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Iridium-Catalyzed Sequential sp^3 C–H Alkylation of an *N*-Methyl Group with Alkenes Towards the Synthesis of α-Substituted Amines

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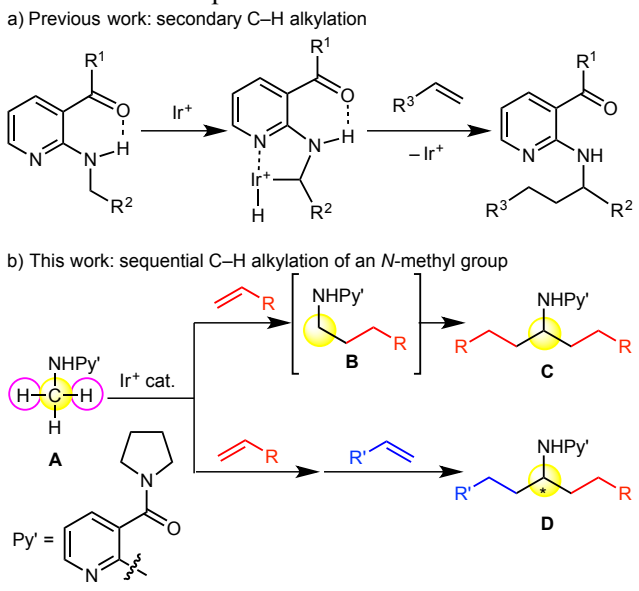
Abstract. Iridium-catalyzed sequential sp^3 C–H alkylation of an *N*-methyl group proceeded to give α-substituted amines, where, in addition to the achiral amines, chiral amines were prepared in one pot via sequential reactions with two different alkenes.

Keywords: Iridium; C–H activation; Amines; Alkenes; Asymmetric synthesis

Direct C–H functionalization catalyzed by transition metals provides step and atom economical processes for organic synthesis.[1] Recent rapid progress of this field has included many successful examples of the C–H functionalization through sp^2 C–H bond activation, and research efforts have also been devoted for sp^3 C–H bond activation.[2] In this respect, the activation of sp^3 C–H bonds[3] adjacent to a nitrogen atom of 2-(alkylamino)pyridine derivatives has been studied under several metal catalysis.[4,5] For example, Jun[6] and Murai,[7] independently, reported catalytic alkylation of sp^3 C–H bonds of 2-(dimethylamino)pyridines with alkenes. Shibata and co-workers have developed enantioselective C–H alkylation of 2-(alkylamino)pyridines with alkenes using Ir catalysts.[8] Opatz[9] and Yu[10] also recently reported Ir-catalyzed C–H alkylation of aminoalkyl groups. In this context, we recently reported that a cationic iridium complex efficiently catalyzes the alkylation of 3-carbonyl-2-(alkylamino)pyridines, where the presence of the substituents at the 3-position was essential for the efficient C–H activation (Scheme 1a).[11a] The finding of the high reactivity of 3-carbonyl-2-(alkylamino)pyridines prompted us to apply the iridium catalysis to the synthesis of α-substituted amines via a sequential alkylation of an *N*-methyl group (Scheme 1b). Thus, alkylation of the *N*-methyl group on **A** with an alkene gives 2-(alkylamino)pyridine **B**, which undergoes alkylation with the same alkene will give achiral α-substituted amine **C**. The use of a different alkene in the second alkylation in one-pot will give chiral α-substituted amine **D**, and the method enables the asymmetric synthesis of the α-substituted amine. In this communication, we wish to report the iridium-catalyzed sequential alkylation of the *N*-methyl group with alkenes via sp^3 C–H bond activation.

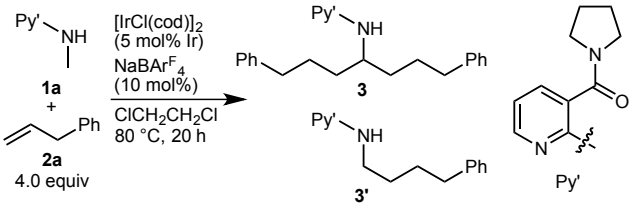


Scheme 1. Ir-Catalyzed sp^3 C–H Alkylation

The C–H dialkylation leading to an α-substituted amine took place very successfully (Table 1). Thus, treatment of **1a** bearing an amide group at the 3-position of the pyridyl substituent with four equiv of allylbenzene (**2a**) in the presence of $[IrCl(cod)]_2$ (5 mol% of Ir, cod = 1,5-cyclooctadiene) and $NaBAr^F_4$ [Ar^F = 3,5-$(CF_3)_2C_6H_3$] (10 mol%) in 1,2-dichloroethane at 80 ºC for 20 h brought about the selective formation of dialkylation product **3aa** in 88% yield (entry 1).[12] The reaction of 1.0 mmol of **1a** in the presence of a reduced amount of the Ir catalyst (2 mol% of Ir) proceeded well to give **3aa** in 92% yield (entry 2). Toluene and 1,4-dioxane were also good solvents (entries 3 and 4), but the reaction in ethylene carbonate was slow giving

monoalkylation product **3aa'** in 56% yield as a major product (entry 5). The presence of a small amount of water significantly decreased the yield of **3aa** because of fast isomerization of allylbenzene into β-methylstyrene in the presence of water (entry 6).[13] The reaction catalyzed by an Ir^{+}/binap complex [binap = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl] was slower than that catalyzed by the Ir^{+}/cod complex (entry 7). In sharp contrast to the high reactivity of **1a**, the reaction of 2-(methylamino)pyridine (**1b**) gave only a trace of the monoalkylation product (entry 8). A rhodium complex $[RhCl(cod)]_2$ displayed no catalytic activity (entry 9).

Table 1. Dialkylation of the *N*-Methyl Group on **1a**[a]

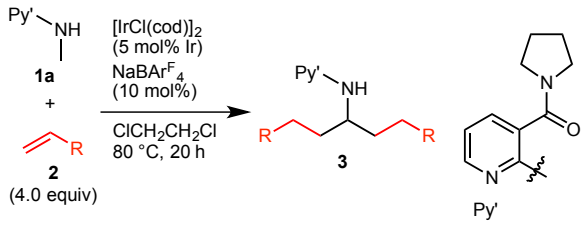


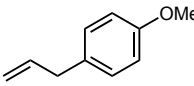
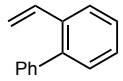
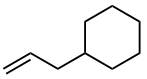
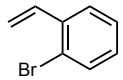
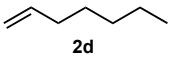
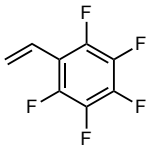
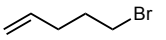
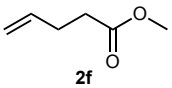
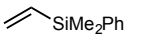
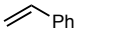
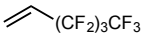
Entry	1	Solvent	Yield [%][b]	3	Yield [%][b]	3'
1	**1a**	$ClCH_2CH_2Cl$	88	(**3aa**)	0	(**3aa'**)
2[c]	**1a**	$ClCH_2CH_2Cl$	92[d]	(**3aa**)	0	(**3aa'**)
3	**1a**	Toluene	88	(**3aa**)	0	(**3aa'**)
4	**1a**	1,4-Dioxane	91	(**3aa**)	0	(**3aa'**)
5	**1a**	Ethylene Carbonate	12	(**3aa**)	57	(**3aa'**)
6[e]	**1a**	$ClCH_2CH_2Cl$	18	(**3aa**)	56	(**3aa'**)
7[f]	**1a**	$ClCH_2CH_2Cl$	15	(**3aa**)	33	(**3aa'**)
8	**1b**	$ClCH_2CH_2Cl$	0	(**3ba**)	<1	(**3ba'**)
9[g]	**1a**	$ClCH_2CH_2Cl$	0	(**3aa**)	0	(**3aa'**)

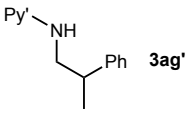
[a] Reaction conditions: **1a** (0.20 mmol), **2** (0.80 mmol), $[IrCl(cod)]_2$ (5 mol% of Ir), and $NaBAr^{F}_4$ (10 mol%) in solvent (0.8 mL) at 80 °C for 20 h. [b] Determined by ^1H NMR. [c] The reaction of 1.0 mmol of **1a** in the presence of 1 mol% of $[IrCl(cod)]_2$. [d] Isolated yield. [e] In the presence of 1 drop of H_2O. [f] With binap (6 mol%). [g] With $[RhCl(cod)]_2$ (5 mol% of Rh) instead of $[IrCl(cod)]_2$.

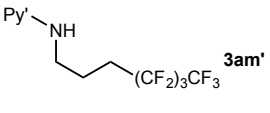
A variety of terminal alkenes can be applied to the dialkylation of the *N*-methyl group (Table 2). The reactions of substituted allylbenzene **2b**, simple alkenes **2c** and **2d**, alkenes having bromo (**2e**) and an ester moiety (**2f**), styrene derivatives **2g**–**j**, and vinyl silanes **2k** and **2l**, gave high yields of the corresponding α-substituted amines **3ab**−**al** (entries 1−11). In the reaction of styrene (**2g**), formation of branched product **3ag'** was observed (entry 6), while *ortho*-substituted styrenes **2h**–**j** underwent the linear selective alkylation giving the dialkylation products (entries 7–9). The reactivity of alkene **2m** substituted with a perfluoroalkyl group was different from those of other simple alkenes; monoalkylation of the *N*-methyl group occurred to give **3am'** in 93% yield even in the presence of an excess of **2m**.[14]

Table 2. Dialkylation of the *N*-Methyl Group[a]



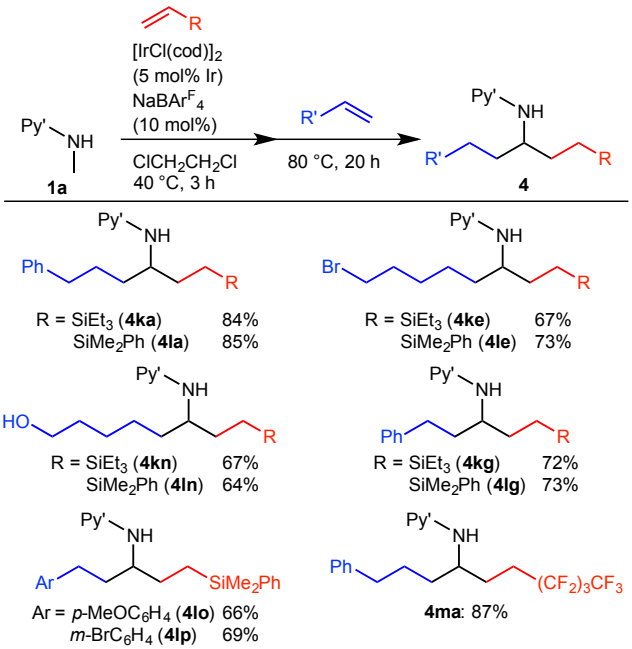
Entry	2	Yield [%]	Entry	2	Yield [%]
1	 **2b**	92 (**3ab**)	7	 **2h**	88 (**3ah**)
2	 **2c**	85 (**3ac**)	8	 **2i**	90 (**3ai**)
3	 **2d**	85 (**3ad**)	9	 **2j**	90 (**3aj**)
4	 **2e**	85 (**3ae**)			
5	 **2f**	87 (**3af**)	10	 **2k**	80 (**3ak**)
			11	 **2l**	80 (**3al**)
6	 **2g**	73 (**3ag**) 18 (**3ag'**)	12	 **2m**	93 (**3am'**)





[a] Reaction conditions: **1a** (0.20 mmol), **2** (0.80 mmol), $[IrCl(cod)]_2$ (5 mol% of Ir), and $NaBAr^{F}_4$ (10 mol%) in 1,2-dichloroethane (0.8 mL) at 80 °C for 20 h. Isolated yields are shown.

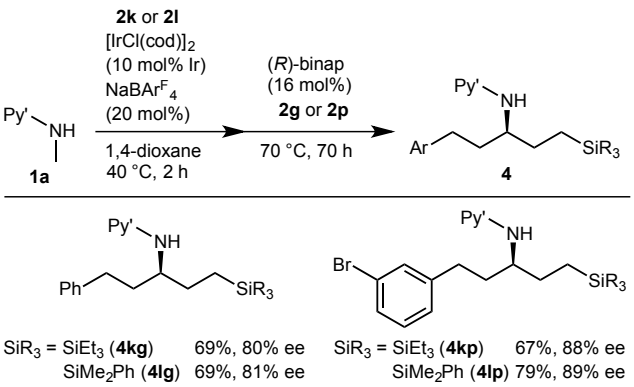
The sequential use of two different alkenes in the present alkylation of the *N*-methyl group enabled the synthesis of chiral α-substituted amines in one pot. The first alkylation was conducted by using 1.1 equiv of vinylsilanes **2k**, **2l** or alkene **2m** (1.5 equiv) substituted with a perfluoroalkyl group at 40 °C for 3 h (80 °C for 3 h for **2m**), and then, a different alkene was added to the reaction mixture and the mixture was stirred at 80 °C for 20 h. As shown in Scheme 2, the sequential reactions gave several chiral α-substituted amines in good yields, although the use of vinylsilanes or **2m** in the first alkylation was essential for the selective formation of the monoalkylation product under mild reaction conditions.



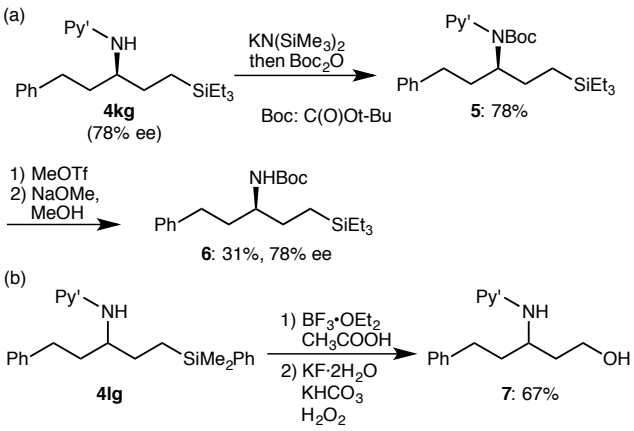
Scheme 2. Ir-Catalyzed sp^3 C–H Alkylation. *Reaction conditions*: **1a** (0.20 mmol), **2k** (0.22 mmol), **2l** (0.22 mmol), or **2m** (0.30 mmol), $[IrCl(cod)]_2$ (5 mol% of Ir), and $NaBAr^F_4$ (10 mol%) in 1,2-dichloroethane (0.8 mL) at 40 °C for 3 h (80 °C for 3 h for **2m**), and then, **2** (0.4 mmol) at 80 °C for 20 h. In the reactions of styrene derivatives, 10 mol% of Ir and $NaBAr^F_4$ (20 mol%) were used. See the Supporting Information for details. Isolated yields are shown.

We then focused on the asymmetric synthesis of chiral α-substituted amines.[15] It was found that the enantioselective alkylation of the initially formed *N*-alkyl group was realized by use of binap as a ligand in 1,4-dioxane.[16] In the sequential reaction in one pot, (*R*)-binap was added just before the addition of the second alkenes. As shown in Scheme 3, the enantioselective synthesis of several chiral α-substituted amines was successful in good yields and enantioselectivities (80–89% ee).

The 2-pyridyl group on **4kg** can be replaced by a *tert*-butoxycarbonyl (Boc) group (Scheme 4).[5f] Treatment of **4kg** with potassium bis(trimethylsilyl)amide followed by an addition of di-*tert*-butyl dicarbonate (Boc_2O) gave the corresponding carbamate **5**. Methylation of the pyridine nitrogen and treatment with sodium methoxide in methanol to give **6** without loss of the enantiomeric purity (Scheme 4a). A dimethylphenylsilyl group on **4lg** was able to be converted into a hydroxyl group by Tamao-Fleming Oxidation in good yield (Scheme 4b).[17]



Scheme 3. Asymmetric Synthesis of α-Substituted Amines. *Reaction conditions*: **1a** (0.20 mmol), **2k** or **2l** (0.22 mmol), $[IrCl(cod)]_2$ (10 mol% of Ir) and $NaBAr^F_4$ (20 mol%) in 1,4-dioxane (0.8 mL) at 40 °C for 2 h. (*R*)-binap (16 mol%) at room temperature for 10 min, and then **2g** or **2p** (0.8 mmol) at 70 °C for 70 h. See the Supporting Information for details.



Scheme 4. Transformations.

In summary, we have developed iridium-catalyzed sequential sp^3 C–H alkylation of an *N*-methyl group leading to α-substituted amines. In addition to the achiral α-substituted amines, chiral amines were prepared in one pot via sequential reactions with two different alkenes. Enantioselective synthesis of chiral α-substituted amines was also realized by using (*R*)-binap as a ligand.

Experimental Section

For detailed experimental information and the characterization of compounds, see the supporting information.

A typical procedure for sequential alkylation of 1a with 2a: $NaBAr^F_4$ (18.4 mg, 0.020 mmol, 10 mol%) in a Schlenk tube was dried under vacuumed at 120 °C for 1 h. After the tube was cooled to room temperature under N_2, **1a** (41.1 mg, 0.20 mmol) and $[IrCl(cod)]_2$ (3.4 mg, 0.0050 mmol, 5 mol% of Ir) were added. 1,2-Dichloroethane (0.8 mL) and alkene **2a** (0.80 mmol) were added to the tube successively, and the mixture was stirred at 80 °C for 20 h.

The mixture was concentrated on a rotary evaporator and the residue was subjected to preparative TLC on silica gel to give **3**.

Acknowledgements

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