

Catalytic Intermolecular C(sp³)-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(sp³)-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(sp³)-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 Rh₂(S-tfpttl)₄, a rhodium(II) complex with a well-defined catalytic pocket, with *tert*-butylphenol sulfamate (TBPhsNH₂), 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(sp³)-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(sp³)-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(sp³)-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(sp³)-H amination reactions,^{35–39} the selectivity in intermolecular reactions with competitive substrates has not yet been addressed. Indeed, several catalytic systems have been

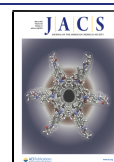
designed for the amination of benzylic^{40–42} (BDE of 85 kcal mol⁻¹) or tertiary^{43,44} (BDE of 96 kcal mol⁻¹) C(sp³)-H bonds. However, in the case of substrates displaying both C(sp³)-H bonds, the more activated benzylic site is always preferentially functionalized irrespective of the sulfamate⁴¹ or the metal catalyst⁴² (Scheme 1a). The same trend determined by the relative BDE is also observed in intermolecular C(sp³)-H amination with azides^{45–50} or involving iodine catalysis⁵¹ (Scheme 1b).

Actually, examples of undirected C(sp³)-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 $\alpha,\alpha,\alpha,\alpha$ -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 Rh₂(S-tfptad)₄ (Figure 1).⁵⁸ Thus, the phthalimido groups induce the formation of a tunable C₄-symmetrical hydrophobic pocket. Such a pocket cannot be found in the Rh₂(esp)₂ complex

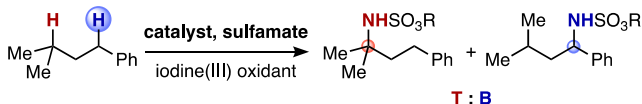
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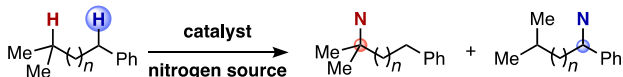
Scheme 1. Site-Selectivity in Catalytic Intermolecular C(sp³)-H Amination ReactionsPrevious studies: Selective intermolecular benzylic C(sp³)-H amination

a) with iodine(III) oxidant



Tces: 2,2,2-trichloroethoxysulfonyl Rh₂(esp)₂, TcesNH₂: 1 : 8 (Ref 41)
 Dfs: 2,6-difluorophenylloxysulfonyl Rh₂(esp)₂, DfsNH₂: 1 : 1.5 (Ref 41)
 Mn(ClPc), TcesNH₂: 1 : >20 (Ref 42)

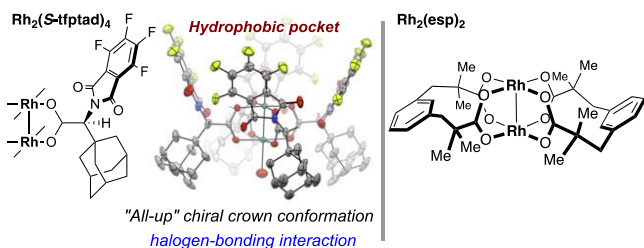
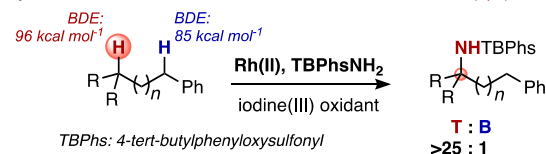
b) Other reaction conditions



With azides

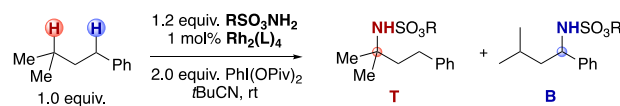
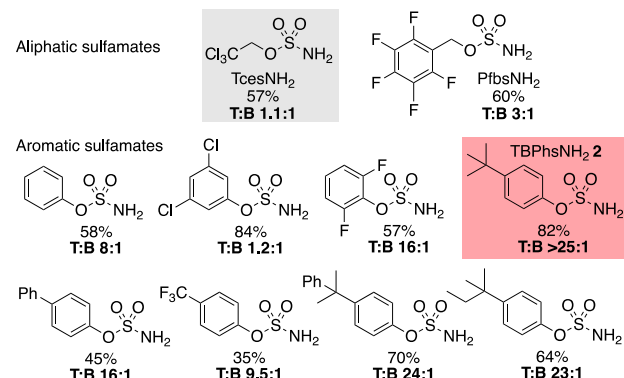
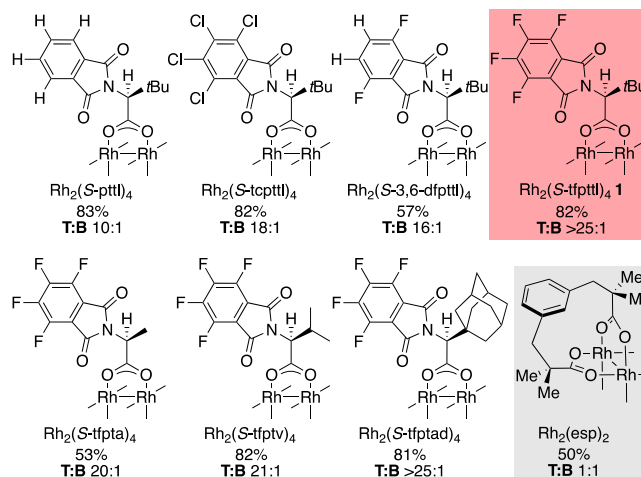
Mes-Acr + RSO₂N₃, blue LED $n = 0 - 40\%$; ~1 : 1 (Ref 46)Cu(II)-TMSN₃-NFSI $n = 1 - 71\%$; 1 : 25 (Ref 47)Mn(salen), NaN₃, $n = 1 - 47\%$; 1 : 3 (Ref 49)Cp*Co(LX), TrocN₃, NaBar^F₄ $n = 1 - 64\%$; 1 : >20 (Ref 50)

Iodine catalysis

I₂, TiNH₂, Ph(OCO₂Ar)₂, blue LED $n = 0 - 67\%$; 1 : >20 (Ref 51)c) This work: Selective intermolecular amination of 3° C(sp³)-H bondsFigure 1. Structures of the Rh₂(S-tftpd)₄ and Rh₂(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 (Rh₂(S-tfpttl)₄ **1**). The use of aliphatic sulfamates such as TcesNH₂⁴⁰ or the pentafluorobenzyl sulfamate (PfbNH₂),⁵⁸ both previously developed for catalytic benzylic C(sp³)-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^aScreening of sulfamates with the Rh₂(S-tfpttl)₄ complex **1**Screening of Rh₂(L)₄ complex with the sulfamate TBPhsNH₂ **2**

^aReaction 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 TBPhsNH₂ **2**.

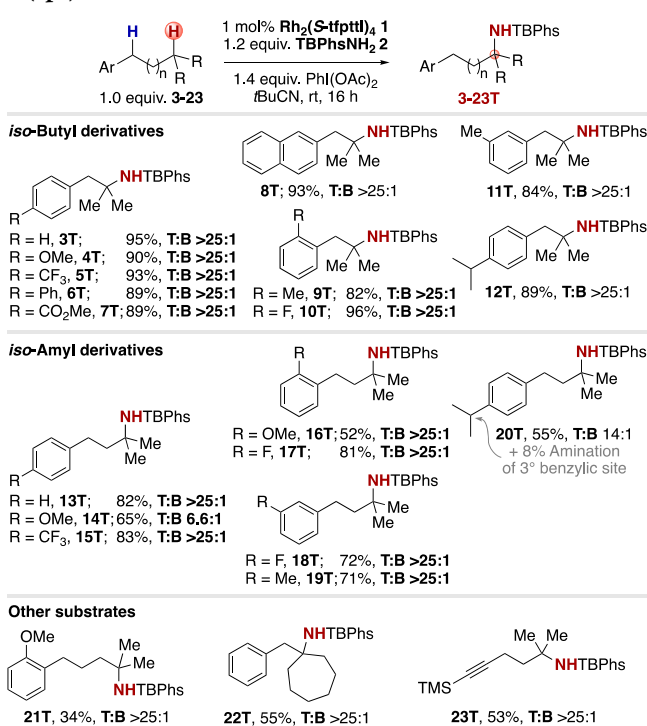
The TBPhsNH₂ reagent **2**, thus, was selected for a parallel evaluation of the rhodium catalysts to determine the key parameters necessary to achieve high yield and site-selectivity. Modification of the nitrogen protecting group of the amino acid ligand first revealed that a perfluorinated phthaloyl 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, Rh₂(S-tfpttl)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 TBPhsNH₂ in the presence of the Rh₂(esp)₂ complex led to a T/B ratio of 1:1, as did the previous combination of TcesNH₂ with Rh₂(S-tfpttl)₄. Together, these results clearly demonstrate

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 $\text{PhI}(\text{OAc})_2$ 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 ^1H NMR of the crude mixture (Scheme 3). The

Scheme 3. Scope of the Selective Amination of Tertiary $\text{C}(\text{sp}^3)\text{--H}$ Bonds^a

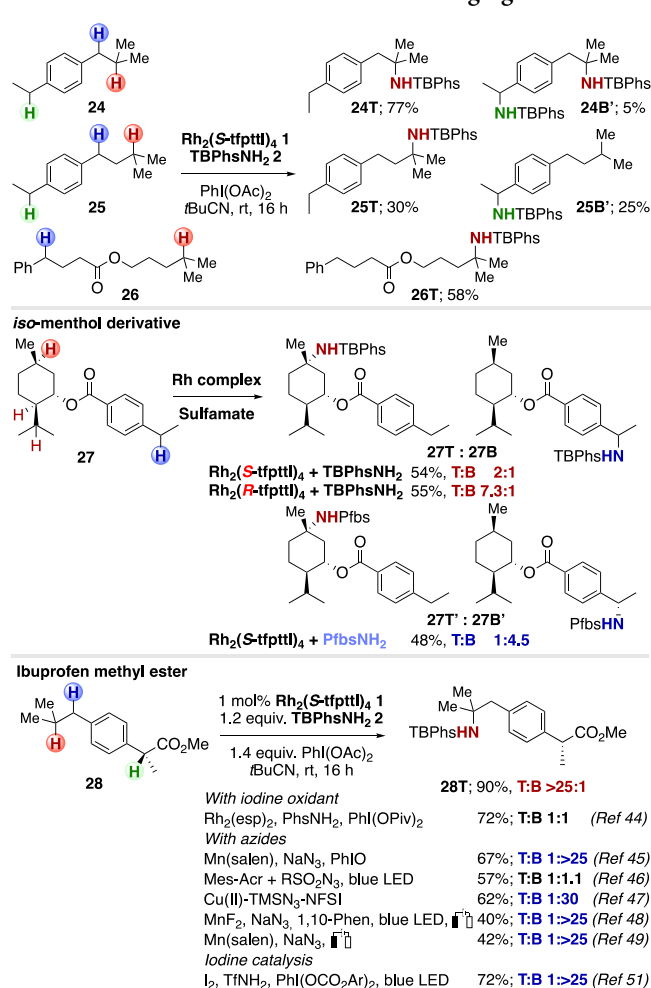


^aReaction conditions: substrate (0.5 mmol), sulfamate (0.6 mmol), $\text{PhI}(\text{OAc})_2$ (0.7 mmol), and rhodium catalyst (1 mol %) in pivalonitrile (0.5 mL) at rt. Isolated yields.

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 $\text{C}(\text{sp}^3)\text{--H}$ 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 $\text{C}(\text{sp}^3)\text{--H}$ 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 $\text{C}(\text{sp}^3)\text{--H}$ 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.

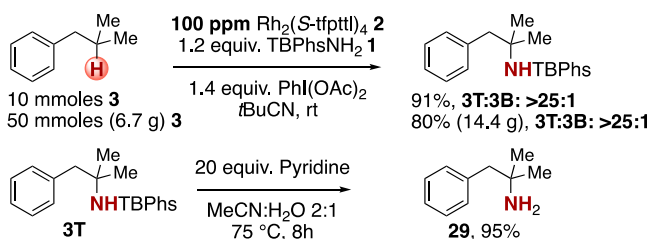
The reactivity of ester **26** demonstrated that the selectivity is maintained between competitive remote positions. This was applied to the amination of the isomenthol derivative **27** that displays three tertiary centers and one secondary benzylic site. In this case, the amination proceeds preferentially at the equatorial tertiary $\text{C}(\text{sp}^3)\text{--H}$ 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 $\text{C}(\text{sp}^3)\text{--H}$ amination reaction are showcased by the two-step

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

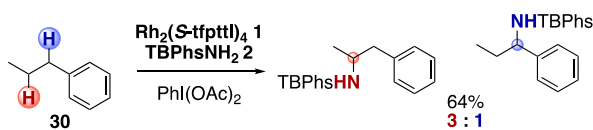


scale led to **3T** in 80% yield. The *tert*-butylphenyloxysulfonyl group could then be removed under mild conditions with pyridine in a 2:1 mixture of acetonitrile and water at 75 °C. The free amine **29** was obtained in 95% yield after a simple extractive workup that also allows the full recovery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

These results demonstrate that the combination of $\text{Rh}_2(\text{S-tfpttl})_4$ **1** and sulfamate TBPhsNH_2 **2** allows us to override the higher reactivity of benzylic $\text{C}(\text{sp}^3)\text{-H}$ 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 $\text{Rh}_2(\text{S-pttl})_4$. 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 $\text{C}(\text{sp}^3)\text{-H}$ 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 $\text{C}(\text{sp}^3)\text{-H}$ 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 $\text{C}(\text{sp}^3)\text{-H}$ 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 $\text{C}(\text{sp}^3)\text{-H}$ 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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Author Contributions

[‡]E.B. and V.B. contributed equally.

Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) Godula, K.; Sames, D. C–H Bond Functionalization in Complex Organic Synthesis. *Science* **2006**, *312*, 67–72.
- (2) Wencel-Delord, J.; Glorius, F. C–H Bond Activation Enables the Rapid Construction and Late-Stage Diversification of Functional Molecules. *Nat. Chem.* **2013**, *5*, 369–375.
- (3) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. The Medicinal Chemist's Toolbox for Late Stage Functionalization of Drug-like Molecules. *Chem. Soc. Rev.* **2016**, *45*, 546–576.
- (4) Chu, J. C. K.; Rovis, T. Complementary Strategies for Directed C(sp³)–H Functionalization: A Comparison of Transition-Metal-Catalyzed Activation, Hydrogen Atom Transfer, and Carbene/Nitrene Transfer. *Angew. Chem., Int. Ed.* **2018**, *57*, 62–101.
- (5) Sambiagio, C.; Schönbauer, D.; Blicke, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. A Comprehensive Overview of Directing Groups Applied in Metal-Catalyzed C–H Functionalisation Chemistry. *Chem. Soc. Rev.* **2018**, *47*, 6603–6743.
- (6) Rej, S.; Ano, Y.; Chatani, N. Bidentate Directing Groups: An Efficient Tool in C–H Bond Functionalization Chemistry for the Expedient Construction of C–C Bonds. *Chem. Rev.* **2020**, *120*, 1788–1887.
- (7) Nechab, M.; Mondal, S.; Bertrand, M. P. 1,n-Hydrogen-Atom Transfer (HAT) Reactions in Which N≠S: An Updated Inventory. *Chem. - Eur. J.* **2014**, *20*, 16034–16059.
- (8) Stateman, L. M.; Nakafuku, K. M.; Nagib, D. A. Remote C–H Functionalization via Selective Hydrogen Atom Transfer. *Synthesis* **2018**, *50* (08), 1569–1586.
- (9) Doyle, M. P.; Liu, Y.; Ratnikov, M. Catalytic, Asymmetric, Intramolecular Carbon-Hydrogen Insertion. *Org. React.* **2012**, *80*, 1–132.
- (10) Hartwig, J. F.; Larsen, M. A. Undirected, Homogeneous C–H Bond Functionalization: Challenges and Opportunities. *ACS Cent. Sci.* **2016**, *2*, 281–292.
- (11) Newhouse, T.; Baran, P. S. If C–H Bonds Could Talk: Selective C–H Bond Oxidation. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362–3374.
- (12) Hartwig, J. F. Catalyst-Controlled Site-Selective Bond Activation. *Acc. Chem. Res.* **2017**, *50*, 549–555.
- (13) Davies, H. M. L.; Liao, K. Dirhodium Tetracarboxylates as Catalysts for Selective Intermolecular C–H Functionalization. *Nat. Rev. Chem.* **2019**, *3*, 347–360.
- (14) White, M. C.; Zhao, J. Aliphatic C–H Oxidations for Late-Stage Functionalization. *J. Am. Chem. Soc.* **2018**, *140*, 13988–14009.
- (15) Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. Thermal, Catalytic, Regiospecific Functionalization of Alkanes. *Science* **2000**, *287* (5460), 1995–1997.
- (16) Liao, K.; Negretti, S.; Musaev, D. G.; Bacsa, J.; Davies, H. M. L. Site-Selective and Stereoselective Functionalization of Unactivated C–H Bonds. *Nature* **2016**, *533*, 230–234.
- (17) Liao, K.; Pickel, T. C.; Boyarskikh, V.; Bacsa, J.; Musaev, D. G.; Davies, H. M. L. Site-Selective and Stereoselective Functionalization of Non-Activated Tertiary C–H Bonds. *Nature* **2017**, *551*, 609–613.
- (18) Liao, K.; Yang, Y.-F.; Li, Y.; Sanders, J. N.; Houk, K. N.; Musaev, D. G.; Davies, H. M. L. Design of Catalysts for Site-Selective and Enantioselective Functionalization of Non-Activated Primary C–H Bonds. *Nat. Chem.* **2018**, *10*, 1048–1055.
- (19) Chen, M. S.; White, M. C. A Predictably Selective Aliphatic C–H Oxidation Reaction for Complex Molecule Synthesis. *Science* **2007**, *318*, 783–787.
- (20) Chen, M. S.; White, M. C. Combined Effects on Selectivity in Fe-Catalyzed Methylene Oxidation. *Science* **2010**, *327*, 566–571.
- (21) Gormisky, P. E.; White, M. C. Catalyst-Controlled Aliphatic C–H Oxidations with a Predictive Model for Site-Selectivity. *J. Am. Chem. Soc.* **2013**, *135*, 14052–14055.
- (22) Yang, Y.; Cho, I.; Qi, X.; Liu, P.; Arnold, F. H. An Enzymatic Platform for the Asymmetric Amination of Primary, Secondary and Tertiary C(sp³)–H Bonds. *Nat. Chem.* **2019**, *11*, 987–993.
- (23) Collet, F.; Dodd, R. H.; Dauban, P. Catalytic C–H Amination: Recent Progress and Future Directions. *Chem. Commun.* **2009**, 5061–5074.
- (24) Zalatan, D. N.; Bois, J. D. Metal-Catalyzed Oxidations of C–H to C–N Bonds. *Top. Curr. Chem.* **2009**, *292*, 347–378.
- (25) Park, Y.; Kim, Y.; Chang, S. Transition Metal-Catalyzed C–H Amination: Scope, Mechanism, and Applications. *Chem. Rev.* **2017**, *117*, 9247–9301.
- (26) Hayashi, H.; Uchida, T. Nitrene Transfer Reactions for Asymmetric C–H Amination: Recent Development. *Eur. J. Org. Chem.* **2020**, *2020*, 909–916.
- (27) Intrieri, D.; Zardi, P.; Caselli, A.; Gallo, E. Organic Azides: “Energetic Reagents” for the Intermolecular Amination of C–H Bonds. *Chem. Commun.* **2014**, *50*, 11440–11453.
- (28) Van Vliet, K. M.; de Bruin, B. Dioxazolones: Stable Substrates for the Catalytic Transfer of Acyl Nitrenes. *ACS Catal.* **2020**, *10*, 4751–4769.
- (29) Chang, J. W. W.; Ton, T. M. U.; Chan, P. W. H. Transition-Metal-Catalyzed Aminations and Aziridinations of C–H and C = C Bonds with Iminoiodinanes. *Chem. Rec.* **2011**, *11*, 331–357.
- (30) Roizen, J. L.; Harvey, M. E.; Du Bois, J. Metal-Catalyzed Nitrogen-Atom Transfer Methods for the Oxidation of Aliphatic C–H Bonds. *Acc. Chem. Res.* **2012**, *45*, 911–922.
- (31) Buendia, J.; Grelier, G.; Dauban, P. Dirhodium(II)-Catalyzed C(sp³)–H Amination Using Iodine(III) Oxidants. *Adv. Organomet. Chem.* **2015**, *64*, 77–118.
- (32) Alderson, J. M.; Corbin, J. R.; Schomaker, J. M. Tunable, Chemo- and Site-Selective Nitrene Transfer Reactions through the Rational Design of Silver(I) Catalysts. *Acc. Chem. Res.* **2017**, *50*, 2147–2158.
- (33) Darses, B.; Rodrigues, R.; Neuville, L.; Mazurais, M.; Dauban, P. Transition Metal-Catalyzed Iodine(III)-Mediated Nitrene Transfer Reactions: Efficient Tools for Challenging Syntheses. *Chem. Commun.* **2017**, *53*, 493–508.
- (34) Hazelard, D.; Nocquet, P.-A.; Compain, P. Catalytic C–H Amination at its Limits: Challenges and Solutions. *Org. Chem. Front.* **2017**, *4*, 2500–2521.
- (35) Fiori, K. W.; Espino, C. G.; Brodsky, B. H.; Du Bois, J. A Mechanistic Analysis of the Rh-Catalyzed Intramolecular C–H Amination Reaction. *Tetrahedron* **2009**, *65*, 3042–3051.
- (36) Paradine, S. M.; Griffin, J. R.; Zhao, J.; Petronico, A. L.; Miller, S. M.; Christina White, M. A Manganese Catalyst for Highly Reactive yet Chemoselective Intramolecular C(sp³)–H Amination. *Nat. Chem.* **2015**, *7*, 987–994.
- (37) Alderson, J. M.; Phelps, A. M.; Scamp, R. J.; Dolan, N. S.; Schomaker, J. M. Ligand-Controlled, Tunable Silver-Catalyzed C–H Amination. *J. Am. Chem. Soc.* **2014**, *136*, 16720–16723.
- (38) Huang, M.; Yang, T.; Paretsky, J. D.; Berry, J. F.; Schomaker, J. M. Inverting Steric Effects: Using “Attractive” Noncovalent Interactions To Direct Silver-Catalyzed Nitrene Transfer. *J. Am. Chem. Soc.* **2017**, *139*, 17376–17386.
- (39) Jung, H.; Schrader, M.; Kim, D.; Baik, M.-H.; Park, Y.; Chang, S. Harnessing Secondary Coordination Sphere Interactions That Enable the Selective Amidation of Benzylic C–H Bonds. *J. Am. Chem. Soc.* **2019**, *141*, 15356–15366.
- (40) Fiori, K. W.; Du Bois, J. Catalytic Intermolecular Amination of C–H Bonds: Method Development and Mechanistic Insights. *J. Am. Chem. Soc.* **2007**, *129*, 562–568.
- (41) Bess, E. N.; DeLuca, R. J.; Tindall, D. J.; Oderinde, M. S.; Roizen, J. L.; Du Bois, J.; Sigman, M. S. Analyzing Site Selectivity in Rh₂(Esp)₂-Catalyzed Intermolecular C–H Amination Reactions. *J. Am. Chem. Soc.* **2014**, *136*, 5783–5789.
- (42) Clark, J. R.; Feng, K.; Sookezian, A.; White, M. C. Manganese-Catalyzed Benzylic C(sp³)–H Amination for Late-Stage Functionalization. *Nat. Chem.* **2018**, *10*, 583–591.
- (43) Roizen, J. L.; Zalatan, D. N.; Du Bois, J. Selective Intermolecular Amination of C–H Bonds at Tertiary Carbon Centers. *Angew. Chem., Int. Ed.* **2013**, *52*, 11343–11346.

- (44) Chiappini, N. D.; Mack, J. B. C.; Du Bois, J. Intermolecular C(sp³)-H Amination of Complex Molecules. *Angew. Chem., Int. Ed.* **2018**, *57*, 4956–4959.
- (45) Huang, X.; Bergsten, T. M.; Groves, J. T. Manganese-Catalyzed Late-Stage Aliphatic C–H Azidation. *J. Am. Chem. Soc.* **2015**, *137*, 5300–5303.
- (46) Margrey, K. A.; Czaplyski, W. L.; Nicewicz, D. A.; Alexanian, E. J. A General Strategy for Aliphatic C–H Functionalization Enabled by Organic Photoredox Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 4213–4217.
- (47) Suh, S.-E.; Chen, S.-J.; Mandal, M.; Guzei, I. A.; Cramer, C. J.; Stahl, S. S. Site-Selective Copper-Catalyzed Azidation of Benzylic C–H Bonds. *J. Am. Chem. Soc.* **2020**, *142*, 11388–11393.
- (48) Niu, L.; Jiang, C.; Liang, Y.; Liu, D.; Bu, F.; Shi, R.; Chen, H.; Chowdhury, A.; Lei, A. Manganese-Catalyzed Oxidative Azidation of C(sp³)-H Bonds under Electrophotocatalytic Conditions. *J. Am. Chem. Soc.* **2020**, *142*, 17693–17702.
- (49) Meyer, T. H.; Samanta, R. C.; Vecchio, A. D.; Ackermann, L. Manganese(III/IV)Electro-Catalyzed C(sp³)-H Azidation. *Chem. Sci.* **2021**, *12*, 2890–2897.
- (50) Lee, J.; Jin, S.; Kim, D.; Hong, S. H.; Chang, S. Cobalt-Catalyzed Intermolecular C–H Amination of Unactivated Alkanes. *J. Am. Chem. Soc.* **2021**, *143*, 5191–5200.
- (51) Bosnidou, A. E.; Muñoz, K. Intermolecular Radical C(sp³)-H Amination under Iodine Catalysis. *Angew. Chem., Int. Ed.* **2019**, *58*, 7485–7489.
- (52) Liu, W.; Ren, Z.; Bosse, A. T.; Liao, K.; Goldstein, E. L.; Bacsa, J.; Musaev, D. G.; Stolz, B. M.; Davies, H. M. L. Catalyst-Controlled Selective Functionalization of Unactivated C–H Bonds in the Presence of Electronically Activated C–H Bonds. *J. Am. Chem. Soc.* **2018**, *140*, 12247–12255.
- (53) Bakhoda, A.; Jiang, Q.; Badieli, Y. M.; Bertke, J. A.; Cundari, T. R.; Warren, T. H. Copper-Catalyzed C(sp³)-H Amidation: Sterically Driven Primary and Secondary C–H Site-Selectivity. *Angew. Chem., Int. Ed.* **2019**, *58*, 3421–3425.
- (54) Campos, K. R.; Coleman, P. J.; Alvarez, J. C.; Dreher, S. D.; Garbaccio, R. M.; Terrett, N. K.; Tillyer, R. D.; Truppo, M. D.; Parmee, E. R. The Importance of Synthetic Chemistry in the Pharmaceutical Industry. *Science* **2019**, *363*, No. eaat0805.
- (55) DeAngelis, A.; Dmitrenko, O.; Yap, G. P. A.; Fox, J. Chiral Crown Conformation of Rh₂(S-PTTL)₄: Enantioselective Cyclopropanation with α -Alkyl- α -diazoesters. *J. Am. Chem. Soc.* **2009**, *131*, 7230–7231.
- (56) Lindsay, V. N. G.; Lin, W.; Charette, A. B. Experimental Evidence for the All-Up Reactive Conformation of Chiral Rhodium Carboxylate Catalysts: Enantioselective Synthesis of *cis*-Cyclopropane α -Amino Acids. *J. Am. Chem. Soc.* **2009**, *131*, 16383–16385.
- (57) Ghanem, A.; Gardiner, M. G.; Williamson, R. M.; Müller, P. X-ray Structure of a Naphthoyl-Tethered Chiral Dirhodium(II) Complex: Structural Basis for Tether Substitution Improving Asymmetric Control in Olefin Cyclopropanation. *Chem. - Eur. J.* **2010**, *16*, 3291–3295.
- (58) Nasrallah, A.; Boquet, V.; Hecker, A.; Retailleau, P.; Darses, B.; Dauban, P. Catalytic Enantioselective Intermolecular Benzylic C(sp³)-H Amination. *Angew. Chem., Int. Ed.* **2019**, *58*, 8192–8196.
- (59) Okada, M.; Iwashita, S.; Koizumi, N. Efficient General Method for Sulfamoylation of a Hydroxyl Group. *Tetrahedron Lett.* **2000**, *41*, 7047–7051.
- (60) Nasrallah, A.; Lazib, Y.; Boquet, V.; Darses, B.; Dauban, P. Catalytic Intermolecular C(sp³)-H Amination with Sulfamates for the Asymmetric Synthesis of Amines. *Org. Process Res. Dev.* **2020**, *24*, 724–728.
- (61) Nishioka, Y.; Uchida, T.; Katsuki, T. Enantio- and Regioselective Intermolecular Benzylic and Allylic C–H Bond Amination. *Angew. Chem., Int. Ed.* **2013**, *52*, 1739–1742.
- (62) Buendia, J.; Darses, B.; Dauban, P. Tandem Catalytic C(sp³)-H Amination/Sila-Sonogashira-Hagihara Coupling Reactions with Iodine Reagents. *Angew. Chem., Int. Ed.* **2015**, *54*, 5697–5701.
- (63) Vasu, D.; Arriba, A. L. F. de; Leitch, J. A.; Gombert, A. de; Dixon, D. J. Primary α -Tertiary Amine Synthesis via α -C–H Functionalization. *Chem. Sci.* **2019**, *10*, 3401–3407.
- (64) Gildner, P. G.; Gietter, A. A. S.; Cui, D.; Watson, D. A. Benzylolation of Nitroalkanes Using Copper-Catalyzed Thermal Redox Catalysis: Toward the Facile C-Alkylation of Nitroalkanes. *J. Am. Chem. Soc.* **2012**, *134*, 9942–9945.
- (65) Werlé, C.; Goddard, R.; Philipps, P.; Farès, C.; Fürstner, A. Stabilization of a Chiral Dirhodium Carbene by Encapsulation and a Discussion of the Stereochemical Implications. *Angew. Chem., Int. Ed.* **2016**, *55*, 10760–10765.