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

Xing-Ping Zeng,[1] Zhong-Yan Cao,[1] Xin Wang,[2] Long Chen,[1] Feng Zhou,[1] Feng Zhu,[1] Cui-Hong Wang,[1] and Jian Zhou*[1,3]

[1]Shanghai Key Laboratory of Green Chemistry and Chemical Processes, School of Chemistry and Molecular Engineering, East China Normal University, Shanghai, 200062, P R China; [2]College of Chemistry, Sichuan University, Chengdu, 610064, P R China; [3]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, P R China.

ABSTRACT: Phosphoranes **2** are identified as a type 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 by-product Ph_3PO and remaining phosphorane **2a** as co-catalysts for cyanosilylation of α,β,γ,δ-unsaturated enones, providing an 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 TMSCN by phosphorane and Ph_3PO, respectively. This mechanistic insight is supported by NMR, MS, react IR analysis 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.

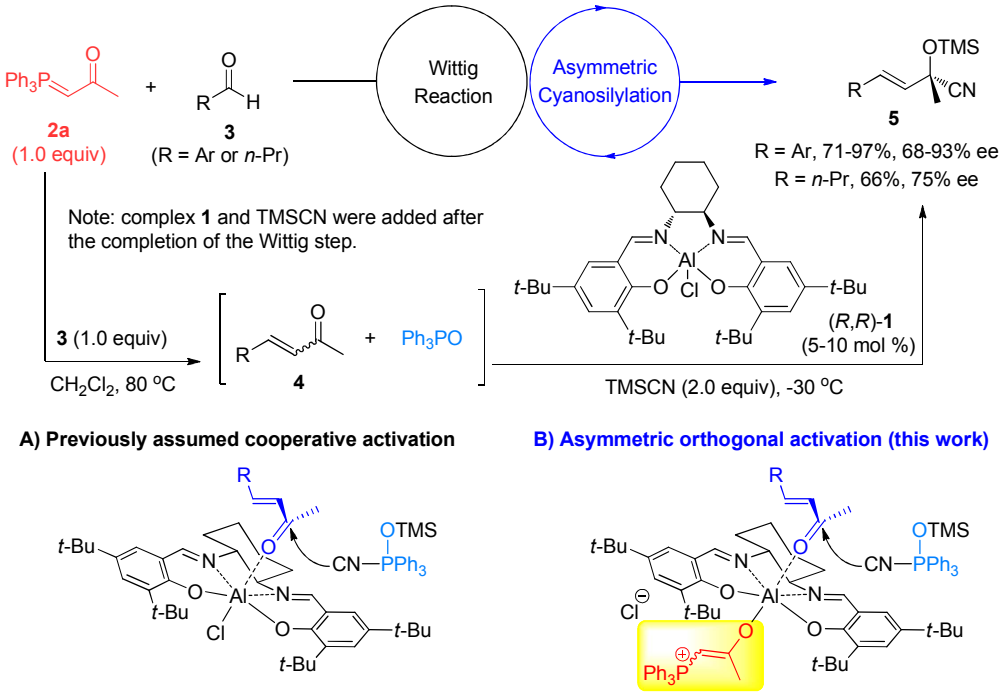
■ INTRODUCTION

To enhance the Lewis acidity of the metal centre 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 non-coordinating anions to secure high electrophilicity of a chiral metal complex.[1] It is also possible to use an achiral Lewis basic co-catalyst 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 re-distribution of electron-density in the resulting Lewis adduct, which polarizes adjacent bonds to form a hypervalent species with enhanced Lewis acidity.[6] Given polarization 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, to improve catalytic activity and enantioselection. In addition, two intriguing beneficial effects may be brought about: (1) Along with the activation of chiral metal complex for better electrophilic activation, it is still possible to use a second co-catalyst to activate the nucleophile. Such an orthogonal activation[7] is promising to develop reactions 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 co-catalyst is useful to develop new chiral ligands. Herein, we wish to report that phosphorane **2** can effectively activate chiral (salen)AlCl complex **1**[9], a privileged catalyst[10] easy to prepare and handle, which contributes to a highly enantioselective cyanosilylation of simple ketones and conjugated enones.

Since its discovery by Jacobsen et al, chiral catalyst **1** has proved to be valuable in a handful of important reactions,[9,11] including Strecker reaction,[9] conjugate addition,[11a-f] Friedel-Crafts[11g] and Passerini-type reaction[11h-j]. Despite significant achievements, it is still important to enhance the Lewis acidity of this neutral complex to expand its application. For example, it alone failed to catalyze ketone cyanosilylation.[12] With the cooperative activation of TMSCN by Ph_3PO to form a more active species $Ph_3P(OTMS)(N{=}C{:})$,[13] Kim et al used complex **1** to realize an asymmetric ketone cyanosilylation, but the enantioselectivity had ample room to improve.[12] Based on this work, we further developed a highly enantioselective tandem Wittig-cyanosilylation sequence, aiming at recycling Ph_3PO to cooperate with complex **1** for cyanosilylation of enone **4** (A, Scheme 1).[14] However, subsequent studies revealed the high efficiency of cyanosilylation step was attributed to orthogonal activation of chiral complex **1** and TMSCN by phosphorane **2a** and Ph_3PO, respectively (B, Scheme 1). This not only suggests the potential of phosphoranes as a type of ligand motifs 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 owing to the importance of cyanohydrins as precursors to 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 in excellent enantioselectivity (≥90% ee).

Scheme 1. Asymmetric tandem Wittig-cyanosilylation reaction

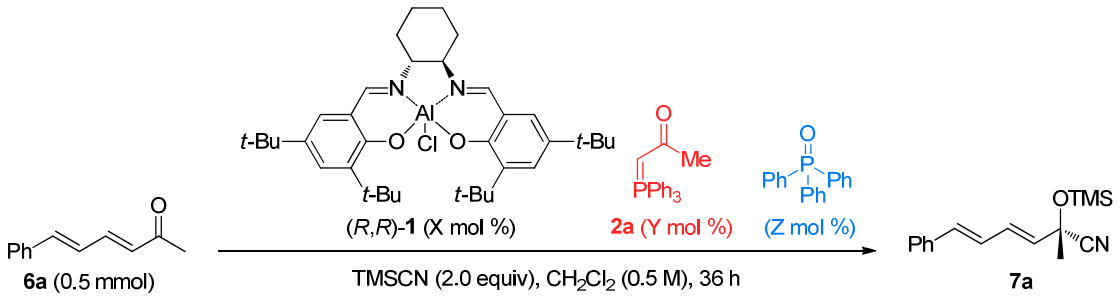


■ RESULTS AND DISCUSSION

Mechanistic Studies. The reaction of α,β,γ,δ-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 1-2). Ph_3PO was used in 100 mol % to mimic the condition in tandem Wittig-cyanosilylation reaction. However, it was very surprising that the merging of 10 mol % complex **1** and 100 mol % Ph_3PO was also inefficient to promote 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, 10 mol % **2a** was added, and the reaction was indeed dramatically accelerated to give product **7a** in 90% yield and 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, 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 to give **7a** in 43% yield with 65% ee after 36 h, and poorly at -30 °C (entries 6-7). These experiments implied that phosphorane **2a** coordinated 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 (entries 7).

Table 1. Control experiments for asymmetric cyanosilylation of enone 6a[a]



Entry	**1** (X)	**2a** (Y)	Ph_3PO (Z)	Temp. (°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 of SI. [b]Isolated yield. [c]Determined by chiral HPLC analysis.

In the following, NMR, MS and React IR analysis were conducted (for details and discussion, see section 2-2, 2-3 and 2-4 of supporting information, SI, respectively), which cast some light on the possible reaction mechanism. First, ^1H and ^{13}C NMR analysis revealed that phosphorane **2a** bound to complex **1** in an *O*-coordination fashion, as shown in B of Scheme 1. In addition, variable temperature ^{31}P NMR analysis revealed that the binding of **2a** to complex **1** was tight, almost undisturbed by the presence of 10 equiv of Ph_3PO. Ph_3PO might bind to 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, react IR analysis of the reaction course confirmed that the role of Ph_3PO was to activate TMSCN to form a more active nucleophile $Ph_3P(OTMS)(N{=}C{:})$.[13]

Now that the binding of phosphorane **2a** to chiral (salen)AlCl complex **1** was confirmed by NMR and MS analysis, 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 Lewis acid.[5a] According to Gutmann's rules,[6] the coordination of **2a** to complex **1** might induce a re-distribution of electron density in the adduct (*R*,*R*)-**1**/**2a**, leading to the polarization of the Al-Cl bond, thereby decrease the electron density at the Al center and increase 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 solvent CH_2Cl_2). In addition, the natural bond orbital (NBO) charge of Al atom in adduct (*R*,*R*)-**1**/**2a** was more positive than that in (*R*,*R*)-**1** (1.983 vs 1.926 in solvent CH_2Cl_2), while the chlorine atom had more negative charge (-0.753 vs -0.671 in solvent CH_2Cl_2). The adduct (*R*,*R*)-**1**/**2a** could easily undergo an ionization of the chloride to form a cationic complex [(*R*,*R*)-**1**/**2a**-Cl]$^+$, with a decrement of Gibbs free energy by only 0.8 kcal/mol. Calculation revealed that the activation of enone **6a** by (*R*,*R*)-**1** was less efficient than 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). The NBO analysis also showed the more positive NBO charge of Al atom in model **II** than that in model **I** (2.080 vs 1.938). Owing to the stronger Lewis acidity of cationic complex [(*R*,*R*)-**1**/**2a**-Cl]$^+$, along with the activation of TMSCN by phosphine oxide, the barrier of the rate-determining C–C bond forming step of cyanosilylation of enone **6a** was lowered down to 21.0 kcal/mol, with 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 up to 50.5 kcal/mol. These results supported that the 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 of SI.

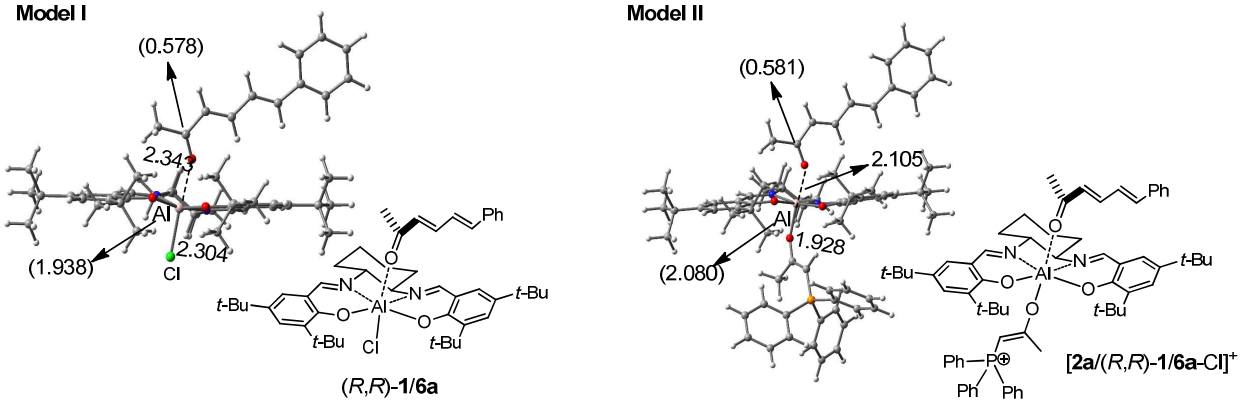


Figure 1. DFT calculation results: Two complexes of (*R*,*R*)-**1**/**6a** and [**2a**/(*R*,*R*)-**1**/**6a**-Cl]$^+$, which were optimized at the B3LYP/6-31G(d)&LANL2DZ level. The bond distances of the optimized structures are in angstroms and the natural bond orbital (NBO) charges are in parentheses.

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 failed to obtain single crystals of Lewis adduct (*R*,*R*)-**1**/**2a** or its analogues. This experiment was inspired by Berrisford' report that the CH_2Cl_2 solution of allyltrichlorosilane became conducting in the presence of Ph_3PO, which was regarded as an evidence for the formation of charged complexes in solution.[19] The electrical conductivity was measured using a two-probe method (see section 2-6 of 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 and 0.68 μS/cm, 0.02 mol/L, 25 °C, respectively), 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**.

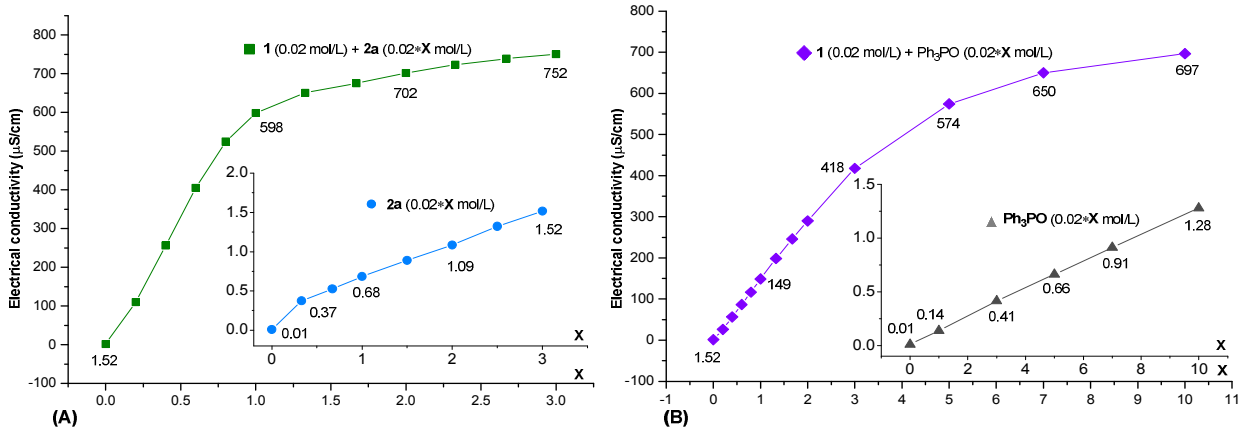
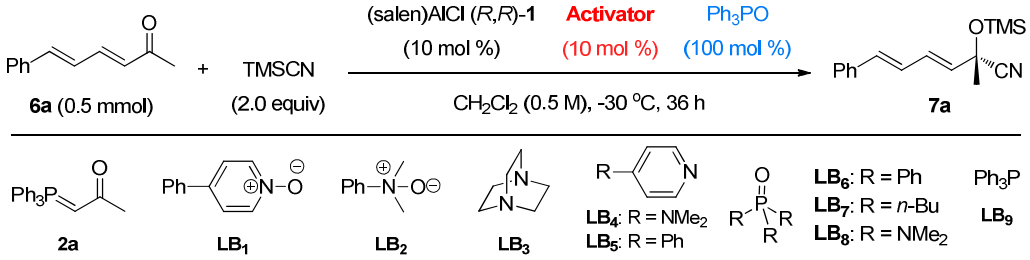


Figure 2. Electrical conductivity experiments: (A) the addition of phosphorane **2a** to the CH_2Cl_2 solution of complex (*R*,*R*)-**1**; (B) the addition of Ph_3PO to the CH_2Cl_2 solution of complex (*R*,*R*)-**1**.

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), which was increased by 98 times when 1.0 equiv of Ph_3PO was added. This result indicated that Ph_3PO was less effective than **2a** in activating (*R*,*R*)-**1** to form ionic complex, which was in accordance with NMR analyses that the binding of **2a** to (*R*,*R*)-**1** was almost undisturbed by the presence of even 10 equivs of Ph_3PO (section 2-2 of 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 (entry 3 of Table 1). This observation intrigued us to determine the changes in electrical conductivity of the CH_2Cl_2 solution 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 conductivity and the performance of these Lewis bases as additives in (*R*,*R*)-**1** catalyzed cyanosilylation of enone **6a**.

Table 2. Compare 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 2-electrode method in anhydrous CH_2Cl_2 at 25 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

It was a well-known strategy to add a Lewis base to improve the reaction outcome of chiral salen complexes catalyzed reactions.[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$_{1\text{-}2}$**, tertiary amine **LB$_3$**, pyridines **LB$_{4\text{-}5}$**, phosphine oxides **LB$_{6\text{-}8}$** 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 of SI).

First, the four Lewis bases (phosphorane **2a** and **LB$_{2\text{-}4}$**), the addition of which to a CH_2Cl_2 solution of complex **1** in 1:1 ratio resulted in the top four highest conductivity, were also the four effective activators in the cyanosilylation of enone **6a** at -30 °C (entries 2 and 4-6), a condition

that the merger of 10 mol% (*R*,*R*)-**1** and 100 mol% Ph_3PO was impotent (entry 1). Other Lewis bases **LB$_{5-8}$** also brought about obvious increase 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 ^oC (entry 2 vs entries 4-6), which suggested the potential of phosphorane as a novel type of ligand motifs. Third, only soft Lewis base Ph_3P was inert in both conductivity experiment and cyanosilylation reaction, possibly because it had no effective interaction with hard Lewis acid Al(III). It should be noted that the role of Lewis bases **LB$_{2-4}$** in accelerating the cyanosilylation was not clear at this stage, as whether or not their binding to complex **1** was undisturbed by the presence of 10 equivs of Ph_3PO was not confirmed.[21]

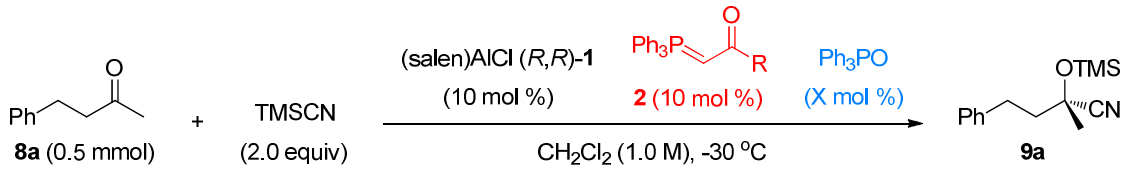
We further examined the performance of cationic aluminum complexes produced from (*R*,*R*)-**1** via halide abstraction using an appropriate silver salt in the cyanosilylation of enone **6a**.[22] Very surprisingly, no reaction took place at all when using either AgOTf or $AgSbF_6$ to activate chiral complex **1** to form the corresponding cationic complex, no matter AgCl was filtered off or not (entries 7-8). 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 7-8). The conductivity of $AgSbF_6$ in CH_2Cl_2 was much higher than that of AgOTf was in part due to its good solubility in CH_2Cl_2. These results unambiguously exhibited that the strategy of Lewis base activation of chiral metal complex had its own advantages, as compared with the alternative strategy of generating cationic chiral catalyst 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 it 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 acid[23] was important in the field of asymmetric catalysis, the conductivity experiment might have more application in the 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 enantioselection. This hypothesis, along with the fact no literature method could achieve more than 90% ee in the cyanosilylation of linear aliphatic ketones,[17] promoted 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 (entry 1, Table 3). The merger of 10

mol % (*R*,*R*)-**1** and 50 mol % Ph_3PO catalyzed the reaction slowly, giving product **9a** in 61% yield and 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 **9a** in 95% yield and 91% ee (entry 3). Finally, it was revealed that a bulkier phosphorane **2e** as the co-catalyst 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), the presence of Ph_3PO obviously accelerated the reaction, and 50 mol % was enough (entries 7, 8-10). 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 salen complex,[24] which contributed to a more effective enantiofacial control.

Table 3. Condition optimization for the asymmetric cyanosilylation of 8a



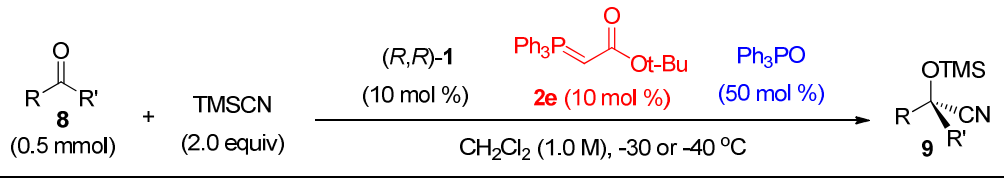
Entry	**2**	Ph_3PO (X)	Time (h)	Yield (%)[a]	Ee (%)[b]
1	-	-	24	No reaction	-
2	-	50	24	61	87
3	**2a**: R = CH_3	50	4	95	91
4	**2b**: R = Ph	50	7	87	88
5	**2c**: R = OMe	50	7	92	91
6	**2d**: R = OEt	50	7	93	92
7	**2e**: R = O*t*-Bu	50	6	97	94
8	**2e**	-	24	36	95
9	**2e**	20	21	90	94
10	**2e**	100	8	96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

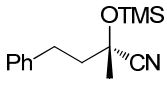
[a] Isolated yield. [b] Determined by chiral HPLC analysis

Based on the above screening, we examined the scope of ketone cyanosilylation catalyzed by a 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 and 90-94% ee. In addition, aryl ketones were also viable substrates, as shown by the synthesis of cyanohydrins **9j-m** in 89-92% ee. Non-methyl ketones were also

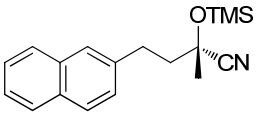
viable substrates. For example, cyclohexyl ethyl ketone gave the desired product **9n** in 90% yield and 95% ee. Nevertheless, cyclohexyl vinyl ketone **8o** afforded product **9o** in diminished 80% ee.

Scheme 2. Scope of catalytic asymmetric ketone cyanosilylation [a]

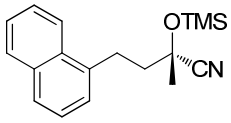




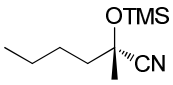
9a: -30 °C, 10 h, 97%, 94% ee
9a: -30 °C, 40 h, 97%, 92% ee[b]



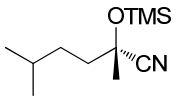
9b: -30 °C, 10 h, 95%, 92% ee



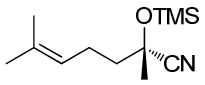
9c: -40 °C, 15 h, 97%, 91% ee



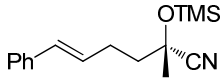
9d: -40 °C, 36 h, 91%, 92% ee



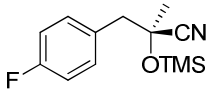
9e: -40 °C, 36 h, 97%, 92% ee



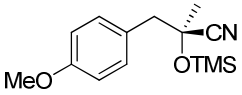
9f: -30 °C, 20 h, 95%, 90% ee



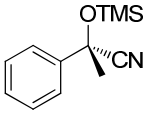
9g: -30 °C, 10 h, 92%, 91% ee



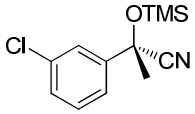
9h: -30 °C, 6 h, 85%, 92% ee



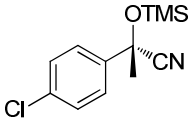
9i: -40 °C, 10 h, 96%, 91% ee



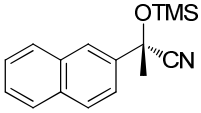
9j: -30 °C, 72 h, 56%, 89% ee



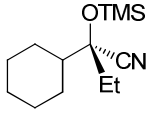
9k: -40 °C, 72 h, 96%, 89% ee



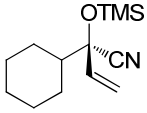
9l: -30 °C, 48 h, 99%, 92% ee



9m: -30 °C, 72 h, 99%, 90% ee

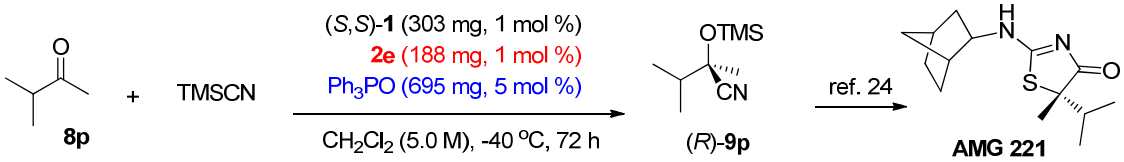


9n: -30 °C, 72 h, 90%, 95% ee



9o: -40 °C, 96 h, 92%, 80% ee

Gram-scale synthesis of a key intermediate to AMG 221



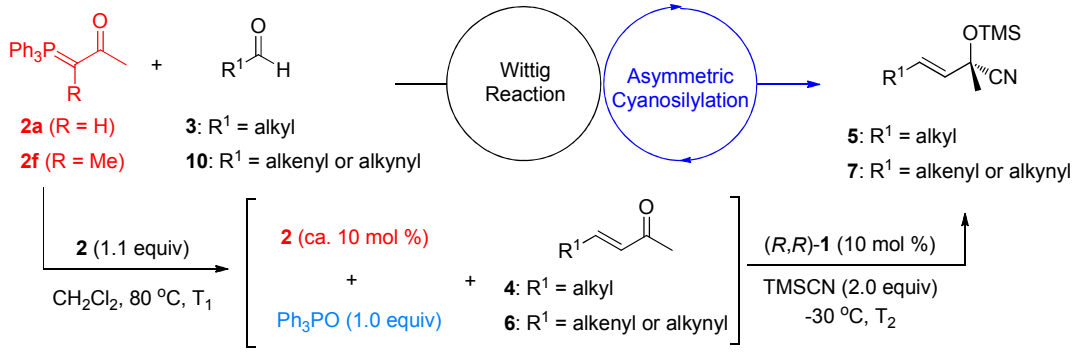
[a] Isolated yield; ee value determined by chiral HPLC analysis. [b] On a 10 mmol scale using 1 mol% of (*R,R*)-**1**, 1 mol % of **2e** and 5 mol % of Ph_3PO in 5 mL CH_2Cl_2.

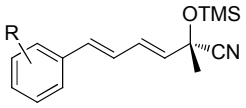
The catalyst loading could be lowered down to 1.0 mol % of (*R*,*R*)-**1**, 1 mol % phosphorane **2e** and 5 mol % of Ph_3PO. For example, the cyanosilylation of ketone **8a** on a 10 mmol scale readily afforded the desired product **9a** in 97% yield and 92% ee. Furthermore, the use of chiral complex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

Tandem Wittig-Asymmetric Cyanosilylation Sequence. Considering that there lacked 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 the completion of initial Wittig reaction of enals **10** with ylide **2a**, carried out in a screw-capped pressure tube using CH_2Cl_2 as the solvent at 80 ^oC, chiral complex **1** and TMSCN were successively added. The following asymmetric cyanosilylation was conducted at -30 or -40 ^oC till completion. It was noteworthy that high ee value of **7a** could be secured with the ratio of phosphorane **2a** to chiral complex **1** ranging from 1.0:5.0 to 2.0:1.0 (see Table S1 of SI), so 1.1 equiv of **2a** was used to ensure the full conversion of aldehydes and the presence of at least 10 mol % phosphorane **2a**.

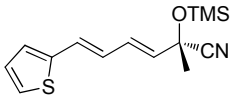
A variety of dienes **7a-o** bearing a tetrasubstituted carbon stereocenter, with two, three or four substituents on alkene functionality, were readily prepared in good yield with high to excellent enantioselectivity. In addition, optically active conjugated trienes **7p**-**q** and enynes **7r**-**t**, with either an aryl or alkyl group, could be accessed in high to excellent enantioselectivity as well, from the corresponding α,β-unsaturated enals. By using DMF as solvent for cyanosilylation step, we further realized highly enantioselective cyanosilylation of β-alkyl substituted enones **4** derived from aliphatic aldehydes and phosphorane **2a**, which was unsuccessful under our previous condition.[14] For example, products **5a**-**f** were all obtained in high yield and excellent enantioselectivity (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 slight excess of **2a**, the use of 6 mol % complex (*S*,*S*)-**1** afforded the desired cyanohydrin (*R*)-**5a** in 3.245 g, 68% yield and 90% ee. Apart from the advantages of using easily available chiral catalyst **1** and higher ee value for (*R*)-**5a**, our protocol was free from the isolation of intermediate enone.

Scheme 3. Substrate scope of tandem Wittig-cyanosilylation sequence [a,b]

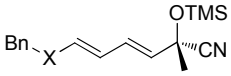




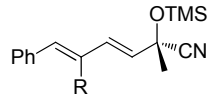
7a (R = H): 25 h/48 h, 70%, 91% ee
7b (R = 3-Me): 25 h/48 h, 71%, 92% ee
7c (R = 2-F): 18 h/36 h, 82%, 93% ee
7d (R = 3-F): 21 h/48 h, 81%, 90% ee
7e (R = 4-Cl): 15 h/48 h, 77%, 91% ee
7f (R = 4-Cl): 16 h/48 h, 80%, 92% ee



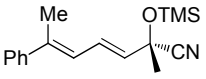
7g: 19 h/48 h, 80%, 92% ee



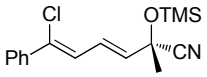
7h (X = CH_2): 21 h/60 h, 60%, 90% ee
7i (X = OCH_2): 21 h/120 h, 42%, 90% ee



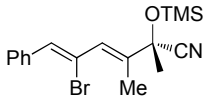
7j (R = Me): 21 h/48 h, 77%, 91% ee
7k (R = Cl): 1 h/24 h, 95%, 92% ee[b]
7l (R = Cl): 1 h/16 h, 96%, 92% ee[b]



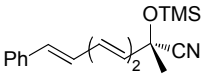
7m (R = Me): 17 h/48 h, 72%, 80% ee



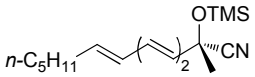
7n: 12 h/14 h, 67%, 80% ee



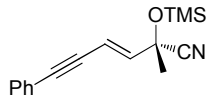
7o: 0.8 h/6 h, 98%, 84% ee[b]



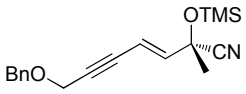
7p: 21 h/60 h, 75%, 91% ee



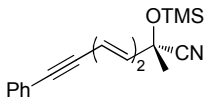
7q: 24 h/72 h, 60%, 92% ee



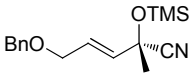
7r: 0.2 h/24 h, 95%, 83% ee



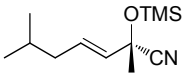
7s: 0.3 h/24 h, 91%, 81% ee



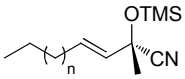
7t: 4 h/26 h, 88%, 90% ee



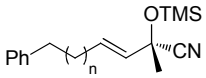
5a: 12 h/72 h
71%, 90% ee



5b: 19 h/48 h
75%, 93% ee

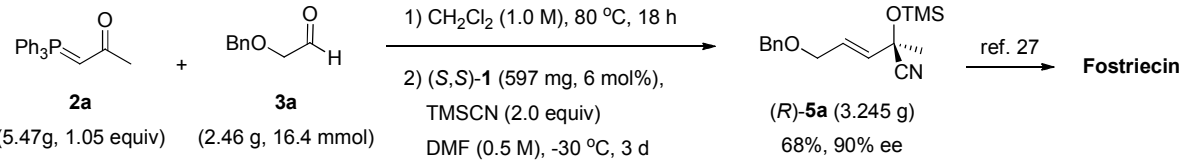


5c (n = 1): 23 h/48 h, 68%, 95% ee
5d (n = 4): 19 h/48 h, 56%, 93% ee



5e (n = 1): 19 h/48 h, 74%, 93% ee
5f (n = 2): 6 h/48 h, 84%, 90% ee

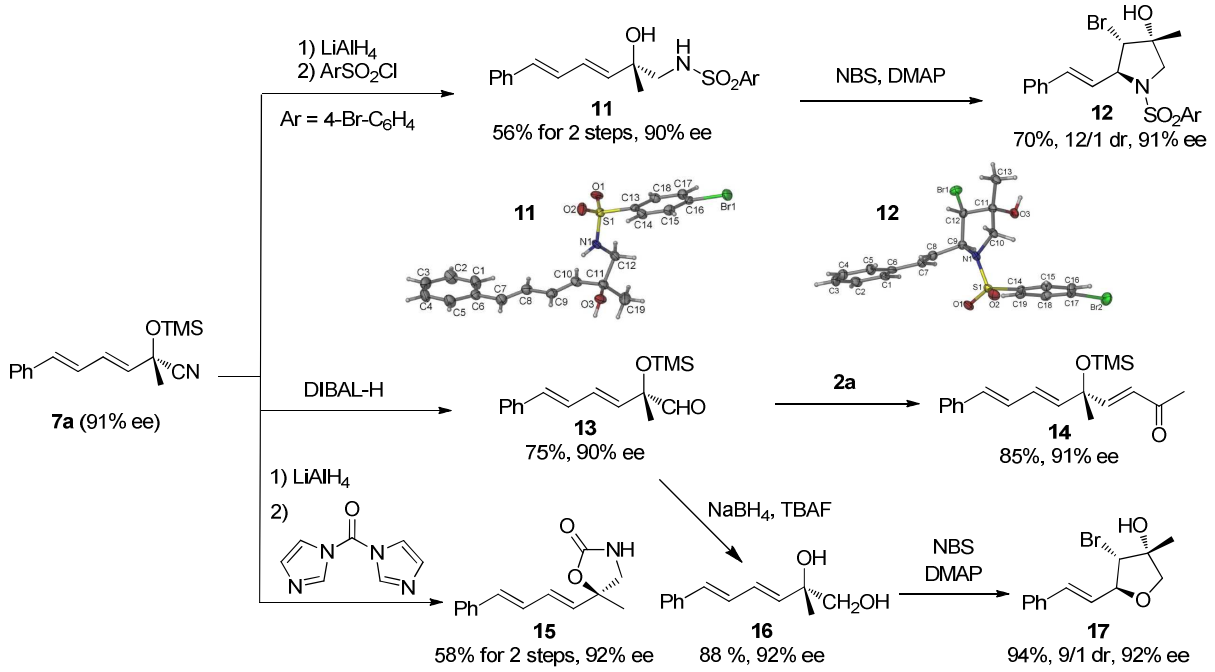
Gram-scale synthesis of a key intermediate to Fostriecin



[a] The results of each product are listed as T_1/T_2, isolated yield/ee value (for details, see section 4&5 of SI). [b] Cyanosilylation run at -40 °C.

An attractive feature of the above sequence is that both co-catalysts (phosphorane **2a** and Ph_3PO) required for asymmetric cyanosilylation step are the remaining reagent or by-product 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, helpful in reducing waste generation. It is worth mentioning that despite progresses, tandem reactions that internally reuse waste to benefit downstream catalytic asymmetric step are still very limited,[14, 28] as it requires rational design to put waste into use whilst avoiding the deactivation of chiral catalyst. This research outlines a promising strategy characterized by merging the waste with a chiral catalyst to form a multicatalyst system,[29] to realize an asymmetric reaction unattainable by the chiral catalyst itself. This is complementary to the strategy pioneered by Shibasaki et al, namely the recycling waste as an additive to improve reactivity and stereoselectivity.[28a] Furthermore, the unexpected finding of phosphorane as a powerful co-catalyst capable of activating chiral (salen)AlCl complex exhibits 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.

Scheme 4. Product elaboration



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 compounds **7a** and found it could be readily converted to aminoalcohol **11**, aldehyde **13**, enone **14**, oxazoline **15** and diol **16** with a conjugated diene moiety at the tetrasubstituted carbon stereocenter (Scheme 4). More, 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

In conclusion, we have identified phosphoranes as a type of potent co-catalysts capable of effective activation of chiral (salen)AlCl complex **1** via mechanistic studies of tandem Wittig-asymmetric cyanosilylation reaction. A three-component catalyst system consisting of complex **1**, phosphorane **2** and Ph_3PO is then developed for highly enantioselective cyanosilylation of a broad scope of ketones and conjugated enones. The high efficiency of this catalyst system is originated from orthogonal activation of (salen)AlCl complex **1** and TMSCN by phosphorane and Ph_3PO, respectively, which further exhibits that asymmetric orthogonal activation of the chiral catalyst and both reactants is promising to develop enantioselective reactions 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 phosphorane as a novel type of ligand motifs to develop chiral metal catalyst. Considering the powerfulness of chiral (salen)AlCl **1**,[9,11] the development of chiral salen-yilde aluminum complexes to exploit new enantioselective reactions is in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, copies of NMR spectra, and HPLC traces for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

jzhou@chem.ecnu.edu.cn

Notes

The authors declare no competing financial interests.

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(4) See for two examples with detailed mechanistic studies. First, Shibasaki et al reported in the cyanosilylation of ketones, the addition of Bu_3PO reduced the Lewis acidity of a chiral aluminum complex (a) Hamashima, Y.; Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 2641. (b) Hamashima, Y.; Sawada, D.; Nogami, H.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2001**, *57*, 805. Second, Evans et al reported that even the binding of solvent THF molecule may reduce the Lewis acidity of bisoxazoline derived copper complex: (c) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686.

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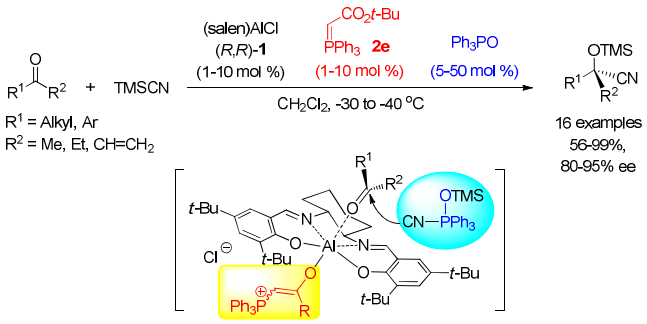
(salen)AlCl
(R,R)-1
(1-10 mol %)
CO2t-Bu
PPh3 2e
(1-10 mol %)
Ph3PO
(5-50 mol %)
TMSCN
CH2Cl2, -30 to -40 °C
R1 = Alkyl, Ar
R2 = Me, Et, CH=CH2
OTMS
CN
16 examples
56-99%,
80-95% ee
t-Bu
OTMS
CN—PPh3
Cl
Ph3P
R