Published in final edited form as:

J Am Chem Soc. 2006 November 8; 128(44): 14264–14265. doi:10.1021/ja0657859.

Kinetic Resolutions of Indolines by a Non-Enzymatic Acylation Catalyst

Forrest O. Arp and Gregory C. Fu

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

An indoline subunit that bears a stereocenter in the 2 position is found in a range of natural products,¹ as well as in an array of biologically active non-natural products.² Few catalytic processes have been reported that generate such indolines in highly enantioenriched form.³

One strategy for achieving this objective is the kinetic resolution⁴ of a racemic mixture of indolines. A number of enzyme-based methods for the resolution of amines via N-acylation have been described,⁵ although not for indolines. Progress in the development of *non*-enzymatic N-acylation catalysts for the kinetic resolution of amines has been extremely limited--not only have there been no reports of success with indolines, but only two effective methods have been described for amines of any type (certain primary amines⁶ and 2-oxazolidinones (Birman)⁷). In this communication, we establish that a chiral, non-enzymatic catalyst can achieve the kinetic resolution of a third family of amines, specifically, 2-substituted indolines (eq 1).

(1)

In an earlier study, we reported that planar-chiral PPY derivative **2** serves as a catalyst for the kinetic resolution of benzylic primary amines (eq 2; *s* = selectivity factor = (rate of fast-reacting enantiomer)/(rate of slow-reacting enantiomer)⁴).⁶ Disappointingly, when we applied these conditions to indolines, we observed no reaction even at 0 °C, due to the comparatively low nucleophilicity of the indoline.

(2)

Fortunately, after considerable effort we were able to develop a process by which a 2-substituted indoline can be kinetically resolved with good selectivity (Table 1). Under these conditions, as for those depicted in eq 2, the C_5Me_5 -substituted PPY derivative (**2**) is virtually inactive (entry 1).^{8,9} Fortunately, replacement of C_5Me_5 by C_5Ph_5 leads to a more effective acylation catalyst that can achieve the desired kinetic resolution with a useful selectivity factor (entry 2).

In a study of desymmetrizations of meso epoxides catalyzed by planar-chiral pyridine-*N*-oxides,¹⁰ we determined that increasing the steric demand of a C_5Ph_5 group of the catalyst via meta substitution¹¹ provided a more effective chiral environment,¹² as manifested by enhanced enantioselectivity. We attempted to exploit this strategy for the first time in the context of planar-chiral PPY derivatives, in order to enhance the efficiency of these kinetic resolutions of indolines. We were pleased to determine that the incorporation of methyl substituents in the meta positions of the phenyl rings does indeed lead to an improvement in the selectivity factor (entry 2 vs. entry 3). However, a further increase in the bulk of the “bottom” cyclopentadienyl ring (Me $\rightarrow$ Et) is not beneficial for stereoselection (entry 4).

On the basis of exploratory studies of kinetic resolutions of indolines by stoichiometric chiral reagents (e.g., higher *s* values when *N*-acylated **3** with a halide counterion¹³ was employed), we hypothesized that the addition of halide salts might be advantageous for selectivity.¹⁴ This has proved to be the case; in particular, the presence of LiBr/18-crown-6 leads to the highest *s* value that we have observed to date (entry 3). The use of smaller crown ethers results in lower selectivity (entries 5 and 6),¹⁵ as does the omission of 18-crown-6 (entry 7). Under otherwise identical conditions but in the absence of LiBr (entry 8) or in the presence of other halide sources (e.g., entries 9-11), the kinetic resolution proceeds with diminished efficiency.

By conducting the acylation at room temperature, the reaction time can be shortened,¹⁶ at the expense of a lower *s* value (entry 12). In the presence of commercially available acylating agents, essentially no selectivity (acetic anhydride, acetyl chloride, and methyl chloroformate) or no reactivity (vinyl acetate) is observed. Finally, Birman’s method, which is outstanding for the kinetic resolution of 2-oxazolidinones,⁷ is not effective for indolines (*s* < 1.1).

We have established that an array of 2-substituted indolines, including functionalized compounds, can be kinetically resolved with good selectivity factors under the optimized reaction conditions (Table 2, entries 1-4).¹⁷ Furthermore, 2,3-disubstituted indolines are suitable substrates (entries 5-9); as might be anticipated, the process is more efficient for the *cis* isomer than for the corresponding *trans* isomer (entry 7 vs. entry 8). It is worth noting that

2,3-disubstituted indolines cannot be accessed in high ee via the asymmetric hydrogenation of indoles.^{3a} Finally, substituents in the 5 position are tolerated (entries 9-11).^{18,19}

There are a number of features of this process that warrant future mechanistic investigation, such as the critical role played by LiBr and 18-crown-6. In addition, we are intrigued by the fact that catalyst **1**, but not **2**, is effective for the kinetic resolution of indolines, whereas **2**, but not **1**, is useful for the resolution of primary benzylic amines (eq 2). Through ¹H NMR studies, we have made the interesting observation that the resting state of the catalyst during indoline resolutions is the free catalyst, which contrasts with the process depicted in eq 2, for which the resting state is the N-acylated catalyst.^{6,20,21}

In conclusion, we have reported the first method, enzymatic or non-enzymatic, for the kinetic resolution of indolines through catalytic N-acylation. To improve the selectivity factor, we synthesized a new planar-chiral PPY derivative (**1**) wherein the chiral environment was tuned through the use of a more bulky cyclopentadienyl group. In light of the very limited success that has been described in the development of non-enzymatic acylation catalysts for the resolution of amines, we believe that our study represents an interesting step forward in addressing this difficult challenge. Future work will be directed at gaining an improved understanding of this process and applying that knowledge to the design of more versatile and efficient catalysts for the kinetic resolution of amines and related compounds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

We thank Luke Firmansjah and Dr. Peter Mueller for assistance with X-ray crystallography. Support has been provided by the NIH (National Institute of General Medical Sciences: R01-GM57034), Merck Research Laboratories, and Novartis. Funding for the MIT Department of Chemistry Instrumentation Facility has been furnished in part by NSF CHE-9808061 and NSF DBI-9729592.

References

- (1). For example, see: GueritteFFahyJCraggGMKingstonDGINewmanDJAnticancer Agents from Natural Products2005123135CRC PressBoca Raton, Florida
- (2). For leading references to drug candidates that bear a 2-methylindoline subunit, see: Nicolaou KC, Roecker AJ, Pfefferkorn JA, Cao G-Q. J. Am. Chem. Soc 2000;122:2966–2967.
- (3). (a) For example, see: Ruthenium catalyzed hydrogenation of N-protected indoles: Kuwano R, Sato K, Kurokawa T, Karube D, Ito Y. J. Am. Chem. Soc 2000;122:7614–7615. Kuwano R, Kashiwabara M, Sato K, Ito T, Kaneda K, Ito Y. Tetrahedron: Asymmetry 2006;17:521–535. Kuwano R, Kashiwabara M. Org. Lett 2006;8:2653–2655. [PubMed: 16737337] (b) Palladium-catalyzed cyclization of N-acyl anilines: Yip K-T, Yang M, Law K-L, Zhu N-Y, Yang D. J. Am. Chem. Soc 2006;128:3130–3131. [PubMed: 16522078] (c) Enzyme-catalyzed hydrolysis of racemic N-Boc-indoline-2-carboxylic esters: Kurokawa M, Sugai T. Bull. Chem. Soc. Jpn 2004;77:1021–1025.
- (4). (a) For reviews, see: Kagan HB, Fiaud JC. Top. Stereochem 1988;18:249–330. (b) Keith JM, Larrow JF, Jacobsen EN. Adv. Synth. Catal 2001;1:5–26. (c) Robinson DEJE, Bull SD. Tetrahedron: Asymmetry 2003;14:1407–1446. (d) Vedejs E, Jure M. Angew. Chem. Int. Ed 2005;44:3974–4001.
- (5). For examples and leading references, see: van Rantwijk F, Sheldon RA. Tetrahedron 2004;60:501–519.
- (6). Arai S, Bellemin-Laponnaz S, Fu GC. Angew. Chem., Int. Ed 2001;40:234–236.
- (7). Birman VB, Jiang H, Li X, Guo L, Uffman EW. J. Am. Chem. Soc 2006;128:6536–6537. [PubMed: 16704235]
- (8). A preliminary study suggests that, when catalyst **2** is N-acetylated, it is a poor electrophile for an indoline.

- (9). In the absence of a catalyst, <1% acetylation is observed.
- (10). Tao B, Lo MM-C, Fu GC. J. Am. Chem. Soc 2001;123:353–354. [PubMed: 11456531]
- (11). Pentaarylcyclopentadienes (C_5Ar_5H) can be synthesized from Ar-Br in a single step: Dyker G, Heiermann J, Miura M, Inoh J-I, Pivsa-Art S, Satoh T, Nomura M. Chem. Eur. J 2000;6:3426–3433.
- (12). For a discussion of catalyst design, see: Fu GC. Acc. Chem. Res 2000;33:412–420. [PubMed: 10891059]
- (13). For an earlier study of kinetic resolutions of 1-phenylethylamine by such stoichiometric chiral acylating agents, see: Ie Y, Fu GC. Chem. Commun 2000:119–120.
- (14). Mioskowski and Wagner have reported a spectacular salt effect (*n*-Oct₃NMeCl) for N-acetylations of racemic 1-phenylethylamine by a stoichiometric chiral acylating agent: Arseniyadis S, Subhash PV, Valleix A, Mathew SP, Blackmond DG, Wagner A, Mioskowski C. J. Am. Chem. Soc 2005;127:6138–6139. [PubMed: 15853296]
- (15). For an interesting compilation of log K_a values for various crown ethers and alkali-metal cations, see: AnslynEVDoughertyDAModern Physical Organic Chemistry2006227University Science BooksSausalito, CA See also: Izatt RM, Pawlak K, Bradshaw JS. Chem. Rev 1991;91:1721–2085.
- (16). Clearly, long reaction times are not ideal. On the other hand, this kinetic-resolution method avoids protection/deprotection of the indole, which is necessary for the most general alternative approach to the catalytic synthesis of enantioenriched indolines (Reference 3a).
- (17). Acylation of 2-isopropylindoline proceeds extremely slowly and with moderate selectivity ($s \sim 8$). Initial studies indicate that, if the 2-substituent is sp^2 -hybridized, low selectivity is observed.
- (18). (a) However, an indoline that bears two electronegative fluorine substituents (4,5-difluoro-2-methylindoline) reacts very slowly and with moderate selectivity ($s \sim 7$). (b) Catalyst **1** can be recovered in good yield (>80%).
- (19). We have been able to achieve the kinetic resolution of a 2-substituted pyrrolidine with $s \sim 4$. To the best of our knowledge, this is the first example of a kinetic resolution of a *dialkyl*amine with promising selectivity by a non-enzymatic acylation catalyst.
- (20). (a) Preliminary studies of the dependence of the selectivity factor on the catalyst ee provide no evidence for the presence of species that contain more than one catalyst molecule. Johnson DW Jr. Singleton DA. J. Am. Chem. Soc 1999;121:9307–9312. (b) KaganHBLuukasTOJacobsenENPfaltzAYamamotoHComprehensive Asymmetric Catalysis1999SpringerNew YorkChapter 4.1.
- (21). This may be a consequence of the enhanced acidity of the N-bound proton of an indoline, relative to a primary benzylic amine.

Table 1

Effect of Reaction Parameters on the Efficiency of the Kinetic Resolution of 2-Methylindoline

entry	change from the optimized conditions	% conversion	s
1	(+)-2 instead of (+)-1	4	<2
2	(+)-3 instead of (+)-1	48	10
3	none	54	23
4	(+)-4 instead of (+)-1	58	19
5	15-crown-5 instead of 18-crown-6	54	20
6	12-crown-4 instead of 18-crown-6	43	3
7	no 18-crown-6	16	6
8	no LiBr	55	<2
9	Bu Bu ₄ NBr instead of LiBr/18-crown-6	49	2
10	NBr LiCl instead of LiBr	43	14
11	LiI instead of LiBr	12	12
12	r.t. instead of 0 °C (2 days)	49	11

All data are the average of two runs.

Table 2

Kinetic Resolutions of Indolines

entry	indoline	s	ee of resolved indoline
1	R = Me	25	94% ee (55% conversion)
2	R = <i>n</i> -Pr	26	90% ee (53% conversion)
3	R = $\text{CH}_2\text{CH}_2\text{Ph}$	18	98% ee (60% conversion)
4	R = CH_2OTBS	14	90% ee (56% conversion)
5	R = CH_2OTBS	9.8	91% ee (64% conversion)
6	R = $(\text{CH}_2)_n$, $n = 1, 2$	31	91% ee (51% conversion)
7	R = Me, cis	18	91% ee (55% conversion)
8	R = Me, trans	9.5	94% ee (64% conversion)
9	R = Me, CO_2Et	19	95% ee (58% conversion)
10	R = Me, X = OMe	13	92% ee (60% conversion)
11	R = Me, X = Br	11	90% ee (60% conversion)

The selectivity factor is the average of two runs. The ee and percent conversion are for a particular run.