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RESEARCH ARTICLE

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Highly Enantioselective Synthesis of Propargyl Amide with Vicinal Stereocenters through Ir-Catalyzed Hydroalkynylation

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Supporting information for this article is given via a link at the end of the document.

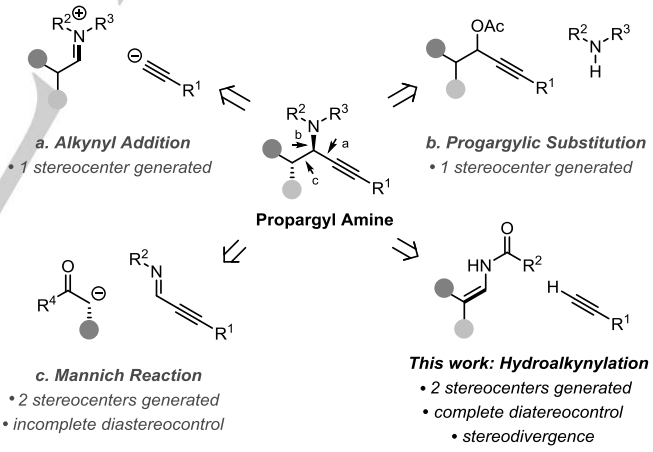
Abstract: Chiral propargyl amines are valuable synthetic intermediates for the preparation of biologically active compounds and functionalized amines. Catalytic methods to access propargyl amines containing vicinal stereocenters with high diastereoselectivity are particularly rare. We report an unprecedented strategy for the synthesis of enantioenriched propargyl amines with two stereogenic centres. An iridium complex, ligated by a phosphoramidite ligand, catalyses the hydroalkynylation of *β*,*β*-disubstituted enamides to afford propargyl amides in a highly regio-, diastereo-, and enantioselective fashion. Stereodivergent synthesis of all four possible stereoisomers was achieved using this strategy.

Introduction

Chiral amines, including those containing vicinal stereocenters, frequently occur in a range of natural products and drug molecules.[1] In particular, enantioenriched propargyl amines are valuable synthetic intermediates frequently used for the preparation of various bioactive molecules.[2] This is due to the rich chemistry of the alkyne group, enabling the transformation of propargyl amines to diverse chiral amine compounds.[3]

Several important strategies have been developed for the catalytic asymmetric synthesis of propargyl amines (Scheme 1). The prevailing strategy involves the coupling of an aldehyde, an amine, and a terminal alkyne (A3 coupling).[4],[5] While synthetically useful, this method generates propargyl amine with a single stereocenter through the alkynyl addition step.[6] The second strategy, namely propargylic substitution,[7] delivers chiral propargyl amines through catalytic substitution of propargylic electrophile with an amine.[8] Similarly, only one stereocenter is formed in the propargylic amine product. Alternatively, enantioselective Mannich reaction between carbonyl compound and C-alkynyl imine has been developed using metal or small molecule catalyst.[9],[10] Enantioenriched propargyl amines with vicinal stereocenters were produced through this strategy. However, the diastereoselectivity is highly dependent on the substrate, and modest diastereoselectivities were observed in many cases. In addition, reversal of the diastereoselectivity to selectively afford the other diastereoisomer was not possible through this method. Despite the important synthetic value of propargyl amines with vicinal stereocenters, a general catalytic method to access these compounds with both high diastereo- and enantio-control remains to be developed.[11]

We envisioned that a catalytic asymmetric hydroalkynylation of enamide could provide a potential solution to this synthetic challenge.[12] Previously, we have developed Rh- and Ir-catalyzed enantioselective hydroalkynylation of enamide to access chiral propargyl amides and homopropargyl amides with a single stereocenter, respectively.[13] A prominent feature of this chemistry is that it proceeds through a stereospecific hydroalkynylation of the alkene rather than alkynylation of an imine (as in A3 coupling). This intrinsic stereospecificity provides a previously unrecognized opportunity to access stereodefined propargyl amide containing multiple stereocenters. More importantly, the stereospecificity of the hydroalkynylation strategy would enable the diastereoselectivity to be precisely controlled. In addition, reversal of the diastereoselectivity could be achieved by switching the olefin geometry. Therefore, a novel stereodivergent synthesis of all the possible stereoisomers could be achieved through this strategy, which is not viable by previous methods.



Scheme 1. Strategies for the preparation of propargyl amines.

However, our previous Rh- and Ir-based catalyst systems did not work for *β*,*β*-disubstituted enamide because the reactivity of the *β*,*β*-disubstituted enamide is significantly lower than that of *β*-monosubstituted enamide due to the increased steric hindrance. Therefore, identification for a new catalytic system is necessary. In addition, the regioselectivity must be controlled because the alkene has two potential reaction sites. Furthermore, the catalyst effective for the hydroalkynylation must not catalyze alkene isomerization,[14] as it would lead to erosion of enantioselectivity and diastereoselectivity. In fact, despite the progress made in enantioselective alkynyl addition reactions,[15],[16],[17] catalytic asymmetric hydroalkynylation of nonactivated tri-substituted olefins is rare,[18] and no such

example has been reported for the diastereoselective generation of two stereocenters.

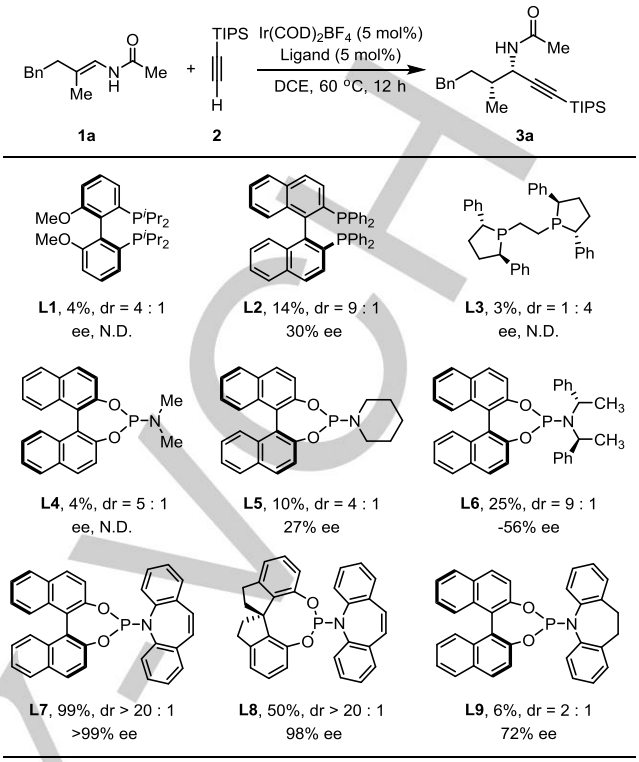
Here, we report an iridium-catalyzed asymmetric hydroalkynylation of *β,β*-disubstituted enamides for the synthesis of propargyl amides with vicinal stereocenters. In addition to high enantioselectivity, complete diastereo-control was observed by leveraging the stereospecificity of the hydrofunctionalization event. Moreover, this strategy enables stereodivergent synthesis of all possible stereoisomers by changing the olefin geometry and ligand configuration.[19] Computational studies support a mechanism involving C-C forming reductive elimination at the iridium center.

Results and Discussion

Reaction development. The catalytic reaction of enamide **1a** with terminal alkyne **2** was evaluated in the presence of a rhodium catalyst with a variety of phosphine ligands. However, none of these reactions provided significant amount of the product (see Supporting Information). Thus, we turned our attention to iridium based catalyst (Table 1). With **L1** as a ligand, the hydroalkynylation product was observed in low yield and diastereoselectivity. The yield and diastereoselectivity were slightly improved with BINAP (**L2**) as a ligand. A reversal of the diastereoselectivity was observed with Ph-BPE ligand (**L3**), indicating that significant alkene isomerization occurred. Reactions with phosphoramidite ligands provided promising results. Although catalytic hydroalkynylation with ligand **L4**-**L6** delivered the product in low yield, reaction with **L7** provided the product in high yield.[20] Furthermore, complete diastereoselectivity and excellent enantioselectivity were observed. The importance of the pendent olefin in **L7** was demonstrated by the reaction with **L9** as a ligand, which formed the product with diminished yield, diastereo- and enantioselectivity.

Substrate scope. We further probed the scope of this method (Table 2). The substituent on the amide group does not have a significant impact on the yield and selectivity, as demonstrated by the catalytic hydroalkynylations with *i*-Pr, *t*-Bu, and phenyl substituted enamides (**3b**-**3d**). However, the hydroalkynylation product was not observed for substrates containing a carbamate or an *N*-methyl amide group (**3e**-**3f**). The catalytic system worked well for a range of dialkyl substituted enamides, affording the corresponding propargyl amides in high yields, diastereo-, and enantioselectivities (**3h**-**3r**). Slightly decreased diastereoselectivity was observed in the hydroalkynylation of *β*-ethyl enamide (**3q**), due to the increase of the temperature to 80 °C.

Table 1. Evaluation of Ligands[a]

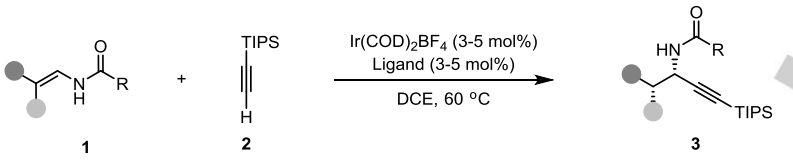


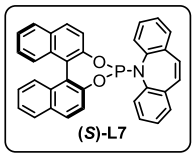
[a] Reaction conditions: **1a** (0.10 mmol), **2** (0.20 mmol), $Ir(COD)_2BF_4$ (5 mol%) and ligand (5 mol%) in DCE at 60 °C for 12 hours. Yields were determined by GC using dodecane as an internal standard. The dr values were determined by crude ^1H NMR. The ee values were determined by chiral HPLC. DCE, 1,2-dichloroethane; N.D., not determined.

For less reactive *β*-aryl substituted enamides, a H_8-binol based ligand was used because of the higher activity of the catalyst formed from this ligand. An array of propargyl amides with a *β*-aryl substituent were produced in good yields (**3s**-**3z**). Similarly, high diastereo- and enantioselectivities were observed in all cases. The absolute configurations of the products **3c** and **3s** were determined by X-ray analysis (see Supporting Information).

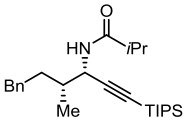
Stereodivergent synthesis. Next, we investigated the stereodivergent synthesis through this method (Scheme 2). Catalytic hydroalkynylation of *E*-**1a** with (*S*)-**L7** generated the *syn*-product (*S,R*)-**3a**. The *anti*-product (*S,S*)-**3a** was obtained by switching the enamide geometry. Unlike our previous observation,[13] the olefin geometry does not have a significant impact on the yield and enantioselectivity. With (*R*)-**L7** as a ligand, hydroalkynylations of *E*- and *Z*-**1a** afforded the other two stereoisomers. Thus, this hydroalkynylation strategy provides access to all possible stereoisomers through catalyst control and tuning substrate geometry.

Table 2. Substrate Scope of Ir-Catalyzed Hydroalkynylation[a]

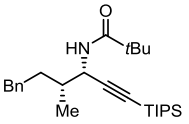




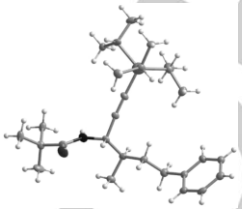
For β,β-dialkyl enamide

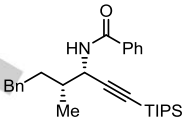


3b
99%, >99% ee
dr = 20 : 1

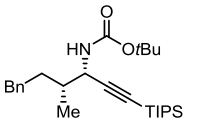


3c
99%, >99% ee
dr > 20 : 1

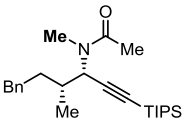




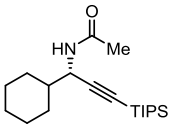
3d
83%, >99% ee
dr > 20 : 1



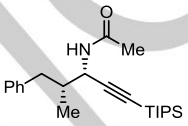
3e
<5%



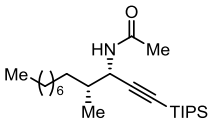
3f
<5%



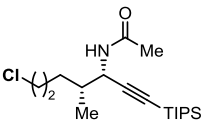
3g
99%, >99% ee



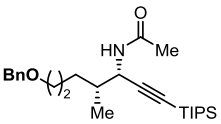
3h
97%, >99% ee
dr > 20 : 1



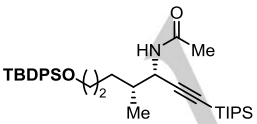
3i
97%, >99% ee
dr = 20 : 1



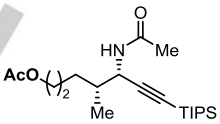
3j
99%, >99% ee
dr > 20 : 1



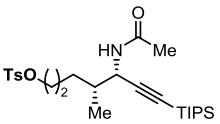
3k
70%, >99% ee
dr > 20 : 1



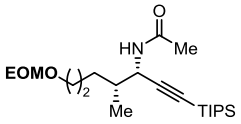
3l
82%, >99% ee
dr > 20 : 1



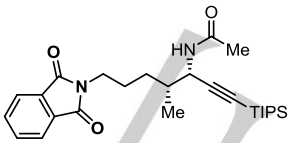
3m
96%, >99% ee
dr > 20 : 1



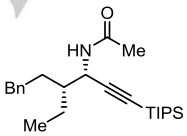
3n
99%, >99% ee
dr > 20 : 1



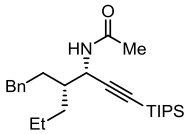
3o
91%, >99% ee
dr > 20 : 1



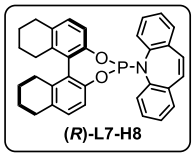
3p
99%, >99% ee
dr > 20 : 1



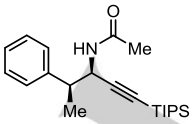
3q
95%, >99% ee
dr = 10 : 1



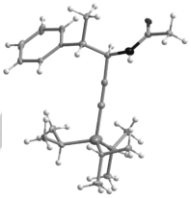
3r
86%, >99% ee
dr > 20 : 1

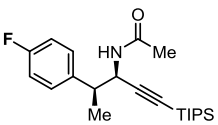


For β,β-alkyl,aryl enamide

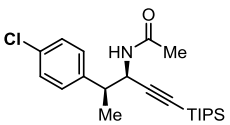


3s
73%, 98% ee
dr > 20 : 1

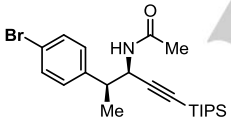




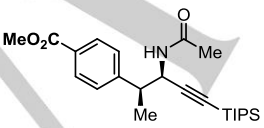
3t
61%, >99% ee
dr > 20 : 1



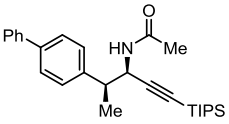
3u
85%, 97% ee
dr > 20 : 1



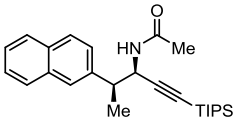
3v
65%, >99% ee
dr > 20 : 1



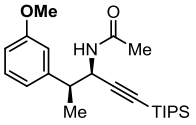
3w
64%, >99% ee
dr > 20 : 1



3x
68%, >99% ee
dr > 20 : 1

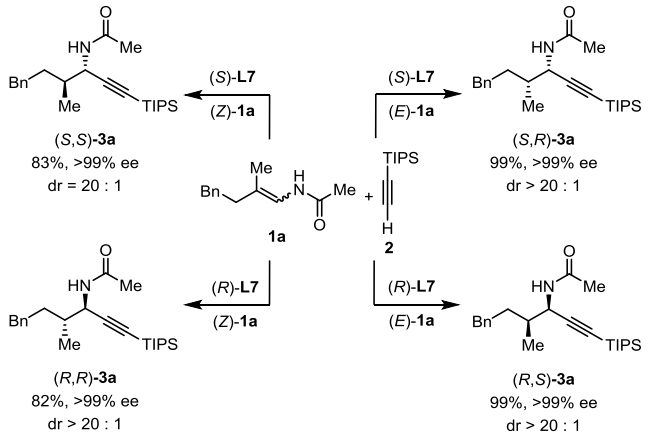


3y
70%, 98% ee
dr > 20 : 1



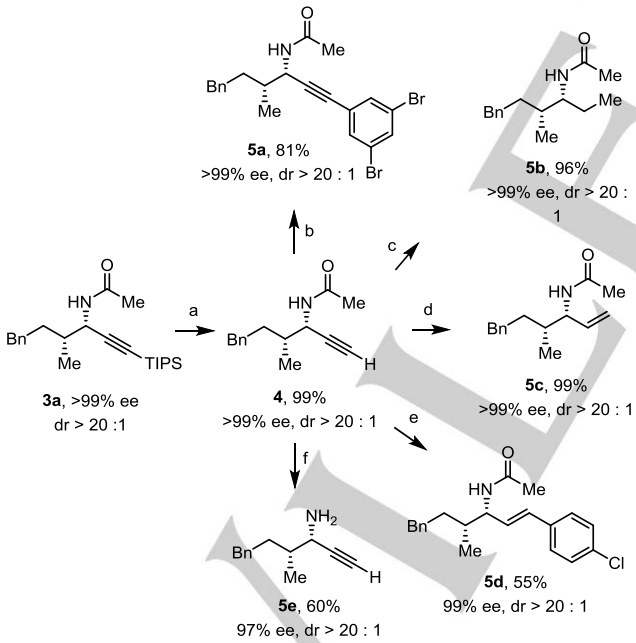
3z
59%, >99% ee
dr > 20 : 1

[a] Reactions were conducted at 0.10 mmol scale. Isolated yields were reported. The dr values were determined by crude ^{1}H NMR. The ee values were determined by chiral HPLC. **3k**, **3p**, **3q**, 80 °C. **3s-3z**, 100 °C. See Supporting Information for details.



Scheme 2. Stereodivergent synthesis.

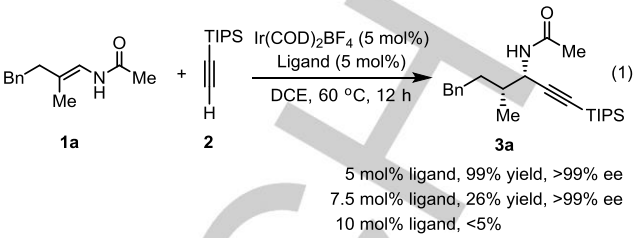
Transformation of products. After deprotection of the silyl group, the resulting propargyl amide **4** underwent diverse subsequent functionalizations (Scheme 3). For example, a Pd-catalyzed Sonogashira coupling of **4** generates **5a** in high yield. Hydrogenation, *semi*-hydrogenation, and hydroarylation of **4** deliver the alkyl and allyl amine compounds **5b**-**5d**. Finally, the amide group could be deprotected to form a free propargyl amine **5e**. Thus, the asymmetric hydroalkynylation enables facile preparation of various chiral amine compounds from easily available starting materials.



Reaction conditions: (a) TBAF, THF. (b) 1,3-dibromo-5-iodobenzene, $PdCl_2(PPh_3)_2$, CuI, NEt_3, THF, 60 °C, Ar, 12 h. (c) H_2, Pd/C, MeOH, rt, 12 h. (d) H_2, Lindlar's catalyst, MeOH, rt, 12 h. (e) 4-chlorophenylboronic acid, $Ni(acac)_2$, PPh_3, Cs_2CO_3, 1,4-dioxane, EtOH, 90 °C, Ar, 12 h. (f) Me_3OBF_4, DCM, rt, then 10% HCl (aq), THF, rt, 4 h. Neutralized by aqueous NaOH.

Scheme 3. Derivatization of hydroalkynylation product.

Metal to ligand ratio. To gain information about the metal to ligand ratio of the active catalyst, we conducted the catalytic hydroalkynylation by varying the amount of the ligand. Although the enantioselectivity did not change significantly, the best yield was obtained with a 1:1 metal to ligand ratio (Equation 1). Therefore, it is likely that only one phosphoramidite ligand coordinates to the metal center during catalysis.[21]



To provide further support for the 1:1 metal to ligand ratio during catalysis, experiments were conducted to probe the non-linear effect. However, no non-linear effect was observed (Figure 1). The absence of a non-linear effect is consistent with 1:1 metal to ligand ratio in this alkynylation reaction.

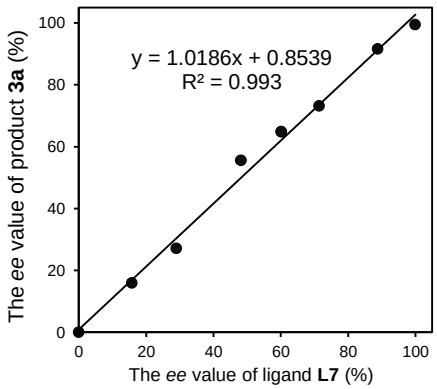


Figure 1. Absence of non-linear effect

Computational studies. Previously, we have showed that catalytic hydroalkynylation of enamide occurs at the *α* position with a rhodium catalyst and at the *β* position with an iridium catalyst.[13] Our experimental and computation studies suggested that a Chalk-Harrod mechanism is operative in the Rh-catalyzed *α*-alkynylation. For the Ir-catalyzed *β*-alkynylation, computational studies by Lin and co-workers indicated that a modified Chalk-Harrod mechanism is more favorable.[22]

To distinguish which mechanism is operative for the current Ir-catalyzed *α*-alkynylation, computational studies were conducted (see Supporting Information for more details). First, the energy profile of a catalytic cycle through the modified Chalk-Harrod mechanism was computed. The reaction pathway with the lowest activation barrier was shown in Figure 2A. It starts with oxidative addition of the C-H bond to the metal center to afford an enamide bound iridium acetylide **Int-2a**. Migratory insertion of the alkene into the Ir-C bond followed by C-H forming reductive elimination delivers the hydroalkynylation product. Similar to the computation by Lin and co-workers, migratory insertion of the alkene into the Ir-C bond has the highest activation barrier (**TS-2a**). However, an activation free energy of 33.7 kcal/mol is unusually high for a reaction conducted at 60 °C. This high activation barrier likely reflects the difficulty associated with the migratory insertion into a sterically more hindered, trisubstituted alkene.

Subsequently, the energy profile of a catalytic cycle through the Chalk-Harrod mechanism was computed. The pathway with the lowest activation barrier was shown in Figure 2B. Oxidative

addition of the alkyne forms intermediate **Int-2b**. It undergoes an intramolecular isomerization[23] to generate an octahedral complex **Int-3b**. Subsequent migratory insertion of the alkene into the iridium hydride occurs, furnishing an iridacycle **Int-4b**. Finally, C-C forming reductive elimination at the iridium center generates the hydroalkynylation product. The computed energies indicated that migratory insertion of the alkene into the iridium hydride bond is a relatively fast step, possibly due to the chelation assistance[18] (no such chelation in **TS-2a**) and the higher intrinsic reactivity of a metal hydride compared to a metal carbon bond.[22] C-C forming reductive elimination at the iridium center has the highest activation barrier (**TS-3b**). This activation barrier is significantly lower than that for the modified Chalk-Harrod catalytic cycle (**TS-2a**). Therefore, the computed energies indicated that the Chalk-Harrod mechanism is more favorable. The low activation barrier observed for C-C forming reductive elimination at the iridium center is likely a result of the ligand effect. Because the phosphoramidite is less electron-donating than a bisphosphine ligand, the electron density at the metal center is reduced, thus facilitating the reductive elimination to occur more rapidly.[24]

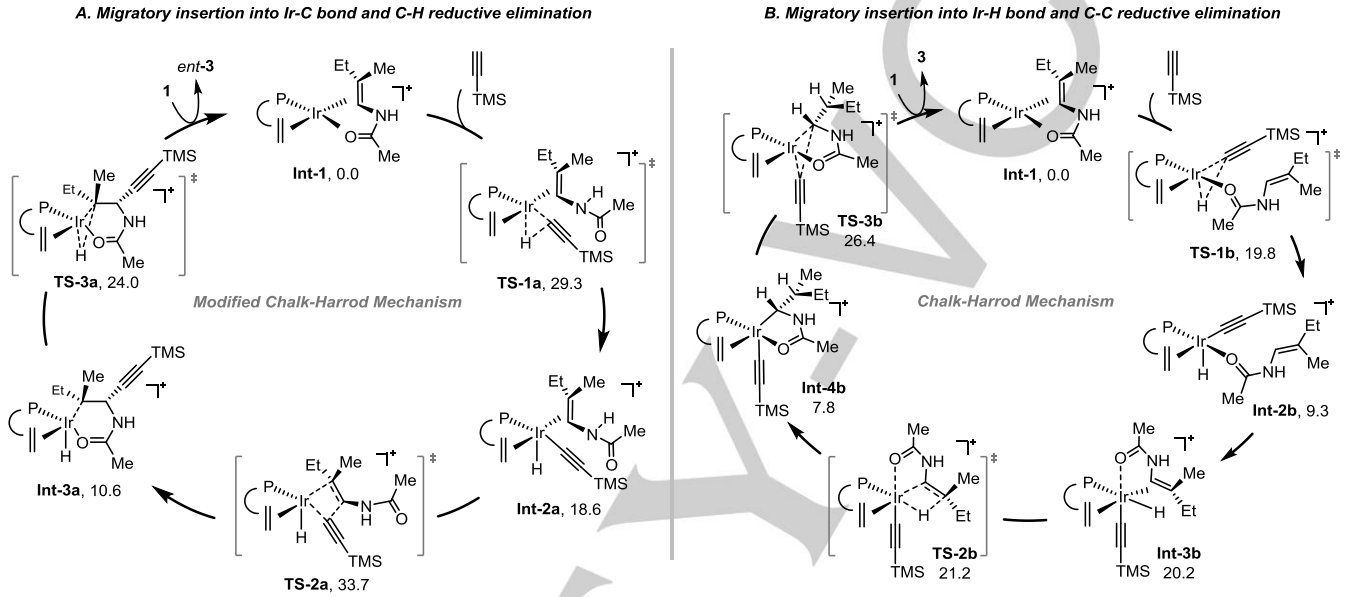
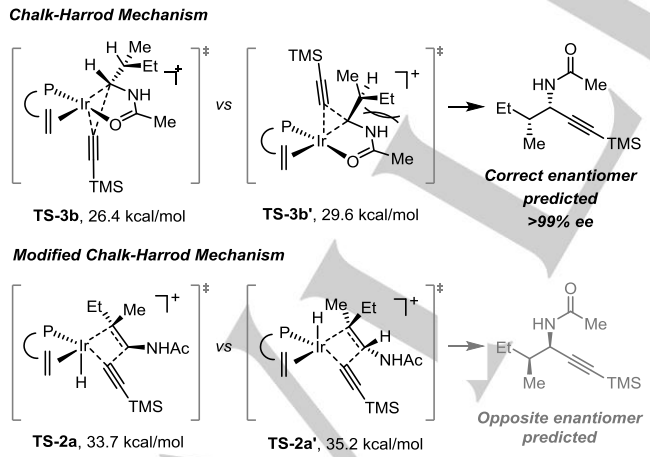


Figure 2. Computed energies for Chalk-Harrod and modified Chalk-Harrod mechanisms. Calculations were carried out at the M06/6-311++g(d,p)/SDD//B3LYP/6-31g(d,p)/Lanl2dz level of theory.



Scheme 4. Competing transition states.

The Chalk-Harrod mechanism not only is lower in computed energy, but also predicts the correct enantiomer observed in the experiment (Scheme 4). The competing transition state **TS-3b'** has an activation energy of 29.6 kcal/mol. Thus, the product was predicted to be formed in more than 99% ee. This is in good agreement with the experiment. In contrast, the modified Chalk-Harrod mechanism predicts that the opposite enantiomer would be formed in moderate ee. Therefore, the Chalk-Harrod mechanism is more consistent with our experimental observation.

In transition state structure **TS-3b'**, the lower naphthyl ring on the ligand positions in a way that it compels the alkyl group to tilt toward the amide group. Significant steric interaction was observed between the ethyl group and the NH moiety. This repulsive interaction likely contributes to the higher energy observed for this competing transition state and consequently leads to excellent enantioselectivity.

Conclusion

In summary, we have developed an iridium-catalyzed enantioselective hydroalkynylation of *β,β*-disubstituted enamides. Excellent regio-, diastereo-, and enantioselectivities were observed for the hydroalkynylation products. The diastereo-control by the stereospecificity and enantio-control by the catalyst provided an opportunity for the stereodivergent synthesis. Computational studies indicated that a Chalk-Harrod mechanism is operative under the current reaction conditions. Further investigation into the detailed mechanism is currently ongoing in our laboratory.

Experimental Section

Preparation of *E*-enamide 1c: $AlMe_3$ (2.0 M in hexane, 20 mmol) was added dropwise to a solution of Cp_2ZrCl_2 (10 mmol) in DCE (15 mL) at 0 °C. After stirring for 1 h, 4-phenyl-1-butyne (10 mmol) was added at 0 °C. The reaction mixture was stirred for 24 h at room temperature and then cooled to 0 ºC before I_2 (12 mmol) in THF (15 mL) was added. After 5 h, the mixture was quenched with H_2O carefully. The organic layer was extracted with DCM, washed with $Na_2S_2O_3$, dried with Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography to afford vinyl iodide as a single isomer (76% yield).

A Schlenk tube was charged with pivalamide (20 mmol), copper iodide (20 mmol), and Cs_2CO_3 (20 mmol). Vinyl iodide (10 mmol) and *N*,*N*'-dimethylethylenediamine (20 mmol) in THF were added under argon. The mixture was stirred at 60 ℃ for 12 h. After filtration over Celite, the mixture was diluted with DCM and washed with water. The organic extract was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography to afford *E*-enamide **1c** (92% yield).

Preparation of *Z*-enamide 1a': To a cooled mixture (-78 °C) of bromomethyltriphenylphosphonium bromide (10.5 mmol) in THF (80 mL) under N_2 was added *t*-BuOK (10.7 mmol). After 1 h at -78 °C, a solution of benzylacetone (10 mmol) in 5.0 mL of dry THF was added dropwise and the mixture was stirred for 1 h. The reaction mixture was warmed up to room temperature and poured into 50 mL of pentane while Ph_3PO precipitated out of the solution. After filtration, the solution was concentrated and the residue was purified by flash chromatography to afford vinyl bromide as an *E* and *Z* mixture (1:1 ratio, 60%). Further amidation of the vinyl bromide using the procedure described above afforded a mixture of *E*-**1a** and *Z*-**1a'** from which *Z*-**1a'** was separated by column chromatography (30% over two steps).

Procedure for catalytic hydroalkynylation: In an N_2-filled glovebox, enamide **1a** (0.10 mmol, 1.0 equiv), $Ir(COD)_2BF_4$ (2.5 mg, 0.0050 mmol), (*S*)-**L7** (2.5 mg, 0.0050 mmol) were weighed into a one-dram screw-capped vial. Subsequently, DCE (0.30 mL) and alkyne (0.20 mmol, 2.0 equiv) were added via syringes. The vial was capped with a Teflon-lined screw cap, and the resulting solution was then removed from the glovebox, placed in a pre-heated aluminum block at 60 °C for 12 h. The reaction mixture was concentrated and the residue was purified directly by column chromatography to afford 38.2 mg of propargyl amide **3a** as an oil (99%).

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Keywords: propargyl amide • alkynylation • enamide • asymmetric catalysis • vicinal stereocenters

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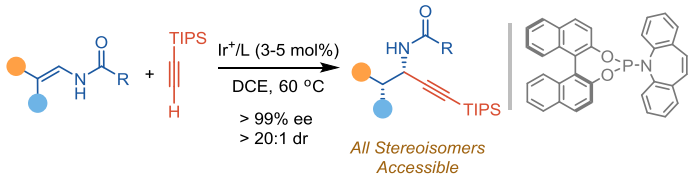

We have developed a hydroalkynylation strategy for the synthesis of enantioenriched propargyl amines with two stereogenic centers. The diastereo-control by the stereospecificity and enantio-control by the catalyst provided an opportunity for the stereodivergent synthesis.