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Iridium-Catalyzed γ-Selective Hydroboration of γ-Substituted Allylic Amides

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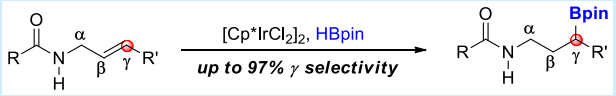
ABSTRACT: Reported here for the first time is the Ir-catalyzed γ-selective hydroboration of γ-substituted allylic amides under mild reaction conditions. A variety of functional groups could be compatible with reaction conditions, affording γ-branched amides in good yields with ≤97% γ-selectivity. We have also demonstrated that the obtained borylated products could be used in a series of C−O, C−F, C−Br, and C−C bond-forming reactions.



Transition-metal-catalyzed hydroboration of alkenes has been recognized as one of the most efficient methods for obtaining alkyl boronic acid and its derivatives.[1] As a result, a great number of strategies have been developed for the synthesis of these compounds in chemo-, regio-, and stereoselective manners. However, most of these successful methods are limited to terminal alkenes,[2] activated alkenes,[3] and styrene derivatives.[2d,4] The regioselective hydroboration of aliphatic internal alkenes as well as other hydrofunctionalization reactions[5] remains a distinct challenge, which has in part arisen from difficulty in the differentiation of two sterically and electronically similar sp^2 carbons. The first example of transition-metal-catalyzed amide-directed regioselective hydroboration of aliphatic internal alkenes was not reported until the 1990s,[6] although the Rh-catalyzed hydroboration of terminal alkenes was developed as early as the 1980s.[7] The key to the success of regioselectivity is the chelation of the substrate to the metal center. Later, a number of elegant regio- and stereoselective hydroboration reactions of a variety of aliphatic internal alkenes were developed by the group of Takacs.[4l,8] In addition to the chelation mechanism, the inductive effect could also be used as the key factor to control regioselectivity. In 2016, the Hartwig group reported a Cu-catalyzed regio- and stereoselective hydroboration of homoallylic alcohol and amine derivatives, affording the desired products in excellent regioselectivity.[9] Notably, both substrate chelation and the inductive effect give rise to the formation of a C−B bond at the sp^2 carbon that is proximal to the directing groups.[10] Recently, we developed an Ir-catalyzed hydroboration of β,γ- and γ,δ-unsaturated carbonyl compounds with high γ- and δ-selectivity.[11] The DFT calculation reveals that the reaction undergoes an unusual Ir(III)/Ir(V) catalytic cycle, and the regioselectivity is dominated by steric repulsion.[11] In the development of this field, further extending the reaction types is desirable.

γ-Branched amine derivatives are important building blocks in synthetic chemistry and widespread subunits in a number of bioactive compounds (Figure 1).[12] In stark contrast to well-developed methods for the α- and β-branched amine derivatives,[13] the catalytic methods for the synthesis of γ-branched ones remain underdeveloped (Scheme 1A). A practical way to synthesize these compounds was accomplished by acid- or base-catalyzed nucleophilic addition to the azetidine derivatives (Scheme 1A, a).[14] In addition, Wu and co-workers reported an efficient Rh-catalyzed reductive amination of γ,γ-disubstituted allylic amine derivatives to prepare γ-branched amines (Scheme 1B, b).[15] However, substrates require preinstallation of γ-substituents, which sometimes costs extra steps and reagents. Therefore, direct regioselective hydrofunctionalization of γ-substituted allylic amine derivatives could provide an attractive alternative to the γ-branched amines. In this context, γ-selective hydroboration could be an appealing candidate in combination with well-established C−B bond transformations.[16] Herein, we report an Ir-catalyzed γ-selective hydroboration of allylic amides under mild reaction conditions, affording the corresponding γ-borylated products with ≤97% γ-selectivity (Scheme 1B, c).

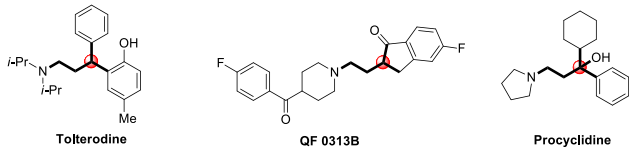


Figure 1. Selected examples of bioactive γ-branched amine derivatives.

Our research commenced with the optimization of the reaction conditions. We chose **1a** as our pilot substrate. The reaction of **1a** with HBpin (1.6 equiv) in the presence of a

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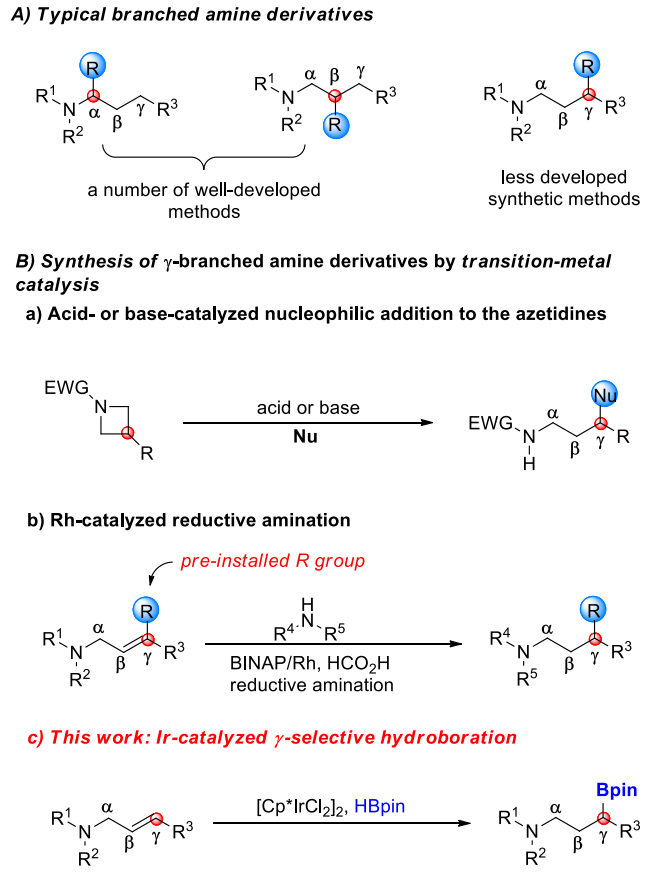
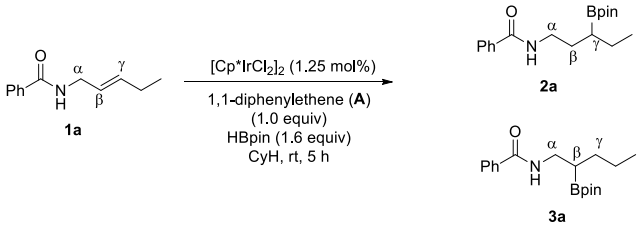
Scheme 1. Typical Branched Amine Derivatives and Transition-Metal-Catalyzed Synthesis of γ-Amine Derivatives



catalytic amount of $[Cp^*IrCl_2]_2$ (1.25 mol %) and a stoichiometric amount of 1,1-diphenylethene (**A**) (1.0 equiv) in cyclohexane for 5 h afforded γ-borylated product **2a** in 78% yield with 90% γ-selectivity (Table 1, entry 1). Replacement of the Ir catalyst with its Rh analogue afforded only a trace amount of the product with 81% γ-selectivity (Table 1, entry 2). Neither CpIr(cod) (**I**) (cod = 1,5-cyclooctadiene) nor chiral CpIr(cod) (**II**) showed reactivity for this reaction (Table 1, entry 3).[17] The use of Crabtree's catalyst also showed no reactivity (Table 1, entry 4). When styrene was used in lieu of **A**, almost the same level of regioselectivity was observed. However, **2a** was obtained in inferior yield (Table 1, entry 5). A low yield was observed (29%) when the reaction was carried out without **A** (Table 1, entry 6). The role of **A** was to act as the hydrogen acceptor to inhibit the hydrogenation byproduct of **1a**, which was evidenced by the 1,1-diphenylethane (44% yield) observed by ^{1}H NMR of the crude reaction mixture under standard reaction conditions (Table 1, entry 1). We next investigated the effect of phosphine ligands on the current reaction. However, none of them could further enhance the performance of the reaction in terms of the outcome of product **2a** (Table 1, entries 7–9). Further examination of solvent effects revealed that cyclohexane was optimal in terms of both yield and regioselectivity (Table 1, entry 1 vs entries 10 and 11).

With optimized reaction conditions in hand (Table 1, entry 1), we then determined the additional substrate scope of the current Ir-catalyzed γ-selective hydroboration of γ-substituted allylic amides as shown in Scheme 2. First, a variety of N

Table 1. Optimization of Reaction Conditions for the Ir-Catalyzed γ-Selective Hydroboration of 1a[a]



entry	variations	2a:3a[b]	yield of 2a (%)[c]
1	none	90:10	78
2	$[Cp^*RhCl_2]_2$ was used instead of $[Cp^*IrCl_2]_2$	81:19	trace
3	**I** or **II** was used instead of $[Cp^*IrCl_2]_2$	NR	–
4	Crabtree's catalyst was used instead of $[Cp^*IrCl_2]_2$	NR	–
5	styrene in lieu of **A**	89:11	65
6	without **A**	92:8	29
7	Davephos (2.5 mol %) was added	89:11	75
8	PPh_3 (2.5 mol %) was added	ND	NR
9	Xantphos (2.5 mol %) was added	88:12	70
10	THF was used instead of CyH	84:16	65
11	1,4-dioxane was used instead of CyH	84:16	71

[a]Unless otherwise noted, all of the reactions were carried out with **1a** (0.20 mmol) and HBpin (0.32 mmol) in solvent (1.0 mL) at room temperature for 5 h. [b]The **2a**:**3a** ratio was determined by GC analysis. [c]Isolated yield.

substituents are investigated when R′ is an ethyl group (**1a–h**). All of the reactions could reach completion within 5 h in moderate to good yields (**2a–h**, 64–80%). The regioselectivity strongly depended on the substituent. For example, *o*-methyl-substituted **2b** gave higher γ-selectivity (92%) while a *para* substituent usually gave inferior results (**2c–h**, 82–90% γ-selectivity). The reaction was also tolerated with a thiophenyl group, although only 80% regioselectivity was observed (**2i**). We next focused on the variation of the R′ group. When R′ is a methyl group, the reaction afforded the products in 63–80% isolated yields with γ-selectivity ranging from 86% to 90% (**2j–l**). The regioselectivity remained at the same level when the chain length of R′ was extended to *n*-propyl (**1m**) and *n*-butyl (**1n**). In addition to alkyl substrates, benzyl and homobenzyl groups (**1o** and **1p**, respectively) were also compatible with reaction conditions. In particular, an excellent γ-selectivity (97%) was observed when R′ was a benzyl group. The moderate isolated yield (45%) is due to the partial decomposition of **2o** upon column chromatography. The lower stability of **2o** is probably due to its C–B bond being closer to the inductively electron-withdrawing sp^2 carbon of the phenyl ring compared to that of **2p**. Apart from arylamides, alkylamide (**1q**) could also undergo the hydroboration smoothly to afford the product (**2q**) in 68% yield with inferior γ-selectivity (86%) compared to the reaction of **1j**. We then surveyed the compatibility of other relatively sensitive functionalities. Fortunately, ester (**1r**), ether (**1s**), aldehyde (**1t**), and free hydroxy (**1u**) groups were well tolerated, affording **2r–2u**, respectively, in 57–69% isolated yields with γ-selectivity ranging from 85% to 91%. Although isolated olefin was not compatible, the bishydroborated product (**2v**) was obtained in 66% yield with 90% γ-selectivity. To further extend the generality of the current protocol, we examined the

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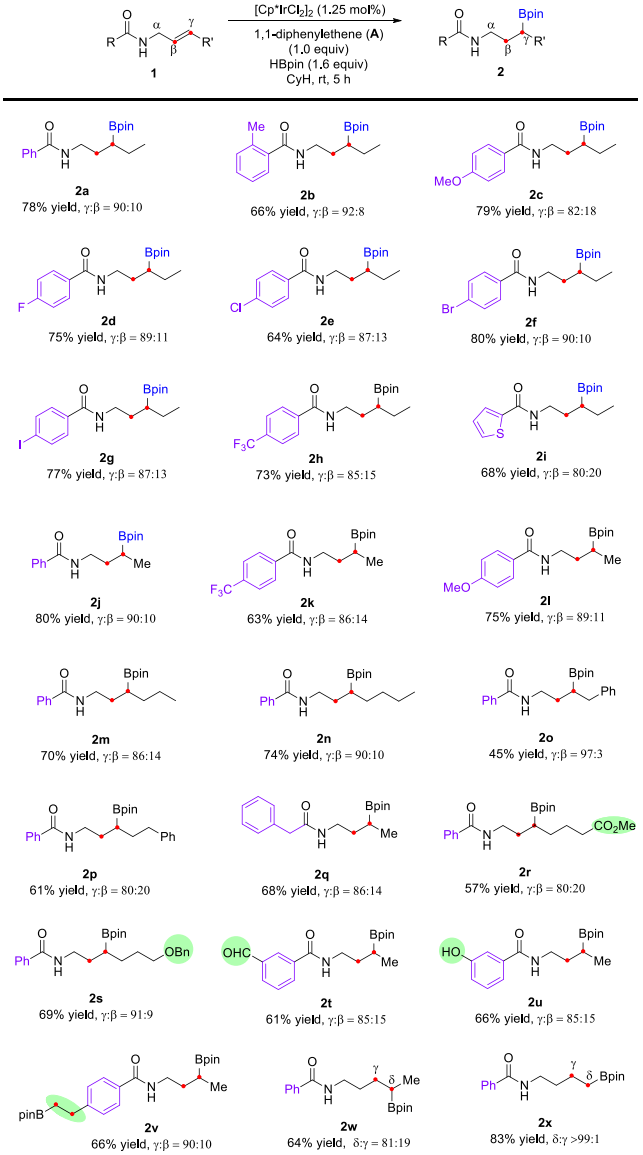
Scheme 2. Substrate Scope for the Ir-Catalyzed γ-Selective Hydroboration of 1[a]



[a]Unless otherwise noted, all of the reactions were carried out with **1** (0.20 mmol), **A** (0.20 mmol), and HBpin (0.32 mmol) in CyH (1.0 mL) at room temperature for 5 h. The regioisomeric ratios were determined by GC analysis.

performance of homoallylic amides. An internal alkene (**1w**) gave inferior distal selectivity (81% δ) compared to that of its allylic analogue (**1j**). Pleasingly, the exclusive δ-borylated product (**2x**) was observed with a terminal alkene (**1x**).

To demonstrate the synthetic utility of the current protocol, a gram-scale reaction of **1a** and several transformations of **2a** were conducted as shown in Figure 2. The reaction of **1a** (5 mmol) under standard reaction conditions afforded **2a** in 68% isolated yield (1.05 g) with 88% γ-selectivity. The C−B bond could be transformed into other functional groups. For example, oxidation of **2a** with $NaBO_3·4H_2O$ gave 1,3-aminoalcohol derivative **3** in 96% isolated yield.[10a] Fluorinated product **5** was obtained in 80% yield when the reaction of **2a** was carried out with Selectfluor in the presence of a catalytic amount of $AgNO_3$.[18] The reaction of **2a** with electron-deficient aryl lithium followed by addition of NBS could provide γ-

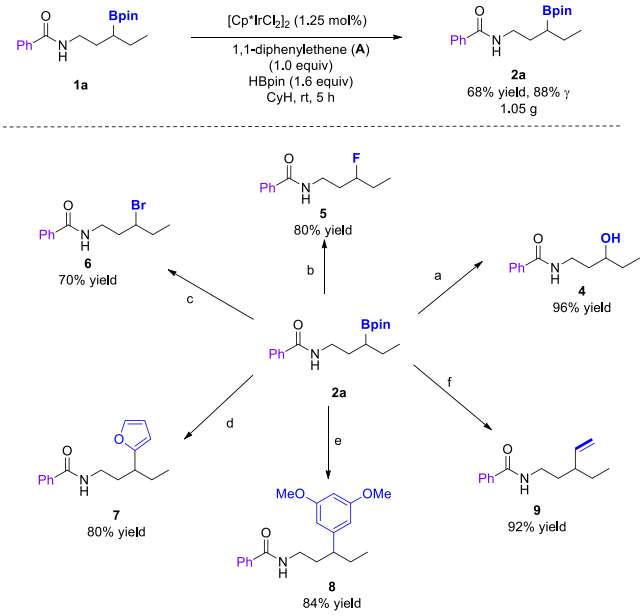


Figure 2. Gram-scale hydrobration of **1a** and synthetic application of borylated product **2a**. Conditions: (a) $NaBO_3·4H_2O$, THF/H_2O, rt; (b) $AgNO_3$ (20 mol %), Selectfluor, CH_2Cl_2/H_2O, 50 °C; (c) 3,5-$(CF_3)_2C_6H_3Br$, *n*BuLi, −78 °C, then NBS, rt; (d) 3,5-$(CF_3)_2C_6H_3Br$, *n*BuLi, −78 °C, then NBS, −78 °C to rt; (e) furan, *n*BuLi, −78 °C, then NBS, −78 °C; (e) 3,5-$(MeO)_2C_6H_3Br$, *n*BuLi, −78 °C, then NBS, −78 °C to rt; (f) C_2H_3MgBr, THF, 0 °C to rt, then I_2 in MeOH, −78 °C, then NaOMe in MeOH, −78 °C to rt.

bromo amide **6** in 70% yield.[19] On the other hand, treatment of **2a** with electron-rich aryl lithium followed by NBS afforded arylated products **7** and **8** in 80% and 84% yields, respectively.[20] Finally, treatment with **2a** with vinylmagnesium bromide followed by sequential addition of I_2 and NaOMe resulted in olefination product **8** in 92% yield.[21]

In conclusion, we have developed Ir-catalyzed γ-selective hydroboration of γ-substituted allylic amides under mild reactions for the first time. A variety of functional groups could be well-tolerated, affording γ-borylated products in good yields with ≤97% γ-selectivity. We have also demonstrated that the obtained borylated products could be used in the synthesis of a series of γ-branched amides. Further exploration of regioselective hydroboration of other types of aliphatic internal alkenes is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00977.

Experimental procedures and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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