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Giulio Bertuzzi, Alessandro Sinisi, Lorenzo Caruana, Andrea Mazzanti, Mariafrancesca Fochi,* and Luca Bernardi**

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

Giulio Bertuzzi, Alessandro Sinisi, Lorenzo Caruana,* Andrea Mazzanti, Mariafrancesca Fochi,* and Luca Bernardi*

Department of Industrial Chemistry "Toso Montanari" and INSTM RU Bologna, Alma Mater Studiorum - University of Bologna, V. Risorgimento 4, 40136 Bologna (Italy).

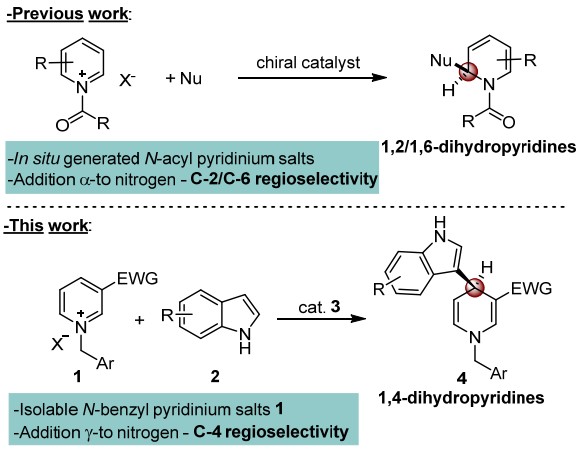
ABSTRACT: The catalytic enantioselective dearomatization of pyridines with nucleophiles represents a direct and convenient access to highly valuable dihydropyridines. Available methods, mostly based on *N*-acyl pyridinium salts, give addition to the C-2/C-6 of the pyridine nucleus rendering 1,2-/1,6-dihydropyridines. 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]

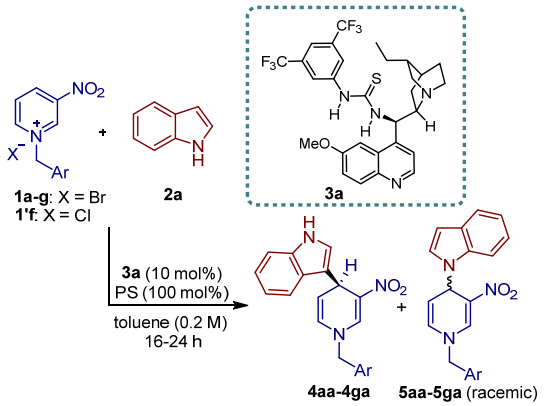


Scheme 1 Catalytic asymmetric dearomatization of pyridines.

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).

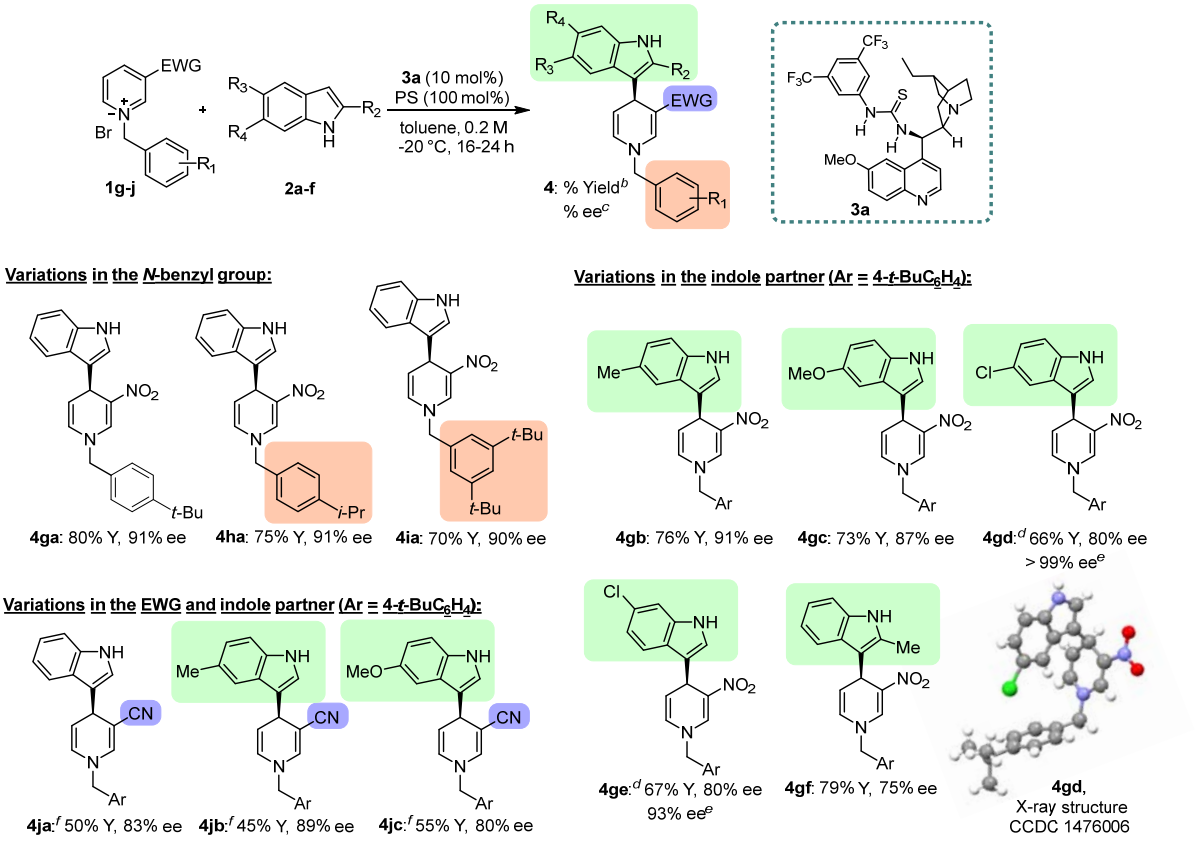
Table 1. Representative optimization results.[a]



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]

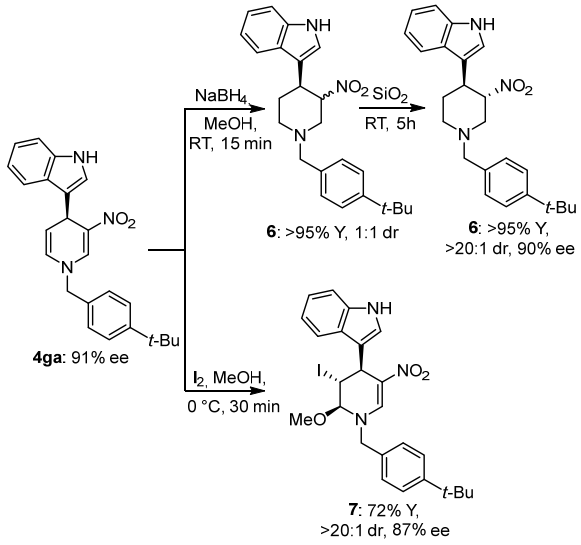


Scheme 2. Scope of the reaction.[a]

[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**.

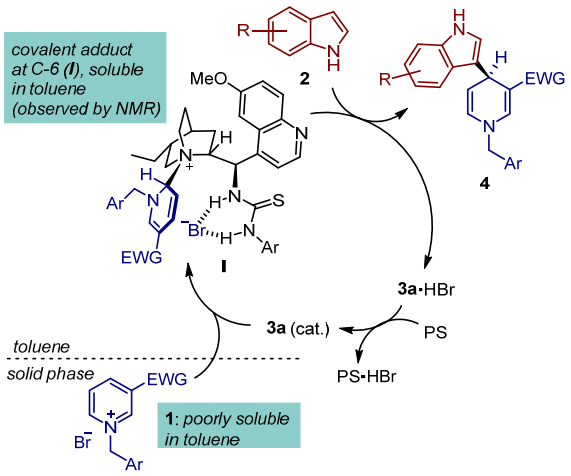
The 1,4-dihydripyridines **4** bear two enamine-type double bonds amenable to various synthetic manipulations (Scheme 3). For example, treatment of **4ga** with excess NaBH4 in methanol afforded piperidine **6** as an equimolar mixture of epimers at C-3, which, upon adsorption and standing on silica, 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.

AUTHOR INFORMATION

Corresponding Author

* E-mail: lorenzo.caruana2@unibo.it; mariafrancesca.fochi@unibo.it; luca.bernardi2@unibo.it

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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(20) While adduct **I** of catalyst **3a** with pyridinium **1g** was clearly observed by ^{1}H NMR, its regiochemistry was inferred from the simpler ^{1}H and ^{13}C NMR spectra of the corresponding quinuclidine-**1g** adduct. Quinuclidine and **3a** showed comparable reactivity and regioselectivity as reaction promoters.

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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.