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Catalytic Enantioselective Friedländer Condensations: Facile Access to Quinolines with Remote Stereogenic Centers

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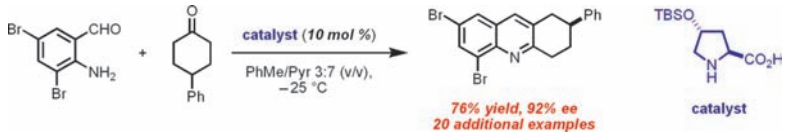
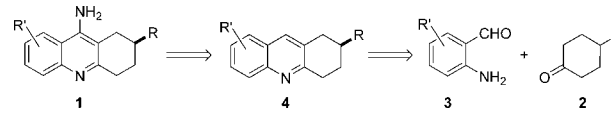
ABSTRACT



Enamine catalysis enables the first catalytic enantioselective Friedländer reaction. The desymmetrization of 4-substituted cyclohexanones upon reaction with *o*-aminobenzaldehydes allows for the synthesis of quinolines with remote stereogenic centers. These heterocycles, which are obtained with high levels of enantioselectivity, serve as precursors for chiral tacrine analogues.

Tacrine (**1**, R = R′ = H) and its derivatives (Scheme 1) have shown efficacy in the treatment of cognitive disorders such as Alzheimer's disease.[1] Tacrine's mode of action is attributed to its potent acetylcholinesterase inhibitor activities,[1b,c] and compounds **1** are also known to inhibit other enzymes including butylcholinesterase[1e] and monoamine oxidase.[1d] In addition, other pharmacological uses of tacrine, such as blockage of potassium channels and inhibition of neuronal monoamine uptake processes, have been reported.[1g] Given their important functions in medicinal chemistry, the synthesis and evaluation of new tacrine analogues continues to be of significant interest.

Scheme 1. Retrosynthesis of Chiral Tacrine Analogues



We envisioned that chiral nonracemic tacrine derivatives **1** may be derived from their corresponding quinolines **4**. The asymmetric synthesis of these quinolines, which are interesting compounds in their own right, would be most conveniently accomplished via catalytic enantioselective Friedländer condensations of *o*-aminobenzaldehydes **3** and ketones **2**.[2] Here we report the first successful realization of such a process.

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Since the renaissance of enamine catalysis in the early 2000s, this organocatalytic mode of activation has been developed into a powerful synthetic tool for the preparation of valuable chiral building blocks.[3,4] Enamine catalysis provides a mild and general solution for the in situ transformation of aldehydes and ketones into their corresponding enolate equivalents. In the past decade, a number of reactions were developed that employ this strategy, including aldol reactions,[5] Mannich reactions,[6] Michael additions,[7] and others.[8] However, relatively few studies have focused on reactions that involve the desymmetrization of prochiral ketones,[9] one of the prerequisites for the targeted Friedländer condensation. Whereas enamines are considered to be important intermediates in the classical Friedländer process, relatively harsh reaction conditions are typically required.[10] Interestingly, proline has recently been used as a catalyst in the Friedländer synthesis of achiral quinolines.[11] However, this reaction appears to be limited to the use of highly activated amino-trifluoromethylketones while simultaneously requiring mild heating.

From the outset of our study, it was clear that several challenges would have to be addressed. First, compared to the relatively electron-poor benzaldehydes that have been used predominantly in enamine-catalyzed asymmetric aldol reactions, the corresponding *o*-aminobenzaldehydes are appreciably more electron-rich and thus represent less reactive electrophiles. Second, it was not clear if it would be possible to conduct the necessary elimination step of the Friedländer sequence under mild enough conditions that would simultaneously allow for a highly enantioselective process. In addition, it is well-known that *o*-aminobenzaldehydes tend to self-condense, even under mild conditions.[12]

With these considerations in mind, we opted to investigate the reaction of commercially available and relatively electron poor 3,5-dibromoaminobenzaldehyde (**3a**) with 4-phenylcyclohexanone (**2a**). Among the readily available organocatalysts tested, only amino acids gave acceptable rates and selectivities.[13] As summarized in Table 1, proline derivatives provided the best results. *trans*-4-Hydroxyproline (**7a**) gave rise to a slightly higher ee as compared to proline itself. Given the poor solubility of proline and *trans*-4-hydroxyproline in nonpolar solvents, more soluble silicon protected *trans*-4-hydroxyproline derivatives were prepared.[14] Gratifyingly, the reactivity and selectivity of these catalysts proved to be very similar to that of unmodified *trans*-4-hydroxyproline.

To improve the rate and selectivity of the reaction, catalyst **7b** was tested in a broad range of solvents (Table 2).[15] Several interesting observations were made in the course of this study. Apolar solvents containing aromatic rings such

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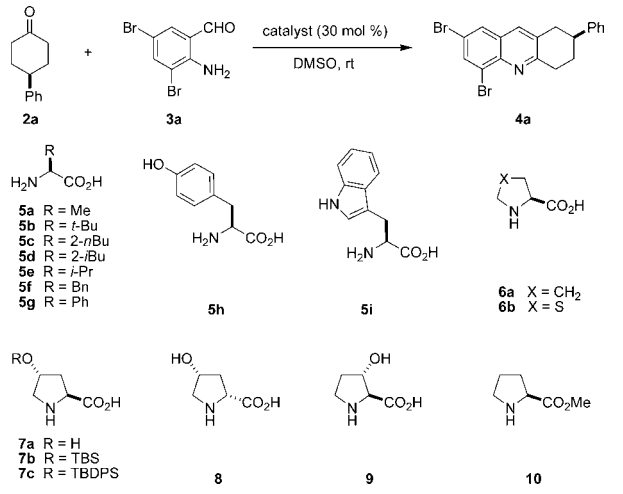
Table 1. Evaluation of Catalysts[a]

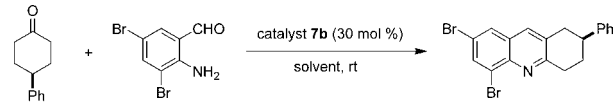


entry	catalyst	time (d)	yield (%)[b]	ee (%)
1	**5a**	3	73	66
2	**5b**	3	75	72
3	**5c**	3	74	70
4	**5d**	3	75	66
5	**5e**	3	70	70
6	**5f**	3	70	47
7	**5g**	3[c]	ND	62
8	**5h**	3	65	50
9	**5i**	3	65	47
10	**6a**	1	83	74
11	**6b**	2	68	67
12	**7a**	1	78	79
13	**7b**	1	82	78
14	**7c**	1	83	76
15	**8**	1	75	−67
16	**9**	1	80	66
17	**10**	3[c]	<5	ND

[a] Reactions were performed at rt on a 0.2 mmol scale in anhydrous DMSO (0.2 M) with 3.0 equiv of cyclohexanone. Reactions were run to full conversion as judged by TLC analysis. The ee's were determined by HPLC analysis. [b] Isolated yields. [c] The reaction was incomplete.

as toluene and xylenes gave rise to high selectivities but reactions were very slow (incomplete in 3 days at rt). On the other hand, more polar solvents gave rise to faster reaction rates, albeit at the expense of selectivity. A closer inspection revealed that solvent polarity alone does not directly correlate with reaction rate.[16] Rather, the presence of basic sites on the solvent appeared to be a factor that significantly impacts reaction rate.[17] These collective observations led us to evaluate pyridine as a reaction medium since it combines apparently favorable attributes of other solvents. Indeed, a reaction conducted in pyridine went to completion in only 12 h while giving rise to product **4a** with 83% ee (Table 2, entry 16). This increase in reactivity allowed for the reaction to be performed at a lower temperature. At −20 °C, product **4a** was recovered with 90% ee (entry 17). Ultimately, a toluene/pyridine solvent mixture was found to provide the best compromise between selectivity and yield. Further optimization also enabled the reduction of catalyst loading to 10 mol %.

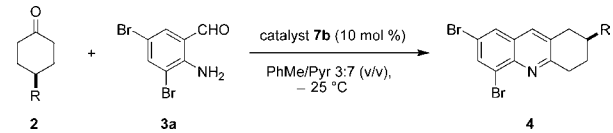
Table 2. Evaluation of Solvents[a]



entry	solvent	time (h)	yield (%)[b]	ee (%)
1	DMSO	16	82	79
2	DMF	24	80	79
3	MeCN	36	83	81
4	EtOAc	48	78	82
5	THF	48	75	82
6	dioxane	36	78	81
7	$CHCl_3$	72[c]	65	79
8	CH_2Cl_2	72[c]	65	79
9	CCl_4	72[c]	65	83
10	cyclohexane	72[c]	45	76
11	PhMe	72[c]	67	87
12	xylenes	72[c]	65	87
13	$PhCF_3$	72[c]	65	82
14	anisole	72[c]	78	86
15	NMI	10	80	76
16	pyridine	12	80	83
17[d]	pyridine	72	75	90
18[e]	pyridine	96[c]	65	93

[a] Reactions were performed at rt on a 0.2 mmol scale in anhydrous solvent (0.2 M) with 3 equiv of cyclohexanone. Reactions were run to full conversion as judged by TLC analysis. The ee's were determined by HPLC analysis. [b] Isolated yields. [c] The reaction was incomplete. [d] The reaction was run at −20 °C. [e] The reaction was run at −35 °C.

Table 3. Scope of Cyclohexanones[a]

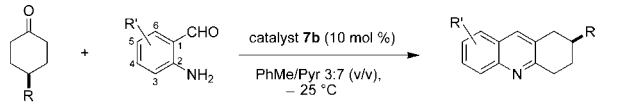


entry	R	product	method[c]	yield (%)[b]	ee (%)
1	Ph	**4a**	A	76	92
2	4-OH-Ph	**4b**	A	60	92
3	4-MeO-Ph	**4c**	A	75	93
4	3-MeO-Ph	**4d**	A	73	92
5	4-CF_3-Ph	**4e**	A	60	90
6	Me	**4f**	B[d]	62	91
7	Et	**4g**	B[d]	85	94
8	*i*-Pr	**4h**	B	80	93
9	*n*-Pr	**4i**	B	81	94
10	*t*-Bu	**4j**	B	82	91
11	*n*-pentyl	**4k**	B	80	95

[a] Reactions were performed at −25 °C on a 0.5 mmol scale in anhydrous solvent for 72 h. The ee's were determined by HPLC analysis. [b] Isolated yields. [c] Method A: 2 equiv of cyclohexanone and solvent (0.5 M). Method B: 2 equiv of cyclohexanone and solvent (0.2 M). [d] 5 equiv of cyclohexanone was used.

To illustrate the scope of this methodology, different 4-substituted cyclohexanones were tested under the optimized conditions (Table 3). A number of aliphatic and aromatic functional groups with different electronic properties were

Table 4. Scope of Amino Benzaldehydes[a]



2 3 11

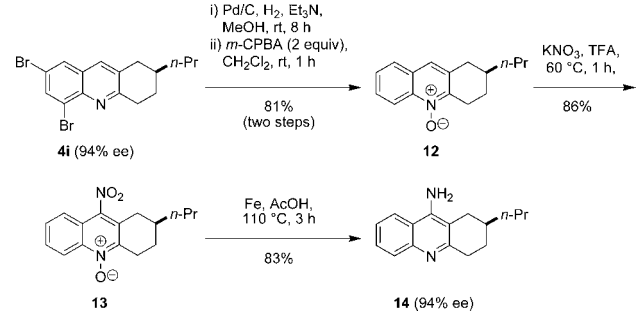
entry	R	R′	product	method[c]	yield (%)[b]	ee (%)
1[d]	*n*-Pr	H	**11a**	A	62	87
2[d]	Ph	H	**11b**	B	60	87
3[d]	*n*-Pr	4-Cl	**11c**	A	73	87
4[d]	Ph	4-Cl	**11d**	B	60	87
5	*n*-Pr	4-CF_3	**11e**	A	70	90
6	Ph	4-CF_3	**11f**	B	60	92
7	*n*-Pr	4-CO_2Me	**11g**	A	88	90
8	Ph	4-CO_2Me	**11h**	B	81	90
9	*n*-Pr	3,5-Cl_2	**11i**	A	77	93
10	Ph	3,5-Cl_2	**11j**	B	70	92

[a] Reactions were performed at −25 °C on a 0.5 mmol scale in anhydrous solvent for 72 h. The ee's were determined by HPLC analysis. [b] Isolated yields. [c] Method A: 5 equiv of cyclohexanones and solvent (0.2 M). Method B: 2 equiv of cyclohexanones and solvent (0.5 M). [d] Reactions were performed at −5 °C.

readily accommodated. Generally, quinoline products were obtained in good yields and with excellent levels of selectivity. As summarized in Table 4, a number of *o*-aminobenzaldehydes were evaluated in combination with 4-*n*-Pr- and 4-Ph-substituted cyclohexanones. Due to their attenuated reactivity, more electron-rich *o*-aminobenzaldehydes required slightly higher reaction temperatures. Satisfactory yields and ee's were obtained for these substrates.

With the chiral quinoline products in hand, a facile sequence was developed to access the corresponding tacrine analogues. Following the straightforward sequence outlined in Scheme 2, the highly enantioenriched tacrine derivative **14** was obtained in good yield and without loss of ee.

Scheme 2. Synthesis of an Enantioenriched Tacrine Analogue



In conclusion, we have reported the first catalytic enantioselective Friedländer reaction. Enamine catalysis allowed for the efficient desymmetrization of 4-substituted cyclohexanones in reactions with *o*-aminobenzaldehydes. Quinolines with remote stereogenic centers were obtained in generally good yields and with good to excellent levels of enantioselectivity. Furthermore, a chiral quinoline was converted into a highly enantioenriched tacrine derivative. Our discovery of interesting solvent effects, in particular the rate acceleration observed with pyridine, may have implications for other enamine-catalyzed reactions.

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Supporting Information Available: Experimental procedures, characterization data, and X-ray crystal structure of **4d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For instance, the reaction in dichloromethane (dielectric constant = 9.1) took substantially longer to go to completion as compared to the corresponding reaction in dioxane (dielectric constant = 2.2), while giving rise to a similar level of enantioselectivity.

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