Asymmetric Latent Carbocation Catalysis with Chiral Trityl Phosphate

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Ⓢ *Supporting Information*

ABSTRACT: Stable carbocations such as tritylium ions have been widely explored as organic Lewis acid catalysts and reagents in organic synthesis. However, achieving asymmetric carbocation catalysis remains elusive ever since they were first identified over one century ago. The challenges mainly come from their limited compatibility, scarcity of chiral carbocations, as well as the extremely low barrier to racemization of chiral carbenium ions. We reported here a latent concept for asymmetric carbocation catalysis. In this strategy, chiral trityl phosphate is employed as the carbocation precursor, which undergoes facile ionic dissociation upon mild external stimulation (e.g., acid, H-bonding, polar substrates) to form a catalytically active chiral ion pair for substrate activation and chiral induction. The latent strategy provides a solution for the long sought-after asymmetric carbocation catalysis as illustrated in three different enantioselective transformations.
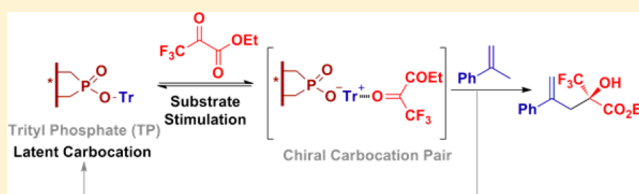
INTRODUCTION

The development of new catalytic motifs remains a frontline in the evolution of asymmetric catalysis.[1] Since the discovery of the first trityl cation in 1901,[2] stable carbocations have been actively pursued as conceptually attractive organic Lewis acid catalysts.[3−5] However, progress along this line has been rather slow, and achieving asymmetric carbocation catalysis remains elusive despite the prevalence of organocatalytic concepts and strategies.[6] The primary reason is the limited compatibility of carbocations with many nucleophilic reactants.[7] As bench stable and easily accessible salts, carbocations such as tritylium ions can still react with most nucleophiles, resulting in the interception of the active centers. Consequently, there have always been concerns regarding the precise nature of carbocation catalysis. For example, hidden proton/silyl catalysis has been noted due to the reaction of carbocations with nucleophilic reactants or even moisture.[8] Last but not the least, regulation of chiral inductions by a sp²-hybridized carbocation is a notoriously challenging task, due to the scarcity of chiral carbocations[9] as well as the extremely low barrier to racemization of chiral carbenium ions.[10] The installation of remote chiral centers to trityl cations has been attempted with unfortunately poor enantioselectivity.[6d] Clearly, a new concept and strategy is required in order to achieve asymmetric carbocation catalysis.
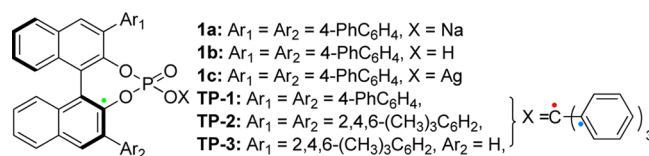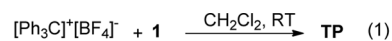
Capitalizing on the known chiral counteranion effect and chiral ion pair catalysis,[11] we propose here a latent carbocation concept for asymmetric carbocation catalysis. Accordingly, chiral trityl phosphates were employed as latent carbocationic species by either in situ mixing chiral phosphate salt and trityl derivatives or separately prepared. The chiral phosphate anion

plays a key role in stabilizing the trityl cation as a neutral species to suppress uncontrolled catalyst interception. With the labile nature of phosphate C−O bonds as known in many chemical[12] and enzymatic[13] processes, the resulting trityl phosphate may undergo facile ionic dissociation upon mild external stimulation (e.g., acid, H-bonding, polar substrates) to form a chiral ion pair,[14−16] which simultaneously participates in catalysis to activate the substrate and to induce stereoselectivity via the known counteranion effect (Figure 1).

RESULTS AND DISCUSSION

Characterizations of Chiral Trityl Phosphate. We started by first examining the properties of chiral trityl phosphate (**TP-1**). Upon in situ mixing sodium phosphate **1a** and Ph₃CBF₄ (eq 1), the typical orange color of a tritylium ion

$$[Ph_3C]^+[BF_4]^- + 1 \xrightarrow{CH_2Cl_2, \, RT} TP \quad (1)$$

1a: Ar₁ = Ar₂ = 4-PhC₆H₄, X = Na
1b: Ar₁ = Ar₂ = 4-PhC₆H₄, X = H
1c: Ar₁ = Ar₂ = 4-PhC₆H₄, X = Ag
TP-1: Ar₁ = Ar₂ = 4-PhC₆H₄,
TP-2: Ar₁ = Ar₂ = 2,4,6-(CH₃)₃C₆H₂,
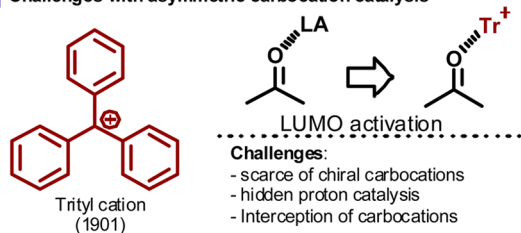**TP-3:** Ar₁ = 2,4,6-(CH₃)₃C₆H₂, Ar₂ = H,   X = C(C₆H₅)₃

solution became colorless. The methine carbon ¹³C signal was completely shifted from 210.8 ppm, characteristic of a deshielded carbenium ion, to 81.9 ppm, corresponding to the formation of the phosphate C−O bond (Figure 2A). An
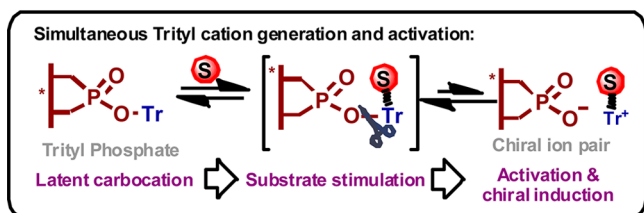
Figure 1. Asymmetric carbocation catalysis.

identical methine carbon signal was also observed when Ph_3C-Br with a C−Br covalent bond (δ = 79.2 ppm) was treated with **1a**. In the UV−vis spectra, a free tritylium ion, such as Ph_3CBF_4, showed a characteristic twin absorption band at λ_{max} = 432 and 411 nm. When a solution of free tritylium ion Ph_3CBF_4 was titrated with sodium phosphate **1a**, the twin absorption was gradually decayed and completely disappeared with 1 equiv of **1a** (Figure 2B and Figure S1 for UV titration spectra). The in situ formed species can be fully characterized as trityl phosphate (e.g., **TP-1**) by ^1H NMR, ^{13}C NMR, ^{31}P NMR, and DOSY spectra (Figure 2 and Supporting Information). Latent trityl carbocation **TP-1** could also be obtained when Ph_3C-OH was treated with free acid **1b** or Ph_3C-Br treated with silver phosphate **1c**. In addition, trityl phosphates with variations on the phosphate moiety such as **TP-2** and **TP-3** can be prepared in situ following the same procedure, and the obtained latent carbocations demonstrated similar spectroscopic properties (Figure 2B).

The Lewis acidity of the latent carbocation was examined by using the Gutmann−Beckett method.[17] The binding of triphenylphosphine oxide (1.0 equiv) to **TP-1** (1.0 equiv) was evaluated on the basis of the change in the ^{31}P NMR chemical shift of OPPh$_3$ upon complexation in CD$_2$Cl$_2$ at room

temperature (eq 2). A change of +5.0 ppm in the ^{31}P NMR chemical shift of OPPh$_3$ was observed. This chemical shift is
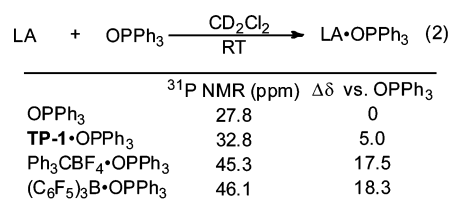
$$LA \ + \ OPPh_3 \xrightarrow[RT]{CD_2Cl_2} LA \cdot OPPh_3 \quad (2)$$

	^{31}P NMR (ppm)	$\Delta\delta$ vs. OPPh$_3$
OPPh$_3$	27.8	0
TP-1·OPPh$_3$	32.8	5.0
Ph$_3$CBF$_4$·OPPh$_3$	45.3	17.5
(C$_6$F$_5$)$_3$B·OPPh$_3$	46.1	18.3

Figure 3. Analytical Lewis acidity of the latent carbocation.

much smaller than the change observed upon binding to B(C$_6$F$_5$)$_3$ ($\Delta\delta$ = +18.3 ppm) and Ph$_3$CBF$_4$ ($\Delta\delta$ = +17.5 ppm) (Figures 3 and S2), suggesting that **TP-1**, as a neutral species, still behaves like a Lewis acid though in a much lower apparent acidity.

The interaction of **TP** with a typical carbonyl compound in Lewis acid catalysis, such as ethyl trifluoropyruvate **2**, was next examined. Upon in situ mixing **TP-1** and ethyl trifluoropyruvate **2**, the colorless solution became yellow (Figure 4A, inset) and the characteristic twin absorption of the trityl cation at λ_{max} = 425 and 405 nm was clearly observed by UV−visible spectra (Figure 4A). The twin absorption signal was gradually enhanced with the addition of trifluoropyruvate, an indication of the increasing formation of a trityl cation (Figure 4A). There seems to also be a threshold concentration of trifluoropyruvate required for effective generation of the trityl cation (Figure 4A, inset). These results suggested that trifluoropyruvate could stimulate the dissociation of trityl phosphate to generate the trityl cation, likely via the known polarization effect, as frequently encountered in S$_N$1-type reactions. The in situ generated trityl cation may simultaneously engage in substrate activation if the stimulator itself is a reaction partner, thus setting the stage for effective catalysis (Figure 4C). UV titration of TrBF$_4$ by trifluoropyruvate **2** confirmed the interception of a free tritylium ion with pyruvate, and this interaction (Figure 4B) could be further verified by ^{19}F NMR (Figure S3).

Asymmetric Catalysis by Trityl Phosphate. *Friedel− Crafts Reactions of α-Ketoesters and Indoles.*[18−20] We next investigated whether the latent carbocation could facilitate an asymmetric catalytic reaction via the in situ formed chiral carbocationic ion pair (Figure 1). To implement this strategy,
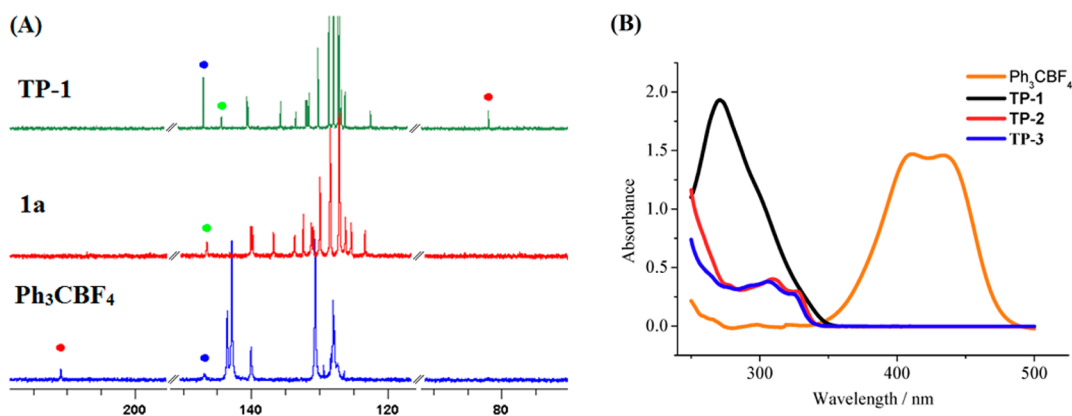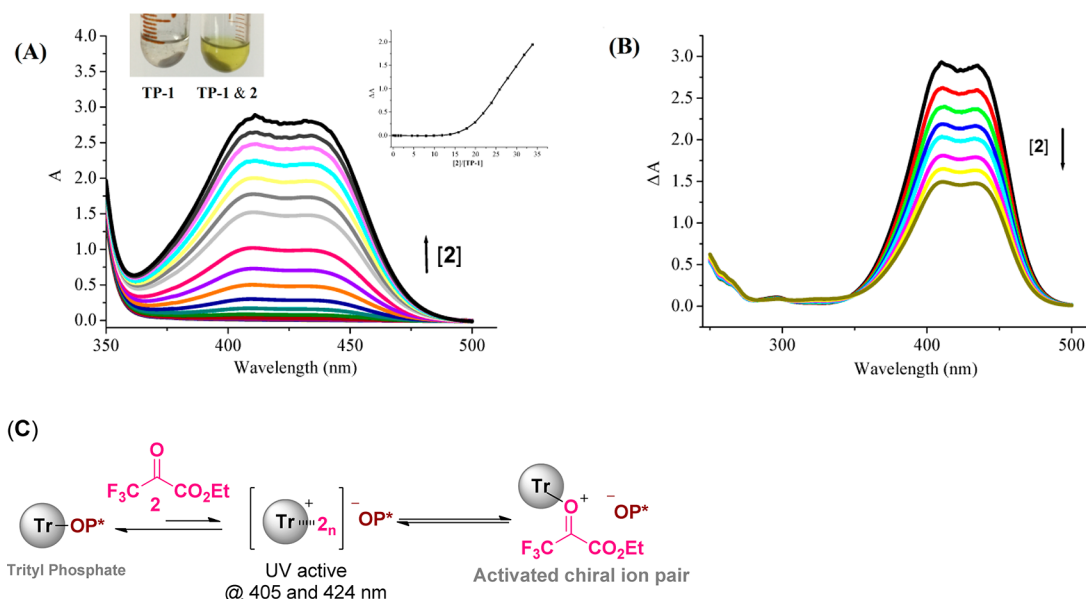

Figure 2. Characterizations of chiral trityl phosphate. (A) ^{13}C NMR (CD$_2$Cl$_2$) spectra of compounds Ph$_3$CBF$_4$, **1a**, and **TP-1**; the red, blue, and green dots represent the responding carbon signal in the structure of **TP-1**. (B) UV−vis absorption spectra of Ph$_3$CBF$_4$ (0.1 mM) and **TP-1**, **2**, and **3** (0.05 mM) in CH$_2$Cl$_2$ at room temperature.

Figure 4. UV−vis titrations of carbocation with ethyl trifluoropyruvate **2**. (A) UV−vis absorption spectra of **TP-1** (2.5 mM in 2.0 mL of CH$_2$Cl$_2$) upon the addition of **2** (0−84.7 mM) at room temperature. The insets show a plot of ΔA at 405 nm against [**2**]/[**TP-1**]. (B) UV−vis absorption spectra of Ph$_3$CBF$_4$ (0.25 mM in 1.0 mL of CH$_2$Cl$_2$) upon the addition of **2** (0, 0.25, 0.50, 1.00, 1.50, 2.50, 3.50, 5.0 mM) at room temperature. (C) Illustration of simultaneous trityl cation generation and substrate activation.

Table 1. Optimization Studies for Asymmetric Catalyzed Friedel−Crafts Reaction by Carbocations[a]


entry	TrX	1	yield (%)[b]/5a	ee (%)[c]
1	TrBF$_4$		<10	
2	TrBF$_4$	1a	62	83
3	TrClO$_4$	1a	65	90
4	TrBr	1a	72	93
5[d]	TrBr	1a	82	92
6	TrBr		trace	
7		1a	trace	
8	TrOH	1b	75	88
9	TrBr	1c	75	91
10[d,e]	TrBr	1a	81	96

[a]General conditions: **3a** (0.1 mmol), **4a** (0.12 mmol), TrX (10 mol %), and **1** (10 mol %) in CH$_2$Cl$_2$ (0.5 mL) at −70 °C for 4 h. [b]Yields of isolated products. [c]Determined by HPLC analysis on a chiral stationary phase. [d]**1a** (5 mol %) and TrBr (5 mol %). [e]Toluene (0.5 mL) as reaction solvent.

different trityl cations, chiral phosphoric acids, or salts **1**[21,22] and their combinations were then examined in the model reactions of indole **3a** and α-ketoester **4a**. In experiments, trityl derivatives were first treated with chiral phosphate salt, such as **1a**, to ensure their complete conversion to trityl phosphate before they were subjected to a catalytic test. We were gratified to find that the joint use of **1a** and trityl cation Ph$_3$CBF$_4$ (10 mol %) led to the desired adduct **5a** with 62% yield and in 83% ee at −70 °C for 4 h (Table 1, entry 2). In sharp contrast, the use of Ph$_3$CBF$_4$ only led to minor desired product (Table 1, entry 1), with the trityl cation being completely intercepted and isolated as the side adduct **5a′**. Trityl phosphates derived from other trityl derivatives and chiral phosphates have also been examined, giving consistently high enantioselectivity (Table 1, entries 3, 8, and 9). Finally, the combination of Ph$_3$CBr and

sodium phosphate **1a** was identified to give the best results (Table 1, entry 4, 72% yield and 93% ee); note that neither Ph$_3$CBr nor **1a** alone was active for the reaction (Table 1, entries 6 and 7). This is a strong indication that the formation of trityl phosphate (**TP-1**) is critical for effective catalysis. The catalysis of **TP-1** derived from Ph$_3$CBr/**1a** could be further improved when conducted in toluene, and under this condition, 5 mol % of loading of catalyst was sufficient to give 81% yield and 96% ee (Table 1, entry 10).[23]

The catalysis of **TP-1** (5 mol %) could be applied to other α-ketoesters and indoles to give the desired 1,4-addition products **5a−h** in good yields and high enantioselectivities (Table 2, entries 1−8). Aliphatic β,γ-unsaturated α-ketoesters **4i** were examined in the current catalysis and gave poor enantioselectivity but good reactivity (Table 2, entry 9). The reaction

**Table 2. Enantioselective Friedel−Crafts Reactions of α-Ketoesters and Indoles**[a]
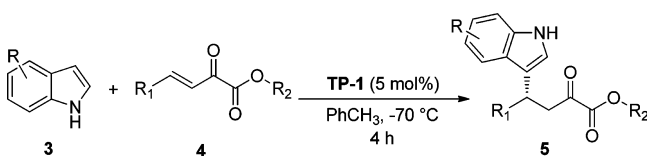
entry	R	R_1	R_2	yield (%)[b]	ee (%)[c]
1	H	Ph	CH₃, **5a**	81	96
2	H	4-Cl-Ph	CH₃, **5b**	75	95
3	H	4-Br-Ph	CH₃, **5c**	80	90
4	H	3,4-Cl₂-Ph	CH₃, **5d**	80	99
5	H	4-CH₃-Ph	CH₃, **5e**	88	93
6	H	4-CH₃O-Ph	CH₃, **5f**	79	93
7	H	2-thiophene	CH₃, **5g**	75	96
8	6-F	Ph	CH₃, **5h**	75	92
9	H	CH₃	C₂H₅, **5i**	71	26

[a]General conditions: **3** (0.1 mmol), **4** (0.12 mmol), TrBr (5 mol %), and **1a** (5 mol %) at −70 °C in PhCH₃ (0.5 mL) for 4 h. [b]Yields of isolated products. [c]Determined by HPLC analysis on a chiral stationary phase.

could also be successfully applied in a similar Friedel−Crafts reaction of simple phenol **6**. In previous studies, it was found that the free phosphoric acid **1b** did not catalyze the reaction in the absence of Lewis acid.[20c] To our delight, the latent carbocation **TP-1** turned out to be a much more effective Lewis acid catalyst for the reaction than the corresponding Brønsted acid, giving the 1,4-adduct **7** with 59% yield and in 84% ee (eq 3).
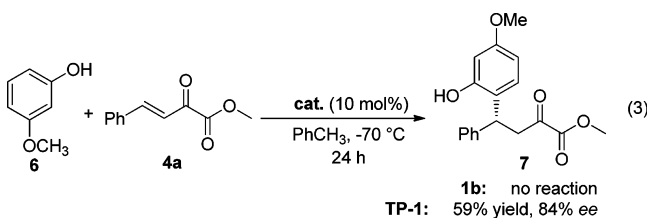

Asymmetric Inverse-Electron-Demanding Hetero-Diels−Alder Reaction.[24,25] It was found that the latent carbocation could also catalyze asymmetric inverse-electron-demanding hetero-Diels−Alder reactions (HDA) of α-ketoester **4a** and cyclopentadiene **8** (Scheme 1). The latent carbocation **TP-2** (5 mol %) derived from Ph₃COH/**1d** in the presence of 4 Å molecular sieves could smoothly catalyze the reaction to afford cycloadduct **9a** (HDA/DA = 70:30) in 99% yield and 90% ee. Importantly, the free phosphoric acid **1d** only gave
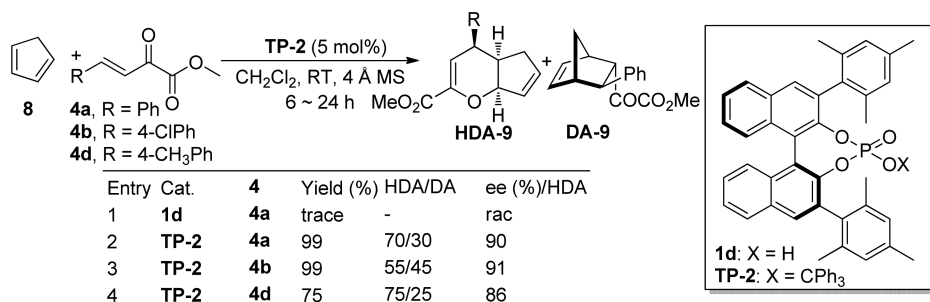
trace racemic adduct **9a**, indicating that the latent carbocation as a Lewis acid plays a pivotal role in the reaction. Moreover, α-ketoesters bearing either an electron-withdrawing or an electron-donating group can be applied in the reactions with cyclopentadiene to give the desired HDA products **HDA-9** and DA products **DA-9** in good yields (HDA/DA up to 75:25) and excellent enantioselectivity for **HDA-9** (up to 91% ee).

Asymmetric Carbonyl-ene Reaction.[26] Furthermore, we found that the asymmetric carbonyl-ene reaction between trifluoropyruvate and α-methylstyrene derivatives **10** could also be achieved with the latent carbocation (Scheme 2). Trityl phosphate **TP-3** (5 mol %), derived from 3-substituted unsymmetric BINOLs, was identified to give 61% yield and 84% ee, while the corresponding Brønsted acid (52% yield and 69% ee for **11a**) and sodium phosphate (28% yield and 27% ee) were much less effective in terms of both activity and stereoselectivity. The electron-withdrawing and electron-donating α-methylstyrenes (**10b** and **10c**) were tolerated to give 78 and 84% ee, respectively.

Mechanistic Studies of Latent Cation Catalysis. *Exclusion of Free Acid Catalysis.* One of the most important issues in carbocation catalysis is to rule out that trace acids, either present as impurities or formed during the reaction, are the "hidden" catalytic active species. In our case, the control experiment with free phosphoric acid **1b** (10 mol %) could give 61% yield and 82% ee (Table 3, entry 1). Generally, two processes, depending on the reacting nucleophile, can be invoked to account for the consumption of tritylium ions to generate free phosphoric acid (eqs 4 and 5):
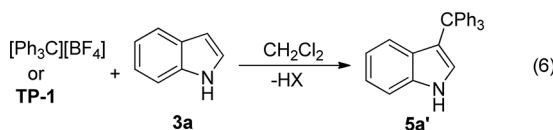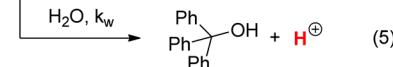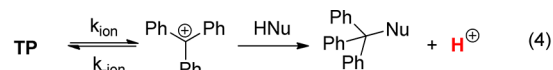
First, we examined the reactivity of a carbocation with a typical nucleophile indole, **3a**, by using in situ IR (Figure 5A). **TP-1** could still react with indole **3a** to form tetraarylated adduct **5a′** at room temperature (eq 6), but with an initial rate 15 times slower than that of Ph₃CBF₄, and this reactivity can be largely suppressed at lower temperature (−70 °C) (Figure 5A), highlighting the critical role of the phosphate anion in stabilizing the carbocation. To our delight, in the presence of

Scheme 1. Asymmetric HDA Reaction

Entry	Cat.	4	Yield (%)	HDA/DA	ee (%)/HDA
1	**1d**	**4a**	trace	-	rac
2	**TP-2**	**4a**	99	70/30	90
3	**TP-2**	**4b**	99	55/45	91
4	**TP-2**	**4d**	75	75/25	86

Scheme 2. Asymmetric Carbonyl-ene Reaction

11a
61% yield, 84% ee

11b
59% yield, 78% ee

11c
64% yield, 84% ee
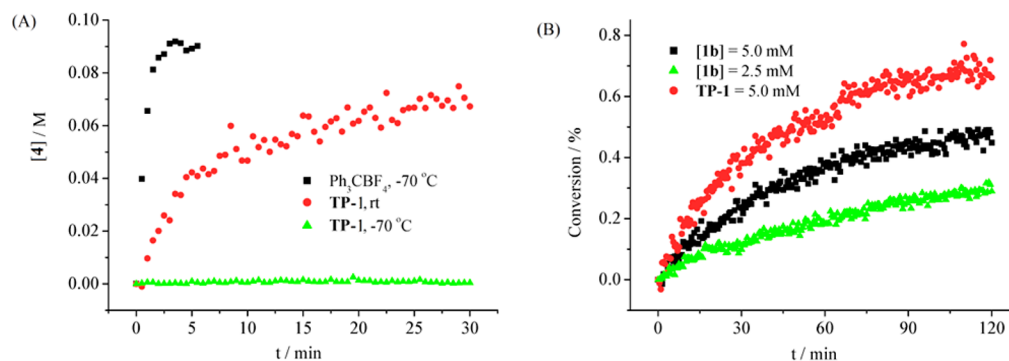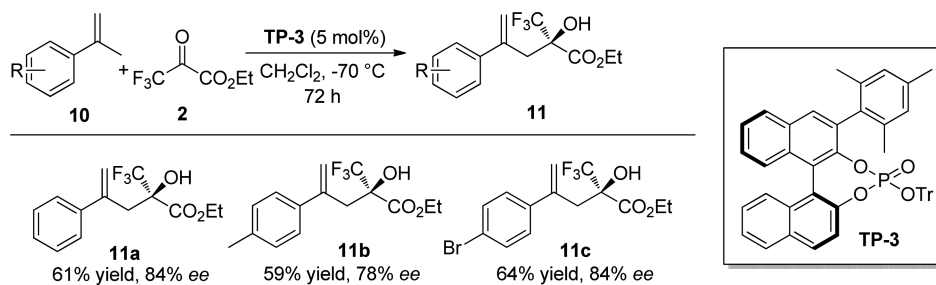
Figure 5. (A) Kinetic profiles of the reaction of indole **3a** and **TP-1** relative to Ph_3CBF_4 to give adduct **5a'**, monitored by in situ IR at 1105 cm^{-1}. (B) Conversion of asymmetric Friedel−Crafts reaction of α-ketoester **5a** and indole **2a** catalyzed by **1b** (2.5−5 mol %) or **TP-1** (5 mol %), monitored by in situ IR at 1737 cm^{-1} (C═O, ester).

α-ketoester **4a**, no tetraarylated adduct **5a** was obtained even at room temperature. Thus, we excluded the generation of free phosphoric acid via electrophilic substitution of **TP-1** with indole **3a**. Moreover, we found that even a trace of chiral phosphoric acid **1b** in the carbocation catalysis could give lower results. In a control experiment, **TP-1** (10 mol %) was first treated with indole **3a** (1.0 equiv) at room temperature to afford chiral phosphoric acid **1b**; the resulting mixture was then treated with ketoester at −70 °C to give 52% yield and 81% ee (eq 7). This result indicates that free phosphoric acid, if present, would lead to reduction of both yield and enantioselectivity.

(7)

5a
52% yield, 81% ee
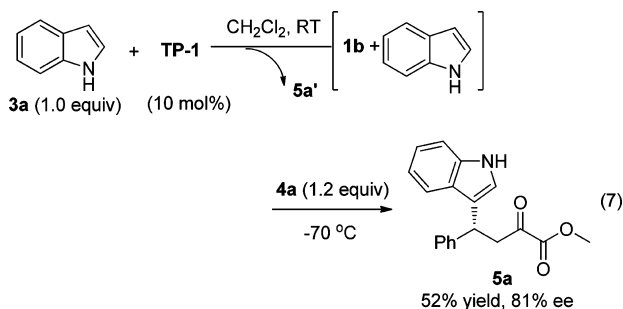
The other pathway may involve the reaction of the carbocation with traces of water to form free phosphoric acid **1b** (eq 5). However, it is known that trityl ester is quite stable and only undergoes hydrolysis under a high concentration of water.[7b] In fact, the reaction worked equally well even in the presence of 5.0 equiv of water (Table 3, entry 6),[27] suggesting that the existence of trace water may only have a negligible effect on the reaction.

Next, the use of non-nucleophilic base to exclude acid catalysis has been explored (Table 3, entries 3 and 4). An

Table 3. Comparison Experiments[a]

entry	catalyst	additive	yield (%)[b]	ee (%)[c]
1	**1b**		61	82
2	**1b**	DBPy (10 mol %)	trace	
3	**1b**	Na$_2$CO$_3$ (1.0 equiv)	<10	
4	**TP-1**	DBPy[d] (10 mol %)	45	72
5	**TP-1**	Na$_2$CO$_3$ (1.0 equiv)	66	92
6	**TP-1**	H$_2$O (5.0 equiv)	83	91

[a]General conditions: **3a** (0.1 mmol), **4a** (0.12 mmol), and catalyst (10 mol %) in CH$_2$Cl$_2$ (0.5 mL) at −70 °C for 4 h. [b]Yields of isolated products. [c]Determined by HPLC analysis on a chiral stationary phase. [d]DBPy = 2,6-di-*tert*-butylpyridine.

organic base such as 2,6-bis(*tert*-butyl)pyridine reacted with the carbocation, leading to its decomposition and thus the depletion of activity. A similar observation has also been reported in carbocation catalysis.[5a] In fact, it has even been shown the use of organic base may induce acid catalysis rather than inhibit it. Nevertheless, the model reaction, conducted in the presence of inorganic Na$_2$CO$_3$ (1.0 equiv) at −70 °C in CH$_2$Cl$_2$,[28] proceeded smoothly to give the desired adduct **5a** in 66% yield and with 92% ee (Table 3, entry 5). In contrast, the catalysis with free acid **1b** was largely suppressed by the addition of Na$_2$CO$_3$ (1.0 equiv) in CH$_2$Cl$_2$ (Table 3, entry 3).

We further compared the kinetic profiles of carbocation catalysis and free acid catalysis. As shown in Figure 5B, the kinetic profile of the **1b** (2.5−5.0 mol %) catalyzed reaction was found to be significantly different from that of the **TP-1** (5.0

mol %) process, with the latter being much faster, showing that they are different in catalytic nature.[29]

Taken together, the above observations exclude the possibility of free acid catalysis in **TP-1** catalyzed reactions.

Verification of the Carbocation Catalysis. In experiments, we have noticed that different TPs, such as **TP-1−TP-3**, showed dramatically different performance in terms of both activity and stereoselectivity (eq 8 and Figure S6). Given the
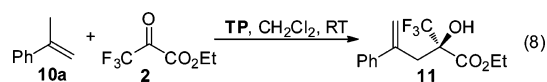
TP-1: 5.0 mol%, -9% ee; **TP-1**: 2.5 mol%, <-5% ee;
TP-2: 5.0 mol%, 15% ee; **TP-2**: 2.5 mol%, 8% ee;
TP-3: 1.0 mol%, 32% ee; **TP-3**: 5.0 mol%, 48% ee

common trityl cation involved in **TP-1−TP-3**, these results showed that the chiral phosphate moiety could tune both the reactivity and stereoinductions. To probe the nature of the cationic catalysis with a trityl phosphate, we have determined the kinetics as well as its dependence on in situ generated active trityl cations (Figure S6), and the ene reaction between α-methylstyrene **10a** and ethyl trifluoropyruvate **2** was chosen for the model studies as this reaction was readily monitored by both IR and UV spectroscopy. The stimulated trityl cation generation was probed by UV under otherwise identical (with catalytic reaction) but dilute conditions in the presence of **2** (Figure 6A). As shown, TPs bearing a different phosphate moiety showed varied tendency to dissociate into free trityl ion pair, with **TP-2** as the most active (Figures 6A and S6). A quick analysis revealed that the initial reaction rates correlated linearly

with the determined trityl cation concentration, proving unequivocally the involvement of the free cation as the catalytic active species (Figure 6B). An estimation based on UV absorption showed that ca. 6% of **TP-2** was dissociated into trityl cation at the onset of the reaction, and the solutions exhibited a bright yellow color (Figure S8). As the reaction proceeded, it was found that the concentration of free trityl cation gradually decreased and the reaction became colorless once the reaction was complete at room temperature (Figure 6C,D). Independent tests indicated that neither alkene nor the ene product **11a** was able to induce or intercept a tritylium ion. Taken together, these results highlight the latent nature of the catalysis, with the active tritylium ion returning back to its latent form as trityl phosphate once the stimulating substrate was consumed.

■ CONCLUSION

We have developed a latent strategy for the long sought-after enantioselective carbocation catalysis. Chiral trityl phosphate was found to undergo facile dissociation to form a catalytic active chiral trityl ion pair under the stimulus by the reacting substrate. The latent strategy bypasses the typical pitfalls associated with active carbocations and provides an enabling solution to organic Lewis acid catalyzed transformations, as illustrated in a Friedel−Crafts alkylation reaction, a hetero-Diels−Alder reaction, and a carbonyl-ene reaction. We believed that the latent carbocation catalysis would provide a complementary strategy to the typical chiral Brønsted/Lewis acid catalysis, and enormous potentials along this line are anticipated with the structural flexibility and versatility of
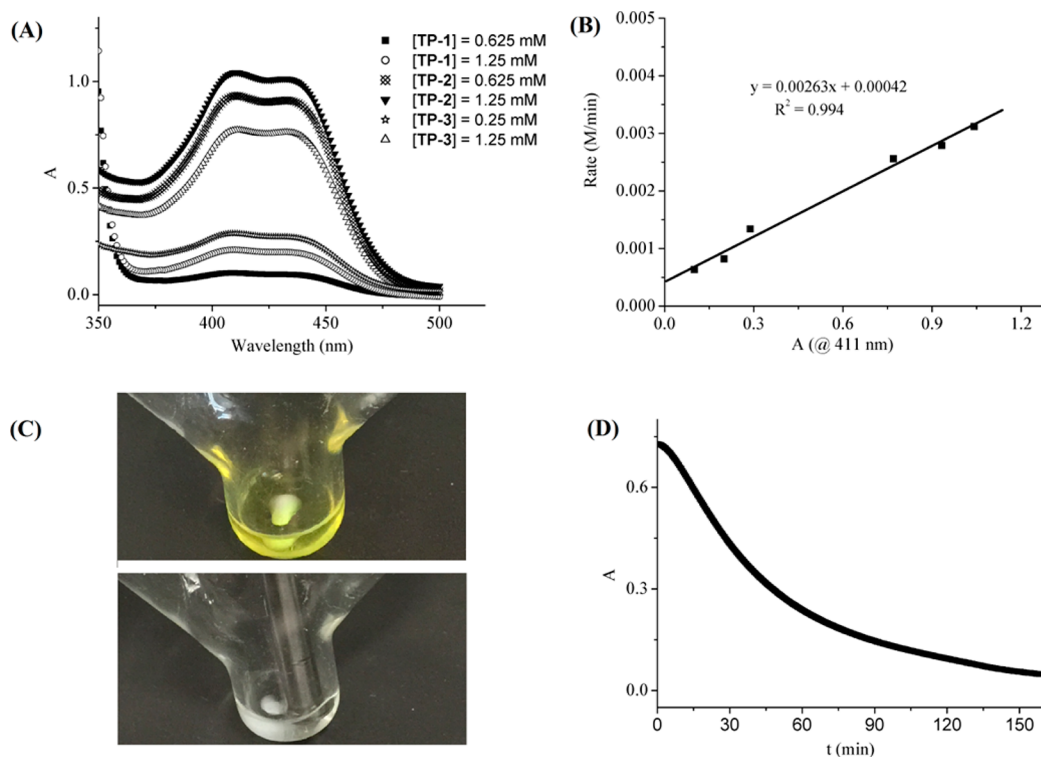
Figure 6. Asymmetric carbonyl-ene reaction catalyzed by TP. (A) UV−vis absorption spectra of **TP** in the presence of ethyl trifluoropyruvate **2** (0.025 M). (B) Correlation between the initial rate and the determined apparent UV−vis absorbance of trityl cations; initial rates of the reaction were determined in the interval between 0 and 20% conversions of the reaction. (C) Color change of the reaction mixture, before adding alkene **10a** (top) and after the reaction complete (bottom). (D) Track of the formation of free trityl cation by UV−vis at 403 nm in **TP-2** (5 mol %) catalyzed reaction of α-methylstyrene **10a** (0.075 M) and **2** (0.025 M) at room temperature.

stabilized carbocations, such as the tritylium ion. Further investigations to develop the scope of this latent carbocation system and to explore chiral carbocation catalysis are currently in progress in our laboratory.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11085.

Experimental details and characterization of new compounds (PDF)

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Notes
The authors declare no competing financial interest.

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