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Iridium(I)-catalyzed α-C(sp^3)–H Alkylation of Saturated Azacycles

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ABSTRACT

Saturated azacycles are commonly encountered in bioactive compounds and approved therapeutic agents. The development of methods for functionalization of the α-methylene C–H bonds of these highly privileged building blocks is of great importance, especially in drug discovery. While much effort has been dedicated towards this goal by using a directed C–H activation approach, the development of directing groups that are both *general*, as well as *practical*, remains a significant challenge. Herein, the design and development of novel amidoxime directing groups is described for Ir(I)-catalyzed α-C(sp^3)–H alkylation of saturated azacycles using readily available olefins as coupling partners. This protocol extends the scope of saturated azacycles to piperidines, azepane, and tetrahydroisoquinoline that are incompatible with our previously reported directing group. A variety of olefin coupling partners, including previously unreactive di-substituted terminal olefins and internal olefins, are compatible with this transformation. The selectivity for a branched α-C(sp^3)-alkylation product is also observed for the first time when acrylate is used as the reaction partner. The development of practical, one-step installation and removal protocols further add to the utility of amidoxime directing groups.

INTRODUCTION

Saturated azacycles constitute a prevalent structural motif in bioactive natural products and pharmaceutical compounds (Figure 1).[1] The development of methods that enable rapid synthesis and late-stage diversification of these heterocycles is appealing from the standpoint of drug discovery.[2] Not surprisingly, a variety of methods have been developed for the functionalization of C(sp^3)–H bonds adjacent to nitrogen in saturated azacycles.[3] Important progress has been made in the direct functionalization of these heterocycles through iminium ion,[4] α-amino carbanion,[5] α-amino radical,[6] carbene insertion[7], and other innovative pathways.[8] Functionalizations proceeding via transition-metal-catalyzed α-C(sp^3)–H bond activation have also been developed.[9-16] These transformations usually entail the installation of a directing group on the azacycle nitrogen for recruitment of the transition-metal catalyst near to the α-C(sp^3)–H bond of interest.[17] Although additional steps are required for the installation and eventual removal of the directing group, a directed C–H activation approach offers important advantages over other methods.[4-8] First, regioselectivity can be controlled in the presence of multiple equally reactive C–H bonds; for example, when more than one amino-alkyl groups are present within the substrate. Second, the formation of a discrete carbon–metal bond in the intermediate allows for diverse transformations that may not be possible with other approaches.[4-8] Third, the directing group can be used as a functional handle for modulating the reactivity and selectivity of a transformation, thus allowing access to different isomers of the product.

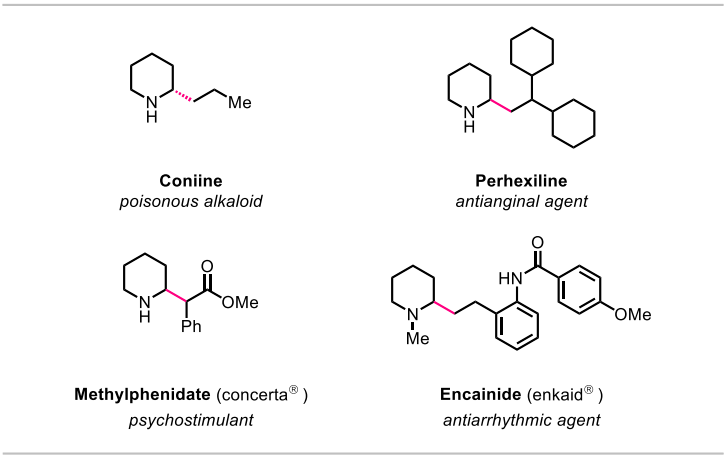
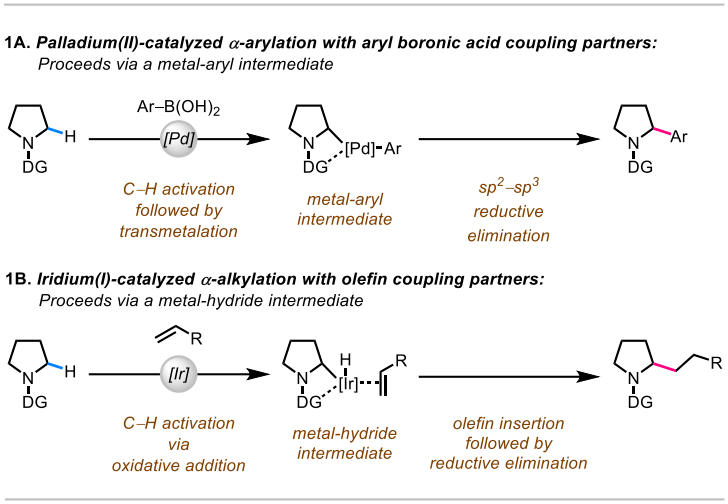


Figure 1. Some biologically significant compounds containing *α*-alkylated saturated azacycles.

In the realm of transition-metal-catalyzed directed *α*-C(sp^3)–H activation of saturated azacycles, several arylation transformations have been developed.[9] In 2014, our group reported the first example of a palladium(II)-catalyzed directed *α*-arylation of saturated azacycles using aryl boronic acids as coupling partners (Scheme 1A).[18] Our efforts towards developing an alkylation transformation using alkyl boronic acids as coupling partners have met with limited success;[19] possibly due to a challenging sp^3–sp^3 reductive elimination and competing *β*-hydride elimination side reactions from the corresponding metal-alkyl intermediate. In contrast, iridium(I)-catalyzed *α*-alkylation using olefins as coupling partners is a promising approach.[20] Such alkylation reactions proceed via the intermediacy of a metal-hydride species, which reacts with olefin coupling partners to affect a net alkylation transformation (Scheme 1B).

Scheme 1. Palladium(II)- and Iridium(I)-catalyzed Directed α-C(sp^3)–H Activation Reactions of Saturated Azacycles. DG = Directing Group.

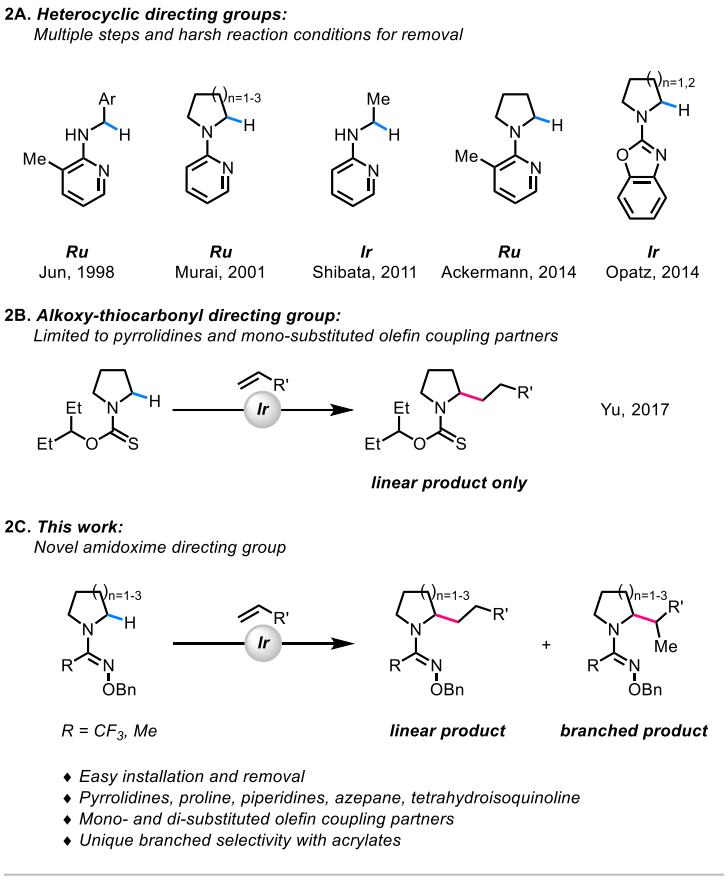


In 1998, Jun et al. reported the first example of a directed α-C(sp^3)–H alkylation of benzylamines using a ruthenium(0) catalyst.[10a] Later in 2001, a ruthenium-catalyzed directed α-C(sp^3)–H alkylation of saturated azacycles was reported by Murai and co-workers.[10b] In 2011, the first example of an iridium-catalyzed directed α-C(sp^3)–H alkylation of aliphatic amines was developed by Shibata and co-workers.[11a] Since these pioneering studies, several groups have developed directed approaches for α-C(sp^3)–H alkylation of saturated azacycles via ruthenium[10c-e] and iridium catalysis[11b-g] (Scheme 2A). However, the utility of these approaches is limited due to the use of heterocyclic directing groups which require multiple steps and harsh reducing reaction conditions for their removal. Additionally, over-alkylation has been a frequently encountered problem.

Recently, our group reported an alkoxy-thiocarbonyl directing group for α-C(sp^3)–H alkylation of saturated azacycles using a cationic iridium(I) catalyst (Scheme 2B).[21] Although the one-step installation and removal of this directing group was advantageous over previous reports

employing heterocyclic directing groups, the synthetic utility of the transformation was limited for the following reasons. First, while pyrrolidines could be alkylated in moderate yields, the alkylation of other azacycles proved to be challenging. Second, the olefin coupling partner scope was limited to only mono-substituted olefins. Third, the alkoxy-thiocarbonyl directing group promoted over-alkylation.

Scheme 2. Evolution of Directing Groups for Transition-metal-catalyzed α-C(sp^3)–H Alkylation of Amines with Olefin Coupling Partners.



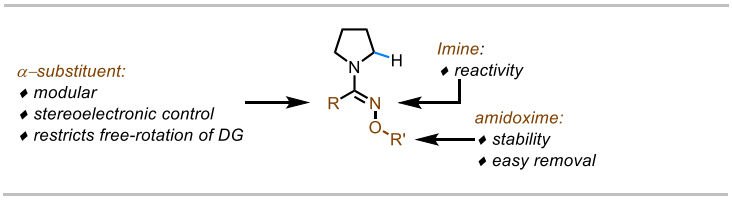
These limitations highlight the challenge associated with designing a practical, as well as a general directing group. Herein, we disclose the design and discovery of novel amidoxime directing groups for an iridium(I)-catalyzed α-C(sp^3)–H alkylation of saturated azacycles (Scheme

2C). The amidoxime directing groups are compatible with a wide range of saturated azacycles and olefin coupling partners, while also being easy to install and remove. During our study, we observed an unprecedented selectivity for branched α-C(sp^3)-alkylation products with ethyl acrylate as the olefin coupling partner.[22] This observation showcases one of the advantages of using a directed C–H activation approach, wherein a new directing group may impact the reactivity of the catalytic intermediate, thus enabling access to new mechanistic pathways and products.

RESULTS AND DISCUSSION

We designed the amidoxime directing groups (Scheme 3) based on the following considerations: 1) an imine moiety to direct the metal insertion, inspired by the high reactivity afforded by heterocyclic directing groups in Scheme 2A, 2) amidoxime moiety to allow easy removal under mild conditions (in comparison with previous reports of amidine directing groups[5a, 9a]), and 3) a modular α-substituent which can be tuned to improve the reactivity and selectivity.

Scheme 3. Design Principles of Amidoxime Directing Groups.

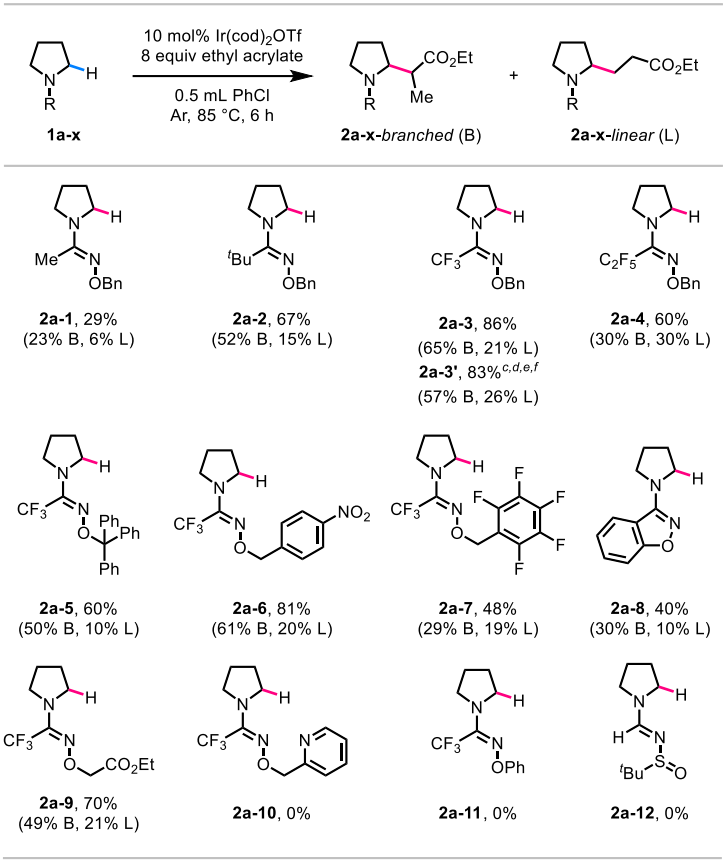


Borrowing reaction conditions from our previous work on iridium(I)-catalyzed α-alkylation of pyrrolidines with an alkoxy-thiocarbamate directing group,[21] we evaluated various amidoxime directing groups using pyrrolidine as the model substrate and ethyl acrylate as the olefin coupling partner (Table 1). We began our studies with an α-methyl substituted *O*-benzyl amidoxime directing group and obtained the α-alkylated product in a total yield of 29% (**2a-1**) as a mixture of branched (B) and linear (L) regioisomers. Keeping the oxime moiety constant, we changed the α-

substituent of the directing group to a bulkier *tert*-butyl group and observed an increase in the total yield to 67% (**2a-2**). The introduction of an electron-withdrawing trifluoromethyl group as the α-substituent further increased the total yield to 86% (**2a-3**). On the other hand, using a perfluoroethyl group as the α-substituent lowered the total yield to 60% (**2a-4**). Next, we varied the oxime moiety while fixing the α-substituent as a trifluoromethyl group. Changing the benzyl oxime to a sterically bulky trityl oxime lowered the total yield to 60% (**2a-5**). Next, we altered the electronics of the oxime moiety by using a *para*-nitro benzyl oxime which gave a slightly lower total yield of 81% (**2a-6**) as compared to the simple benzyl oxime. Increasing the electron-withdrawing nature of the oxime moiety further by using a perfluorobenzyl oxime reduced the total yield to 48% (**2a-7**). In order to test the importance of a pendant benzyl oxime unit, we tied it into a benzoxazole heterocycle and observed a drop in the total yield to 40% (**2a-8**). Increasing the coordination ability of the pendant oxime unit with a weakly coordinating ester afforded product in 70% total yield (**2a-9**), while a strongly coordinating pyridine completely shut down the reaction (**2a-10**). Next, reaction using an *O*-phenyl amidoxime directing group suffered from poor mass balance and no desired product was observed (**2a-11**). Employing a *tert*-butanesulfinyl imine as the directing group did not give any product (**2a-12**). We next screened the reaction conditions with trifluoromethyl *O*-benzyl amidoxime as the optimal directing group, and were able to lower the catalyst loading to 5 mol% and the ethyl acrylate loading to 4 equivalents to afford a total yield of 83% (**2a-3'**) of α-alkylated pyrrolidine products. As seen from Table 1, the regioisomeric product ratio was found to be dependent on the structure of the directing group. Attempts at improving the regioisomeric product ratio by further screening of the reaction conditions were unsuccessful. Moreover, the regioisomeric ratio was affected by the identity of

solvent, the catalyst counteranion, and the diene ligand on iridium (see the Supporting Information for details).

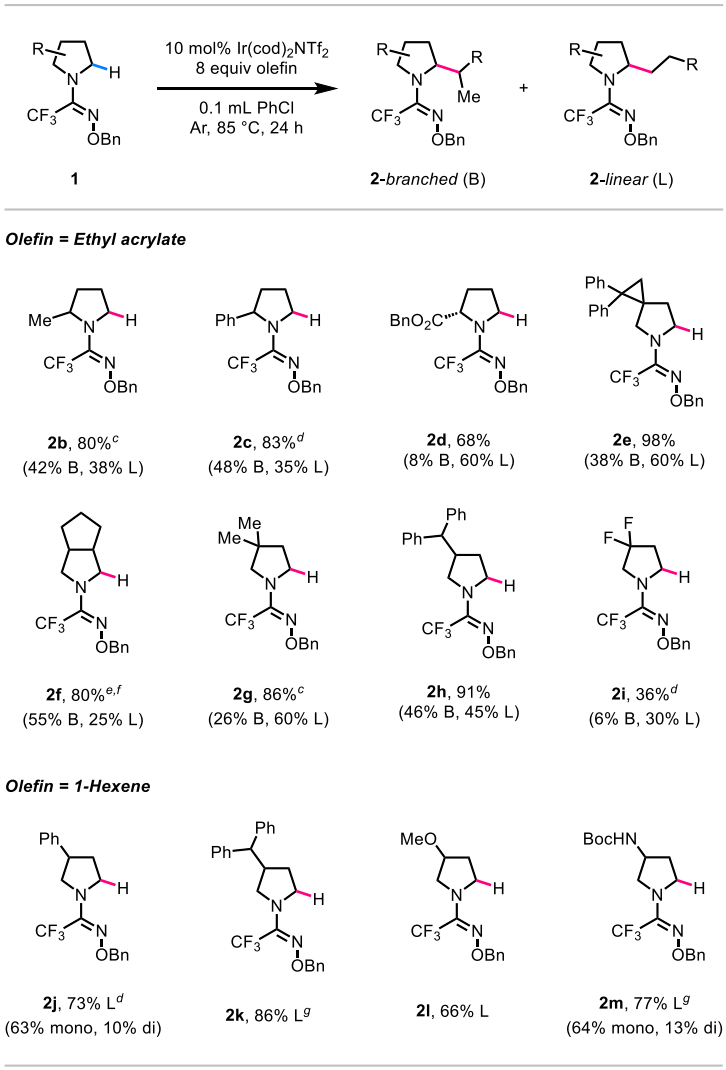
Table 1. Directing Group Evaluation for α-C(sp^3)–H Alkylation of Pyrrolidine.[a,b]



[a]Reaction conditions: **1a-1** to **1a-11** (0.1 mmol, 1.0 equiv), $Ir(cod)_2OTf$ (0.01 mmol, 0.1 equiv), ethyl acrylate (0.8 mmol, 8.0 equiv), degassed PhCl (0.5 mL), 85 °C, under Ar, 6 h. [b]Yields were determined by ^1H NMR analysis of the crude products using mesitylene as the internal standard. [c]0.05 equiv of $Ir(cod)_2OTf$ (0.005 mmol). [d]4.0 equiv of ethyl acrylate (0.4 mmol). [e]0.1 mL of degassed PhCl. [f]Yield after isolation by chromatography is shown.

We then tested the trifluoromethyl *O*-benzyl amidoxime directing group against a variety of substituted pyrrolidine substrates (Table 2). When ethyl acrylate was used as the olefin coupling partner, separable mixtures of branched and linearly α-alkylated products were obtained (**2b-2i**), the ratios of which were dependent on the nature of substituents on the pyrrolidine substrates. On the other hand, when 1-hexene was used as the olefin coupling partner, only linearly α-alkylated products were obtained (**2j-2m**). With ethyl acrylate as the olefin coupling partner, 2-methyl and 2-phenyl substituted pyrrolidine substrates afforded products in total yields of 80% (**2b**) and 83% (**2c**), respectively. A benzyl protected proline substrate was also compatible and afforded product in a total yield of 68% (**2d**). Spirocyclic and bicyclic pyrrolidine substrates, which are relevant to various medicinal chemistry campaigns,[23] reacted in good yields of 98% (**2e**) and 80% (**2f**), respectively. Pyrrolidine substrates with 3-alkyl substituents also reacted in good yields (**2g, 2h**). On the other hand, an electron deficient 3,3-difluoropyrrolidine substrate gave a low yield of 36% (**2i**). With 1-hexene as the olefin coupling partner, 3-phenyl, 3-alkyl, 3-methoxy, and 3-amino substituted pyrrolidine substrates afforded products in 73% (**2j**), 86% (**2k**), 66% (**2l**), and 77% (**2m**) yields, respectively. We were pleased to find that the use of trifluoromethyl *O*-benzyl amidoxime directing group (with adequate substrate-specific tuning of the reaction conditions) prevented over-alkylation of a variety of substituted pyrrolidine substrates, thus addressing one of the major limitations with previous directing group designs.[9,10]

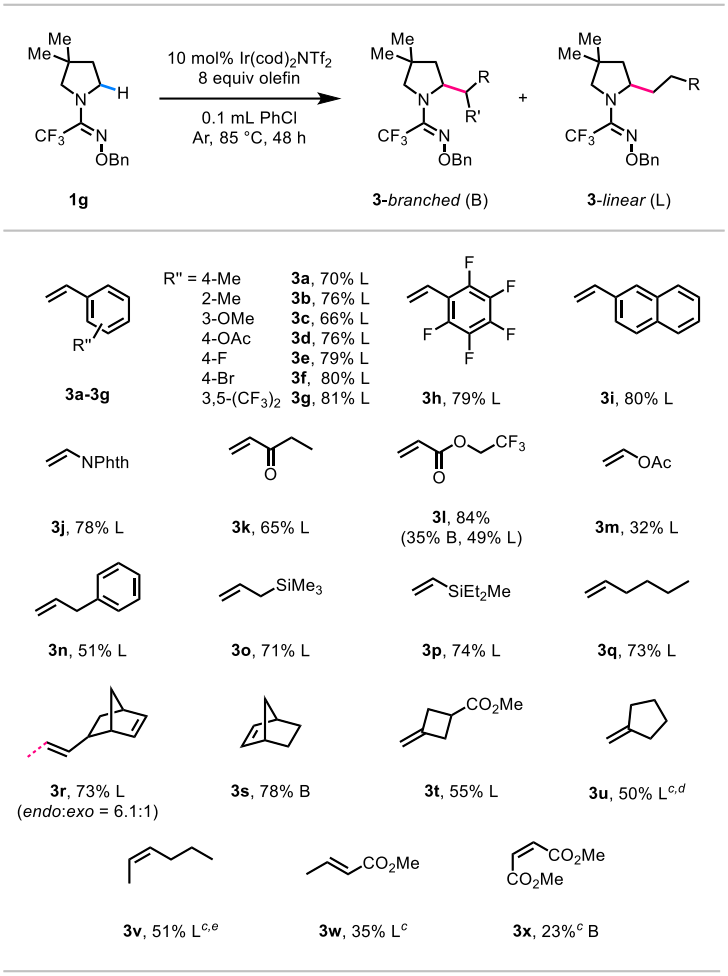
Table 2. Pyrrolidine Substrate Scope.[a,b]



[a]Reaction conditions: **1b** to **1m** (0.1 mmol, 1.0 equiv), $Ir(cod)_2NTf_2$ (0.01 mmol, 0.1 equiv), ethyl acrylate (0.8 mmol, 8.0 equiv), degassed PhCl (0.1 mL), 85 °C, under Ar, 24 h. [b]Yields after isolation by chromatography are shown. [c]$Ir(cod)_2OTf$ instead of $Ir(cod)_2NTf_2$. [d]0.1 equiv of $HBF_4.Et_2O$ (0.01 mmol) as additive. [e]0.05 equiv of $Ir(cod)_2OTf$ (0.005 mmol). [f]12 h instead of 24 h. [g]48 h instead of 24 h.

Having established the scope of pyrrolidine substrates with the trifluoromethyl *O*-benzyl amidoxime directing group, we next investigated the scope of olefin coupling partners using 3,3-dimethyl pyrrolidine (**1g**) as the standard substrate (Table 3). Olefins with a wide variety of steric and electronic properties proved to be efficient coupling partners. A wide range of styrene analogues, including 4-bromostyrene, afforded the respective linearly α-alkylated products in good yields of 66%-81% (**3a-3i**). Electron deficient olefins such as vinyl phthalimide and ethyl vinyl ketone also proceeded to give linearly α-alkylated products in 78% (**3j**) and 65% (**3k**) yields, respectively. Alternate ester protecting groups on the acrylate were well tolerated (**3l**) to give a mixture of branched and linearly α-alkylated regioisomeric products. However, vinyl acetate reacted in a low yield of 32% (**3m**) to give linearly α-alkylated product. Electron neutral olefins all gave their corresponding linearly α-alkylated products selectively. While allylbenzene (**3n**) reacted in a moderate yield of 51%, allyl silane, vinyl silane, and 1-hexene reacted in good yields of 71% (**3o**), 74% (**3p**), and 73% (**3q**), respectively. When vinyl norbornene was used as the olefin coupling partner, the reaction occurred regioselectively at the vinyl position in 73% yield (**3r**). Moreover, a selectivity of 6.1:1 was observed in favor of the *endo*-isomer over the *exo*-isomer of vinyl norbornene. In contrast, in the absence of a vinyl group, simple norbornene reacted in 78% yield (**3s**). The reaction also tolerated di-substituted terminal olefins in moderate yields of 55% (**3t**) and 50% (**3u**), respectively. When cis-2-hexene was used as the olefin coupling partner, an isomerized linear product was obtained in a moderate yield of 51% (**3v**). We also observed isomerization of methyl crotonate to give a linear product, albeit in a low yield of 35% (**3w**).[24] A sterically hindered maleate ester also reacted in 23% yield (**3x**). To the best of our knowledge, this is the first example of an iridium(I)-catalyzed α-C(sp^3)–H alkylation reaction which can utilize di-substituted terminal olefins and internal olefins as effective coupling partners.

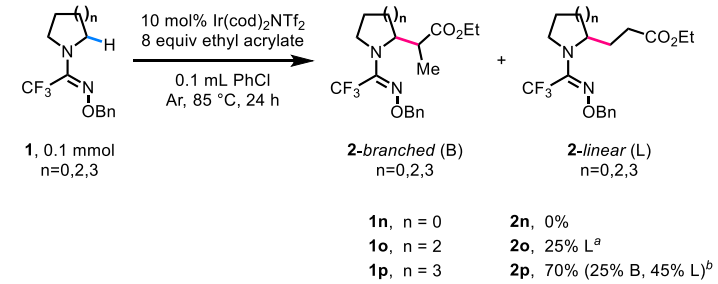
Table 3. Olefin Coupling Partner Scope.[a,b]



[a]Reaction conditions: **1g** (0.1 mmol, 1.0 equiv), $Ir(cod)_2NTf_2$ (0.01 mmol, 0.1 equiv), olefin coupling partner (0.8 mmol, 8.0 equiv), degassed PhCl (0.1 mL), 85 °C, under Ar, 48 h. [b]Yields after isolation by chromatography are shown. [c]**1a** instead of **1g**. [d]mono:di = 4:1. [e]mono:di = 7.5:1.

After establishing the performance of the trifluoromethyl *O*-benzyl amidoxime directing group with a variety of substituted pyrrolidine substrates and olefin coupling partners, we next tested the efficacy of this directing group for azacycles of other ring sizes (Scheme 4). When we subjected the azetidine substrate (**1n**) to the optimized reaction conditions with ethyl acrylate as the olefin coupling partner, no product was observed. The piperidine substrate afforded a linearly α-alkylated product in a low yield of 25% (**2o**). In contrast, the azepane substrate reacted in a good yield of 70% (**2p**) and afforded a mixture of separable branched and linearly α-alkylated regioisomers. A similar reactivity trend has been observed in previous reports where piperidines were found to be a more challenging class of substrates than pyrrolidines and azepanes.

Scheme 4. Evaluation of the Trifluoromethyl *O*-Benzyl Amidoxime Directing Group for α-C(sp^3)–H Alkylation of Azetidine, Piperidine, and Azepane.

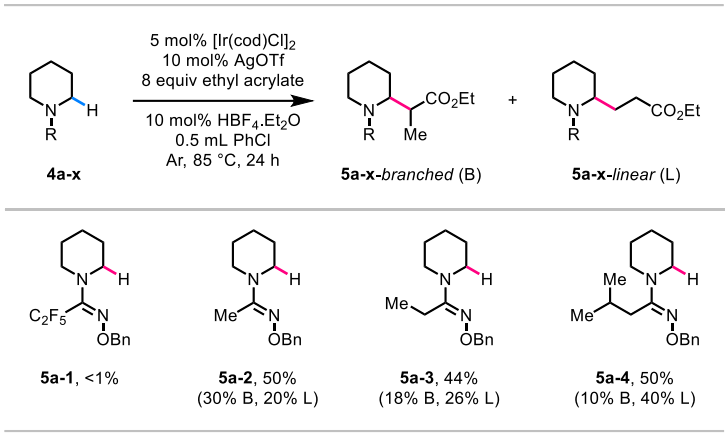


[a]Yield was determined by ^{1}H NMR analysis of the crude product using mesitylene as the internal standard. [b]Yield after isolation by chromatography is shown.

We reasoned that a lower reactivity for the piperidine substrate (**2o**) relative to the pyrrolidine and azepane substrates might be associated with an unfavorable conformation of the six-membered saturated azacycle. This led us to consider that a different directing group might be required for

the piperidine substrate. Leveraging the modular nature of the amidoxime directing groups, we re-evaluated directing groups for the piperidine substrate as shown in Table 4. Under the optimized reaction conditions, with ethyl acrylate as the olefin coupling partner, changing the α-substituent to a perfluoroethyl group had deleterious effect on reactivity (**4a-1**). On the other hand, a variety of alkyl groups such as, methyl (**4a-2**), ethyl (**4a-3**), and isobutyl (**4a-4**), all worked as efficient α-substituents and gave a mixture of branched and linearly α-alkylated regioisomers in moderate yields. A bulkier alkyl α-substituent in the directing group led to a higher yield of the linearly α-alkylated regioisomer. We selected methyl *O*-benzyl amidoxime as the optimal directing group for piperidines because we anticipated that a smaller directing group would have an easier removal protocol.

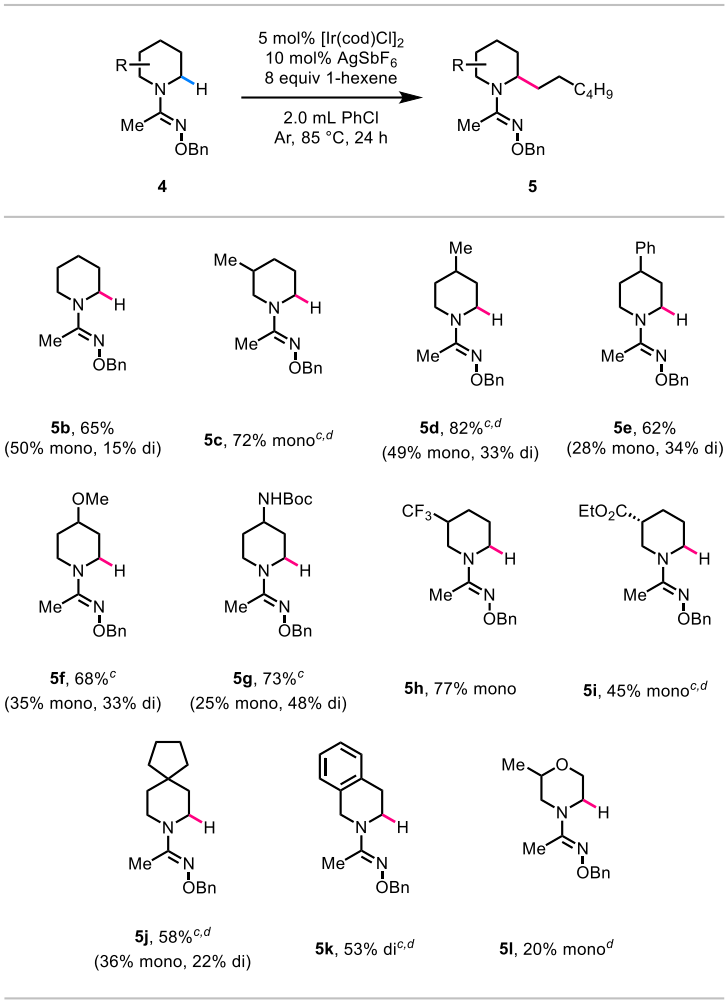
Table 4. Directing Group Evaluation for α-C(sp^3)–H Alkylation of Piperidine.[a,b]



[a]Reaction conditions: **4a-1** to **4a-4** (0.1 mmol, 1.0 equiv), $[Ir(cod)Cl]_2$ (0.005 mmol, 0.05 equiv), AgOTf (0.01 mmol, 0.1 equiv), ethyl acrylate (0.8 mmol, 8.0 equiv), $HBF_4.Et_2O$ (0.01 mmol, 0.1 equiv), degassed PhCl (0.5 mL), 85 °C, under Ar, 24 h. [b]Yields were determined by ^{1}H NMR analysis of the crude products using mesitylene as the internal standard.

With the optimal directing group for piperidine in hand, we further optimized the reaction conditions using 1-hexene as the olefin coupling partner (see the Supporting Information for details). As shown in Table 5, simple piperidine reacted to give a separable mixture of mono- and di-alkylated products in a total yield of 65% (**5b**). Next, we tested the methyl *O*-benzyl amidoxime directing group against a variety of substituted piperidine substrates (**5c-5j**). 3-Methyl piperidine substrate reacted to give mono-alkylated product in 72% yield (**5c**). 4-Methyl and 4-phenyl substituted piperidine substrates also reacted in 82% (**5d**) and 62% (**5e**) yields, respectively, giving a mixture of separable mono- and di-alkylated products. Piperidine substrates containing various functional groups such as 4-methoxy (**5f**), 4-amino (**5g**), 3-trifluoromethyl (**5h**), and 3-ester (**5i**) were also compatible and reacted in moderate to good yields. A spirocyclic piperidine substrate yielded a separable mixture of mono- and di-alkylated products in a total yield of 58% (**5j**). Tetrahydroisoquinoline was also a compatible substrate and reacted to give di-alkylated product in 53% yield (**5k**). 3-Methyl morpholine was a challenging substrate and gave the corresponding mono-alkylated product in a low yield of 20% (**5l**). However, complete site-selectivity was achieved for the α-C(sp^3)–H bonds next to the nitrogen atom in the presence of the α-C(sp^3)–H next to an oxygen atom. Finally, the di-alkylation favored *anti*-stereochemistry; where **5b-di**, **5d-di**, and **5k** were isolated as single diastereomers (see the Supporting Information for details on diastereoselectivity).

Table 5. Piperidine Substrate Scope.[a,b]

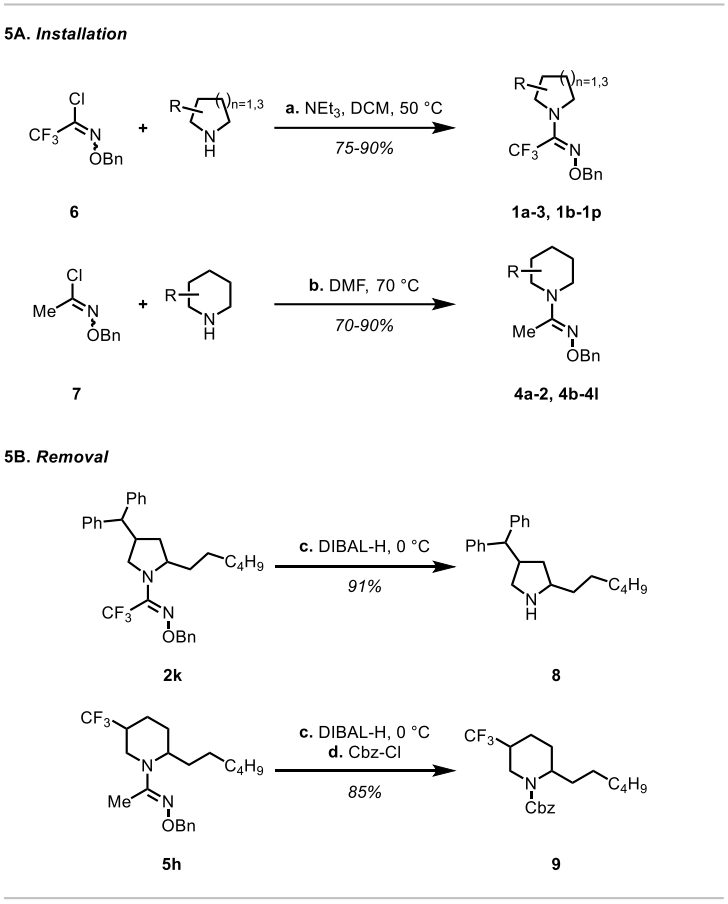


[a]Reaction conditions: **4b** to **4l** (0.1 mmol, 1.0 equiv), $[Ir(cod)Cl]_2$ (0.005 mmol, 0.05 equiv), $AgSbF_6$ (0.01 mmol, 0.1 equiv), 1-hexene (0.8 mmol, 8.0 equiv), degassed PhCl (2.0 mL), 85 °C, under Ar, 24 h. [b]Yields after isolation by chromatography are shown. [c]0.1 equiv of $Ir(cod)_2NTf_2$ (0.01 mmol) instead of $[Ir(cod)Cl]_2$ and $AgSbF_6$. [d]48 h instead of 24 h.

Scheme 5A shows the one-step installation protocols developed for both the trifluoromethyl *O*-benzyl amidoxime and the methyl *O*-benzyl amidoxime directing groups

starting from precursors **6** and **7** (see the Supporting Information for details). These precursors were used for the synthesis of the azacycle substrates (**1a-3**, **1b-1p**, **4a-2**, **4b-4l**) in a divergent manner. Scheme 5B shows the removal protocols for two representative products, **2k** and **5h**. Both the directing groups were cleaved effectively under DIBAL-H reduction at 0 °C in a single step.

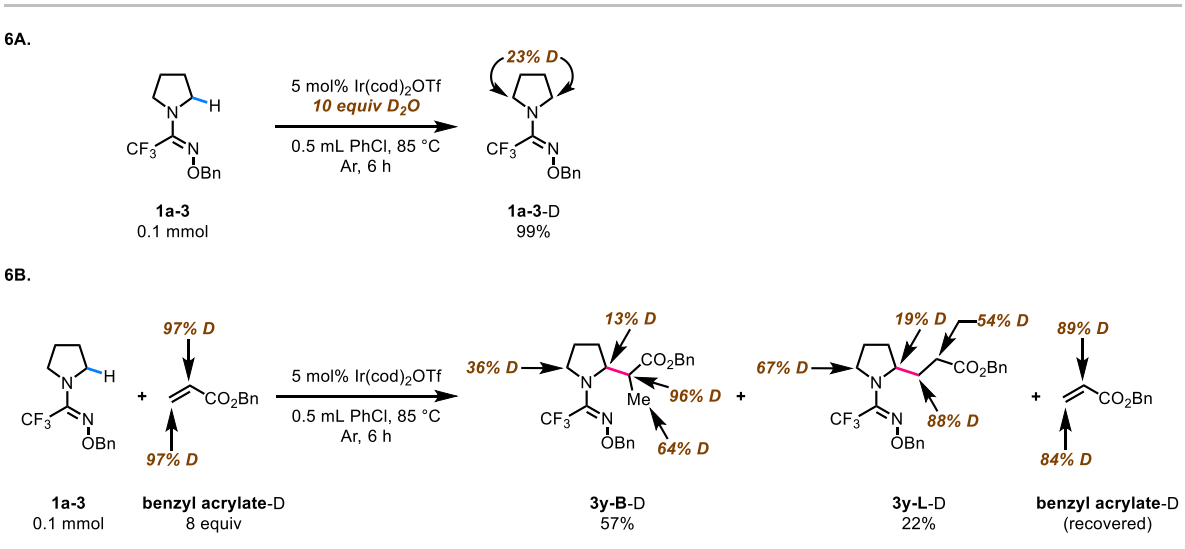
Scheme 5. Installation and Removal of Amidoxime Directing Groups.[a]



[a]Reaction conditions: (a) Azacycle (1.0 equiv), **6** (1.2 equiv), triethylamine (1.2 equiv), DCM, 50 °C, under air, 12 h. (b) Azacycle (1.0 equiv), **7** (1.2 equiv), DMF, 70 °C, under air, 12 h. (c) **2k** or **5h** (0.1 mmol, 1.0 equiv), DIBAL-H (0.5 mmol, 5.0 equiv), toluene (0.5 mL), 0 °C, under N_2, 30 min. (d) CbzCl (0.3 mmol, 3.0 equiv), Et_3N (0.3 mmol, 3.0 equiv), DCM (1.0 mL), rt, under N_2, 12 h.

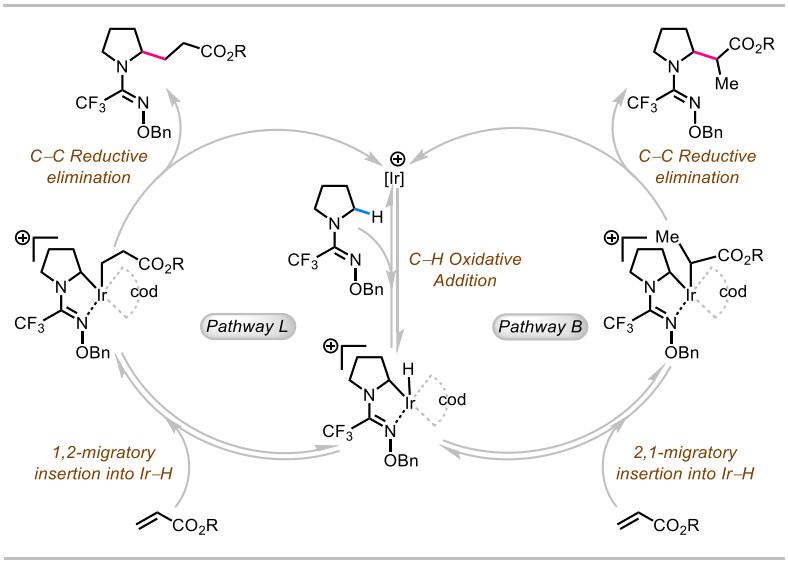
Due to the observation of unconventional branch-selective α-alkylation with acrylates, we performed deuterium labelling experiments (Scheme 6). When substrate **1a-3** was subjected to the reaction conditions in the presence of D_2O and in the absence of an olefin coupling partner, deuterium incorporation at the α- and α'-positions of the pyrrolidine substrate was observed (Scheme 6A). This result implies that the α-C(sp^3)–H bond of **1a-3** is cleaved under the present reaction conditions, without the involvement of an olefin coupling partner. Next, the reaction of substrate **1a-3** with deuterated benzyl acrylate was examined (Scheme 6B). Incorporation of deuterium atoms was detected at the α- and α'-positions of both the branched and linearly alkylated products (**3y-B**, **3y-L**). Moreover, the recovered benzyl acrylate coupling partner was found to have a reduced deuterium content. These observations indicate that the catalytic cycle consists of reversible C–H bond activation and olefin insertion steps. The experimentally observed isomerization of internal olefins to give linearly α-alkylated products (**3v**, **3w**) lends further support for a reversible olefin insertion step.

Scheme 6. Deuterium labelling experiments.



On the basis of the above labelling experiments, the proposed mechanism for the amidoxime-directed Ir(I)-catalyzed α-C(sp^3)–H alkylation reaction of pyrrolidine with an acrylate coupling partner is shown in Scheme 7. Since the reaction yield and selectivity were found to be dependent on the diene ligand (see the Supporting Information), it is likely that one unit of the diene ligand remains coordinated to iridium.[25] The first step involves the directed α-C–H activation of the pyrrolidine substrate via an oxidative addition mechanism, leading to the formation of a cationic Ir(III) intermediate. Next, a molecule of acrylate may react reversibly with this iridium-hydride species in two different ways - thus giving rise to Pathways L and B. In Pathway L, acrylate undergoes a sterically-controlled 1,2-migratory insertion into the Ir–H bond, leading to a linear Ir-alkyl species, which upon a C–C reductive elimination gives the linearly α-alkylated product. In Pathway B, acrylate undergoes an electronically-controlled 2,1-migratory insertion into the Ir–H bond leading to a branched Ir-alkyl species, which upon a C–C reductive elimination gives the branched α-alkylated product.

Scheme 7. Proposed Mechanistic Pathways.



CONCLUSION

In summary, we report the design and discovery of novel amidoxime directing groups for the iridium(I)-catalyzed α-C(sp^3)–H alkylation of saturated azacycles using readily available olefins as coupling partners. A trifluoromethyl *O*-benzyl amidoxime directing group was developed for substituted pyrrolidines, proline, and azepane substrates. This transformation is applicable on wide arrays of olefin coupling partners with diverse steric and electronic properties, including previously unreactive di-substituted terminal olefins and internal olefins. For more challenging substrates, such as substituted piperidines and tetrahydroisoquinoline, a methyl *O*-benzyl amidoxime directing group was developed. The selectivity for a branched α-C(sp^3)–H alkylation product is observed for the first time when acrylate was used as the reaction partner. New protocols enabling practical, one-step installation and removal of these directing groups were also developed. Future work from our group will focus on developing enantioselective α-C(sp^3)–H alkylation of saturated azacycles and on exploiting the potential of amidoxime directing groups for other interesting substrates and transformations.

EXPERIMENTAL SECTION

A 2-dram vial was charged with the substrate (0.1 mmol, 1.0 equiv) and taken inside an argon glovebox. $Ir(cod)_2NTf_2$ (6.9 mg, 0.01 mmol, 0.1 equiv, unless otherwise noted) was added followed by a magnetic stir bar. The vial was sealed with a PTFE septum and taken out of the glovebox. Degassed PhCl (0.1 mL, unless otherwise noted) and olefin coupling partner (0.8 mmol, 8.0 equiv, unless otherwise noted) were added to the vial. The solution was stirred at 85 °C for 24 hours (unless otherwise noted). Upon completion, the reaction mixture was cooled to rt and diluted

with 2 mL EtOAc. The mixture was filtered through a pad of celite. The celite was washed thoroughly with EtOAc and the combined organics were concentrated *in vacuo*. The crude reside was purified by preparative TLC to provide the alkylated product(s).

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Detailed experimental procedures and characterization of new compounds (PDF)

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Notes

The authors declare no competing financial interests.

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