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Activation of Chiral (Salen)AlCl Complex by Phosphorane for Highly Enantioselective Cyanosilylation of Ketones and Enones

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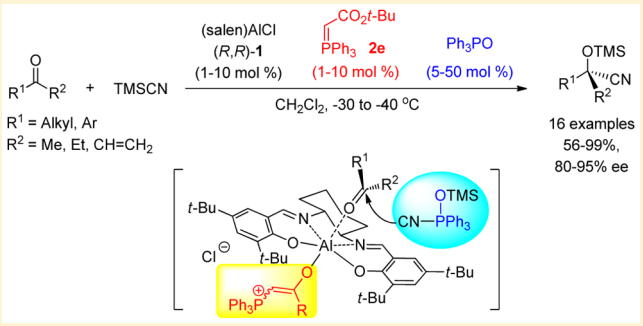
Supporting Information

ABSTRACT: Phosphoranes **2** are identified as a class of effective Lewis bases to activate chiral (salen)AlCl complex **1** to enhance its electrophilicity. Accordingly, a three-component catalyst system consisting of complex **1**, phosphorane **2e**, and Ph_3PO is developed as a powerful tool for asymmetric ketone cyanosilylation. In particular, an unprecedented highly enantioselective cyanosilylation of linear aliphatic ketones is achieved. A tandem Wittig−cyanosilylation sequence starting from phosphorane **2a** and enals **10** is further achieved, which internally utilizes the Ph_3PO byproduct and remaining phosphorane **2a** as cocatalysts for cyanosilylation of $\alpha,\beta,\gamma,\delta$-unsaturated enones, providing atom-efficient access to valuable chiral conjugated dienes and enynes. The high efficiency of the cyanosilylation originates from orthogonal activation of both (salen)AlCl complex **1** and cyanotrimethylsilane by the phosphorane and Ph_3PO, respectively. This mechanistic insight is supported by NMR, MS, and ReactIR analyses and DFT calculations. Furthermore, the formation of charged complexes through the activation of chiral complex **1** by phosphorane **2a** is confirmed by electrical conductivity experiments.



INTRODUCTION

Enhancement of the Lewis acidity of the metal center of a chiral metal complex often plays an important role in achieving a high catalytic activity for reaction development. In this context, a routine and powerful strategy is to introduce weakly or noncoordinating anions to secure high electrophilicity of a chiral metal complex.[1] It is also possible to use an achiral Lewis basic cocatalyst to activate a chiral metal complex, but this conceptually different strategy is much less explored,[2] possibly because such a type of ligand-accelerated catalysis[3] contradicts commonly held views that the binding of a Lewis base to a chiral metal complex will lead to reduced Lewis acidity.[4] According to the Lewis base catalysis defined by Denmark,[5] the activation of a chiral metal complex by a Lewis base may originate from a redistribution of electron density in the resulting Lewis adduct, which polarizes adjacent bonds to form a hypervalent species with enhanced Lewis acidity.[6] If the polarization is strong enough, ionization may occur to produce cationic species with greatly enhanced electrophilicity. Therefore, it is interesting and rewarding to exploit powerful Lewis bases to effectively activate easily available chiral metal complexes in order to improve the catalytic activity and enantioselection. In addition, two intriguing beneficial effects may be brought about: (1) Along with activation of the chiral metal complex for better electrophilic activation, it is still possible to use a second cocatalyst to activate the nucleophile. Such orthogonal activation[7] is promising to develop reactions that are unattainable by common cooperative catalysis,[8] in which the chiral catalyst is not activated. (2) It offers the promise to identify new ligand motifs, as the structural feature of a powerful cocatalyst is useful to develop new chiral ligands. Herein we report that phosphoranes **2** can effectively activate chiral (salen)AlCl complex **1**,[9] a privileged catalyst[10] that is easy to prepare and handle, which contributes to a highly enantioselective cyanosilylation of simple ketones and conjugated enones.

Since its discovery by Jacobsen and co-workers, chiral catalyst **1** has proved to be valuable in a handful of important reactions,[9,11] including the Strecker reaction,[9] conjugate addition,[11a−f] Friedel−Crafts reactions,[11g] and Passerini-type reactions.[11h−j] Despite significant achievements, it is still important to enhance the Lewis acidity of this neutral complex to expand its application. For example, alone it failed to catalyze

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Scheme 1. Asymmetric Tandem Wittig–Cyanosilylation Reaction

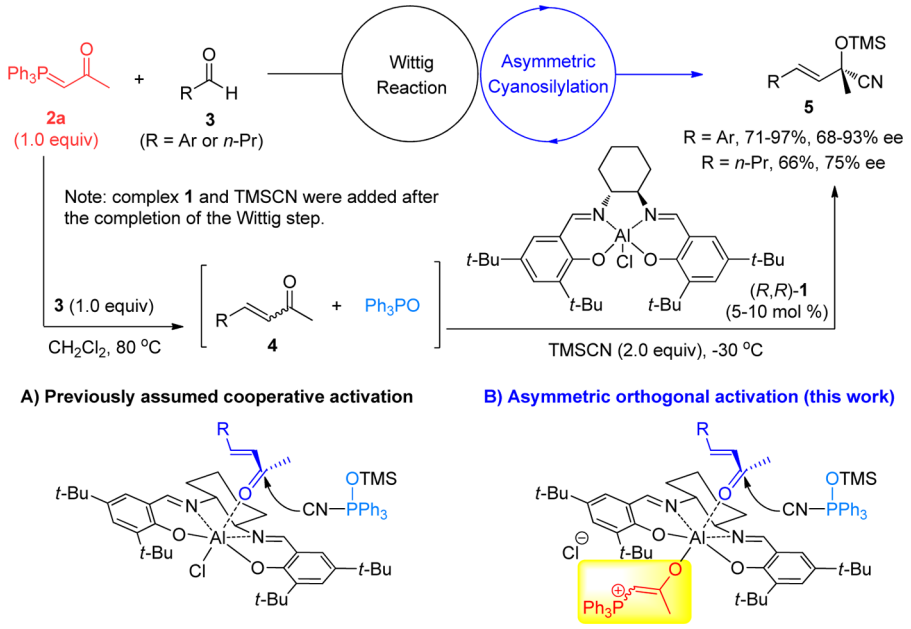
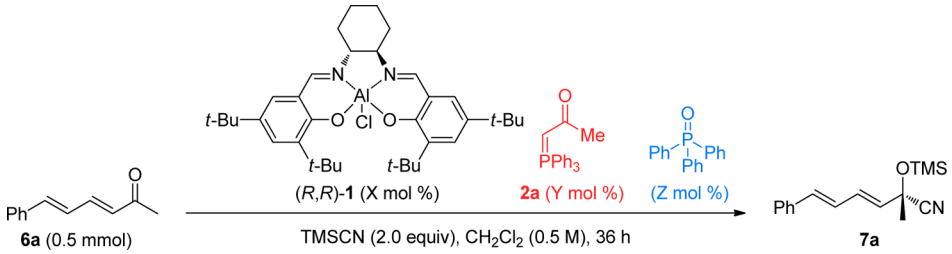


Table 1. Control Experiments for the Asymmetric Cyanosilylation of Enone 6a[a]



entry	1 (X)	2a (Y)	Ph_3PO (Z)	T (°C)	yield (%)[b]	ee (%)[c]
1	10	–	–	25	no reaction	–
2	–	–	100	25	no reaction	–
3	10	–	100	−30	<5	88
4	10	10	100	−30	90	92
5	–	10	–	−30	92	–
6	10	10	–	25	43	65
7	10	10	–	−30	<5	76

[a]For details, see section 2-1 in the SI. [b]Isolated yields. [c]Determined by chiral HPLC analysis.

ketone cyanosilylation.[12] With the cooperative activation of cyanotrimethylsilane (TMSCN) by Ph_3PO to form the more active species $Ph_3P(OTMS)(N{=}C{:})$,[13] Kim and Kwak[12] used complex **1** to realize an asymmetric ketone cyanosilylation, but the enantioselectivity had ample room to improve. On the basis of that work, we further developed a highly enantioselective tandem Wittig–cyanosilylation sequence, aiming to recycle Ph_3PO to cooperate with complex **1** for cyanosilylation of enone **4** (Scheme 1A).[14] However, subsequent studies revealed that the high efficiency of the cyanosilylation step was due to orthogonal activation of chiral complex **1** and TMSCN by phosphorane **2a** and Ph_3PO, respectively (Scheme 1B). This not only suggests the potential of phosphoranes as a type of ligand motif to develop chiral metal catalysts,[15] an untrodden path in the chemistry of ylides, but paves the way to a powerful catalyst system consisting of (salen)AlCl complex **1**, phosphorane **2e**, and Ph_3PO for asymmetric ketone cyanosilylation. It is worth mentioning that because of the importance of cyanohydrins as precursors of tetrasubstituted α-hydroxy carbonyl derivatives, much effort has been devoted to cyanation of ketones.[16] However, while several outstanding catalyst systems have been devised for highly enantioselective cyanosilylation of alkyl aryl ketones,[17] linear aliphatic ketones still present a challenge as a substrate class, and the newly identified catalyst system first enables the transformation of a number of linear aliphatic ketones to the corresponding cyanohydrins with excellent enantioselectivity (≥90% ee).

RESULTS AND DISCUSSION

Mechanistic Studies. The reaction of $\alpha,\beta,\gamma,\delta$-unsaturated enone **6a** and TMSCN was first undertaken to probe the role of each component of the catalytic system (Table 1). As expected, no reaction took place in the presence of either chiral complex **1** or Ph_3PO at 25 °C (entries 1 and 2). Ph_3PO was used at a loading of 100 mol % to mimic the condition in the tandem Wittig–cyanosilylation reaction. However, it was very

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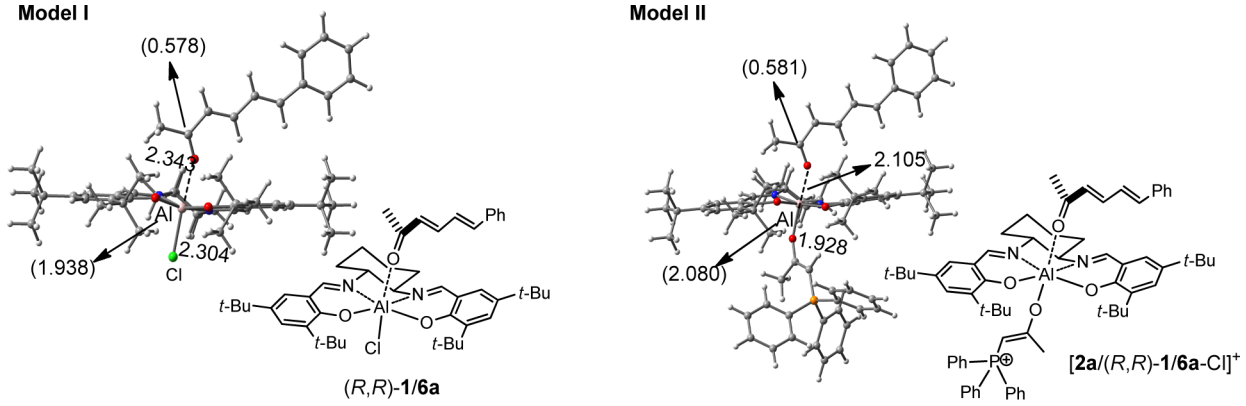

Figure 1. DFT calculation results for the two complexes (*R*,*R*)-**1**/**6a** and [**2a**/(*R*,*R*)-**1**/**6a** − Cl]$^+$, which were optimized at the B3LYP/6-31G(d) &LANL2DZ level. The bond distances of the optimized structures are given in angstroms, and the natural bond orbital (NBO) charges are shown in parentheses.

surprising that the merging of 10 mol % complex **1** and 100 mol % Ph_3PO was also inefficient in promoting the cyanosilylation at −30 °C, the previously used condition,[14] giving product **7a** in less than 5% yield even after 36 h (entry 3). Considering that in the tandem protocol there might be some phosphorane **2a** remaining from the Wittig step, we added 10 mol % **2a**, and the reaction was indeed dramatically accelerated to give product **7a** in 90% yield with 92% ee (entry 4). To understand the role of phosphorane, more control experiments were conducted. First, it was surprising that the use of 10 mol % phosphorane **2a** mediated the reaction efficiently at −30 °C to give **7a** in 92% yield (entry 5). To the best of our knowledge, the use of phosphorane as an organic promoter to trigger a reaction is unprecedented.[18] Second, without the cooperation of Ph_3PO, the merger of complex **1** and **2a** (10 mol % each) catalyzed the reaction inefficiently at 25 °C, giving **7a** in 43% yield with 65% ee after 36 h, and poorly at −30 °C (entries 6 and 7). These experiments implied that phosphorane **2a** coordinates to complex **1** to form an enhanced chiral aluminum catalyst (*R*,*R*)-**1**/**2a** (entry 1 vs 6); otherwise, free phosphorane would cause severe racemic background reaction. On the other hand, the presence of Ph_3PO was also important to secure high reactivity and enantioselectivity, as the Lewis adduct (*R*,*R*)-**1**/**2a** was impotent to mediate the reaction efficiently by itself at −30 °C (entry 7).

Next, NMR, MS, and ReactIR analyses were conducted (for details and discussion, see sections 2-2, 2-3, and 2-4 in the Supporting Information (SI), respectively), which cast some light on the possible reaction mechanism. First, ^{1}H and ^{13}C NMR analysis revealed that phosphorane **2a** binds to complex **1** in an O-coordination fashion, as shown in Scheme 1B. In addition, variable-temperature ^{31}P NMR analysis revealed that the binding of **2a** to complex **1** is tight, as it was almost undisturbed by the presence of 10 equiv of Ph_3PO. Ph_3PO might bind to the aluminum of adduct (*R*,*R*)-**1**/**2a** as well, but this interaction was labile enough to allow facile coordination of enone **6a** via ligand exchange. Second, MS analysis detected a characteristic signal [**2a** + (*R*,*R*)-**1** + **6a** − Cl]$^+$ at *m*/*z* 1061.6, consistent with the complex derived from complex **1**, phosphorane **2a**, and enone **6a**, although it was weak. Furthermore, ReactIR analysis of the reaction course confirmed that the role of Ph_3PO was to activate TMSCN to form the more active nucleophile Ph_3P(OTMS)(N═C:).[13]

After the binding of phosphorane **2a** to chiral (salen)AlCl complex **1** was confirmed by NMR and MS analyses, the enhanced electrophilicity of the resulting adduct (*R*,*R*)-**1**/**2a** could be viewed as a result of n−σ*-type Lewis base activation of the Lewis acid.[5a] According to Gutmann's rules,[6] coordination of **2a** to complex **1** might induce a redistribution of electron density in the adduct (*R*,*R*)-**1**/**2a**, leading to polarization of the Al−Cl bond, thereby decreasing the electron density at the Al center and increasing the electron density at the chlorine atom. Such a hypervalent state might further result in ionization of the chloride to afford a cationic aluminum complex with enhanced Lewis acidity. Indeed, density functional theory (DFT) calculations supported that the binding of **2a** to complex **1** easily polarized the Al−Cl bond, as the Al−Cl distance in adduct (*R*,*R*)-**1**/**2a** was obviously longer than that in (*R*,*R*)-**1** (2.538 vs 2.286 Å in CH_2Cl_2 solvent). In addition, the natural bond orbital (NBO) charge of the Al atom in adduct (*R*,*R*)-**1**/**2a** was more positive than that in (*R*,*R*)-**1** (1.983 vs 1.926 in CH_2Cl_2 solvent), while the chlorine atom had more negative charge (−0.753 vs −0.671 in CH_2Cl_2 solvent). The adduct (*R*,*R*)-**1**/**2a** could easily undergo ionization of the chloride to form the cationic complex [(*R*,*R*)-**1**/**2a** − Cl]$^+$, with a decrement of the Gibbs free energy by only 0.8 kcal/mol. Calculations revealed that the activation of enone **6a** by (*R*,*R*)-**1** was less efficient than that by complex [(*R*,*R*)-**1**/**2a** − Cl]$^+$ (model **I** vs **II**; Figure 1), since the Al−O distance in model **I** was longer than that in model **II** (2.343 vs 2.105 Å). NBO analysis also showed a more positive NBO charge of the Al atom in model **II** than in model **I** (2.080 vs 1.938). Because of the stronger Lewis acidity of the cationic complex [(*R*,*R*)-**1**/**2a** − Cl]$^+$ along with the activation of TMSCN by phosphine oxide, the barrier for the rate-determining C−C bond-forming step in the cyanosilylation of enone **6a** was lowered to 21.0 kcal/mol, representing a substantial decrease in the total activation energy by 15.3 kcal/mol from 36.3 kcal/mol (calculation based on complex **1**). On the other hand, without any catalyst the reaction proceeded with a high reaction barrier of up to 50.5 kcal/mol. These results supported the conclusion that coordination of phosphorane **2a** to complex **1** made the aluminum more electrophilic, which effectively stabilized the transition state and decreased the activation energy. For details, see section 2-5 in the SI.

In addition to DFT calculations, electrical conductivity experiments also strongly supported the formation of a cationic aluminum complex via the ionization of chloride, although we

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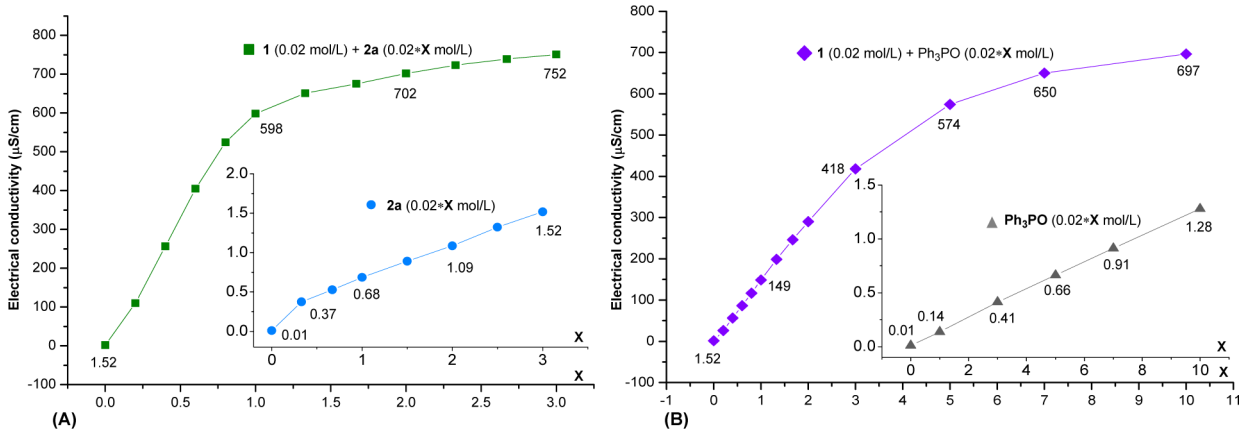
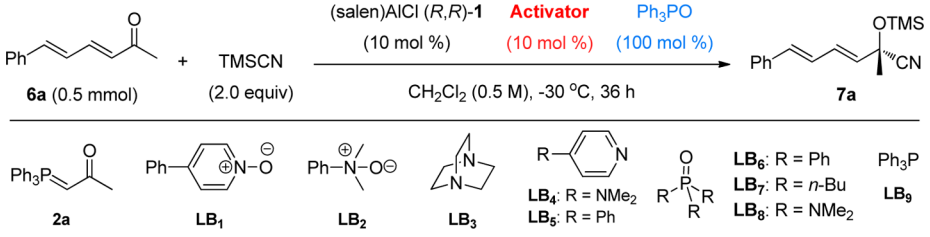


Figure 2. Electrical conductivity experiments: (A) addition of phosphorane **2a** to a CH_2Cl_2 solution of complex (*R*,*R*)-**1**; (B) addition of Ph_3PO to a CH_2Cl_2 solution of complex (*R*,*R*)-**1**.

Table 2. Comparison of Phosphorane 2a with Other Activators in the Cyanosilylation of Enone 6a



Entry	Activator	Electrical Conductivity (μS/cm)[a]		Yield (%)[b]	Ee (%)[c]
		Activator (0.02 M)	Activator/(*R*,*R*)-1 (1:1, 0.02 M)		
1	-	-	1.52	<5	88
2	**2a**	0.685	598	90	92
3	**LB_1**	0.322	245	trace	-
4	**LB_2**	1.644	255	31	91
5	**LB_3**	0.294	308	65	90
6	**LB_4**	2.84	386	45	89
7	AgOTf	0.469	37	-	
8	$AgSbF_6$	68.3	188	-	-

[a]The electrical conductivity experiments were conducted using the two-electrode method in anhydrous CH_2Cl_2 at 25 °C. [b]Isolated yields. [c]Determined by chiral HPLC analysis.

failed to obtain single crystals of Lewis adduct (*R*,*R*)-**1**/**2a** or its analogues. This experiment was inspired by Berrisford' report that a CH_2Cl_2 solution of allyltrichlorosilane became conducting in the presence of Ph_3PO, which was regarded as evidence for the formation of charged complexes in solution.[19] The electrical conductivity was measured using a two-probe method (see section 2-6 in the SI). Very interestingly, as shown in Figure 2A, although the conductivity of either complex **1** or phosphorane **2a** in CH_2Cl_2 was weak (1.52 or 0.68 μS/cm, respectively, at 0.02 mol/L, 25 °C), the addition of phosphorane **2a** to a CH_2Cl_2 solution of complex **1** dramatically increased the conductivity of the resulting solution, which soared by around 400 times to 598 μS/cm when 1.0 equiv of **2a** was added. This observation strongly supported the formation of ionic complexes via the activation of complex (*R*,*R*)-**1** by phosphorane **2a**.

On the other hand, the addition of Ph_3PO to a CH_2Cl_2 solution of complex (*R*,*R*)-**1** enhanced the conductivity as well (Figure 2B): the conductivity increased 98-fold when 1.0 equiv of Ph_3PO was added. This result indicated that Ph_3PO is less effective than **2a** in activating (*R*,*R*)-**1** to form an ionic complex, which is in accordance with NMR analyses showing that the binding of **2a** to (*R*,*R*)-**1** was almost undisturbed by the presence of even 10 equiv of Ph_3PO (section 2-2 in the SI), and the fact that the merger of 10 mol % (*R*,*R*)-**1** and 100 mol % Ph_3PO was unable to mediate the cyanosilylation of enone **6a** at −30 °C (Table 1, entry 3). This observation intrigued us to determine the changes in electrical conductivity of CH_2Cl_2 solutions of (*R*,*R*)-**1** after the addition of 1.0 equiv of typical Lewis bases and to examine whether there was a relationship between the thus-obtained conductivities and the performance

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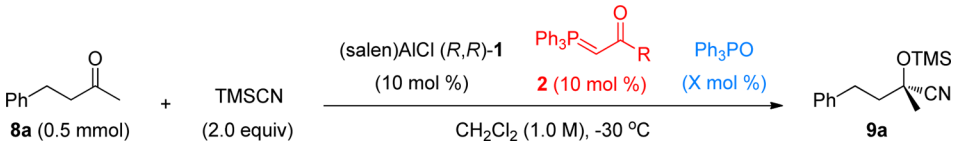
Table 3. Optimization of Conditions for the Asymmetric Cyanosilylation of 8a



entry	2	Ph_3PO (X)	time (h)	yield (%)[a]	ee (%)[b]
1	–	–	24	no reaction	–
2	–	50	24	61	87
3	**2a**: R = CH_3	50	4	95	91
4	**2b**: R = Ph	50	7	87	88
5	**2c**: R = OMe	50	7	92	91
6	**2d**: R = OEt	50	7	93	92
7	**2e**: R = O*t*-Bu	50	6	97	94
8	**2e**	–	24	36	95
9	**2e**	20	21	90	94
10	**2e**	100	8	96	94

[a]Isolated yields. [b]Determined by chiral HPLC analysis.

of these Lewis bases as additives in the (*R*,*R*)-**1**-catalyzed cyanosilylation of enone **6a**.

It is a well-known strategy to add a Lewis base to improve the outcome of reactions catalyzed by chiral salen complexes.[20] For example, 4-phenylpyridine *N*-oxide (**LB_1**) was used in chiral (salen)MnCl complex-catalyzed epoxidation to facilitate the generation and stabilization of reactive intermediates.[20a−f] In the cyanation of nitroolefins catalyzed by complex **1**, **LB_1** was proposed to serve as an axial ligand to activate complex **1** and as a Lewis base to activate TMSCN as well.[11f] It was also reported that pyridines or amines might bind to complex **1** to form (base·[Al(salen)]) complexes that showed enhanced enantioselection but diminished catalytic activity in indole alkylation.[11g] Although the role of different additive bases might vary in the cyanosilylation reaction, we compared phosphorane **2a** with some typical Lewis bases such as *N*-oxides **LB_1** and **LB_2**, tertiary amine **LB_3**, pyridines **LB_4** and **LB_5**, phosphine oxides **LB_6**−**LB_8**, and tertiary phosphine **LB_9** in both electrical conductivity experiments and cyanosilyation of enone **6a** at −30 °C (for details and discussion, see section 2-6 in the SI).

First, the four Lewis bases **2a** and **LB_2**−**LB_4**, the addition of which to CH_2Cl_2 solutions of complex **1** in a 1:1 ratio resulted in the top four highest conductivities, were also the four effective activators in the cyanosilylation of enone **6a** at −30 °C (Table 2, entries 2 and 4−6), a condition under which the merger of 10 mol % (*R*,*R*)-**1** and 100 mol % Ph_3PO was impotent (entry 1). Other Lewis bases **LB_5**−**LB_8** also brought about obvious increases in conductivity, but all failed to accelerate the reaction, possibly because they could not effectively activate complex **1**. Second, it turned out that phosphorane **2a** was the most efficient one in increasing conductivity and accelerating the cyanosilylation reaction at −30 °C (entry 2 vs entries 4−6), which suggested the potential of phosphorane as a novel type of ligand motif. Third, only the soft Lewis base Ph_3P was inert in both the conductivity experiment and the cyanosilylation reaction, possibly because it had no effective interaction with the hard Lewis acid Al(III). It should be noted that the role of Lewis bases **LB_2**−**LB_4** in accelerating the cyanosilylation was not clear at this stage, as whether their binding to complex **1** was undisturbed by the presence of 10 equiv of Ph_3PO was not confirmed.[21]

We further examined the performance of cationic aluminum complexes produced from (*R*,*R*)-**1** via halide abstraction using an appropriate silver salt in the cyanosilylation of enone **6a**.[22] Very surprisingly, no reaction at all took place when either AgOTf or $AgSbF_6$ was used to activate chiral complex **1** to form the corresponding cationic complex, regardless of whether AgCl was filtered off or not (Table 2, entries 7 and 8). In addition, the conductivity of the CH_2Cl_2 solution of (*R*,*R*)-**1** with 1.0 equiv of AgOTf or $AgSbF_6$ was much lower than that of (*R*,*R*)-**1** with 1.0 equiv of phosphorane **2a** (entry 2 vs entries 7 and 8). The conductivity of $AgSbF_6$ in CH_2Cl_2 was much higher than that of AgOTf, which is due in part to its good solubility in CH_2Cl_2. These results unambiguously demonstrated that the strategy of Lewis base activation of chiral metal complexes has its own advantages compared with the alternative strategy of generating cationic chiral catalysts by halide abstraction.

Noticeably, the use of electrical conductivity experiments to detect the formation of charged complexes via the activation of chiral metal complexes was unprecedented. Our results suggested that it is possible to use this cost-effective and convenient method for rapid screening of Lewis bases that could effectively activate a chiral metal complex, although it was inappropriate to directly correlate the conductivity with the extent to which a chiral catalyst was activated. In addition, as the strategy of Lewis base activation of Lewis acids[23] was important in the field of asymmetric catalysis, conductivity experiments might have more application in mechanistic studies.

Enantioselective Cyanosilylation of Simple Ketones. The finding that phosphorane **2a** could activate complex **1** implied the possibility of varying its substituent to improve the enantioselection. This hypothesis, along with the fact no literature method could achieve more than 90% ee in the cyanosilylation of linear aliphatic ketones,[17] prompted us to tune the substituent of phosphorane **2** in the cyanosilylation of ketone **8a** to identify a highly enantioselective catalyst system based on chiral (salen)AlCl complex **1** for ketone cyanosilylation. As expected, (*R*,*R*)-**1** failed to mediate this reaction by itself (Table 3, entry 1). The merger of 10 mol % (*R*,*R*)-**1** and 50 mol % Ph_3PO catalyzed the reaction slowly, giving product **9a** in 61% yield with 87% ee after 24 h (entry 2). This result suggested that aliphatic ketone **8a** was more active than enone **6a**. The addition of 10 mol % phosphorane **2a** greatly accelerated the reaction to finish within 4 h, giving product

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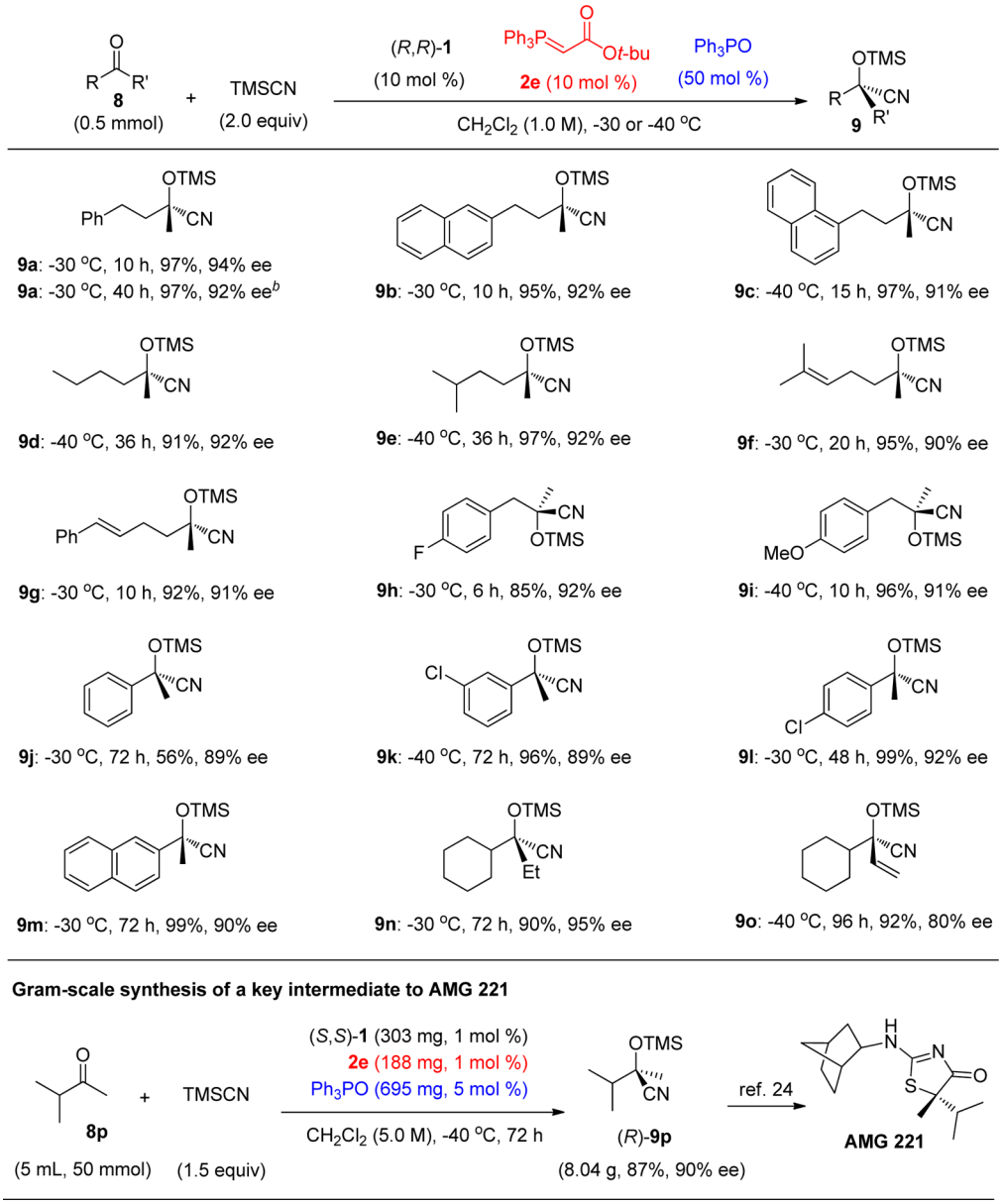
Scheme 2. Scope of Catalytic Asymmetric Ketone Cyanosilylation[a]



[a]Isolated yields are shown; ee values were determined by chiral HPLC analysis. [b]On a 10 mmol scale using 1 mol % (*R*,*R*)-**1**, 1 mol % **2e**, and 5 mol % Ph_3PO in 5 mL of CH_2Cl_2.

9a in 95% yield with 91% ee (entry 3). Finally, it was revealed that the use of bulkier phosphorane **2e** as the cocatalyst could improve the enantioselectivity to 94% (entry 7). In addition, the merger of (*R*,*R*)-**1** and **2e** (10 mol % each) could also catalyze the reaction slowly at −30 °C (entry 8), while the presence of Ph_3PO obviously accelerated the reaction, and 50 mol % was enough (entries 7−10). Generally, higher enantioselectivity was observed when any of phosphoranes **2a**−**e** was used as an activator (entries 3−7 vs entry 2). Possibly, the binding of a bulky phosphorane as an axial ligand to (salen)Al complex **1** tuned the overall conformation of the salen complex,[24] which contributed to more effective enantiofacial control.

On the basis of the above screening, we examined the scope of ketone cyanosilylation catalyzed by the combined system of (*R*,*R*)-**1**, phosphorane **2e**, and Ph_3PO (Scheme 2). Very impressively, a variety of differently substituted aliphatic ketones worked well to give the desired cyanohydrins **9a**−**i** in 85−97% yield with 90−94% ee. In addition, aryl ketones were also viable substrates, as shown by the synthesis of cyanohydrins **9j**−**m** with 89−92% ee. Non-methyl ketones were also viable substrates. For example, cyclohexyl ethyl ketone gave the desired product **9n** in 90% yield with 95% ee. Nevertheless, cyclohexyl vinyl ketone (**8o**) afforded product **9o** with diminished enantioselectivity (80% ee).

The catalyst loading could be lowered to 1.0 mol % (*R*,*R*)-**1**, 1 mol % phosphorane **2e**, and 5 mol % Ph_3PO. For example, the cyanosilylation of ketone **8a** on a 10 mmol scale readily afforded the desired product **9a** in 97% yield with 92% ee. Furthermore, the use of chiral complex (*S*,*S*)-**1** allowed the gram-scale synthesis of cyanohydrin (*R*)-**9p** from methyl isopropyl ketone (**8p**) (8.04 g, 87% yield, 90% ee), which is the key intermediate in the synthesis of AMG 21, an inhibitor of 11β-hydroxysteroid dehydrogenase type 1.[25]

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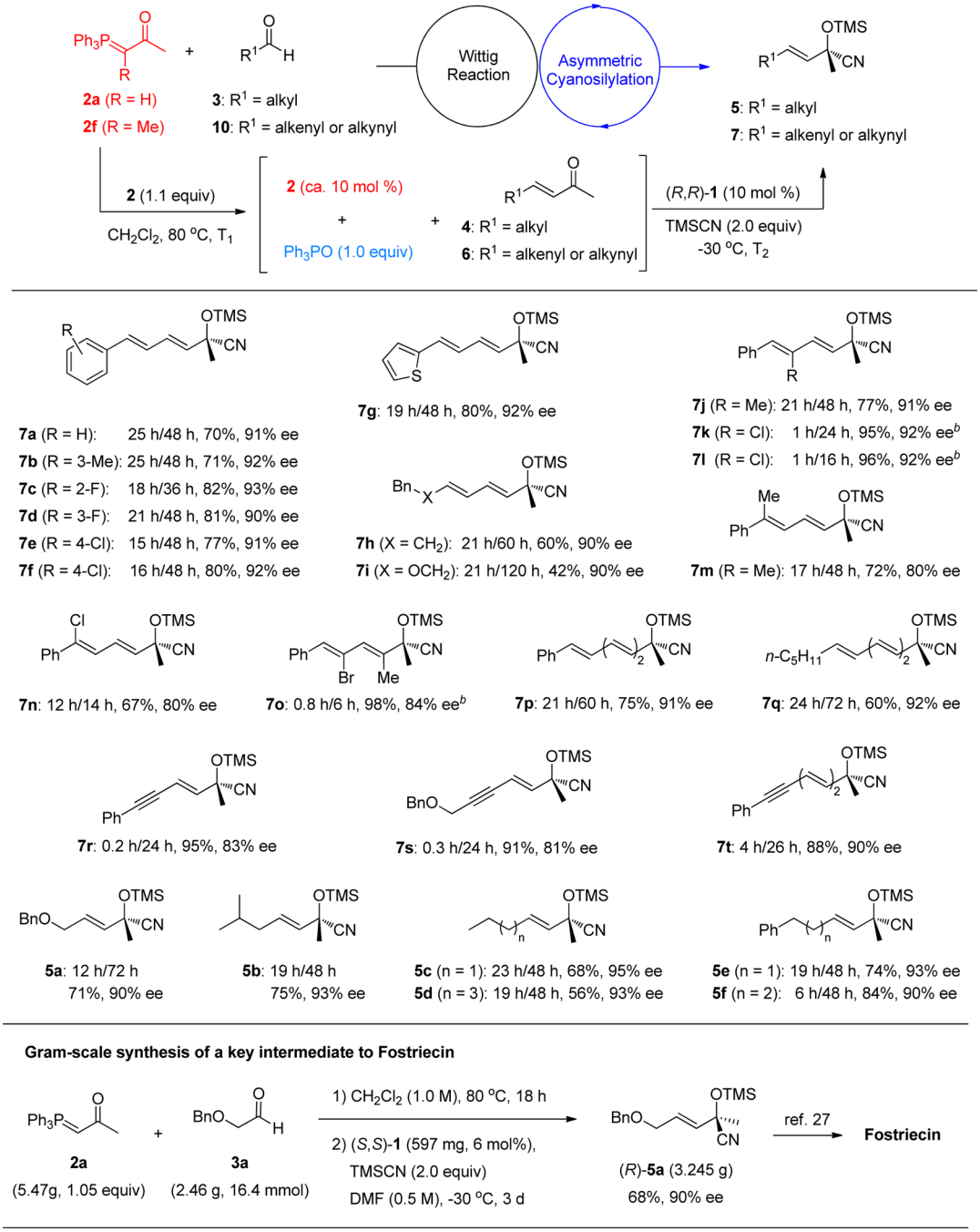
Scheme 3. Substrate Scope of the Tandem Wittig–Cyanosilylation Sequence[a,b]



[a]The results of each product are listed as T_1/T_2, isolated yield/ee value (for details, see sections 4 and 5 in the SI). [b]The cyanosilylation was run at −40 °C.

Tandem Wittig–Asymmetric Cyanosilylation Sequence. Considering the lack of a highly enantioselective cyanosilylation of α,β,γ,δ-unsaturated enones,[16,17] we further developed a tandem Wittig–cyanosilylation sequence starting from phosphorane **2a** and α,β-unsaturated enals **10** for the atom-efficient synthesis of optically active cyanohydrins bearing a conjugated diene or enyne group as a synthetically versatile handle,[26] as shown in Scheme 3. The one-pot procedure was operationally simple. After completion of the initial Wittig reaction of enal **10** with ylide **2a**, carried out in a screw-capped pressure tube using CH_2Cl_2 as the solvent at 80 °C, chiral complex **1** and TMSCN were successively added. The following asymmetric cyanosilylation was conducted at −30 or −40 °C until completion. It was noteworthy that a high ee value of **7a** could be secured when the ratio of phosphorane **2a** to chiral complex **1** ranged from 1.0:5.0 to 2.0:1.0 (see Table S1 in the SI), so 1.1 equiv of **2a** was used to ensure full conversion of the aldehyde and the presence of at least 10 mol % phosphorane **2a**.

A variety of dienes **7a–o** bearing a tetrasubstituted carbon stereocenter with two, three, or four substituents on the alkene functionality were readily prepared in good yields with high to excellent enantioselectivities. In addition, optically active conjugated trienes **7p** and **7q** and enynes **7r–t** with either an

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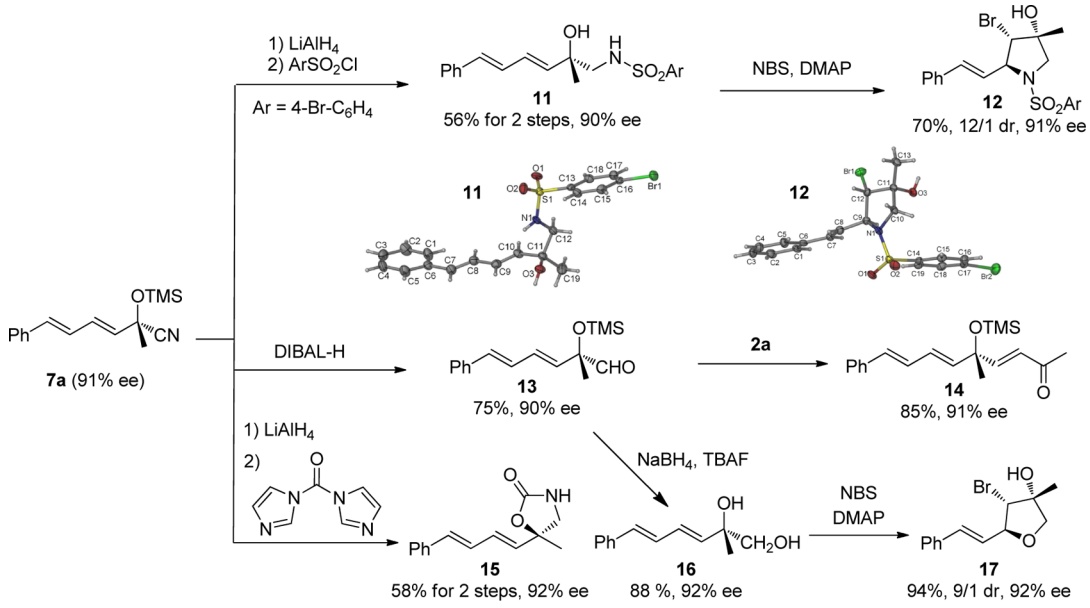
Scheme 4. Product Elaboration



aryl or alkyl group could also be accessed with high to excellent enantioselectivities from the corresponding α,β-unsaturated enals. By using *N*,*N*-dimethylformamide (DMF) as the solvent for the cyanosilylation step, we further realized the highly enantioselective cyanosilylation of β-alkyl-substituted enones **4** derived from aliphatic aldehydes and phosphorane **2a**, which was unsuccessful under our previous conditions.[14] For example, products **5a**–**f** were all obtained in high yields with excellent enantioselectivities (Scheme 3). To show the practical use of our tandem sequence, we tried a gram-scale synthesis of cyanohydrin (*R*)-**5a**, which was used as the key synthon for the total synthesis of fostriecin,[27] a natural antibiotic. Starting from aldehyde **3a** and a slight excess of **2a**, the use of 6 mol % complex (*S*,*S*)-**1** afforded the desired cyanohydrin (*R*)-**5a** in 68% yield (3.245 g) with 90% ee. Apart from the advantages of using easily available chiral catalyst **1** and the higher ee value for (*R*)-**5a**, our protocol was free from the isolation of the intermediate enone.

An attractive feature of the above sequence is that both of the cocatalysts required for asymmetric cyanosilylation step (phosphorane **2a** and Ph_3PO) are the remaining reagent or byproduct from the Wittig step. This represents a unique advantage of such tandem reactions, as the internal reuse of waste alleviates the use of extra substances, which is helpful in reducing waste generation. It is worth mentioning that despite some progress, tandem reactions that internally reuse waste to benefit downstream catalytic asymmetric steps are still very limited,[14,28] as putting waste into use while avoiding the deactivation of the chiral catalyst requires rational design. This research outlines a promising strategy characterized by merging the waste with a chiral catalyst to form a multicatalyst system[29] in order to realize an asymmetric reaction unattainable by the chiral catalyst itself. This is complementary to the strategy pioneered by Shibasaki and co-workers, namely, recycling of the waste as an additive to improve the reactivity and stereoselectivity.[28a] Furthermore, the unexpected finding of phosphorane as a powerful cocatalyst capable of activating the chiral (salen)AlCl complex demonstrates that the development of tandem reactions that internally reuse waste is not always the simple combination of known knowledge but offers the promise to discover new chemistry.

Product Elaboration. While the versatility of cyanohydrins as building blocks had been well-documented,[16] the elaboration of cyanohydrins **7** featuring a conjugated diene group had not been reported. Therefore, we examined the synthetic potential of compound **7a** and found that it could be readily converted to amino alcohol **11**, aldehyde **13**, enone **14**, oxazoline **15**, and diol **16** with a conjugated diene moiety at the tetrasubstituted carbon stereocenter (Scheme 4). Moreover, the synthesis of polysubstituted pyrrolidine **12** and tetrahydrofuran **17** from **7a** was also achieved. The absolute configuration of **11** was determined to be *S* by X-ray analysis, and that of **7a** was accordingly assigned to be *S*. The relative configuration of pyrrolidine **12** was assigned by X-ray analysis.

CONCLUSION

We identified phosphoranes as a class of potent cocatalysts capable of effective activation of chiral (salen)AlCl complex **1** via mechanistic studies of a tandem Wittig–asymmetric cyanosilylation reaction. A three-component catalyst system consisting of complex **1**, phosphorane **2**, and Ph_3PO was then developed for the highly enantioselective cyanosilylation of a broad scope of ketones and conjugated enones. The high efficiency of this catalyst system originates from orthogonal activation of (salen)AlCl complex **1** and TMSCN by the phosphorane and Ph_3PO, respectively, which further exhibits that asymmetric orthogonal activation of the chiral catalyst and both reactants is a promising approach to develop enantioselective reactions that are unattainable by monocatalysis or common cooperative catalysis. The fact that phosphorane **2a** is more efficient than some common Lewis bases in accelerating asymmetric ketone cyanosilylation suggests the potential of phosphoranes as a novel type of ligand motif to develop chiral metal catalysts. In view of the powerfulness of chiral (salen)AlCl complex **1**,[9,11] the development of chiral salen–ylide aluminum complexes to exploit new enantioselective reactions is in progress in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11476.

Crystallographic data for **11** (CIF)
Crystallographic data for **12** (CIF)
Experimental procedures, characterization data and details of DFT calculations (PDF)
Copies of NMR spectra and HPLC traces for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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