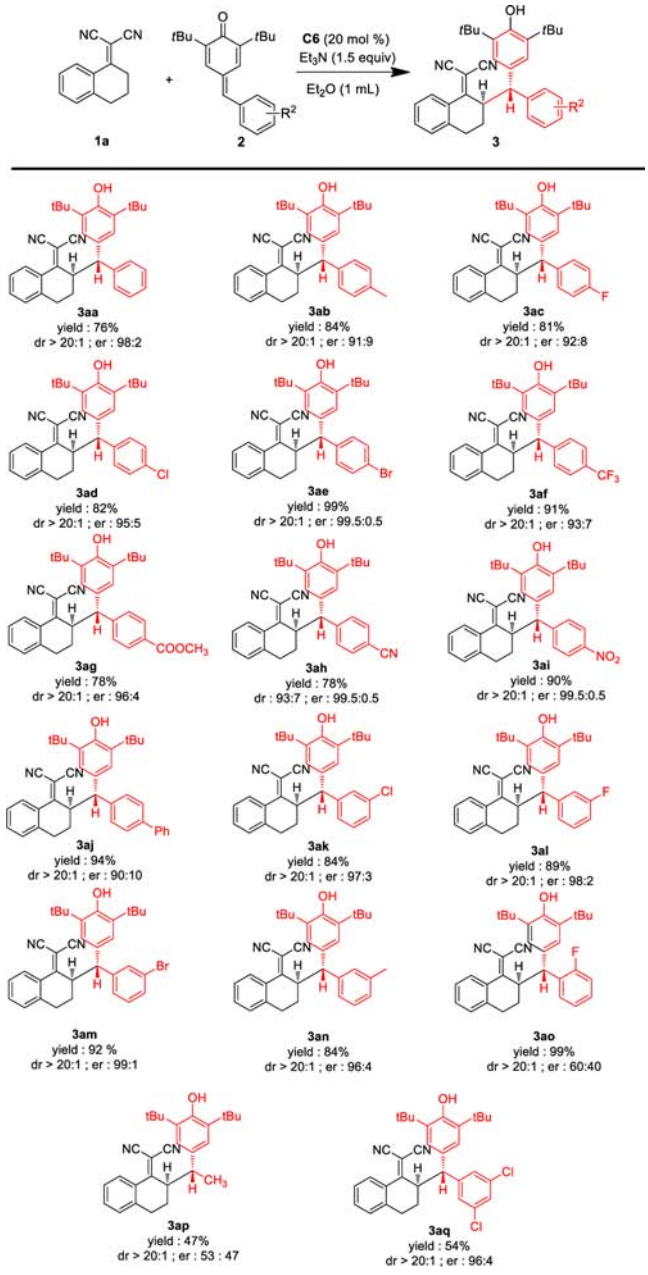


entry	cat.	*t* (°C)	solvent	yield (%)	dr	er
1	C1	rt	CH_2Cl_2	61	>20:1	50:50
2	C2	rt	CH_2Cl_2	37	>20:1	50:50
3	C3	rt	CH_2Cl_2	74	88:12	57:43
4	C4	rt	CH_2Cl_2	78	84:16	60:40
5	C5	rt	CH_2Cl_2	31	>20:1	57:43
6	C6	rt	CH_2Cl_2	78	88:12	64:36
7	C6	−40	CH_2Cl_2	80	>20:1	92:8
8	C6	−40	toluene	94	>20:1	95:5
9	C6	−40	mesitylene	82	>20:1	95:5
10	C6	−40	chlorobenzene	80	>20:1	93:7
11	C6	−40	*m*-xylene	80	>20:1	95:5
12	C6	−40	DME	82	95:5	55:45
13	C6	−40	Et_2O	76	>20:1	98:2

[a]Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.1 mmol, 1.0 equiv), catalyst (20 mol %), and Et_3N (0.15 mmol, 1.5 equiv) in solvent (1 mL). [b]Isolated yield.

With the optimized conditions in hand, we tested an array of substituted *p*-QMs and dicyanoolefins to explore the generality of this asymmetric 1,6-conjugate addition reaction. The results are summarized in Schemes 2 and 3. The substrates bearing a methyl group at the 4-position of the arene afforded the corresponding product **3ab** in 84% yield with 91:9 er and 20:1 dr. The halogen (F, Cl, Br) substituted **2c**–**2e** offered **3ac**–**3ae** in 81%–99% yields with 92:8–99.5:0.5 er. The absolute configuration of **3ae** was determined by X-ray crystal structure analysis (Figure 2).[12] Functional groups, such as the CF_3 group,

Scheme 2. Scope of the *p*-QMs[a,b]



[a]Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2** (0.1 mmol, 1.0 equiv), **C6** (20 mol %), Et_3N (0.15 mmol, 1.5 equiv) in Et_2O (1 mL) at −40 °C for 48 h. [b]Isolated yields.

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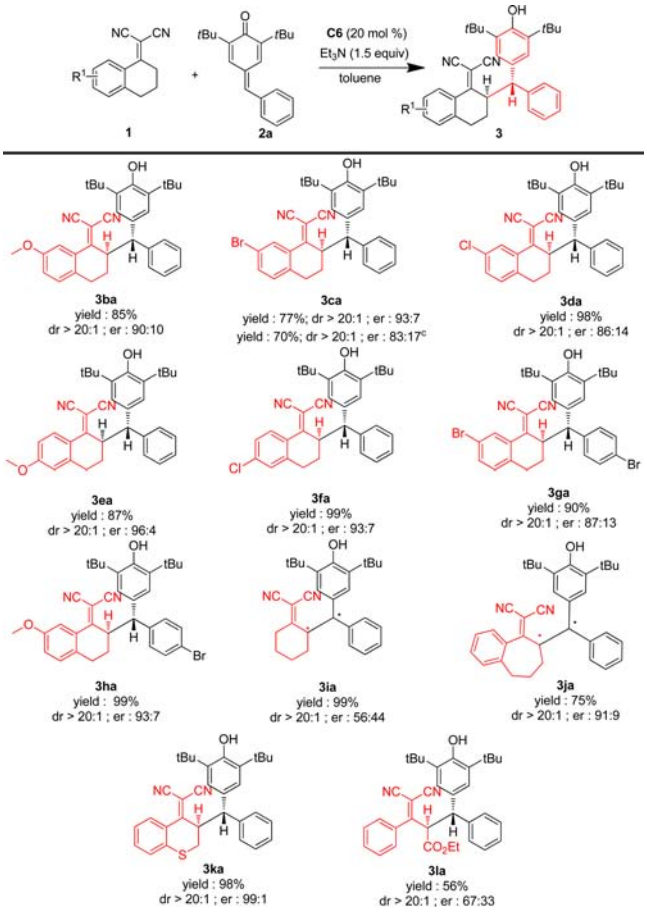
Scheme 3. Scope of Dicyanoolefins[a,b]



[a]Reaction conditions: **1** (0.1 mmol, 1.0 equiv), **2a** (0.1 mmol, 1.0 equiv), **C6** (20 mol %), Et_3N (0.15 mmol, 1.5 equiv) in toluene (1 mL) at −40 °C for 48 h. [b]Isolated yields. [c]Et_2O (1 mL) as solvent.

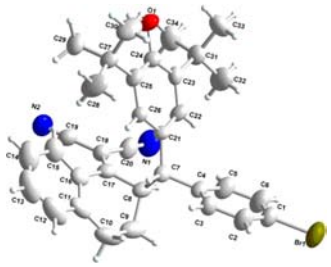


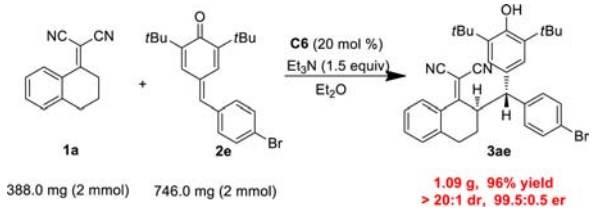
Figure 2. X-ray structure of enantiopure **3ae**. Thermal ellipsoids are shown at 30% probability.

an ester group, a CN group, and a NO_2 group, were all well tolerated under the reaction conditions, leading to products **3af**−**3ai** in 78%−91% yields with 93:7−99.5:0.5 er. Phenyl group substituted *p*-QM provided the desired product **3aj** in 94% yield with 90:10 er. Substrates with *meta*-substituents (Cl, F, Br, Me) at benzene rings such as **2k**, **2l**, **2m**, and **2n** offered the desired products **3ak**−**3an** in 84%−92% yields with 96:4−99:1 er. A substrate with an *ortho*-substituent at the phenyl ring (**2o**) gave the desired product **3ao** in 99% yield and 20:1 dr while the er was low. Alkyl substituent *p*-QM was also attempted, and the 1,6-conjugate addition product **3ap** was obtained in 47% yield with 53:47 er. Disubstituted *p*-QM was also examined, and the product **3aq** was obtained in 96:4 er.

Next, we turned our attention to the dicyanoolefin scope. It was found that the enantiomeric ratio of **3ca** could be improved from 83:17 to 93:7 when toluene was chosen as the solvent instead of Et_2O. As a consequence, we chose toluene as solvent for the dicyanoolefin scope study. The substrates derived from 7-substituted 1-tetralone worked well and gave the corresponding products **3ba**−**3da** in 77%−98% yields with 86:14−93:7 er. 6-Substituted dicyanoolefins afforded **3ea**−**3fa** in 87%−99% yields with 93:7−96:4 er. The more flexible 2,2-dicyanoolefin prepared from cyclohexanone was also tested, and **3ia** could be obtained in 99% yield and 20:1 dr with a low er value. When the 2,2-dicyanoolefin derived from a seven-membered ring ketone was tested, **3ja** was obtained in 75% yield with 91:9 er. When the dicyanoolefin derived from thiochroman-4-one was tested, the desired product **3ka** was obtained in 98% yield with 20:1 dr and 99:1 er. The acyclic dicyanoolefin (**1l**) could also give the desired product **3la** in 56% yield with 20:1 dr and 67:33 er.

To test the synthetic utility of our method, **3ae** was prepared on a gram scale (Scheme 4). The reaction of **1a** (2 mmol, 388.0 mg) with **2e** (2 mmol, 746.0 mg) under the optimal reaction conditions afforded **3ae** in 1.09 g (96% yield) maintaining the dr and er values. Removal or functionalization of the *tert*-butyl groups and dicyanoolefin could not be realized in our system at the present stage.[13]

Scheme 4. Gram-Scale Synthesis of 3ae



To gain insight into the mechanism of our asymmetric 1,6-conjugate addition, we carried out a series of mass spectrometric studies,[14] and a representative result is shown in Scheme 5. When catalyst **C6** was mixed with **1a**, **2a**, and Et_3N in Et_2O for 40 min, a new peak characterized by m/z = 885.5 was detected and assigned to be **C6** + **2a**, which provided evidence that the catalyst **C6** activated **2a** through intermolecular hydrogen-bond interaction. The role of the phosphorus atom in the catalytic cycle is unclear, but it may play a role as a Lewis base to act on dicyanoolefin. Based on previous work[10f] and our experimental clue, we propose an activation mode between the catalyst and the two reactants as shown in Scheme 6. The dicyanoolefin was much more accessible to attack the active *p*-QM from the *Si* face, affording the major stereoisomer.

In conclusion, we have developed the first example of chiral thiourea catalyzed asymmetric 1,6-conjugate addition of *p*-QMs with dicyanoolefins. This protocol provided facile access to diarylmethine stereogenic centers in good yields, excellent diastereoselectivity, and good to excellent enantioselectivity. The preliminary mechanistic study showed that in our catalytic system the remote stereocontrol was achieved through intermolecular hydrogen-bond interaction between the chiral thiourea catalyst and the *p*-QMs. Further reaction mechanistic study is underway in our group.

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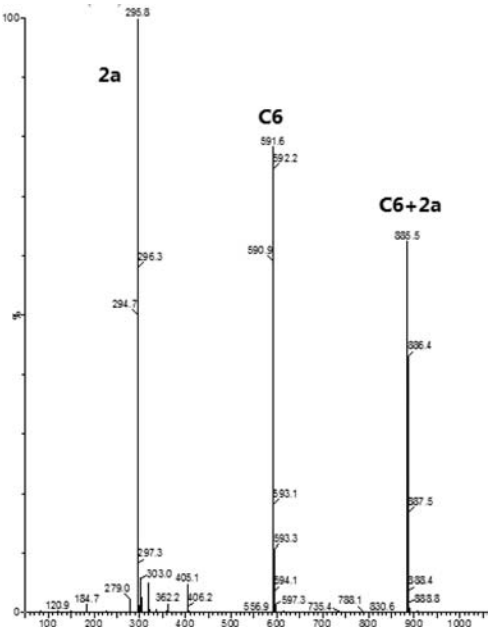
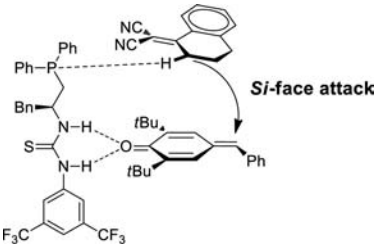
Scheme 5. Species Detected by MS (ESI) Analysis of 1a and 2a after the Addition of Et_3N and Catalyst C6



Scheme 6. Proposed Mode of Activation of the Substrate and Catalyst System



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03471.

^1H and ^{13}C NMR spectra for all new compounds (PDF)
X-ray crystallographic data for **3ae** (CIF)

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Notes

The authors declare no competing financial interest.

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(12) CCDC 1436969 contains the supplementary crystallographic data (Supporting Information)

(13) See Supporting Information for details of removal or functionalization of the *tert*-butyl groups and dicyanoolefin.

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