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Thiourea-Catalyzed Highly Diastereo- and Enantioselective Conjugate Additions of α-Substituted Cyanoacetates to Maleimides: Efficient Construction of Vicinal Quaternary-Tertiary Stereocenters

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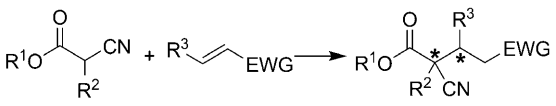
Abstract: A highly diastereo- and enantioselective conjugate addition of α-substituted cyanoacetates to maleimides in the presence of a chiral bifunctional thiourea-tertiary amine catalyst has been investigated for the first time. The procedure was capable of tolerating a relatively wide range of substrates with respect to α-substituted cyanoacetates and maleimides, providing a series of substituted succinimidates bearing two vicinal quaternary-tertiary stereocenters in excellent yields (up to 97%) with excellent diastereo- (up to 98:2) and enantioselectivities (up to 98%) under mild reaction conditions.

Keywords: bifunctional thioureas; maleimides; Michael addition; organocatalysis; α-substituted cyanoacetates

Two vicinal quaternary-tertiary stereocenters are ubiquitious and important structural motifs in natural products and pharmaceuticals. Developing efficient catalytic asymmetric methods for the construction of vicinal quaternary-tertiary stereocenters in complex molecular structures remains a challenging goal in organic synthesis.[1] In this regard, the reaction between α-substituted cyanoacetates as nucleophiles and appropriate electrophiles has emerged to be one of the most feasible methods of access to chiral vicinal quaternary-tertiary stereocenters contained in various molecular architectures. Consequently, a great deal of interest has been devoted to the development of efficient methodologies for the asymmetric conjugate addition of α-substituted cyanoacetates to various Michael acceptors (Scheme 1).[2] Moreover, there are several reasons for the wide application of α-substituted cyanoacetates in asymmetric transformation, including (i) α-substituted cyanoacetates are highly reactive, (ii) α-substituted cyanoacetates are readily epimerizable and thus offer the possibility of generating a configurationally stable quaternary stereocenter under kinetic control, and (iii) α-substituted cyanoacetates comprise several functional groups (e.g., ester, nitrile, etc.), which make possible the rapid access to some highly functionalized building blocks such as quaternary α- and β-amino acids.[3] Therefore, developing new and efficient methods with α-substituted cyanoacetates as nucleophiles for the direct and stereocontrolled construction of diverse molecular structures bearing adjacent quaternary-tertiary stereocenters still retains undiminished synthetic significance in organic synthesis and is highly desirable, in spite of the numerous great strides made in the asym-



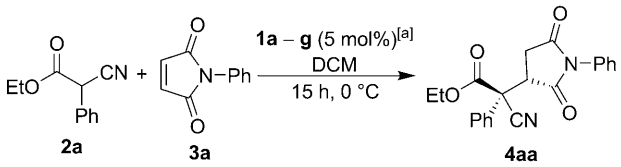
Scheme 1. Conjugate addition of α-substituted cyanoacetates to Michael acceptors.

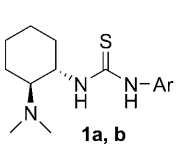
metric conjugate addition reactions with α-substituted cyanoacetates as nucleophiles.[2,4,5]

The Michael addition is certainly one of the most powerful C–C bond-forming transformations, and the diversity in donors and acceptors that can be combined is remarkable. Indeed, numerous Michael acceptors have been employed in the reaction with α-substituted cyanoacetates (Scheme 1).[2,4,5] However, to the best of our knowledge, there were no reports on the catalytic asymmetric conjugate addition of α-substituted cyanoacetates to maleimides for C–C bond formation. Maleimides are one of the most versatile reagents that participate in a wide range of organic reactions manifesting into valuable scaffolds, building blocks, and heterocycles, for example, acting as dienophiles or dipolarophiles in cycloadditions,[6] or as Michael acceptors in conjugated additions.[7] Notably, the asymmetric conjugate addition to maleimides is a very useful strategy for the construction of substituted succinimidates that are found in many biological interesting substances, such as certain anticonvulsant drugs.[8] On the other hand, due to its operational and economic advantages, asymmetric organocatalysis has been proven to be a powerful tool for the synthesis of optically pure compounds.[9] Particularly, among the supreme achievements gained in asymmetric organocatalysis, bifunctional thiourea catalysts with various chiral scaffolds have been successfully applied in a range of asymmetric transformations.[10] As a continuation of our efforts in the investigation on catalytic asymmetric reactions based on organocatalysis,[11] herein we wish to report the first asymmetric conjugate addition reaction of α-substituted cyanoacetates to maleimides with chiral bifunctional thiourea-tertiary amine compounds as catalysts. In this protocol, the bifunctional catalysts successfully impart both high diastereoselectivity and enantioselectivity in a sterically demanding, intermolecular C–C bond formation that simultaneously creates both a quaternary and a tertiary stereocenter.

As a model reaction, we chose to study the reaction of ethyl α-phenylcyanoacetate (**2a**) with maleimide **3a**. As shown in Scheme 2, the readily available Takemoto's thiourea catalyst **1a**[12] was identified to be the most selective catalyst as judged by reactivity, diastereo- and enantioselectivity under the same reaction conditions. Catalyst **1a** smoothly promoted the addition of ethyl α-phenylcyanoacetate (**2a**) with **3a** to generate **4aa** in 97% yield with 90:10 *dr* and 80% *ee*. Based on these results, a further optimization of the reaction conditions with **1a** as the most promising catalyst was carried out.

The subsequent screening of solvent was performed in the presence of 5 mol% **1a** in chlorinated solvents such as CH_2Cl_2, $CHCl_3$, 1,2-dichloroethane (DCE), and CCl_4 at 0 °C. It was revealed that the conjugate

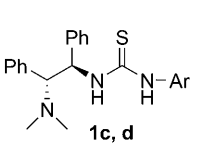




1a, b

1a: Ar = 3,5-$(CF_3)_2C_6H_3$
yield[b] 97%
dr[c] 90:10
ee[d] (–)80%

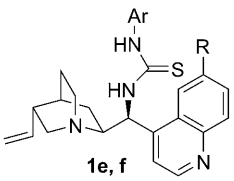
1b: Ar = 4-FC_6H_4
yield 93%
dr 90:10
ee (–)77%



1c, d

1c: Ar = 3,5-$(CF_3)_2C_6H_3$
yield 42%
dr 80:20
ee (+)52%

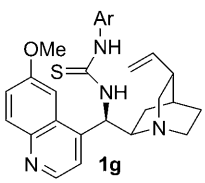
1d: Ar = 4-$NO_2C_6H_4$
yield 49%
dr 80:20
ee (+)34%



1e, f

1e: Ar = 3,5-$(CF_3)_2C_6H_3$
R = H
yield 83%
dr 71:29
ee (–)70%

1f: Ar = 3,5-$(CF_3)_2C_6H_3$
R = OMe
yield 69%
dr 74:26
ee (–)40%



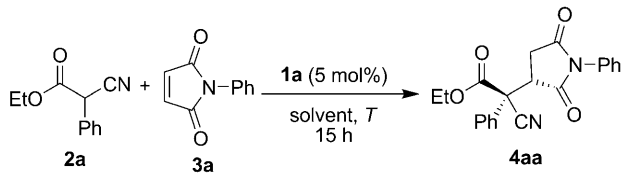
1g

1g: Ar = 3,5-$(CF_3)_2C_6H_3$
yield 83%
dr 80:20
ee (+)74%

[a] *Reaction conditions*: **2a** (0.12 mmol), **3a** (0.1 mmol), and catalyst **1** (5 mol %) were stirred in CH_2Cl_2 (1.0 mL) at 0 °C for 15 h.
[b] Isolated yield.
[c] Determined by ^1H NMR.
[d] Determined by chiral HPLC analysis for major diastereoisomer.

Scheme 2. Model reaction and catalysts studied.

Table 1. Optimization of reaction conditions.[a]



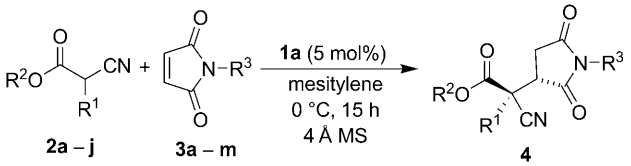
Entry	Solvent	T [°C]	Yield [%][b]	dr[c]	ee [%][d]
1	CH_2Cl_2	0	97	90:10	80
2	$CHCl_3$	0	94	91:9	76
3	DCE	0	98	88:12	79
4	CCl_4	0	94	90:10	84
5	toluene	0	98	91:9	81
6	xylene	0	97	93:7	86
7	mesitylene	0	94	95:5	89
8	THF	0	72	95:5	42
9	Et_2O	0	93	96:4	79
10	$PhOCH_3$	0	97	93:7	76
11	mesitylene	−20	95	95:5	90[e]
12	mesitylene	−40	89	96:4	90[e]
13	mesitylene	0	97	92:8	91[f]
14	mesitylene	0	97	93:7	93[g]
15	mesitylene	0	96	93:7	91[h]
16	mesitylene	0	96	93:7	94[g,i]
17	mesitylene	0	76	96:4	95[g,j]
18	mesitylene	0	96	97:3	97[g,k]
19	mesitylene	r.t.	95	93:7	93[g,k,l]

[a] *Reaction conditions* (unless otherwise noted): **2a** (0.12 mmol), **3a** (0.1 mmol), and catalyst **1a** (5 mol%) were stirred in the specified solvent (1.0 mL) at the stated temperature for 15 h.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] Determined by chiral HPLC analysis for major diastereoisomer.
[e] Run for 24 h.
[f] **2a**/**3a** = 0.1 mmol/0.2 mmol.
[g] **2a**/**3a** = 0.1 mmol/0.15 mmol.
[h] **2a**/**3a** = 0.2 mmol/0.1 mmol.
[i] In 2.0 mL solvent.
[j] In 5.0 mL solvent.
[k] 4 Å MS (60 mg) was used.
[l] *Reaction conditions:* 2 mol% catalyst and 4 Å MS (60 mg) in 1.0 mL solvent run for 10 h.

addition proceeded smoothly and gave the desired product in very high yield with good *dr* and *ee* values, respectively (Table 1, entries 1–4). Under the same reaction conditions, we then further evaluated other solvents (Table 1, entries 5–10), and found that the best result was achieved in mesitylene (Table 1, entry 7). Lowering the reaction temperature did not result in any significant improvement in stereoselectivity and yield in spite of an extension of the reaction time to 24 h (Table 1, entries 11 and 12). Furthermore, the ratio of the two substrates (**2a** to **3a**) was revealed to be optimal at 1.0 to 1.5 (Table 1, entry 14 *vs.* entries 12 and 13). Subsequently, the substrate concentration was probed, it was observed that a 94% *ee* value was obtained and without any negative effects on yield and diastereoselectivity in 2.0 mL of solvent (Table 1, entry 16). However, in 5.0 mL of solvent, the *dr* and *ee* values were satisfactory but the yield decreased from 97% to 76% (Table 1, entry 17). Fortunately, addition of 4 Å molecular sieves (MS) led to higher diastereo- and enantioselectivity (97:3 *dr*, 97% *ee*) (Table 1, entry 18). Notably, product **4aa** could also be smoothly obtained with 2 mol% catalyst in 95% yield with 93:7 *dr* and 93% *ee* in 1.0 mL mesitylene at room temperature for 10 h (Table 1, entry 19).

Under the optimum reaction conditions, we turned our attention to the scope and limitations of the transformations. As shown in Table 2, a substrate scope study revealed that *N*-arylmaleimides **3b–i** bearing a range of aryl groups of varying electronic properties underwent efficient asymmetric addition with ethyl α-phenylcyanoacetate (**2a**), providing structurally diverse succinimides **4ab–ai** bearing vicinal quaternary-tertiary stereocenters in excellent diastereoselectivities, good to excellent enantioselectivities and excellent yields (entries 1–8). In addition, the reaction was also applicable to *N*-alkylmaleimides **3j** and **k** albeit, compared to their congeners, **3j** and **3k** were less active as Michael acceptor for the addition and provided the corresponding products in acceptable yields with good diastereo- and enantioselectivies (entries 9 and 10). Unfortunately, in the cases of *N*-alkylmaleimides **3l** and **3m** as Michael acceptor, their corresponding adducts were observed in only trace amounts even with 20 mol% catalyst loading at room temperature for 24 h (entries 11 and 12). This further proved the *N*-alkylmaleimides showed lower reactivity than *N*-arylmaleimides in this experimental protocol. To further expand the scope of this methodology, we subsequently investigated the conjugate addition with various α-aryl cyanoacetates **2b–e** to *N*-phenyl maleimide **3a** (entries 13–16). In all cases, the reactions proceeded smoothly to give the desired adducts in excellent yields and with excellent diastereoselectivities and good to excellent enantioselectivities. Notably, an excellent yield and stereoselectivity could also be obtained with an α-heteroaryl α-cyanoacetate (entry 17). Moreover, we were pleased to find that variation of the ester group of α-phenylcyanoacetates showed no negative effects on the reactivity, giving the corresponding adducts in very good results (entries 18 and 19). In addition to the foregoing, we subsequently investigated the Michael reactions of α-alkylcyanoacetates **2i** and 3**j** and *N*-phenylmaleimide **3a**, respectively (entries 20 and 21). The corresponding adducts were smoothly obtained in high yields, but with poor diastereoselectivities and good enantioselectivities (entries 20 and 21).

Table 2. Asymmetric conjugate addition of α-substituted cyanoacetates **2** and maleimides **3**.[a]



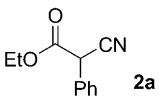
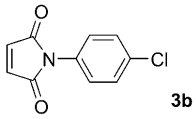
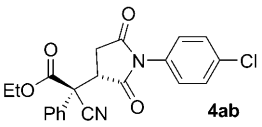
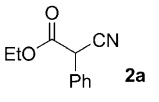
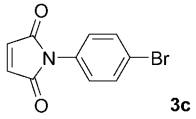
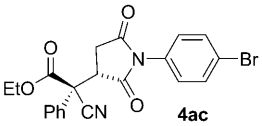
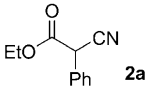
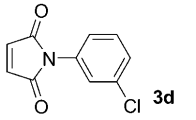
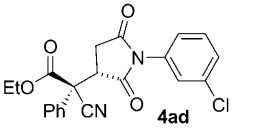
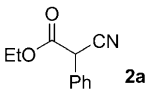
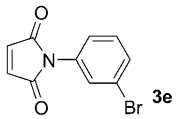
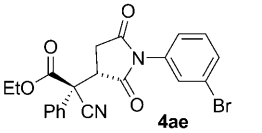
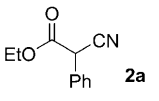
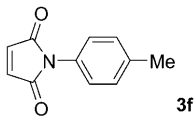
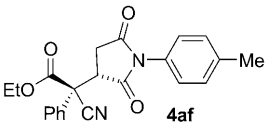
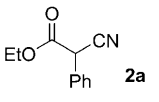
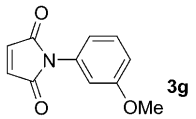
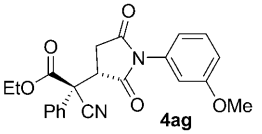
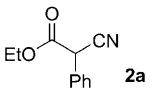
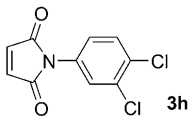
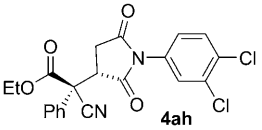
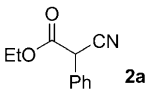
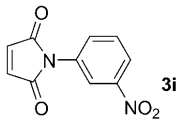
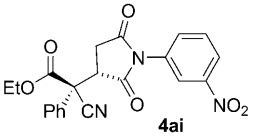
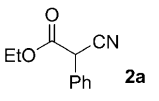
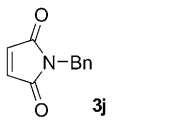
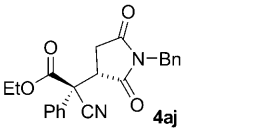
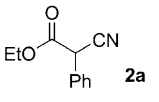
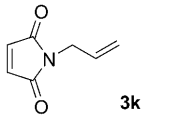
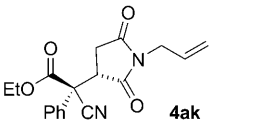
Entry	2	3	4	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	 **2a**	 **3b**	 **4ab**	94	96:4	98
2	 **2a**	 **3c**	 **4ac**	92	97:3	98
3	 **2a**	 **3d**	 **4ad**	95	98:2	96
4	 **2a**	 **3e**	 **4ae**	93	98:2	96
5	 **2a**	 **3f**	 **4af**	93	98:2	97
6	 **2a**	 **3g**	 **4ag**	96	97:3	96
7	 **2a**	 **3h**	 **4ah**	93	96:4	96
8	 **2a**	 **3i**	 **4ai**	97	93:7	88
9[e]	 **2a**	 **3j**	 **4aj**	84	83:17	82
10[e]	 **2a**	 **3k**	 **4ak**	65	90:10	81[e]

Table 2. (Continued)

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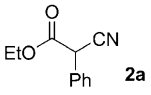
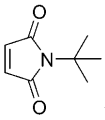
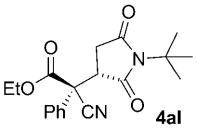
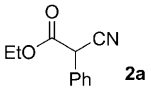
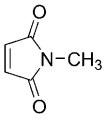
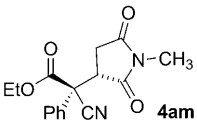
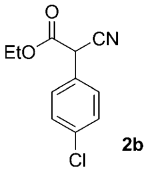
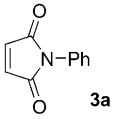
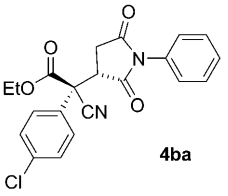
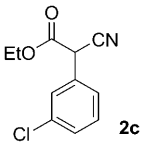
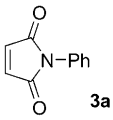
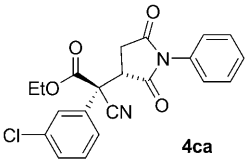
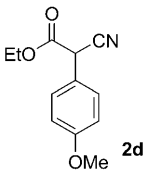
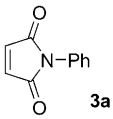
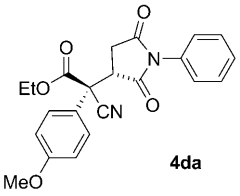
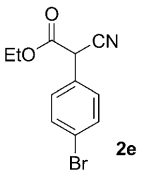
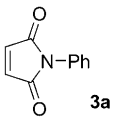
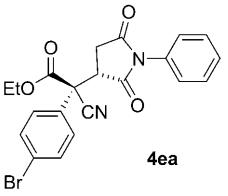
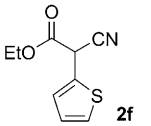
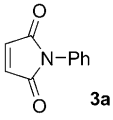
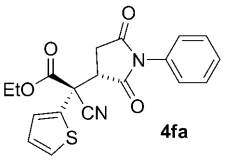
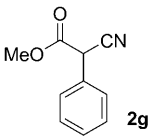
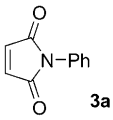
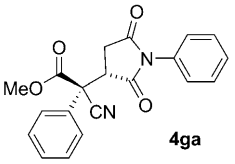
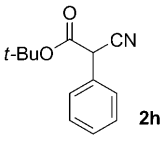
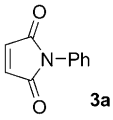
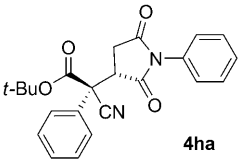
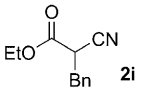
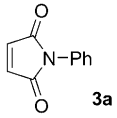
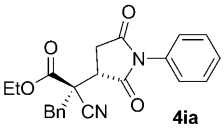
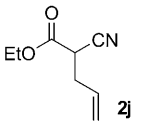
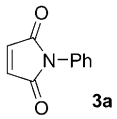
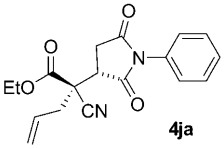
11[e]	 **2a**	 **3l**	 **4al**	trace	–[f]	–[f]
12[e]	 **2a**	 **3m**	 **4am**	trace	–[f]	–[f]
13	 **2b**	 **3a**	 **4ba**	96	98:2	96
14	 **2c**	 **3a**	 **4ca**	94	95:5	94
15	 **2d**	 **3a**	 **4da**	96	95:5	96
16	 **2e**	 **3a**	 **4ea**	95	94:6	96
17	 **2f**	 **3a**	 **4fa**	95	93:7	94
18	 **2g**	 **3a**	 **4ga**	96	96:4	87
19	 **2h**	 **3a**	 **4ha**	92	92:8	93

Table 2. (Continued)

Entry	2	3	4	Yield [%][b]	*dr*[c]	*ee* [%][d]
20[e]	 **2i**	 **3a**	 **4ia**	92	52:48	68[d]/3[g]
21[e]	 **2j**	 **3a**	 **4ja**	90	69:41	11[d]/76[g]

[a] *Reaction conditions* (unless otherwise noted): **2a** (0.2 mmol), **3** (0.3 mmol), catalyst **1a** (5 mol%), and 60 mg 4 Å MS in mesitylene (2 mL) were stirred at 0 °C for 15 h.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] Determined by chiral HPLC analysis for major diastereoisomer.
[e] 20 mol% **1a** was used, at 25 °C for 24 h.
[f] Not measured.
[g] Enantiomeric excess of the minor diastereoisomer, determined by chiral HPLC analysis.

A large scale experiment with 5 mol% of **1a** was performed at 0 °C to test the utility of the current catalytic system (Scheme 3). While a somewhat prolonged reaction time (24 h) was required, product **4aa** was isolated in high yield and with excellent diastereo- and enantioselectivity.

To determine the relative and absolute configurations of the asymmetric Michael addition products, a single crystal of compound **4ab** was obtained and the structure was confirmed by X-ray diffraction analysis. As shown in Figure 1, compound **4ab** contains a (C9*S*,C11*R*) configuration.[13] The configurations of the other products in this work were tentatively assigned by assuming that a similar catalytic mechanism was followed.

In light of the above data, we tentatively propose a working model as shown in Figure 2. The thiourea moiety activates the maleimide *via* double hydrogen bonding interaction. On the other hand, a single hydrogen bonding interaction was generated between the OH group of the enolate and the tertiary amine moiety of the catalyst, in addition, a weak hydrogen bonding interaction might be formed concurrently between the OR group of the enolate and an NH of the thiourea moiety. Subsequently, *Re*-face attack of the

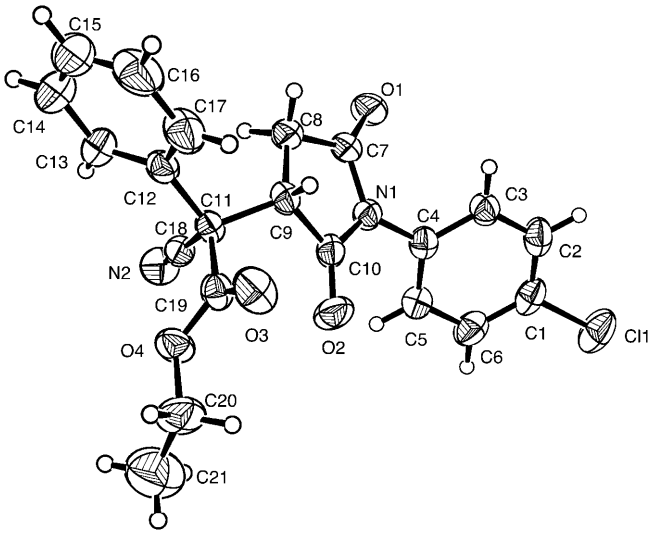
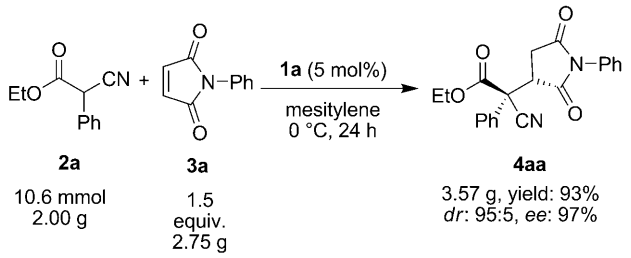


Figure 1. X-ray structure of compound **4ab**.



Scheme 3. Catalytic asymmetric Michael addition of α-phenylcyanoacetate **2a** to maleimide **3a** on a large scale.

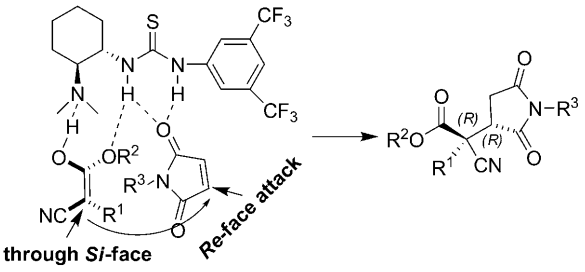


Figure 2. A proposed working model for α-substituted cyanoacetates Michael addition to maleimides.

maleimide *via* the *Si*-face of the enolate of the α-substituted cyanoacetate will create the corresponding product with (*S,R*)-configuration (Figure 2).[14]

In summary, we have developed the first highly diastereo- and enantioselective conjugate addition of α-substituted cyanoacetates to maleimides. The addition reactions employed a readily available chiral thiourea organocatalyst and an experimentally simple protocol with mild reaction conditions. In particular, the procedure was capable of tolerating a relatively wide range of substrates with respect to α-substituted cyanoacetates and maleimides, providing a series of substituted succinimidates bearing two vicinal quaternary-tertiary stereocenters in excellent yields (up to 97%) with excellent diastereo- (up to 98:2) and enantioselectivities (up to 98%). Furthermore, high yield, excellent *dr* and *ee* values also were able to be obtained on a large scale, which showed the potential value of the catalyst system. These features should render this method a viable and attractive route to synthetically and biologically important chiral α-succinimidate compounds. Further studies on other valuable transformations with some distinct advantages including high efficiency, operational simplicity and environmentally friendly conditions are actively being pursued in our laboratory.

Experimental Section

Typical Procedure for the Asymmetric Conjugate Addition of α-Phenylcyanoacetate 2a and Maleimide 3a with Organocatalyst 1a

A solution of α-phenylcyanoacetate **2a** (0.2 mmol), *N*-substituted maleimide **3a** (0.3 mmol), bifunctional thiourea catalyst **1a** (0.01 mmol) and 60 mg 4 Å MS in mesitylene (2 mL) was stirred at 0 °C for 15 h. And then the reaction mixture was directly subjected to flash column chromatography on silica gel (petroleum ether:ethyl acetate = 8:1) to furnish the corresponding product **4aa** as a white solid; yield: 96%; 97:3 *dr*; 97% *ee*; $[\alpha]_D^{20}$: −61.5 (*c* 1.08, $CHCl_3$); mp 111.7–114.1 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.32$ (t, $J = 7.2$ Hz, 3H), 2.55 (dd, $J = 6.6$ Hz, 18.6 Hz, 1H), 2.82 (dd, $J = 9.3$ Hz, 18.6 Hz, 1H), 4.24–4.44 (m, 3H), 7.30–7.33 (m, 2H), 7.42–7.49 (m, 6H), 7.64–7.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 13.6$, 31.5, 46.8, 55.3, 64.1, 115.8, 126.4, 128.9, 129.2, 129.6, 129.8, 131.1, 165.9, 172.9, 174.0; IR (KBr): $\nu =$ 3056, 2242, 1746, 1713, 1594, 1497, 1393, 1238, 693 cm^{-1}; HR-MS (ESI): $m/z = 385.1163$, calcd. for $C_{21}H_{18}N_2NaO_4$ $[M+Na]^+$: 385.1159; HPLC (Chiralcel AD-H column, *i*-PrOH/hexane 30:70, flow rate 1.0 mL min^{-1}, UV detection at 254 nm): $t_{major} = 40.61$ min, $t_{minor} = 26.13$ min.

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[13] CCDC 810819 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[14] A similar working model involving multiple hydrogen bonding interactions was proposed by Chen in ref.[3a] based on the relevant computational studies.

