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Enantioselective Alkylation of 2-Alkylpyridines Controlled by Organolithium Aggregation

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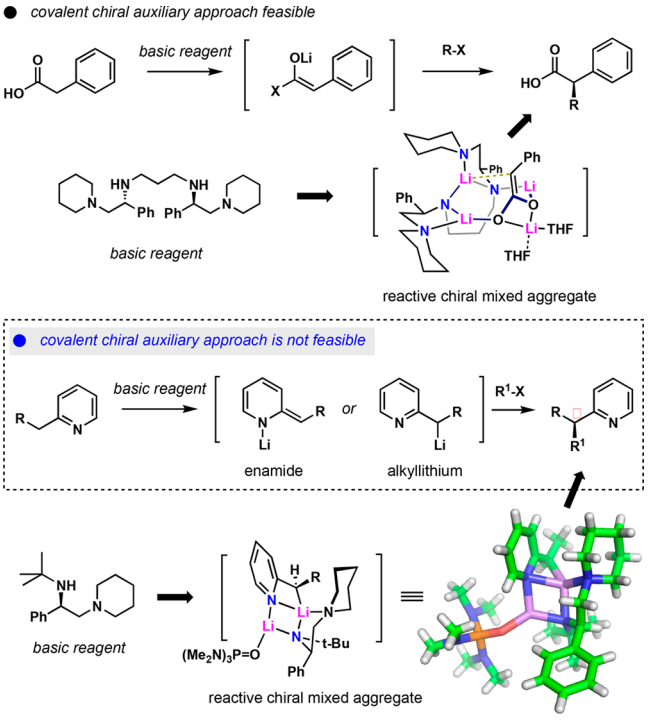
Supporting Information

ABSTRACT: Direct enantioselective α-alkylation of 2-alkylpyridines provides access to chiral pyridines via an operationally simple protocol that obviates the need for prefunctionalization or preactivation of the substrate. The alkylation is accomplished using chiral lithium amides as noncovalent stereodirecting auxiliaries. Crystallographic and solution NMR studies provide insight into the structure of well-defined chiral aggregates in which a lithium amide reagent directs asymmetric alkylation.

Enantioselective alkylation is a fundamentally important transformation in organic synthesis. For enolate-based carbanions, asymmetric alkylations have been historically achieved using covalently attached chiral auxiliaries,[1−4] and these reactions have extensive applications in the synthesis of natural products and pharmaceuticals on scales spanning several orders of magnitude.[5,6] However, this strategy is not readily applicable to carbanions derived from noncarbonyl precursors. Building on discoveries by Shioiri[7] and subsequently Koga,[8] we previously demonstrated that chiral lithium amides (CLAs) function as noncovalent stereodirecting reagents enabling highly effective enantioselective transformations of dianionic enediolates derived directly from carboxylic acids.[9−11] The asymmetric alkylation is achieved by virtue of mixed aggregation[12] between the enediolate and CLA, providing the chiral environment for subsequent functionalization (Scheme 1).[13] CLAs derived from amines shown in Scheme 1 produce mixed aggregates with a broad range of organolithium reagents with a remarkably conserved three-dimensional architecture.[14] Such well-defined aggregation suggests that CLAs can potentially direct the stereochemistry of alkylations for nonenolate monoanionic carbanions for which no covalent chiral auxiliary is feasible.[15,16]

We became interested in α-alkylation of 2-alkylpyridines for an initial examination of this approach. Pyridines bearing C2-alkyl substituents are privileged ligands in asymmetric catalysis; however, their preparation often involves cumbersome multistep synthesis. Moreover, pyridines are the second most frequently occurring nitrogen-containing heterocycles in pharmaceuticals, with C-2 substitution appearing in more than 60%.[17] While several approaches have been developed to access chiral C2-substituted pyridines in some form,[18−25] each has its limitations in substrate scope profile, and no direct enantioselective alkylation has been reported.

Scheme 1. Chiral Lithium Amides in Enolate Alkylation versus Alkylpyridine Alkylation



Herein, we report a general procedure for the direct asymmetric alkylation of C2-alkylpyridines. This approach circumvents the need to incorporate a synthetic handle into the substrate or preactivate the pyridine nucleus prior to alkylation, thus offering an advantage over previously reported methods of accessing chiral pyridines.[19−26] We also report isolation and structural characterization of the mixed aggregates between the chiral lithium amide and α-lithio-2-alkylpyridines, supporting a hypothesis for the origin of enantiocontrol.

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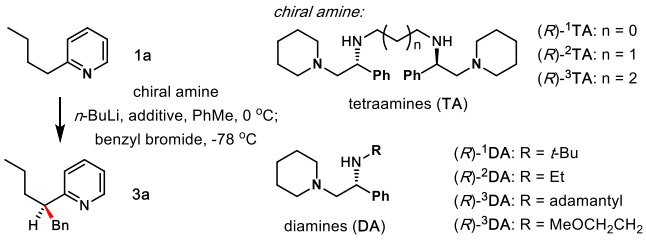
To identify the optimal reagent for the enantioselective alkylation, several chiral amines were screened first (Table 1).

Table 1. Identification of the Optimal Reaction Conditions for Benzylation of 2-Butylpyridine[a]



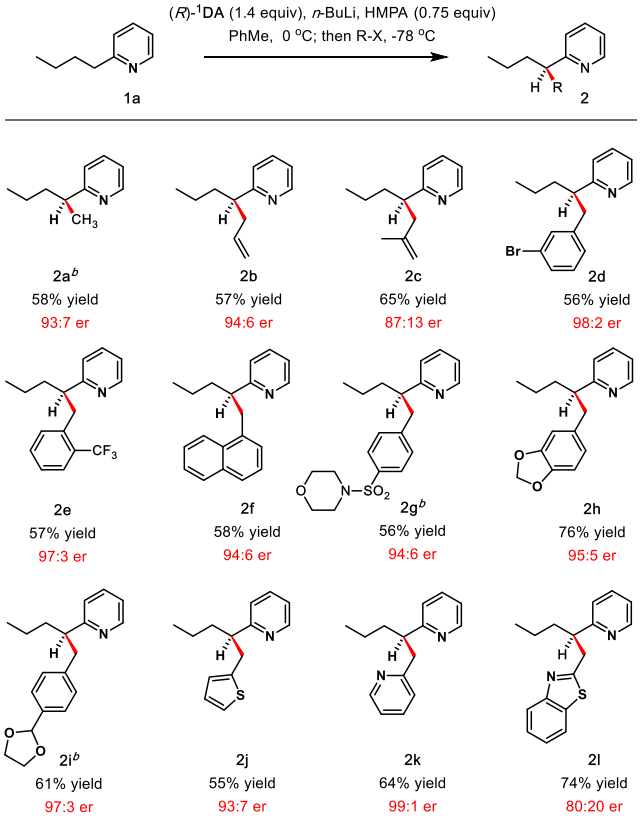
entry	amine	additive	yield (%)	er, **2a**
1	(*R*)-^{1}**TA**[b]	–	31	74:26
2	(*R*)-^{2}**TA**[b]	–	45	78:22
3	(*R*)-^{3}**TA**[b]	–	20	53:47
4	(*R*)-^{2}**TA**[b]	HMPA	65	65:35
5	(*R*)-^{1}**DA**	–	22	87:13
6	(*R*)-^{2}**DA**	–	25	64:36
7	(*R*)-^{3}**DA**	–	21	73:27
8	(*R*)-^{4}**DA**	–	32	79:21
9	(*R*)-^{1}**DA**	LiBr	11	91:9
10	(*R*)-^{1}**DA**	HMPA	55	97:3
11	(*R*)-^{1}**DA**	DMPU	25	80:20
12	(*R*)-^{1}**DA**	TMEDA	70	50:50

[a]Reaction conditions: 0.44 mmol butyl pyridine, 0.90 mmol *n*-BuLi, 0.45 mmol amine, 0.22 mmol additive, 0.53 mmol BnBr, toluene (5.0 mL), see the Supporting Information for details. Isolated yields are shown. Enantiomeric ratios (er) were determined by high performance liquid chromatography (HPLC) analysis. [b]3.03 equiv of *n*-BuLi were used.

C_2-Symmetrical amines (*R*)-^{1}**TA**-^{3}**TA** that gave excellent enantioselectivity in enediolate alkylation provided only moderate level of enantiocontrol (entries 1−3). In contrast, diamines such as (*R*)-^{1}**DA**-^{4}**DA** showed an improved enantiomeric ratio (er), with *N*-*tert*-butyl-substituted amine (*R*)-^{1}**DA** being the best (entries 5−8). Given the importance of additives for aggregation states of organolithium compounds,[12] we screened the effect of common lithium ligands. HMPA displayed an enhancement in both conversion (from 22% to 55%) and er (from 87:13 to 97:3, entries 5,10). While LiBr also produced an increased er, the conversion was suppressed due to incomplete lithiation of the substrate. We found that in general, lithiation of **1a** was inhibited by lithium compounds, including *n*-BuLi itself. Toluene proved to be the optimal solvent; ethereal solvents (tetrahydrofuran, Et_2O, 1,4-dioxane, 1,2-dimethoxyethane) resulted in no enantioselectivity, while the use of hydrocarbon solvents (hexane, cyclohexane) encountered solubility problems.

High enantioselectivity was obtained upon reaction of **1a** with a range of activated electrophiles (Table 2). Methylation proceeded with enantiomer ratio of 93:7 (**2a**). Allyl bromide and methallyl bromide afforded alkylation products in 94:6 er and 87:13 er, respectively (**2b**, **2c**). High enantioselectivity was observed for a variety of benzylic bromides (**2d**−**2i**). Highly reactive heteroaromatic benzylic bromides proved to be effective alkylating agents. 2-Thienyl bromide and 2-(bromomethyl)pyridine reacted rapidly to form **2j** in 93:7 er and **2k** in 99:1 er. Despite attempted additional refinement of reaction conditions, alkylation with 2-(bromomethyl)-1,3-benzothiazole afforded **2l** in 80:20 er.

Table 2. Scope of Alkyl Halide



[a]Reaction conditions: All reactions were carried out on a 0.44 mmol scale unless otherwise noted. Isolated yields are shown. Results are normalized to bases with the *R* configuration, enantiomeric ratios (er) measured by HPLC analysis. [b]0.5 equiv of HMPA and 1.0 equiv of (*R*)-^{1}**DA** were used.

The scope of 2-alkylpyridines was investigated by enantioselective benzylation employing the conditions developed for **1a**; however, for several substrates improved results were achieved by modifying the stoichiometry of HMPA and the chiral lithium amide (Table 3). Increasing the length of the alkyl chain (**3b**) produced results similar to those observed during benzylation of **1a**. Benzylation of 2-ethylpyridine (**1c**) occurred in similar yield (76%) but diminished er (85:15) compared to **1a**. When the stoichiometry of the chiral amine and HMPA was reduced, the reaction proceeded with greater er (92:8) and somewhat reduced yield (58%).

Alkylation of tetrahydroquinoline **3d** proceeded smoothly in very good yield and enantioselectivity. Branching at the γ-position of the C-2 alkyl chain (**3e**, **3f**) had a detrimental impact on enantioselectivity under the standard conditions; however, when the amount of HMPA and chiral lithium amide was reduced, excellent enantioselectivity was observed with only slightly diminished conversion.

Substrates containing β-branching (**3g**, **3h**) were initially alkylated in poor er (<3:1) under the original procedure, but good results were observed by adjusting the quantity of HMPA to 1.25 equiv while lowering the amount of (*R*)-^{1}**DA** to 1.0 equiv. Substrates with β,γ-unsaturation were alkylated with poor er (<2:1), but γ,δ- and δ,ε-unsaturation was tolerated furnishing **3i** and **3j** with good enantioselectivity. Pyridine **3k**

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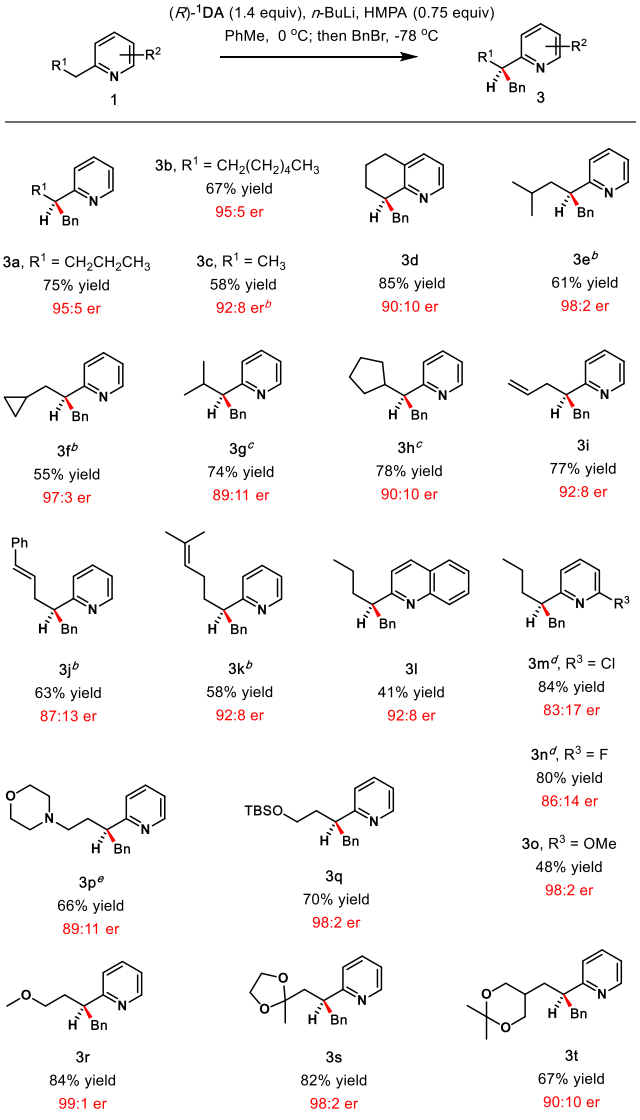
Table 3. Scope of 2-Alkyl Pyridines



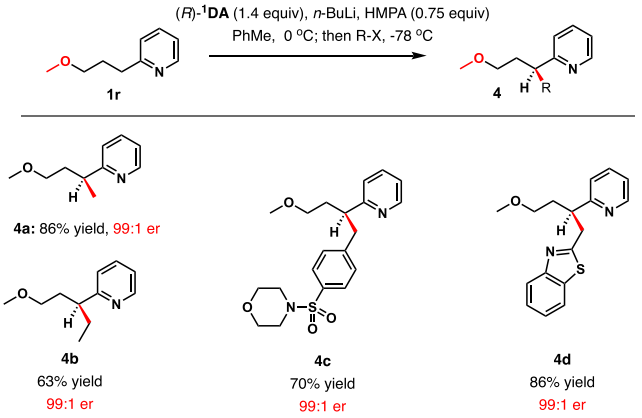
[a]Reaction conditions: All reactions were performed on a 0.44 mmol scale unless otherwise noted. Isolated yields are shown. Results are normalized to bases with the *R* configuration, enantiomeric ratios (er) measured by HPLC analysis. [b]0.5 equiv of HMPA and 1.0 equiv of (*R*)-**1DA** were used. [c]1.0 equiv of (*R*)-**1DA** and 1.25 equiv of HMPA. [d]1.4 equiv of (*R*)-**1DA** and 1.0 equiv of HMPA. LDA used instead of *n*-BuLi. [e]1.0 equiv of (*R*)-**1DA** and no HMPA.

gave results identical to those observed for benzylation of 2-ethylpyridine, **3c**. Quinolines are useful compounds in medicinal chemistry.[17,26] Quinoline **3l** was accessed with very good enantioselectivity by this protocol. Halogen substitution at the 6-position resulted in moderate erosion of enantioselectivity (**3m**, **3n**). In contrast, C6-substitution with a methoxy group enhanced enantioselectivity, furnishing **3o** in 98:2 er. The presence of a morpholine group was detrimental, resulting in racemic product under the original conditions. Remarkably, in the absence of HMPA, a strong boost in er to 89:11 was observed (**3p**), potentially due to internal chelation.

When an ether or ketal are present at the γ-position, an exceptional increase in enantioselectivity is observed (**3q**, **3r**, **3s**). Benzylation of **1q** also proceeded in very good yield (80%) and excellent er (97:3) in the absence of HMPA when (*R*)-**1DA** was replaced with the chiral amide (*R*)-**3TA**. Notably, no enhancement was observed upon alkylation of the 1,3-dioxane **3t**, in which no internal chelation by the γ-alkoxy group is feasible.

We explored this intriguing enhancement of enantioselectivity by the γ-alkoxy substituents in greater detail, testing additional electrophiles with **1r** (Table 4). Methylation

Table 4. Enantioselective Alkylation of 2-(3-Methoxy-1-propyl)pyridine (1r)



[a]Reaction conditions: Reactions were performed on a 0.44 mmol scale unless otherwise noted. Isolated yields are shown. Results are normalized to bases with the *R* configuration, enantiomeric ratios, determined by HPLC analysis.

occurred in very good yield and excellent enantioselectivity (**4a**, er 99:1). Alkylation was also successful with less reactive electrophiles. Ethylation of **1a** resulted in only 14% conversion, however, under identical conditions **1r** reacted with iodoethane to furnish **4b** in 63% yield and 99:1 er. Reaction with significantly more functionalized *N*-(4-bromomethylbenzenesulfonyl)morpholine proceeded smoothly to afford **4c**. High er enhancement versus **1a** was also observed in the reaction of **1r** with 2-(bromomethyl)benzothiazole, which afforded **4d** in greater than 99:1 er versus 80:20 for **2l**.

Given the growing evidence of the strong correlation between stereocontrol and aggregation states in organolithium chemistry,[14,27] a critical part of these investigations was the crystallographic study of the central mixed aggregates involved in the alkylation reaction. We were especially interested in comparing the structures of the more generic 2-alkyl pyridine-derived aggregates to those from 2-(3-methoxy-1-propyl)-pyridine **1r**, which afforded a significant boost in enantioselectivity. Initial efforts at crystallization of the reactive aggregate from 2-butylpyridine were unproductive. On the other hand, we succeeded in obtaining high-quality crystals from 2-ethyl pyridine and **1r** upon treatment with (*R*)-**1DA**, *n*-BuLi, and HMPA in pentane at −25 °C. Figure 1 shows the rendering of the aggregate structures obtained by X-ray diffraction studies. In both cases, the aggregate has a general structure of (2-Py)(R)CHLi·(*R*)-Li**1DA**·HMPA in a 1:1:1 stoichiometry.

The structural study revealed significant pyramidalization at the lithiated α-carbon consistent with the sp^3 character of an alkyllithium reagent rather than sp^2 character of the enolate-like Li enamide tautomer.[28−30] Despite the presence of the internally chelating OMe group in **1r**, the similarities in arrangement and orientation are striking. The most significant

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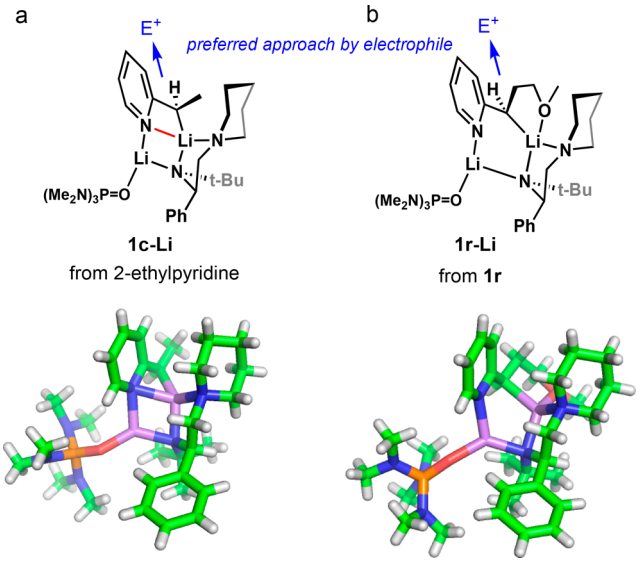


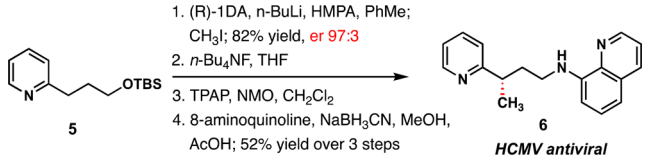
Figure 1. Structures of mixed aggregates determined by X-ray diffraction study of crystals obtained from (a) 2-ethylpyridine (**1c-Li**); or (b) **1r** (**1r-Li**), (*R*)-[1]**DA**, *n*-BuLi, and HMPA in pentane.

difference between the structures is the disruption of the central four-membered Li−N−Li−N cluster to a six-membered cyclic structure with internal complexation to the OMe group in **1r**. We confirmed that the sense of absolute configuration of alkylation products derived from 2-ethylpyridine and **1r** is identical and consistent with inversion of configuration at C−Li bond in an apparent S_E2 mechanism. It is plausible that the 10-fold increase in enantiomer ratio from about 10:1 to 100:1, corresponding to ∼1.4 kcal/mol free energy difference in the competing transition structure, is due to the small differences in bond angles; however, it appears to be unlikely. Our current hypothesis for the boost in enantioselectivity observed in alkylation of **1r** is that it forms a more stable aggregate minimizing the nonselective background alkylation. This observation is supported by high sensitivity of er to the stoichiometry of HMPA, pointing to a dynamic equilibrium between two or more aggregates of varying reactivity. Racemization by product deprotonation was excluded by deuterium quench experiments, as the product displayed no deuterium incorporation.

Subsequent solution-state studies by ^{6}Li and ^{31}P NMR spectroscopy further corroborate the structures **1c-Li** and **1r-Li**. For example, the ^{31}P NMR spectrum for **1r-Li** has a single resonance at 24.88 ppm (J_{PLi} = 3.50 Hz), while the ^{6}Li spectrum features two resonances at 2.47 (d, J_{PLi} = 3.50 Hz) and 1.64 ppm, in a 1:1 ratio, as expected. These spectra also clearly indicate the presence of a minor isomer (10−15%) at −80 °C. Detailed structural investigations of the dynamic aggregation states along with density functional theory computational examination of the alkylation are the subject of a separate, ongoing study.

The utility of this method for medicinal chemistry applications is illustrated by an expedient enantioselective synthesis of anti-HCMV compound **6** studied by Forge Life Sciences (Scheme 2).[31] Direct, asymmetric methylation of **5** afforded the product in 82% yield and 97:3 er. Desilylation, oxidation, and reductive amination with 8-aminoquinoline provided the target structure without erosion of enantiomeric purity.

Scheme 2. Synthesis on HCMV Antiviral Compound 6 by Direct Asymmetric Alkylation



In summary, an operationally straightforward procedure for asymmetric alkylation of 2-alkylpyridines is described. The chiral amine reagent is readily available in bulk in two simple steps from styrene oxide, and can be readily recovered by aqueous pH-controlled extraction. This reaction validates CLAs as reagents for alkylation of nonenolate-derived organolithium reagents. Valuable insight into the mechanism of enantiocontrol were revealed by X-ray diffraction studies of mixed aggregates obtained by cocrystallization of (*R*)-[1]**DA** with ethylpyridine or **1r** upon lithiation with *n*-BuLi. These structural studies provide a defined view of the intermediate aggregates involved in the alkylation reactions and allow for a structure-based design of new lithium amide reagents for expanded applications in the future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b08659.

Full experimental procedures (PDF)
Copies of ^{1}H, ^{13}C NMR spectra (PDF)
Copies HPLC traces (PDF)
Crystallographic data for **1c-Li** (CIF)
Crystallographic data for **1r-Li** (CIF)

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Notes

The authors declare no competing financial interest.

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