α-Branched amines by catalytic 1,1-addition of C–H bonds and aminating agents to terminal alkenes

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Abstract

α-Branched amines are present in hundreds of pharmaceutical agents and clinical candidates and are important targets for synthesis. Here we show the convergent synthesis of α-branched amines from three readily accessible starting materials: aromatic C–H bond substrates, terminal alkenes, and aminating agents. This reaction proceeds by an intermolecular formation of C–C and C–N bonds at the sp^3 carbon branch site through an uncommon 1,1-alkene addition pathway. The reaction is carried out under mild conditions and has high functional group compatibility. Ethylene and propylene feedstock chemicals are effective alkene inputs with ethylene in particular providing for the one step synthesis of α-methyl branched amines, a motif prevalent in drug structures. The reaction is scalable, and 1% loading of an air stable dimeric rhodium precatalyst is effective for several different types of products. The use of chiral catalysts also enables the asymmetric synthesis of α-branched amines.

Graphical Abstract
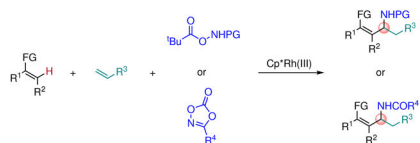
α-Branched amines displaying an exceedingly broad range of functionality have been incorporated into many approved pharmaceuticals and clinical candidates (Fig. 1a)[1–7]. The synthesis of α-branched amines by formation of a C–C bond at the sp^3 carbon branch site is strategic because it enables a convergent preparation from smaller precursors with

simultaneous introduction of a stereogenic centre[8]. Indeed, one of the most powerful approaches for the preparation of this class of compound is the addition of nucleophiles such as organometallic reagents to imines, with new methods for catalysing this process continuing to be developed (Fig. 1b)[9–16]. Recently, C–C bond formation at the α-position of a preexisting amine has been applied to the synthesis of α-branched amines also with simultaneous introduction of a stereocentre at the branch site (Fig. 1c)[17–20].

We sought a new approach for the synthesis of α-branched amines by simultaneous C–C and C–N bond formation at the branch site from three rather than two inputs, specifically, readily available C–H bond substrates, aminating agents, and alkenes (Fig. 1d). Because the approach does not involve organometallic reagents and should not require strongly acidic or basic conditions, we anticipated that it would be compatible with functionalities present in pharmaceuticals that interfere with many of the other C–C bond forming reactions for α-branched amine synthesis. However, to implement this method, a new mode of catalysis needed to be developed for the ordered intermolecular 1,1-addition of a C–H bond and an aminating agent to the C–C π-bond of an alkene. The requisite 1,1-addition pathway is in stark contrast to much more common 1,2-additions with a bond formed at each carbon of the reacting C–C π-bond[21,22].

Herein we report the synthesis of α-branched amines by Cp*Rh(III)-catalysed 1,1-addition of C–H bonds and aminating agents to terminal alkenes. Different aminating agents were used to directly prepare α-branched amines protected with the common Boc, Cbz, Fmoc and toluenesulfonyl protecting groups and also as alkyl, aryl and heteroaryl amide derivatives. In addition to terminal alkenes displaying a large variety of functionality, the bulk chemical feedstocks ethylene and propylene were also effective inputs. For several different α-branched amine products, a 1% loading of an air stable dimeric rhodium precatalyst was effective, and at this catalyst loading, the reaction was shown to be scalable. The asymmetric synthesis of α-branched amines was also achieved with chiral catalysts. Finally, through information obtained from reactions with isotopically labelled substrates, we propose a mechanism that explains the uncommon 1,1-alkene addition observed for this three-component transformation.

Results

Optimization studies.

Two types of aminating agents were carefully chosen to provide useful derivatives of α-branched amine products (Fig. 2). O-Acyl hydroxamic acids were selected to give the carbamates and sulfonamides that represent the most extensively used protected amine classes and can be readily cleaved to access free amines[23–25]. Dioxazolones were selected to directly provide diverse amides given that a high percentage of α-branched amines present in drugs and drug candidates are incorporated within amide structures[25,26].

To optimize the reaction, we focused on the preparation of α-branched amine **1** protected with the most popular and extensively used *tert*-butyloxycarbonyl (Boc) protecting group (Fig. 2). A cationic Cp*Rh(III) catalyst was determined to be the most effective after extensive investigation of a number of different transition metal catalysts and variations of

reaction parameters (see Supplementary Tables 1 and 2). Under the optimal reaction conditions, [Cp*RhCl$_2$]$_2$ was employed as an air and water stable precatalyst with AgSbF$_6$ as the halide abstracting agent. The reaction was performed at 0.2 M in the limiting C–H bond substrate with dichloroethane (DCE) as solvent at 30 °C. For oxime C–H bond substrates the addition of one equivalent of NaHCO$_3$ resulted in 10–15% higher yields than the reaction performed in the absence of the additive. However, for amide and triazole C–H bond substrates, pivalic acid (PivOH) was found to be a more effective additive[27]. Significantly, undesired 1,2-addition products were not observed.

Scope and limitations of the reaction.

The transformation could be broadly applied to the direct, one-step preparation of α-branched amines protected with other common amine protecting groups (Fig. 2, **1**-**4**). In addition to α-branched amine **1** protected with the acid labile Boc-group, we also prepared amine **2** protected with the hydrogenolytically labile carbobenzoxy (Cbz) group, amine **3** protected with the base labile 9-fluorenylmethoxycarbonyl (Fmoc) group, and amine **4** protected with the robust toluenesulfonyl (Ts) group.

We next explored styrene as the alkene, which provided protected amines **5**-**8** in comparable yields to that observed for hexene as the alkene input. While the stabilizing nature of the phenyl substituent in styrene might be expected to facilitate formation of 1,2-addition products, only the desired α-branched amine product resulting from 1,1-addition was observed. Although the scope of the reaction was broadly explored with 5 mol % of the [Cp*RhCl$_2$]$_2$ precatalyst, much lower catalyst loadings could be used in some cases. Indeed, when only 1 mol % of [Cp*RhCl$_2$]$_2$ and 4 mol % of AgSbF$_6$ were employed at a 1 M concentration in the limiting C–H bond substrate, *N*-Boc amine **5** was obtained in 63% isolated yield, which compares favorably to the 60% yield obtained at 5 mol % catalyst loading.

To directly obtain diverse α-branched amide derivatives in a single step, 1,4,2-dioxazol-5-ones were used as the aminating agents (**9**-**17**). By using different 1,4,2-dioxazol-5-ones, aromatic and heteroaromatic amides as well as linear and branched alkyl amides were prepared.

An attractive feature of the approach presented here is the opportunity to vary all three inputs to obtain a broad range of α-branched amine products. This beneficial aspect was highlighted by successful inclusion of different C–H bond substrates. Commonly encountered nitrogen heterocycles such as pyridine (**18** and **19**), pyrimidine (**20** and **21**), triazole (**22** and **23**) and pyrazole (**24** and **25**) were effective directing groups to provide the desired α-branched amines. For the pyrazole directing group, an example of a sterically challenging *ortho*-substituted arene was investigated and coupled efficiently to give **25**. Interestingly, both secondary (**26**) and tertiary (**27–31**) amides were also effective directing groups. For amide product **27** the yield was maintained at 1 mol % precatalyst simply by increasing the reaction temperature to 70 °C. The synthesis of α-branched amine **30** is notable because it required activation of a heteroaromatic C–H bond, and amine product **31** is of interest as an example of a fused bicyclic amide motif. Branched amines were also

obtained in good yields for a related fused bicyclic oxime (**32**) and for the fused heterocycle *N*-pyrimidinyl indole (**33**).

The broad availability and low cost of terminal alkenes enables straightforward introduction of diverse functionality (Fig. 3). A β-branched alkene (**34**), allylbenzene (**35**), and sterically more demanding α-branched alkenes (**36** to **38**) provided the desired products under the standard conditions. The reaction showed very broad functional group compatibility, including for acidic primary alcohol (**39**) and carbamate (**40** and **41**) functionality, and for electrophilic epoxide (**42**), primary alkyl halide (**43**), aldehyde (**44**), ketone (**45**) and ester (**46** and **47**) functionality. Many of these functional groups are not compatible with the organometallic reagents that have traditionally been used for imine additions (see Fig. 1b). It is also notable that the highly electron deficient α,β-unsaturated acrylate esters are effective alkene inputs with only the 1,1-addition products, β-amino esters **46** and **47**, obtained despite the potential for stabilization of 1,2-addition intermediates by the ester group[28]. Styrenes substituted at the *para-*, *meta-* and *ortho-*positions also provided the desired products (**48** to **52**), including for organoboron (**48**) and bromo (**49**) substituted products amenable to further elaboration by cross-coupling. Not all of the alkenes that were investigated were effective inputs. For example, vinyl chlorides and ethers and a variety of disubstituted alkenes did not undergo three-component addition (Supplementary Figure 1 depicts unsuccessful alkene inputs).

Use of Feedstock Alkenes.

The bulk commodity chemicals ethylene and propylene are also effective inputs and can readily be introduced to the reaction flask simply by sparging these gaseous alkenes over several minutes (Fig. 4a and b)[29]. Ethylene is particularly useful because it provides α-methyl branched amines (Fig. 4a), a sub-class of α-branched amines present in many pharmaceuticals. For this reason, performing the reaction under a pressurized ethylene atmosphere, which is readily applicable to larger reaction scales, was also carried out (see **53** and **54**). The scalability of this approach was demonstrated by the preparation of α-methyl branched amine **54** from 5 g of the C–H bond substrate at 1 M concentration with only 1 mol % loading of the precatalyst [Cp*RhCl$_2$]$_2$ (Fig. 4c).

Catalytic Asymmetric Reactions.

Given the recent advances in asymmetric C–H bond functionalization with chiral Rh(III) catalysis[30–33], we also investigated a number of chiral catalysts for the asymmetric synthesis of α-methyl branched amines (see Supplementary Table 3). The Rh-complex **59** employing Cramer's elegantly designed chiral ligand[34], gave the most promising initial results with 86:14 to 92:8 enantiomer ratios obtained for α-methyl branched amines **60**-**63** incorporating different directing groups and both electron-poor and electron rich aromatic amides[7] (Fig 4d).

Mechanistic Studies.

A catalytic cycle is proposed in Fig. 5 based upon the bond connectivity of the α-branched amine products and is supported by a series of mechanistic studies (Fig. 6a–d). The reaction is initiated by reversible *ortho* C–H bond activation by concerted metalation deprotonation to

give **A** (See Supplementary Figure 2). Alkene coordination and subsequent migratory insertion leads to seven-membered rhodacycle **B**, which undergoes syn β-H elimination to generate alkene-bound Rh-H intermediate **C**. An exocyclic, syn H-reinsertion of the alkene generates six-membered rhodacycle **D**. Rigorous stoiochiometric studies on the related conversion of a seven- to a more stable six-membered Cp*Rh(III) rhodacycle via a β-H elimination and reinsertion sequence provide support of the proposed pathway from **B** to **D**[35]. Coordination of the amidating agent followed by C–N bond formation with retention of configuration and simultaneous release of CO_2 provides the seven-membered rhodacycle **E**[25]. Subsequent protodemetallation leads to α-branched amine **27** while ensuring catalytic turnover.

The stereospecific nature of the β-H elimination, re-insertion and amidation steps were established by employing α-deuterostyrene, which provided **64** as a single stereo- and regioisomer (Fig. 6a and Supplementary Figure 3). The stereospecific nature of the reaction was further confirmed by employing β,β-di-deuterostyrene, which similarly provided **65** as a single stereo- and regioisomer (Fig. 6b and Supplementary Figure 4). When perdeuterated styrene was employed, intramolecular migration of deuterium to give **66** was observed consistent with the proposed β-hydride elimination and reinsertion steps (Fig. 6c and Supplementary Figure 5). However, this reaction proceeded more slowly with an extended reaction time or elevated temperature necessary to achieve high conversion to **66**, suggesting that cleavage of a bond to deuterium might be involved in the rate determining step. Indeed, determination of the relative initial rates of reaction for styrene and perdeuterated styrene provided a kinetic isotope effect of $K_H/K_D = 3.6$, confirming that β-H elimination and/or reinsertion are rate determining step(s) for this reaction (Fig. 6d, Supplementary Figure 7, 8 and Supplementary Tables 4–6)[36].

The interplay of all three components in the catalytic cycle is an essential feature of this transformation. When only two out of the three components are submitted to Rh(III) catalysis, different products result in each case. It is well-documented that reaction of the C–H bond substrate solely with an alkene results in C–H bond addition to the alkene[14], whereas reaction solely with the dioxazolone results in C–H bond amidation[25]. Alkenes, including terminal alkenes, have also recently been reported to readily undergo Rh(III)-catalysed reaction with dioxazolones via allylic C–H insertion to give allylic amines[37–39]. Nevertheless, when all three of the components are present under appropriate conditions, reaction to give the α-branched amine product outcompetes all of the two component reactions.

Conclusion

In summary, we have described a multicomponent approach for the convergent synthesis of α-branched amines that proceeds under mild conditions from three readily accessible starting materials. The high functional group compatibility, potential for asymmetric synthesis, and scalability are additional desirable features. The complete selectivity for 1,1-addition regardless of the electronic properties of the alkene provides an avenue for the development of other intermolecular C–H bond addition reactions that proceed with this type of bond connectivity.

Methods

General procedure:

In a N_2-filled glove box, a 2–5 mL microwave vial was charged with $[Cp*RhCl_2]_2$ (9.3 mg, 0.015 mmol, 0.050 equiv), $AgSbF_6$ (21 mg, 0.060 mmol, 0.20 equiv), and, if indicated, an additive (0.300 mmol, 1 equiv). 1,2-Dicholoroethane (1.5 mL, 0.2 M) was added followed by the indicated C–H bond substrate (0.300 mmol, 1.0 equiv), alkene (0.600 mmol, 2 equiv), and amine substrate (0.450 mmol, 1.50 equiv). The reaction vial was equipped with a magnetic stir bar, sealed with a microwave cap, and taken outside the glove box. The reaction mixture was stirred at 30 or 70 °C in a preheated oil bath. After 20 h, the reaction mixture was allowed to cool to room temperature. The reaction mixture was filtered through a small celite plug, (1 cm long in a pipette), which was washed with ethyl acetate. The resulting mixture was then concentrated and purified by the corresponding chromatographic method to afford the desired product.

Data availability:

Much of the data that support the results of this study are available in the Supplementary Information. Additional data is available from the corresponding author upon reasonable request.. X-ray crystal data for structure **62** that established its absolute configuration is shown in Supplementary Figure 9, Supplementary Tables 7–13 and is available free of charge from the Cambridge Crystallographic Data Centre (https://www.ccdc.cam.ac.uk/) under reference number CCDC 1903974.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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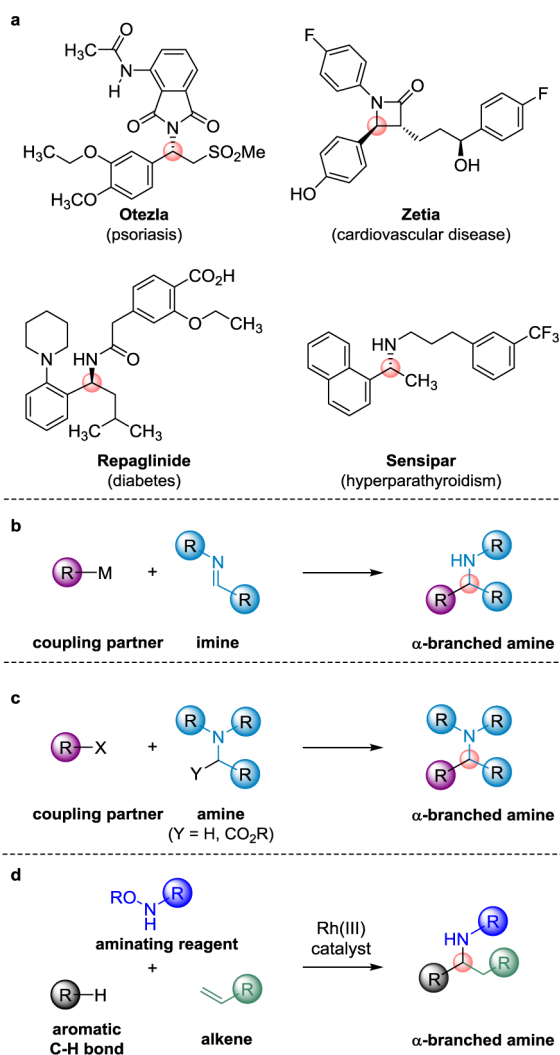
Fig. 1. α-Branched amines.
a, Representative examples of hundreds of approved pharmaceuticals that contain α-branched amine motifs (branch site highlighted by pink spheres). **b**, α-Branched amine synthesis with C–C bond formation at the branch site by addition of organometallic reagents to imines. **c**, α-Branched amine synthesis with C–C bond formation at the branch site from preexisting amines. **d**, Single step method to form α-branched amines from readily available C–H bond substrates, alkenes and aminating agents with formation of both C–C and C–N bonds at the branch site.
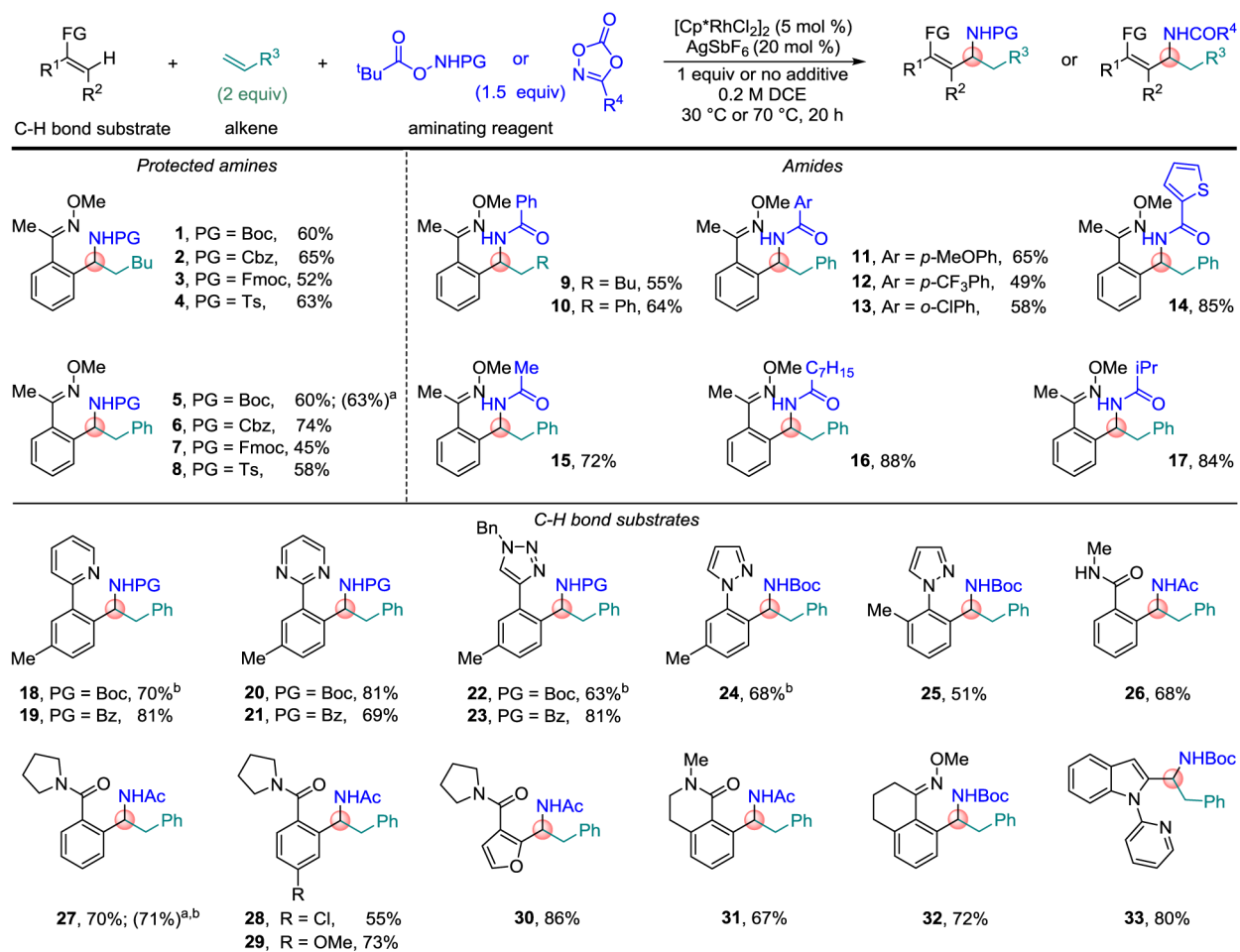
Fig. 2. Aminating agent and C–H bond substrate scope for α-branched amine synthesis.
Reactions were performed on 0.3 mmol scale at [0.2 M] with respect to C–H bond substrates. Ratio of C–H bond substrate: aminating agent: alkene (1:1.5:2). One equivalent of $NaHCO_3$ was used as an additive for oxime C–H bond substrates and one equivalent of pivalic acid (PivOH) was used as an additive for triazole and amide C–H bond substrates. Isolated yields of product after purification by chromatography are reported. See Supplementary Methods for experimental details. [a] Reactions performed with 1 mol % of $[Cp*RhCl_2]_2$ and 4 mol % of $AgSbF_6$. [b] Reactions performed at 70 °C.
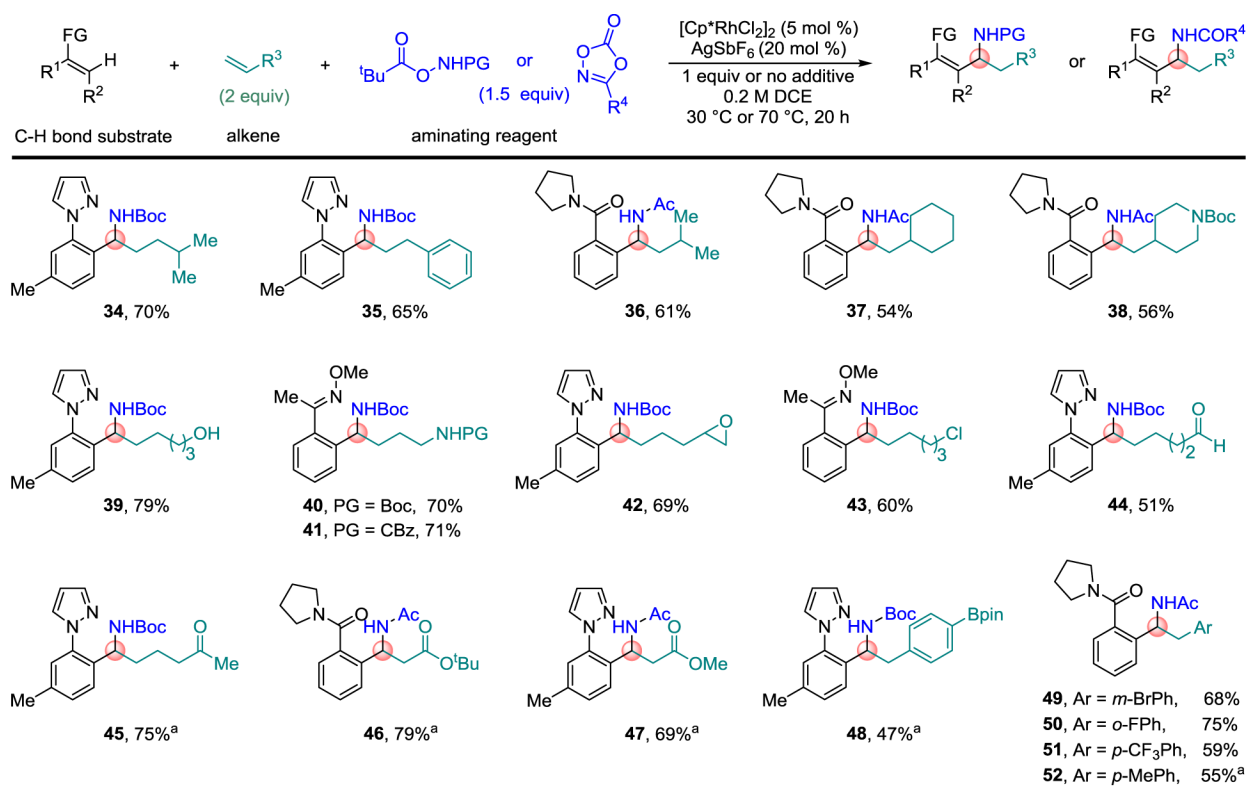
Fig. 3. Alkene scope for the modular synthesis of α-branched amines.

Reactions were performed on 0.3 mmol scale at [0.2 M] with respect to C–H bond substrates. Ratio of C–H bond substrate: aminating agent: alkene (1:1.5:2). One equivalent of $NaHCO_3$ was used as an additive for oxime C–H bond substrates and one equivalent of pivalic acid (PivOH) was used as an additive for amide C–H bond substrates. Isolated yields of product after purification by chromatography are reported. See Supplementary Methods for experimental details. [a] Reactions performed at 70 °C.
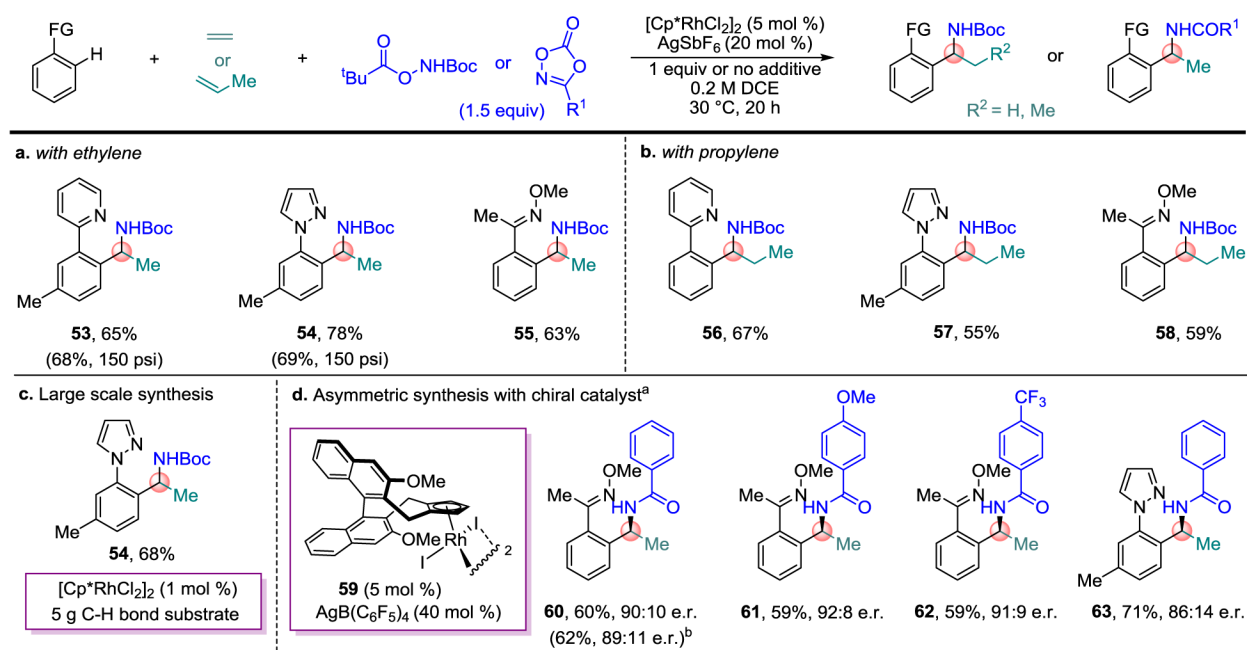
Fig. 4. Use of Feedstock Alkenes and Asymmetric Synthesis.

a and **b**, Synthesis of α-methyl and α-ethyl branched amines from the feedstock chemicals ethylene and propylene, respectively. **c**, Large scale (> 5 g) modular synthesis of Boc-protected α-methyl branched amine with 1 mol % [Cp*RhCl$_2$]$_2$ loading. **d**, Asymmetric catalysis with chiral catalyst **59**. One equivalent of NaHCO$_3$ was used as an additive for oxime C–H bond substrates. [a] Reactions performed on 0.05 mmol scale. [b] Reaction performed on 0.2 mmol scale.
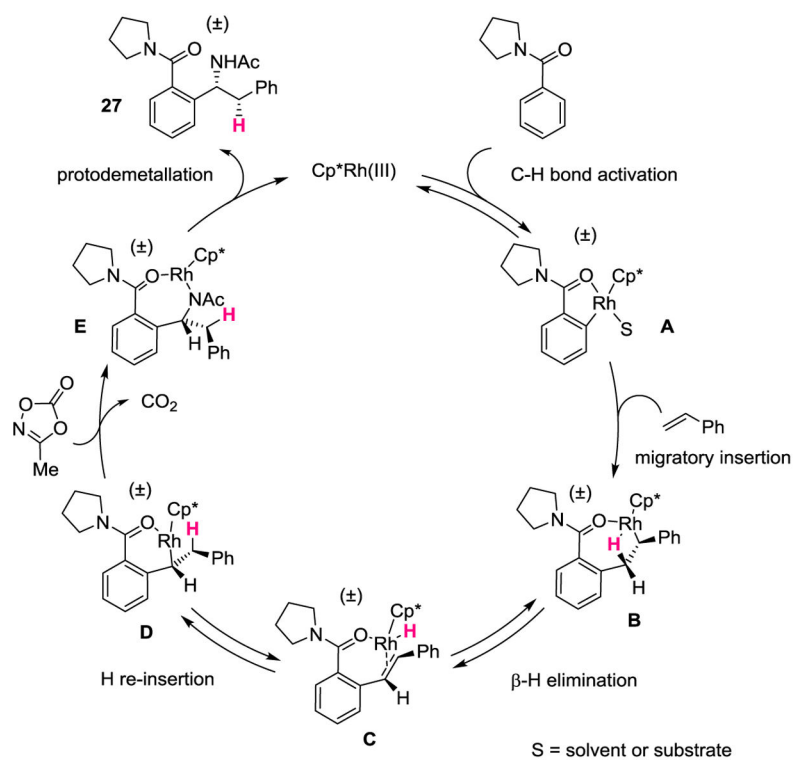
Fig. 5. Proposed catalytic cycle.
The transformation proceeds through a reversible C–H bond activation (**A**), followed by migratory insertion into styrene to give **B**. Syn β-hydride elimination and hydride re-insertion lead to the species **D**, which coordinates with the dioxazolone and inserts into it to give **E**. Protodemetallation provides the product **27** and releases the Rh(III) species to maintain catalytic turnover.
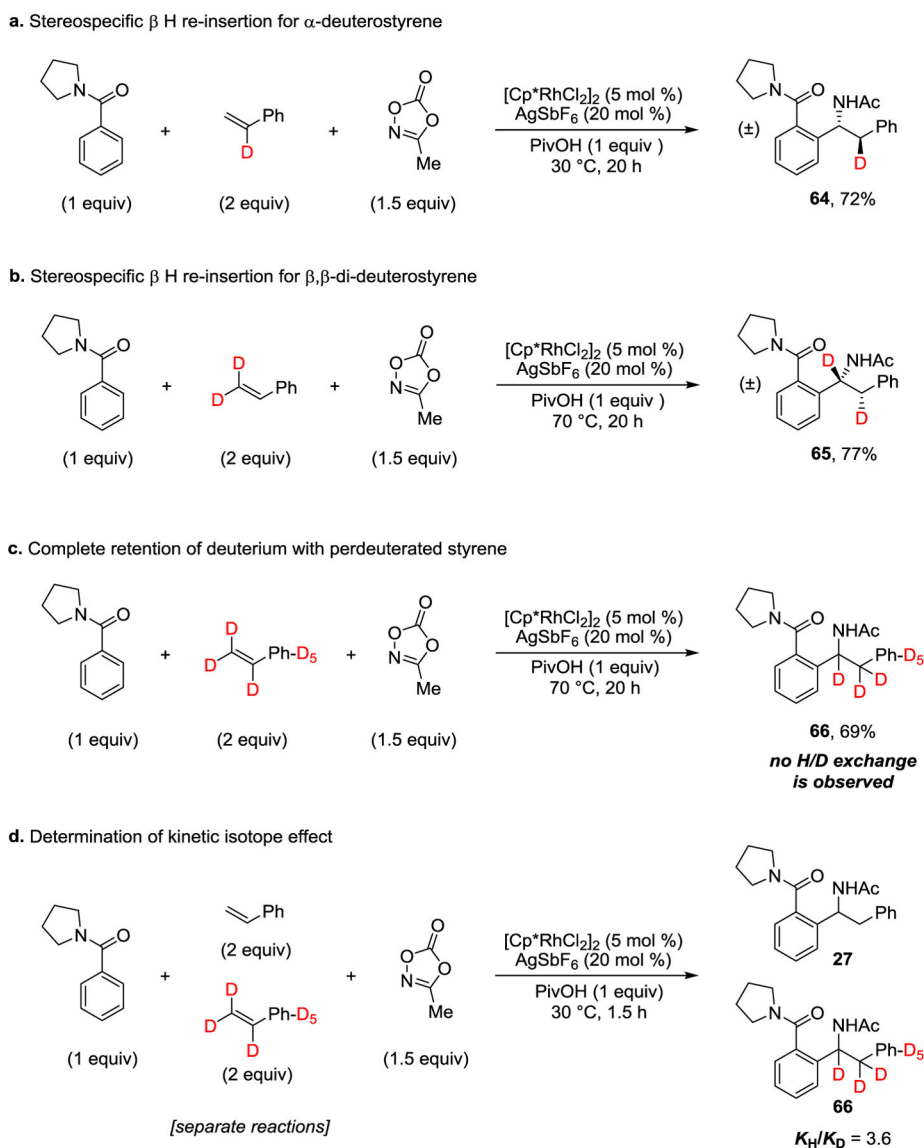
a. Stereospecific β H re-insertion for α-deuterostyrene

b. Stereospecific β H re-insertion for β,β-di-deuterostyrene

c. Complete retention of deuterium with perdeuterated styrene

d. Determination of kinetic isotope effect

Fig. 6. Mechanistic experiments.

a, Stereospecific H re-insertion demonstrated with α-deuterostyrene. **b**, Stereospecific H re-insertion verified with β,β-dideuterostyrene. **c**, Migration of β-deuterium to the α-position with perdeuterated styrene. **d**, Relative initial rates of reactions with styrene and perdeuterated styrene.