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Synthesis of Amides with Remote Stereocenters by Catalytic Asymmetric γ-Alkynylation of α,β-Unsaturated Amides

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Supporting Information

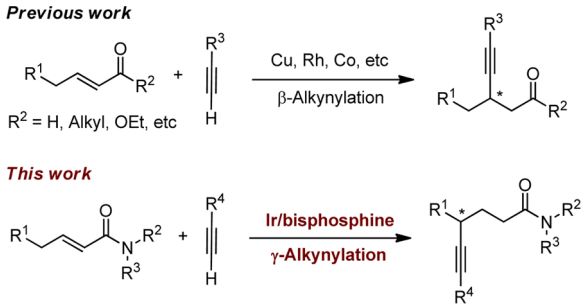
ABSTRACT: An iridium-catalyzed enantioselective hydroalkynylation of α,β-unsaturated amides was described. The selectivity of this reaction is distinct from that observed in many catalytic hydroalkynylations of α,β-unsaturated carbonyl compounds. It occurs selectively at the γ instead of the β position. Preliminary mechanistic studies suggest that the reaction proceeds through alkene isomerization followed by hydroalkynylation. This method provides a straightforward route for the synthesis of amides with a remote stereocenter at the γ position.

In organic synthesis γ-alkynyl carbonyl compounds are important building blocks. Through subsequent functional group manipulations, γ-alkynyl carbonyl compounds can be transformed into useful structural motifs during the synthesis of many natural products and bioactive molecules.[1] The synthesis of chiral γ-alkynyl carbonyl compounds, however, is nontrivial. Current synthetic methods of these compounds are usually indirect and require multiple steps.[1,2] Although catalytic asymmetric synthesis of carbonyl compounds with stereocenters at α and β positions is well established,[3] very limited approaches have been disclosed for metal-catalyzed direct construction of carbonyl compounds bearing remote stereogenic centers.[4,5]

Asymmetric conjugated alkynylation is an efficient method to access β-alkynylated carbonyl compounds. Since the early work by Carreira and Hayashi, several catalytic systems have been developed for the asymmetric hydroalkynylations of α,β-unsaturated ketone,[6] ester,[7] thioamide,[8] and aldehyde[9] with terminal alkynes.[10−12] These catalytic systems create stereocenters exclusively at the β position and are not amenable to enantioselective γ-alkynylation. Our lab has been interested in asymmetric hydroalkynylation reactions,[13] and our effort has accumulated in an iridium-catalyzed enantioselective hydroalkynylation of α,β-unsaturated amides. Unexpectedly, the alkynylation occurs regio- and enantioselectively at γ instead of the β position. This finding represents the first example of a catalytic asymmetric γ-alkynylation of α,β-unsaturated carbonyl compounds. This approach allows direct preparation of amide compounds with remote stereocenters from easily available starting materials. Formally, this γ-alkynylation proceeds through an enantioselective and redox-neutral allylic C−H functionalization process (see Scheme 1).[14]

Catalytic reactions of unsaturated amide **1a** with triisopropylsilyl acetylene **2** were conducted to identify an optimal catalyst for the hydroalkynylation reaction (Table 1). We began

Scheme 1. Catalytic Hydroalkynylation Reactions



by testing Me-Duphos (**L1**) and Ph-BPE (**L2**), which were effective ligands for iridium-catalyzed hydroalkynylation of enamides.[13] However, neither of them promoted any hydroalkynylation of α,β-unsaturated amide **1a**. Nonetheless, when BINAP (**L3**) was used as a ligand, high yield of hydroalkynylation product (**3a**) was observed. In contrast to the expected conjugated addition, the alkynylation occurred at the γ position. Less than 5% of the β-alkynylation product was observed. Additionally, the reaction was enantioselective. An 85.5:14.5 enantiomeric ratio (er) was obtained for the γ alkynylation product. The use of a spirocyclic ligand[15] (**L4**) provided low yield of alkynylation product. The yields of the reactions with CTH-P-Phos (**L5**), DifluoroPhos (**L6**), and Segphos (**L8**) as ligands were lower than that of the reaction with BINAP as a ligand, although similar enantioselectivities were obtained in these reactions. With Xyl-BINAP (**L7**) as the ligand, we observed improved enantioselectivity compared to the result obtained with BINAP but in lower yield of the desired product. However, when the ligand was switched from Segphos (**L8**) to DM-Segphos (**L9**), γ-hydroalkynylation product **3a** was afforded in significantly higher yield and enantioselectivity. Further increase of the sterics on the Segphos ligand (DTBM-Segphos, **L10**) led to significantly decreased yield. Thus, fine-tuning of the ligand structure allows the identification of an efficient catalyst for the regio- and enantioselective γ-alkynylation of α,β-unsaturated amides.

Having developed a catalyst system for the asymmetric γ-alkynylation of α,β-unsaturated amide, we next set out to investigate the scope of this methodology. As summarized in Table 2, α,β-unsaturated amides derived from a variety of amines underwent selective γ-alkynylation (Table 2). The steric hindrance on the nitrogen atom did not have a significant

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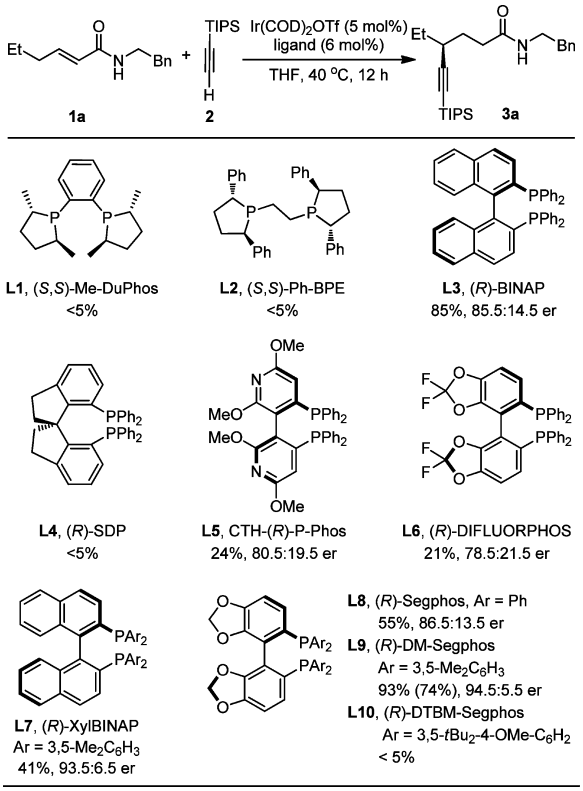
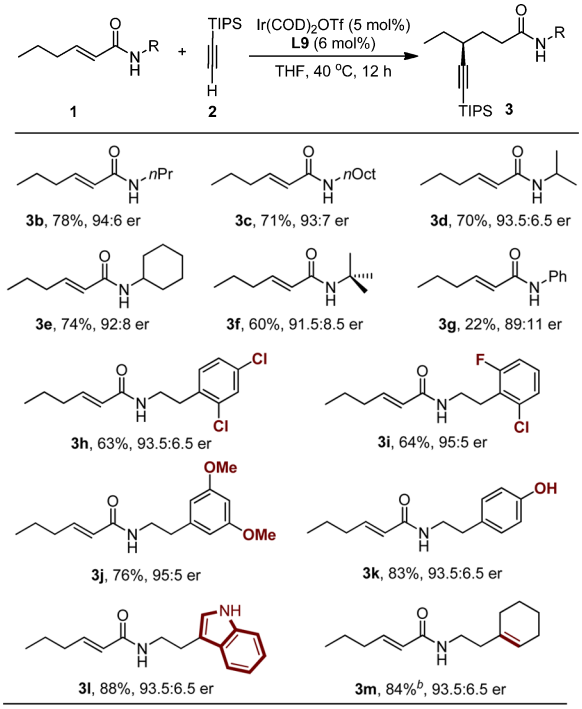
Table 1. Evaluation of Bisphosphine Ligands



[a]Reaction conditions: **1a** (1.0 equiv), **2** (3.0 equiv), $Ir(COD)_2OTf$ (5 mol %), ligand (6 mol %), 40 °C, 12 h. Yields were determined by ^1H NMR using CH_2Br_2 as an internal standard. Isolated yield in parentheses. The er values were determined by HPLC on a chiral stationary phase.

Table 2. Scope of *N*-Substituted *α,β*-Unsaturated Amides

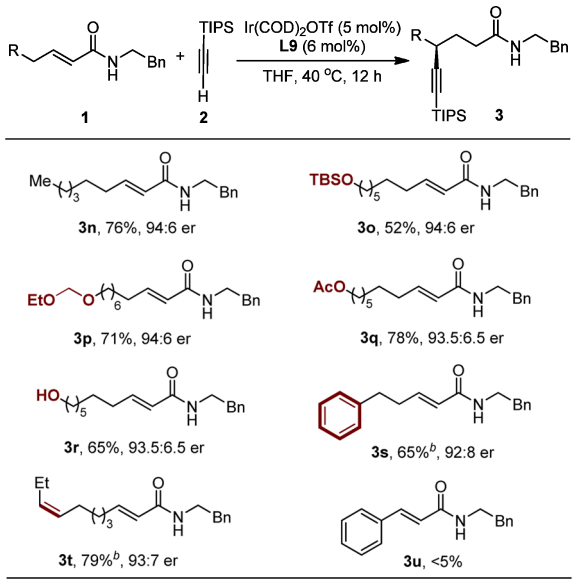


[a]See SI for details. [b]10 mol % catalyst.

impact on the yield and enantioselectivity (**3b**–**3f**). However, hydroalkynylation of *N*-phenyl amide gave significantly lower yield (**3g**), presumably because of the electron-withdrawing nature of the phenyl ring, compared to alkyls, that decreased the coordinating ability of the amide oxygen to the Ir center. Furthermore, the current catalytic system tolerated a range of functional groups (**3h**–**3l**). Additionally, *α,β*-unsaturated amide containing a pendant alkene underwent *γ*-selective alkynylation with complete chemoselectivity (**3m**).

α,β-Unsaturated amides synthesized from a range of *α,β*-unsaturated acids underwent selective *γ*-alkynylation as well (Table 3). Functional groups including silyl ether, acetal, ester,

Table 3. Scope of Substituted Secondary Alkenyl Amides



[a]See SI for details. [b]10 mol % catalyst.

and hydroxyl groups were tolerated (**3n**–**3s**). Chemoselective hydroalkynylation was also observed for *α,β*-unsaturated amides containing a disubstituted *cis*-alkene (**3t**). To probe whether the phosphine-Ir catalyst would promote hydroalkynylation at the *β*-carbon when the substrate does not have an available *γ* site, we tested the reaction of cinnamyl amide. In this case, the substrate remained largely intact, and less than 5% of the *β*-alkynylation product was observed (**3u**).

The reaction is also applicable to *α,β*-unsaturated tertiary amides (Table 4). Catalytic alkynylation of acyclic and cyclic tertiary amides provided slightly higher er's (>95:5 er, **3v**–**3ae**) than the alkynylation of secondary amides. Morpholine amide, a Weinreb amide analogue, underwent alkynylation in 60% yield and 95.5:4.5 er (**3aa**).

Although the current catalytic system is limited to the use of silyl acetylene due to the fast oligmerization of aryl and alkyl substituted alkynes,[6c,d,g,7c,d,9] the TIPS group on the alkynylation product could be easily removed by TBAF, and the resulting terminal alkyne could be further transformed to access a number of useful functionalities; representative cases were shown in Scheme 2.[16] For example, a Pd-catalyzed Sonogashira coupling of the alkyne gave aryl substituted alkyne **5a** in good yield. The absolute configuration of compound **5a** was determined by X-ray crystallography. In addition, the *γ*-alkynylation product underwent desilylation and selective semihydrogenation or click-reaction, affording *γ*-alkenylation

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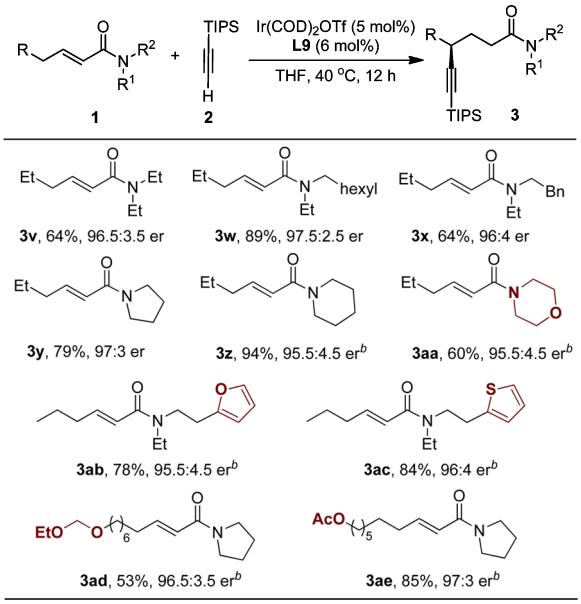
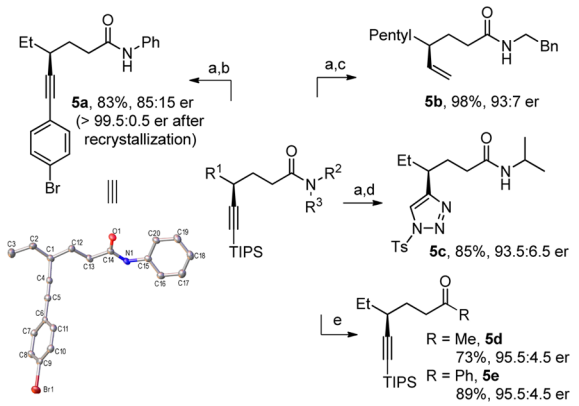
Table 4. Scope of Tertiary Alkenyl Amides



[a]See SI for details. [b]10 mol % catalyst, 50 °C.

Scheme 2. Synthetic Transformation of Alkynylation Products.[a]

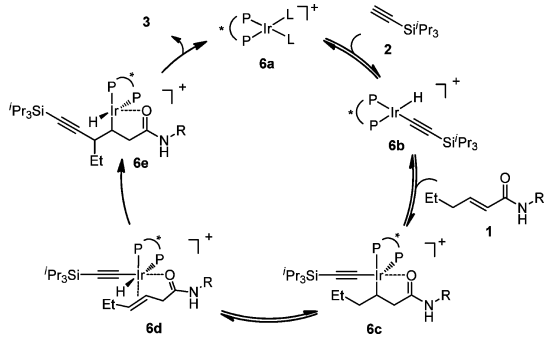


[a]Reaction conditions: (a) TBAF,THF, RT. (b) 4-BrC_6H_4I, $PdCl_2(PPh_3)_2$, CuI, NEt_3/THF, 45 °C. (c) H_2, Lindlar's catalyst, MeOH, RT. (d) CuTC, TsN_3, RT. (e) RMgBr, THF, RT. Enantioselectivities of the starting materials: **3g**, 89:11 er, **3a**, 94.5:4.5 er, **3d**, 93.5:6.5 er, **3aa**, 95.5:4.5 er.

and γ-heteroarylation products in high yields, respectively (**5b**, **5c**). The reactions of the alkynylation product **3aa** with Grignard reagents afforded the ketone products selectively (**5d**, **5e**). This two-step sequence provides an alternative method for the synthesis of the γ-alkynylated ketone product.

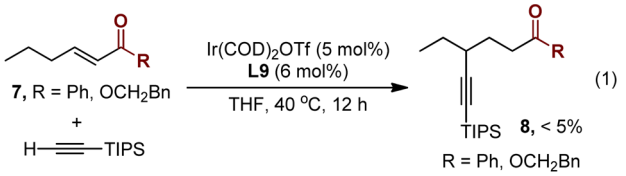
To account for the unusual γ selectivity, a proposed mechanism is shown in Scheme 3. Oxidative addition of terminal alkyne **2** to the bisphosphine-ligated iridium center affords an alkynyl iridium hydride **6b**. It adds to the α,β-unsaturated amide to give a five-membered iridacycle **6c** in which the β carbon of the amide is attached to the iridium center. Because the direct C−C bond-forming reductive elimination product was not observed under these conditions, we propose that the five-membered iridacycle undergoes a β-hydride elimination to generate an iridium hydride **6d** coordinated by a β,γ-unsaturated amide.[17] Complex **6d**

Scheme 3. Proposed Mechanism

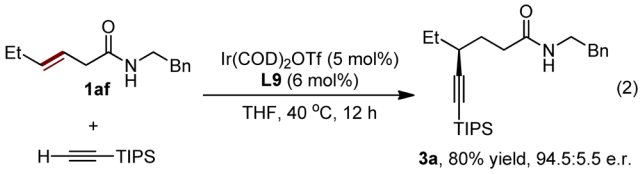


undergoes irreversible migratory insertion of the alkene into the Ir−C bond followed by C−H bond-forming reductive elimination.

To probe the effect of the coordinating group on the reactivity and selectivity of Ir-catalyzed hydroalkynylation, we tested α,β-unsaturated ester and ketone **7** under the standard reaction conditions. As we expected, **7** containing a weak coordinating ester or ketone group failed to serve as an effective substrate in hydroalkynylation; <5% of product **8** was obtained (eq 1). This example highlighted the importance of the amide group for the γ alkynylation reaction.[18]



In the proposed mechanism, the α,β-unsaturated amide is isomerized to the unconjugated unsaturated amide before the final hydroalkynylation event. The yield and enantioselectivity observed in the reaction of β,γ-amide **1af** were comparable to that obtained in the reaction of α,β-unsaturated amide (eq 2). The similar reactivity between **1a** and **1af** provides support for the isomerization-hydroalkynylation mechanism.



To gain further insight into the isomerization process, a deuterium labeling experiment was conducted. Analysis of the products from the reactions of deuterated alkyne and deuterated amide revealed that deuterium was incorporated into various carbons on the alkyl chain (eqs 3 and 4). No other isomeric alkynylation products were observed under these conditions. These results provide further evidence for an extensive alkene isomerization process prior to the alkynylation step (see the SI for details). The observed γ selectivity could be attributed to the formation of a requisite five-membered iridacycle through migratory insertion of the alkynyl group.

In conclusion, we have developed an iridium-catalyzed hydroalkynylation of α,β-unsaturated amides. The reaction occurs with complete γ-selectivity and high enantioselectivity.

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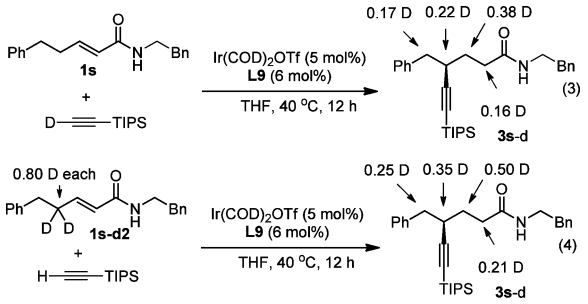

Further investigation on the origin of the distinct regioselectivity is ongoing in our lab.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b10415.

Experimental procedures, characterization of new compounds, and spectroscopic data (PDF)
Crystallographic data (CIF) (CIF)

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Notes

The authors declare no competing financial interest.

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