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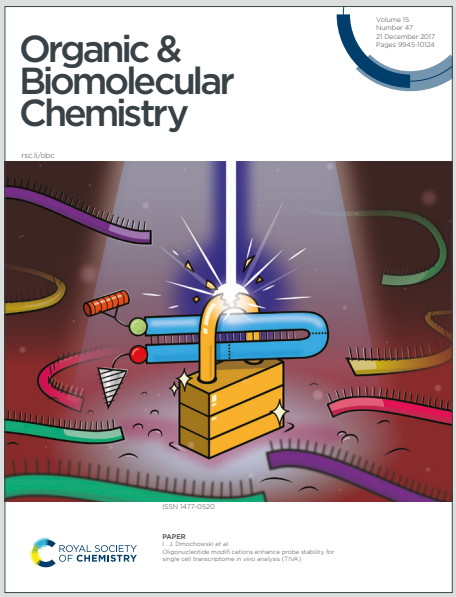

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COMMUNICATION

Alkyl Lithium-Catalyzed Benzylic C–H Bond Addition of Alkyl Pyridines to α-Alkenes

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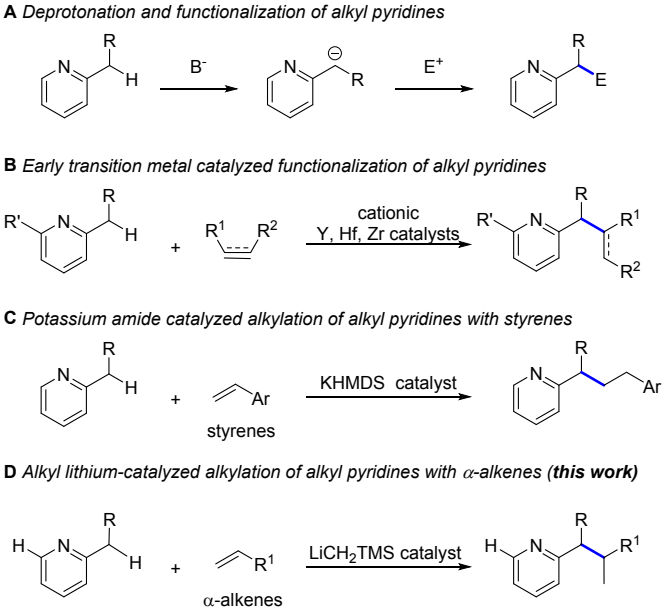
Brønsted base catalyzed C–C bond formation reactions have been extensively utilized as reliable, efficient, and atom economical methods in organic synthesis. However, the electrophiles were mostly limited to polar ones such as imines, carbonyl compounds, α, β-unsaturated compounds, styrenes and conjugated dienes. The use of α-alkenes as electrophiles in C–C bond formation reaction always needs transition metal catalysts. Herein, we reported an alkyl lithium-catalyzed benzylic C–H bond addition of alkyl pyridines to α-alkenes. The alkyl lithium catalyst displayed quite different selectivity from the transition metal catalysts.

An alkyl pyridine motif exists widely and behaves importantly in many natural products, pharmaceuticals, ligands, and functional materials.[1] In various approaches to the alkyl pyridines synthesis, the benzylic C–H bond functionalization reaction is the most frequently used method. The deprotonation of an alkyl pyridine with a strong base could easily afford a benzylic anion, which could successfully undergo the substitution or addition reactions with a series of electrophiles such as halides,[2,3] carbonyl groups,[1,4] imines[5] and α, β-unsaturated carbonyl compounds (Scheme 1A).[6] Using Lewis acid catalysts or transition metal catalysts, the catalytic alkylation of alkyl pyridines could be achieved but mostly with highly reactive imines and enones.[5, 6e] It was not until the early transition metal complexes got involved as catalysts that the scope of electrophiles was greatly extended to simple alkenes and alkynes (Scheme 1B).[7] Hou and co-workers reported the catalytic addition of benzylic C–H bonds of alkyl pyridines to various alkenes with cationic yttrium catalysts.[7b,c] Yao and co-workers later reported the similar alkylation reactions with cationic zirconium catalyst.[7d,e] Mashima and co-workers reported the coupling of 2,6-lutidine with internal alkynes catalyzed by alkylhafnium complexes.[7f,g] However, the early transition metal catalysts prefers the alkylation of the *ortho*-pyridyl C–H bond rather than the benzylic ones. Thus, only if the *ortho*-pyridyl C–H bonds were inhibited, the benzylic C–H bonds underwent the catalytic alkylation reactions.[8]



Scheme 1 C–H Functionalization of Alkyl pyridines.

Brønsted base catalyzed C–C bond formation reactions had been widely used in organic synthesis for their reliability, efficiency, and atom economy.[9] With the great efforts from Kobayashi, Walsh and Schneider groups, the pronucleophiles scope was greatly extended from carbonyl compounds to alkyl pyridines and even toluenes.[10] The electrophiles, however, were mainly limited to imines, α, β-unsaturated amides, styrenes and conjugated dienes. Actually as early as 1956, Pines and co-workers reported the alkylation of alkyl pyridines with alkenes using metal sodium or potassium as catalysts.[11] The alkylation reactions of picoline with ethylene and propene were carried out under harsh conditions, giving the products in low yields and in poor selectivity from the multi-alkylation reactions.[11a-c] We recently reported the catalytic alkylation of alkyl pyridines with styrenes by using potassium amide as catalyst (Scheme 1C).[12] Herein, we report the alkyl lithium-catalyzed benzylic alkylation of alkyl pyridines with α-alkenes (Scheme 1D).

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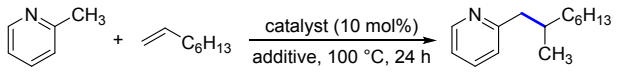
Table 1 Catalytic Alkylation of 2-Methylpyridine with 1-Octene.[a]



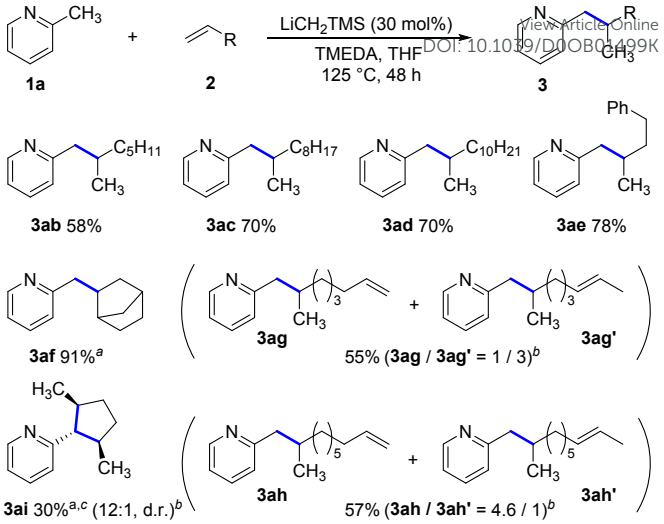
1a 2a 3aa

entry	catalyst	additive	**3aa** yield (%)[b]
1	LDA	Et_2O	9
2	LiTMP	Et_2O	9
3	LiHMDS	Et_2O	NR
4	NaDA	Et_2O	NR
5	KDA	Et_2O	NR
6	n-BuLi / hexane	Et_2O	10
7	$LiCH_2TMS$	Et_2O	17
8	$LiCH_2TMS$	—	11
9	$LiCH_2TMS$	THF	19
10	$LiCH_2TMS$	THF + TMEDA	25
11	$LiCH_2TMS$	THF + TMEDA	29[c]
12	$LiCH_2TMS$	THF + TMEDA	81 (76)[d]

[a]Conditions: 2-methylpyridine (**1a**) (0.5 mmol), 1-octene (**2a**) (1.0 mmol), catalyst (10 mol%), additive (0.1 mL), 100 °C, 24 h. [b]NMR yields based on 2-methylpyridine with 2-methoxynaphthalene as an internal standard, isolated yield in parenthesis. [c]$LiCH_2TMS$ (20 mol%). [d]$LiCH_2TMS$ (30 mol%), 1-octene (**2a**) (3.5 mmol), 125 °C, 48 h.

We firstly carried out the reaction between 2-methylpyridine and 1-octene at 100 °C with lithium amides as catalysts and Et_2O as additive (Table 1, entries 1-3). Lithium diisopropylamide (LDA) and lithium 2,2,6,6-tetramethylpiperidine (LiTMP), 24 hours later, afforded the alkylation product **3aa** in 9% yields, suggesting a stoichiometric reaction of the lithium amides rather than a catalytic one. Sodium and potassium amides as catalysts were tested in the reaction but failed to give any alkylation product (entries 4 and 5). Alkyl lithium compounds were also subjected into the reaction as catalysts (entries 6 and 7); to our delight, $LiCH_2TMS$ achieved the alkylation reaction catalytically even though the turn over number is pretty low (entry 7, 17% yield). The reaction in absence of the additive Et_2O, however, gave the alkylation product in a lower yield of 11% (entry 8). THF as additive under the same conditions resulted in a yield of 19% (entry 9). The further addition of TMEDA as another additive gave an even better yield of 25% (entry 10). Under the enhanced conditions of more catalyst and 1-octene, higher temperature and longer reaction time, we could finally complete the catalytic alkylation of 2-methylpyridine and get the product in a good yield of 81% (entry 12).

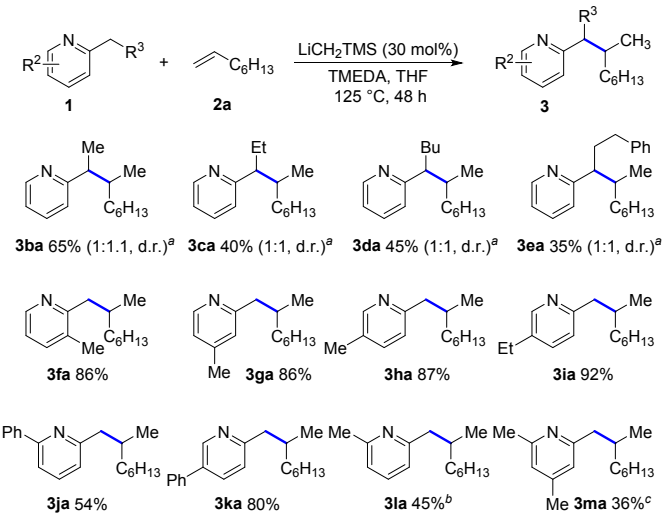
With the optimized conditions in hand, we next evaluated the scope of alkenes in the alkyl lithium-catalyzed alkylation of 2-picoline (Scheme 2). Olefins such as 1-heptylene, 1-decene, 1-laurylene and 4-phenyl-1-butene reacted smoothly with 2-methylpyridine, and afforded the corresponding alkylation products in good yields (**3ab-3ae**). Norbornene exhibited high activity and gave the alkylation product in 91% yield (**3af**). Cyclopentene and cyclohexene were also subjected into the



Scheme 2 Substrate Scope of Alkenes. Conditions: 2-methylpyridine (**1a**) (1.0 mmol), alkenes (**2**) (7.0 mmol), $LiCH_2TMS$ (30 mol%), THF (0.2 mL), TMEDA (0.2 mL), 125 °C, 48 h, isolated yields are based on the amount of (**1a**). [a]THF (0.2 mL), 100 °C, 48 h. [b]Ratios determined by ^1H NMR. [c]47% yield with 50 mol% of $LiCH_2TMS$.

reaction but failed to provide any alkylation product. For the dienes such as 1,7-octadiene and 1,9-decadiene, only one of the two double bonds reacted with 2-methylpyridine to afforded pyridine substituted alkenes (**3ag** and **3ah**), accompanying with their alkene isomerization products (**3ag'** and **3ah'**). In the case of 1,5-hexadiene, however, both of the double bonds underwent the alkylation reaction with the benzylic C–H bonds to form a substituted cyclopentane product **3ai** in a low yield of 30% (see Supporting Information). Quite different from the scandium catalyzed continuous insertion reaction of 1,5-hexadiene,[13] the alkyl lithium catalyst achieved twice alkylation at the same benzylic position, revealing that there was an intramolecular deprotonation before the insertion of the second double bond. We carried out this reaction further with 50 mol% of $LiCH_2TMS$, and got the cyclopentane product in 47% yield, suggesting a stoichiometric reaction based on the alkyl lithium reagent. A possible reason for the change from the catalytic reactions to this stoichiometric one is the tertiary lithium intermediate, which is crowd enough to prevent the coordination and deprotonation with another 2-methylpyridine.

Beside 2-methylpyridine, some other alkyl pyridines including 2-ethylpyridine, 2-propylpyridine, 2-pentylpyridine and 2-(3-phenylpropyl)pyridine were also allowed to react with 1-octene. With the increase of the steric hindrance at the benzylic position, the alkyl pyridine products bearing a tertiary alkyl group were isolated in moderate to low yields (Scheme 3, **3ba-3ea**). Multi-substituted 2-methylpyridines such as 2,3-dimethylpyridine, 2,4-dimethylpyridine, 2,5-dimethylpyridine, 5-ethyl-2-methylpyridine, 2-methyl-5-phenylpyridine and 2-methyl-6-phenylpyridine were also subjected into the catalytic alkylation reactions and the alkylation products were obtained in good to high yields (**3fa-3ka**). 2,6-Dimethylpyridine and 2,4,6-trimethylpyridine smoothly reacted with 1-octene to give the alkylation products in 45% and 36% yields (**3la** and **3ma**), along with some 2,6-dialkylation by-products (**3la'** and **3ma'**, see

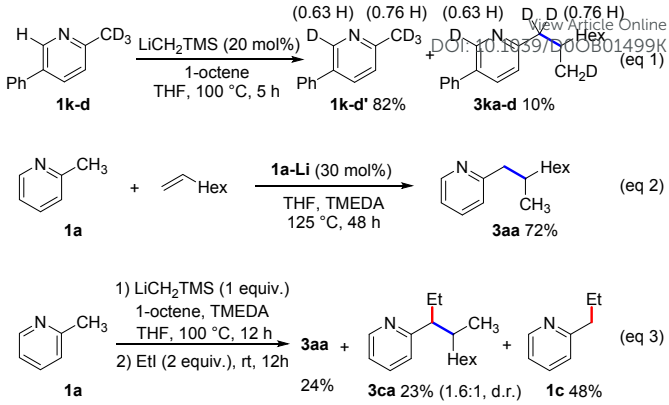


Scheme 3 Substrate Scope of Alkyl pyridines. Conditions: alkyl pyridines (**1**) (1.0 mmol), 1-octene (**2a**) (7.0 mmol), $LiCH_2TMS$ (30 mol % of **1**), THF (0.2 mL), TMEDA (0.2 mL), 125 °C, 48 h, isolated yields based on the amount of alkyl pyridines. [a]Determined by GC analysis. [b]Dialkylation product **3la'** was obtained in 33% yield. [c]Dialkylation product **3ma'** was obtained in 47% yield.

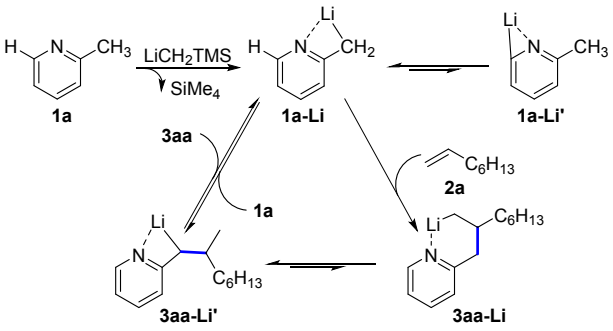
Supporting Information). It is worthy to note that this transformation displayed good selectivity: only the 2-methyl groups undergo the C–H bond alkylation reaction. The 4-methyl group of the alkyl pyridine, which has even more acidic C–H bonds, was inert in the catalytic alkylation reaction. These results suggested that the coordination between the nitrogen atom and the lithium catalyst is crucial for the addition (insertion) reaction with alkenes.

In the reaction of deuterated 2-methyl-5-phenylpyridine (**1k-d**) with 1-octene, the H–D exchange between the benzylic C–D bond and the *ortho*-pyridyl C–H bond was observed (Scheme 4, eq 1), suggesting there is an equilibrium between benzylic metal species and pyridyl metal species, similarly with the cationic early transition metal complexes.[8c,e] However, distinct from the early transition metal catalysts, alkyl lithium catalyst prefers the alkylation of the benzylic C–H bond rather than the *ortho*-pyridyl C–H bond of the alkyl pyridine. The similar deuterium distribution (*ortho*-pyridyl position: 0.63H; benzylic position: 0.76H) of the alkylation product **3ka-d** and recovered reactant **1k-d'** revealed the fast equilibrium between the reactant and the product. To further explore the reaction mechanism, we carried out the direct deprotonation of 2-methylpyridine with n-BuLi in diethyl ether at -20 ˚C to prepare the intermediate 2-picolyllithium (**1a-Li**), which was reported to exist in a dimer structure in its solid state.[14] 2-Picolyllithium can efficiently catalyze the alkylation reaction, suggesting that 2-picolyllithium intermediate is possibly involved in the catalytic cycle (Scheme 4, eq 2). The in-situ quenching of a reaction with iodoethane gave the ethylation products at the benzylic position of both the reactant and product (Scheme 4, eq 3), suggesting that the two benzylic lithium intermediates exist as the privilege species in the catalytic cycle.

On the basis of these observations, we proposed a possible process for the catalytic alkylation reaction shown in Scheme 5.



Scheme 4 Control Experiments.



Scheme 5 A Plausible Reaction Pathway.

The deprotonation of 2-methylpyridine with alkyl lithium catalyst takes place easily to afford the benzylic lithium intermediate **1a-Li**. Although there is an equilibrium between benzylic lithium species (**1a-Li**) and pyridyl lithium species (**1a-Li'**), only the former slowly undergoes the following addition to 1-octene to generate a new alkyl lithium intermediate (**3aa-Li**). This intermediate quickly goes through an intramolecular deprotonation reaction to afford a more stable benzylic lithium intermediate **3aa-Li'**, which would further undergo the deprotonation equilibrium with another 2-methylpyridine to give the alkylation product and regenerate the benzylic lithium species.

Conclusions

In summary, we for the first time achieved the alkyl lithium-catalyzed benzylic C–H bond addition of alkyl pyridines to α-alkenes. The alkyl lithium catalyst displayed quite different selectivity with early transition metal catalysts in the selective benzylic C–H bond alkylation of 2-alkyl pyridine as well as the reaction with 1,5-hexadiene. Considering the easy availability and good selectivity of the alkyl lithium catalyst, this method could provide a practical approach for synthesis of alkyl pyridines.

Conflicts of interest

There are no conflicts to declare.

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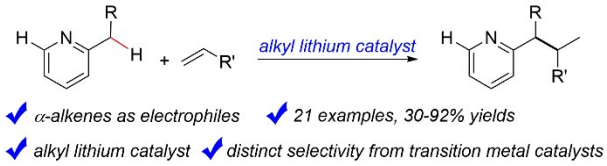

The alkyl lithium catalyst successfully achieved the benzylic C–H bond addition of alkyl pyridines to α-alkenes, and displayed distinct selectivity from the transition metal catalysts.