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Nucleophilic Dearomatization of Pyridines under Enamine Catalysis: Regio-, Diastereo-, and Enantioselective Addition of Aldehydes to Activated *N*-Alkylpyridinium Salts

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Supporting Information

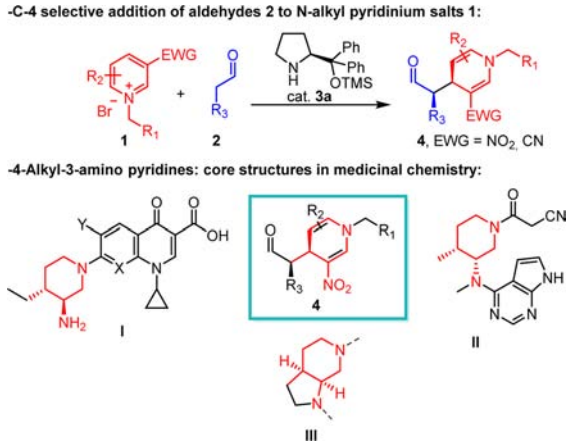
ABSTRACT: Catalytic addition of chiral enamines to azinium salts is a powerful tool for the synthesis of enantioenriched heterocycles. An unprecedented asymmetric dearomative addition of aldehydes to activated *N*-alkylpyridinium salts is presented. The process exhibits complete C-4 regioselectivity along with high levels of diastereo- and enantiocontrol, achieving a high-yielding synthesis of a broad range of optically active 1,4-dihydropyridines. Moreover, the presented methodology enables the synthesis of functionalized octahydropyrrolo[2,3-*c*]pyridines, the core structure of anticancer peptidomimetics.

Catalytic asymmetric dearomatizing addition[1] of aldehydes to azinium cations, proceeding via enamine activation, is a powerful tool for the synthesis of enantioenriched nitrogen-containing heterocycles. After an intramolecular dearomatization of *N*-alkylisoquinolinium salts, reported by Jørgensen in 2005,[2] in 2014 Cozzi and co-workers disclosed an intermolecular version, exploiting more activated *N*-acyl substrates.[3] More recently, quinolinium salts have been employed in this type of reaction with four nearly simultaneous contributions by Pineschi, Rueping, Liu, Gualandi, and Cozzi.[4] Pyridinium cations,[5] more challenging substrates for dearomatization processes,[6,7] have not been employed so far in catalytic dearomative addition of aldehydes.

N-Alkylpyridium salts **1**, substituted at the 3-position by an EWG, are bench-stable solids, readily prepared from the corresponding pyridines.[8] The EWG activates the pyridine nucleus for nucleophilic additions and stabilizes the dihydropyridine adduct. Addition occurs at C-4 or C-6, depending on the nucleophile type and reaction conditions. These compounds have been largely employed in diastereoselective alkaloid syntheses;[5,8] however, their engagement in catalytic enantioselective reactions is limited to a rhodium-catalyzed C-6 selective addition of aryl boronic acids reported in 2011[6g] and to our very recent disclosure of a C-4 selective indole addition.[7b] Herein, we present an asymmetric addition of aldehydes **2** to pyridinium salts **1**, catalyzed by secondary amine **3a**[9] (Scheme 1), furnishing highly enantioenriched 1,4-dihydropyridines **4**.

The presence of a 3-nitro group in some products **4**, combined with full C-4 regioselectivity, renders this process useful to give precursors of 4-alkyl-3-aminopiperidines.[10] These scaffolds are common in medicinally relevant compounds, as exemplified in Scheme 1 for piperidine quinolones **I**, a class of antibacterial agents,[11] and tofacitinib **II**, a potent Janus Kinase inhibitor

Scheme 1. Dearomatization of Pyridinium Salts 1 under Enamine Catalysis



commercialized as Xeljanz and Jakvinus for the treatment of rheumatoid arthritis.[12] Furthermore, the aldehyde and nitro functions in products **4** can be exploited for further manipulations. For example, cyclization processes render synthetically challenging bicyclic motives related to octahydropyrrolo[2,3-*c*]pyridines **III**, core structures of anticancer peptidomimetics.[13]

Initially, we treated pyridinium salt **1a** with 2 equiv of 3-phenylpropionaldehyde **2a** in the presence of 20 mol % of catalyst **3a** and 1 equiv of TEA (Et_3N) as stoichiometric base (HBr is formed as the reaction proceeds) in DCM for 6 h.

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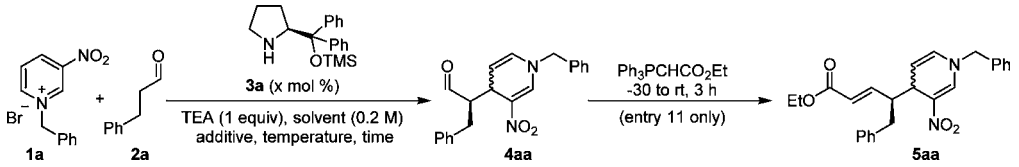
Table 1. Representative Optimization Results[a]



entry	solvent	temp (°C)	time (min)	**3a** (mol %)	additive[b]	conv[c,d] (%)	dr (*syn*:*anti*)[c]	ee *syn*/ee *anti*[e] (%)
1	DCM	rt	360	20	none	>95	50:50	*rac*/*rac*
2	DCM	rt	10	20	none	>95	75:25	6/60
3	DCM	−30	35	20	none	60	86:14	40/40
4	DCM	−60	90	20	none	>95	90:10	35/45
5	PhMe	−30	60	20	none	>95	92:8	92/94
6	PhMe	−30	120	20	none	>95	86:14	73/76
7	PhMe	−30	60	20	$PhCH_2CO_2H$	83	92:8	96/91
8	PhMe	−30	60	10	$PhCH_2CO_2H$	>95	91:9	92/89
9	PhMe	−30	150	10	$PhCH_2CO_2H$	>95	88:12	90/87
10	PhMe	−30	60	5	$PhCH_2CO_2H$	41	88:12	37/60
11[f]	PhMe	−30	60	10	$PhCH_2CO_2H$	86[g] (80)[h]	93:7 (>95:5[i])	99/-[j]

[a]Reaction conditions: **1a** (0.05 mmol), **2a** (0.1 mmol), TEA (0.05 mmol), **3a** (0.01 or 0.005 or 0.0025 mmol), solvent (250 μL). [b]Equimolar with **3a**. [c]Determined on the crude mixture by ^{1}H NMR. [d]Overall conversion in the two diastereoisomers. [e]Enantiomeric excess of crude **4aa** determined by CSP HPLC. [f]Reaction conditions as before, then Ph_3PCHCO_2Et (0.6 mmol), −30 °C to rt, 3 h. [g]Isolated yield of product **5aa** after column chromatography. [h]Isolated yield on a 1.0 mmol scale. [i]Diastereomeric ratio of isolated **5aa**. [j]Enantiomeric excess of isolated **5aa**.

Although the process proved to be feasible (complete conversion), no diastereo- or enantioselectivity was observed (Table 1, entry 1). Since the reaction seemed to be almost instantaneous, we tried to reduce considerably the reaction time and the temperature, as post addition epimerization can be a considerable issue in chiral enamine-catalyzed α-alkylation of aldehydes (entries 2−4).[14] The diastereomeric ratio increased considerably, but the maximum value of enantiomeric excess (40% ee for *syn*-**4aa**), observed at −30 °C, remained unsatisfactory. Gratifyingly, upon changing the reaction solvent from DCM to toluene, very good values of diastereoselectivity (92:8) and enantioselectivity (92% ee for *syn*-**4aa**) were reached for the first time (entry 5). At this point, many different auxiliary bases were tested, giving similar or worse results compared to TEA, which was thus confirmed as optimal (see the SI for more detailed data). However, at this stage of optimization, the reaction protocol did not prove to be robust enough, as, for example, simply increasing the reaction time from 1 to 2 h led to significant erosion in both diastereo- and enantioselectivity values (compare entry 6 with entry 5). We then found that an acidic co-catalyst (phenylacetic acid, equimolar with **3a**) led to better results in terms of enantiocontrol (92:8 dr, 96% ee for *syn*-**4aa**, entry 7) and that lowering the catalyst loading to 10 mol % led only to slightly inferior results (91:9 dr, 92% ee for *syn*-**4aa**, entry 8). The process, run under these latter conditions, proved to be much more robust than before: upon prolonging the reaction time to 2.5 h only a very small detriment in the enantiomeric excess and the diastereomeric ratio (88:12 dr, 90% ee for *syn*-**4aa**) was observed (compare entries 8 and 9 with entries 5 and 6). For a tentative rationalization of the role of the acid, see the SI. On the other hand, by further diminishing the catalyst loading to 5 mol %, all of the results dropped considerably (entry 10). We therefore chose 10 mol % as the best value (for an additional catalyst screening, see the SI). Finally, to avoid small deviations from the primary outcomes of the reaction during isolation, due to the instability of product **4aa**, we chose to transform the aldehyde group into a less labile α,β-unsaturated ester by Wittig reaction. Product **5aa** proved thus to be stable enough for column chromatography and was isolated as a single diastereoisomer in 86% yield (80% on a 1.0 mmol scale) and 99% ee (entry 11).

Having optimized the parameters required for optimal results, we sought to verify the reaction scope. Besides 3-phenylpropanal **2a**, a variety of aldehydes were successfully employed in the present dearomatization (Scheme 2). Short- (*n*-butanal **2b**), medium- (*n*-hexanal **2c**), and long-chained (*n*-dodecanal **2d**) linear aldehydes along with 4-methylpentanal **2e** and 3-cyclohexylpropanal **2f** furnished in good yields (65%−89%) and very good enantiomeric excesses (96%−99% ee) the respective dearomatized products **5ab**−**af** isolated as single diastereoisomers. Isovaleraldehyde **2g** proved to be less reactive than the other aldehydes employed: the reaction temperature was therefore raised to 0 °C and the time prolonged to 2 h. Since in this case the Wittig reaction proved to be quite slow, product **6ga** was obtained through acetalization of the aldehyde group, in moderate yield (43%) but good enantiomeric excess (94%). Other aldehydes, bearing functional groups on the β-carbon, such as heterocycles (**2h**), aromatic polycycles (**2i**), and ethers (**2j**) could also be employed without loss of reaction efficiency or diastereo- and enantiocontrol.

Thereafter, we tested the possible changes on pyridinium partner **1** (Scheme 3). Since the nitrogen protecting group strongly influenced the reaction outcomes in our previous report,[7b] we thought that exploration of this moiety could be of some interest. Both an electron-poor (**1b**) and an electron-rich (**1c**) aromatic ring along with simple aliphatic chains (**1d**) were all suitable for the present process, giving products **5ba**−**da** with excellent results (82%−92% yield, 90%−99% ee). We next moved to salt **1e**, bearing a methyl substituent on the C-6 of the pyridinium ring. This is a particularly challenging substrate, given the observed tendency of this electrophile to undergo side reactions under the basic conditions required in this reaction.[15] Nevertheless, we were able to isolate product **5ea**, albeit in moderate yield (35%), as a single diastereoisomer and with excellent optical purity (98% ee). Substitution on the C-5 was also explored: products **5fa** and **5ga** were obtained in useful

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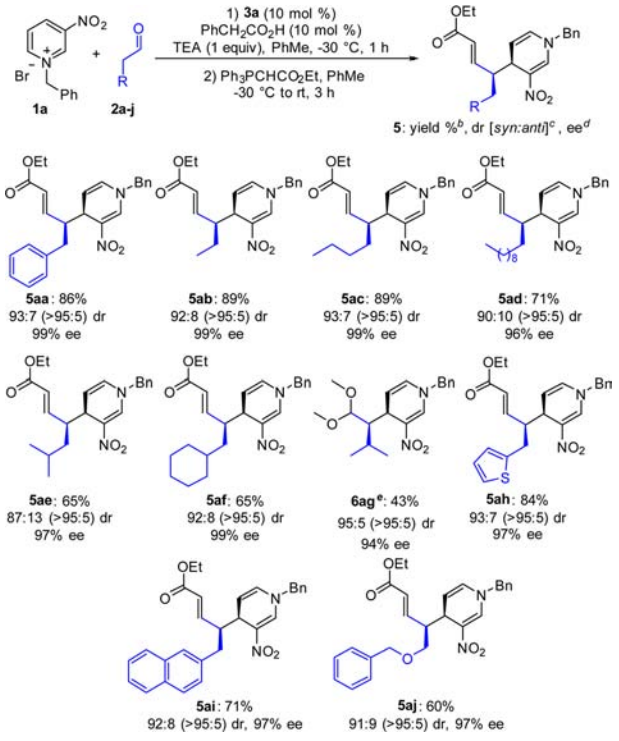
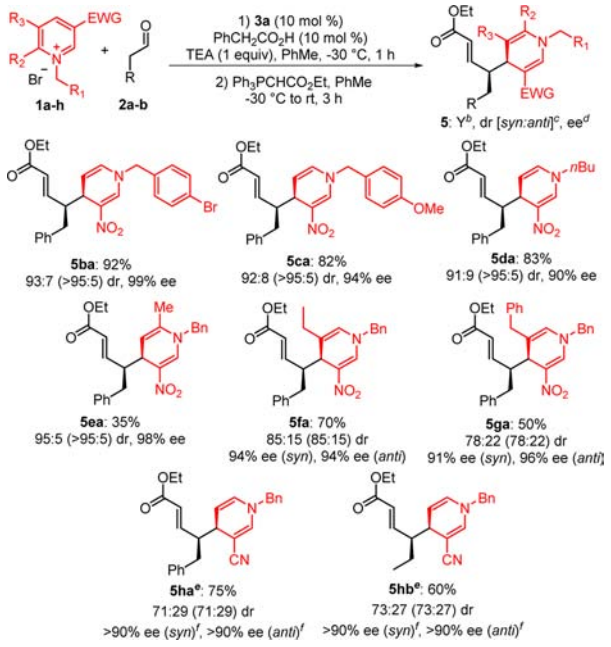
Scheme 2. Aldehyde 2 Substrate Scope[a]



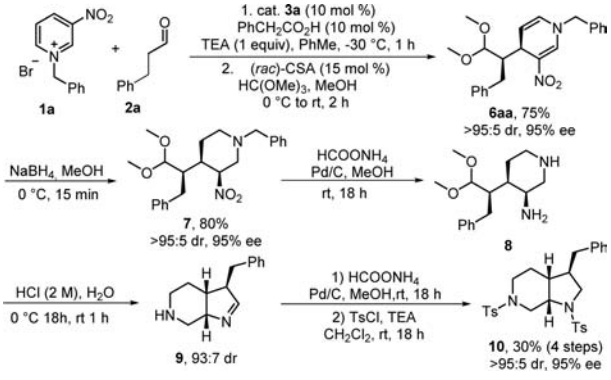
[a]Conditions: **1a** (0.1 mmol), **2** (0.2 mmol), **3a** (0.01 mmol), $PhCH_2CO_2H$ (0.01 mmol), TEA (0.1 mmol), PhMe (500 μL), −30 °C, 1 h; then Ph_3PCHCO_2Et (0.6 mmol), −30 °C to rt, 3 h. [b]Yield of isolated product. [c]Determined by ^1H NMR analysis on the crude mixture (dr of isolated product after column chromatography shown in parentheses). [d]Determined by CSP HPLC. [e]Reaction run at 0 °C for 2 h. Acetalization conditions: SiO_2 plug, then $HCO(Me)_3$ (1.0 mmol), *p*-TSA (0.15 mmol), MeOH (250 μL), 0 °C to rt, 2 h.

Scheme 3. Pyridinium Salt 1 Substrate Scope[a]



[a]Conditions: **1** (0.1 mmol), **2** (0.2 mmol), **3a** (0.01 mmol), $PhCH_2CO_2H$ (0.01 mmol), TEA (0.1 mmol), PhMe (500 μL), −30 °C, 1 h; then Ph_3PCHCO_2Et (0.6 mmol), −30 °C to rt, 3 h. [b]Yield of isolated product. [c]Determined by ^1H NMR analysis on the crude mixture (dr of isolated product after column chromatography shown in parentheses). [d]Determined by CSP HPLC. [e]Reaction run at 0 °C for 2 h. [f]Determined by ^1H NMR spectroscopy using a chiral shift reagent (Pirkle's alcohol).

Scheme 4. Synthesis of Product 10



synthetic yields (70%−50%) and high enantiomeric excesses (94%−91% ee for the *syn* isomer), although with decreased diastereoselectivity. The possibility of changing the EWG on the pyridinium ring was also investigated. A cyano group was found to activate the pyridinium cation enough to promote the dearomatization. Substrate **1h** was therefore reacted with aldehydes **2a** and **2b** to render products **5ha** and **5hb**, as diastereomeric mixtures, in 75% and 60% yield, respectively. The enantiomeric excesses of both diastereoisomers were very good (>90% ee) in both cases. Unfortunately, less activated substrates such as *N*-benzyl-3-acetylpyridinium and *N*-benzyl-3-methoxycarbonylpyridinium bromides did not show sufficient reactivity.

The relative configuration of product **5aa** was assigned as *syn* by NMR spectroscopy, while the absolute configuration of **5da** (*S*,*S*) was assigned by comparing the calculated (TD-DFT) with the experimental ECD spectra.[16] These were extended for analogy to all other products **5** and **6**. Both the relative and the absolute configurations are in agreement with the reported conjugate additions of aldehydes to *trans*-nitroolefins catalyzed by **3a**.[9a] We therefore envisioned that the same transition-state model,[17] proposed to explain the stereochemical outcomes of that reaction, could be also successfully applied to our case (see the SI for more details).

As mentioned previously, we envisioned that the present dearomatization would be suitable for the construction of medicinally relevant bicyclic structures of type **III** (see Scheme 1). As shown in Scheme 4, after application of the standard addition protocol to salt **1a** and aldehyde **2a**, product **4aa** was transformed into acetal **6aa**, obtained as a single diastereoisomer in 76% yield and 95% ee. Treatment of **6aa** with excess $NaBH_4$ in methanol[7b] afforded fully saturated piperidine **7** (80% yield, 95% ee) with complete diastereocontrol of the newly formed stereocenter, which was found to be in an 1,2-*cis* relationship with the contiguous one. Under standard hydrogenation conditions (ammonium formate and Pd/C in methanol), **7** underwent simultaneous nitro-group reduction and benzyl group cleavage to afford 3-aminopiperidine **8**. Crude **8** was directly subjected to acetal deprotection−cyclization by reaction with aqueous HCl at 0 °C for 18 h and then at room temperature for 1 h. These reaction conditions were found to be an optimal compromise between diastereopurity (93:7 dr) and conversion (95% by ^1H NMR, see the SI). Bicyclic imine **9** was reduced to

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obtain a diamine, conveniently isolated as ditosylated product **10** in 30% overall yield (four steps, 75% yield per step) and 95% ee. Product **10** afforded enantiopure single crystals which, upon X-ray diffraction analysis (see SI), provided its configuration as 3*R*,3a*R*,7a*S* in complete agreement with the previous assignments by NMR and ECD spectroscopy on adducts **5aa** and **5da**.

To summarize, we have developed an organocatalytic nucleophilic dearomatization of activated *N*-alkylpyridinium salts **1** with aldehydes **2** under chiral enamine catalysis. The process exhibits complete C-4 regioselectivity along with high levels of diastereo- and enantiocontrol, enabling a high-yielding synthesis of a broad range of optically active 1,4-dihydropyridines (**5** or **6**). The utility of the present protocol was demonstrated by successfully employing one of the obtained products in the catalytic stereoselective preparation of a synthetically challenging functionalized octahydropyrrolo[2,3-*c*]pyridine, a core structure of anticancer peptidomimetics.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03824.

Additional optimization results, determination of the relative and absolute configurations, experimental details, copies of NMR spectra, and HPLC traces (PDF)
Crystallographic data for **10** (CIF)

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Notes

The authors declare no competing financial interest.

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