JOC Notes

Hammett Correlation of Nornicotine Analogues in the Aqueous Aldol Reaction: Implications for Green Organocatalysis

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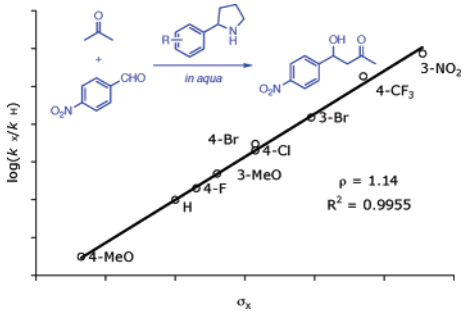

A series of meta- and para-substituted 2-arylpyrrolidines were synthesized and examined for their ability to catalyze an aqueous aldol reaction under buffered conditions. Kinetic analysis of arylpyrrolidine-catalyzed reactions displayed a linear Hammett correlation with $\rho = 1.14$ ($R^2 = 0.996$), indicating that the reaction is accelerated by electron-withdrawing aryl rings. These results show promise for the development of a synthetically viable aqueous organocatalyst.

The use of tobacco products is the leading cause of death in the United States, and is known to contribute to a wide variety of pathologies, including certain types of cancer.[1] In light of the serious health consequences and addictive nature of nicotine, we have recently initiated a research program aimed at studying the chemical reactivity of nicotine metabolites. Nornicotine, a minor nicotine metabolite with an extended half-life,[2] has been demonstrated by our laboratory to perform iminium-based chemistry in water; for example, we have shown the aberrant glycation of proteins in vivo,[3] as well as the fortuitous glycation of the amyloid β-peptide.[4] Through a related mechanism, nornicotine can also utilize enamine intermediates to catalyze aqueous aldol reactions under physiological conditions (Scheme 1).[5] The unprecedented ability of a xenobiotic secondary metabolite to catalyze carbon−carbon bond formation led us to further investigate the role of nornicotine in aqueous aldol catalysis. In addition to the biological implications of this reaction, an understanding of the basis of rate enhancement could expand the impact of organocatalysis,[6] and provide the impetus for the discovery of a synthetically relevant green organocatalyst.

Initial computational studies into the nornicotine-catalyzed aqueous aldol reaction validated the proposed enamine-based mechanism;[7] however, it offered no particular insight into the structural basis for enhanced catalysis relative to the related organocatalysts proline[8] and pyrrolidine. In our first report of this reaction, it was observed that altering the position of the pyridyl nitrogen had little effect on catalysis. Replacing the pyridyl ring with a phenyl substituent, however, reduced activity by 40%, while the use of pyrrolidine led to an 80% reduction in activity. These results caused us to speculate as to the relationship of the rate of the reaction on the electronic nature of the aryl ring. We now report our experimental findings into the stereoelectronic nature of arylpyrrolidine-based aqueous aldol catalysis, and its potential for the design of "green" organocatalysts.

To test the electronic dependence of the nornicotine-catalyzed aqueous aldol reaction, we synthesized a variety of 2-arylpyrrolidines with Hammett values in the range $-0.83 \leq \sigma_x \leq 0.71$. Compounds with electron-donating or mildly electron-withdrawing substituents were synthesized according to a lithium-catalyzed anionic 5-*endo*-*dig* cyclization method developed by Yus et al. (Scheme 2).[9] In this route, the appropriate arylaldehyde was treated with 3-chloropropylamine in the presence of triethylamine and magnesium sulfate.[10] The resulting *N*-arylmethylene-3-chloropropylamines were then reacted with lithium metal in the presence of catalytic (20 mol %) di-*tert*-butylbiphenyl (DTBB) providing 2-arylpyrrolidines **1b**−**5b** in high yields (85−95% over two steps).

In their report, Yus et al. primarily considered this method on substrates with electron-donating groups.[9] Unfortunately, lithium-catalyzed cyclization failed for substrates with substituents more electron withdrawing

(1) (a) Nelson, D. E.; Kirkendall, R. S.; Lawton, R. L.; Chrisom, J. H.; Merritt, R. K.; Arday, D. A.; Giovino, G. A. *Morbid. Mortal. Wkly. Rep*. **1994**, *43*, 1−8. (b) *Reducing the Health Consequences of Smoking. 25 Years of Progress. A Report of the Surgeon General*; U.S. Department of Health and Human Services; Public Health Services: Rockville, MD, 1989.

(2) Kisaki, T.; Tamaki, E. *Arch. Biochem. Biophys*. **1961**, *92*, 351−355.

(3) Dickerson, T. J.; Janda, K. D. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 15084−15088.

(4) Dickerson, T. J.; Janda, K. D. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 8182−8187.

(5) Dickerson, T. J.; Janda, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 3220−3221.

(6) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed*. **2004**, *43*, 5138−5175.

(7) Dickerson, T. J.; Lovell, T.; Meijler, M. M.; Noodleman, L.; Janda, K. D. *J. Org. Chem.* **2004**, *69*, 6603−6609.

(8) (a) List, B. *Synlett* **2001**, *11*, 1675−1686. (b) List, B. *Acc. Chem. Res*. **2004**, *37*, 548−557. (c) Notz, W.; Tanaka, F.; Barbas, C. F., III *Acc. Chem. Res*. **2004**, *37*, 580−591.

(9) Yus, M.; Soler, T.; Foubelo, F. *J. Org. Chem.* **2001**, *66*, 6207−6208.

(10) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400−13401.

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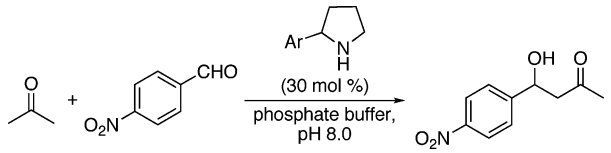
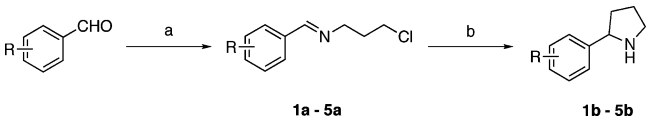
SCHEME 1. Nornicotine Catalyzed Aldol Reaction (Ar = 3-pyridyl)



SCHEME 2. Synthesis of 2-Arylpyrrolidines, Route A[a]



[a] Reagents and conditions: (a) 3-chloropropylamine·HCl, Et_3N, $MgSO_4$, CH_2Cl_2. (b) Li wire, DTBB, THF, −78 °C.

than 3-methoxy ($\sigma_{3-MeO} > 0.12$). When exposed to a solution of lithium di-*tert*-butylbiphenylide, these substrates formed stabilized aryl radicals, which reacted to form a variety of side products with no pyrrolidine detectable by GC analysis. To synthesize the full range of electron-withdrawing 2-arylpyrrolidines, several other routes were attempted, all of which proceeded through myosmine analogues, that were reduced with sodium borohydride to afford the desired 2-arylpyrrolidine (Scheme 3).

The 4-bromo and 4-chlorophenyl analogues, **6a** and **7a**, were readily synthesized from commercially available chlorobutyrophenones by displacement of the alkyl chloride with NaN_3. The crude azide was then smoothly reduced with PPh_3 to afford the desired myosmine analogue.[11] While this route provided the pyrrolidine product in good yield (~75% over three steps), commercially available chlorobutyrophenones were limited to 4-substituted ortho/para directing groups. For meta halide-containing members, Weinreb amides were reacted with protected Grignard reagent **11** at 0 °C for 12 h, followed by treatment with 10% HCl in EtOH to induce concomitant deprotection of the amine and imine formation in modest yields (50−65%).[12,13] Stronger electron-withdrawing groups, such as nitro or trifluoromethyl, could not be synthesized with this route due to facile dialkylation, even at lower temperatures (−78 °C). Consequently, these compounds were synthesized from the corresponding ethyl esters, which were treated with 1-vinyl-2-pyrrolidinone and sodium hydride in refluxing THF, followed by acidification in refluxing HCl.[14] Although yields for this route were poor (~30%),[13] suitable quantities of pure myosmine analogue could be obtained after distillation.

With the desired compounds in hand, the k_{obs} for the nornicotine analogues in the aqueous aldol reaction were determined under pseudo-first-order conditions with use of acetone as the donor and 4-nitrobenzaldehyde as the acceptor (Table 1). Using the Hammett eq 1,[16] we found

$$\log\left(\frac{k_x}{k_H}\right) = \rho\sigma_x \qquad (1)$$

that the relationship between the log of the relative rate constant[17] and σ_x was linear over the entire domain of tested compounds ($\rho = 1.14$, $R^2 = 0.996$) with the exception of 4-Me_2N ($\sigma = -0.81$), which did not have activity over the uncatalyzed aldol reaction (Figure 1). Indeed, according to the Hammett equation derived from our data, the substituent on an arylpyrrolidine must have a Hammett value ≥ −0.70 before any catalytic activity is observed. These results show that the mere presence of a 2-aryl ring is not enough for rate enhancement, but that the appearance of aldol catalysis is critically dependent on the electronic nature of the ring. For example, the observed rate constant of pyrrolidine[5] is close to that of 4-MeO analogue **2b**.

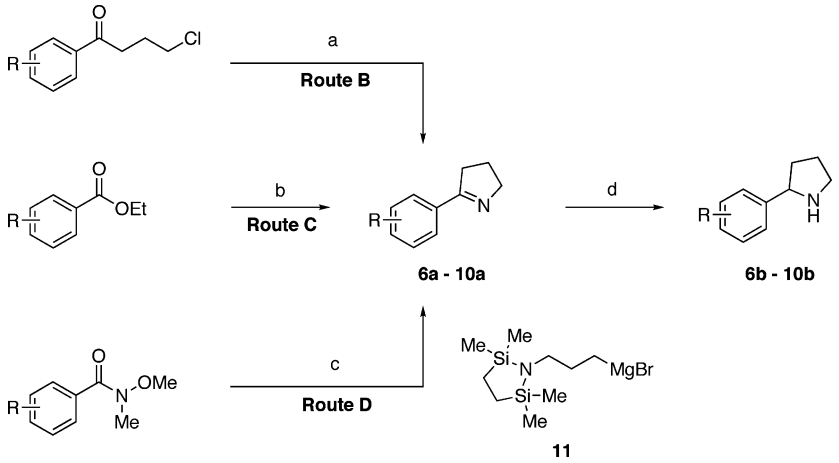
The positive slope of the Hammett plot validates earlier observations of the aqueous aldol reaction, that is, that an electron-withdrawing aryl ring improves catalysis. To our knowledge, prior to this report no pyrrolidine-based catalyst has exhibited aqueous catalytic activity significantly greater than that of nornicotine.[18] We found that substituents with Hammett values greater than $\sigma_x \geq 0.39$ have improved catalysis relative to nornicotine. In fact, 3-NO_2 analogue **10b** has a rate approximately double that of nornicotine and represents the most efficient pyrrolidine-based aqueous aldol catalyst reported to date.

A possible explanation for the improved rates of arylpyrrolidines substituted with electron-withdrawing groups is that these substituents lower the pK_a of the pyrrolidine nitrogen, effectively increasing the concentration of available catalyst. In this context, nornicotine is an effective aqueous aldol catalyst relative to pyrrolidine or proline because the 3-pyridyl ring is sufficiently electron withdrawing to perturb the pK_a of the pyrrolidine nitrogen. Similarly, **1b** does not catalyze aldol formation because the 4-Me_2N phenyl ring is sufficiently electron donating to make the pyrrolidine nitrogen predominantly protonated at pH 8.0, leaving only trace amounts of active free amine catalyst. One may speculate that eventually the electron-withdrawing nature of the aryl ring could become too strong, and as such, the rate of aldol catalysis would be expected to no longer increase linearly with σ_x.

In summary, these results show promise for the development of improved aldol catalysts in aqueous media. The field of green chemistry has received much attention in recent years as a method to develop envi-

(11) De Kimpe, N.; Tehrani, K. A.; Stevens, C.; De Cooman, P. *Tetrahedron* **1997**, *53*, 3693−3706.
(12) Basha, F. Z.; DeBernardis, J. F. *Tetrahedron Lett.* **1984**, *25*, 5271−5274.
(13) Yields refer to the isolated yield of 2-arylpyrrolidine and were not optimized.
(14) Maryanoff, B. E.; McComsey, D. F.; Gardocki, J. F.; Shank. R. P.; Costanzo, M. J.; Nortey, S. O.; Schneider, C. R.; Setler, P. E. *J. Med. Chem.* **1987**, *30*, 1433−1454.
(15) (a) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195. (b) Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lein, E. J. *J. Med. Chem.* **1973**, *16*, 1207−1216.
(16) (a) Topsom, R. D. *Prog. Phys. Org. Chem.* **1976**, *12*, 1. (b) Uger, S. H.; Hansch, C. *Prog. Phys. Org. Chem.* **1976**, *12*, 91. (c) Levitt, L. S.; Widing, H. F. *Prog. Phys. Org. Chem.* **1976**, *12*, 119.
(17) The relative rate refers to the rate constant of the 2-arylpyrrolidine-catalyzed reaction divided by the rate constant of the 2-phenylpyrrolidine (**3b**)-catalyzed reaction.
(18) (a) Reymond, J.-L.; Chen, Y. *J. Org. Chem.* **1995**, *60*, 6970−6979. (b) Córdova, A.; Notz, W.; Barbas, C. F., III *Chem. Commun.* **2002**, *24*, 3024−3025. (c) Peng, Y.-Y.; Ding, Q.-P.; Li, Z.; Wang, P. G.; Cheng, J.-P. *Tetrahedron Lett.* **2003**, *44*, 3871−3875. (d) Hartikka, A.; Arvidsson, P. I. *Tetrahedron*: *Asymmetry* **2004**, *15*, 1831−1834.

SCHEME 3. Synthesis of 2-Arylpyrrolidines, Routes B, C, and D[a]



[a] Reagents and conditions: Route B: (a) (i) NaN_3, NaI, DMSO, 55 °C, (ii) PPh_3, hexane. Route C: (b) (i) 1-vinyl-2-pyrrolidinone, NaH, THF, (ii) 4.6 M HCl. Route D: (c) (i) **11**, THF, 0 °C, (ii) 10% HCl/EtOH. (d) $NaBH_4$, 20% AcOH/MeOH, −45 °C.

TABLE 1. k_{obs} for 2-Arylpyrrolidine-Catalyzed Aqueous Aldol Reactions

compd	substituent	route	yield (%)[a]	σ_x[b]	k_{obs}[c] (10^{-3} min^{-1})
1b	4-Me_2N	A	91	−0.83	0.7 ± 0.1
2b	4-MeO	A	94	−0.27	3.1 ± 0.2
3b	H	A	88	0.00	4.6 ± 0.1
4b	4-F	A	85	0.06	4.8 ± 0.1
5b	3-MeO	A	97	0.12	6.3 ± 0.1
6b	4-Cl	B	76	0.23	8.4 ± 0.2
7b	4-Br	B	79	0.23	9.1 ± 0.1
8b	3-Br	D	63	0.39	12.5 ± 0.4
9b	4-CF_3	C	34	0.54	18.0 ± 0.9
10b	3-NO_2	C	32	0.71	23.8 ± 1.7
	nornicotine				10.1[d]
	pyrrolidine				2.4[d]
	uncatalyzed reaction				0.7 ± 0.1

[a] Unoptimized isolated yield of 2-arylpyrrolidine. [b] Hammett values, σ_x, taken from ref 15. [c] Initial rates were measured in 10% DMSO/200 mM phosphate buffer (pH 8.0) at 37 °C with 240 mM acetone, 2.4 mM catalyst, and initiated by the addition of 1−8 mM aldehyde. The reaction was followed by monitoring the generation of aldol addition product by reverse-phase HPLC. Values for k_{obs} were calculated by using linear regression analysis. [d] Values from ref 5.

ronmentally benign chemical processes.[19] Our data provide a clearer picture into the nature of aqueous pyrrolidine-based organocatalysts and suggest that with suitable design, synthetically useful catalysts are attainable.

Experimental Section

General Procedure for *N*-Arylmethylene-3-chloropropyl-1-amines. Triethylamine (2.2 mmol, 0.31 mL) was added to a mixture of 3-chloropropylamine hydrochloride (0.29 g, 2.2 mmol) and $MgSO_4$ (0.48 g, 4.0 mmol) in 10 mL of CH_2Cl_2. After stirring at room temperature for 1 h, the appropriate aldehyde (0.2 mmol) was added and the suspension was allowed to continue to stir at ambient temperature, or heated to reflux for 12 h. Upon completion, the $MgSO_4$ was filtered and washed with CH_2Cl_2. The filtrate was washed sequentially with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. Compounds were used without any further purification.

General Procedure for Li/DTBB-Catalyzed Cyclizations. Lithium wire (20 equiv) was prepared by scraping its surface under kerosene oil, cutting it into small pieces, and placing the oil-covered pieces into a flask. The oil was removed by washing the pieces with dry hexanes followed by THF under a stream of Ar. To the prepared lithium wire was slowly added di-*tert*-butylbiphenyl (0.2 equiv) as a concentrated solution in THF. The resulting green suspension was diluted with THF, the mixture was cooled to −78 °C, and the appropriate *N*-arylmethylene-3-chloropropyl-1-amine (1 equiv) was added as a solution in THF, quenching the green color. After the green color reappeared (ca. 2 h), the reaction was quenched by the slow addition of water (20 mL), and the mixture was allowed to warm to room temperature. The solution was acidified with 2 N HCl and washed twice with Et_2O. The aqueous layer was then brought to pH 12−13 with 4 M NaOH, and the product was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo to afford 2-arylpyrrolidine, which was purified by bulb-to-bulb distillation.

General Procedure for Synthesis of Myosmine Analogues from 4-Chlorobutyrophenones (Route B). A flask containing the appropriate 4-chlorobutyrophenone (38 mmol), NaN_3 (3.73 g, 57 mmol), and NaI (0.19 g, 1.3 mmol) in DMSO was warmed to 55 °C. After 15 h, the solution was poured into water and extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Triphenylphosphine (9.69 g, 37 mmol) was added to a suspension of the resulting crude azide (35 mmol) in hexanes. The resulting mixture was stirred for 14 h at room temperature before being filtered. The solids were washed with cold Et_2O and the filtrate was evaporated. The residue was dissolved in Et_2O: hexane (1:1) and filtered. The filtrate was evaporated, affording the crude myosmine analogue.

General Procedure for Synthesis of Myosmine Analogues from Aryl Esters (Route C). To a solution of NaH (0.86 g, 36 mmol) in THF was added 1-vinylpyrrolidinone (31 mmol, 3.3 mL) and aryl ethyl ester (26 mmol) as a solution in THF. After being stirred at ambient temperature for 15 min, the resulting mixture was warmed to reflux for 1 h. The flask was then cooled to room temperature and treated with 4.6 M HCl. The THF was evaporated, and the solution was treated with another portion of 4.6 M HCl. The flask was then warmed to reflux for 15 h. After heating, the solution was cooled in an ice bath, and the reaction was basified by 50% NaOH. After extraction with Et_2O, the combined organic layers were washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo.

General Procedure for Synthesis of Myosmine Analogues from Weinreb Amides (Route D). To a flask containing Mg (0.17 g, 6.8 mmol) was added a few small crystals of iodine. The flask was sealed and warmed with a heat-gun until

(19) (a) Kirchhoff, M. M. *Environ. Sci. Technol.* **2003**, *37*, 5349−5353. (b) Anastas, P. T.; Warner, J. C. *Green Chemistry*: *Theory and Practice*; Oxford: New York, 1998.

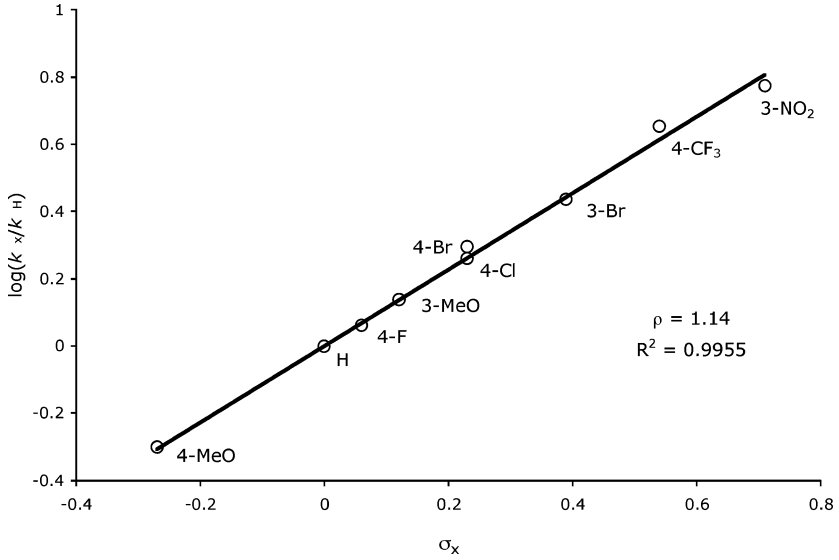


FIGURE 1. Hammett correlation of the log of relative rate for aldol catalysis versus Hammett value, σ_x (taken from ref 15), where $k_H = k_{obs}$ for **3b**, and $k_x = k_{obs}$ for the tested compound.

the iodine vaporized. After the Mg metal was stirred in the vapor for 30 min, the flask was purged with argon. After the iodine was removed, a small amount of THF was added, followed by the dropwise addition of 1-(3-bromopropyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane (6.2 mmol, 1.53 mL). During the addition, the flask was warmed with a heat-gun at such a rate to maintain reflux. Once the suspension was able to maintain its own reflux, additional THF was slowly added. After being stirred for 1 h, the solution was cannulated into a chilled flask (0 °C) containing Weinreb amide (0.5 g, 2.1 mmol) and THF. Upon completion, the mixture was allowed to warm to room temperature. After 18 h, the reaction was quenched by the addition of 10% HCl in EtOH (20 mL) and stirred an additional 3 h. The solution was then brought to pH 12−13 with 4 M NaOH and washed with EtOAc. The organic fractions were dried (Na_2SO_4) and concentrated to afford crude myosmine analogue.

General Procedure for the Synthesis of Pyrrolidines from Myosmine Analogues. $NaBH_4$ (2 equiv) was added to a solution of myosmine analogue in 20% AcOH/MeOH at −41 °C. After being stirred for 1 h the solution was allowed to warm to room temperature. Once the reaction was deemed complete by TLC or GC analysis, the unreacted $NaBH_4$ was quenched by the addition of 2 N HCl. The solution was then diluted with H_2O and ether. The phases were separated, and the aqueous layer was washed with an additional portion of ether. The aqueous layer was basified with 4 M NaOH (pH 12−13) and washed with ethyl acetate. The combined organic extracts were washed with brine, and then dried over Na_2SO_4. Evaporation, followed by bulb-to-bulb distillation afforded pure 2-arylpyrrolidine.

Initial Rate Kinetics. Initial rates and rate constants for 2-arylpyrrolidine catalyzed aldol condensation of 4-nitrobenzaldehyde and acetone were determined by monitoring the formation of 4-hydroxy-4-(4-nitrophenyl)butan-2-one by analytical reverse-phase HPLC. Reactions were conducted at 37 °C with 2.4 mM freshly distilled arylpyrrolidine, 240 mM acetone, and 8.0 mM 4-nitrobenzaldehyde in 10% DMSO/200 mM phosphate, pH 7.4. All reactions were performed in a total volume of 500 μL. To monitor the progress of the reaction, 10-μL aliquots of the above solution were removed at various times during the reaction and diluted to a total volume of 500 μL with phosphate buffer. Then, 20 μL of these samples was injected onto an analytical RP-C18 HPLC, and the amount of 4-hydroxy-4-(4-nitrophenyl)butan-2-one (retention time = 6.2 min) was determined by interpolation of the peak height and area values relative to standard curves. Pseudo-first-order rate constants were measured by varying 4-nitrobenzaldehyde concentrations (1−8 mM) in the above reaction.

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Supporting Information Available: ^1H and ^{13}C NMR spectra data for 2-arylpyrrolidines **1b**−**10b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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