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Communication

Iridium-Catalyzed Asymmetric Hydroalkenylation of Norbornene Derivatives

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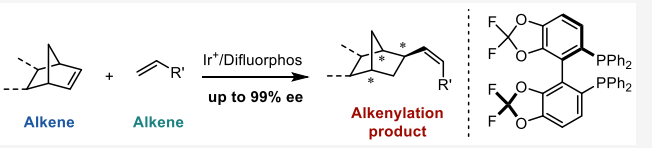
ABSTRACT: Transition-metal-catalyzed asymmetric hydroalkenylation of alkenes provides an atom-economical method to build molecular complexity from easily available materials. Herein we report an iridium-catalyzed asymmetric hydroalkenylation of unconjugated alkenes with acrylamides and acrylates. The catalytic hydroalkenylation of norbornene derivatives occurred to form products with allylic stereocenters with high chemo-, regio-, and stereoselectivities. DFT calculations revealed that the migratory insertion is irreversible and the enantiodetermination step.



The transition-metal-catalyzed Mizoroki−Heck reaction is a powerful method to construct C−C bonds.[1] However, coupling of alkyl halides with terminal alkenes is difficult because of the slow oxidative addition and potential side reactions (Scheme 1a).[2] In particular, catalytic enantioselective coupling of secondary alkyl halides with terminal alkenes remains an important synthetic challenge (Scheme 1b).[3] This process produces useful chiral products containing an allylic stereocenter. Therefore, alternative processes to access these chiral products from alkenes are highly desirable.

Transition-metal-catalyzed asymmetric hydroalkenylation of alkenes provides an atom-economical method to generate these chiral products from easily available alkene substrates

Scheme 1. Challenge of the Mizoroki−Heck Reaction and Hydroalkenylation of Alkenes

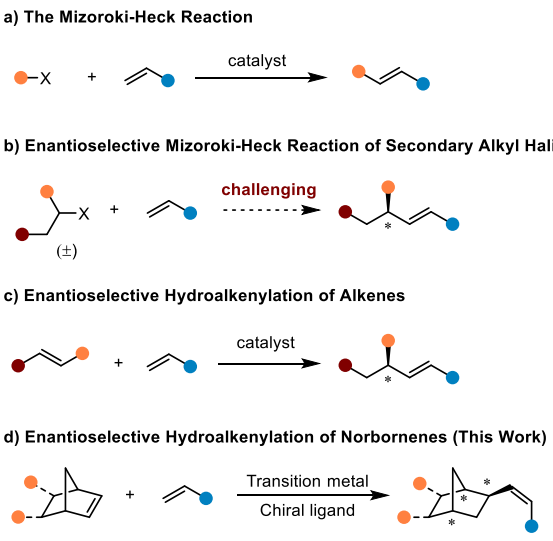
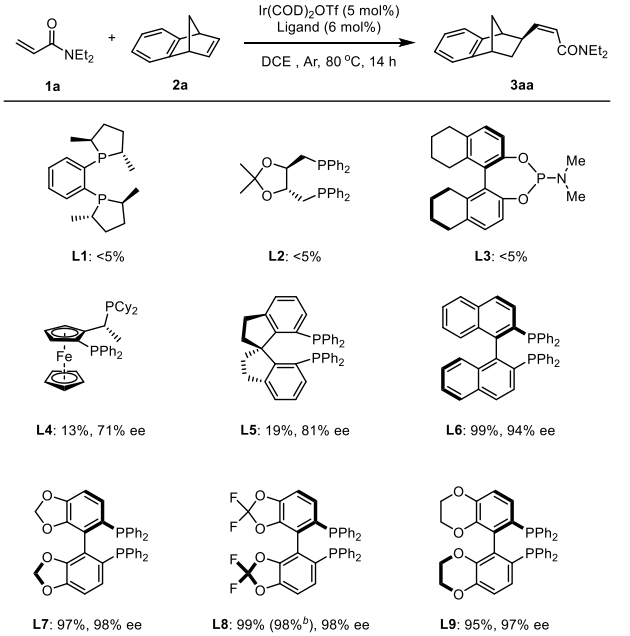


Table 1. Reaction Development[a]



[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.20 mmol), $Ir(COD)_2OTf$ (5 mol %, 0.0050 mmol), ligand (6 mol %, 0.0060 mmol), DCE (0.50 mL), 80 °C, 14 h. Yields were determined by NMR spectroscopy using CH_2Br_2 as an internal standard. [b]Isolated yield.

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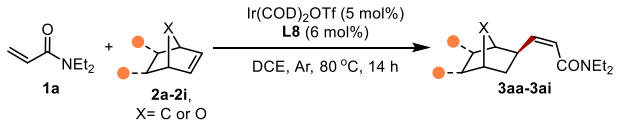
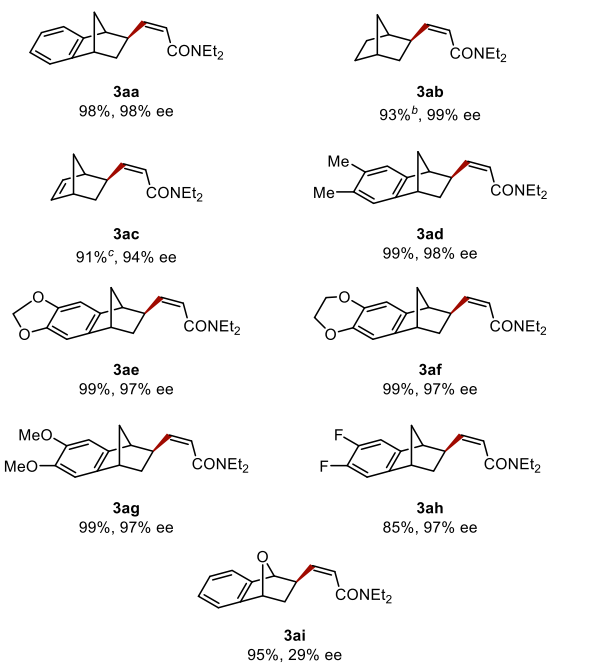
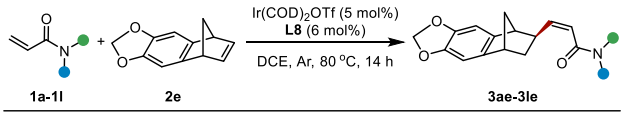
Table 2. Substrate Scope for Norbornene Derivatives[a]

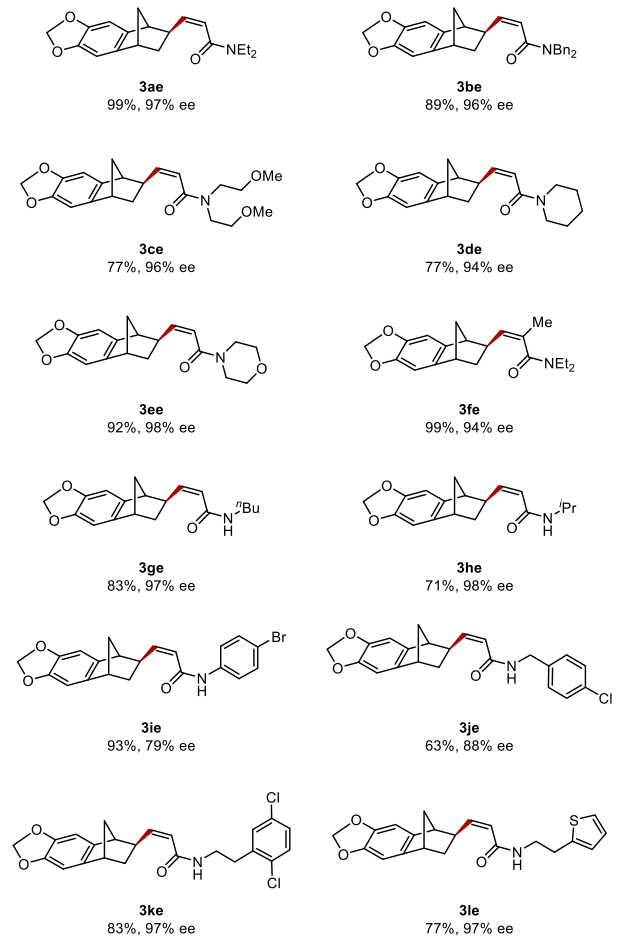




[a]Reaction conditions: **1a** (0.10 mmol), **2a**−**i** (0.20 mmol), $Ir(COD)_2OTf$ (5 mol %, 0.0050 mmol), **L8** (6 mol %, 0.0060 mmol), DCE (0.50 mL), 80 °C, 14 h. Isolated yields are reported. [b]**2b** (0.50 mmol). [c]**2c** (0.50 mmol).

Table 3. Substrate Scope for Acrylamide Derivatives[a]





[a]Reaction conditions: **1a**−**l** (0.10 mmol), **2e** (0.20 mmol), $Ir(COD)_2OTf$ (5 mol %, 0.005 mmol), **L8** (6 mol %, 0.0060 mmol), DCE (0.50 mL), 80 °C, 14 h. Isolated yields are reported.

(Scheme 1c).[4] Since the first example of asymmetric hydrovinylation reported in 1972,[5] catalytic asymmetric hydrovinylations[6] of styrenes,[7] conjugated alkenes,[8] and strained alkenes[9] with ethylene have been reported. In contrast, asymmetric hydroalkenylations involving substituted alkenes are less developed. In such an enantioselective alkene dimerization process, the two alkenes must chemoselectively react with each other. In addition, the regioselectivities on both alkenes and the enantioselectivity of the process must be effectively controlled. Currently, catalytic asymmetric hydroalkenylations using substituted alkenes have been developed mainly for conjugated alkenes such as styrenes[10] and 1,3-dienes.[11] Recently, Hirano described a Ru-catalyzed asymmetric hydroalkenylation of 2,5-dihydrofuran with acrylates to afford the coupling products with good enantioselectivity.[12]

We report here an iridium-catalyzed highly enantioselective coupling of unconjugated alkenes with acrylamides to afford products containing three stereocenters (Scheme 1d).[13,14] In the presence of a coordinating group, the low-valent cationic iridium species selectively cleaves the vinyl C−H bond.[15,16] Further reaction of the vinyliridium intermediate with norbornene generates the hydrovinylation products with high chemo-, regio-, and stereoselectivities. This mechanism is distinct from those in previous reports on hydroalkenylation of conjugated alkenes.[10−12] The catalytic system is applicable to a variety of acrylamide and norbornene derivatives. Further computational studies revealed the origin of the enantioselectivity.

We began our study by testing the hydroalkenylation between *α*,*β*-unsaturated amide **1a** and benzonorbornadiene (**2a**) in the presence of $Ir(COD)_2OTf$ and a series of chiral ligands (Table 1). When Du-Phos (**L1**), DIOP (**L2**), or a phosphoramidite (**L3**) was used, no hydroalkenylation product was observed. However, with Josiphos (**L4**) or SDP (**L5**) as the ligand, the desired product was observed, although in low yield with moderate enantioselectivity. The product could be obtained in high yield and enantioselectivity with BINAP (**L6**) as the ligand. Further variations of the ligand backbone indicated that Difluorphos (**L8**) provided even higher ee in the hydroalkenylation reaction. Importantly, only the *Z* isomer was obtained for the hydroalkenylation product. This is supportive of a directed C−H cleavage mechanism, as only the C−H bond cis to the coordinating group was cleaved (vide infra). In addition, the high *Z* selectivity indicates minimal alkene isomerization in the catalytic system, although an iridium hydride intermediate was involved.

The substrate scope of the asymmetric hydroalkenylation reaction was subsequently investigated (Table 2). The reactions of norbornene and norbornadiene afforded the

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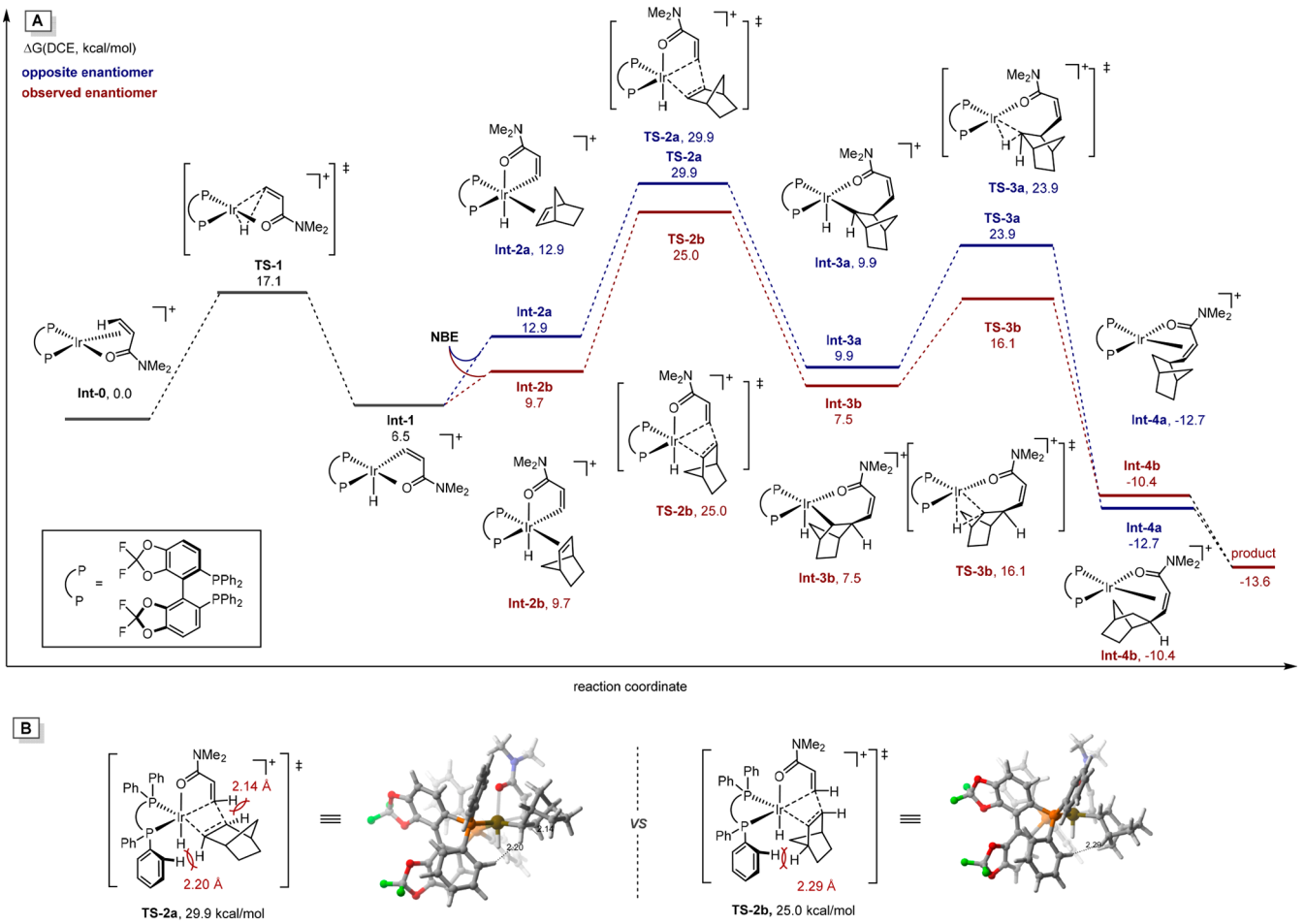
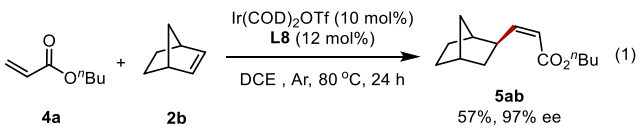


Figure 1. Computational studies for catalytic hydroalkenylation. (A) Energy profile for catalytic hydroalkenylation. (B) Structures of key transition states. Calculations were carried out at the M06/6-311++G(d,p)/SDD//B3LYP/6-31G(d,p)/LANL2DZ level of theory.

corresponding products **3ab** and **3ac** in high yields with high ee's. The absolute configuration of **3ab** was determined by subsequent derivatization and comparison with authentic samples (see the Supporting Information).[9a] Both electron-donating and electron-withdrawing groups on the benzonorbornadiene were tolerated (**3ad**–**ah**). Catalytic hydroalkenylation of 1,4-epoxy-1,4-dihydronaphthalene provided the product **3ai** in high yield, although the ee value was low (see the Supporting Information for discussion).

We further tested the scope of various acrylamides (Table 3). The reaction was applicable to substrates derived from both acyclic amines (**3ae**–**ce**) and cyclic amines (**3de** and **3ee**). The acrylamide with an α-methyl group underwent the hydroalkenylation smoothly and generated the product in high yield with high ee (**3fe**). In addition to tertiary acrylamides, secondary acrylamides were tolerated (**3ge**–**le**). We found that the substituents on the nitrogen had an influence on the ee value. The product was obtained with higher enantioselectivity for an *N*-alkylamide (**3ke**) than for *N*-arylamides (**3ie** and **3je**). Functional groups including aryl halides and thiophene were tolerated.

In addition to acrylamides, acrylates underwent efficient hydroalkenylation. For example, catalytic hydroalkenylation of norbornene with *n*-butyl acrylate afforded product **5ab** with high enantioselectivity, although a higher catalyst loading was necessary (eq 1).



To gain insight into the reaction mechanism, computational studies were conducted (Figure 1). The reaction starts with the oxidative addition of the alkenyl C–H of the acrylamide (**Int-0**) to afford an alkenyliridium hydride intermediate (**Int-1**) with coordination of the carbonyl group (Figure 1A). After coordination of norbornene to the iridium center of **Int-1**, the C=C bond of norbornene undergoes migratory insertion into the Ir–C bond to generate an iridacycle. Finally, C–H bond-forming reductive elimination delivers the hydroalkenylation product. The activation free energies in the reaction profile indicate that migratory insertion (**TS-2b** vs **TS-2a**) is irreversible and determines the enantioselectivity. The transition state leading to the major enantiomer (**TS-2b**) has an activation barrier of 25.0 kcal·mol^{-1} while the competing transition state (**TS-2a**) has an activation free energy of 29.9 kcal·mol^{-1}. Thus, the product was predicted to be formed with >99% ee. The predicted absolute configuration and high enantioselectivity are in good agreement with the experimental results.

Analysis of the two competing transition state structures revealed the origin of the enantioselectivity (Figure 1B). In **TS-2a**, the vinylic C–H bond of norbornene experiences repulsion

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with the vinylic C−H bond of acrylamide (2.14 Å). In addition, the other vinylic C−H bond of norbornene is in close proximity to the aryl group on the ligand (2.20 Å). In contrast, these repulsive interactions are not observed in **TS-2b** because of the orientation of the norbornene. A relatively weak repulsion was found between the tertiary C−H bond and the aryl group on the ligand (2.29 Å). Thus, the stronger repulsion in **TS-2a** compared with that in **TS-2b** contributes to the energy difference and leads to the high enantioselectivity observed.

In summary, we have developed an iridium-catalyzed asymmetric hydroalkenylation reaction of unconjugated alkenes with acrylamides and acrylates. The catalytic hydroalkenylation of norbornene derivatives occurred in high yields with high diastereo- and enantioselectivities. DFT calculations revealed that the migratory insertion is irreversible and the enantiodetermining step. Further expansion of the substrate scope and investigation of the detailed mechanism are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.organomet.0c00811.

Experimental procedures, characterization data for new compounds, and spectroscopic data (PDF)

Cartesian coordinates (XYZ)

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Notes

The authors declare no competing financial interest.

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