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Asymmetric Synthesis

Trio Catalysis Merging Enamine, Brønsted Acid, and Metal Lewis Acid Catalysis: Asymmetric Three-Component Aza-Diels–Alder Reaction of Substituted Cinnamaldehydes, Cyclic Ketones, and Arylamines

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Abstract: A trio catalyst system, composed of arylamine, BINOL-derived phosphoric acid, and $Y(OTf)_3$, enables the combination of enamine catalysis with both hard metal Lewis acid catalysis and Brønsted acid catalysis for the first time. Using this catalyst system, a three-component aza-Diels–Alder reaction of substituted cinnamaldehyde, cyclic ketone, and arylamine is carried out with high chemo- and enantioselectivity, affording a series of optically active 1,4-dihydropyridine (DHP) derivatives are obtained in 91–99% *ee* and 59–84% yield. DHPs bearing a chiral quaternary carbon center are also obtained with good enantioselectivity and moderate yield (three examples). Preliminary mechanistic investigations have also been conducted.

Introduction

The combination of organocatalysis with metal catalysis has emerged as a powerful tool to develop new reactions that cannot be achieved by organocatalysis or metal catalysis independently.[1] The major problem in merging amine organocatalysts with metal Lewis acid catalysts is that acid–base quenching causes catalyst inactivation. An effective strategy to overcome this problem is the incorporation of a soft metal Lewis acid such as Pd^0 or Ag^I with a hard aliphatic amine (Figure 1, top). By using this strategy, very challenging asymmetric direct alkylation reactions have been achieved[1g–q] and a number of de novo reactions based on allylic alkylation have been developed.[1r–u] However, the combination of enamine catalysis with hard metal Lewis acid has turned out to be very difficult, and few organic reactions through cooperative enamine–hard metal Lewis acid catalysis have been reported.[1–3] Nevertheless, a large variety of electrophiles can be activated by hard metal Lewis acids (Figure 1, top), so the development of new strategies to overcome the acid–base self-quenching problem could represent an important breakthrough in organic synthesis and catalysis.

To extend the possibilities for catalytic organic reactions, our group has been engaged in developing new strategies to merge enamine catalysis with hard metal Lewis acid catalysis.[1a–d,2,3] Very recently, our group introduced a new strategy, namely soft–hard reversion, to solve the acid–base quenching problem.[2] In this approach, arylamines replace the well-established and generally used aliphatic amines in enamine catalysis. We demonstrated that arylamine-based enamine catalysis could be successfully combined with hard metal Lewis acid catalysis. Herein, we further demonstrate enamine catalysis merged with both hard metal Lewis acid catalysis and Brøn-

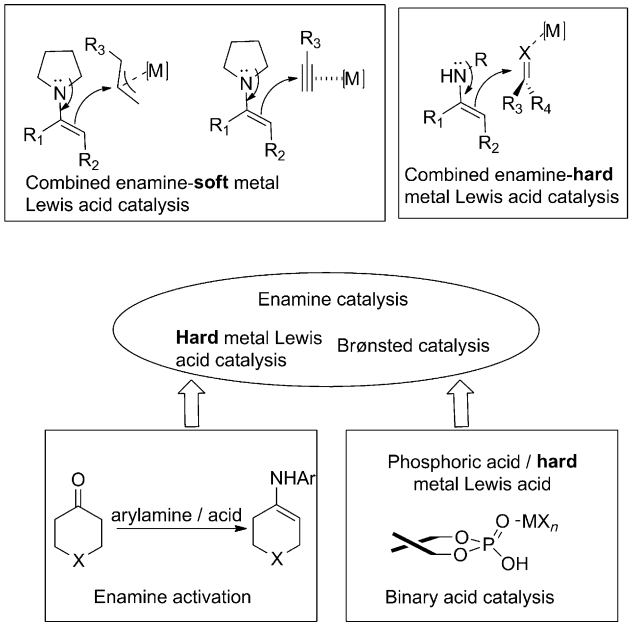

Figure 1. Top: Different reaction modes in cooperative enamine–metal Lewis acid catalysis. Bottom: Trio catalysis incorporating enamine and binary acid catalysis.

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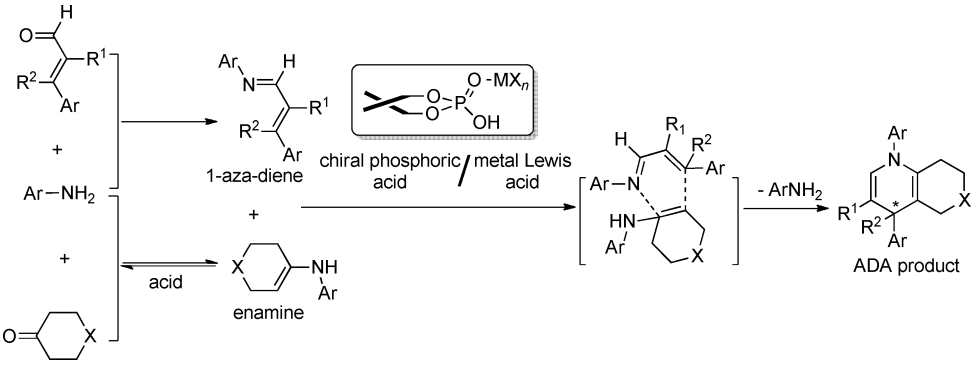
sted acid catalysis, to give a novel trio catalyst system composed of an arylamine, $Y(OTf)_3$, and a BINOL-derived phosphoric acid (Figure 1, bottom). By using this trio catalyst system, a challenging three-component aza-Diels–Alder reaction of substituted cinnamaldehydes, cyclic ketones, and arylamines was developed with excellent chemo- and enantioselectivity.



Scheme 1. Proposed three-component ADA reaction of substituted cinnamaldehyde, cyclic ketone, and arylamine catalyzed by a trio catalytic system.

Results and Discussion

Design of asymmetric three-component aza-Diels–Alder reaction through trio catalysis

In the past several years we have developed several difficult asymmetric organic transformations through combining enamine catalysis with hard metal Lewis acid catalysis.[2,3] Like many other metal Lewis acid-catalyzed reactions, a substrate with a chelating site, such as α-ketoesters, is generally required to attain maximal activation of the electrophiles. To greatly extend the scope of cooperative enamine–hard metal Lewis acid catalysis, new strategies must be developed to activate electrophiles without chelating sites, such as cinnamaldehydes. We considered binary acid catalysis, in which a BINOL-derived chiral phosphoric acid and a metal Lewis acid are synergistically incorporated.[4] The binary acid catalytic systems are designed to attain mutually enhanced acidity/electrophilicity and, very importantly, binary acid catalysts are able to provide extra binding sites for substrates (Figure 1).We previously demonstrated the good compatibility of arylamines with either hard metal Lewis acids or phosphoric acids.[2] As such, binary acid catalysis appears to be an ideal complementary strategy to be integrated with enamine catalysis (Figure 1).

Despite significant advances in the development of asymmetric hetero-Diels–Alder reaction of carbonyl compounds in recent years, there has been little development of inverted-electron-demand aza-Diels–Alder reactions involving enamines as the dienophiles.[5] Cinnamaldehyde and its derivatives represent a diverse class of materials that are easily accessible. Activation of this class of compounds in different reactions would lead to new atom-economy and convenient organic transformations. We were interested in developing an aza-Diels–Alder reaction of cinnamaldehydes with cyclic ketones and aryl amines using the proposed trio catalytic system. In the proposed aza-Diels–Alder reaction (Scheme 1), the arylamine reversibly forms an enamine intermediate with the cyclic ketone serving as the amine catalyst. At the same time, the arylamine also reversibly forms a 1-azadiene with the cinnamaldehyde. Nucleophilic attack of the enamine (dienophile) on the 1-azadiene affords the desired aza-Diels–Alder (ADA) products.

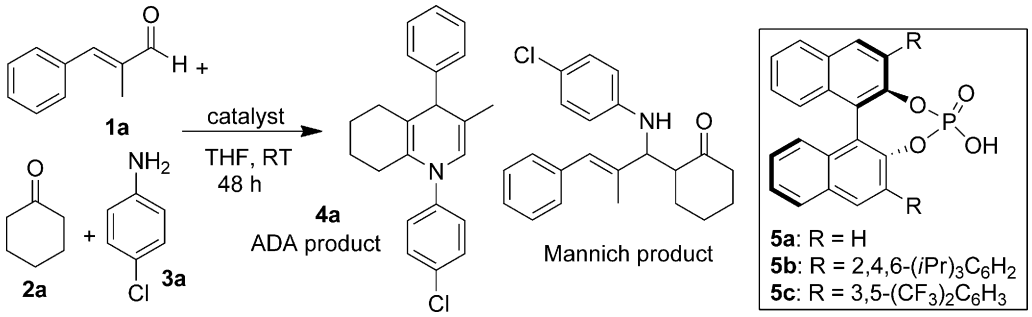
Screening of conditions

We first tested our investigation by using 2-methylcinnamaldehyde **1a**, cyclohexanone, and *p*-chloroaniline as substrates (Table 1). To gain good understanding of the reaction, we initially used a solo acid catalyst. All of the chiral Brønsted acids examined (Table 1, entries 1–5) gave the Mannich product as the major product alongside the ADA product in low to moderate yield (7–24%), indicating that the solo Brønsted acid cannot promote the ADA reaction. These data are consistent with those reported previously.[6] Notably, however, good enantioselectivity (88% *ee*; Table 1, entry 5) was obtained with the phosphoric acid TRIP (**5b**).

The catalytic activity of solo metal Lewis acids was also tested. Most of the metal salts, including $Zn(OTf)_2$, $In(OTf)_3$, $Sm(OTf)_3$, and $Yb(OTf)_3$, also afforded the Mannich product as the major product (see the Supporting Information). Fortunately, when $Y(OTf)_3$ or $La(OTf)_3$ was used, the reaction pathway switched, giving dominantly ADA product (see the Supporting Information). However, the chemoselectivity of this reaction remained low.

We then attempted binary acid catalyst systems (Table 1, entries 7–15) in the hope of obtaining both enantioselectivity and enhanced activity of the ADA reaction. It was encouraging that the combination of a chiral phosphoric acid and a metal Lewis acid led to changes in both chemoselectivity and/or enantioselectivity as compared to the solo acid catalyst systems. These results indicate a possible interaction between the phosphoric acid and the metal Lewis acid. The combination of $Y(OTf)_3$ with chiral phosphoric acids **5a** and **5c** gave decreased chemoselectivity relative to solo $Y(OTf)_3$ (Table 1, entry 6). The use of the more sterically hindered phosphoric acid **5b** alongside $Y(OTf)_3$ was more promising, affording slightly better chemoselectivity than solo $Y(OTf)_3$ (Table 1, entry 8) and very good enantioselectivity (89% *ee*). These results suggest that a binary acid catalytic system had likely formed between $Y(OTf)_3$ and **5b**. The best chemoselectivity (ADAP/MP ratio = 1:0.1) was obtained when **5b** was combined with $Yb(OTf)_3$ (Table 1, entry 10), albeit with decreased enantioselectivity relative to using **5b** only (45 vs. 88% *ee*; Table 1, entry 5). It should be noted that other metal Lewis acids examined with **5b** (Table 1,

Table 1. Catalyst screening for three-component ADA reaction of **1a**, **2a**, and **3a**.



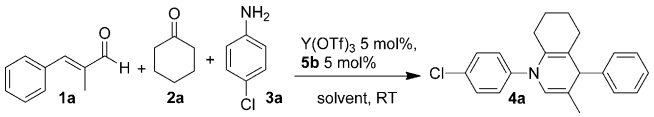
Entry	MLA (5 mol%)	BA (5 mol%)	ADAP/MP	ADAP yield [%][a]	*ee* [%][b]
1	–	TFA	1:5.3	7	–
2	–	benzoic acid	1:2.4	11	–
3	–	(+) CSA	1:7.4	5	0
4	–	**5a**	1:3.4	19	21
5[c]	–	**5b**	1:2.6	24	88
6	$Y(OTf)_3$	–	1:0.45	61	–
7	$Y(OTf)_3$	**5a**	1:0.77	53	18
8	$Y(OTf)_3$	**5b**	1:0.39	62	89
9	$Y(OTf)_3$	**5c**	1:0.95	44	35
10	$Yb(OTf)_3$	**5b**	1:0.1	73	45
11	$Zn(OTf)_2$	**5b**	–	trace	55
12	$La(OTf)_3$	**5b**	1:0.20	59	77
13	$In(OTf)_3$	**5b**	1:0.17	61	64
14	$Sm(OTf)_3$	**5b**	1:0.51	29	74
15	YCl_3	**5b**	–	trace	–

All reactions were conducted using **1a** (0.1 mmol) and *p*-chloroaniline (0.13 mmol) with cyclohexanone (0.05 mL) in THF (0.5 mL) at room temperature. [a] Yields were determined by ^{1}H NMR spectroscopic analysis of crude reaction mixtures; [b] *ee* values were determined by chiral HPLC analysis; [c] the reaction was conducted for 72 h. See the Supporting Information for experimental details. MLA = metal Lewis acid; BA = Brønsted acid; ADAP = product of ADA reaction; MP = product of Mannich reaction.

entries 12–14) were also able to give the ADA product as the major product with moderate enantioselectivities (45–77% *ee*).

We next conducted solvent screening to further improve the chemoselectivity and enantioselectivity of the ADA reaction (Table 2). We decided to choose the $Y(OTf)_3$/**5b** binary acid system for solvent screening, as $Y(OTf)_3$/**5b** displayed the highest enantioselectivity (Table 1, entry 8). Dichloromethane (DCM) and 1,2-dichloroethane (DCE) turned out to be the best solvents, both leading to excellent chemoselectivity (ADAP/MP = 1:0.04 in both cases) and enantioselectivity (98% *ee* in both cases; Table 2, entries 9 and 10).

Table 2. Solvent screening for the three-component ADA reaction of **1a**, **2a**, and **3a**.



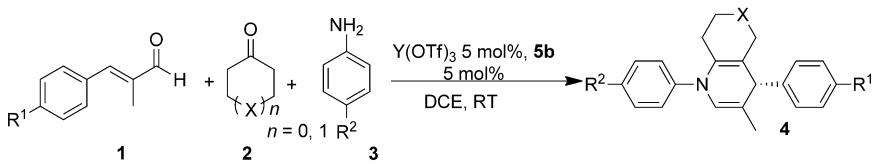
Entry	Solvent	ADAP/MP	ADAP yield [%][a]	*ee* [%][b]	Time [h]
1	toluene	1:0.94	38	92	48
2	CH_3CN	1:0.02	70	35	48
3	Neat	1:2.6	15	80	48
4	MeOH	1:0.3	67	93	48
5	1,4-dioxane	1:0.91	44	43	48
6	H_2O	1:0.68	50	99	48
7	$CHCl_3$	1:0.04	87	69	24
8	acetone	1:0.06	78	88	24
9	DCM	1:0.04	81	98	24
10	DCE	1:0.04	84	98	24

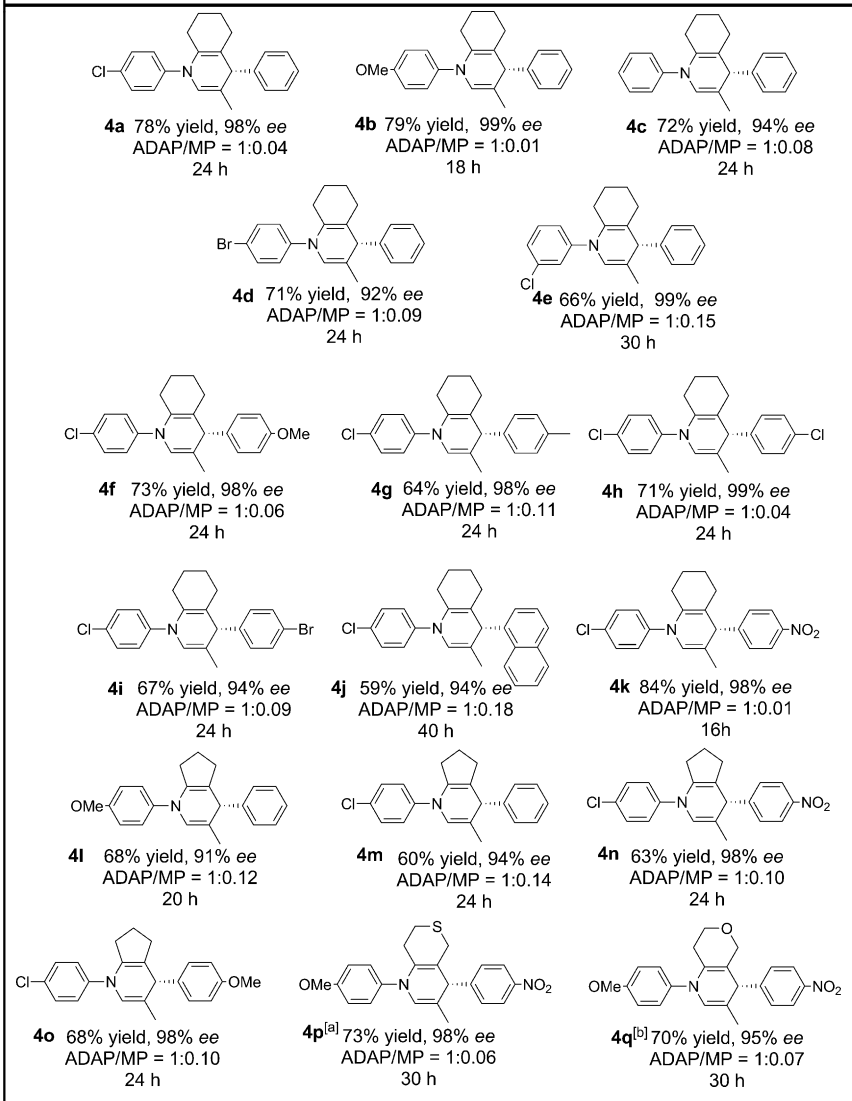
All reactions were conducted using **1a** (0.1 mmol) and *p*-chloroaniline (0.13 mmol) with cyclohexanone (0.05 mL) in dry solvent (0.5 mL) at room temperature. [a] Yields were determined by ^{1}H NMR spectroscopic analysis of crude reaction mixtures; [b] *ee* values were determined by chiral HPLC analysis.

Reaction scope

Having established the feasibility of this trio catalytic system, we explored the scope of this three-component ADA reaction using the optimized conditions (Table 2, entry 10). The scope of the three substrates (arylamines, 2-methylcinnamaldehydes, and cyclic ketones) is summarized in Table 3. Both electron-rich *p*-methoxyaniline (**4b**), and more electron-deficient arylamines, including aniline (**4c**), *p*-chloroaniline (**4a**), *m*-chloroaniline (**4e**), and *p*-bromoaniline (**4d**), reacted with **1a** and cyclohexanone to produce the ADA products in high enantioselectivities, good yields, and excellent chemoselectivities (Table 3, **4a**–**e**). 2-Methylcinnamaldehydes with both electron-donating and electron-withdrawing aromatic substituents at the β-position reacted smoothly with cyclohexanone and *p*-chloroaniline to afford the ADA product in high to excellent enantioselectivities (94-99% *ee*) and good yields (59–84%; **4f**–**k**). It is notable that 2-methylcinnamaldehyde with an electron-withdrawing aro-

Table 3. Substrate scope of three-component ADA reaction of substituted cinnamaldehydes, cyclic ketones, and arylamine.





All reactions were conducted using **1** (0.2 mmol) and arylamine (0.26 mmol) with cyclic ketone (0.2 mL) in dry DCE (2.0 mL) at room temperature. Yields refer to products isolated by chromatography and *ee* values were determined by chiral HPLC analysis; [a] 1.0 mmol dihydrothiopyran-4-one was used in the reaction; [b] 0.05 mL tetrahydro-4*H*-pyran-4-one was used in the reaction.

matic substituent (NO_2) exhibited higher activity in the ADA reaction (**4k**; $t = 16$ h, 84% yield, 98% *ee*).

Cyclopentanone and heteroatom-containing cyclic ketones were also active for the ADA reaction (**4l–q**). The ADA reactions of cyclopentanone, however, resulted in slightly lower yields (**4l–o**; 60–68% yield, 91–98% *ee*) than those of cyclohexanone. Dihydrothiopyran-4-one and tetrahydro-4*H*-pyran-4-one underwent ADA reactions smoothly, giving **4p** (73% yield, 98% *ee*) and **4q** (70% yield, 95% *ee*) in a reaction time of 30 h in both cases.

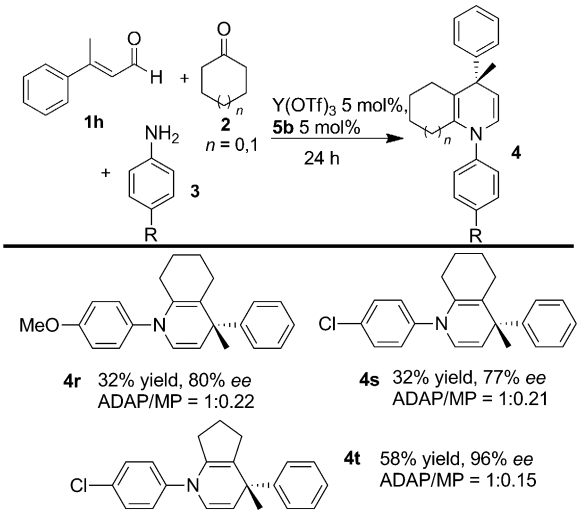
DHPs bearing a chiral quaternary carbon center (Scheme 2, **4r–t**) were also realized. Using β-substituted enal **1h**, the ADA reaction of cyclopentanone, **1h** and *p*-chloroaniline was achieved in moderate yield (58%) with high enantioselectivity (96%; **4t**). The ADA reactions of cyclohexanone, **1h**, and arylamines, however, only produced ADA products (**4r** and **4s**) in low yields (32% in both cases) with moderate enantioselectivities (**4r**: 80% *ee*; **4s**: 77% *ee*). The lower stability of these DHPs accounts partially for the lower yields as a result of decomposition of the compounds on the silica column.

The absolute configuration of **4k** was established as 4*R* by X-ray crystallography of compound **6**.[7] Compound **6** was prepared from **4k** by reduction with $NaBH(OAc)_3$ (Scheme 3).

Study of the trio catalytic system

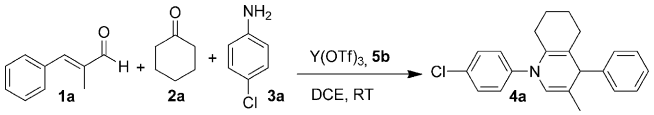
This three-component-catalyzed three-component reaction is complicated in nature. It is possible that this reaction involves one or more transition states. To further elucidate this novel system, we performed a ratio study of **5b** and $Y(OTf)_3$ (Table 4). The ratio study suggested that the most active binary acid catalyst was formed in a 1:1 molar ratio, in good agreement with the study of Luo et al.[4b–d,i] ESI-MS spectra (anionic mode) of a solution containing **5b** and $Y(OTf)_3$ revealed one dominant peak at *m/z* 1287, corresponding to TRIP·$Y(OTf)_3$. The mass spectrometric analysis further confirmed that the **5b**/$Y(OTf)_3$ complex was formed in a 1:1 molar ratio.

To better understand the roles that both the phosphoric acid and $Y(OTf)_3$ play, we treated the catalytic systems with triethylamine (Scheme 4). When TRIP was mixed with triethylamine in the absence of $Y(OTf)_3$, no reaction occurred, indicating that the acid functionality of phosphoric acid was fully



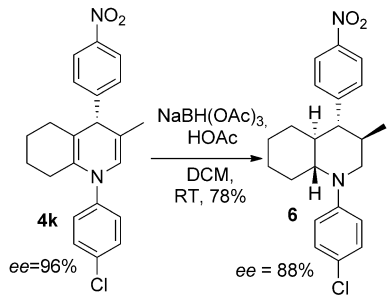
Scheme 2. ADA reactions of β-substituted enal **1h**.

Table 4. Ratio study of binary acid catalyst **5b**/$Y(OTf)_3$.



Entry	$Y(OTf)_3$ [mol%]	**5b** [mol%]	ADAP/MP	ADAP yield [%][a]	*ee* [%][b]	Time [h]
1	5	–	1:1.21	21	–	48
2	–	5	1:0.45	47	99	48
3	2.5	5	1:0.11	72	98	48
4	5	5	1:0.04	84	98	24
5	10	5	1:0.21	62	70	24

All reactions were conducted using **1a** (0.1 mmol) and *p*-chloroaniline (0.13 mmol) with cyclohexanone (0.05 mL) in dry DCE (0.5 mL) at room temperature. [a] Yields were determined by ^{1}H NMR spectroscopic analysis of crude reaction mixtures; [b] *ee* values were determined by chiral HPLC analysis.

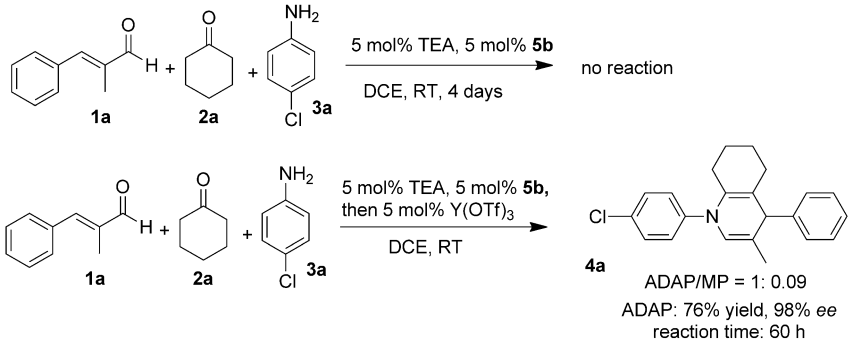


Scheme 3. Reduction of **4k** and crystal structure of compound **6**.

quenched by the base; however, when $Y(OTf)_3$ was added into the system, quantitative ADA product was obtained, albeit in a much longer reaction time (60 h) than the reaction without triethylamine (24 h, Table 2, entry 10), indicating that the presence of the phosphoric acid significantly facilitates the reaction.

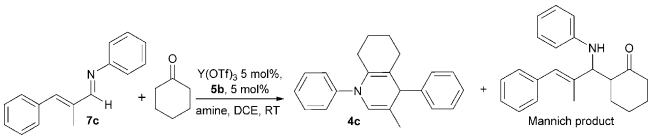
We demonstrated in our previous work that arylamines can serve as effective amine catalysts in enamine catalysis by combining with either a strong metal Lewis acid or a Brønsted acid.[2] We believe that the arylamines in this trio catalyst system play the same role. To further investigate this, we set up parallel reactions using preformed 1-azadiene and cyclohexanone, and studied the effect on the reaction with different amines (Table 5). In the presence of a primary (aniline) or a secondary arylamine (indoline), the two-component reactions proceeded the fastest (Table 5, entries 1 and 5). Without the addition of an amine (Table 5, entry 6), reaction still occurred. This was an expected result, because 1-azadiene easily decomposed back to the corresponding aldehyde and amine (Table 5, entry 7), converting the reaction into a three-component reaction. In the presence of a tertiary arylamine (Table 5, entry 2), the reaction was much slower than those with primary and secondary arylamines. It was also slower than the reaction without addition of an arylamine. It is likely that the tertiary amine interferes with the catalytic system by reversibly combining with the metal Lewis acid and/or the Brønsted acid. These data are similar to those obtained in our previous work,[2] suggesting that enamine catalysis is taking place. We also attempted reactions with an aliphatic primary amine (hexylamine) and an aliphatic secondary amine (pyrrolidine). As expected, these reactions did not give any product, confirming once again that aliphatic amines (hard bases) are not compatible with hard metal Lewis acids and strong Brønsted acids.

Based on these data and the results in previous work involving binary acid catalysis[4b–i] and BINOL-derived phosphoric acid,[8] we proposed a possible transition state for this transformation (Figure 2). In this model, Y^{III} coordinates to one of the oxygen atoms of phosphoric acid; the nitrogen atom of (*E*)-1-azadiene binds to Y^{III} and thus is activated; the hydrogen of the enamine intermediate forms a hydro-



Scheme 4. Three-component ADA reactions catalyzed by trio catalytic systems with triethylamine.

Table 5. Effect of amine on two-component ADA reaction.



Entry	Amine (mol%)	Time [h]	Conversion [%][a]
1	aniline (130)	<18	100
2	*N*,*N*-dimethylaniline (130)	19	69
3	pyrrolidine (130)	20	0
4	hexylamine (130)	20	0
5	indoline (130)	19	91
6	–	21	82
7[b]	–	24	17

All reactions were conducted using **7c** (0.2 mmol) with cyclohexanone (0.2 mL) in dry DCE (2 mL) at room temperature. [a] Conversions were determined by ^{1}H NMR spectroscopic analysis of crude reaction mixtures; [b] no cyclohexanone was included in this reaction; the conversion is the conversion of **7c** to the corresponding aldehyde and arylamine.

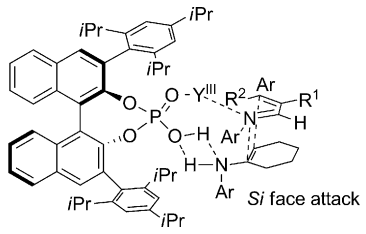


Figure 2. Proposed transition state for ADA reaction.

gen bond with another oxygen of the phosphoric acid and approaches the 1-azadiene via an *endo*-selective mode; the binaphthyl skeleton, possessing axial chirality, shields the *Re* face of the 1-azadiene and the enamine attacks from the *Si* face. The proton of the phosphoric acid is likely to participate through hydrogen bonding to stabilize the enamine intermediate and transition state. This proposed transition state explains well the observed phenomena. The absolute configuration of the chiral Diels–Alder product derived from this model also matches well with the X-ray crystal structure.

Conclusion

It is very challenging to develop multiple catalyst-mediated multicomponent reactions. In this work, we have developed novel trio catalysis involving chiral phosphoric acid, hard metal Lewis acid, and arylamine. This three-component catalytic system integrates enamine catalysis with both stronger Brønsted acid catalysis and hard metal Lewis acid catalysis for the first time and was used to effect a new asymmetric three-component ADA reaction of substituted cinnamaldehydes, cyclic ketones, and arylamines. In the presence of the binary acid TRIP/Y(OTf)$_3$, a wide range of arylamines and cyclic ketones reacted with substituted cinnamaldehydes leading to the formation of DHPs with good yields and good to excellent enantioselectivities (up to 99% *ee*). DHPs bearing a chiral quaternary carbon center at C4 were also obtained with moderate to high enantioselectivities and moderate yields.

The three-component catalytic system also allows combinational flexibility of arylamine, metal Lewis acid, and chiral phosphoric acid, offering easily tunable catalytic activity. The trio catalysis introduced herein provides a new tool in asymmetric catalysis, in particular in the growing field of combining amine organocatalysts with transition metal catalysts. We expect broad applications of this new concept in the development of new asymmetric organic transformations in the near future.

Experimental Section

General procedure for asymmetric three-component ADA reaction: To a Schlenk tube charged with argon was added Y(OTf)$_3$ (5.36 mg, 0.01 mmol, 5 mol%) and **5b** (0.01 mmol, 5 mol%). Distilled anhydrous DCE (2 mL) was added to the mixture. After stirring at room temperature for 2 h, aldehyde **1** (0.2 mmol, 1.0 equiv), arylamine (0.26 mmol, 1.3 equiv), and cyclic ketone (0.2 mL, 1.93 mmol) were added under argon protection. The resulting solution was stirred at room temperature until the reaction was completed (monitored by TLC). The reaction mixture was filtered through an aluminum oxide plug, and the filtrate was concentrated. The residue was purified by column chromatography on aluminum oxide (eluent = 8:1 hexane/ethyl acetate) to give the pure products **4**.

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FULL PAPER

Asymmetric Synthesis

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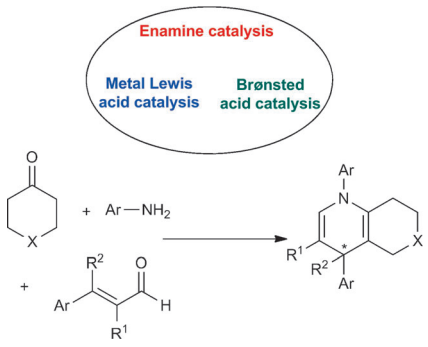
Trio Catalysis Merging Enamine, Brønsted Acid, and Metal Lewis Acid Catalysis: Asymmetric Three-Component Aza-Diels–Alder Reaction of Substituted Cinnamaldehydes, Cyclic Ketones, and Arylamines



Once, twice, thrice a catalyst: A three-component aza-Diels–Alder reaction of substituted cinnamaldehydes, cyclic ketones, and arylamines was developed with high chemo- and enantioselectivities (up to 99% *ee*), by using trio catalysis involving enamine, metal Lewis acid, and Brønsted acid catalysts.