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Primary–Tertiary Diamine/Brønsted Acid Catalyzed C–C Coupling between *para*-Vinylanilines and Aldehydes

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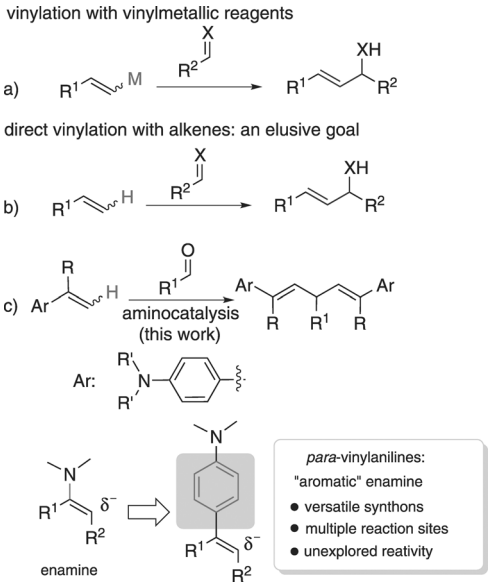
Vinylation of carbonyls or iminines represents one of the most straightforward approaches for the synthesis of versatile allylic compounds.[1] Traditionally, stoichiometric amounts of vinyl metal reagent, either preformed or generated in situ, are employed in the reactions (Scheme 1a).[2–7] In this context, direct vinylation of carbonyl compounds



Scheme 1. Vinylation reactions.

with alkenes by C–H functionalization would be highly desirable as handling sensitive vinyl organomatellic species can be avoided and such a process is also highly atom-economic with readily available alkenes as the feed stocks.[8] To this end, novel catalytic strategies have been developed and the successes so far have been mainly achieved with transition-metal catalysts, such as Pd, Rh, and Ni.[9–11] However, organocatalytic direct vinylation reactions are rare and have not yet been reported.

Recently we found that *para*-vinylanilines (e.g. **1a**) are unique nucleophiles in reacting with aldehydes, furnishing vinylation-type products under mild organocatalytic conditions (Scheme 1c). Mechanistically, the remote *para*-amino group enhances the nucleophilicity of the olefin bond by electron-delocalization via the conjugated phenyl ring.[12] The *para*-vinylanilines, endowed with a nucleophilic terminal carbon atom, in a manner, closely resemble the well-known enamine intermediates, and may be regarded as aromatics intervened enamine (aromatic enamine). Surprisingly, these seemingly well-known structural moieties have not been well explored as synthons in C–C bond formation reactions, not to mention their synthetic potentials in many catalytic systems. Provided with the now quite well-established strategies for C–N and C–H transformations of aniline derivatives,[13] direct vinylation reactions with *para*-vinylanilines would deliver versatile synthetic pathways for multifunctional conjugate molecules, that are of significant potential in organic electronics. In fact, the parent vinylanilines serve as important building blocks for a number of leuco dyes.[14–18] Herein, we report an effective aminocatalytic C–C coupling reaction between *para*-vinylanilies and aldehydes, formulating a rare example of an organocatalytic direct vinylation reaction.

Preliminary studies started with the examination of the nucleophilic addition of vinylaniline **1a** to benzaldehyde. Previously, the coupling of vinylaniline **1a** and aldehyde has been disclosed in patents to react under rather harsh conditions (reflux in the presence of excess acid).[19] The resulting bis(allylic) adducts (e.g. **3a**) can be used as charge control agents in electroreprographic toners and as colour formers, particularly in transfer imaging, pressure sensitive and thermal-responsive carbonless duplicating systems.[19] In our studies, it was found that a catalytic amount of Brønsted acid, such as benzoic acid or TfOH, demonstrated rather low activity at room temperature (Table 1, entries 2 and 3). In contrast, the combined use of Brønsted acids and a primary amine, such as *N*,*N*-dimethylethylene diamine **4a**, a proved biomimetic aminocatalytic motif,[20] was found to be an effective catalyst for the reaction to furnish a bis(allylic) adduct **3a** (entry 7).[21] In this regard, a range of acidic additive has been screened with **4a** as the initial aminocatalyst and the strongest acid TfOH gave the optimal results (entries 4–9). The acid/base catalytic feature is reminiscent of

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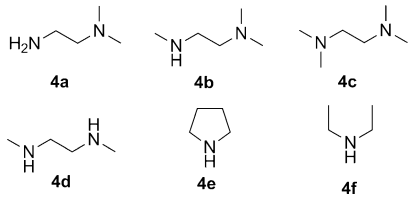
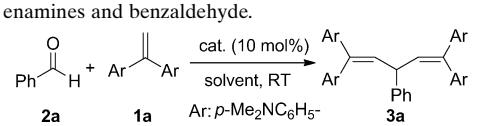


the typical iminium-based Knoevenagel reaction. To seek the optimal amine catalysts, a number of amines including both primary and secondary amines have been screened and the simple primary–tertiary diamine **4a** turned out to be the preferred aminocatalyst in this reaction (Table 1, entries 9–14). Similar diamines, such as tertiary–tertiary diamine **4c** and secondary–secondary diamine **4d**, gave much lower activity (entries 11 and 12). These results together with the observation of virtually inactive secondary amines, such as pyrrolidine **4e** and diethylamine **4f** (entries 13 and 14) highlight the critical role of the primary amine moiety in the catalysis.[20] In a further optimization of the reactions, ethanol was identified as the favourable solvent (entries 15–20) and the reaction gave 88% yield in 17 h with 10 mol% of **4a**/TfOH (entry 19).

Under the optimized conditions (10 mol% of **4a**/TfOH in EtOH, RT), we next probed the scope of the vinylation reaction for a variety of aldehydes and the results were presented in Table 2. The scope of aldehyde is quite general. Aromatic aldehydes bearing either electron-donating or -withdrawing groups are equally applicable in the reactions

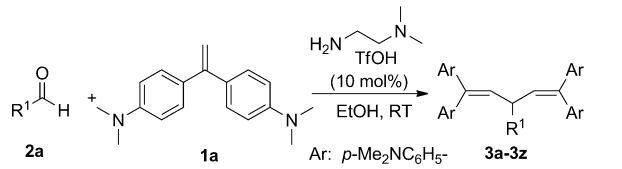
Table 1. Screening of different catalysts and solvents for the reaction of aromatic enamines and benzaldehyde.



Entry[a]	Catalyst[b]	Solvent	t [h]	Yield [%][c]
1	none	EtOH	11	none
2	PhCOOH	EtOH	11	<5
3	TfOH	EtOH	11	<5
4	**4a**	EtOH	11	<5
5	**4a**/AcOH	EtOH	11	<5
6	**4a**/PhCOOH	EtOH	11	<5
7	**4a**/TFA	EtOH	11	65
8	**4a**/TsOH	EtOH	11	49
9	**4a**/TfOH	EtOH	11	85
10	**4b**/TfOH	EtOH	11	57
11	**4c**/TfOH	EtOH	11	<5
12	**4d**/TfOH	EtOH	11	7
13	**4e**/TfOH	EtOH	11	10
14	**4f**/TfOH	EtOH	11	5
15	**4a**/TfOH	CH_2Cl_2	17	84
16	**4a**/TfOH	DMF	17	31
17	**4a**/TfOH	Et_2O	17	85
18	**4a**/TfOH	$PhCH_3$	17	81
19	**4a**/TfOH	EtOH	17	94 (88)[d]
20	**4a**/TfOH	CH_3CN	17	80

[a] General conditions: **1a** (26.6 mg, 0.1 mmol), benzaldehyde (0.06 mmol), solvent (0.4 mL), catalyst (10 mol%), RT. [b] TfOH: trifluoromethanesulfonic acid; TsOH: benzenesulfonic acid; TFA: trifluoroacetic acid. [c] NMR spectroscopic yield. [d] Isolated yield.

Table 2. Scope of aldehydes.



Entry[a]	R^1	Product	t [h]	Yield [%][b]
1	Ph	**3a**	17	88
2	4-ClPh	**3b**	48	97
3	4-CF_3Ph	**3c**	24	98
4	2-BrPh	**3d**	32	80
5	4-OHPh	**3e**	32	50
6	3-CH_3Ph	**3f**	24	63
7	3-NO_2Ph	**3g**	24	97
8[c]	2-NO_2Ph	**3h**	22	98
9	4-FPh	**3i**	24	90
10[d]	2-FPh	**3j**	22	97
11[e]	4-*N,N*-dimethylPh	**3k**	12 (36)[f]	71 (70)
12[g]	4-BrPh	**3l**	32	96
13[h]	4-NO_2Ph	**3m**	32	95
14	4-MeOPh	**3n**	32 (36)[f]	88 (91)
15	2-Br-5-ClPh	**3o**	22	90
16	3,4-dimethoxylPh	**3p**	40	85
17	2-F-4-CF_3Ph	**3q**	17	82
18	2-F-4-BrPh	**3r**	29	95
19	2-F-4-MeOPh	**3s**	29	52
20	2-F-3-Cl-4-CF_3Ph	**3t**	5	98
21[i]	2-thiophene	**3u**	10	89
22	2-furan	**3v**	36	75
23[d]	*n*Pr	**3w**	30	82
24[d]	*i*pr	**3x**	30	70
25	*n*Bu	**3y**	4 days	67
26[d]	$PhCH_2CH_2$	**3z**	30	86

[a] General conditions: **1a** (53.2 mg, 0.2 mmol), aldehyde (0.12 mmol), solvent (0.8 mL), catalyst (10 mol%), RT. [b] Isolated yield. [c] Catalyst loading was 40 mol%. [d] Catalyst loading was 20 mol%. [e] At 40°C. [f] **1a** (5 mmol), aldehyde (3 mmol), solvent (20 mL), catalyst (4 mol%), 40°C. [g] **1a** (5 mmol), aldehyde (3 mmol), solvent (20 mL), catalyst (20 mol%), 40°C. [h] **1a** (2 mmol), aldehyde (1.2 mmol), solvent (8 mL), catalyst (20 mol%), 40°C. [i] At 80°C.

with the latter generally favoured. *Ortho*-substituted benzaldehydes reacted much slower than their *para* and *meta* derivatives (Table 2, entry 7 versus 8; entry 9 versus 10), which indicates the presence of steric effects in these cases, and good yields were obtained by increasing the loading of catalyst or raising the reaction temperature. The reactions with heterocyclic aldehydes, such as 2-furan-carbaldehyde and 2-thiophene-carbaldehyde also worked very well to afford the desired bis(allylic) adducts in high yields (entries 21 and 22). Notably, aliphatic aldehydes also served as reactive substrates for the reactions, affording the products **3w–z** in moderate to good yields (entries 23–26). The crystal structure of **3w** has been determined, showing unequivocally the bis(allylic) motif (Figure 1). The reaction with a bis-(aldehyde), 1,4-phthalaldehyde, has also been examined in reacting with excess vinylaniline **1a** and tetra-allylated adduct **3a′** was isolated in a moderate 26% yield (Scheme 2). The use of activated ketones, such as trifuoromethyl ketones, has also been tested, showing no reaction under the present conditions.

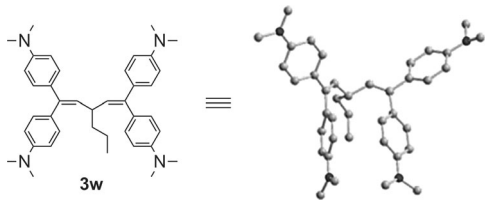
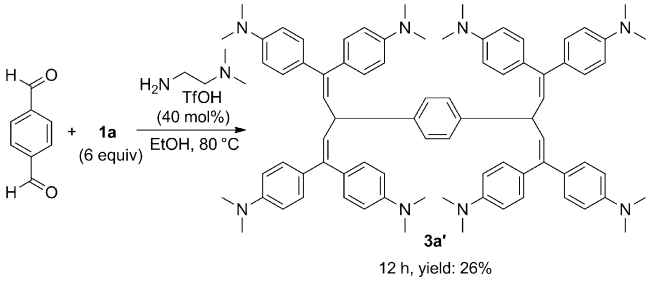


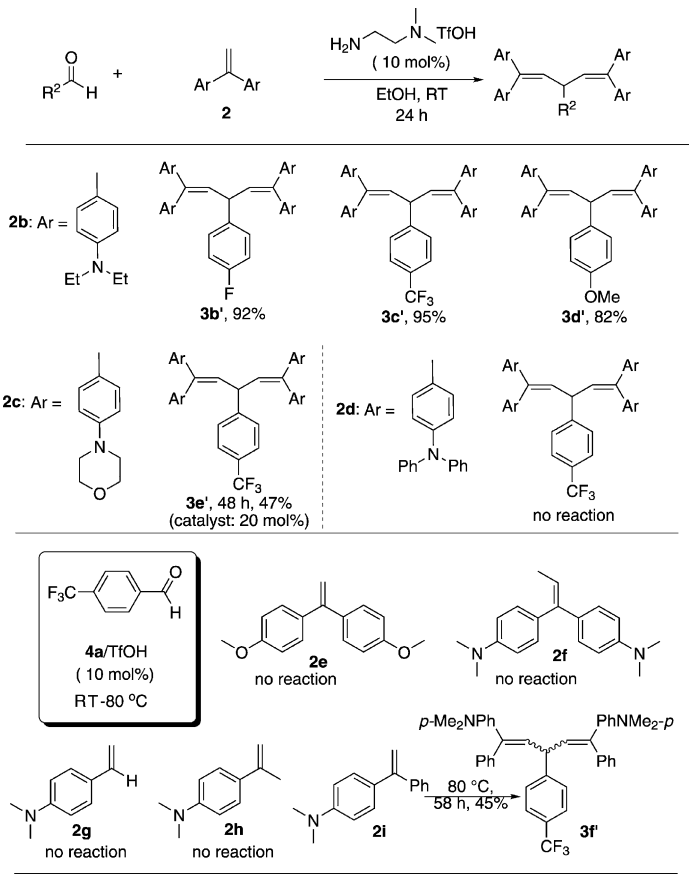
Figure 1. X-ray crystal structure of adduct **3w** (H atoms are omitted for clarity).



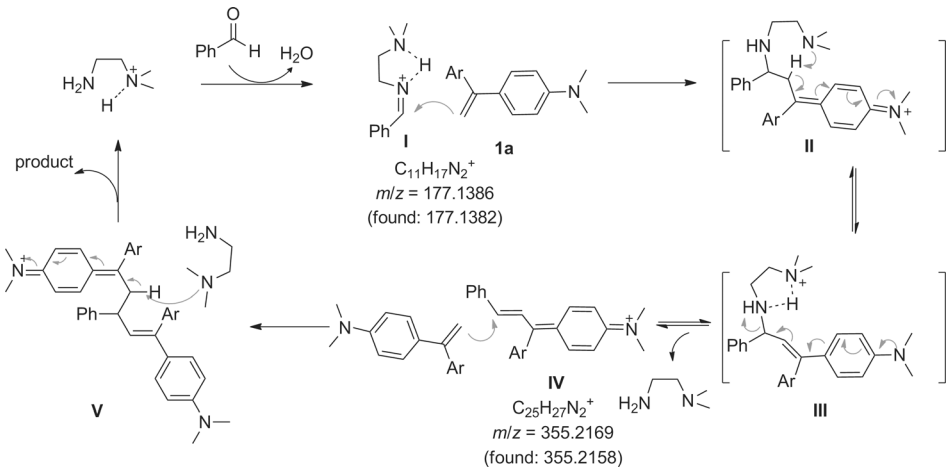
Scheme 2. Coupling of 1,4-phthalaldehyde with vinylaniline **1a**.

The scope of the *para*-vinylanilies was next explored. Alkyl substitutes on the *para*-amino group, such as in **2b** and **2c** are tolerated and the corresponding adducts **3b′**–**3e′** can be obtained with moderate to good yields (Scheme 3). Unfortunately, the triarylamine **2d** was found to be inert, likely as a result of its unfavoured electronic delocalization. Replacement of the dialkylamino group with a methoxyl group also depletes the reactivity as observed with **2e** (Scheme 3). The impact of the olefinic substitution has also been examined. In this regard, no reactions were observed with terminal substituted **2f** or replacing one aniline moiety with H or methyl substitute, as in **2g** and **2h**, respectively. Interestingly, vinyl aniline **2i**, of which one aniline moiety is replaced with a phenyl ring, demonstrated moderate activity to give the bis(allylic) adduct **3f′** in 45% yield (Scheme 3).

On the basis of the above experimental observations, we propose an iminium-based catalytic cycle as shown in Scheme 4. The reaction is initialized by the nucleophilic addition of **1a** to iminium ion **I**. The resulting iminium ion **II** undergoes an iminiu–enamine-type tautomerization, followed by elimination of diamine **4a** and then affords a highly conjugated iminium **IV**, which reacts readily with the second molecule of nucleophilic **1a** to give the desired bis(allylic) adduct. Though pure acid catalysis cannot be completely ruled out, the fact that **4c**, a dimethylated derivative of **4a**, is nearly inactive for the reaction (Table 1, entry 11), suggests that the acid catalysis, if present, should be minor under the current conditions. In addition, ESI-MS analysis of the reaction mixture showed *m*/*z* bands at 177 and 355, consistent with iminium intermediates **I** and **IV** (see the Supporting Information), respectively, adding further support to the proposed mechanism.



Scheme 3. Scope of vinylanilines.



Scheme 4. Proposed catalytic cycle.

In conclusion, we have uncovered *para*-vinylanilines as a new type of nucleophilic synthons, closely resembling enamines. A simple primary amine in concert with TfOH has been found to promote effectively C–C coupling of *para*-vinylanilines and aldehydes, affording bis(allyic) adducts as potential organic electronic materials in high yields under rather mild conditions. Further explorations of the nucleophilic features of *para*-vinylanilines in catalysis as well as the applications of the obtained conjugated molecules are ongoing.

Experimental Section

General procedure for the coupling of 1a and aldehyde: Compounds **2a** (12.7 mg, 0.12 mmol) and **1a** (53.2 mg, 0.2 mmol) were added to a solution of *N*,*N*-dimethylethylenediamine/TfOH (2.4 mg, 10 mol%) in EtOH (0.8 mL). The resulting solution was stirred at room temperature for 17 h. After complete conversion as indicated by TLC analysis, the product was purified by silica gel column chromatography (EtOAc/PE 1:10) to give product **3a** as a white solid (yield: 88%).

Acknowledgements

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Keywords: C–C bond formation · enamines · iminium activation · organocatalysis · primary amines

[1] For selected reviews, see: a) E. Skucas, M. Ngai, V. Komanduri, M. J. Krische, *Acc. Chem. Res.* **2007**, *40*, 1394–1401; b) P. Wipf, C. Kendall, *Chem. Eur. J.* **2002**, *8*, 1778–1784; c) A. Lumbroso, M. L. Cooke, B. Breit, *Angew. Chem.* **2013**, *125*, 1942–1986; *Angew. Chem. Int. Ed.* **2013**, *52*, 1890–1932.

[2] a) P. Wipf, C. Kendall, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2003**, *125*, 761–768; b) H. Li, P. J. Walsh, *J. Am. Chem. Soc.* **2004**, *126*, 6538–6539; c) H. Li, P. J. Walsh, *J. Am. Chem. Soc.* **2005**, *127*, 8355–8361.

[3] W. Huang, J. Chan, T. F. Jamison, *Org. Lett.* **2000**, *2*, 4221–4223.

[4] a) K. Takai, S. Sakamoto, T. Isshiki, *Org. Lett.* **2003**, *5*, 653–655; b) G. M. Mahandru, G. Liu, J. Montgomery, *J. Am. Chem. Soc.* **2004**, *126*, 3698–3699.

[5] A. Kakuuchi, T. Taguchi, Y. Hanzawa, *Tetrahedron Lett.* **2003**, *44*, 923–926.

[6] H. Y. Jang, R. R. Huddleston, M. J. Krische, *J. Am. Chem. Soc.* **2004**, *126*, 4664–4668.

[7] P. Wipf, C. R. J. Stephenson, *Org. Lett.* **2003**, *5*, 2449–2452.

[8] a) R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413–4450; b) M. C. Willis, *Chem. Rev.* **2010**, *110*, 725–748.

[9] Ni: a) C. Y. Ho, S. S. Ng, T. F. Jamison, *J. Am. Chem. Soc.* **2006**, *128*, 5362–5363; b) S. S. Ng, T. F. Jamison, *J. Am. Chem. Soc.* **2005**, *127*, 7320–7321; c) S. S. Ng, T. F. Jamison, *J. Am. Chem. Soc.* **2005**, *127*, 14194–14195; d) C. Ho, T. F. Jamison, *Angew. Chem.* **2007**, *119*, 796–799; *Angew. Chem. Int. Ed.* **2007**, *46*, 782–785; e) S. S. Ng, C. Ho, T. F. Jamison, *J. Am. Chem. Soc.* **2006**, *128*, 11513–11528.

[10] Pd: a) Y. Xie, J. Hu, Y. Wang, C. Xia, H. Huang, *J. Am. Chem. Soc.* **2012**, *134*, 20613–20616; Rh:b) Y. Li, X. Zhang, Q. Zhu, Z. Shi, *Org. Lett.* **2012**, *14*, 4498–4501.

[11] Reductive coupling of alkenes and aldehydes: a) N. M. Kablaoui, S. L. Buchwald, *J. Am. Chem. Soc.* **1995**, *117*, 6785–6786; b) W. E. Crowe, M. J. Rachita, *J. Am. Chem. Soc.* **1995**, *117*, 6787–6788.

[12] a) A. Mishra, R. K. Behera, P. K. Behera, B. K. Mishra, G. B. Behera, *Chem. Rev.* **2000**, *100*, 1973–2011; b) T. Akio, K. Ikuo, N. Akihisa, N. Yutaka, I. Hidetoshi, *J. Org. Chem.* **1997**, *62*, 2658–2661; c) M. Gates, *J. Am. Chem. Soc.* **1944**, *66*, 124–130.

[13] a) G. Guillena, D. J. Ramón, M. Yus, *Chem. Rev.* **2010**, *110*, 1611–1641; b) T. Suzuki, *Chem. Rev.* **2011**, *111*, 1825–1845; c) E. Wenkert, A. Han, C. J. Jenny, *J. Chem. Soc. Chem. Commun.* **1988**, 975–976; d) V. I. Stenberg, V. R. Srinivas, R. J. Baltisberger, N. F. Woolsey, *J. Org. Chem.* **1983**, *48*, 1107–1110; e) N. A. Paras, B. Simmons, D. W. C. MacMillan, *Tetrahedron* **2009**, *65*, 3232–3238; f) S. B. Blakey, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 6046–6047; g) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 7894–7895.

[14] a) J. Fabian, H. Nakazumi, M. Matsuuoka, *Chem. Rev.* **1992**, *92*, 1197–1226; b) R. O. Loutfy, A. M. Hor, C. K. Hsiao, G. Baranyi, P. Kazmaier, *Pure. Appl. Chem.* **1988**, *60*, 1047–1054.

[15] M. P. Shandura, Y. M. Poronik, Y. P. Kovtun, *Dyes Pigm.* **2005**, *66*, 171–177.

[16] a) Y. Son, S. Kim, *Dyes Pigm.* **2007**, *72*, 403–405; b) Q. Wang, C. Sun, S. Sui, Z. Liu, X. Zhang, Y. Liu, *Youji Huaxue.* **1998**, *18*, 175–179.

[17] S. Hünig, M. Kemmer, H. Wenner, F. Barbosa, G. Gescheidt, I. F. Perepichka, P. Bäuerle, A. Emge, K. Peters, *Chem. Eur. J.* **2000**, *6*, 2618–2632.

[18] a) K. Yoshida, T. Koujiri, N. Oga, M. Ishiguro, Y. Kubo, *J. Chem. Soc. Chem. Commun.* **1989**, 708–710; b) M. Matsuoka, T. Hikida, K. Murobushi, Y. Hosoda, *J. Chem. Soc. Chem. Commun.* **1993**, 299–301.

[19] a) G. Peter, H. Nigel, EP 0289122, **1988**; b) U. Yoshiaki, S. Mutsuo, M. Kozo, T. Katsuhiko, JP 63272581, **1988**; c) W. M. Hung, US 4870050, **1989**.

[20] L. Zhang, S. Luo, *Synlett* **2012**, 1575–1589.

[21] For similar aminocatalytic carbaacetalization reactions, see: a) B. List, C. Castello, *Synlett* **2001**, 1687–1689; b) D. B. Ramachary, C. F. Barbas III, *Chem. Eur. J.* **2004**, *10*, 5323–5331.

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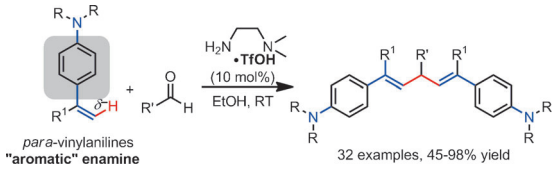

Aromatic enamines: *para*-Vinylanilines were identified as unique nucleophiles, closely resembling enamines, to undergo C–C coupling with aldehydes catalyzed by a simple primary-tertiary diamine/Brønsted acid. The resulting bis(allylic) adducts, which have potential as functional materials, were obtained in high yields under rather mild conditions (see scheme).

Organocatalysis

*L. Cui, Y. Zhu, S. Luo,**
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Primary–Tertiary Diamine/Brønsted Acid Catalyzed C–C Coupling between *para*-Vinylanilines and Aldehydes