JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

Organocatalytic Enantioselective Direct Additions of Aldehydes to 4-Vinylpyridines and Electron-Deficient Vinylarenes and Their Synthetic Applications

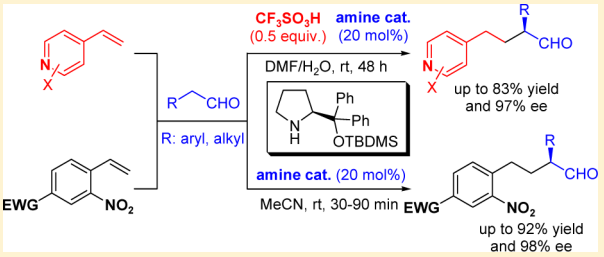
Sinan Wang,[†] Xiangmin Li,[†,‡] Hongwei Liu,[†] Li Xu,[†] Jinchen Zhuang,[†] Jian Li,[†] Hao Li,*[,†] and Wei Wang*[,†,‡]

[†]Shanghai Key Laboratory of New Drug Design, School of Pharmacy, and State Key Laboratory of Bioengineering Reactor, East China University of Science and Technology, 130 Mei-long Road, Shanghai 200237, China

[‡]Department of Chemistry and Chemical Biology, University of New Mexico, Albuquerque, New Mexico 87131-0001, United States

Supporting Information

ABSTRACT: We describe a synergistic catalysis strategy for the asymmetric direct addition of simple aldehydes to 4-vinylpyridines. By means of independent activation of weakly electrophilic 4-vinylpyridines by the Brønsted acid CF_3SO_3H (TfOH) and aldehydes by chiral diphenylprolinol *tert*-butyldimethylsilyl (TBDMS) ether-catalyzed formation of nucleophilic enamines in a cooperative manner, the previously unattainable highly enantioselective addition process has been realized for the first time. Notably, the power of the addition process is fueled by its high efficiency in the production of synthetically valued chiral pyridines. ^{1}H NMR studies of the process suggested that the nucleophilic enamine formed in situ from the chiral amine catalyst and the aldehyde is directly added to the trimeric 4-vinylpyridinium-derived species as a highly active electrophile generated from the 4-vinylpyridine in the presence of TfOH. Moreover, inspired by the similar electronic natures of pyridine and nitrobenzene, we have achieved an unprecedented chiral diphenylprolinol TBDMS ether-promoted, highly enantioselective direct addition of aldehydes to 2-nitrostyrenes without the use of TfOH as a cocatalyst. In this approach, introducing a strong electron-withdrawing group such as NO_2, CF_3, SO_2Me, etc. on the 2-nitrostyrene creates a highly electrophilic vinyl moiety, which enables the direct addition of the in situ-formed enamine derived from the chiral amine promoter and the aldehyde. This method significantly expands the scope of the enantioselective addition process. While the electron-withdrawing nitro group is essential for activation of the vinyl group, we have demonstrated that it can be readily transformed to diverse functionalities. Furthermore, as shown, a chiral pyridine adduct serves as a key building block in the synthesis of the potent fibrinogen receptor antagonist L-734,217.



INTRODUCTION

Twelve therapeutics containing a pyridine moiety in the top 200 pharmaceutical products by U.S. retail sales in 2012, including the top one, Nexium, manifest the "privileged" status of the heteroaromatic structure in synthesis and medicinal chemistry.[1] Among the heteroarenes, pyridine perhaps is the most studied system because of its broad utility. In addition to their ubiquitous distribution in biologically active natural products, pharmaceuticals, and agrochemicals,[2] pyridines are also widely employed as ligands in catalysis and molecular recognition.[3] Therefore, the capacity to functionalize the privileged structure would leverage new broad-ranging applications.[4]

Direct addition of nucleophiles to electrophilic alkenylpyridines is a viable strategy for the facile synthesis of pyridine derivatives.[5] In this context, readily available 2- and 4-vinylpyridines have been subjected to intensive studies in a nonasymmetric fashion. It is noteworthy that as a result of their lower reactivity compared with classic α,β-unsaturated systems as Michael acceptors in conjugate additions, strong nucleophiles such as indoles,[6] malonates and their derivatives,[7] amines,[8] and thiols[9] are generally used. Moreover, these processes are often performed under basic or acidic conditions or with the assistance of transition metals and/or at high temperature for effective transformations.

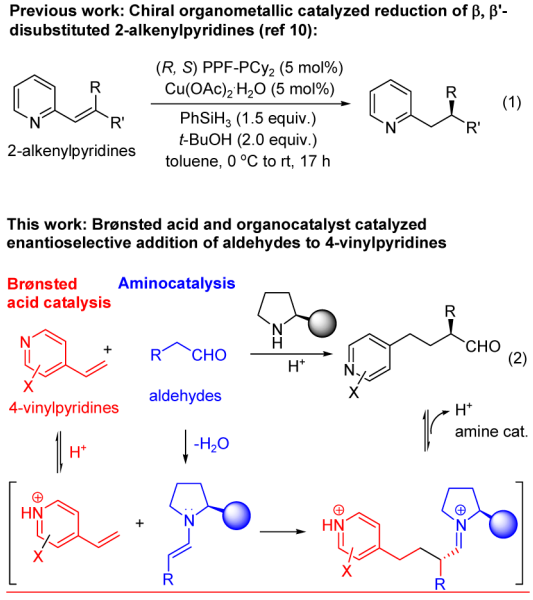
Despite the significant value and broad application of chiral pyridine building blocks in organic synthesis and medicinal chemistry, the development of catalytic enantioselective 1,4-conjugate addition processes with 2- and 4-vinylpyridines has been difficult. To date, to the best of our knowledge, only four catalytic processes to effect enantioselective conjugate addition processes have been investigated. In 1993, Houpis and co-workers reported the first asymmetric addition reaction of Grignard and organozinc reagents to 4-alkenylpyridines catalyzed by a nickel catalyst, but the products were obtained with less than 15% ee.[10] The breakthrough in this field came 16 years later, when Lam and colleagues uncovered the Cu(II)–

Received: October 29, 2014
Published: January 28, 2015

DOI: 10.1021/ja511143b
J. Am. Chem. Soc. 2015, 137, 2303–2310

Josiphos complex-catalyzed highly enantioselective reduction of electron-deficient β,β'-disubstituted 2-alkenylpyridines and other heteroarenes with $PhSiH_3$ (Scheme 1, eq 1).[11] More recently, the same group reported an elegant arylation reaction of alkenylpyridines and -heteroarenes catalyzed by a chiral Rh complex with high enantioselectivity (up to 98% ee).[12] Similar chemistry has been nicely carried out by Lautens and co-workers[13] in a Rh/Pd-cocatalyzed cascade process for the one-pot synthesis of chiral aza-dihydrodibenzoxepines. Unfortunately, these chiral transition-metal-catalyzed processes display poor efficiency on 4-alkenylpyridines because of the difficulty of complexation with the Lewis acid for activation of these substrates.

Scheme 1. Catalytic Enantioselective Addition Reactions with Alkenylpyridines



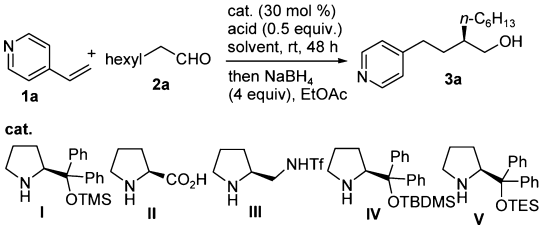
Herein we report an alternative catalytic strategy using a Brønsted acid and chiral amine as cocatalysts in promoting the enantioselective direct addition of aldehydes to 4-vinylpyridines for the first time (Scheme 1, eq 2).[14] The Brønsted acid (e.g., CF_3SO_3H (TfOH)) activates the 4-vinylpyridine to generate a highly active electrophilic trimeric 4-vinylpyridinium ion, while the amine promotes the formation of a nucleophilic enamine from the corresponding aldehyde. Notably, the cooperative catalysis achieves high enantioselectivities (up to 97% ee) and good yields (up to 83%). Furthermore, trigged by the similar electronic natures of pyridine and nitrobenzene, we have successfully designed electron-deficient-substituted 2-nitrostyrenes as effective acceptors for the highly enantioselective addition of aldehydes using a chiral amine as the catalyst. Although the electron-withdrawing nitro group is essential for activation of the vinyl group, it can be conveniently transformed to new diverse functional groups. Furthermore, as demonstrated experimentally, a chiral pyridine adduct serves as a key building block in the efficient synthesis of the potent fibrinogen receptor antagonist L-734,217.

RESULTS AND DISCUSSION

1. Conjugate Addition to 4-Vinylpyridines. *a. Design Plan.* In light of the poor reactivity of 4-vinylpyridines in nucleophilic addition reactions, we proposed a synergistic catalysis approach.[15] Through independent activation of separate electrophilic and nucleophilic substrates by two distinct catalysts, this synergistic catalytic strategy may enable a new, previously unattainable addition process. Specifically, a Brønsted acid activates the 4-vinylpyridines through acid–base interactions[16] while a chiral amine promotes the formation of highly active nucleophilic enamines from their precursor aldehydes[17] (Scheme 1, eq 2). The two resultant active species may allow for an unprecedented enantioselective addition reaction of 4-vinylpyridines with aldehydes.

b. Exploration and Optimization of the Reaction Conditions. To demonstrate the feasibility of the novel process, we embarked on the model reaction of 4-vinylpyridine (**1a**) (1.0 mmol) and *n*-octanal (**2a**) (3.0 mmol) in the presence of diphenylprolinol trimethylsilyl (TMS) ether (**I**) (30 mol %) and CF_3SO_3H (0.5 equiv) as cocatalysts in 1 mL of *N*,*N*-dimethylformamide (DMF) at room temperature (rt) for 48 h (Table 1, entry 1). Under the reaction conditions, fast racemization of the aldehyde product was observed. Accordingly, it was reduced to alcohol **3a** by $NaBH_4$ for characterization. To our delight, the desired product **3a** was obtained in good yield (75%), but the enantioselectivity was poor (23% ee). Various amine catalysts were then screened (entries 2–4). L-Proline (**II**) and (*S*)-pyrrolidine sulfonamide **III** failed to promote this process (entries 2 and 3). The more hindered

Table 1. Optimization of Reaction Conditions for the Addition of Aldehydes to 4-Vinylpyridines[a]



entry	cat	acid	solvent	yield (%)[b]	ee (%)[c]
1	**I**	CF_3SO_3H	DMF	75	23
2	**II**	CF_3SO_3H	DMF	trace	nd
3	**III**	CF_3SO_3H	DMF	trace	nd
4	**IV**	CF_3SO_3H	DMF	74	33
5	**IV**	CF_3SO_3H	THF	45	41
6	**IV**	CF_3SO_3H	toluene	33	35
7	**IV**	CF_3SO_3H	DMF/H_2O (9:1)	77	80
8	**IV**	CF_3SO_3H	DMF/H_2O (8:2)	81	86
9	**IV**	CF_3SO_3H	DMF/H_2O (7:3)	76	86
10	**IV**	–	DMF/H_2O (8:2)	0	nd
11	**IV**	AcOH	DMF/H_2O (8:2)	0	nd
12	**IV**	HCl	DMF/H_2O (8:2)	45	90
13	**IV**	HNO_3	DMF/H_2O (8:2)	52	88
14	**IV**	H_2SO_4	DMF/H_2O (8:2)	50	91
15[d]	**IV**	CF_3SO_3H	DMF/H_2O (8:2)	81	92
16[d,e]	**IV**	CF_3SO_3H	DMF/H_2O (8:2)	56	91
17[d,f]	**IV**	CF_3SO_3H	DMF/H_2O (8:2)	72	92
18[g]	**IV**	CF_3SO_3H	DMF/H_2O (8:2)	73	92

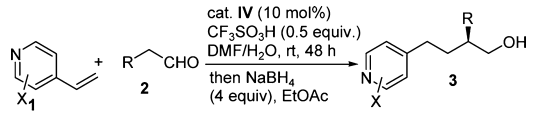
[a]Unless otherwise specified, a mixture of **1a** (1.0 mmol) and **2a** (3.0 mmol) in the presence of the catalyst (30 mol %) and CF_3SO_3H (0.5 equiv) in the indicated solvent (1.0 mL) was stirred at rt for 48 h. [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d]**IV** (10 mol %) was used. [e]CF_3SO_3H (0.4 equiv) was used. [f]CF_3SO_3H (0.6 equiv) was used. [g]**IV** (5 mol %) was used.

DOI: 10.1021/ja511143b
J. Am. Chem. Soc. 2015, 137, 2303–2310

catalyst diphenylprolinol *tert*-butyldimethylsilyl (TBDMS) ether (**IV**) afforded better enantioselectivity without loss of yield (33% ee, 74% yield; entry 4). Although a slight improvement in the enantioselectivity was observed in less polar solvents (tetrahydrofuran (THF) and toluene), lower yields were obtained as a result of the poor solubility of the formed pyridinium salt, which was precipitated out during the course of the reaction (entries 5 and 6). Further optimization of the reaction conditions revealed H_2O to be critical for the enantioselectivity (entries 7–9). A mixture of DMF and H_2O (9:1 v/v) as the solvent led to a dramatic increase in the enantioselectivity (80% ee; entry 7). Further fine-tuning of the ratio showed 8:2 to be the optimal choice (entries 8 and 9). The acid catalyst had a significant impact on the reaction. No reaction took place without acid or with a weaker acid (AcOH) (entries 10 and 11). This suggests that activation of the 4-vinylpyridine is essential in this synergistic catalysis, proving our working hypothesis. Strong acids such as HCl, HNO_3, and H_2SO_4 afforded the alkylation products with excellent enantioselectivities in moderate yields (entries 12–14). When the loading of the amine catalyst was decreased to 10 mol %, the reaction gave rise to a significantly improved yield while maintaining excellent enantioselectivity (entry 15). Further decreasing the catalyst loading to 5 mol % led to a lower reaction yield despite similarly high enantioselectivity (entry 18). In contrast, using a smaller (0.4 equiv) or larger amount (0.6 equiv) of CF_3SO_3H deteriorated the yield (entries 16 and 17).

c. Reaction Scope. With the optimal conditions in hand, we then probed the scope of the new addition process (Table 2).

Table 2. Scope of the Asymmetric Addition of Aldehydes to 4-Vinylpyridines[a]



entry	X	R	yield (%)[b]	ee (%)[c]
1	H	*n*-hexyl	81 (**3a**)	92
2	H	Et	70 (**3b**)	93
3	H	*n*-butyl	74 (**3c**)	93
4	H	*n*-octyl	82 (**3d**)	93
5	H	isopropyl	62 (**3e**)	97
6	H	cyclohexyl	62 (**3f**)	96
7	H	Bn	83 (**3g**)	90
8	H	$(CH_2)_3CO_2Me$	73 (**3h**)	92
9	H	$(CH_2)_4NHBoc$	71 (**3i**)	94
10	H	$(CH_2)_3NH(Cbz)CH_2CO_2Et$	76 (**3j**)	95
11	2-Me	*n*-hexyl	83 (**3k**)	97
12	2-$HOCH_2$	*n*-hexyl	76 (**3l**)	97
13	3-NHAc	*n*-hexyl	73 (**3m**)	92
14	3-CO_2Me	*n*-hexyl	43 (**3n**)	93

[a]See the Supporting Information for the experimental protocol. [b]Isolated yields. [c]Determined by chiral HPLC analysis.

The results showed that the catalytic addition reaction serves as a general approach to structurally diverse products **3**. A wide range of aldehydes and various 4-vinylpyridines could engage in the process, affording the corresponding products with excellent enantioselectivities in overall good to high yields. Structure variation of the aldehyde reactant could be tolerated. The length and size of the aldehyde have a limited effect on the enantioselectivity (entries 1–6), and it appears that sterically demanding branched aldehydes are beneficial to the enantioselectivity (entries 5 and 6). Furthermore, aldehydes bearing a diverse array of functional groups, including aromatic ring, ester, and amine, reacted smoothly under the optimal conditions to give the desired products (entries 7–10). It is recognized that 4-vinylpyridines with electron-donating substituents on the pyridine ring delivered excellent results in terms of yield and enantioselectivity (entries 11–13). However, electron-withdrawing moieties decreased the reactivity of the 4-vinylpyridine, presumably because of a reduction in the basicity of the pyridine for activation by CF_3SO_3H. A low yield but still a high level of enantioselectivity were achieved (entry 14). The absolute configurations of the products were determined on the basis of single-crystal X-ray diffraction analysis of compound **4** derived from aldehyde **5i** by two-step conversion (Figure 1; also see the Supporting Information).[18]

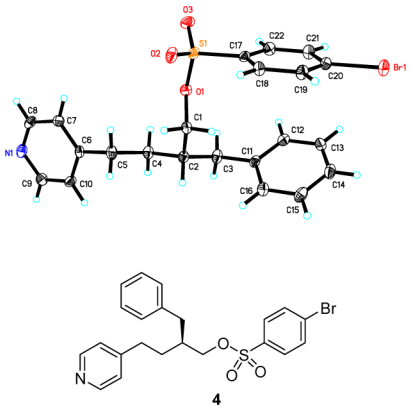
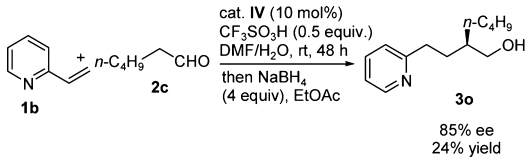


Figure 1. X-ray crystal structure of compound **4**.

We then turned our attention to 2-vinylpyridine (**1b**) as the reactant in the **IV**-promoted enantioselective addition process (Scheme 2). It was found that under the same reaction

Scheme 2. IV-Catalyzed Addition of *n*-Hexanal (2c) to 2-Vinylpyridine



conditions, the process proceeded with good enantioselectivity (85% ee) but low yield (24%). This outcome is consistent with that observed by Gray and co-workers in their studies of the acid-catalyzed morpholine–isobutyraldehyde-derived enamine, where only a 13% yield was obtained.[14b] It is believed that the poor reactivity of 2-vinylpyridine is attributable to its much lower basicity (pK_a = 4.92) compared with 4-vinylpyridine (pK_a = 5.62).[19] Its poor protonation efficiency makes it difficult to form the more active pyridinium ion. This is also in agreement with what was observed in our mechanistic investigations (see below). In the presence of CF_3SO_3H, it is difficult for 2-vinylpyridine to form the corresponding pyridinium trimer, the actual active species for the catalytic addition process.

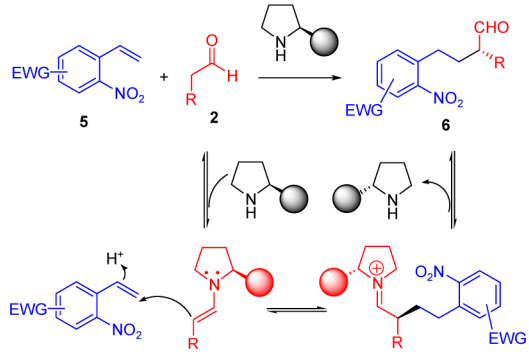
DOI: 10.1021/ja511143b
J. Am. Chem. Soc. 2015, 137, 2303–2310

Finally, we probed ketones, including acetone and cyclohexanone, as nucleophiles in the **IV**-catalyzed addition reaction with 4-vinylpyridine. Unfortunately, the processes did not take place. This is presumably due to the lower reactivity of ketones compared with aldehydes that is often seen in enamine catalysis. Other pyridine-derived heterocycles such as 2- and 4-vinylpyrimidines and 2-vinylpyrazine also were explored in this reaction, but no reactions were observed either. We reasoned that similar to 2-vinylpyridine, these heterocycles cannot form the corresponding active trimers because the basicity is diminished by the electron-withdrawing "N" atoms.

2. Conjugate Addition to Substituted 2-Nitrostyrenes.

a. Design Plan. Having established the organocatalyzed enantioselective direct addition of aldehydes to electron-deficient 4-vinylpyridine C=C double bonds with the assistance of the Brønsted acid CF_3SO_3H for the synthesis of useful chiral pyridine derivatives, we questioned whether this strategy could be applied to other vinyl structures, as the successful realization of these processes would significantly expand the scope of the useful asymmetric addition reaction. In the addition of aldehydes to 4-vinylpyridines, the acid cocatalyst was necessary for activation of the pyridine. It is accepted that the electronic nature of pyridine is similar to that of nitrobenzene. To make the vinyl group have reactivity comparable to that of the vinyl group in 4-vinylpyridines, which is further activated by CF_3SO_3H, we surmised that introducing into 2-nitrostyrene an additional strong electron-withdrawing group such as NO_2, CF_3, or SO_2Me may lead to a highly active vinyl group for the addition reaction (Scheme 3).

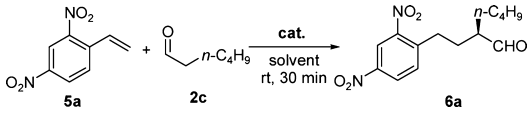
Scheme 3. Catalytic Enantioselective Addition Reactions with Electron-Deficient Styrenes



Such activation may sufficiently polarize the vinyl moiety to enable the addition reaction with aldehydes. Subsequently, a chiral enamine formed in situ from its corresponding aldehyde precursor as an electron donor could be added to the C=C double bond.

b. Exploration and Optimization of the Reaction Conditions. In the exploratory study, we conducted a model reaction between 2,4-dinitro-1-vinylbenzene (**5a**) (0.2 mmol) and *n*-hexanal (**2c**) (0.6 mmol) in the presence of 30 mol % organocatalyst **I** in CH_3CN at rt (Table 3). To our delight, the process was complete in 30 min and gave the desired alkylation product **6a** in high yield with good enantioselectivity (entry 1). The more bulky catalysts **V** and **IV** significantly improved the enantioselectivity from 83% to 92% and 94%, respectively (entries 2 and 3), while **II** failed to promote this process (entry 4). Probing the solvent effects with catalyst **IV** revealed that a lower reaction yield and enantioselectivity were obtained when

Table 3. Optimization of the Reaction Conditions for the Addition of Aldehydes to 2-Nitrostyrenes[a]



entry	cat (mol %)	solvent	yield (%)[b]	ee (%)[c]
1	**I** (30)	CH_3CN	82	83
2	**V** (30)	CH_3CN	83	92
3	**IV** (30)	CH_3CN	85	94
4	**II** (30)	CH_3CN	0	–
5	**IV** (30)	DMF	34	70
6	**IV** (30)	THF	56	96
7	**IV** (30)	CH_2Cl_2	73	95
8	**IV** (30)	toluene	51	97
9[d]	**IV** (20)	CH_3CN	85	98
10[d,e]	**IV** (10)	CH_3CN	65	91
11[d,f]	**IV** (20)	CH_3CN	87	89
12[d,g]	**IV** (20)	CH_3CN	92	86

[a]Reaction conditions: unless otherwise specified, see the Experimental Section in the Supporting Information. [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d]MeCN (0.2 mL) was used. [e]The reaction mixture was stirred for 2 h. [f]**2c** (0.4 mmol) was used. [g]**2c** (0.3 mmol) was used.

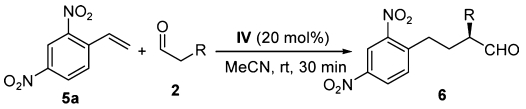
the reaction was performed in DMF, and a significant amount of self-condensation product from the aldehyde was obtained (entry 5). Other solvents such as THF, CH_2Cl_2, and toluene gave high levels of enantioselectivity but lower yields (entries 6–8). Lowering the loading of catalyst **IV** from 30 to 20 mol % and increasing the reaction concentration afforded both high enantioselectivity and yield (entry 9). Further decreasing the catalyst loading to 10 mol % led to decrease in reaction yield and enantioselectivity (entry 10). Moreover, a drop in the ee value was observed when the **2c**:**5a** ratio was decreased (entries 11 and 12). Therefore, we chose the following reaction conditions to probe the scope of the reaction: 1.0 equiv of **5a** with 3.0 equiv of **2c** in the presence of 20 mol % organocatalyst **IV** in CH_3CN at rt.

c. Reaction Scope. We first examined the impact of the structural features of aldehydes **2** on the **IV**-catalyzed process. As shown in Table 4, the reactions proceeded smoothly in high yields (65–90%) with excellent levels of enantioselectivity (93–98% ee). It appears that significant structural variation in the aldehyde can be tolerated. Linear (entries 2–4) and branched (entries 5 and 6) systems efficiently participate in the process. Furthermore, a similar trend was observed with aldehydes bearing various functional groups (entries 7–12). For example, aromatic (entries 8 and 9), heterocyclic (entry 10), ester (entry 11), and Boc-protected amino (entry 12) moieties were included in these studies. Therefore, structurally diverse chiral arylethyl aldehydes **6** are produced.

Next, we probed the reaction scope with respect to structural variation of the aromatic system **5** (Table 5). In addition to 2,4-dinitrobenzene as a reliable electron acceptor (entry 1), 2-nitro-3-trifluoromethyl and 2-nitro-4-methylsulfonyl were also effective ones (entries 2 and 3). High enantioselectivities (96 and 94% ee, respectively) and good yields (57 and 63%) were obtained. It should be noted that 30 mol % **IV** and 3.0 equiv of **2c** added in three portions were required for efficient transformation. This may be attributed to the weaker electron-withdrawing capacity of CF_3- and $MeSO_2-$ compared

DOI: 10.1021/ja511143b
J. Am. Chem. Soc. 2015, 137, 2303–2310

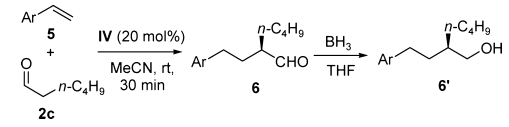
Table 4. Scope of the IV-Catalyzed Enantioselective Alkylation of Vinylarenes[a]

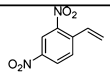
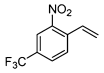
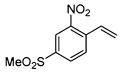
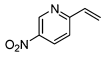


entry	R, 6	yield (%)[b]	ee (%)[c]
1	n-C_4H_9, **6a**	85	98
2[d]	C_2H_5, **6b**	68	94
3[e]	n-C_6H_{13}, **6c**	90	95
4[e]	n-C_8H_{17}, **6d**	92	97
5[d,f]	i-Pr, **6e**	65	96
6[e]	cyclohexyl, **6f**	82	97
7	Bn, **6g**	84	94
8	4-$MeOC_6H_4CH_2$, **6h**	83	95
9	4-$ClC_6H_4CH_2$, **6i**	84	93
10	2-furanyl, **6j**	86	93
11[e]	$MeO_2C(CH_2)_3$, **6k**	90	95
12[d]	$BocNH(CH_2)_4$, **6l**	76	95

[a]Reaction conditions: unless otherwise specified, see footnote *a* of Table 3 and the Experimental Section in the Supporting Information. [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d]Catalyst (30 mol %) was used. [e]The reaction finished in 20 min. [f]**5a** (0.4 mmol) and aldehyde (1.2 mmol) were used.

Table 5. Scope of IV-Catalyzed Enantioselective α-Arylethylation of *n*-Hexanal with Different Styrenes[a]



entry	5	6 or 6′	% yield[b]	% ee[c]
1		**6a**	85	98
2[d,f]		**6m′**	68	94
3[d,f,g]		**6n′**	90	95
4		**6o**	76	95

[a]Reaction conditions: unless otherwise specified, see the Experimental Section in the Supporting Information. [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d]Catalyst (30 mol %) was used. [e]Three 1.0 equiv portions of aldehyde were added at 30 min intervals; the total reaction time was 90 min. [f]The product **6** was directly reduced to the alcohol **6′** by BH_3 for chiral HPLC analysis. [g]Three 1.0 equiv portions of aldehyde were added at 10 min intervals.

with $-NO_2$. Finally, heterocyclic 5-nitro-2-vinylpyridine was an effective acceptor, providing a high yield with high enantioselectivity under the optimized reaction conditions (entry 4). The absolute configurations of the products were determined on the basis of single-crystal X-ray diffraction analysis of compound **7** derived from aldehyde **6i** by two-step conversion (Figure 2; alos see the Supporting Information).[20]

3. Synthetic Applications. *a. Synthesis of Key Intermediate 9 of Fibrinogen Receptor Antagonist L-734,217 from Chiral Pyridine Adducts.* Chiral pyridines are versatile

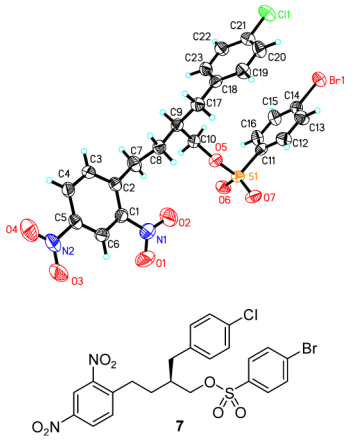
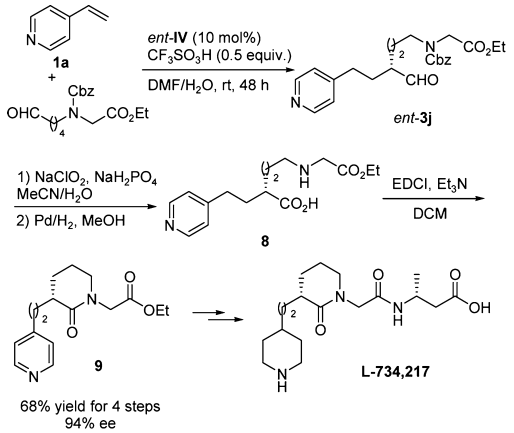


Figure 2. X-ray crystal structure of compound 7.

synthetic building blocks in organic synthesis. To probe the utility of the chiral pyridine adducts produced from this addition process, we developed a synthetic approach to the important chiral intermediate **9**, which serves as a key component of the synthesis of L-734,217, a potent fibrinogen receptor antagonist (Scheme 4).[21] The reported synthetic

Scheme 4. Synthesis of Chiral Intermediate 9 Leading to L-734,217



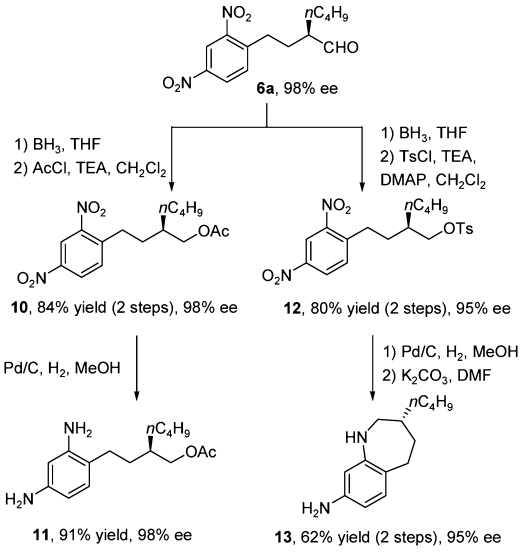
method relies on resolution, and the highest yield for the synthesis of this chiral intermediate was very low (ca. 26%). The strategy we developed is much more efficient, involving one single purification operation. The required chiral aldehyde *ent*-**3j** was rapidly accessed from simple 4-vinylpyridine **1a** and the *N*-Cbz-protected aldehyde precursor in the presence of CF_3SO_3H (0.5 equiv) and *ent*-**IV** (10 mol %). The resulting crude product was directly used for the subsequent oxidation without purification. Treatment of the aldehyde with the oxidant $NaClO_2$ and NaH_2PO_4 furnished the corresponding acid. After Pd-catalyzed hydrogenation to remove the Cbz group, intramolecular cyclization of the amine and the carboxylic acid using 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDCI) as a coupling reagent afforded chiral lactam **9** in 68% yield for the total four-step transformation without isolation of these intermediates. It is noted that no ee erosion was observed in these conversions. By means of the reported procedures, the lactam can be readily converted to the target L-734,217 in three steps.[21]

DOI: 10.1021/ja511143b
J. Am. Chem. Soc. 2015, 137, 2303−2310

b. Synthetic Elaboration of Chiral Adducts **6.** The strong electron-withdrawing nitro group(s) on the aromatic ring is essential for creating highly active electronic acceptors in the **IV**-promoted α-arylethylation of aldehydes. Nevertheless, from the synthetic utility point of view, the nitro moiety should be conveniently transformed into new functionalities. Therefore, we carried out studies using products **6a** and **6m** as examples (Schemes 5 and 6).

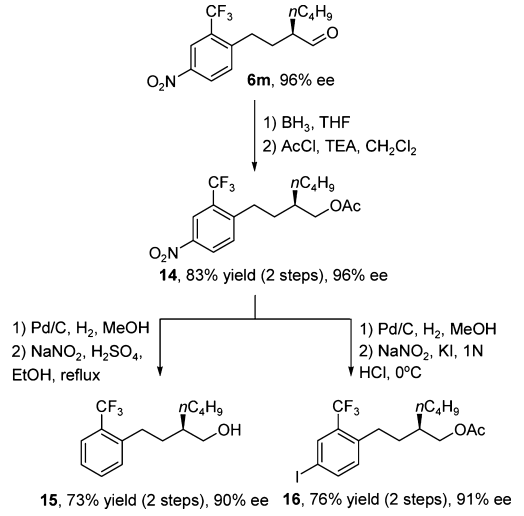
The BH_3-mediated reduction of aldehyde **6a** gave the corresponding alcohol, which was then converted to esters **10** and **12** in high yields by treatment with AcCl and TsCl, respectively (Scheme 5). Pd-catalyzed reduction of both nitro groups in **10** with H_2 gave rise to amine **11** in 91% yield. The amine formed by reduction of **12** underwent a cyclization in the presence of K_2CO_3 to afford benzazepine **13**, one member of a class of biologically important "privileged" molecules.[22] It is noteworthy that in these transformations, no or minimal racemization was observed.

Scheme 5. Synthetic Elaboration of Compound 6a



Furthermore, the nitro group can be removed or transformed to H or I, as demonstrated using compound **6m** (Scheme 6).

Scheme 6. Synthetic Elaboration of Compound 6m



By means of similar strategies, the aldehyde was converted to ester **14** in two steps by reaction with BH_3 and then AcCl. Hydrogenation of the nitro moiety catalyzed by Pd/C offered an amine. Diazotization of the amine in the presence of $NaNO_2$ under acidic conditions with reflux led to denitronation to afford compound **15** in 73% yields in two steps. The nitro group could also be transferred to iodide using a similar protocol in the presence of KI, affording **16** in 76% yield. In these transformations, only slight racemization was observed.

4. Mechanistic Studies. Singerman and Danishefsky proposed a cycloaddition pathway involving pyridylcyclobutane intermediates for the conjugate addition reactions of enamines with 2- and 4-vinylpyridines.[14a] The intermediates were then observed by Gray and co-workers only with enamines of α,α-diasubstituted aldehydes and only under conditions of acid catalysis.[14b] Preformed enamines were used in their cases, while we employed a catalytic process for in situ formation of the enamines. We questioned whether the catalytic process involved a similar cycloaddition process with the pyridylcyclobutane intermediate. Therefore, ^{1}H NMR studies were performed using the reaction of *n*-hexanal **2c** and 4-vinylpyridine **1a** as an example under the standard reaction conditions we identified, except for the use of DMSO-d_6 instead of DMF-d_7 as the reaction medium (Figure 3).

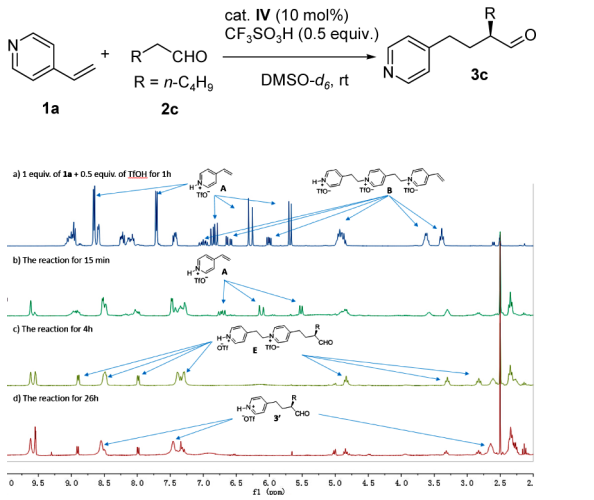


Figure 3. ^{1}H NMR studies of the reaction of 4-vinylpyridine (**1a**) with *n*-hexanal (**2c**) cocatalyzed by **IV** and TfOH. (a) Spectrum of a mixture of **1a** (0.5 mmol) and TfOH (0.25 mmol) in DMSO-d_6 (0.5 mL) after 1 h. (b–d) A mixture of **1a** (0.5 mmol), TfOH (0.25 mmol), and DMSO (0.17 mmol) in DMSO-d_6 (0.5 mL) was shaken for 10 min, and then catalyst **IV** (0.05 mmol) and **2c** (0.5 mmol) were added; the reaction was monitored by ^{1}H NMR spectroscopy after (b) 15 min, (c) 4 h, and (d) 26 h.

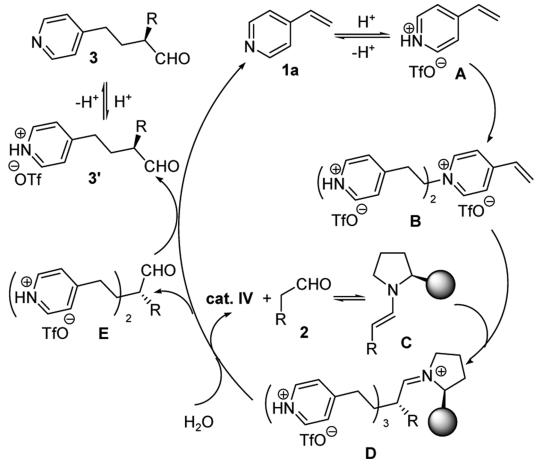
However, we did not observe the pyridylcyclobutane intermediate. Instead the pyridinium trimer species **B** (as a mixture of protonated and unprotonated forms) was formed on the basis of ^{1}H NMR analysis. The unexpected outcome prompted us to carry out a deeper investigation. First, to verify the formation of the intermediate from TfOH-catalyzed trimerization of 4-vinylpyridine, we performed the experiment by simply mixing **1a** (0.5 mmol) with TfOH (0.25 mmol) in DMSO-d_6 (0.5 mL) and then shaking the mixture for 1 h. ^{1}H NMR monitoring (Figure 3a). It was found that the trimer of 4-vinylpyridinium ion, **B**, was quickly formed as the dominant species with the copresence of the protonated form of 4-

DOI: 10.1021/ja511143b
J. Am. Chem. Soc. 2015, 137, 2303–2310

vinylpyridine, **A**, which was first observed by Fife and colleagues.[23] The trimer structure **B** was determined by 3:8 ratio of the vinyl protons to the alkyl protons. Without TfOH, no **B** was produced, indicating that the acid plays a key role in the formation of **B** through **A**. To confirm that **B** was the actual active electrophile for the direct addition reaction with the in situ-formed chiral enamine without the involvement of a pyridylcyclobutane, we added catalyst **IV** and aldehyde **2c** into the mixture and monitored the reaction process by ^{1}H NMR spectroscopy (Figure 3b). The cyclobutane intermediate was not observed by ^{1}H NMR analysis. Trimer **B** disappeared rapidly and was transformed to the dimeric adduct **E**. After 4 h, both **A** and **B** were consumed, and the new protonated product **3′** was generated. The ratio of **E** to **3′** was about 1:1 (Figure 3c). This suggests that **3′** was produced from **E**. Furthermore, the transformation of **E** to **3′** seems to be the rate-determining step (Figure 3d). Even after 48 h of reaction, there was still about 10% **E** left (see the Supporting Information).

On the basis of the ^{1}H NMR experimental studies of the **IV**-catalyzed conjugate addition of **2c** to **1a**, we propose a catalytic cycle for this reaction (Scheme 7). TfOH catalyzes the formation of the more electrophilic trimeric pyridinium salt **B** from protonated 4-vinylpyridinium species **A**. The resulting highly active electrophile enables the addition of the nucleophilic enamine created from the chiral amine catalyst **IV** and the corresponding aldehyde to form the adduct **D**. Since water is employed as the cosolvent for the reaction, **D** is facilely hydrolyzed to recycle the catalyst and concurrently release the dimer aldehyde adduct **E** and **1a**. Finally, the aldehyde salt product **3′** and **1a** are slowly released from **E**. Workup of the reaction mixture by treatment with a mixture of aqueous Na_2CO_3 and EtOAc gives a relatively clean ^{1}H NMR spectrum of product **3**. We found that under the same reaction conditions, mixing 2-vinylpyridine with TfOH in DMSO-d_6 did not lead to the expected trimer of 2-vinylpyridine. This can help to rationalize its poor reactivity in the **IV**-cocatalyzed process. Moreover, the acidity of the acid is critical for the formation of trimeric pyridinium salt **B**. On the basis of ^{1}H NMR studies, strong acids such TfOH and nitric acid can promote the formation of **B**, while it is difficult for the weak acid AcOH to do so.

Scheme 7. Proposed Catalytic Cycle for IV-Catalyzed Addition of Aldehydes to 4-Vinylpyridines



CONCLUSION

We have developed a synergistic catalysis strategy to realize for the first time a catalytic asymmetric direct addition of simple aldehydes to 4-vinylpyridines. Activation of weakly electrophilic 4-vinylpyridines by the Brønsted acid CF_3SO_3H and aldehydes by the chiral diphenylprolinol TBDMS ether-catalyzed formation of nucleophilic enamines in a cooperative manner enables the new, previously unattainable highly enantioselective addition process. The power of the addition process is underscored by its mild reaction conditions and high efficiency in the production of synthetically valued chiral pyridines with a broad substrate scope. ^{1}H NMR studies of the reaction process revealed a trimeric 4-vinylpyridinium species as the actual highly active electrophile for the direct addition of the chiral-amine-promoted nucleophilic enamine. Moreover, inspired by the similar electronic natures of pyridine and nitrobenzene, we have successfully expanded the reaction scope beyond 4-vinylpyridines, realizing the novel chiral diphenylprolinol TBDMS ether-promoted, highly enantioselective direct addition of aldehydes to substituted 2-nitrostyrenes without the use of CF_3SO_3H as a cocatalyst. In this approach, introducing a strong electron-withdrawing group such as NO_2, CF_3, SO_2Me, etc. on 2-nitrostyrene creates a highly electrophilic vinyl moiety, which displays reactivity comparable to that of protonated 4-vinylpyridines in the chiral-amine-catalyzed addition of aldehydes. The processes exhibit a broad substrate scope for both electron donors and acceptors. While the electron-withdrawing nitro group is essential for activation of the vinyl group, we have demonstrated that it can be readily transformed to diverse functionalities. Furthermore, a chiral pyridine adducts serves as a key building block in the synthesis of the fibrinogen receptor antagonist L-734,217. Further exploration of the strategy and the application of this methodology in the synthesis of biologically relevant molecules are under investigation in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental details, spectroscopic data, and crystallographic data for **4** and **7** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Authors

*wwang@unm.edu
*hli77@ecust.edu.cn

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support of this research from the program for Professor of Special Appointment (Eastern Scholar) at Shanghai Institutions of Higher Learning (201226 to H. Li), the National Natural Science Foundation of China (21372073 to W.W.), the Fundamental Research Funds for the Central Universities and East China University of Science and Technology (startup funds to H. Li and W.W.), the China 111 Project (Grant B07023 to H. Li and W.W.), the Chinese Scholarship Council (X.L.) and the National Science Foundation (CHE-1057569 to W.W.) is gratefully acknowledged.

DOI: 10.1021/ja511143b
J. Am. Chem. Soc. 2015, 137, 2303−2310

REFERENCES

(1) http://www.pharmacytimes.com/publications/issue/2013/July2013/Top-200-Drugs-of-2012 (accessed Oct 29, 2014).

(2) (a) Qiao, J. X. In *Heterocyclic Chemistry in Drug Discovery*; Li, J. J., Ed.; Wiley: Hoboken, NJ, 2013; p 398. (b) Chaubey, A.; Pandeya, S. N. *Asian J. Pharm. Clin. Res.* **2011**, *4*, 5. (c) Kiuru, P.; Yli-Kauhaluoma, J. In *Heterocycles in Natural Product Synthesis*; Majumdar, K. C., Chattopadhyay, S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2011; p 267. (d) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043. (e) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science: Cambridge, U.K., 2000; p 63. (f) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627. (g) Kim, J.; Movassaghi, M. *Chem. Soc. Rev.* **2009**, *38*, 3035. (h) Bagley, M. C.; Dale, J. W.; Merritt, E. A.; Xiong, X. *Chem. Rev.* **2005**, *105*, 685. (i) Mishra, A.; Ma, C.-Q.; Bäuerle, P. *Chem. Rev.* **2009**, *109*, 114.

(3) (a) Chelucci, G. *Coord. Chem. Rev.* **2013**, *257*, 1887. (b) Kilah, N. L.; Beer, P. D. *Top. Heterocycl. Chem.* **2010**, *24*, 301.

(4) (a) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, *112*, 2642. (b) Nakao, Y. *Synthesis* **2011**, 3209. (c) Hill, M. D. *Chem.—Eur. J.* **2010**, *16*, 12052.

(5) (a) Bergmann, E. D.; Ginsburg, D.; Pappo, R. *Org. React.* **1959**, *10*, 179. (b) Giam, C. S. In *Pyridine and Its Derivatives*; Abramovitch, R. A., Ed.; Wiley: New York, 1974; Suppl. part 3, p 112. (c) Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 4, pp 10 and 77. (d) Klumpp, D. A. *Synlett* **2012**, *23*, 1590.

(6) Gray, A. P.; Archer, W. P. *J. Am. Chem. Soc.* **1957**, *79*, 3554.

(7) (a) Leonard, F.; Tschannen, W. *J. Med. Chem.* **1966**, *9*, 140. (b) Gimbert, C.; Lumbierres, M.; Marchi, C.; Moreno-Manas, M.; Sebastian, R. M.; Vallribera, A. *Tetrahedron* **2005**, *61*, 8598. (c) Siperko, L. G.; Smith, F. X. *Synth. Commun.* **1979**, *9*, 383. (d) Yoneda, A.; Newkome, G. R.; Theriot, K. J. *J. Organomet. Chem.* **1991**, *401*, 217. (e) Dryanska, V.; Ivanov, C. *Synthesis* **1983**, 143. (f) Devaux, G.; Nuhrich, A.; Dufour, R.; Canellas, J. *Bull. Soc. Pharm. Bordeaux* **1975**, *114*, 70.

(8) (a) Han, X.; Civiello, R. L.; Mercer, S. E.; Macor, J. E.; Dumowchik, G. E. *Tetrahedron Lett.* **2009**, *50*, 386. (b) Tucci, F. C.; Zhu, Y.-F.; Guo, Z.; Gross, T. D.; Connors, P. J., Jr.; Struthers, R. S.; Reinhart, G. J.; Saunders, J.; Chen, C. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3317. (c) Safak, C.; Erdogan, H.; Palaska, E.; Sunal, R.; Duru, S. *J. Med. Chem.* **1992**, *35*, 1296. (d) Taylor, E. C.; Martin, S. F. *J. Am. Chem. Soc.* **1972**, *94*, 6218.

(9) (a) Klemm, L. H.; McCoy, D. R.; Shabtai, J.; Kiang, W. K. T. *J. Heterocycl. Chem.* **1969**, *6*, 813. (b) Momose, Y.; Meguro, K.; Ikeda, H.; Hatanaka, C.; Oi, S.; Sohda, T. *Chem. Pharm. Bull.* **1991**, *39*, 1440.

(10) Houpis, I. N.; Lee, J.; Dorziotis, I.; Molina, A.; Reamer, B.; Volante, R. P.; Reider, P. J. *Tetrahedron* **1998**, *54*, 1185.

(11) Rupnicki, L.; Saxena, A.; Lam, H. W. *J. Am. Chem. Soc.* **2009**, *131*, 10386.

(12) (a) Pattison, G.; Piraux, G.; Lam, H. W. *J. Am. Chem. Soc.* **2010**, *132*, 14373. (b) Saxena, A.; Lam, H. W. *Chem. Sci.* **2011**, *2*, 2326.

(13) Friedman, A. A.; Panteleev, J.; Tsoung, J.; Huynh, V.; Lautens, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 9755.

(14) For noncatalytic examples of reactions between enamines and vinyl heterocycles, see: (a) Singerman, G.; Danishefsky, S. *Tetrahedron Lett.* **1964**, *5*, 2249. (b) Heitmeier, D. E.; Hortenstine, J. T.; Gray, A. P. *J. Org. Chem.* **1971**, *36*, 1449.

(15) The main efforts have been focused on the organocatalytic- and transition-metal-cocatalyzed reactions. For reviews, see: (a) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2009**, *38*, 2745. (b) de Armas, P.; Tejedor, D.; García-Tellado, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 1013. (c) Zhong, C.; Shi, X.-D. *Eur. J. Org. Chem.* **2010**, 2999. (d) Rueping, M.; Koenigs, R. M.; Atodiresei, I. *Chem.—Eur. J.* **2010**, *16*, 9350. (e) Zhou, J. *Chem.—Asian J.* **2010**, *5*, 422. (f) Han, Z.-Y.; Wang, C.; Gong, L.-Z. In *Science of Synthesis: Asymmetric Organocatalysis*; Maruoka, K., Ed.; Georg Thieme Verlag: Stuttgart, Germany, 2012; Vol. 2, p 697. (g) Loh, C. C. J.; Enders, D. *Chem.—Eur. J.* **2012**, *18*, 10212. (h) Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.* **2012**, *3*, 633. (i) Patil, N. T.; Shinde, V. S.; Gajula, B. *Org. Biomol. Chem.* **2012**, *10*, 211. (j) Pellissier, H. *Tetrahedron* **2013**, *69*, 7171. (k) Du, Z.-T.; Shao, Z.-H. *Chem. Soc. Rev.* **2013**, *42*, 1337. (l) Ceban, V.; Putaj, P.; Meazza, M.; Pitak, M. B.; Coles, S. J.; Vesley, J.; Rios, R. *Chem. Commun.* **2014**, *50*, 7447. (m) Meazza, M.; Ceban, V.; Pitak, M. B.; Coles, S. J.; Rios, R. *Chem.—Eur. J.* **2014**, *20*, 16853.

(16) The studies by Klumpp show that acids can activate vinylpyridines in the addition reaction with benzene. See: (a) Zhang, Y.; Sheets, M. R.; Raja, E.; Boblak, K.; Klumpp, D. A. *J. Am. Chem. Soc.* **2011**, *133*, 8467. (b) Zhang, Y.; Briski, J.; Zhang, Y.; Rendy, R.; Klumpp, D. A. *Org. Lett.* **2005**, *7*, 2505.

(17) For a review of enamine catalysis, see: Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

(18) CCDC-1031100 contains the supplementary crystallographic data for compound **4**. These data can be obtained from the Cambridge Crystallographic Data Centre free of charge via www.ccdc.cam.ac.uk.

(19) Pietrzyk, A.; Wiley, R.; MoDaniel, D. *J. Org. Chem.* **1957**, *22*, 83.

(20) CCDC-966469 contains the supplementary crystallographic data for compound **7**. These data can be obtained from the Cambridge Crystallographic Data Centre free of charge via www.ccdc.cam.ac.uk.

(21) Chung, J. Y. L.; Hughes, D. L.; Zhao, D.; Song, Z.; Song, Z.; Mathre, D. J.; Ho, G.-J.; McNamara, J. M.; Douglas, A. W.; Reamer, R. A.; Tsay, F.-R.; Varsolona, R.; McCauley, J.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1996**, *61*, 215.

(22) DeSimone, R. A.; Currie, R. A.; Mitchell, S. A.; Darrow, J. W.; Pippin, D. A. *Comb. Chem. High. Throughput Screening* **2004**, *7*, 473.

(23) Fife, W. K.; Ranganathan, P.; Zeldin, M. *J. Org. Chem.* **1990**, *55*, 5610.

DOI: 10.1021/ja511143b
J. Am. Chem. Soc. 2015, 137, 2303−2310