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FULL PAPER

Enantioselective Cyanosilylation of α,α-Dialkoxy Ketones Catalyzed by Phosphine-Thiourea Dual-Reagent Catalysis

Qi-Wen Yu, Lu-Ping Wu, Tian-Chen Kang, Jin Xie, Feng Sha, and Xin-Yan Wu*[a]

Abstract: The first highly enantioselective cyanosilylation of α,α-dialkoxy ketones enabled by a dual-reagent catalysis has been developed. With the combination of a chiral bifunctional phosphine-thiourea and methyl acrylate, the key organophosphorus zwitterion intermediate was generated *in situ* as a novel Lewis base, which catalyzed the enantioselective cyanosilylation reaction in excellent yields (up to 99%) with good-to-excellent enantioselectivities (up to 94% *ee*).

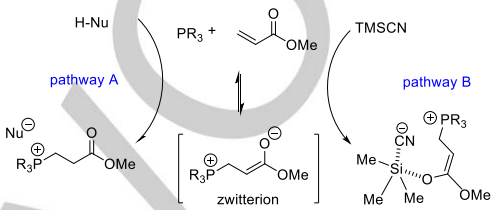

Figure 1. The activation mode of the dual-reagent catalysis

Introduction

In the past two decades, chiral phosphine organocatalysis has emerged as a powerful strategy for the enantioselective synthesis of various useful compounds.[1] Typically, the catalytic cycle is initiated by the addition of a phosphine as the Lewis base to an activated alkene/allene reactant, and then the resulting intermediate reacts with activated electrophilic partners.[2] This category includes (*aza*)-Morita-Baylis-Hillman reactions,[3] Rauhut-Currier reactions,[4] phosphine-catalyzed annulation reactions[5] and other reactions.[6] However, the catalytic mode is limited to the reactions involving electron-deficient alkenes, allenes or alkynes. Recently, Lu[7a] and Zhao[8] developed an *in situ* generated phosphonium resulted from a bifunctional phosphine and an acrylate. This so-called "asymmetric dual-reagent catalysis" mode has been successfully applied to the asymmetric conjugate addition,[7] Mannich-type reactions,[9] and Strecker reactions.[10] In this strategy, a catalytic amount of an activated alkene was cooperated with the chiral phosphine, which formed the key zwitterion as an *in situ* generated chiral Brønsted base (pathway A, Figure 1) or chiral Lewis base (pathway B, Figure 1) during the enantioselective reactions.

Catalytic asymmetric cyanation of prochiral compounds could afford versatile building blocks for pharmaceuticals, agrochemicals and specialty materials, providing an immense opportunity for the synthesis of various chiral compounds.[11] Early works on cyanohydrin syntheses were generally carried out with hydrogen cyanide as the cyanide source,[11] while the applications were limited due to its volatility and extreme toxicity. By far the most universal cyanide source, however, is trimethylsilyl cyanide (TMSCN).[12] In recent years, a couple of chiral organocatalysts have been explored for the asymmetric cyanation reactions of aldehydes, ketones and imines, with TMSCN as the cyanide source. The catalytic systems involve chiral oxazaborolidinium ions,[13] cinchona-derived organic chiral Lewis bases,[14] bifunctional tertiary amines,[15] N,N'-dioxide compounds,[16] sulfonamides,[17] amino acid salts,[18] dual-reagent catalysts[10] and so on.[19] In spite of these achievement, asymmetric cyanation of ketones are very limited.[14a,15a,16b,18] To the best of our knowledge, metal-free chiral phosphine-catalyzed cyanosilylation of carbonyl compounds is still vacant.[20] In 2010, Tian and co-workers[21] reported a racemic dual-reagent catalyzed cyanosilylation of carbonyl compounds, using triphenylphosphine and methyl acrylate as an efficient nucleophilic catalyst. Encouraged by Tian's report and with our continuing interest in enantioselective phosphine catalysis, herein, we report an asymmetric cyanosilylation reaction between TMSCN and α,α-dialkoxy ketones with a dual-reagent catalysis system, which consists of a chiral phosphine-thiourea organocatalyst and methyl acrylate.

Results and Discussion

Initially, the enantioselective cyanosilylation reaction between TMSCN and acetophenone **1a** was selected as the model reaction. The reactions were performed with different bifunctional organophosphine catalysts (Figure 2) in CH_2Cl_2 at -30 °C, and the results were summarized in Table 1. Firstly, the chiral cyclohexane-based bifunctional phosphines with different Brønsted acid group were investigated.[22] The results indicated that the H-bonding donator in the bifunctional phosphines affected the enantioselective reaction, and thiourea catalyst **C4** provided

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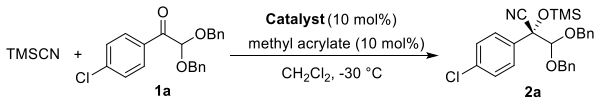
better yield and enantioselectivity than squaramide **C1**, amide **C2** and **C3** (entries 1-4). To improve the stereoselectivity, variant phosphine-thioureas were evaluated. In general, the phosphine-thioureas containing aromatic scaffolds provided higher enantioselectivities than the aliphatic analogues (entry 4-11). The highest enantioselectivity was obtained using chiral catalyst **C7** (62% *ee*, entry 7).

Table 1. Screening of the chiral bifunctional phosphine organocatalysts[a]



Entry	Catalyst	Time (h)	Yield (%)[b]	*Ee* (%)[c]
1	**C1**	3	96	4
2	**C2**	1	90	7
3	**C3**	1	87	8
4	**C4**	1	99	46
5	**C5**	3	88	48
6	**C6**	1	99	55
7	**C7**	1	99	62
8	**C8**	1	98	59
9	**C9**	1	92	59
10	**C10**	1	97	54
11	**C11**	1	89	53
12	**C12**	1	97	33
13	**C13**	1	99	-72
14	**C14**	1	90	3
15	**C15**	1	99	-78
16	**C16**	1	94	60
17	**C17**	1	96	-54

[a] The reactions were performed with TMSCN (0.2 mmol), ketone **1a** (0.1 mmol), Catalyst (0.01 mmol) and methyl acrylate (0.01 mmol) in CH_2Cl_2 (0.5 mL). [b] Isolated yields. [c] The *ee* values were determined by HPLC using a Chiralpak AD-H column. The absolute configurations of **2a** were determined by comparison of the optical rotation values reported.[14a]

In our previous work on Morita-Baylis-Hillman reaction, the phosphine-thiourea with an additional chiral group could enhance the enantioselectivity, and there was a chirality match between the chiral backbone and the additional chiral group.[23] The same effects were observed when the diastereomer **C5** and **C6** were used as catalyst for the model reaction (entries 5 and 6 vs entry 4, Table 1). Incorporation of a carbohydrate motif to the chiral thiourea catalysts might improve the enantioselectivity.[24] As predicted, the stereoselectivity of the cyanosilylation reaction was controlled by the chiral cyclohexane backbone, and gratifyingly, 78% *ee* enantioselectivity was achieved with catalyst **C15** (entries 12-17). These results indicated the (*S*,*S*)-configuration of 2-amino-1-(diphenylphosphino)cyclohexane matched well with *β*-*D*-galactose to enhance the stereochemical control.

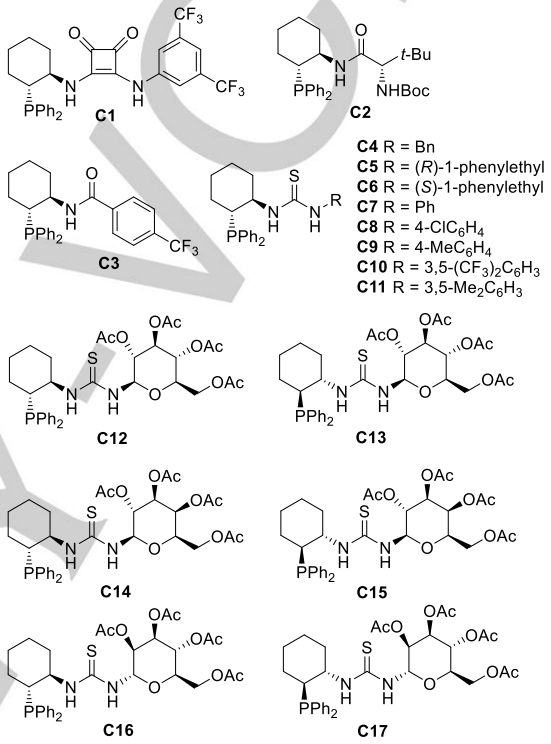
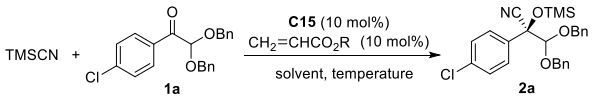


Figure 2. Structure of the chiral phosphines screened.

Subsequently, the optimization of reaction conditions was carried out with chiral phosphine **C15** (Table 2). In all the solvents examined except Et_2O, product **2a** was obtained in excellent yields (entry 1-7). Only a trace amount of product was detected with Et_2O as the solvent, probably due to the poor solubility of catalyst **C15** in Et_2O (entry 4). Compared with other solvents, MTBE turns out to be the most suitable one, which afforded product **2a** in the highest yield and enantioselectivity (1.5 h, 97% yield and 81% *ee*, entry 5). In the absence of methyl acrylate, no product was detected. The result strongly supported our hypothesis that the zwitterion generated *in situ* acted as the "real" catalyst for the enantioselective cyanosilylation reaction (entry 8). The enantioselectivity could not be improved using other acrylates, such as phenyl acrylate and butyl acrylate (entry 9-10)[8]. Lowering the reaction temperature to -78 °C enhanced the enantioselectivity significantly to give a 91% *ee*, in spite of a slightly lower yield of 92% and a prolonged reaction time of 24 h (entry 12). Furthermore, reducing the catalyst loading from 10 mol% to 5 mol% led to a loss of yield and enantioselectivity (entry

13 vs entry 12). Therefore, the optimal reaction conditions have been identified as follows: α,α-dialkoxy ketone **1** and TMSCN in MTBE (0.1 M) at -78 °C, with 10 mol% of galactose-based phosphine-thiourea **C15** and 10 mol% methyl acrylate as the chiral catalyst.

Table 2. Optimization of the reaction conditions[a]

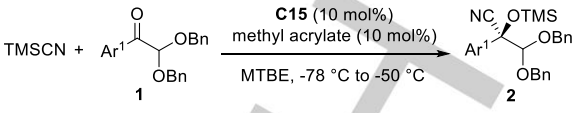


Entry	R	Solvent	Temp (°C)	Time (h)	Yield (%)[b]	*Ee* (%)[c]
1	Me	Toluene	-30	1	82	75
2	Me	CH_2Cl_2	-30	1	99	78
3	Me	$CHCl_3$	-30	1	90	79
4	Me	Et_2O	-30	120	trace	nd[d]
5	Me	MTBE	-30	1.5	97	81
6	Me	THF	-30	2	86	76
7	Me	CH_3CN	-30	1	95	71
8[e]	-	MTBE	-30	120	trace	nd
9	*t*-Bu	MTBE	-30	6	94	79
10	Ph	MTBE	-30	1.5	97	80
11	Me	MTBE	-60	6.5	96	88
12	Me	MTBE	-78	24	92	91
13[f]	Me	MTBE	-78	24	87	86

[a] Unless stated otherwise, the reactions were performed with TMSCN (0.2 mmol), ketone **1a** (0.1 mmol), catalyst **C15** (0.01 mmol) and acrylate (0.01 mmol) in solvent (0.5 mL). [b] Isolated yields. [c] The *ee* values were determined by HPLC using a Chiralpak AD-H column. [d] Referred to not detected. [e] In the absence of methyl acrylates. [f] Using 5 mol% (0.005 mmol) **C15** and methyl acrylate.

Under the established optimal reaction conditions, the substrate scope of the cyanosilylation reaction was investigated (Table 3). In general, the catalytic system showed excellent efficiency for all the substrates examined, providing good-to-excellent yields and high enantioselectivities. However, the acetal ketones with a strong electron-withdrawing group such as 4-NO_2, as well as the heterocyclic ketones exhibited relatively low enantioselectivity (entries 5 and 17), probably due to a hydrogen-bond interaction with the chiral catalyst. A certain number of acetal ketones were inert under the gelid temperature of -78 °C, and therefore the reaction temperature was raised to -60 °C or -50 °C (entries 3, 4, 6-9 and 13-17).

Table 3. Substrate scope of the acetal ketones [a]



Entry	Ar^1	Temp (°C)	Time (h)	Yield (%)[b]	*Ee* (%)[c]
1	4-ClC_6H_4	-78	20	**2a**, 89	91
2	C_6H_5	-78	20	**2b**, 89	92
3	4-FC_6H_4	-60	16	**2c**, 96	88
4	4-BrC_6H_4	-60	6	**2d**, 99	87
5	4-$NO_2C_6H_4$	-78	16	**2e**, 92	75
6	4-MeC_6H_4	-60	20	**2f**, 89	88
7	4-$MeOC_6H_4$	-60	48	**2g**, 80	79
8	3-MeC_6H_4	-50	12	**2h**, 88	86
9	3-$NO_2C_6H_4$	-50	12	**2i**, 95	87
10	3-ClC_6H_4	-78	20	**2j**, 86	94
11	2-FC_6H_4	-78	24	**2k**, 93	88
12	2-ClC_6H_4	-78	24	**2l**, 97	85
13	2-MeC_6H_4	-60	24	**2m**, 92	91
14	2,4-$Me_2C_6H_3$	-50	24	**2n**, 86	83
15	3,5-$Cl_2C_6H_3$	-60	24	**2o**, 81	88
16	2-naphthyl	-60	48	**2p**, 88	90
17	2-furyl	-50	72	**2q**, 98	66

[a] The reactions were performed with TMSCN (0.2 mmol), ketone **1** (0.1 mmol), catalyst **C15** (0.01 mmol) and methyl acrylate (0.01 mmol) in MTBE (0.5 mL). [b] Isolated yields. [c] The *ee* values were determined by chiral HPLC analysis.

Alkyl acetal ketones were also tolerated for the cyanosilylation reaction (Scheme 1). Notably, compound **4a** was achieved in 91% *ee* with 20 mol% **C15** and methyl acrylate, which could be converted to analogues of the Bisorbicillinoids.[25] According to the optical rotation values reported[14a], the absolute configuration of product **4b** was assigned as *S*-configuration.

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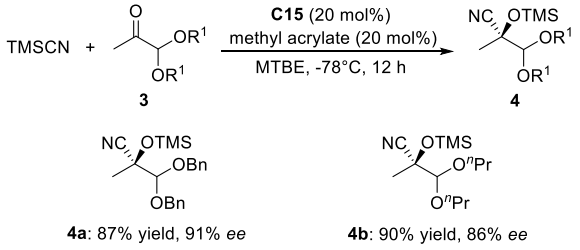
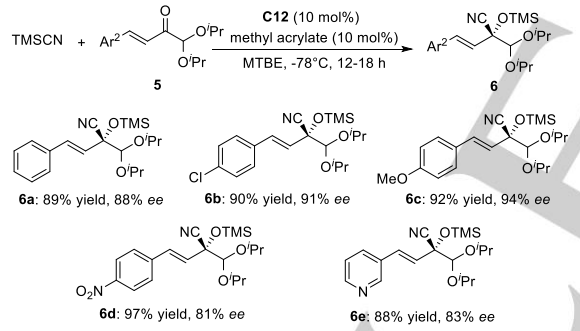
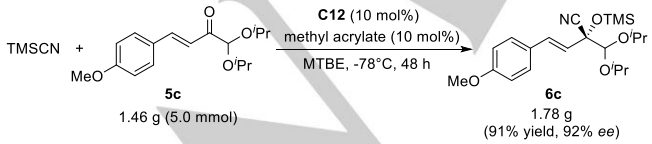


Scheme 1. The enantioselective cyanosilylation reaction between TMSCN and alkyl acetal ketones **3**

When α,β-unsaturated acetal ketone **5a** was used as substrate under the typical reaction conditions mentioned above, only 44% *ee* was obtained, which suggested that phosphine-thiourea **C15** might not be a suitable catalyst for the cyanosilylation of substrate **5a**. After screening a series of chiral bifunctional phosphine catalysts, compound **C12** was proved to be the optimal one for the enantioselective cyanosilylation reaction between TMSCN and α,β-unsaturated ketones (See ***Table S1*** and ***S2*** in the Supporting Information). Generally, the enantioselective cyanosilylation reaction of α,β-unsaturated acetal ketones and TMSCN proceeded with high 1,2-regioselectivity to afford the corresponding products **6a-6e** in high yields and good enantioselectivities (Scheme 2).



Scheme 2. The enantioselective cyanosilylation reaction between TMSCN and α,β-unsaturated acetal ketones **5**.



Scheme 3. Gram scale reaction between TMSCN and ketone **5c**

To demonstrate the practical application of this methodology, a gram-scale synthesis of product **6c** was performed (Scheme 3). The desired product was achieved in 1.78 grams with excellent yield and enantioselectivity (91% yield, 92% *ee*).

To study the mechanism of the dual-reagent catalytic system, ^{31}P NMR spectroscopy was used to explore the reaction process (Figure 3). The catalyst **C15** alone showed a ^{31}P resonance signal at -8.94 ppm. No change was observed when TMSCN was mixed with catalyst **C15** in 1:1 mole ratio. When compound **C15** was mixed with methyl acrylate in a mole ratio of 1:1, a new chemical shift of the *in situ* generated zwitterion appeared at 35.81 ppm. Moreover, in a mixture of catalyst **C15**, TMSCN and methyl acrylate (1:1:1 mole ratio), another new chemical shift was observed at 48.19 ppm, which suggested the efficient interaction between TMSCN and the zwitterion intermediate. The result also revealed the *in situ* generated zwitterion was the active species for the catalytic reaction..

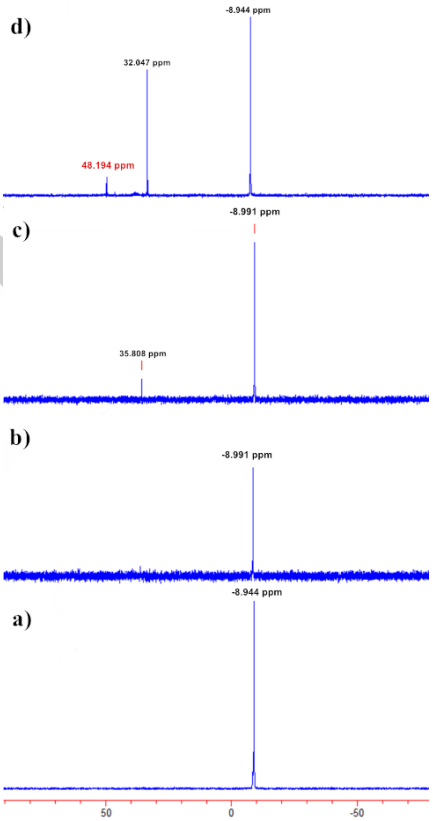


Figure 3. a) ^{31}P NMR spectrum of catalyst **C15** in $CDCl_3$. **b**) ^{31}P NMR spectrum of **C15** and TMSCN in $CDCl_3$. **c**) ^{31}P NMR spectrum of **C15** and methyl acrylate in $CDCl_3$ **d**) ^{31}P NMR spectrum of **C15**, methyl acrylate and TMSCN in $CDCl_3$.

Conclusions

In conclusion, we have developed an efficient dual-reagent catalyst system for the enantioselective cyanosilylation reaction of α,α-dialkoxy ketones. In the presence of bifunctional phosphine-thiourea **C12** or **C15** with methyl acrylate, the

cyanosilylation reaction was achieved in excellent yields (up to 99%) and with high enantioselectivities (up to 94% *ee*). Features of this asymmetric cyanation reaction include the wide substrate scope, excellent yields, highly chemo- and enantioselectivity. Further studies on enantioselective organophosphine catalysis and other potential applications of the dual-reagent catalytic system are currently underway in our group.

Experimental Section

General procedure: To a vial containing a solution of **C12** or **C15** (10 mol%) and methyl acrylate (10 mol%) in MTBE (0.5 mL) was added TMSCN (0.2 mmol) at particular temperature, followed by the addition of α,α-dialkoxyl ketone [14a,16b] (0.1 mmol). The resulting mixture was stirred at this temperature until the reaction completed (monitored by TLC). The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (petroleum ether/EtOAc) to provide enantioselective cyanohydrin trimethylsilyl ethers.

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Keywords: asymmetric catalysis • organocatalysis • dual-reagent catalysis • chiral phosphine • cyanosilylation reaction

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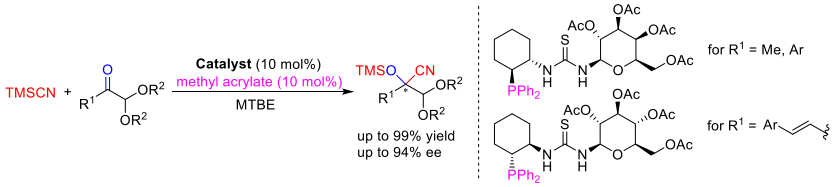

An organophosphine-catalyzed enantioselective cyanosilylation of carbonyl compounds has been disclosed for the first time. This process, the dual-reagent catalysis serves as a powerful tool, affording the desired cyanohydrin trimethylsilyl ethers in excellent yields (up to 99%) and good-to-excellent enantioselectivities (up to 94% *ee*).

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