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by

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# Catalytic Enantioselective Addition of Indoles to Activated *N*-Benzyl Pyridinium Salts: Nucleophilic Dearomatization of Pyridines with Unusual C-4 Regioselectivity

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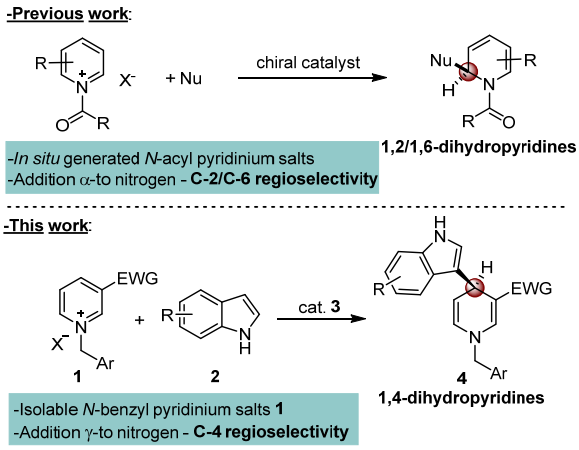
**ABSTRACT:** The catalytic enantioselective dearomatization of pyridines with nucleophiles represents a direct and convenient access to highly valuable dihydropyridines. Available methods, mostly based on *N*-acyl pyridinium salts, give addition to the C-2/C-6 of the pyridine nucleus rendering 1,2-/1,6-dihydropyridines. Herein, we present an alternative approach to this type of dearomatization reaction, employing activated *N*-benzyl pyridinium salts in combination with a bifunctional organic catalyst. Optically active 1,4-dihydropyridines resulting from the addition of the nucleophile (indole) to the C-4 of the pyridine nucleus are obtained as major products, rendering this method for nucleophilic dearomatization of pyridines complementary to previous approaches.

**KEYWORDS**: *asymmetric catalysis, dearomatization, indole, organocatalysis, pyridines*

Enantioselective dearomatization of pyridines represents a convenient access to highly valuable dihydropyridine and piperidine scaffolds. Besides reductions,[1] available methodologies include mainly nucleophilic dearomatizations[2] relying on stoichiometric chiral auxiliaries or transition metal catalyzed reactions.[3] Various organometallic catalysts were demonstrated to be able to induce stereoselectivity in the addition of different nucleophiles (cyanide,[4] alkynes,[5] alkyl/arylzinc)[6] to the C-2/C-6 of *N*-acyl activated pyridinium ions (Scheme 1, top). A recent report[7] introduced organocatalysis, and in more detail anion binding by multiple hydrogen bond donors,[8] as a suitable approach to this kind of reaction, using a silylketeneacetal as nucleophilic partner. Variable C-2 or C-4 selectivities, depending on the substitution pattern at the pyridine ring, were observed.[7] Previous asymmetric organocatalytic examples were all limited to less demanding dearomatization of *N*-acyl quinolinium and isoquinolinium substrates.[9]

We envisioned that *N*-alkyl pyridinium salts **1**, more stable and easy to handle compared to their *N*-acyl analogues, may provide an alternative platform with unforeseen opportunities in catalytic enantioselective nucleophilic dearomatization of pyridines. *N*-alkyl pyridinium salts bearing an electron-withdrawing group at C-3, to render more electrophilic the pyridine nucleus and to stabilize the dihydropyridine adducts, have been widely applied in alkaloid synthesis (i.e. the "Wenkert procedure").[3,10] However, only one catalytic asymmetric reaction with these substrates – a C-6 selective [Rh]-catalyzed addition of aryl and alkenyl boronic acids to *N*-benzyl nicotinates – has been reported to date.[11,12] Herein, we present an asymmetric nucleophilic dearomatization of *N*-benzyl pyridinium salts **1**, using indoles **2** as nucleophiles (Scheme 1, bottom).[13] A key feature of this organocatalytic reaction is the formation of the 1,4-dihydropyridine regioisomers **4** as the major products, thus providing a new platform for nucleophilic pyridine dearomatization reactions complementary in several aspects to existing methodologies.[4-7]

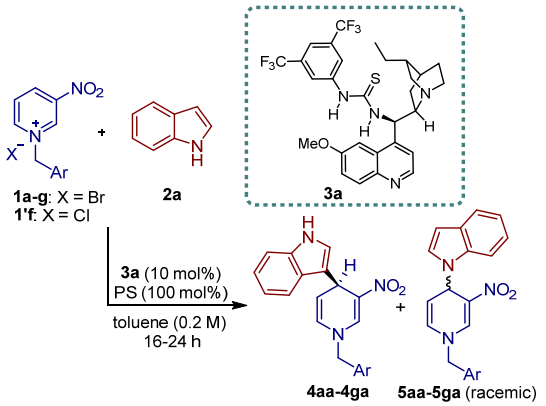



**Scheme 1** Catalytic asymmetric dearomatization of pyridines.

Our initial plan involved a reactivity enhancement of pyridinium salts **1** by drifting apart the tightly bound halide counterion. Exploiting the low solubility of salts **1** in apolar organic solvents, an inverted phase-transfer catalytic approach[8b] was first attempted, followed by an anion binding activation strategy using typical Jacobsen-type thioureas.[8a,i-m] Whereas these approaches failed (see the Supporting Information), further experiments demonstrated that catalysts bearing tertiary amine basic moieties could promote the C-4 selective addition of indole **2a** to *N*-benzyl

3-nitropyridinium bromide **1a**, affording the 1,4-dihydropyridine product **4aa** in enantioenriched form. A screening (see Supporting Information) of basic catalysts and auxiliary bases, to neutralize the HBr formed in the reaction, led to the identification of the conditions outlined in Table 1, entry 1 as a promising hit result. In more detail, a catalyst such as **3a**, bearing not only a basic tertiary amine moiety, but also an acidic thiourea group,[14] and a stoichiometric amounts of the "thermodynamic"[15] base 1,8-bis(dimethylamino)naphthalene (proton sponge, PS), were required to achieve both good conversion and enantioselectivity in the reaction. In all these preliminary screening experiments, adduct **4** was accompanied by substantial amounts of the indole *N*-alkylation product **5**, as a racemate in all cases. Further optimization showed that lowering the reaction temperature gave better enantioselectivity in **4**, without giving a great detriment in conversion (entries 1-3). The **4**/**5** ratio was also slightly improved. Variations in the aryl ring of the *N*-benzyl substituent were then explored. Substrates **1b-e** bearing electron-withdrawing groups (**1b**, entry 4 and **1c**, entry 5) and additional aromatic rings (**1d**, entry 6 and **1e**, entry 7) gave lower enantioselectivities, compared to the unsubstituted substrate **1a** (entry 3), accompanied by variable conversions. In contrast, an electron-donating methoxy substituent (**1f**, entry 8) incremented slightly the enantioselectivity. Interestingly, the reaction outcome worsened considerably when employing the pyridinium salt **1'f**, bearing chloride, instead of bromide, as the counterion (entry 9, compare with entry 8). We were instead pleased to find that a bulky substituent, such as *t*-Bu (**1g**), gave a remarkable improvement in both reactivity and enantioselectivity, along with a promising selectivity for product **4ga** vs **5ga** (entry 10). This positive result may be rationalized taking into account the sandwich-like structure of substrates **1**, inferred from the X-ray structure of related *N*-benzyl pyridinium salts,[16] in which the halide is fitted between the two aromatic rings. A bulky (and electron-rich) substituent may open this structure rendering the bromide anion more available for thiourea coordination (vide infra). Finally, we found that the undesired isomer **5** is apparently generated as a background PS-promoted process. Thus, we envisioned that a controlled addition of this auxiliary base would have resulted in a selectivity improvement. Indeed, when PS was added portion-wise over 10 hours, a good 91:9 ratio in favor of the desired product **4ga**, along with a satisfactory 91% ee, was achieved (entry 11).

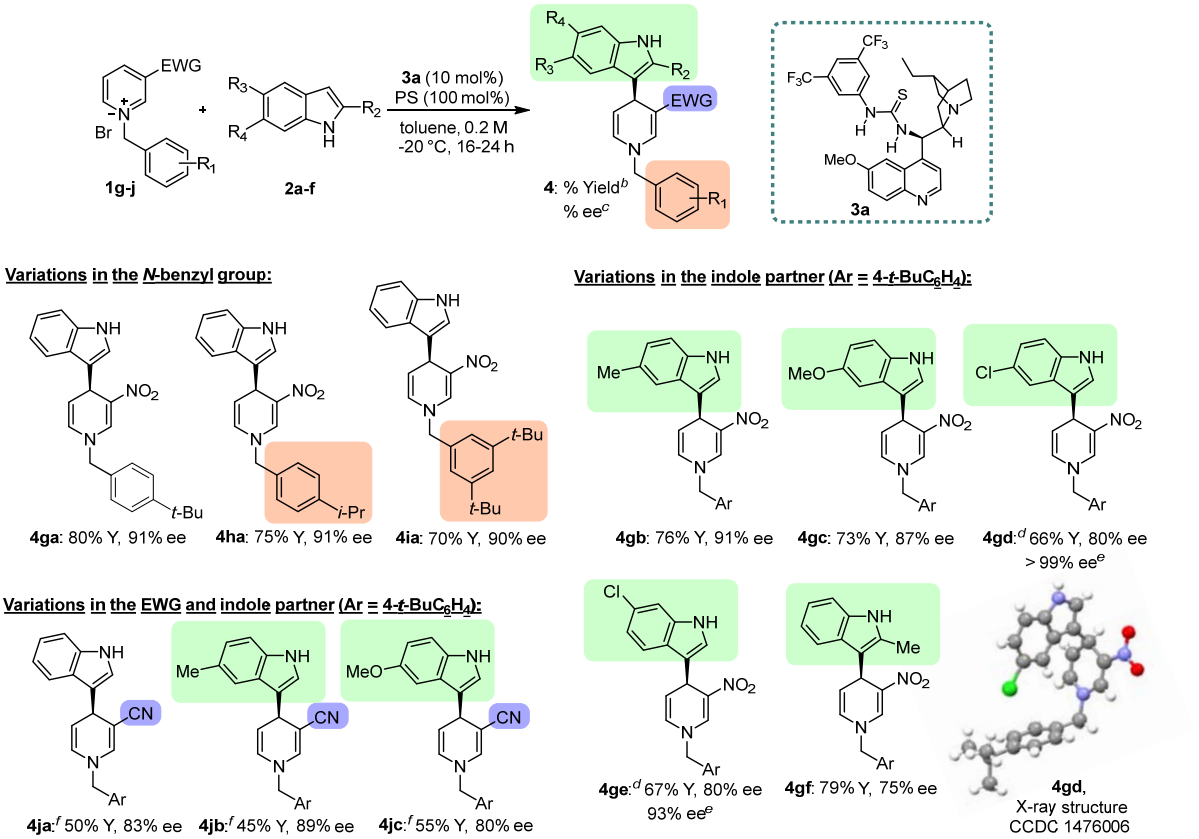
**Table 1.** Representative optimization results.[a]




| Entry | T [°C] | **1a-g**, Ar | Conv. (%)[b,c] | **4**/**5**[b] | ee (%)[d] |
|---|---|---|---|---|---|
| 1 | RT | **1a**, Ph | 60 | 55:45 | 68 |
| 2 | 0 | **1a**, Ph | 50 | 55:45 | 75 |
| 3 | -20 | **1a**, Ph | 50 | 70:30 | 75 |
| 4 | -20 | **1b**, 4-$BrC_6H_4$ | 52 | 80:20 | 70 |
| 5 | -20 | **1c**, 3,5-$(CF_3)_2C_6H_4$ | 89 | 71:29 | 63 |
| 6 | -20 | **1d**, 2-naphtyl | 51 | 88:12 | 67 |
| 7 | -20 | **1e**, 4-$PhC_6H_4$ | 13 | 95:5 | 45 |
| 8 | -20 | **1f**, 4-$MeOC_6H_4$ | 52 | 82:18 | 82 |
| 9 | -20 | **1'f**, 4-$MeOC_6H_4$ | 31 | 76:24 | 58 |
| 10 | -20 | **1g**, 4-*t*-$BuC_6H_4$ | 88 | 71:29 | 87 |
| 11[e] | -20 | **1g**, 4-*t*-$BuC_6H_4$ | 92 | 91:9 | 91 |

[a] Reaction conditions: salts **1a-g** or **1'f** (0.05 mmol), indole **2a** (0.065 mmol), **3a** (10 mol%), PS (0.05 mmol), toluene (250 μL), 16-24 h. [b] Overall conversion in products **4** and **5**. [c] Determined on the crude mixture by $^1$H NMR. [d] ee of products **4**, determined by CSP HPLC. [e] 0.2 equiv. of PS were added every 2 h: overall 1 equiv. in 10 h.

Having identified reaction conditions and substrate requirements for optimal results, the reaction scope was investigated (Scheme 2). Variation of the bulky substituent in the *N*-benzyl moiety afforded dearomatized products **4ha** and **4ia** in similar yields (75-70%) and enantioselectivities (91-90%) to adduct **4ga**. Variation at the indole **2** reaction partner showed that methyl and methoxy substituents at the 5-position were well tolerated (**4gb** and **4gc** 73-76% yield and 91-87% ee). Indoles **2d,e** bearing an electron withdrawing group (Cl) at 5- and 6- positions afforded the desired adducts **4gd** and **4ge** with moderate enantiomeric excess (80% ee). Their lower reactivity required 15 mol% catalyst **3a** and a reaction temperature of 0 °C to afford satisfactory yields (66-67%). Crystallization of compound **4gd** afforded enantiopure single crystals which, upon X-ray analysis,[17] provided the absolute configuration S at the C-4-stereocenter, extended by analogy to all other compounds **4**. Also the more challenging 2-methylindole **2f** was a suitable nucleophile, affording product **4gf** in good yield (79%) and a moderate ee value of 75%.[18]

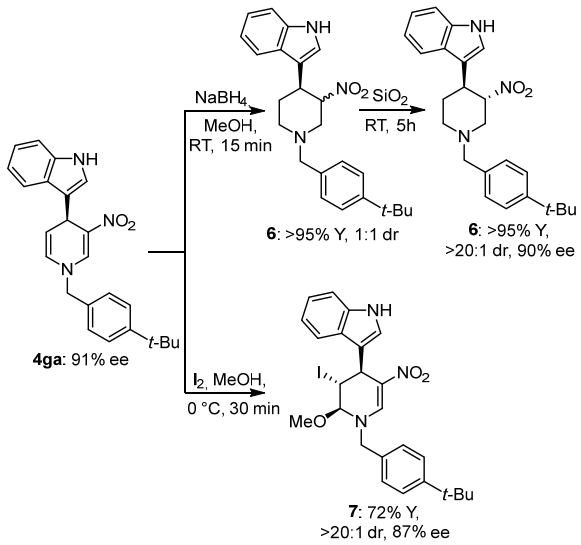



**Scheme 2**. Scope of the reaction.[a]

[a] Conditions: **1g-j** (0.15 mmol), **2a-f** (0.195 mmol), **3a** (10 mol%), toluene (750 µL), -20 °C. Reaction was set up without PS, then 0.2 equiv. (0.03 mmol) of PS were added every 2 h: overall 1 equiv. [b] Yields of isolated products **4**. [c] ee determined by CSP HPLC. [d] Reaction performed at 0 °C with 15 mol% **3a**. [e] After one crystallization. [f] Reaction performed at RT with 15 mol% **3a**.

We then explored the possibility of changing the EWG at the C-3 of pyridinium salts **1**. While 3-acetyl and 3-methoxycarbonyl derivatives did not show sufficient reactivity, we were pleased to find that compound **1j** bearing a cyano group was a competent substrate for the present nucleophilic dearomatization. Although its lower reactivity compared to **1g-i** forced us to increase the reaction temperature and the catalyst loading (15 mol%), dihydropyridines **4ja-jc** were obtained with useful results (45-55% yield, 80-89% ee) in the reactions with indoles **2a-c**. Possibly due to the higher temperature, the isomeric ratios **4**/**5** of these reactions were found to be lower than in the previous examples (see Supporting Information) accounting for the lower yields obtained with this less activated substrate **4j**.

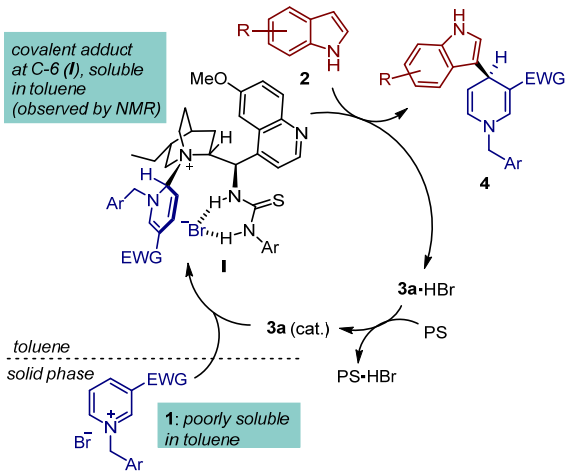
The 1,4-dihydripyridines **4** bear two enamine-type double bonds amenable to various synthetic manipulations (Scheme 3). For example, treatment of **4ga** with excess NaBH4 in methanol afforded piperidine **6** as an equimolar mixture of epimers at C-3, which, upon adsorption and standing on silica, converted to the more stable 3,4-*trans*-diastereoisomer in quantitative yield with retainment of the enantiomeric excess. On the other hand, exposure of **4ga** to an oxidative functionalization with I2 in methanol[19] afforded the highly substituted tetrahydropyridine **7** as a single diastereoisomer, in 72% yield and 87% ee.




**Scheme 3**. Synthetic elaborations on 1,4-dihydropyridine **4ga**.

Several control experiments (see the Supporting Information) were carried out to gain insights about the pathway followed by this transformation. $^{1}$H and $^{13}$C NMR studies pointed to the extraction of the insoluble pyridinium salt **1** in the apolar reaction medium through formation of

the covalent adduct **I** with the catalyst, resulting from the addition of the tertiary amine to the C-6 of the pyridinium ring (Scheme 4).[20] Assistance of the thiourea moiety, through coordination of the bromide, could also be inferred. Although in substrates **1** the C-6 position can be considered the most reactive, while C-4 products are thermodynamically favored,[21] the nature of the nucleophilic species and the reaction conditions can heavily influence the regioselectivity of the reaction.[3,10,13] In the present case, the C-6 adduct with the catalyst (**I**) is favoured both kinetically and thermodynamically. In contrast, the addition of indole **2** occurs at C-4, plausibly through a two-step SN2'-like[22] pathway from adduct **I**.[23] Subsequent rearomatization of the indole nucleus leads to products **4** and to protonated (i.e. inactive) catalyst **3a**. PS scavenges HBr ensuring catalyst turnover. However, this base is also able to promote the slow *N*-alkylation of indoles with substrates **1**, rendering isomers **5** in racemic form.[24] Its controlled addition is thus required to achieve good selectivity and yields in the catalytic reactions.




**Scheme 4**. Proposed reaction pathway.

To summarize, we have developed a catalytic asymmetric dearomatization reaction of activated *N*-benzyl pyridinium bromides **1** with indoles **2** as nucleophile partners. The 1,4-dihydropyridine adducts **4** were obtained with good results in terms of yields and enantioselectivities. A peculiar feature of the present reaction is the addition of the nucleophile to the C-4 of the pyridine. This regioselectivity is unusual in catalytic enantioselective nucleophilic pyridine dearomatization reactions, rendering this approach complementary to previous methodologies. Current efforts in our laboratory are directed at exploring *N*-benzyl pyridinium salts **1** as a useful synthetic platform for the preparation of different 1,4-dihydropyridines, employing different nucleophilic reaction partners and catalytic approaches.

## ASSOCIATED CONTENT

**Supporting Information**. Additional optimization results, control experiments, experimental details, copies of NMR spectra and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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## ABBREVIATIONS

CSP, chiral stationary phase; PS, proton sponge; EWG, electron withdrawing group.

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(17) CCDC 1476006 contains the crystallographic data of **4gd**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

(18) Indoles bearing substituents at other positions were tested, without giving useful results: 3-methyl indole gave exclusively the *N*-alkylation product (**5**); *N*-methylindole afforded only a small amount (<15%) of the expected adduct, and in racemic form.

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(23) For additional discussion, including a tentative rationalization of the poor performance of *N*-methylindole in this reaction,[18] see the Supporting Information.

(24) This *N*-alkylation promoted by PS might proceed at the more reactive C-6 of **1** first, followed by slow conversion to more stable C-4 products **5** (see ref.[21]). Although we were unable to isolate this hypothetical C-6 adduct, possibly due to its poor stability, $^{1}$H NMR analysis of crude mixtures of uncatalyzed reactions performed with PS showed signals (ca. 20-30% compared to the signals of **5**) compatible with its structure.