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Rh(II)-Catalyzed C−H Alkylation of Benzylamines with Unactivated Alkenes: The Influence of Acid on Linear and Branch Selectivity

Amrita Das and Naoto Chatani*

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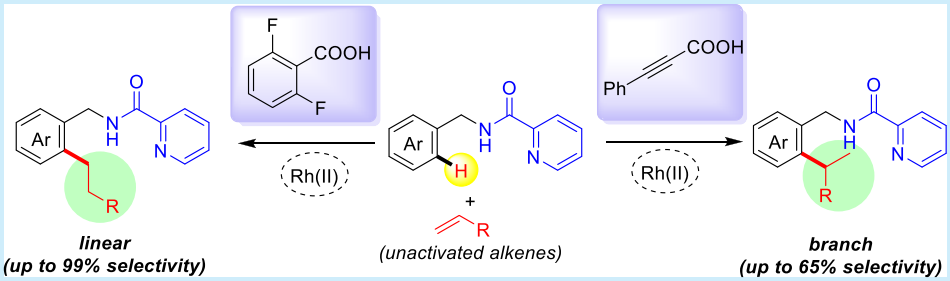
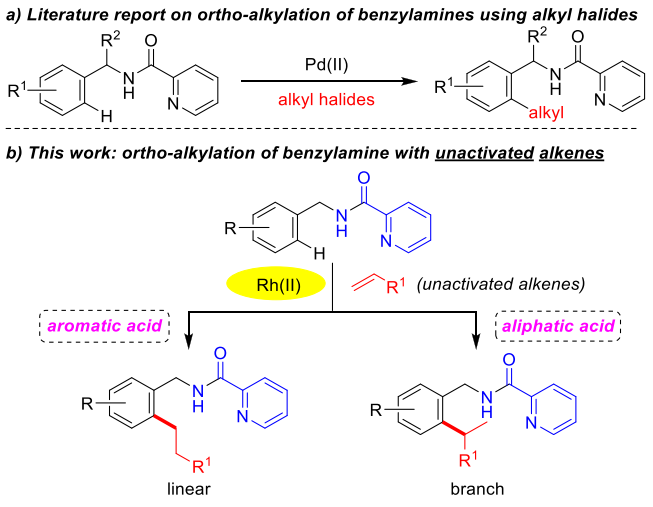


ABSTRACT: The Rh-catalyzed C−H alkylation of benzylamine derivatives with unactivated 1-alkenes that proceeds via a picolinamide directing group is reported. The crucial role of an acid additive in this transformation is confirmed. Aromatic acids showed high linear selectivity, and aliphatic acids provided branched alkylation products as the major product. The reaction has a broad scope for benzylamines and alkenes. Deuterium labeling experiments suggest that a Rh-carbene intermediate is involved in the case of linear product formation. A different reaction pathway, however, appears to be involved in the case of branched alkylation products, and this pathway also appeared to be a minor pathway in linear-selective reactions.

The formation of C−C bonds via reactions using unactivated alkenes is a subject of current interest in the field of C−H bond activation.[1] A pioneering example of C−H alkylation with alkenes was reported by Murai in 1993 who used ruthenium catalysts in conjunction with a ketone as a directing group to achieve *ortho*-C−H selective alkylation.[2] Since then, many reports on this subject have appeared but the scope of alkenes in C−H alkylation is still limited to activated alkenes, such as α,β-unsaturated carbonyl compounds, styrene derivatives, and norbornene.[1] Furthermore, only a few cases of branch-selective C−H alkylation using unactivated alkenes have been reported.[3]

Given the fact that benzylamine skeletons are widely found in various pharmaceutical and synthetic molecules,[4] its C−H functionalization with unactivated alkenes is a subject of interest. The reported method for the C−H alkylation of benzylamines involves the use of alkyl halides as coupling partners with the use of stoichiometric amounts of a base,[5] which results in the generation of hazardous products as waste materials (Scheme 1a).[6] On the other hand, C−H alkylation with alkenes offers a much more environmentally friendly reaction because all the molecules of the substrates and alkenes are fully utilized in forming the desired products. Given our ongoing interest in C−H alkylation reactions,[7] we investigated the *ortho*-alkylation of benzylamines with unactivated alkenes. In our previous work, we reported the Rh-catalyzed linear-selective, picolinamide chelation assisted C−H alkylation of benzylamine derivatives with activated alkenes, such as

Scheme 1. *ortho*-Alkylation of Benzylamines



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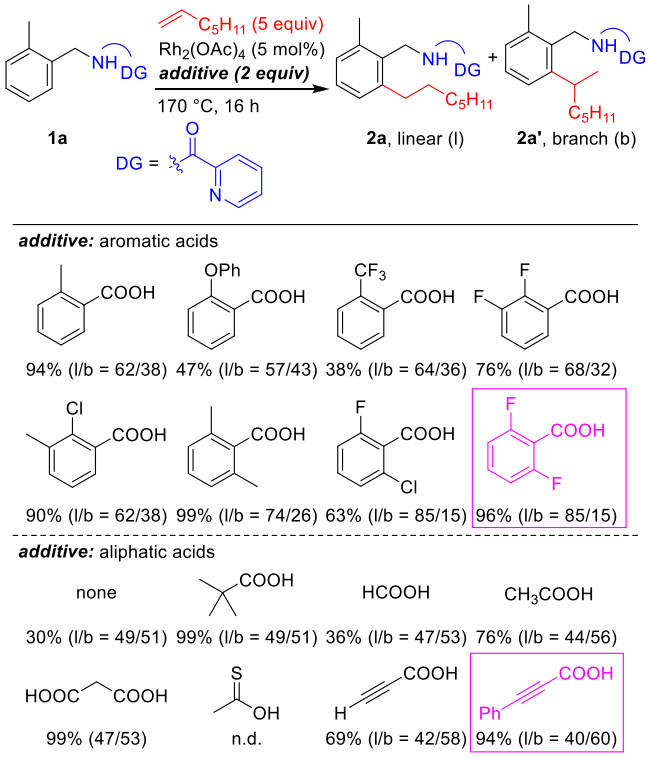
acrylates, styrenes, and maleimides.[71] Our objective in this study was to pursue the C−H alkylation of benzylamine derivatives with unactivated 1-alkenes. The results of our investigation highlight the crucial role of acid additives in achieving a high linear selectivity as well as methods for tuning the regioselectivity between linear and branch products (Scheme 1b). The results of deuterium labeling experiments suggest that two different reaction pathways are operative, one for linear and another for branch products.

The reaction was optimized by using the *N*-pyridinecarbonyl protected 2-methylbenzylamine **1a** and 1-heptene as model substrates. We screened a series of acid additives[8] for this reaction using 5 mol % of $Rh_2(OAc)_4$ as a catalyst and 5 equiv of 1-heptene at 170 °C under neat conditions for 16 h (Table 1). We initially examined aromatic acids as additives, and

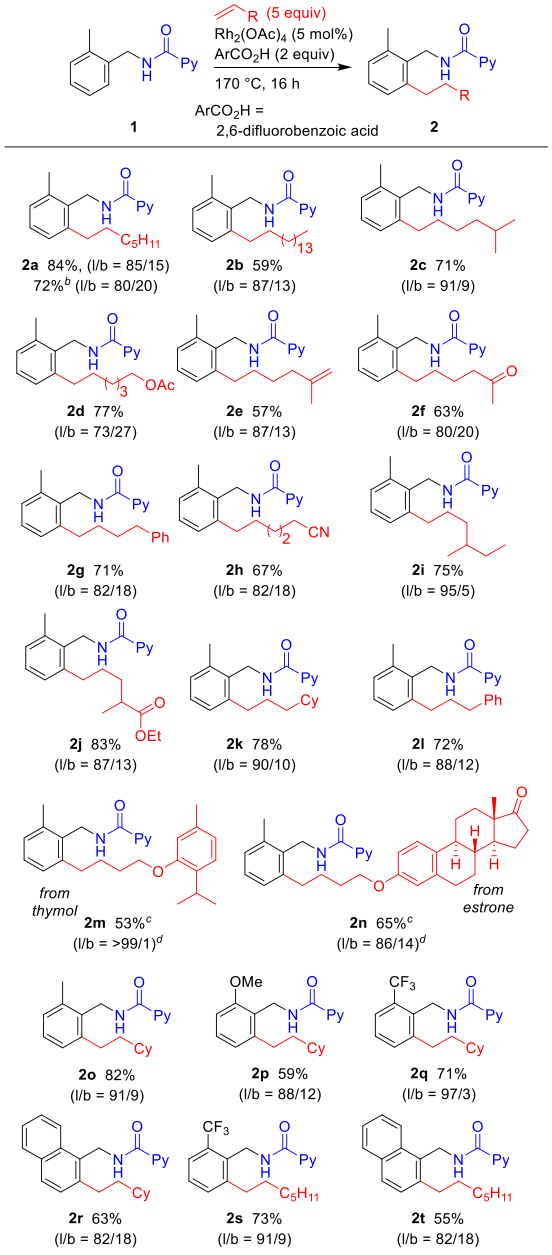
Table 1. Effect of an Additive in the C−H Alkylation of 1a with 1-Heptene[a]



[a]Reaction conditions: **1a** (0.2 mmol), 1-heptene (1.0 mmol), $Rh_2(OAc)_4$ (0.01 mmol), acid additive (0.4 mmol) at 170 °C for 16 h. Yields and linear/branch (l/b) ratios were determined by ^{1}H NMR analysis of the crude mixture. n.d. = not detected.

among them, 2-trifluoromethylbenzoic acid provided 64% linear selectivity. Finally, to our delight, the use of 2,6-difluorobenzoic acid gave excellent yields (96% NMR yield) of **2a** and **2a′** with a linear/branch ratio of 85/15. In the absence of an acid additive, only a 30% yield of product was observed with a nearly 1:1 ratio of linear and branch products. After screening several aliphatic acids, we found that the formation of the branched product was slightly favored over the linear product. Finally, phenylpropiolic acid provided the desired product in high yield with the ratio 60/40 in favor of the branched product **2a′**. We were not able to improve the ratio for branch selectivity further. However, it is noteworthy that the acid used in the reaction plays a crucial role in tuning the

Scheme 2. Scope of Alkenes and Amines (Linear Selective)[a]



[a]Reaction conditions: **1** (0.2 mmol), 1-alkene (1.0 mmol), $Rh_2(OAc)_4$ (0.01 mmol), 2,6-difluorobenzoic acid (0.4 mmol) at 170 °C for 16 h. Linear/branch (l/b) ratio was determined by ^{1}H NMR analysis of the crude mixture. Isolated yields are shown. [b]Gram scale (5 mmol scale) reaction was performed where 2 mL toluene was additionally used as solvent. [c]0.5 mL of toluene was additionally used as solvent. [d]Due to the complexity of the NMR spectrum of the crude material, the linear/branch (l/b) ratio was determined after isolation.

ratio of linear and branched alkylation products and the reaction involves a rare example of branch-selective C−H alkylation with unactivated alkenes.

With the optimized reaction conditions in hand, we next examined the substrate scope for this linear-selective alkylation reaction by using 2 equiv of 2,6-difluorobenzoic acid as an additive (Scheme 2). The reaction of **1a** with 1-heptene gave the desired product **2a** in 84% isolated yield with an 85/15 = l/b (linear/branch) ratio. The use of 5-methyl-1-hexene gave **2c** in good yield and high selectivity (71%, l/b = 91/9). Some

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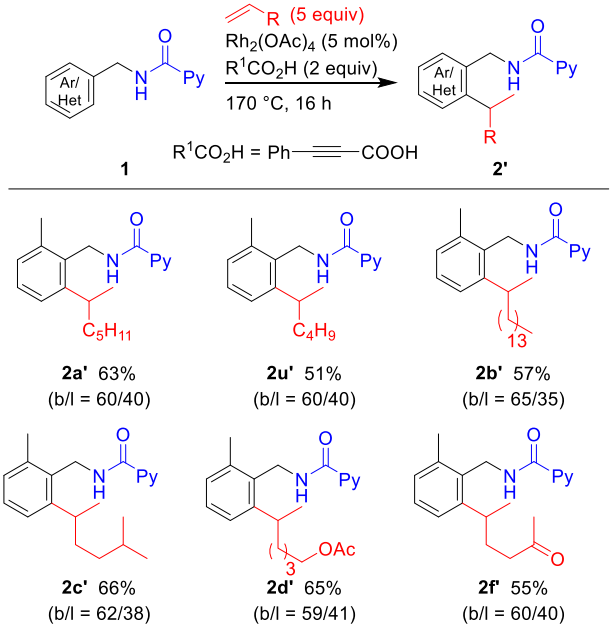
functional groups were suitable for use in this reaction, such as acetate (**2d**), ketone (**2f**), and cyano (**2h**), and all provided the desired products in good to high yields. This alkylation reaction was selective for monosubstituted alkenes over disubstituted alkene moieties; thus, **2e** was exclusively obtained and the disubstituted alkene moiety remained intact. 4,4-Disubstituted and allyl substituted alkenes (**2i**–**2l**) generally showed an increased ratio of linear/branch products containing an ester (**2j**) and other functionalities with satisfactory yield and up to 95% linear selectivity (**2i**). Biologically active substrates[9] also reacted to afford the corresponding alkylation products (**2m** and **2n**). Vinylcyclohexene was one of the more suitable alkenes for this reaction, providing **2o** in high yield and with high selectivity. Next, the scope of benzylamines for this reaction was examined. The 2-methoxybenzylamine derivative was reacted with vinylhexane to obtain **2p** in good yield with high selectivity. The electron-deficient 2-trifluoromethyl substituent also provided the desired product **2q** in high yield and excellent regioselectivity (l/b = 97/3). A naphthylmethylamine (**2r**) derived substrate was well tolerated for this reaction.

The scope for branch-selective reaction was then investigated using phenylpropiolic acid as the additive (Scheme 3).

Scheme 3. Scope of Alkenes (Branch Selective)[a]

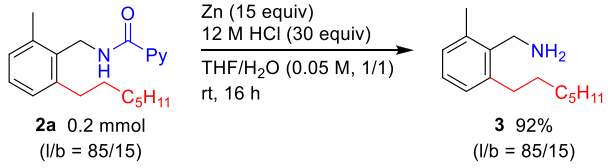


[a]Reaction conditions: **1** (0.2 mmol), 1-alkene (1.0 mmol), $Rh_2(OAc)_4$ (0.01 mmol), phenylpropiolic acid (0.4 mmol) at 170 °C for 16 h. Branch/linear (b/l) ratio was determined by ^1H NMR analysis of the crude mixture. Isolated yields were shown.

It was found that 1-hexadecene (**2b′**) also gave the desired products with up to 65% branch selectivity and **2c′** was obtained from 5-methyl-1-hexene in high yield with a 62/38 ratio. Some functional groups such as ester (**2d′**) and ketone (**2f′**)-containing alkenes successfully led to the formation of branch products as major products. These results are only preliminary results, indicating that the reaction was branch-selective, but that further optimization would still be needed.

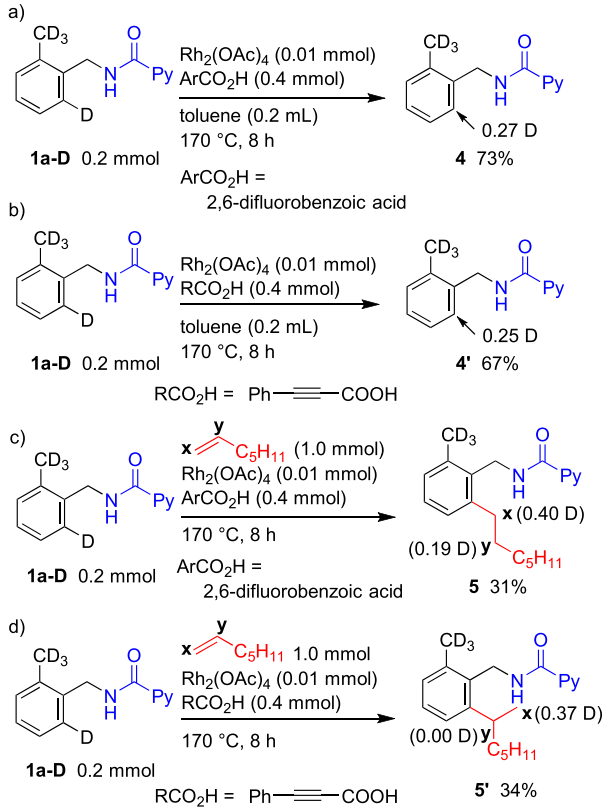
After the successful removal of the picolinamide directing group,[10] an excellent yield was achieved with the complete retention of linear/branch (l/b) selectivity (Scheme 4).

Scheme 4. Deprotection of Directing Group



Deuterium labeling experiments were conducted in order to elucidate the reaction mechanism for this alkylation reaction (Scheme 5). When the substrate **1a-D** was reacted in the absence of the alkene coupling partner in both systems, H/D scrambling at the *ortho*-position was observed in the recovered starting material in both cases (Scheme 5a and b), indicating that the *ortho*-C–H bond cleavage is reversible. When the deuterated substrate **1a-D** was reacted with 1-heptene under the optimized catalytic conditions using 2,6-difluorobenzoic acid as the additive for a shorter reaction time, 0.40 D was incorporated at the x position (Scheme 5c). However, deuterium incorporation was also observed at the y position although to a lesser extent (0.19 D). These data imply that the deuterium atom of the *ortho* C–D bond in **1a-D** is transferred to both the x and y positions. It therefore appears that the reaction proceeds via two different mechanisms for the formation of linear-selective product. On the other hand, when the branch-selective reaction was carried out using **1a-D** in the presence of phenylpropiolic acid as the additive, deuterium incorporation was only observed at the x position (0.37 D) and no deuterium incorporation was detected at the y position (0.00 D) (Scheme 5d). This result suggests that the branch-selective reaction proceeds via one major pathway

Scheme 5. Deuterium Labelling Experiments



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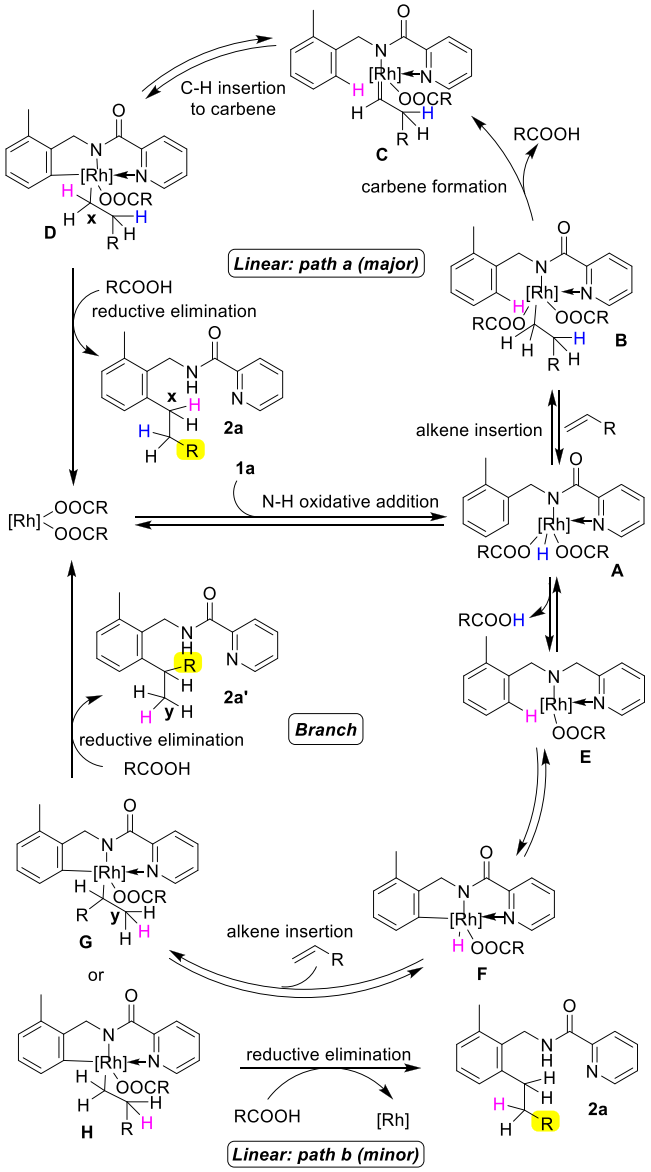
where the deuterium atom from *ortho* C−D bond is transferred only to the x position.

A reaction mechanism is proposed based on the results of deuterium labeling experiments (Scheme 6). Throughout the

Scheme 6. Proposed Catalytic Cycle



proposed catalytic cycle, we used the term [Rh] as a rhodium center because no clear evidence was obtained to confirm that the structure of the actual catalytic species of rhodium was either monometallic or bimetallic.[3h,11] The oxidative addition of a N−H bond to a Rh-center gives the Rh(IV) species **A**.[12] Two different catalytic cycles from the rhodium intermediate **A** are proposed to explain the formation of linear and branch products. Alkene insertion into the Rh−H bond in **A** gives the intermediate **B**.[7l] In the next step, α-elimination of the carboxylic acid in **B** results in the formation of a carbene intermediate **C** which appears to be the major pathway for producing the linear alkylation product.[7e,j,l] From **C**, C−H insertion into the carbene occurs to give intermediate **D**.[13] This is consistent with the deuterium labeling experiment in which a deuterium atom of the *ortho* C−D bond is largely transferred to the x position (Scheme 5c). Finally, reductive elimination occurs in the presence of the carboxylic acid to give the desired linear product **2a** and regeneration of the Rh-species continues the catalytic cycle. The other mechanism for the formation of branched products involves the elimination of the carboxylic acid from **A** to generate the intermediate **E**. Oxidative addition of the *ortho* C−H bond in **E** leads to the formation of **F** via a reversible pathway. As a result, H/D scrambling occurs at the *ortho* C−D bond (Scheme 5a and b). An alkene insertion generates both intermediate **G** (as evidenced by the incorporation of 0.37 D at the x position of **5′**, Scheme 5d) or **H** (as evidenced by the incorporation of 0.19 D at the y position of **5**, Scheme 5c). Subsequent reductive elimination in the presence of a carboxylic acid takes place from **G** to furnish the branch product **2a′** and from **H** to give the linear product **2a**. In this pathway, the *ortho* C−H bond is transferred to the y position in the branch product **2a′**. This path also appears to be the minor pathway for the linear alkylation reaction **2a**.

In summary, we report herein the Rh(II)-catalyzed C−H alkylation of benzylamine derivatives with unactivated alkenes by utilizing a picolinamide directing group. The crucial role of acid additives for producing high yields as well as a high linear/branch ratio was realized. Though there is still room for improving the branch selectivity, it is noteworthy that this preliminary investigation reports a rare example of the production of branch-selective alkylation products with unactivated alkenes. Mechanistic investigations indicate that two different reaction pathways are operative for product formation. A carbene mechanism is proposed as a major pathway for the formation of a linear product, and a reversible hydrometalation pathway is operative in the case of the formation of the branch product as well as the minor pathway for linear alkylation. Further studies directed to improving branch selectivity and a detailed understanding of the role of the acid additive in tuning the branch/linear ratio are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01224.

Experimental procedures and characterization data of all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Naoto Chatani − *Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan*; orcid.org/0000-0001-8330-7478; Email: chatani@chem.eng.osaka-u.ac.jp

Author

Amrita Das − *Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c01224

Notes

The authors declare no competing financial interest.

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