JOC Article

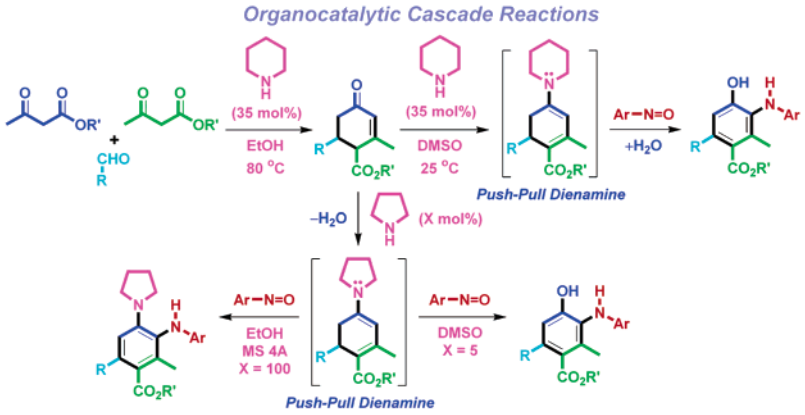
Organocatalytic Cascade Reactions Based on Push−Pull Dienamine Platform: Synthesis of Highly Substituted Anilines

Dhevalapally B. Ramachary,* Kinthada Ramakumar, and Vidadala V. Narayana

School of Chemistry, University of Hyderabad, Central University (PO), Hyderabad 500 046, India

ramsc@uohyd.ernet.in

Received November 15, 2006

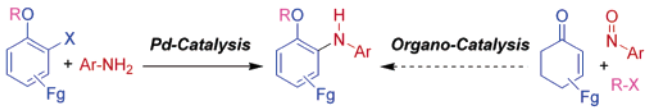


A practical and novel one-pot organocatalytic selective process for the cascade synthesis of highly substituted *o*-hydroxydiarylamines and *o*-pyrrolidin-1-yldiarylamines is reported. Direct combination of amine-catalyzed cascade Knoevenagel/Michael/aldol condensation/decarboxylation and cascade enamine amination/isoaromatization of alkyl acetoacetates, aldehydes, and nitrosoarenes furnished the highly functionalized anilines with high yields.

Arylamines are of considerable importance in a variety of industries. As such, the development of new and more general methods for their preparation is of significant interest.[1] Recently, palladium catalysis has emerged for the reactions of aryl halides with primary and secondary amines in the presence of strong base to provide a general route to a variety of arylamines in good yields (Scheme 1).[2]

Herein, we discovered a metal-free, novel, and green technology for the synthesis of highly substituted *o*-hydroxydiarylamines, *o*-pyrrolidin-1-yldiarylamines, and *o*-alkyloxydiarylamines by using direct organocatalytic cascade enamine amination/isoaromatization (EA/IA) and enamine amination/isoaromatization/alkylation (EA/IA/A) reactions from commercially available enones, nitrosobenzenes, and alkyl halides (Scheme 1). Direct combination of amine-catalyzed cascade Knoevenagel/Michael/aldol condensation/decarboxylation (K/M/A/DC) and cascade enamine amination/isoaromatization (EA/IA) of alkyl acetoacetates, aldehydes, and nitrosoarenes has been developed in one pot as shown in Scheme 2. *o*-Hydroxydiarylamines are useful materials as additives for rubbers and plastics, antioxidants, antibacterial activity, anti-fibrillant activity, and hair dyes.[3]

SCHEME 1. Synthesis of Highly Substituted Anilines



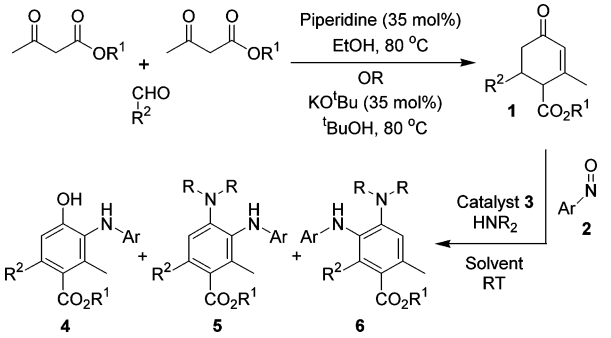
In continuation of our recent discovery of in situ generation and application of novel push−pull dienamines[4] in tandem reactions, we initiated our studies of the cascade EA/IA reaction by screening a number of known and novel organocatalysts for

(1) (a) Knolker, H. J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303−4427. (b) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901−7902. (c) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; pp 641−677.

(2) (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067. (b) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 6066−6068. (c) Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268−1273. (d) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264−1267. (e) Marcoux, J. F.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1568−1569. (f) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133−1135. (g) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215−7216. (h) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217−7218. (i) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1995**, *34*, 1348−1350.

10.1021/jo0623639 CCC: $37.00
Published on Web 01/20/2007

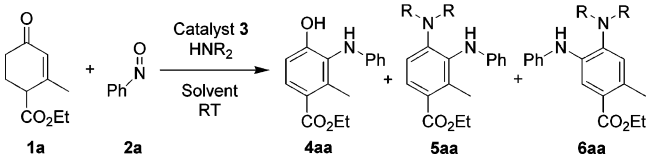
SCHEME 2. Organocatalytic Cascade Approach to the Synthesis of Highly Substituted Anilines



the amination of a variety of Hagemann's esters **1** with different nitrosoarenes **2** as shown in Scheme 2. For developing this novel cascade EA/IA reaction, we need a library of Hagemann's esters **1**, and we synthesized these esters **1** in good yields with minor modifications of known methods of direct piperidine- or KO^t-Bu-catalyzed cascade K/M/A/DC reactions (Scheme 2 and Table S1, see the Supporting Information).[5]

We initiated our studies of the cascade EA/IA reaction by screening a number of known and novel organocatalysts for the amination of Hagemann's ester **1a** using 0.5−1.0 equiv of nitrosobenzene **2a** as shown in Table 1.[6] Proline-catalyzed the formation of *o*-hydroxydiarylamine **4aa** in moderate yields in DMSO and DMF solvents (Table 1, entries 1 and 2) (in all compounds denoted **4xy**, **5xy**, and **6xy**, **x** is incorporated from reactant enones **1** and **y** is incorporated from the reactant nitrosoarenes **2**). Interestingly, catalyst diamine generated the cascade product **4aa** in very good yield in DMSO (Table 1, entry 3). Secondary amines like piperidine and morpholine catalysts also furnished the cascade product **4aa** in very good yields with excellent regioselectivity in DMSO solvent (entries 5 and 6). The primary amine, benzylamine, also catalyzed the formation of cascade product **4aa** in good yield (entry 7). The simple amine, pyrrolidine, catalyzed the cascade EA/IA reaction to produce **4aa** in 88% yield, which was accompanied by 1:1 regioisomers of *o*-pyrrolidin-1-yldiarylamines **5aa** and **6aa** in 8% yield (entry 8). Amine-catalyzed cascade EA/IA reactions are solvent dependent and also autocatalyzed reactions as shown in Table 1, entries 10−14. The use of 5 mol % of **4aa** catalyzed the cascade EA/IA reaction of **1a** and **2a** to produce product **4aa** in 35% yield. This is a good demonstration of the involvement of autocatalysis in the present reactions (Table 1, entry 13). We envisioned the optimized condition to be 25 °C in DMSO under 5 mol % of pyrrolidine catalysis to furnish *o*-hydroxydiarylamine **4aa** in 85% yield (entry 9).

TABLE 1. Optimization of Direct Organocatalytic Cascade Synthesis of *o*-Hydroxydiarylamines[a]



entry	catalyst (20 mol %)	solvent (0.3 M)	Hagemann's ester **1a** (equiv)	time (h)	products yield[b] (%) **4aa**	**5aa**	**6aa**
1	proline	DMSO	1.0	6	46		
2	proline	DMF	1.0	6	32		
3	**diamine**[c]	**DMSO**	**2.0**	**1**	**90**		
4	glycine	DMSO	2.0	36	30		
5	piperidine	DMSO	2.0	1	87		
6	**morpholine**	**DMSO**	**2.0**	**1**	**88**		
7	benzylamine	DMSO	2.0	1	83		
8	**pyrrolidine**	**DMSO**	**2.0**	**1**	**88**	**4**	**4**
9[d]	**pyrrolidine**	**DMSO**	**2.0**	**1**	**85**	**2**	**2**
10	pyrrolidine	DMSO	1.0	1	70	2	2
11	pyrrolidine	CH_3CN	2.0	10	40	10	10
12	pyrrolidine	EtOH	2.0	10	35	10	10
13	**4aa** (5 mol %)	DMSO	2.0	72	35		
14		DMSO	2.0	72			

[a] Reactions were carried out in solvent (0.3 M) with 1.0−2.0 equiv of **1a** relative to the **2a** in the presence of 20 mol % of catalyst. [b] Yield refers to the column purified product. [c] (*S*)-1-(2-Pyrrolidinylmethyl)pyrrolidine. [d] 5 mol % of pyrrolidine used.

In the investigation of EA/IA cascade reactions under pyrrolidine catalysis, product **4aa** was accompanied by interesting diamination products **5aa** and **6aa** with good conversion in EtOH via self-catalysis (Table 1, entry 12). To further exploit formation of this novel structure, we initiated our studies of the cascade EA/IA reaction by screening a number of known amines for the diamination of Hagemann's ester **1a** by 0.5 to 1.0 equiv of both nitrosobenzene **2a** and amines **3** as shown in Table 2.

The use of proline, diamine, and glycine as reagents in cascade reactions did not furnish the expected diamination products **5**/**6** in EtOH via self-catalysis and produced only amination product **4aa** (not shown in Table 2). Interestingly, pyrrolidine as reagent in self-catalyzed cascade reactions in

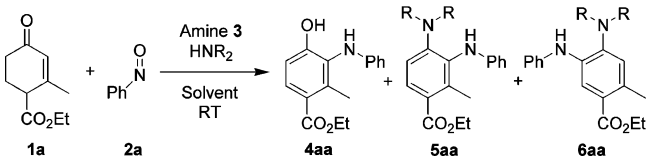
(3) (a) Gaina, L.; Lovasz, T.; Cristea, C.; Silberg, I. A.; Deleanu, C. *Rev. Roum. Chim.* **2003**, *48*, 549−554. (b) Suzuki, T.; Goto, F. Jpn. Kokai Tokkyo Koho 2003, 6 pp. CODEN: JKXXAF JP 2003096032 A2 20030403, CAN 138:271374 (Patent written in Japanese). (c) Yamamura, T.; Suzuki, K.; Yamaguchi, T.; Nishiyama, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 413−419. (d) Wahlig, H.; Henning, H. M.; Hepding, L.; Bertram, H. J. *Arzneim.-Forsch.* **1962**, *12*, 1123−1127. (e) Schmitt, J.; Suquet, M.; Callet, G.; Raveux, R. *Bull. Soc. Chim. Fr.* **1962**, 444−455. (f) Protiva, M.; Jilek, J. O.; Kolinsky, J.; Sustr, M.; Urban, J. *Chem. Listy. Vedu Prum.* **1949**, *43*, 254−257. (g) Bolton, P. D.; Glenn, R. W. U.S. Pat. Appl. Publ. 2006, 17 pp. CODEN: USXXCO US 2006032002 A1 20060216, CAN 144:239220.

(4) Ramachary, D. B.; Ramakumar, K.; Kishor, M. *Tetrahedron Lett.* **2005**, *46*, 7037−7042.

(5) (a) Chong, B. D.; Ji, Y. I.; Oh, S. S.; Yang, J. D.; Baik, W.; Koo, S. *J. Org. Chem.* **1997**, *62*, 9323−9325. (b) Shiv Kumar, S. N.; Bhaduri, A. P. *Indian J. Chem.* **1983**, *22B*, 524−525. (c) Ahmed, M. G.; Ahmed, S. A.; Romman, U. K. R.; Akhter, K.; Chowdhury, M. A.; Kiuchi, F. *Indian J. Chem.* **2001**, *40B*, 710−712. (d) Banerjee, M.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. Kr. *J. Org. Chem.* **2006**, *71*, 2787−2796. (e) Zhang, S.-W.; Mitsudo, T.-a.; Kondo, T.; Watanabe, Y. *J. Organomet. Chem.* **1995**, *485*, 55−62. (f) McCurry, P. M., Jr.; Singh, R. K. *Synth. Commun.* **1976**, *6*, 75−79. (g) Brunke, E. J.; Bielstein, H.; Kutschan, R.; Rehme, G.; Schuetz, H. J.; Wolf, H. *Tetrahedron* **1979**, *35*, 1607−1613. (h) Smith, W. T., Jr.; Eftax, D. S. P. *J. Org. Chem.* **1956**, *21*, 174−176. (i) Smith, W. T., Jr.; Eftax, D. S. P. *J. Am. Chem. Soc.* **1953**, *75*, 4356−4357.

(6) (a) Four decades ago,the Mukaiyama and Moskal research groups independently reported the KOH-catalyzed nitroso aldol reaction of active methylenes with nitrosobenzene to produce azomethine derivatives; see: Nohira, H.; Sato, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1963**, *36*, 870−872. Mirek, J.; Moskal, J.; Moskal, A. *Tetrahedron* **1975**, *31*, 2145−2149. (b) For an early reaction of aromatic nitroso compounds with enamines, see: Lewis, J. W.; Myers, P. L.; Ormerod, J. A. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2521−2524. (c) For an excellent review of reactions with nitroso compounds, see: Yamamoto, H.; Momiyama, N. *Chem. Commun.* **2005**, 3514−3525. (d) For,an electrophilic aromatic substitution with nitrosoarenes, see: Sokolov, A. V. *Int. J. Quantum Chem.* **2004**, *100*, 1−12. Hubig, S. M.; Kochi, J. K. *J. Am. Chem. Soc.* **2000**, *122*, 8279−8288. Eckert-Maksic, M.; Hodoscek, M.; Kovacek, D.; Maksic, Z. B.; Primorac, M. *Theochem* **1997**, *417*, 131−143. White, E. H. *Tetrahedron Lett.* **1997**, *38*, 7649−7652. Corbett, M. D.; Corbett, B. R. *Biochem. Pharmacol.* **1986**, 35, 3613−21. Bowden, W. L.; Little, W. F.; Meyer, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 5605−5607. Abramovitch, R. A.; Challand, S. R.; Scriven, E. F. V. *J. Org. Chem.* **1972**, *37*, 2705−2710. Shudo, K. *Yakugaku Zasshi* **1982**, *102*, 111−126.

TABLE 2. Optimization of Direct Self-Catalyzed Cascade Synthesis of *o*-Aminediarylamines



entry	amine **3**	solvent (0.3 M)	Hagemann's ester **1a** (equiv)	time (h)	products yield[a] (%) **4aa**	**5** & **6**	ratio **5/6**
1[b]	pyrrolidine	DMSO	2.0	0.5	85	11	2:1
2[b]	pyrrolidine	MeOH	2.0	1	35	45	1:1
3[b]	pyrrolidine	EtOH	2.0	1	35	45	3:1
4[b]	pyrrolidine	DCM	2.0	0.5	35	45	10:1
5[c]	pyrrolidine	MeOH	1.0	1	10	80	10:1
6[c]	**pyrrolidine**	**EtOH**	**1.0**	**1**	**10**	**80**	**10:1**
7[c]	piperidine	EtOH	1.0	0.5	85	-	-
8[d]	**pyrrolidine**	**EtOH**	**2.0**	**1**	**10**	**90**	**33:1**

[a] Yield refers to the column purified product. [b] All reactants pyrrolidine (0.3 mmol), nitrosobenzene **2a** (0.3 mmol), and Hagemann's ester **1a** (0.6 mmol) were mixed at the same time in solvent (0.3 M) and stirred at room temperature. [c] To the mixture of Hagemann's ester **1a** (0.3 mmol) and amine **3** (0.6 mmol) in solvent (0.5 mL) was added a 0.5 mL solution of nitrosobenzene **2a** (0.3 mmol) over a period of 0.5 h and the mixture stirred at rt. [d] To the mixture of Hagemann's ester **1a** (0.6 mmol), pyrrolidine (0.3 mmol), and MS 4A (300 mg) in solvent (0.5 mL) was added a 0.5 mL solution of nitrosobenzene **2a** (0.3 mmol) over a period of 0.5 h and the mixture stirred at rt.

DMSO furnished the amination product **4aa** as the major product and diamination products **5/6** as minor products (Table 2, entry 1). The same reaction in protic solvents furnished the amination **4aa** and diamination **5aa/6aa** products with poor regioselectivity (entries 2 and 3). Slow addition of nitrosobenzene **2a** to Hagemann's ester **1a** under pyrrolidine self-catalysis in EtOH furnished the expected *o*-pyrrolidin-1-yldiarylamines **5aa** and **6aa** in 80% yield with good selectivity (entry 6). We envisioned the optimized condition to be slow addition of **2a** to the mixture of **1a**, **3**, and MS 4A at 25 °C in EtOH to furnish *o*-pyrrolidin-1-yldiarylamines **5aa/6aa** in 90% yield with 33:1 regioselectivity (entry 8). A mechanistic aspect of this cascade EA/IA reaction is discussed in the next section.

With an efficient organocatalytic cascade protocol in hand, the scope of the auto- and self-catalyzed EA/IA cascade reactions was investigated with various Hagemann's esters **1a**−**m** and nitrosoarenes **2a**−**c**.[7] A series of 6-substituted Hagemann's esters **1a**−**m** were reacted with 0.5 equiv of nitrosoarenes **2a**−**c** catalyzed by 5 mol % of pyrrolidine or piperidine at 25 °C in DMSO (Table 3). The *o*-hydroxydiarylamines **4** were obtained as single isomers with excellent yields. The reaction of **1a** with 1-methyl-2-nitrosobenzene **2b** furnished the *o*-hydroxydiarylamine **4ab** as a single isomer, in good yield (Table 3). Synthesis of *o*-hydroxydiarylamine **4ac** from **1a**, **2c**, and **3** at 25 °C required a longer reaction time (12 h), but reaction at 65 °C furnished the product **4ac** with good yield within 2.5 h (Table 3). Both aliphatic- and aromatic-substituted Hagemann's esters **1d**−**m** generated the expected *o*-hydroxydiarylamines **4** with nitrosoarenes **2a**−**c** in excellent yield (Table 3). The rates of EA/IA cascade reactions are accelerated by in situ generated products **4**, and these reactions are ideal examples for the biomimetic autocatalysis of functionalized amines in organic reactions.[8] Structure and regiochemistry of *o*-hydroxydiarylamines **4** was confirmed by X-ray structure analysis on **4aa** as shown in Figure S1 (see the Supporting Information).[9]

With the success of cascade synthesis of highly functionalized *o*-hydroxydiarylamines **4**, we continued our investigation for generation of a highly functionalized diversity-oriented library of cascade *o*-pyrrolidin-1-yl-diarylamines **5** under self-catalysis. The results in Table 4 demonstrate the broad scope of this novel green methodology covering a structurally diverse group of Hagemann's esters **1a**−**m**, pyrrolidine, and nitrosobenzenes **2a**−**c**. Cascade EA/IA reaction of Hagemann's esters **1b**,**c**, nitrosobenzene **2a**, and pyrrolidine furnished the regioselective diamines **5ba** and **5ca** in 11:1 ratio with >85% yield (Table 4). Unexpectedly, cascade product **5ab** furnished with moderate yield in 3:1 isomeric ratio from **1a**, pyrrolidine, and **2b**. 4-*N*,*N*-Dimethylnitrosobenzene **2c** did not furnish the expected cascade EA/IA product **5ac** at 25 °C, but gave only <5% of expected **5ac** along with 40% of *o*-hydroxydiarylamine **4ac** at 65 °C in EtOH; this may be due to the electronic factor of the NMe_2 group. Interestingly, all 6-substituted Hagemann's esters **1d**−**m** furnished the expected *o*-pyrrolidin-1-yldiarylamines **5da**−**ma** with good yields as single isomers in self-catalyzed EA/IA cascade reactions as shown in Table 4. The structure and regiochemistry of *o*-pyrrolidin-1-yldiarylamines **5** were confirmed by X-ray structure analysis on **5ia** (Figure S2, see the Supporting Information).[9]

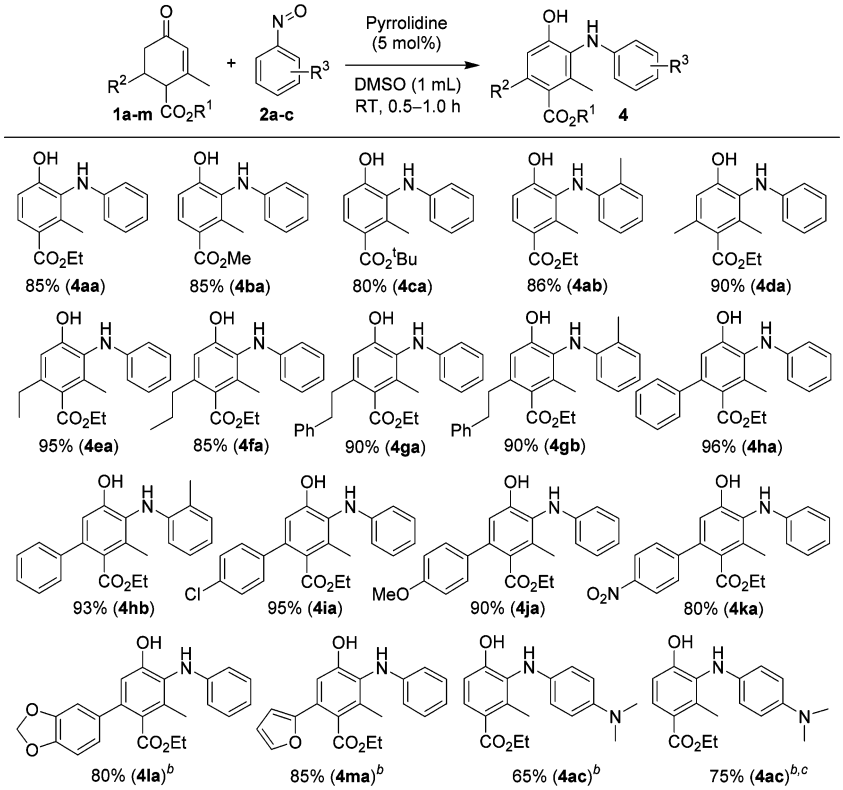
After successful demonstration of the piperidine-catalyzed cascade K/M/A/DC and EA/IA reactions, we decided to investigate the combination of these two cascade reactions in one pot. Reaction of 2 equiv of ethyl acetoacetate and benzaldehyde under piperidine catalysis in EtOH at 80 °C for 3−6 h furnished the expected Hagemann's ester **1h**, which on treatment with nitrosobenzene **2a** at 25 °C in same solvent did not furnish the expected *o*-hydroxydiarylamine **4ha** in good yield, but removing the solvent EtOH by vacuum pump and adding solvent DMSO, 20 mol % of piperidine, and nitrosobenzene **2a** to the reaction mixture of cascade K/M/A/DC furnished the expected *o*-hydroxydiarylamine **4ha** in good yield as shown in Table 5. Successful combination of two cascade K/M/A/DC and EA/IA reactions under piperidine catalysis was demonstrated by two more examples as shown in Table 5, and this one-pot synthetic strategy will have a great impact on the synthesis of functionalized small molecules.

(7) Many of nitrosoarenes **2** are commercially available, and suitable methods are known to prepare them. For excellent methods for synthesis of nitroso compounds, see: (a) Priewish, B.; Ruck-Braun, K. *J. Org. Chem.* **2005**, *70*, 2350−2352. (b) Defoin, A. *Synthesis* **2004**, 706−710. (c) Porta, F.; Prati, L. *J. Mol. Catal.* **2000**, *157*, 123−129. (d) Tollari, S.; Cuscela, M.; Porta, F. *J. Chem. Soc., Chem. Commun.* **1993**, 1510−1511.

(8) (a) Ramachary, D. B.; Babul, Reddy, G. *Org. Biomol. Chem.* **2006**, *4*, 4463−4468. (b) Ramachary, D. B.; Kishor, M.; Babul Reddy, G. *Org. Biomol. Chem.* **2006**, *4*, 1641−1646. (c) Iwamura, H.; Mathew, S. P.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 11770−11771. (d) Iwamura, H.; Wells, D. H.; Mathew, S. P.; Klussmann, M.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 16312−16313. (e) Mathew, S. P.; Iwamura, H.; Blackmond, D. G. *Angew. Chem. Int. Ed.* **2004**, *43*, 3317−3321.

(9) Crystal structure data for **4aa**: $C_{16}H_{17}NO_3$, $M_r = 271.31$, monoclinic, space group $P2_1/c$, $a = 10.9755(12)$ Å, $b = 8.2031(9)$ Å, $c = 16.2285(18)$ Å, $\alpha = 90°$, $\beta = 107.064(2)°$, $\gamma = 90°$, $V = 1396.8(3)$ Å^3, $T = 293(2)$ K, 13983 reflections collected. Crystal structure data for **5ia**: $C_{26}H_{27}ClN_2O_2$, $M_r = 434.95$, triclinic, space group *P*-1, $a = 10.602(2)$ Å, $b = 10.735(2)$ Å, $c = 11.281(2)$ Å, $\alpha = 77.344(3)°$, $\beta = 67.507(3)°$, $\gamma = 83.509(3)°$, $V = 1156.8(4)$ Å^3, $T = 293(2)$ K, 12012 reflections collected. CCDC-611665 for **4aa** and CCDC-611666 for **5ia** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or e-mail to deposit@ccdc.cam.ac.uk. See the Supporting Information for the crystal structures.

TABLE 3. Chemically Diverse Libraries of *o*-Hydroxydiarylamines[a]



[a] Yield refers to the column purified product. [b] Piperidine (5 mol %) used as catalyst. [c] Reaction performed at 65 °C.

With pharmaceutical applications in mind, we extended the two-component cascade EA/IA reactions to a novel amine/Cs_2CO_3-catalyzed three-component EA/IA/A reaction of **1a**, **1d**, and **2a** with allyl and propargyl bromides in one pot as shown in Table 6. *o*-Alkyloxydiarylamines **7** were constructed in good yields with high selectivity as shown in Table 6, and this method will have a great impact on the synthesis of carbazole alkaloids.[1a]

The possible reaction mechanism for regioselective synthesis of cascade products **4** and **5** through reaction of Hagemann's ester **1a**, nitrosobenzene **2**, and pyrrolidine **3** is illustrated in Scheme 3. First, reaction of pyrrolidine **3** with Hagemann's ester **1a** generates the imine cation **8**, which will transform into both dienamines **9** (thermodynamic stable product, major) and **15** (kinetic product, minor) on the basis of reaction conditions. The energy difference (ΔH) between the two dienamines **9** and **15** is 4.698 kcal/mol based on AM1 and 4.367 kcal/mol based on PM3 calculations. Minimized structures of **9** and **15** are depicted in the Supporting Information. Since the difference in ΔH's between the two dienamines of **9** and **15** are >4 kcal/mol, formation of thermodynamic stable dienamine **9** will be major under mild organocatalysis conditions. Slow addition of nitrosoarenes **2** to the reaction mixture of **1** and **3** controlled the formation of kinetic dienamine **15**, which may be due the basic nature of nitrosoarenes **2**, and this was supported by results in Tables 2 and 4.

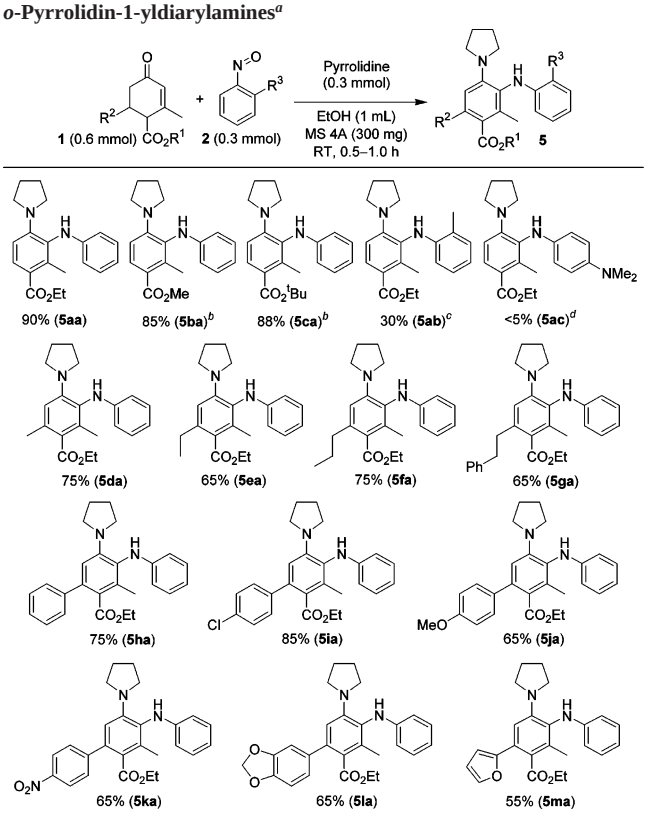
The reaction of push−pull dienamine **9** with **2** furnishes the selectively nitroso aldol product **11**, which will give imine product **12** by losing the hydroxide ion. Hydrolysis followed by isoaromatization of imine product **12** converted into highly substituted *o*-hydroxydiarylamine **4** under amine catalysis. Imine product **12** was transformed into highly substituted *o*-pyrrolidin-1-yldiarylamines **5** via isoaromatization under suitable conditions (EtOH and MS 4A). Hydrolysis of imine **12** is more solvent dependent as shown in Tables 1 and 2, which means this hydrolysis step is faster in DMSO than in EtOH, perhaps due to more interactions with water. In a similar manner, regioisomer **6** was also furnished from kinetic dienamine **15**. As discussed above, these cascade reactions are autocatalyzed and product **4** can catalyze the nitroso aldol reaction of enolate **1a′** of **1a** with **2** to form **17** via hydrogen-bonding transition state **16**, which will transform into the expected product **4** through imine **13** as shown in Scheme 3 (see Table 1, entries 13 and 14).

In summary, we have developed the metal-free synthesis of highly substituted anilines **4**, **5**, and **7** from simple starting materials via cascade EA/IA, K/M/A/DC/EA/IA, and EA/IA/A reactions under amine catalysis. The cascade reaction proceeds in good yields with high selectivity using pyrrolidine or piperidine as the catalyst. Furthermore, we have demonstrated the biomimetic auto- and self-catalysis in amine-catalyzed cascade reactions. Further work is in progress to utilize novel EA/IA, K/M/A/DC/EA/IA, and EA/IA/A reactions in synthetic chemistry.

Experimental Section

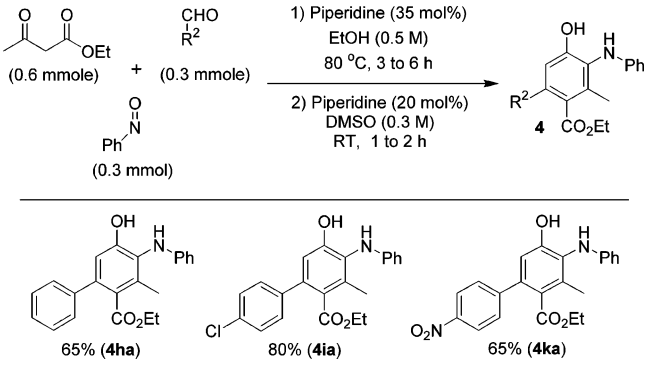
General Experimental Procedures for the Cascade Amination Reactions: Pyrrolidine-Catalyzed, Two-Component, Cascade Enamine Amination/Isoaromatization Reactions. In an ordinary glass vial equipped with a magnetic stirring bar, to 0.6 mmol of the Hagemann's esters **1** was added 1.0 mL of solvent, and then the catalyst pyrrolidine (0.015 mmol, 2.5 μL) was added and the reaction mixture was stirred at 25 °C for 0.5 h; then 0.3 mmol of nitrosoarenes **2** was added in one portion, and the reaction mixture

TABLE 4. Chemically Diverse Libraries of *o*-Pyrrolidin-1-yldiarylamines[a]



[a] In all reactions, 10−35% of the corresponding substituted *o*-hydroxydiarylamines **4** were isolated. Yield refers to the column purified product. [b] 11:1 ratio of regioisomers **5/6** are isolated. [c] 3:1 ratio of **5/6** are isolated. [d] Reaction performed at 65 °C for 2.5 h, and 40% of product **4ac** was isolated.

TABLE 5. Combination of Cascade Knoevenagel/Michael/Aldol Condensation/Decarboxylation and Cascade Enamine Amination/ Isoaromatization Reactions in One Pot[a,b]

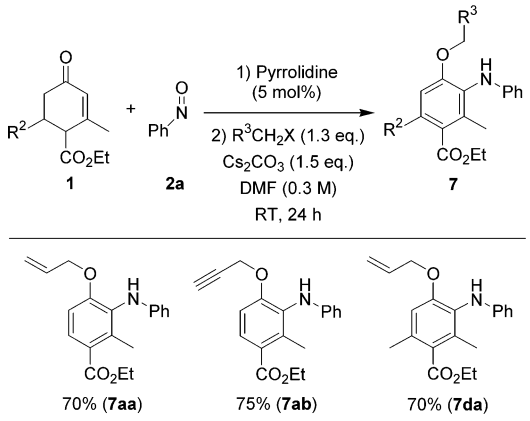


[a] See the Experimental Section. [b] Yield refers to the column purified product.

was stirred at 25 °C for the time indicated in Tables 1 and 3. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous workup, and pure cascade products **4** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

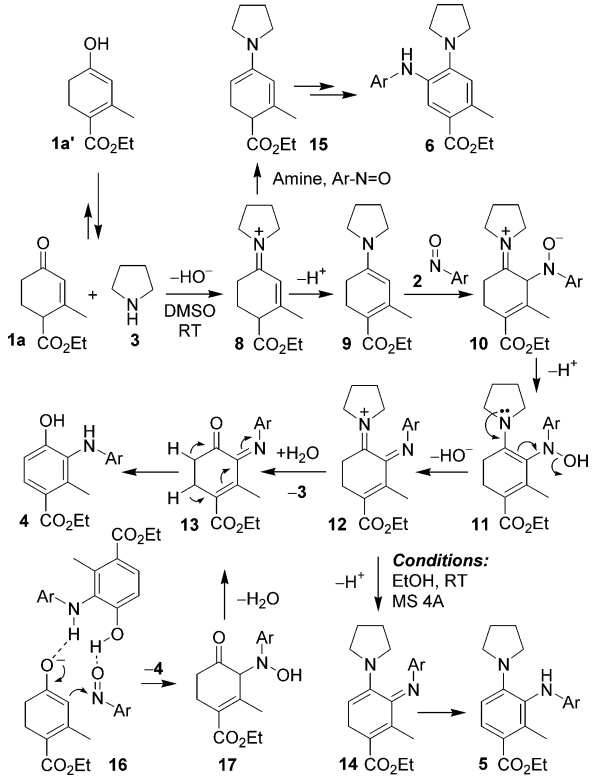
Self-Catalyzed, Three-Component, Cascade Enamine Amination/Isoaromatization Reactions. In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of the pyrrolidine, 0.6 mmol of Hagemann's esters **1**, and 300 mg of MS 4A was added 0.5 mL of solvent, and then the 0.5 mL solution of nitrosoarene (0.3 mmol) **2** was added dropwise for 0.5 h and the

TABLE 6. Amine−Cs_2CO_3-Catalyzed Enamine Amination/ Isoaromatization/Alkylation Reactions in One Pot[a,b]



[a] See the Experimental Section. [b] Yield refers to the column purified product.

SCHEME 3. Proposed Reaction Mechanism



reaction mixture was stirred at 25 °C for the time indicated in Tables 2 and 4. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure cascade products **5** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Piperidine-Catalyzed Combination of Cascade Knoevenagel/Michael/Aldol Condensation/Decarboxylation and Cascade Enamine Amination/Isoaromatization Reactions in One Pot. To a stirred solution of ethyl acetoacetate (0.6 mmol) and aldehydes (0.3 mmol) in EtOH (1 mL) was added a catalytic amount of piperidine (0.1 mmol, 35 mol %), and the reaction mixture was stirred at 80 °C for 3 h. Solvent ethanol and piperidine were evaporated by vacuum pump, then catalyst piperidine (0.06 mmol, 20 mol %), nitrosobenzene **2a** (0.3 mmol), and solvent DMSO (1 mL) were added, and

the reaction mixture was stirred at 25 °C for 1−2 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure one-pot products **4** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Pyrrolidine/Cs_2CO_3-Catalyzed Three-Component Enamine Amination/Isoaromatization/Alkylation Reactions in One Pot. In an ordinary glass vial equipped with a magnetic stirring bar, to 0.6 mmol of the Hagemann's esters **1** was added 1.0 mL of solvent, and then the catalyst pyrrolidine (0.015 mmol, 2.5 μL) was added and the reaction mixture was stirred at 25 °C for the 0.5 h. A 0.3 mmol portion of nitrosoarenes **2** was added in one portion, and the reaction mixture was stirred at 25 °C for the time indicated in Table 6. To the reaction mixture were added alkyl halide (0.39 mmol) and Cs_2CO_3 (0.45 mmol), and stirring was continued at rt for 24 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure one-pot products **7** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Acknowledgment. This work was made possible by a grant from The Department of Science and Technology (DST), New Delhi. K.R. and V.V.N. thank the Council of Scientific and Industrial Research (CSIR), New Delhi, for their research fellowships. We are thankful to Prof. A. Srikrishna and his research group, Department of Organic Chemistry, IISc, Bangalore, for their help in obtaining HRMS data of all reported compounds. We thank Pallepogu Raghavaiah for X-ray structural analysis.

Supporting Information Available: General experimental procedures, compound characterization, X-ray crystal structures, and analytical data (^1H NMR, ^{13}C NMR, and HRMS) for all new compounds. Copies of ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0623639