Organic LETTERS

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Enantioselective Cyano-Alkoxycarbonylation of α-Oxoesters Promoted by Brønsted Acid–Lewis Base Cooperative Catalysts

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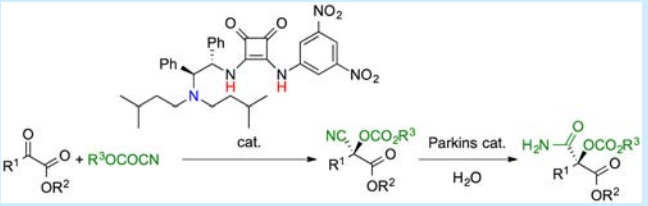
Supporting Information

ABSTRACT: The highly enantioselective cyano-alkoxycarbonylation of α-oxoesters with alkyl cyanoformates is promoted by a new chiral Brønsted acid–Lewis base cooperative organocatalyst. The present catalysis can be performed at room temperature under nitrogen or air.



Optically active cyanohydrins serve as highly versatile synthetic building blocks in biologically active compounds. However, cyanohydrins are not very stable and readily decompose under basic conditions. In particular, it is difficult to develop the catalytic enantioselective addition of cyanides to ketones due to the rapid reversibility of the reaction. Thus, procedures that allow for direct access to *O*-protected non-racemic cyanohydrins are needed to avoid the reversibility of the cyanide addition and a decrease in enantioselectivity.[1]

Enantioselective cyano-alkoxycarbonylation is one of the most powerful methods for preparing *O*-protected non-racemic cyanohydrins because alkyl cyanoformate is an easy-to-handle and user-friendly cyanide source.[2−8] There have been numerous successful examples of the catalytic cyano-alkoxycarbonylation reaction of aldehydes since the report by Shibasaki et al. in 2002.[2,3] In sharp contrast, there are a few examples of the use of ketones.[4,5,7] The first success with unconjugated ketones was achieved by Deng et al. in 2001.[4] They used modified cinchona alkaloids as chiral Lewis base catalysts. In 2014, we developed the enantioselective cyano-alkoxycarbonylation of isatins catalyzed by chiral β-aminothiourea **1** as an acid–base cooperative catalyst (Figure 1 and Scheme 1).[5] As shown in Scheme 1, catalyst **1** initially activates ethyl cyanoformate as an ammonium cyanohydrinate intermediate, which reacts with *N*-protected

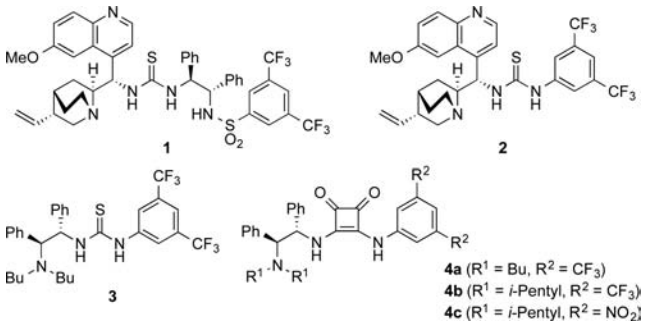
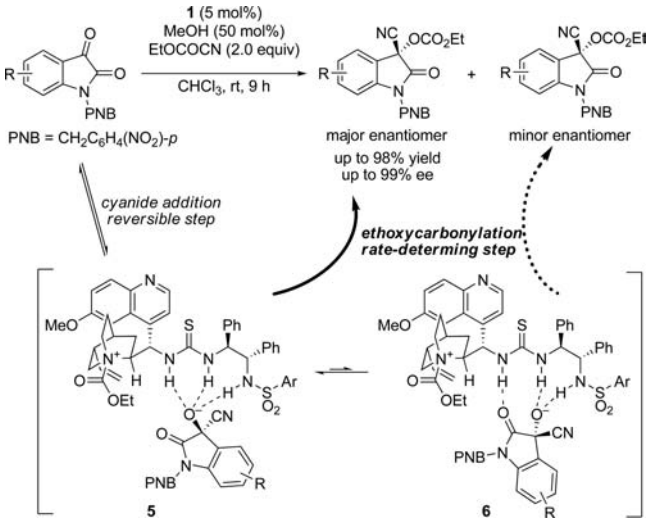


Figure 1. Brønsted acid–Lewis base cooperative organocatalysts.

Scheme 1. Our Previous Work



isatins to generate a diastereomeric mixture of **5** and **6**. The first step is in equilibrium. The subsequent alkoxycarbonylation is the rate-determining step, and the final product is obtained with high enantioselectivity through dynamic kinetic resolution of deprotonated cyanohydrin. Mechanistic studies by Deng et al.[4] also support this proposed mechanism.

Tertiary cyanohydrin derivatives derived from α-oxoesters are very valuable as optically active compounds with a multifunctionalized carbon center. To the best of our knowledge, three successful examples have been reported. In 2004, Johnson et al. reported tandem enantioselective cyanation/Brook rearrangement/*C*-acylation reactions of benzoylsilanes catalyzed by a chiral (salen)aluminum complex to give α-aryl-α-cyano-α-silyloxyacetates.[6] The enantioselectivity was good to moderate, and aliphatic acylsilanes were unreactive. In 2009, Moberg et al.

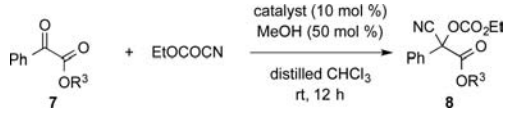
Received: October 26, 2015
Published: December 4, 2015

DOI: 10.1021/acs.orglett.5b03093
Org. Lett. 2015, 17, 6070–6073

reported the first enantioselective cyano-acetylation of α-oxoesters catalyzed by cinchonidine.[7] The substrate was limited to alkyl 2-oxo-2-phenylacetates, and the reaction temperature had to be lowered to −40 or −78 °C to induce higher enantioselectivity. In 2010, Ohkuma et al. reported the highly catalytic enantioselective cyanosilylation of α-oxoesters by using a [Ru(phgly)$_2$(binap)]−PhOLi system.[8] The substrate scope was extended to aryl-, heteroaryl-, alkenyl-, and alkylacetates. However, the reaction temperature had to be lowered to −50 or −60 °C. Thus, more efficient methods are needed for the enantioselective synthesis of *O*-protected cyanohydrins derived from α-oxoesters.[9] Here we report the highly enantioselective cyano-alkoxycarbonylation of α-oxoesters with alkyl cyanoformates catalyzed by a new chiral Brønsted acid−Lewis base cooperative catalyst **4** at room temperature.

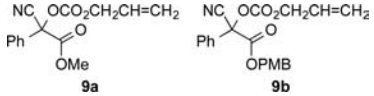
First, **1** was examined as a catalyst for the enantioselective cyano-ethoxycarbonylation of methyl 2-oxo-2-phenylacetate (**7a**) with ethyl cyanoformate in distilled chloroform,[10] based on our previous results.[5] The addition of 50 mol % of methanol was slightly effective for improving the catalytic activity. The desired product **8a** was obtained in quantitative yield with 67% ee. Structurally simpler catalyst **2** gave the same results as with **1** (Table 1, entry 2). Catalyst **3** gave higher enantioselectivity than

Table 1. Screening of the Reaction Conditions[a]



entry	7 (R^3)	cat.	8, yield (%)[b,c]	ee (%)[c,d]
1[e]	**7a** (Me)	**1**	**8a**, >99 [99]	67 [61]
2	**7a** (Me)	**2**	**8a**, [83]	[61]
3	**7a** (Me)	**3**	**8a**, >99 [93]	67 [67]
4	**7a** (Me)	**4a**	**8a**, [92]	[77]
5	**7a** (Me)	**4b**	**8a**, [90]	[79]
6	**7a** (Me)	**4c**	**8a**, 98 [93]	79 [79]
7[f,h]	**7a** (Me)	**4c**	**9a**, 91	81
8[g]	**7b** (Et)	**4c**	**8b**, 88	79
9[g]	**7c** (*i*-Pr)	**4c**	**8c**, 89	71
10[g]	**7d** (CH_2Ph)	**4c**	**8d**, 95	82
11[g]	**7e** (PMB)	**4c**	**8e**, 81	89
12[f,g,h]	**7e** (PMB)	**4c**	**9b**, 98	89
13[g]	**7f** ($CH_2C_6H_4(NO_2)$-*p*)	**4c**	**8f**, 72	84
14[g]	**7g** (CH_2-anthathenyl-9)	**4c**	**8g**, 98	97

[a]Unless otherwise noted, the reaction of **7** (0.2 mmol) with ethyl cyanoformate (2.0 equiv) was carried out in the presence of methanol (50 mol %) and catalyst (10 mol %) in distilled chloroform (0.2 mL) at room temperature for 12 h. [b]Isolated yield. [c]Results without methanol are shown in brackets. [d]Determined by chiral HPLC. [e]Reaction time was 6 h. [f]Reaction was carried out using allyl cyanoformate for 24 h. [g]Distilled chloroform (0.4 mL) was used. [h]

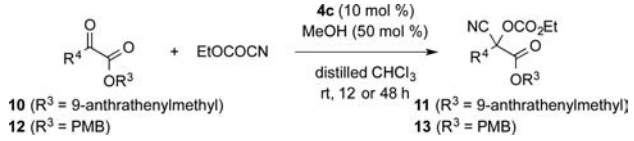


1 and **2** (entry 3). Interestingly, β-aminosquaramide **4**[11] was superior to β-aminothiourea **3** with respect to enantioselectivity (entry 4). Allyl cyanoformate could also be used in place of ethoxycarbonylcyanide (entry 7).

Next, the effect of an alkoxy moiety (R^3) of **7** was explored (entries 6, 8−11, 13, and 14). When 9-anthrathenylmethyl ester **7g** was used as a substrate, the highest enantioselectivity (97% ee) was observed (entry 14). *p*-Methoxybenzyl (PMB) ester **7e** could also be used (entry 11).

To investigate the substrate scope, several 9-anthrathenylmethyl 2-oxoacetates (**10**) and 4-methoxybenzyl 2-oxoacetates (**12**) were examined in the cyano-ethoxycarbonylation under the optimized conditions (Table 2). A series of 2-aromatic, α,β-unsaturated, and aliphatic-group-substituted 2-oxoacetates were converted into the desired products with good to high enantioselectivity.[12]

Table 2. Substrate Scope[a]

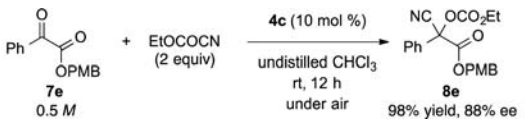


10 (R^3 = 9-anthrathenylmethyl) **11** (R^3 = 9-anthrathenylmethyl)
12 (R^3 = PMB) **13** (R^3 = PMB)

entry	2-oxoacetate (R^4)	product, yield (%)[b]	ee (%)[c]
1	**10a** (*p*-MeC_6H_4)	**11a**, 96	97
2	**10b** (*p*-ClC_6H_4)	**11b**, 76	97
3	**10c** (*p*-BrC_6H_4)	**11c**, 89	98
4	**10d** (4-(MeO)C_6H_4)	**11d**, 80	98
5	**10e** ((3,4-(CH_2O_2)C_6H_3)	**11e**, 88	98
6[d]	**10f** ((*E*)-PhCH=CH)	**11f**, 66	97
7[d]	**10g** ((*E*)-*p*-BrC_6H_4CH=CH)	**11g**, 74	99
8[d]	**10h** ((E)-*m*-BrC_6H_4CH=CH)	**11h**, 87	97
9[d]	**10i** ((*E*)-*p*-$CF_3C_6H_4CH$=CH)	**11i**, 75	97
10	**12a** (*i*-Bu)	**13a**, 93	73
11	**12b** ($PhCH_2CH_2$)	**13b**, 90	80

[a]Unless otherwise noted, the reaction of **10** or **12** (0.2 mmol) with ethyl cyanoformate (2.0 equiv) was carried out in the presence of methanol (50 mol %) and catalyst (10 mol %) in distilled chloroform (0.4 mL) at room temperature for 12 h. [b]Isolated yield. [c]Determined by chiral HPLC. [d]Reaction was carried out in chloroform (0.6 mL) at room temperature for 48 h.

The present organocatalysis proceeded smoothly in commercially available chloroform[10] even under air (eq 1). The addition of methanol was not required because 0.5−1.0% ethanol was included as stabilizer in commercially available chloroform.

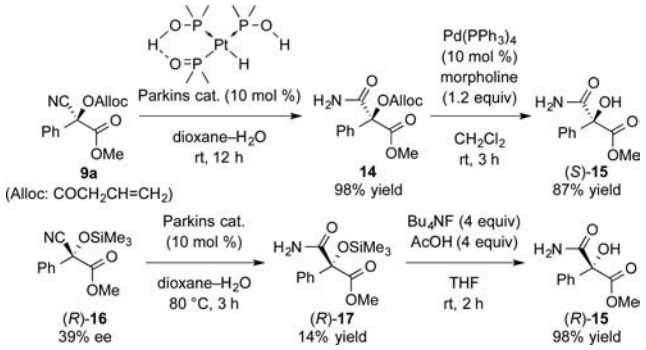


The absolute configuration of product **9a** was determined by transformation to known compound **15** and comparison of their specific rotations, as shown in Scheme 2. It was quite difficult to obtain cyano-alkoxycarbonated products chemoselectively. Fortunately, we found that the chemoselective hydrolysis of **9a** promoted by Parkins catalyst[13] and subsequent deprotection of the alloc group gave **15** in high yield. The authentic sample of (*R*)-**15** was synthesized from (*R*)-**16**, which was prepared by a known method.[8,14] Thus, the absolute configuration of **9a** was determined to be (*S*). Notably, chemoselective hydrolysis of (*R*)-**16** gave (*R*)-**17** in low yield because of the instability of the silyloxy moiety of **16**.

To demonstrate the synthetic utility of cyano-alkoxycarbonated products, we converted primary amide **18** derived from **9b** to 4-methoxybenzyl (*S*)-2,4-dioxo-5-phenyloxazolidine-5-carboxylate (**19**) in high yield in two steps (Scheme 3). The skeletons analogous to **19** are included in vinclozoline as a

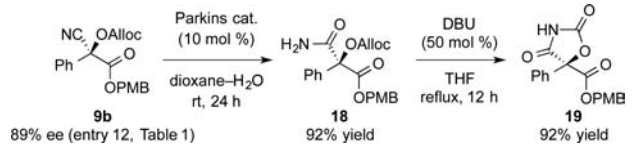
DOI: 10.1021/acs.orglett.5b03093
Org. Lett. 2015, 17, 6070−6073

Scheme 2. Determination of the Absolute Configuration of 9a



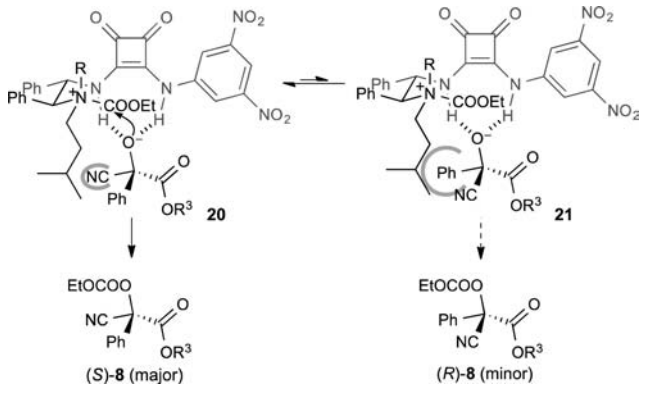
fungicide with antiandrogenic properties, paramethadione as anticonvulsant, etc.

Scheme 3. Chemoselective Transformation from 8e to 19



Finally, a diastereomeric ion pair, **20** and **21**, of a cyanohydrinated oxyanion of **7** and a quaternary ammonium cation via catalyst **4c** were speculated to exist as shown in Scheme 4. The squaramide moiety of **4c** acts as an "oxyanion hole" and

Scheme 4. Proposed Mechanism



contributes to recognition of the enantiomeric oxyanion through multiple hydrogen-bonding interactions.[5,15,16] Enantioselective ethoxycarbonylation may occur through the more-favored ion pair intermediate **20** to give (*S*)-adduct **8** because of the serious steric hindrance between the α-phenyl group of (*R*)-cyanohydrinated oxyanion and the quaternary ammonium moiety in **21**. Moreover, it is expected that $\pi-\pi$ attractive interaction between a 3,5-nitrophenyl moiety and a 9-anthrathenylmethyl group (R^3) contributes to the stability of **20** and the transition from **20** to (*S*)-**8**. Further mechanistic study is in progress.[17−19]

In conclusion, we have developed a highly enantioselective cyano-alkoxycarbonylation of α-oxoesters with alkyl cyanoformates catalyzed by a new chiral chiral Brønsted acid−Lewis base cooperative organocatalyst. The present catalysis at room temperature is of great advantage for large-scale application.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03093.

Experimental details and characterization data for the starting material and products (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support was provided in part by JSPS KAKENHI Grant Number 15H05755 and Program for Leading Graduate Schools "IGER program in Green Natural Sciences", MEXT, Japan. Y.O. is grateful for a JSPS Research Fellowship for Young Scientists.

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(10) Commercially available chloroform includes 0.5−1.0% ethanol as stabilizer. Chloroform was distilled in the presence of P_2O_5 to remove ethanol and water before its use as solvent for the cyano-alkoxycarbonylation.
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(12) The cyano-alkoxycarbonylation of aliphatic-group-substituted 2-oxoacetates **12a** and **12b** gave moderate enantioselectivities (entries 10 and 11, Table 2). In contrast, these 9-anthrathenylmethyl esters were not used as substrates because of their instability, although 9-anthrathenylmethyl esters are expected to be more suitable than PMB esters for inducing higher enantioselectivity. See also ref 19.
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(17) Although the present kinetic studies (see the Supporting Information) and the previous reports support our proposed mechanism,[4,5] we cannot exclude the possibility that asymmetric induction arises solely from the first cyanation step.
(18) Cyanohydrins were not observed during the present cyano-alkoxycarbonylation. This suggests that the cyanohydrinated oxyanion intermediates were highly unstable.
(19) The enantioselectivity in the reaction of aliphatic-group-substituted 2-oxoacetates **12a** and **12b** (entries 10 and 11, Table 2) was slightly lower than that of 2-oxo-2-phenylacetate **7e** (entry 11, Table 1). In the reaction of aliphatic substrates, the equilibrium between diastereomeric intermediates **20** and **21** might not be high enough for high enantioselectivity to be induced in the next step.

DOI: 10.1021/acs.orglett.5b03093
Org. Lett. 2015, 17, 6070−6073