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Vincent Boquet, Junio A Guimaraes Naves, Erwan A Brunard, Ali Nasrallah, Mylène Joigneaux, et al.. Rhodium(II)-Catalyzed Selective C(sp<sup>3</sup>)-H Amination of Alkanes. *European Journal of Organic Chemistry*, 2023, 26 (32), 10.1002/ejoc.202300352 . hal-04209991

**HAL Id: hal-04209991**

**<https://hal.science/hal-04209991>**

Submitted on 18 Sep 2023

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# Rhodium(II)-Catalyzed Selective C(sp<sup>3</sup>)-H Amination of Alkanes

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In memory of David A. Evans

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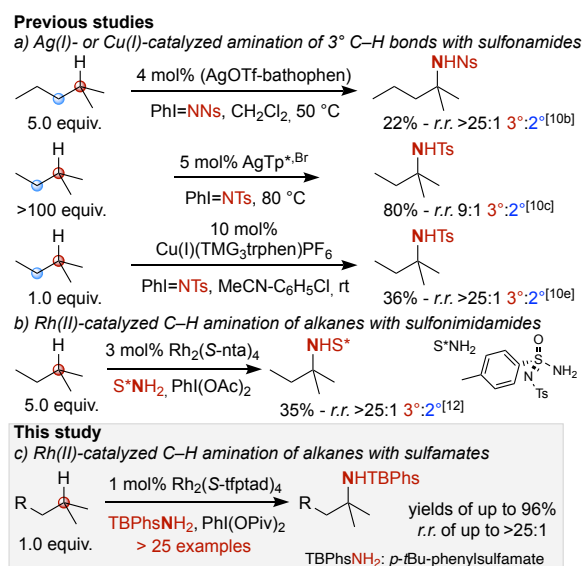
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Supporting information for this article is given via a link at the end of the document.

**Abstract:** The development of an efficient catalytic system enabling the conversion of alkanes to valuable nitrogen-containing building blocks is reported. Light alkanes can be selectively functionalized by an intermolecular C(sp<sup>3</sup>)-H amination reaction that proceeds at room temperature in the presence of only 1 mol% of a dirhodium(II) complex. Selective amination of tertiary C(sp<sup>3</sup>)-H within acyclic or cyclic alkanes used as limiting components leads to the corresponding amides isolated with yields in the 51-96% range. The reaction, that can be performed on a gram-scale, applies with equal levels of efficiency and selectivity to more complex hydrocarbons.

## Introduction

The use of alkanes as a source of energy can be considered as a waste of an abundant carbon-based feedstock. From the organic chemist's eye, they indeed represent a carbon pool for chemical synthesis but their conversion remains a challenge that requires the discovery of efficient and selective reagents.<sup>[1]</sup> To this end, the emergence of catalytic C-H functionalization reactions offers a solution.<sup>[2]</sup> However, because alkanes are devoid of functional groups and possess C-H bonds of similar reactivity with high dissociation energies, the development of efficient reactions is much more challenging, both in terms of yields and selectivity.<sup>[3,4]</sup> Nitrogen is a cornerstone atom in life sciences as well as in asymmetric catalysis.<sup>[5]</sup> Its ubiquity makes any new amination reactions of interest for the design of functional molecules. Needless to say, the introduction of a nitrogen atom into light alkanes represents an appealing strategy to convert them into valuable building blocks. To this end, several processes were reported with the advent of metal catalysis.<sup>[6]</sup> The use of copper(I) complex and *tert*-butyl peroxide led to perform alkane C-H amination *via* Kharasch-Sosnovsky type transformations, which proceeded preferentially at secondary positions.<sup>[7]</sup> Efficient reactions were also reported based on catalytic nitrene C(sp<sup>3</sup>)-H insertions.<sup>[8]</sup> When the nitrene was generated from an azide in the presence of a bulky copper(II) complex or a Cp\*Co(III) complex, the selective formation of secondary or primary amides was observed.<sup>[9]</sup> On the other hand, nitrenes can be produced using halide(III) reagents (Scheme 1a).<sup>[10]</sup> Under these conditions, silver or copper



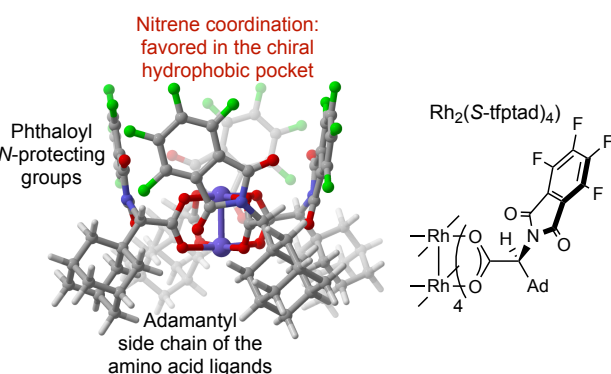
**Scheme 1.** Metal-catalyzed amination of tertiary C(sp<sup>3</sup>)-H bonds of alkanes.

complexes were shown to catalyze the nitrene insertion into tertiary C(sp<sup>3</sup>)-H bonds with high regioselectivity but yields often moderate to low.<sup>[10b,c,e]</sup> Equally selective metal-free conditions involving iminobromanes were also described,<sup>[10d]</sup> however, the efficiency of these methods is limited making the use of an excess of alkanes necessary to reach good yields.

Recent investigations in carbene chemistry demonstrated that dirhodium(II) complexes are unique to mediate the selective functionalization of alkanes.<sup>[11]</sup> These paddlewheel complexes are also competent catalysts for nitrene additions. Our group reported their catalytic activity in the amination of light alkanes with sulfonimidamides as nitrene precursors, albeit with the same aforementioned limitations (Scheme 1b).<sup>[12]</sup> Subsequent studies, however, showed that high yielding selective nitrene C(sp<sup>3</sup>)-H insertions or alkene aziridination can be performed with sulfamates.<sup>[13]</sup> These results convinced us to investigate the selective amination of alkanes under these conditions. In this communication, we present the outcome of our studies that led to develop an efficient catalytic system for the conversion of alkanes to amides (Scheme 1c).

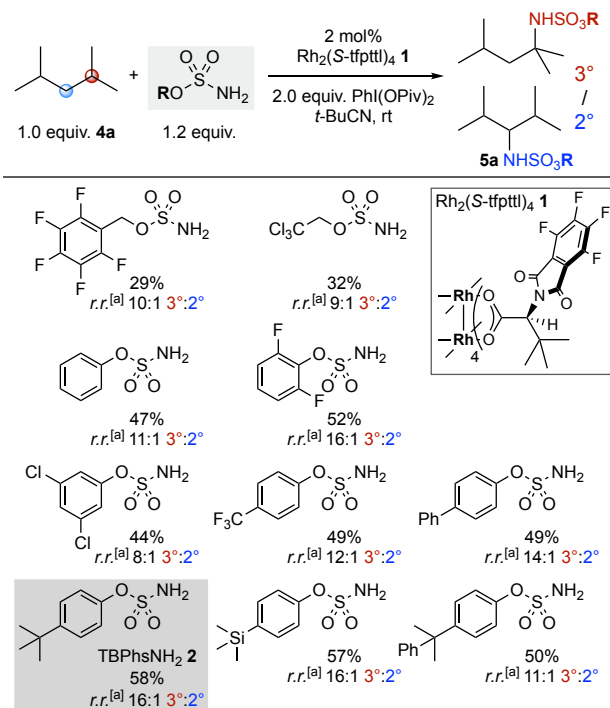
## Results and Discussion

Recent studies highlighted the unique reactivity profile of metal-bound nitrenes generated from sulfamates and easily accessible chiral  $C_4$ -symmetrical dirhodium(II) tetracarboxylates having ligands derived from amino acids. In these complexes, the four imido groups are known to orient in an “all-up” conformation,<sup>[14]</sup> delineating a  $C_4$ -symmetrical pocket into which the rhodium-bound nitrene is formed (Figure 1). This feature led us to develop selective  $C(\text{sp}^3)\text{-H}$  amination reactions either at secondary benzylic or tertiary positions.<sup>[13,15]</sup> These results were a starting point to search for the optimal combination of the rhodium(II) complex and the sulfamate to develop an efficient selective amination of alkanes.

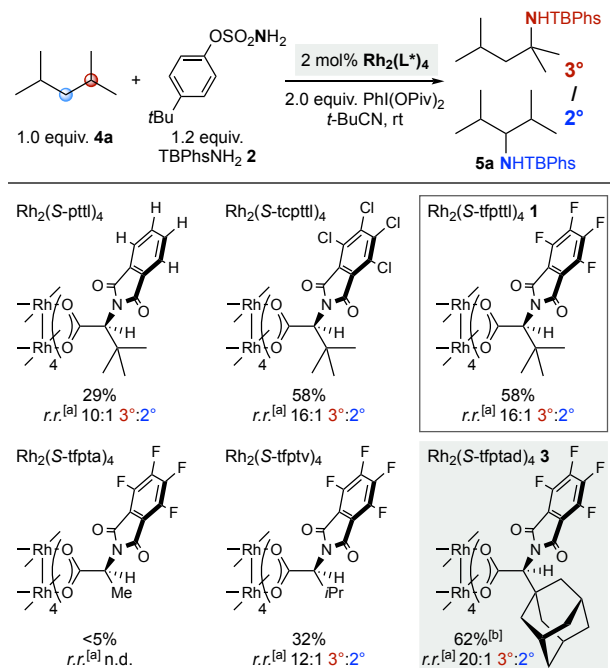


**Figure 1.** Structure of the  $\text{Rh}_2(\text{S-tfptad})_4$  complex obtained by DFT.

Our investigation initially focused on the influence of the sulfamate on both the yield and the site-selectivity for the intermolecular amination of alkanes used as the limiting component (Scheme 2). The reactions were performed in the presence of 2,4-dimethylpentane **4a** and the chiral complex dirhodium(II) tetrakis[*N*-tetrafluorophthaloyl-(*S*)-*tert*-leucinate] ( $\text{Rh}_2(\text{S-tfpttl})_4$  **1**) that was the reference catalyst in our previous studies.<sup>[13c,d]</sup> First experiments indicated that benzylic and aliphatic sulfamates afforded a mixture of  $3^\circ$  and  $2^\circ$  amides with a regioisomeric ratio (r.r.) of 9-10:1 and yields in the 30% range, while products resulting from the amination at primary positions were not observed by NMR. The screening confirmed the higher reactivity of aromatic sulfamates in the amination of tertiary positions, with the best results being obtained in the case of *ortho*- and *para*-substituted reagents.<sup>[13c]</sup> Among the sulfamates evaluated, *p*-*t*Bu-phenyloxysulfonamide (TBPhsNH<sub>2</sub>) **2** proved to be the most reactive and selective since the corresponding tertiary amide derived from 2,4-dimethylpentane was isolated in 58% yield and with a  $3^\circ:2^\circ$  selectivity of 16:1. In addition, *p*-*t*Bu-phenol is cheap and its conversion to the sulfamate is high-yielding. Thus, this sulfamate was chosen to further optimize the reaction conditions. A catalyst screening allowed us to evaluate the influence of both the nitrogen protecting group and the side chain of the amino acid ligand on the course of the reaction (Scheme 3). Regarding the phthalimido group, the presence of halogens on the aromatic ring was important for the reactivity and the site-selectivity. Halogen-bonding interactions between the rings are indeed necessary to maintain the chiral crown conformation of  $C_4$ -symmetrical rhodium(II) tetracarboxylates,<sup>[14]</sup> that delineates the pocket into which the nitrene C–H insertion efficiently takes place.<sup>[13d]</sup>

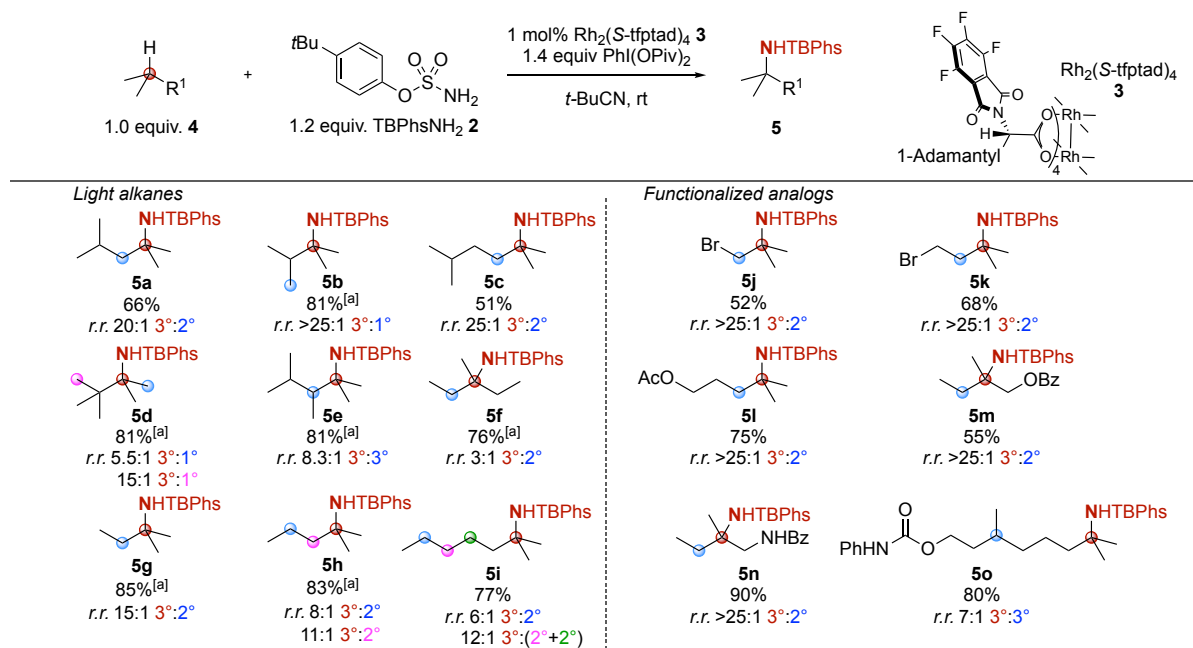


**Scheme 2.** Screening of sulfamates with the  $\text{Rh}_2(\text{S-tfpttl})_4$  complex. [a] Regioisomeric ratio determined by  $^1\text{H}$  NMR of the crude reaction mixture.



**Scheme 3.** Screening of Rhodium(II) complexes with sulfamate TBPhsNH<sub>2</sub> **2**. [a] Regioisomeric ratio determined by  $^1\text{H}$  NMR of the crude reaction mixture. [b] Reaction performed in the presence of 1 mol% of the rhodium complex.

Modification of the side chain also showed that its steric bulk plays a key role on the process. While traces of the aminated product were observed in the presence of a methyl substituent, use of the  $\text{Rh}_2(\text{S-tfptad})_4$  complex **3** having more sterically hindered adamantyl side chains allowed us to isolate the expected product with a better yield of 62% and an improved r.r. of 20:1. The latter might be the result of a tighter pocket, the size of which is



**Figure 2.** Selective amination of acyclic compounds. [a] Yields of isolated products using 2.0 equivalents of alkane and 1.0 equivalent of the sulfamate **2**.

dictated by the steric effects of the side chains on the other side, as supported by DFT analysis (see SI). The highest reactivity of the Rh<sub>2</sub>(S-tftad)<sub>4</sub> complex **3** ultimately led us to lower the catalyst loading to 1 mol% without any loss of reactivity and selectivity. Final optimization of the reaction conditions focused on the screening of the solvent, the iodine(III) oxidant and its quantity, the temperature and the concentration using a combination of sulfamate **2** and the rhodium complex **3** (Tables S1 and S2, Supporting Information). While no effect on the site-selectivity was observed regardless of the modifications, a slight improvement in the yield could be achieved by running the reaction with only 1.4 equivalents of commercially available PhI(OPiv)<sub>2</sub> as the oxidant, at room temperature with a concentration in alkane of 1.0 M in pivalonitrile. Under these conditions, the tertiary amide **5a** derived from 2,4-dimethylpentane was isolated in 66% yield and with r.r. 20:1. These conditions were selected to study the scope of the selective amination of both acyclic and cyclic alkanes. However, starting from alkanes with low boiling points, we decided to run the reaction in the presence of 2.0 equivalents to secure higher yields. Our investigations first focused on acyclic derivatives (Figure 2). The reaction with dimethylalkanes **4a-c** occurred with high level of 3°:2° or 3°:1° selectivity (≥20:1), comparable to the excellent regioselectivities reported in previous studies.<sup>[10]</sup> But the corresponding mono-amides **5a-c** resulting from the selective amination of the tertiary C(sp<sup>3</sup>)-H bond were isolated with competitive yields ranging from 51 to 81%, and with complete chemoselectivity as no diamines resulting from the amination of both 3° sites were obtained.

We then studied the influence of steric hindrance on the course of the reaction at tertiary centers. 2,2,3-Trimethylbutane **4d** with a *tert*-butyl group  $\alpha$ -to the tertiary C(sp<sup>3</sup>)-H bond led to isolate the expected tertiary amide **5d** but the latter was accompanied by two other minor compounds resulting from the amination at the more accessible methyl substituents of either the *t*-butyl or the *i*-propyl group. The formation of the primary amides showed that electronic factors, favoring the reaction of electrophilic nitrenes at

the more electron rich tertiary sites, could be counterbalanced by steric factors. Accordingly, when two tertiary positions having different steric environment were in competition, as in the case of 2,3,4-trimethylpentane **4e**, the reaction took place at the more accessible tertiary site affording compound **5e** with a r.r. of 8.3:1. Steric factors also played a role on the 3°:2° selectivity. Thus, increasing the steric hindrance around tertiary centers led to diminished 3°:2° selectivities. Such a trend could be noticed in the reaction from 3-methylpentane delivering compound **5f** with a r.r. of 3:1 whereas the r.r. obtained in the case of the amide **5h** derived from 2-methylpentane were 8:1 (3° C-H vs. terminal CH<sub>2</sub>) and 11:1 (3° C-H vs. internal CH<sub>2</sub>). Likewise, the C(sp<sup>3</sup>)-H amination of 2-methylbutane proceeded cleanly in 85% yield with a r.r. of 15:1 at the tertiary site (**5g**) while the reaction performed from substrates having a longer alkyl chain such as 2-methylheptane, led to higher amounts of secondary amide side-products (r.r. of 6:1 and 12:1, compound **5i**).<sup>[16]</sup>

With the aim to show the functional group tolerance of the catalytic system, we applied the conditions to functionalized analogs incorporating either a halide, an ester or an amide. The presence of these substituents was well-tolerated and, more importantly, key to improve the level of regioselectivity in favor of 3° centers. These electron-withdrawing groups indeed deactivate the neighboring methylene substituents so that the corresponding tertiary amides **5j-5n** were isolated with yields in the 52-90% range and r.r. greater to 25:1. Fundamentally, because the C-H amination reactions involved the use of a chiral rhodium(II) complex, we also investigated a possible but challenging kinetic resolution to produce enantiomerically enriched amides **5m** and **5n**, however, without significant success as the enantiomeric excess did not exceed 20%.<sup>[17]</sup> Finally, the reaction performed from the 3,7-dimethyloctanol derivative **4o** led to isolate the product **5o** with a r.r. of 7:1 resulting from the selective amination at the tertiary center displaying a *gem*-dimethyl motif. The regioselectivity was rationalized by steric factors but also electronic effects as the other less accessible tertiary C(sp<sup>3</sup>)-H bond is deactivated by the terminal carbamoyl group.

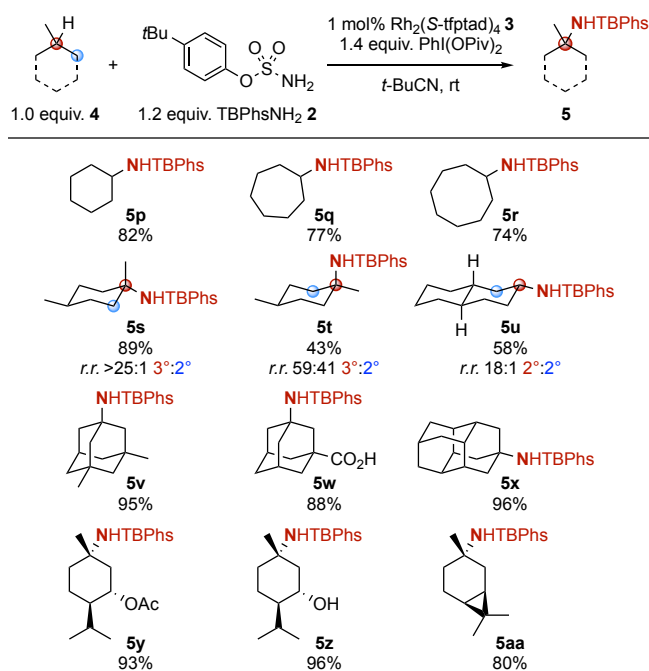


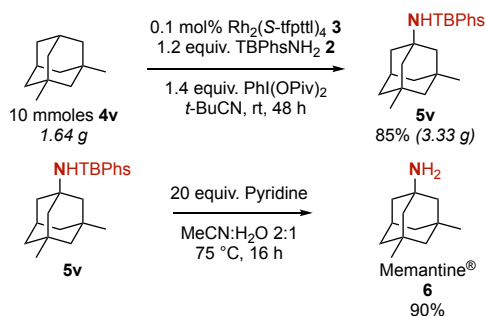
Figure 3. Selective amination of cyclic derivatives.

The reactivity of cyclic alkanes used as the limiting component was then investigated (Figure 3). The amination of simple cycloalkanes **4p-r** proceeded efficiently to afford the corresponding amides with yields ranging from 74% to 82%. Once again, the reaction proved to be chemoselective as the formation of products resulting from multiple aminations was not observed. Then, we evaluated the 3°:2° selectivity issue with substrates displaying a tertiary C(sp<sup>3</sup>)-H bond. In the case of *cis*-1,4-dimethylcyclohexane **4s**, dimethyladamantane **4v** and adamant-1-yl carboxylic acid **5w**, the reaction occurred exclusively at the tertiary equatorial C-H bond. Functionalization of the latter is favored first because of steric factors associated with the strain release phenomenon.<sup>[18]</sup> Moreover, hyperconjugative effects make the equatorial C(sp<sup>3</sup>)-H bond more nucleophilic, hence its better reactivity towards the electrophilic nitrene.<sup>[19]</sup>

On the other hand, the low reactivity of axial tertiary C-H bonds was illustrated by the poor 3°:2° selectivity observed for the C-H amination of *trans*-1,4-dimethylcyclohexane **4t**. Because the two tertiary C-H bonds are axial, the reaction also took place at the equatorial secondary C-H bonds. In the case of *trans*-decaline, the tertiary site was no more reactive with four unfavorable 1,3-diaxial interactions, and the nitrene insertion proceeded at the more accessible secondary center to afford compound **5u** isolated in 52% yield and an enantiomeric excess of around 30%. The difference in reactivity between equatorial and axial C-H bonds was clearly highlighted by the reaction from diamantane. Only the tertiary C-H bond that is fully equatorial with respect to the three cyclohexyl rings was aminated, thus affording compound **5x** in nearly quantitative yield.<sup>[20]</sup> On the other hand, the same excellent level of regioselectivity was observed with the more complex terpene derivatives **5y-aa** that were aminated at the equatorial tertiary center. Particularly worth of mention is the amination of unprotected (+)-*iso*-menthol **4z** that delivers the tertiary amide **5z** with an excellent yield of 96%.

Finally, the capacity to give a synthetic value to alkanes through the catalytic C(sp<sup>3</sup>)-H amination reaction was demonstrated by

the two-step synthesis of the anti-Alzheimer drug Memantine on a gram-scale.



Scheme 4. Gram-scale reaction with reduced catalyst loading and deprotection.

Starting from 10 mmoles of 1,3-dimethyladamantane **4v** in the presence of only 0.1 mol% of the commercially available rhodium complex (Rh<sub>2</sub>(S-tfptad)<sub>4</sub> **1**, the tertiary amide **5v** was isolated in 85% yield (Scheme 4). The *tert*-butylphenyloxysulfonyl group was then removed under mild conditions to afford the corresponding free amine **6** in 90% yield.

## Conclusion

In conclusion, the combination of the *p*-*t*Bu-phenol-derived sulfamate TBPhsNH<sub>2</sub> **2** with the chiral rhodium complex Rh<sub>2</sub>(S-tfptad)<sub>4</sub> **3** in the presence of an iodine(III) oxidant affords a highly reactive and discriminating metal-bound nitrene species. The latter allows to efficiently transform light acyclic and cyclic alkanes into amides in good to excellent yields. Worth of mention is the high level of regioselectivity observed for the functionalization of tertiary C(sp<sup>3</sup>)-H bonds over secondary and primary C(sp<sup>3</sup>)-H bonds. The reaction can be performed on a 10 mmoles scale with equal efficiency and the corresponding products can be easily deprotected under mild conditions. This study therefore highlights the possibility to convert alkanes to valuable nitrogen-containing building blocks that could be further derivatized to pyrrolidines as previously demonstrated in the group.<sup>[21]</sup>

## Experimental Section

**General procedure for the catalytic C-H amination of alkanes:** A tube containing the substrate (0.500 mmol, 1.00 equiv.) was charged with Rh<sub>2</sub>(S-tfptad)<sub>4</sub> **3** (9.2 mg, 5.0 μmol, 1.0 mol%) and 4-*tert*-butylphenyloxysulfonamide **2** (138 mg, 0.600 mmol, 1.20 eq.). 0.5 mL of trimethylacetone nitrile was added and the resulting mixture was stirred until complete dissolution. PhI(OPiv)<sub>2</sub> (284 mg, 0.700 mmol, 1.40 eq.) was then added in one portion and the mixture was stirred at room temperature for 24 h. 1.0 mL of a saturated aqueous solution of thiourea was added followed by 3.0 mL of DCM. The colour turned to dark brown and the resulting mixture was stirred vigorously for 15 minutes. The content was transferred to a separatory funnel and the organic layer was collected. The aqueous layer was extracted twice with DCM. The combined organic extracts were washed with saturated NaHCO<sub>3</sub>, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the expected product from the C(sp<sup>3</sup>)-H amination reaction.

## Supporting Information

Additional references cited within the Supporting Information.<sup>[22-28]</sup>

## Acknowledgements

We wish to thank the French National Research Agency (program n° ANR-11-IDEX-0003-02, CHARMMAT ANR-11-LABX-0039, ANR-15-CE29-0014-01; fellowship to A. N., and ANR-19-CE07-0043-02; fellowship to J. A. G. N.), the Ministère de l'Enseignement Supérieur et de la Recherche (fellowships to V. B. and E. B.), the ICSN for their support. DFT was performed using HPC resources from GENCI-TGCC (Allocation A11 - [A0110810977](https://doi.org/10.101810977)).

## Conflicts of Interest

The authors declare no conflict of interest.

## Data Availability Statement

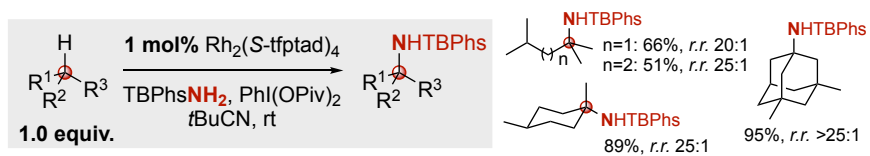
The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** Amination • Alkane • C–H Functionalization • Nitrene • Rhodium

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## Entry for the Table of Contents



Rhodium(II)-catalyzed intermolecular C(sp<sup>3</sup>)-H amination with sulfamates allows to functionalize alkanes used as the limiting component, selectively at tertiary centers. Valuable nitrogen-containing building blocks can be isolated in good to excellent yields.