Mechanistic and Kinetic Studies of the Direct Alkylation of Benzylic Amines: A Formal C(sp³)−H Activation Proceeds Actually via a C(sp²)−H Activation Pathway

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Ⓢ *Supporting Information*

ABSTRACT: Mechanistic investigations of a Rh(I)-catalyzed direct C−H alkylation of benzylic amines with alkenes, formally an C(sp³)−H activation, reveal this reaction to proceed via imine intermediates and, hence, via C(sp²)−H activation. The reaction shows a primary kinetic isotope effect of 4.3 at the benzylic C−H position together with a reversible H−D exchange at the same position, which indicates that there are at least two distinct steps in which the corresponding C−H bonds are broken. The imine intermediates are shown to be converted to the final product under the reaction conditions, and a time course analysis of the alkylated imine intermediate shows that it is formed before the final amine product in the course of the reaction.

KEYWORDS: *heterogeneous reaction, Rh(I) catalysis, C−H activation, cyclometalation, direct alkylation, kinetic isotope effects, reaction mechanism*
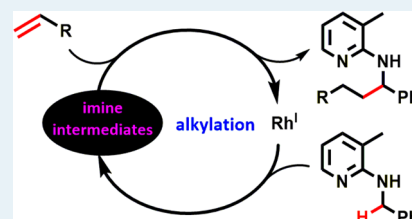
1. INTRODUCTION

In recent years, the development of catalytic C−H activation methods to selectively functionalize organic molecules at unsubstituted carbon atoms has emerged tremendously.[1] Especially, C−H activation of sp²-hybridized C−H bonds is now quite common and well established in the field.[2] On the other hand, C−H activation of sp³-hybridized C−H bonds still remains difficult and is therefore of special interest.[3] To gain a better understanding of these reactions and overcome the difficulties, detailed mechanistic investigations are important. They provide insight into the intrinsic problems and indicate in which step of the catalytic cycle optimization is necessary. A very useful and general method to achieve catalytic C−H activation is cyclometalation, which employs the aid of a nearby coordinating group to direct the catalyst selectively to one specific C−H bond to be activated and functionalized.[4] Our group recently reported several useful methods for the C−H activation of benzylic sp³ C−H bonds directed by 3-substituted pyridin-2-yls, including Ru(0)-catalyzed arylation employing arylboronates[5] and Ru(II)-catalyzed arylation of benzylic amines with aryl halides.[6] Herein, we report detailed mechanistic investigations into a Rh(I)-catalyzed method to alkylate benzylic amines using either alkyl bromides or alkenes. It should be noted that the alkylation of **1** using alkenes catalyzed by Ru(0) was already reported by the group of Jun in 1998;[7] however, to the best of our knowledge, there have not yet been any published reports using Rh(I) catalysis or contributions dedicated to detailed mechanistic investigations of such a transformation.

The initial idea behind this research was to use alkyl halides in direct alkylation reactions of benzylamines carrying a directing group on the amine function. We had developed several direct arylation protocols and gained significant experience and mechanistic understanding with this type of substrate. Therefore, we were confident that we could use the same system for direct alkylation using alkyl halides, a coupling between two sp³-hybridized carbon atoms.

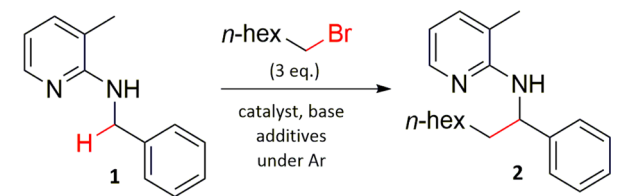## 2. RESULTS AND DISCUSSION

2.1. Screening of Direct C−H Alkylation Reactions. We started the development of direct alkylation of **1** using the conditions optimized for our direct arylation reactions but employing alkyl bromides as the alkyl source (Table 1: entry 1, conditions derived from the aryl chloride protocol; entry 2, conditions derived from the aryl bromide protocol).[6] Initial experiments using 1-bromoheptane as the alkyl source showed promising conversion of substrate **1** of ∼20% to the alkylated product **2** (Table 1, entries 1 and 2), but significant amounts of unreacted **1** (∼40%) remained. After intensively screening reaction conditions employing the [RuCl₂(*p*-cymene)]₂ catalyst without any significant improvements (not shown),[8] it turned out that [RhCl(cod)]₂ gave better conversion (Table 1, entry 3). Further optimizing the reaction conditions showed that the addition of ligands had no beneficial influence, and cyclohexanol proved to be unnecessary (Table 1, entries 5 and 6).[9] The best results were obtained when raising the temperature to 160 °C and changing the solvent to toluene (Table 1, entry 6).

After our optimization efforts, we started investigating the substrate scope with respect to alkyl bromides. We were especially interested in using secondary alkyl bromides because they should lead to branched products. However, when

Table 1. Selected Screening Results for Direct C—H Alkylation of 1 Using Alkyl Bromides

entry	catalyst[a]	base	additive	solvent	temp[b]	time	conversion of 1	conversion to 2
1	[RuCl₂(p-cymene)]₂ (0.1 equiv)	K₂CO₃ (3 equiv)	PPh₃ (0.05 equiv) cyclohexanol (1 equiv)	o-xylene	140 °C	24 h	56%	23%
2	[RuCl₂(p-cymene)]₂ (0.1 equiv)	K₂CO₃ (3 equiv)	KOPiv (0.3 equiv) cyclohexanol (1 equiv)	o-xylene	140 °C	24 h	60%	20%
3	[RhCl(cod)]₂ (0.1 equiv)	K₂CO₃ (3 equiv)	cyclohexanol (1 equiv)	o-xylene	140 °C	24 h	70%	31%
4	[RhCl(cod)]₂ (0.1 equiv)	K₂CO₃ (3 equiv)	cyclohexanol (1 equiv)	toluene	140 °C	24 h	73%	37%
5	[RhCl(cod)]₂ (0.1 equiv)	K₂CO₃ (3 equiv)	cyclohexanol (1 equiv)	toluene	160 °C	24 h	97%	70% (56%)[d]
6	[RhCl(cod)]₂ (0.1 equiv)	K₂CO₃ (3 equiv)		toluene	160 °C	24 h	98%	70%

[a]Equivalents based on monomer unit. [b]Reaction block temperatures and not inside temperatures of the reaction mixtures. [c]Based on GC analysis of the reaction mixture with dodecane as internal standard. [d]Isolated yield.

conducting the reaction with 2-bromobutane, we found that alkylation had taken place at the terminal carbon, and the same product was obtained as in the reaction with 1-bromobutane (Scheme 1).

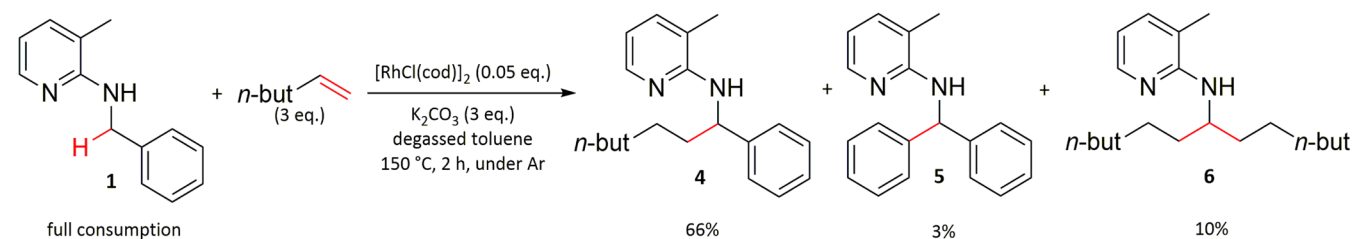**Scheme 1. Direct Alkylation of Benzylic Amine 1 Using Either 1-Bromobutane or 2-Bromobutane**
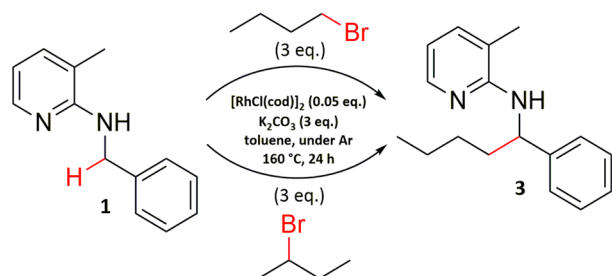
Because β-H-elimination is very common in alkyl complexes of transition metals, we suspected the reaction proceeds via the corresponding terminal alkene.[10] Hence, it was tested whether alkenes would react under these conditions to form the corresponding alkylated products. The first experiments using hex-1-ene gave the corresponding alkylated product **4** in 44% isolated yield. In addition, in experiments using either 1-bromododecane or 1-bromo-2-phenylethane, the correspond-

ing alkenes could be detected in low amounts by means of GC/MS in the reaction mixture. In the absence of [RhCl(cod)]₂, no alkene formation was observed, confirming a crucial role of the catalyst and excluding simple thermal elimination.

Because the conditions applied in the first experiments with alkenes stemmed from optimizing the alkyl bromide protocol, further screening experiments were carried out. Initial experiments showed that the alkylation reaction using alkenes proceeded considerably faster; therefore, the temperature could be reduced to 150 °C. In addition, using degassed toluene accelerated the reaction significantly. The optimized reaction conditions are shown in Scheme 2.

There are several features to be noted here. First, as can be seen in Scheme 2, we observed significant formation of two byproducts, **5** and **6**. At first sight, they seem rather surprising; however, their formation can be explained by C—C activations.[11] We conducted several experiments, discussed later (vide infra), to investigate their formation. Second, small amounts (below 1%) of the corresponding imines of **1** and **4** were detected in the reaction mixture throughout the whole reaction time. Third, K₂CO₃ proved to be absolutely crucial in this reaction because experiments without K₂CO₃ did not show any conversion to the corresponding alkylated product. In the reaction employing alkyl bromides, K₂CO₃ is conceptually needed to catch the HBr formed and, therefore, to drive the reaction to the products. In the case of alkenes, however, there

Scheme 2. Optimized Reaction Conditions for Direct C—H Alkylation of Benzylic Amine 1 Using Alkenes[a]

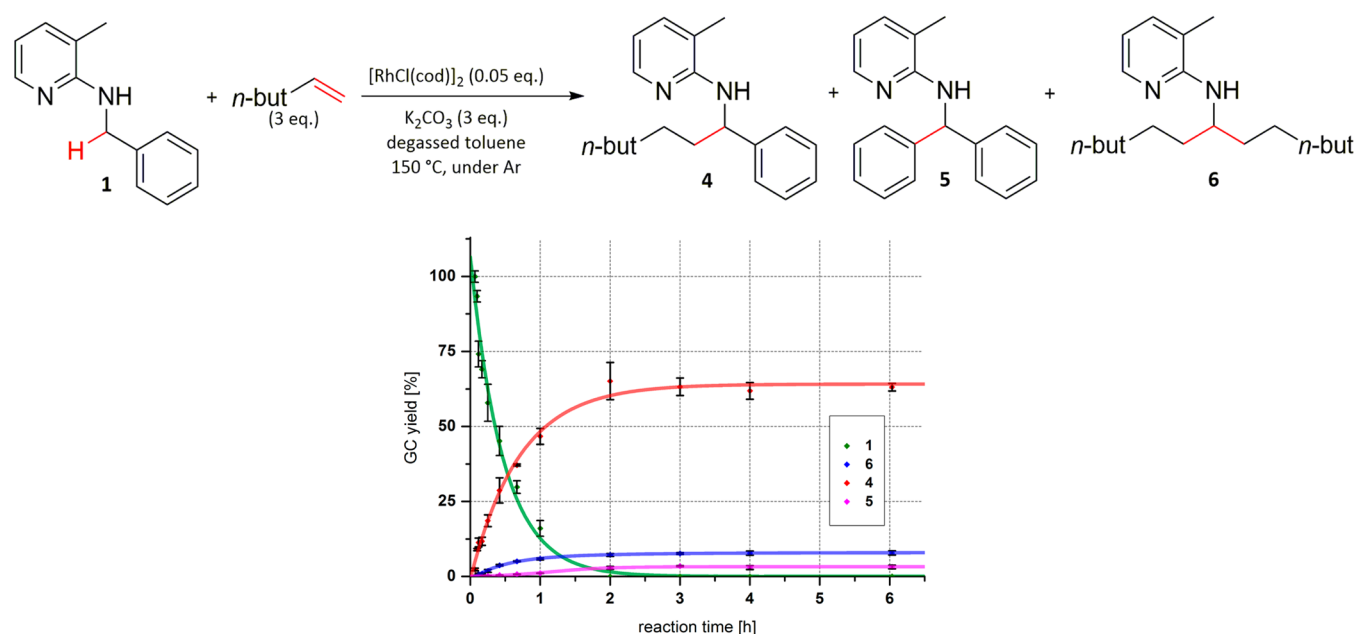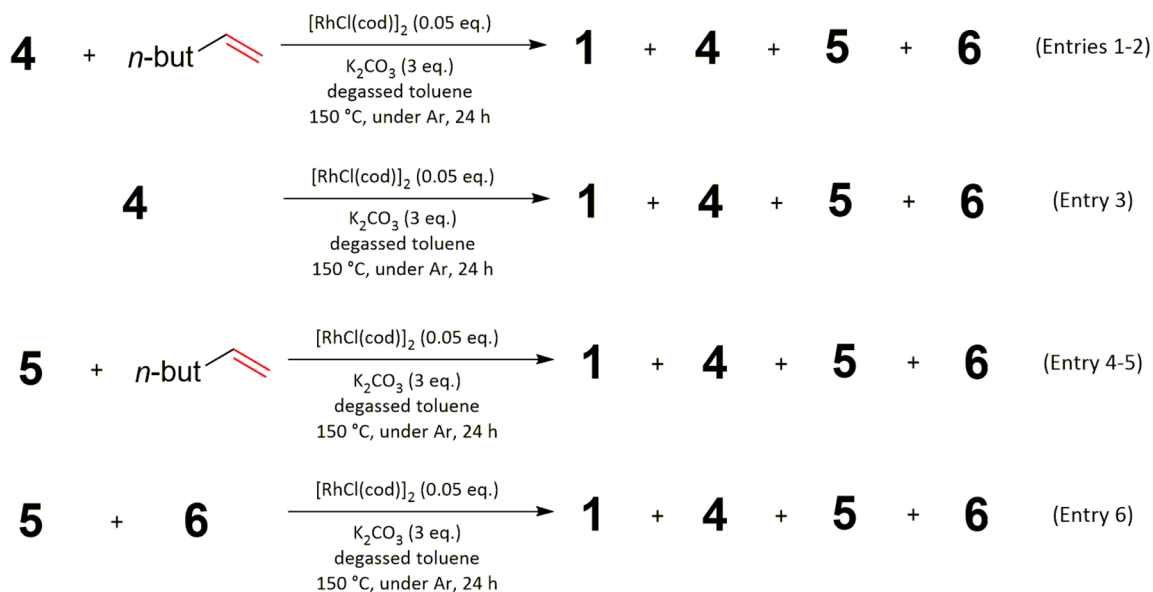

[a]Yields are calibrated GC yields.

Figure 1. Determination of the kinetic time course of direct C−H alkylations of benzylic amine **1** using hex-1-ene.

Table 2. Investigation of the Formation of the By-Products 5 and 6 in the Direct C−H Alkylation Using Hex-1-ene

entry	starting compd(s)	hex-1-ene amt, equiv	compd amt, %[a]			
			1	**4**	**5**	**6**
1	**4** (1 equiv)	3	<0.1	62	5	11
2	**4** (1 equiv)	6	<0.1	72	4	12
3	**4** (1 equiv)	0	2	76	2	3
4	**5** (1 equiv)	3	<0.1	4	68	<0.1
5	**5** (1 equiv)	6	<0.1	6	58	<0.1
6	**5** (0.5 equiv) + **6** (0.5 equiv)[b]	0	<0.1	1	42	46

[a]Determined at the end of the reaction; calibrated GC yields. [b]Sum of amounts of **5** and **6** was considered as 1 equiv.

is no formation of an acidic byproduct because the reaction toward **1** is formally an addition of a C−H bond across a double bond. Finally, only 79% of the initial amount of **1** is found in the products. Because we were not able to detect any other byproducts and the Rh catalyst used is capable of breaking C−C bonds, obviously, we suspect that there is significant decomposition of material to compounds that cannot easily be detected in the reaction mixture.

2.2. Kinetic Profile of the Direct Alkylation of 1 Using Hex-1-ene. As entry point to our mechanistic investigations, we determined the kinetic profile of the olefin alkylation protocol (Figure 1).[12]

There are some features to be noted. First, the reaction is finished after 2 h, and the amounts of **4**, **5**, and **6** remain constant thereafter. This can be rationalized either by inhibition or decomposition of the active catalyst under these conditions or by a reversible reaction among **4**, **5**, and **6**. Second, both **4** and **6** are formed more or less from the beginning, and no significant induction period is observed, except for the time the reaction mixture needs to reach a constant temperature.[13] This is very important because it allows us to easily determine kinetic parameters by using the method of initial rates (vide infra). From this kinetic profile, the initial reaction rate under the optimized reaction conditions was determined (See the Supporting Information for details).

2.3. Side Product Studies.
To gain more information about the side products observed in the reaction using alkenes, several experiments that subjected these side products to the reaction conditions were conducted (Table 2).

Entries 1 and 2 show that the initial product, **4**, can be converted to the two side products **5** and **6** by subjecting it to the reaction conditions. Without any alkene present (entry 3), compound **4** is even converted back to **1**, showing that its formation is reversible under the reaction conditions. Entries 4 and 5 indicate that compound **5** can be converted to **4** under the reaction conditions, showing that its formation is also reversible. Finally, mixing **5** and **6** in the absence of alkene leads to formation of **4** (entry 6). Overall, these experiments demonstrate that the formation of **5** and **6** starting from **4** and the formation of **4** from **1** are, in principle, reversible and that C−C bond cleavages are occurring in the reaction mixture to a significant extent.

Interestingly, no side product deriving from bisalkylation of the benzylic position was detected in any experiment. One possible explanation is that formation of a quaternary carbon is disfavored because of steric hindrance. Alternatively, if the alkylation does not occur on the amine substrate **1** but proceeds via an imine intermediate thereof, formation of a quaternary carbon is impossible. This can be considered as a first finding, pointing toward an imine mechanism. In addition, in a similar system using imines with the same directing group and also employing Rh(I) catalysis, similar C−C activation reactions are already known.[14]

2.4. Base Studies.
In the reaction using alkenes, a very pronounced dependence of the initial rate on the adsorbed water content of K_2CO_3[15] was found, which is depicted in Figure 2. The higher the content of adsorbed water in the base, the higher the observed initial reaction rate.

That water is beneficial for C−H activation reactions is already known in some cases.[16] However, to the best of our knowledge, there has been no report on using a base effectively insoluble in the reaction solvent containing superficially adsorbed water to increase the reaction rate. At present, this significant dependence on the adsorbed water content cannot be satisfactorily interpreted, and further investigations need to be carried out.

2.5. Kinetic Isotope Effect Studies.
To gain more information about the rate-determining step of the reaction, kinetic isotope effect (KIE) studies were conducted. In C−H activation reactions, one major question is always whether the oxidative addition of the metal catalyst into the C−H bond is rate-determining. Therefore, in a first study, the KIE of the benzylic C−H bonds was determined (Scheme 3) by measuring the initial rate of the reaction with the deuterated
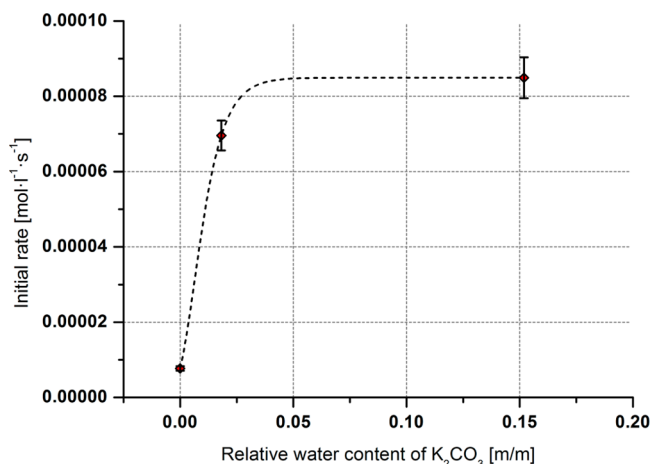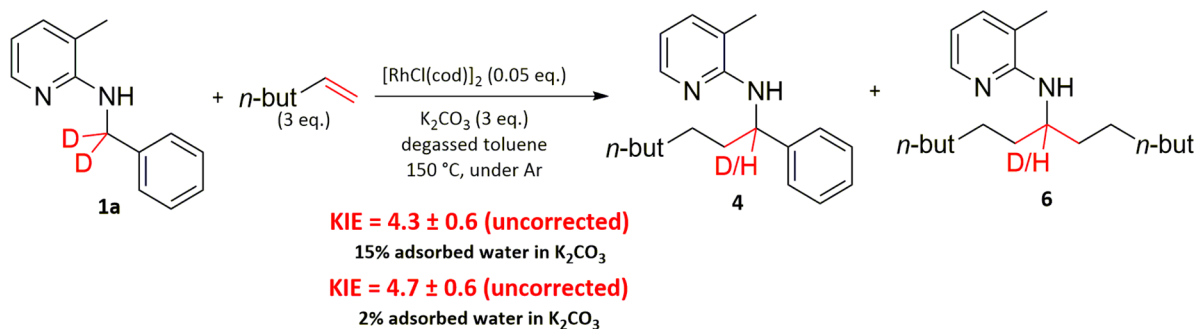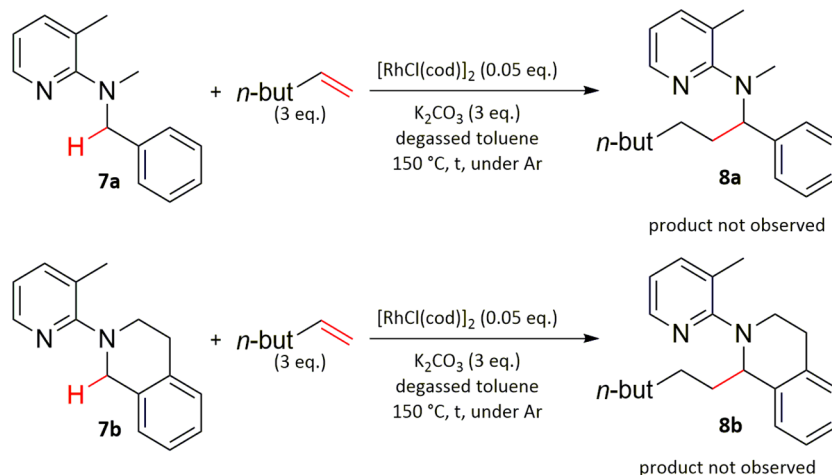

Figure 2. Dependence of the initial reaction rate on the adsorbed water content of K_2CO_3 for the direct C−H alkylation using hex-1-ene in dry toluene.

compound **1a** and comparing it with the initial rate we determined for **1** under the same reaction conditions.

The large observed value indicates a primary KIE and suggests that the benzylic C−H bond is broken in the rate-determining step; that is, oxidative addition into the C−H bond is rate-determining. There are several things to notice. First, the KIE is independent of the adsorbed water content of K_2CO_3. This is very important so that the result can be compared with the KIE study of the N−H bond (vide infra). Second, there is significant H−D exchange observed in unreacted **1a** during the reaction. Actually, the H−D exchange is higher than the total amount of products formed (details in the Supporting Information). This seems contradictory to the primary KIE observed because this would suggest a (compared with the overall reaction rate) fast and reversible C−H activation. However, it makes perfect sense if the reaction proceeds over the corresponding imine via a fast, reversible amine-to-imine interconversion, which would account for the H−D exchange observed. The consecutive oxidative addition into the sp^2-hybridized C−H bond would then be rate-determining, accounting for the large primary KIE.

In a second study, the KIE of the N−H bond was determined (Scheme 4) to find out whether this hypothesis could be supported. The KIE was determined by comparing the initial reaction rate of deuterated compound **1b** and the initial rate obtained for the undeuterated compound **1** under the same reaction conditions. It should be noted that this is not an easy experiment to perform because the N−D readily exchanges with any H_2O that is introduced into the reaction mixture. The concomitant extent of H−D exchange has to be minimized to obtain a meaningful result.

Before the value is discussed, it is important to mention that because of the adsorbed water introduced with K_2CO_3, the H−D exchange in this experiment series was high.[17] Using K_2CO_3 with 2% of adsorbed water resulted in an H−D exchange low enough (even though still 56%) to determine the KIE reliably by correcting the observed initial rate (see the Supporting Information for details). The small KIE value observed for the N−H bond indicates that the N−H bond is not broken in the rate-determining step, excluding a mechanism in which one of the benzylic C−H bonds and the N−H bond are broken simultaneously.[18] However, it rather suggests a secondary KIE, which would support the previously established hypothesis of a

Scheme 3. Determination of the KIE of the Benzylic C−H Bonds in the Direct C−H Alkylation of 1 Using Hex-1-ene

KIE = 4.3 ± 0.6 (uncorrected)
15% adsorbed water in K_2CO_3
KIE = 4.7 ± 0.6 (uncorrected)
2% adsorbed water in K_2CO_3

Scheme 4. Determination of the KIE of the N−H Bond in the Direct C−H Alkylation of 1 Using Hex-1-ene

KIE = 1.3 ± 0.1 (corrected)
2% adsorbed water in K_2CO_3
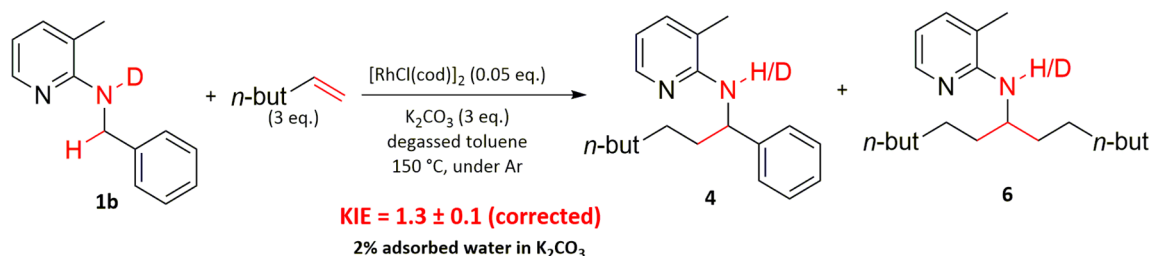
Scheme 5. Attempted Alkylation of Tertiary Benzylic Amines 7a and 7b

product not observed

product not observed

fast, reversible imine formation prior to rate-determining oxidative addition into the C−H bond.

2.6. Substrate Scope Investigation: Tertiary Amines. The simplest experiment series to support or exclude an imine mechanism is to test whether tertiary benzylic amines are converted to the corresponding alkylated products under the reaction conditions (Scheme 5). If the formation of the corresponding products was observed at a similar rate as compared with secondary benzylic amines, this would be evidence against an imine mechanism because the formation of the corresponding iminium ion is not expected to be occurring at a similar rate, if possible at all.[19]

In neither experiment were any alkylated products observed, even after 24 h of reaction time, again supporting the hypothesis of the reaction proceeding over the corresponding imines.

2.7. Imine studies. On the basis of our previous results, the hypothesis is that amine 1 is converted to imine 9 and gets alkylated and the alkylated imine 10 is then converted back to

alkylated amine 4 (Scheme 6). Of course, these interconversions would occur on a rhodium complex. It should be noted that a similar amine-to-imine oxidation prior to alkylation has been proposed previously in the literature.[20] However, in that example, the final reaction product is a ketone, which is formed after hydrolysis of the imine, so the amine-to-imine interconversion was not reversed.

It was hypothesized that if imines 9 and 10 were intermediates in the reaction, they should be converted to the products of the reaction under the reaction conditions. However, subjecting only imine 9 as starting material to the reaction conditions resulted in only a very low conversion (see the Supporting Information for more details). Therefore, crossover experiments were performed using 0.05 equiv of imines 9 and 10, respectively, together with 1 equiv of amine 1c as starting materials (Scheme 7).

In the first crossover experiment, amine 1c was alkylated in the presence of imine 9, which was completely converted to the alkylated amine 4. In the second, the same amine, 1c, was

Scheme 6. Hypothetical General Reaction Course of the Direct C−H Alkylation of Benzylic Amine 1
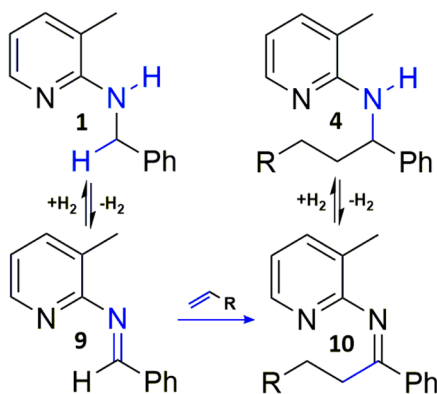
reacted in the presence of alkylated imine **10**. Full consumption of **10** was observed, and it was converted to products **4** (2%), **5** (1%), and **6** (1%) with a total recovery of 80% (4% found from 5% used). These results show that both imine **9** and alkylated imine **10** are transformed to the corresponding amine products under the reaction conditions.

2.8. Investigation of Imine Intermediate Kinetics. All previous experiments are in agreement with a reaction mechanism proceeding via the imines **9** and **10**. Still, a reaction mechanism in which the alkylation takes place at the amine and the imines are formed in off-cycle reactions cannot yet be excluded. All three mechanistic scenarios depicted in Scheme 8 are possible. Either imines **9** and **10** are formed as off-cycle products from **1** and **4**, respectively (scenario 1), or the reaction mechanism is proceeding through imines **9** and **10** as intermediates, with the alkylation taking place at the imine (scenario 2). Scenario 3 is a combination of those two cases in which both pathways occur at a similar rate.

To distinguish between scenarios 1 and 2, we developed a method based on simplified kinetic models. Because compounds **10** and **4** are interconvertible, the change of the ratio of these two compounds over time can deliver the desired information. If the ratio of the concentrations of **10** and **4** is decreasing over time in an initial reaction period, it would mean that **10** is formed before **4** in the course of the reaction, supporting the imine mechanism. If the same ratio is increasing,

the opposite is true.[21] The complete mathematical background of this method is given in the Supporting Information. However, it is also shown in the Supporting Information that experimentally, the third mechanistic scenario is very hard if not impossible to exclude by this method.

Plotting the ratio of imine **10** to amine **4** over time, the following result was obtained (Figure 3). The decreasing ratio of imine **10** to amine **4** over time is in accordance with mechanistic scenario 2 in which the reaction occurs at the imine, not at the amine, and excludes scenario 1. However, as already mentioned, mechanistic scenario 3 in which both pathways occur at a similar rate cannot be excluded. Because mechanistic scenario 2 is the significantly simpler explanation for all our observations, we prefer it over scenario 3. Either way, the reaction would proceed (at least to a significant extent) over the corresponding imines.

2.9. Mechanistic proposal. On the basis of our experimental results, we propose the following general mechanistic outline for the direct C−H alkylation using alkenes (Scheme 9).

The catalytic cycle starts with coordination of **1** to a rhodium species (**I** in Scheme 9), then the corresponding amine complex **II** is reversibly interconverted to the corresponding imine (**III**), which is supported by the H−D exchange observed in unreacted **1** in the KIE studies of the benzylic C−H bond. Imine **9** can then be released from this complex (not depicted in Scheme 9) or it reacts in the rate-determining oxidative addition into the sp²-hybridized C−H bond to form a cyclometalated intermediate, **IV**, which is supported by the large KIE of about 4−5 observed for the benzylic C−H bond. Then, alkylation of intermediate **IV** with alkene yields the rhodium complex **V** of the alkylated imine **10**. This imine can now be reversibly released (not depicted in Scheme 9) or it is converted to the alkylated amine coordinated to Rh (**VI**), which is released as the main product of the reaction. Since the whole reaction is shown to be in principle reversible, all mechanistic steps are also depicted to be reversible.

It should be noted that additional ligands coordinated to Rh were omitted because nothing is known about them on the basis of our experiments. In addition, it is not known how the two hydrogen atoms are bonded to the catalyst. If they would be bonded directly to Rh, the oxidative addition into the C(sp²)−H bond of the imine would result in a Rh(V) species

Scheme 7. Crossover Experiments Investigating Whether Imines 9 and 10 Are Converted to the Corresponding Products of the Direct C−H Alkylation Using Hex-1-ene Together with Benzylic Amine 1c
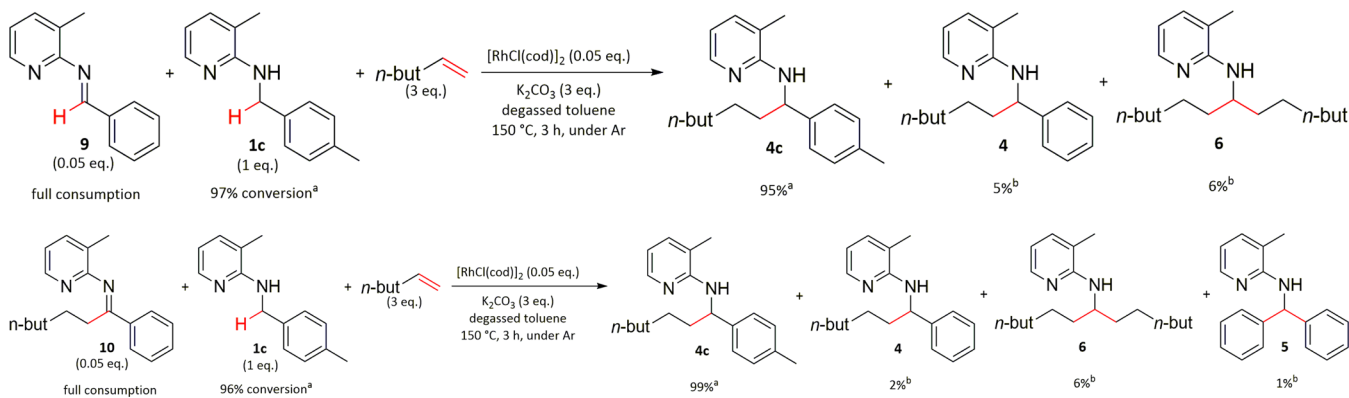
[a]Based on GC analysis of the reaction mixture with dodecane as internal standard, assuming a conversion factor of 1 (not calibrated). [b]Calibrated GC yields.

Scheme 8. Possible Mechanistic Scenarios for the Direct C−H Alkylation of Benzylic Amine 1 Using Alkenes[a]
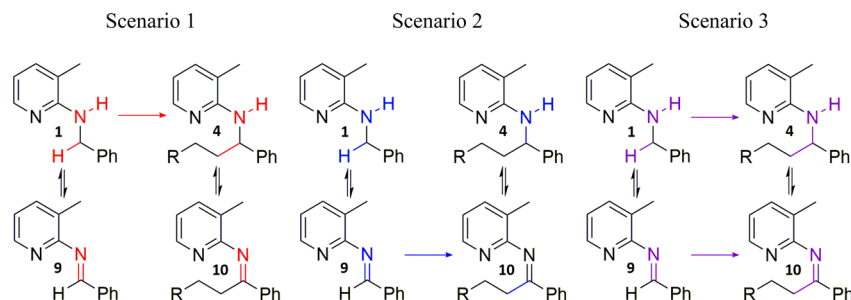
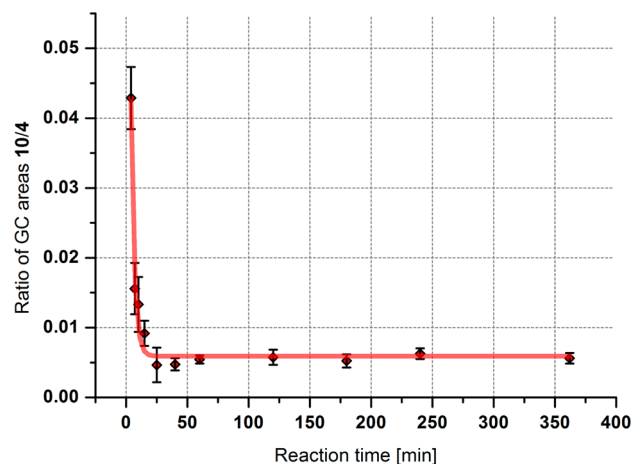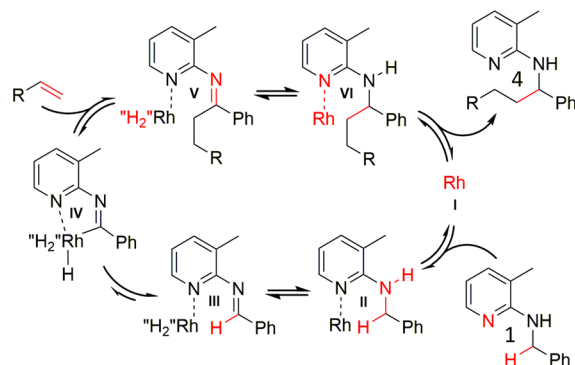[a]For simplicity, schemes are not fully stoichiometrically balanced.

Figure 3. Time course of the ratio of the GC areas under the peaks of imine **10** and amine **4**.

Scheme 9. Mechanistic Proposal for the Direct C−H Alkylation of Benzylic Amines Using Alkenes[a]

[a]The rate-determining step is indicated by a significantly shorter forward reaction arrow. "H₂" emphasizes that it is not known how the two hydrogen atoms are bonded to the catalyst.

that is not very common in literature but was reported on previous occasions, although on different complex systems.[22] Alternatively, the interconversion of amine and imine could also proceed by transfer hydrogenations with a ligand on Rh. Transfer hydrogenations employing rhodium catalysis are quite common in the literature.[23]

Altogether, there are several important issues that remain open in this mechanistic investigation. First, almost nothing is known about the intermediate Rh species involved in the catalytic cycle. Second, the mechanism of the amine-to-imine interconversion is not known, either. Third, the role of K_2CO_3 and the water introduced with it need to be investigated. The last major unresolved issue is how the exchange between H and Ph in the interconversions of **4** and byproducts **5** and **6** actually occurs. These points certainly need to be addressed in follow-up studies, which are under way in our lab to get more insight into the reaction mechanism.

3. CONCLUSION

Benzylic amines were alkylated using both alkyl bromides and alkenes, and the latter transformation was investigated in detail. Kinetic and mechanistic evidence shows that the reaction does not proceed directly over the amines but instead over the corresponding imines, showing that the formal $C(sp^3)$−H activation reaction proceeds mechanistically over an $C(sp^2)$−H activation pathway. Additional experiments need to be performed to investigate the role of K_2CO_3 in the reaction and gain insight into the nature of the rhodium complexes involved in the catalytic cycle. Furthermore, the alkylation using alkyl bromides needs to be investigated and exploited further because gaseous short-chain alkenes could be avoided using the corresponding alkyl bromides.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/cs501924c.

Full experimental details, spectroscopic data for all new compounds, data points from kinetic experiments and full mathematical details (PDF)

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Notes
The authors declare no competing financial interest.

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