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Communication

Catalytic Intermolecular C(sp^3)−H Amination: Selective Functionalization of Tertiary C−H Bonds vs Activated Benzylic C−H Bonds

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ABSTRACT: A catalytic intermolecular amination of nonactivated tertiary C(sp^3)−H bonds (BDE of 96 kcal·mol^{-1}) is reported for substrates displaying an activated benzylic site (BDE of 85 kcal·mol^{-1}). The tertiary C(sp^3)−H bond is selectively functionalized to afford *α,α,α*-trisubstituted amides in high yields. This unusual site-selectivity results from the synergistic combination of Rh_2(*S*-tfpttl)$_4$, a rhodium(II) complex with a well-defined catalytic pocket, with *tert*-butylphenol sulfamate (TBPhsNH$_2$), which leads to a discriminating rhodium-bound nitrene species under mild oxidative conditions. This catalytic system is very robust, and the reaction was performed on a 50 mmol scale with only 0.01 mol % of catalyst. The TBPhs group can be removed under mild conditions to afford the corresponding *NH*-free amines.

The design of site-selective C(sp^3)−H functionalization reactions is a great challenge with important applications in organic synthesis and medicinal chemistry.[1−3] A first general approach to meet this goal is based on directed functionalization reactions that include the use of coordinating groups or intramolecular reactions.[4−9] These processes convert proximal C−H bonds with high levels of selectivity, but substrates devoid of such a directing effect remain out of their scope. Thus, undirected C−H functionalization has emerged as a conceptually different strategy.[10] The site-selectivity for such reactions is mostly driven by inherent parameters of the substrates, i.e., the bond dissociation energy (BDE) of C−H bonds or polar effects.[11] However, unactivated C−H bonds remain inaccessible, so that other undirected processes under catalyst and/or reagent control must be developed to overcome these limitations.[12−14] This challenging approach should enhance the scope of C−H functionalization reactions as shown by the reports on alkane borylation,[15] carbene insertion,[16−18] C−H oxidation,[19−21] or in biocatalysis.[22]

Catalytic C(sp^3)−H amination reactions have emerged as valuable synthetic tools in the 2000s.[23−26] Significant progress has been achieved through the design of catalytic nitrene C−H insertions using azides,[27] *N*-oxy reagents,[28] or iminoiodinanes.[29−34] The latter, particularly, have received much attention with applications in total synthesis and medicinal chemistry. With respect to the site-selectivity issue, nitrene C(sp^3)−H insertion reactions preferentially proceed at benzylic or tertiary positions.[30] However, what happens when these two reacting sites are in competition within the same substrate?

Whereas solutions relying on catalyst modification were developed to address this chemoselectivity issue in intramolecular C(sp^3)−H amination reactions,[35−39] the selectivity in intermolecular reactions with competitive substrates has not yet been addressed. Indeed, several catalytic systems have been designed for the amination of benzylic[40−42] (BDE of 85 kcal mol^{-1}) or tertiary[43,44] (BDE of 96 kcal mol^{-1}) C(sp^3)−H bonds. However, in the case of substrates displaying both C(sp^3)−H bonds, the more activated benzylic site is always preferentially functionalized irrespective of the sulfamate[41] or the metal catalyst[42] (Scheme 1a). The same trend determined by the relative BDE is also observed in intermolecular C(sp^3)−H amination with azides[45−50] or involving iodine catalysis[51] (Scheme 1b).

Actually, examples of undirected C(sp^3)−H functionalization reactions favoring nonactivated alkyl C−H bonds in the presence of an activated secondary benzylic center remain extremely rare.[52,53] In this context, we wish to report a novel catalyst- and reagent-controlled intermolecular C−H amination of tertiary centers in the presence of benzylic positions with T/B ratio of >25:1 (Scheme 1c). The reaction gives access to a variety of *α,α,α*-trisubstituted primary amines that are important motifs in medicinal chemistry.[54]

With the aim of favoring the amination of a tertiary C−H bond in the presence of a secondary benzylic center, we turned our attention to dirhodium(II) tetracarboxylates derived from *α-N*-(phthaloyl)amino acids. Such complexes are known to adopt an *α,α,α,α*-conformation with all the amino acid side chains oriented on one face and the imido groups on the other,[55−57] as shown by the X-ray structure of the Rh_2(*S*-tfptad)$_4$ (Figure 1).[58] Thus, the phthalimido groups induce the formation of a tunable C_4-symmetrical hydrophobic pocket. Such a pocket cannot be found in the Rh_2(esp)$_2$ complex

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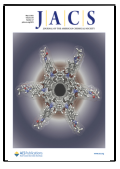

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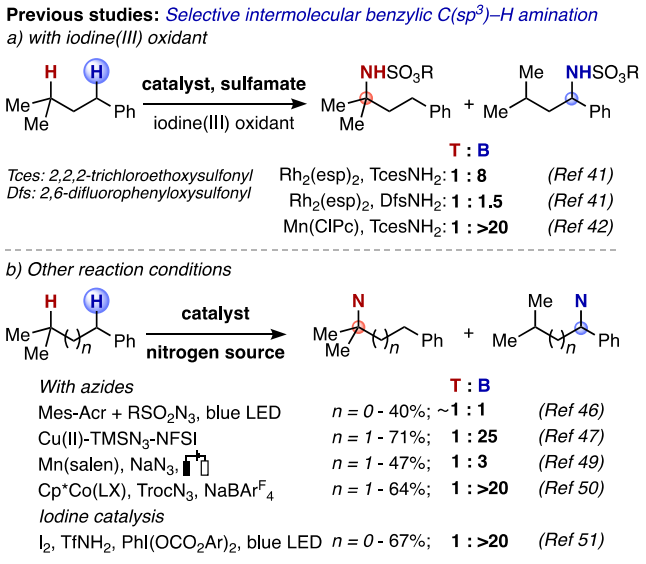
Scheme 1. Site-Selectivity in Catalytic Intermolecular C(sp^3)−H Amination Reactions



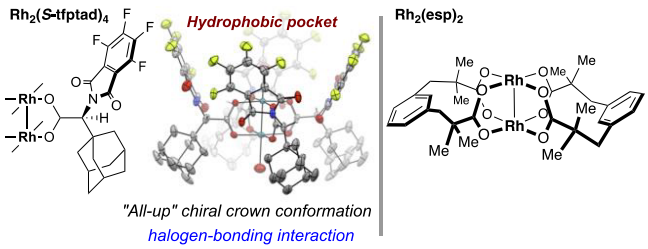
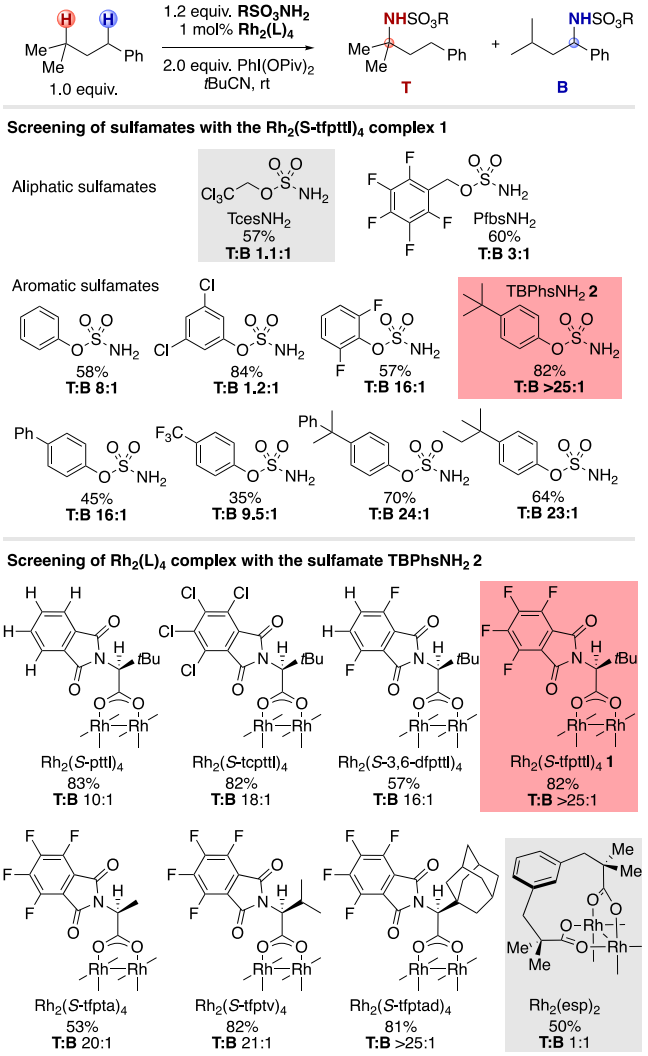


Figure 1. Structures of the Rh_2(*S*-tfptad)$_4$ and Rh_2(esp)$_2$ complexes.

designed for intermolecular C−H amination.[30,40] Importantly, its size and shape can be fine-tuned by changing either the phthaloyl substitution or the side chain. In combination with a sterically demanding nitrene precursor, we thus expected that the pocket could host a discriminating rhodium-bound nitrene species able to induce novel site-selective reactions.

With this hypothesis in mind, we started our investigations by screening several combinations of nitrene precursors and rhodium(II) complexes for the catalytic C−H amination of isoamylbenzene in pivalonitrile as this solvent led to the highest conversions (Scheme 2). We first focused on sulfamates, which were easily prepared by reacting the corresponding alcohols with sulfamoyl chloride,[59] in the presence of the readily available dirhodium(II) tetrakis[*N*-tetrafluorophthaloyl-(*S*)-*tert*-leucinate] complex (Rh_2(*S*-tfptl)$_4$) **1**. The use of aliphatic sulfamates such as $TcesNH_2$[40] or the pentafluorobenzyl sulfamate ($PfbsNH_2$),[58] both previously developed for catalytic benzylic C(sp^3)−H amination, was not satisfactory as the T/B ratio did not exceed 3:1. By contrast, we could observe the preferential amination of tertiary centers by running the reaction with aromatic sulfamates. In particular, high T/B ratios were obtained with

Scheme 2. Screening of Sulfamate/Rhodium(II) Complex Combinations[a]



[a]Reaction conditions: isoamylbenzene (0.20 mmol), sulfamate (0.24 mmol), $PhI(OPiv)_2$ (0.40 mmol), and rhodium catalyst (1 mol %) in pivalonitrile (0.5 mL) at rt. Isolated yields.

sulfamates derived from phenols having a bulky group in the *para* position, with an optimal ratio >25:1 being obtained with the 4-*tert*-butylphenol-derived sulfamate $TBPhsNH_2$ **2**.

The $TBPhSNH_2$ reagent **2**, thus, was selected for a parallel evaluation of the rhodium catalysts to determine the key parameters necessary to achieve high yield and site-selectivity. Modification of the nitrogen protecting group of the amino acid ligand first revealed that a perfluorinated phthaloyl motif was required to maintain a T/B ratio of >25:1. On the other hand, the steric bulk of the amino acid side chain also proved to have an influence. The best results both in terms of yields and T/B ratio were obtained with the *tert*-butyl and the adamantyl derivatives. Importantly, Rh_2(*S*-tfptl)$_4$ **1** is commercially available and easily synthesized in two high-yielding steps from *tert*-leucine so that it was chosen for the rest of the study.

It is worth pointing out that the reaction performed with $TBPhsNH_2$ in the presence of the Rh_2(esp)$_2$ complex led to a T/B ratio of 1:1, as did the previous combination of $TcesNH_2$ with Rh_2(*S*-tfpttl)$_4$. Together, these results clearly demonstrate

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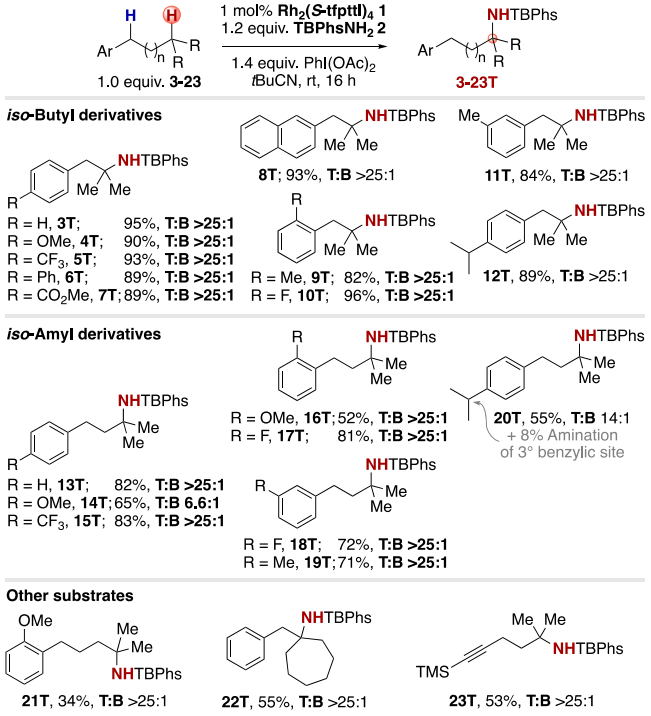
the critical role of both the sulfamate and the rhodium complex on the course of the reaction. Finally, a screening of additional reaction parameters showed that similar levels of reactivity could be achieved with only 1.4 equiv of the cheaper iodine oxidant $PhI(OAc)_2$ at a substrate concentration of 1 M, a relevant observation with the aim of performing reactions on a larger scale (see Table S1).

The optimized conditions were applied to a wide range of isobutyl and isoamyl derivatives used as the limiting reagents. The combination of 1.2 equiv of sulfamate **2** and 1 mol % of the rhodium(II) complex **1** led to the isolation of the corresponding tertiary amides **3**–**20** with yields of up to 96% and high T/B ratio generally greater than 25:1 as indicated by ^{1}H NMR of the crude mixture (Scheme 3). The

Scheme 3. Scope of the Selective Amination of Tertiary C(sp^3)–H Bonds[a]

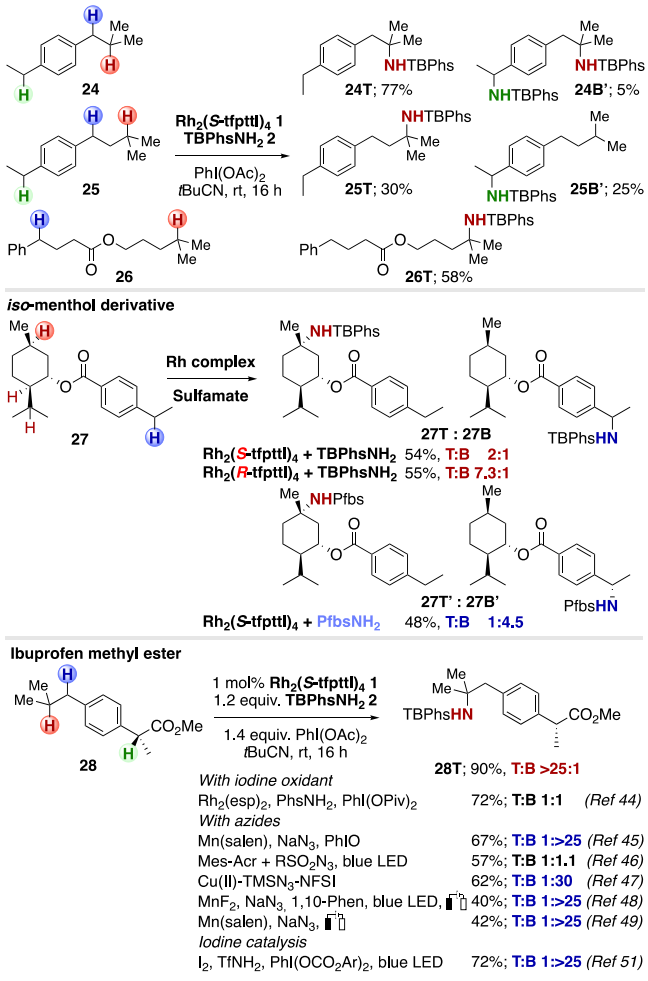


[a]Reaction conditions: substrate (0.5 mmol), sulfamate (0.6 mmol), $PhI(OAc)_2$ (0.7 mmol), and rhodium catalyst (1 mol %) in pivalonitrile (0.5 mL) at rt. Isolated yields.

reaction tolerates both electron-withdrawing (**5**, **7**, **10**, **15**, **17**, **18**) and electron-donating (**4**, **14**, **16**) substituents at the *para*, *meta*, or *ortho* positions. For substrates **4** and **14** in which the benzylic position is even more activated by a *p*-MeO substituent, the amination of the tertiary C(sp^3)–H bond was still favored, respectively, with a T/B ratio of >25:1 and 6.6:1. In addition, regioselective amination of the unactivated tertiary site proceeds efficiently in the presence of a competitive tertiary benzylic C(sp^3)–H bond as shown by products **12** and **20**. The reaction was successfully extended to the substituted higher homologue **21** of isoamylbenzene or cyclic products such as benzylcycloheptane **22**. Finally, compound **23** highlights that a tertiary center preferentially reacts in the presence of propargylic C–H bonds.

We then studied the case of more challenging substrates in terms of site-selectivity (Scheme 4). Attention was first paid to substrates having a *p*-ethyl substituent, since this alkyl group

Scheme 4. Selective Amination of Challenging Substrates



was always selectively functionalized in catalytic intermolecular C(sp^3)–H amination.[60−62] Pleasingly, the isobutyl derivative **24T** was obtained in 77% yield with very high levels of selectivity together with only traces of the diaminated product **24B′**. In contrast, when the isoamyl homologue **25** was reacted, the amination of the tertiary site was slightly favored.

The reactivity of ester **26** demonstrated that the selectivity is maintained between competitive remote positions. This was applied to the amination of the isomenthol derivative **27** that displays three tertiary centers and one secondary benzylic site. In this case, the amination proceeds preferentially at the equatorial tertiary C(sp^3)–H bond of the cyclohexyl ring. However, depending on the catalyst configuration, a match/mismatch effect was observed and a better T/B ratio of 7.3:1 was obtained with the (*R*)-catalyst. Importantly, a switch in the sulfamate reagent favors the amination of the benzylic position, a fundamental result with the aim of producing molecular diversity.

Ultimately, the result obtained with ibuprofen methyl ester **28** perfectly illustrates the unusual chemoselectivity of our catalyst- and reagent-controlled reaction. While previously reported conditions led to mixtures of products or the exclusive formation of the benzylic amine with yields lower than 72%, we isolated the tertiary amide **28T** with an excellent yield of 90% and a T/B ratio >25:1.

Finally, the efficiency and practicality of the catalytic C(sp^3)–H amination reaction are showcased by the two-step

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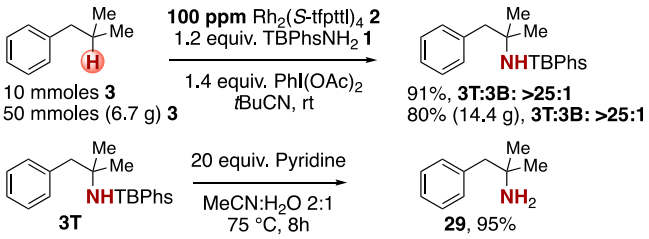
synthesis of the appetite suppressant phentermine on a gram scale.[63,64] Starting from 10 mmol of **3** in the presence of only 100 ppm of the rhodium complex **2**, the crystalline tertiary amide **3T** (see the Supporting Information for the X-ray structure) was isolated in 91% yield and a T/B ratio of >25:1 (Scheme 5). The use of 100 ppm of the catalyst on a 50 mmol

Scheme 5. Gram-Scale Synthesis of Phentermine

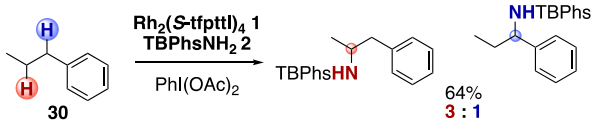


scale led to **3T** in 80% yield. The *tert*-butylphenyloxysulfonyl group could then be removed under mild conditions with pyridine in a 2:1 mixture of acetonitrile and water at 75 °C. The free amine **29** was obtained in 95% yield after a simple extractive workup that also allows the full recovery of 4-*tert*-butylphenol.

These results demonstrate that the combination of Rh_2(*S*-tfpttl)$_4$ **1** and sulfamate $TBPhsNH_2$ **2** allows us to override the higher reactivity of benzylic C(sp^3)−H bonds under C−H amination reaction conditions. Hypotheses to rationalize this observation can be proposed from the X-ray structure of complex **1** (see the Supporting Information for details). The latter confirms that it adopts the aforementioned all-up conformation with the four phthalimido groups on the same side. Thus, they shape a pocket that is wider than the other one delineated by the *t*Bu groups so that the nitrene would bind to that face of the catalyst. The presence of the fluorine atoms also induces secondary interactions with the imide carbonyl groups and the protons α to the carboxylic acid function. This contributes to the rigidification of the tight pocket that is maintained in solution.[56,65] Such a tightening effect is supported by the lower T/B ratio of 10:1 obtained with the nonhalogenated complex Rh_2(*S*-pttl)$_4$. Accordingly, upon coordination of the nitrene, the pocket would be poorly accessible to the benzylic motif of the substrate, thereby disfavoring the benzylic C−H amination reaction for steric reasons. A test reaction with propylbenzene was performed to give support to this hypothetical scenario. Gratifyingly, our catalyst system was found to be sufficiently discriminating to favor the amination of the nonactivated secondary C(sp^3)−H bond (BDE of 98 kcal·mol^{-1}) in the presence of the secondary benzylic site (Scheme 6).

In conclusion, this study demonstrates that the amination of nonactivated C(sp^3)−H bonds can be efficiently performed in the presence of an electronically activated benzylic center. Key to the success of the strategy is the selectivity control by a discriminating rhodium-bound nitrene species. Together with our previously reported protocol for enantioselective benzylic

Scheme 6. Selective Amination of Propylbenzene



amination,[58] these results highlight the possibility to uncover a set of various conditions for the selective amination of different classes of C(sp^3)−H bonds by varying both the rhodium catalyst and the nitrene precursor. We are currently exploring this strategy to obtain new site-selectivity and to apply the C(sp^3)−H amination reaction to the late-stage derivatization of complex natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c03872.

Experimental procedures, characterization data, spectra for all new compounds, and crystallographic data (PDF)

Accession Codes

CCDC 2059571 and 2074077 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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‡E.B. and V.B. contributed equally.

Notes

The authors declare no competing financial interest.

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