Asymmetric Catalysis

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Iridium-Catalyzed Enantioselective Hydroalkynylation of Enamides for the Synthesis of Homopropargyl Amides

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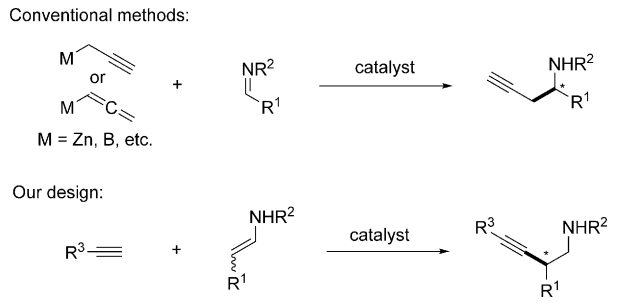
Abstract: *Reported is an iridium-catalyzed asymmetric hydroalkynylation of enamides with terminal alkynes. The reaction occurs regioselectively at the β-position of an enamide to produce homopropargyl amides. Good to high enantioselectivity was observed with an iridium complex ligated by a chiral bis(phosphine) ligand. This method provides a straightforward route to synthesize chiral homopropargyl amides with a stereocenter β to the amide.*

Homopropargyl amides are important synthetic intermediates in organic synthesis.[1] They can be further elaborated to prepare useful fragments during the synthesis of a number of natural products and biologically active molecules.[2] Enantioselective synthesis of homopropargyl amides is usually achieved by diastereoselective propargylation of imines with functionalized propargyl or allenyl metal compounds.[1,3] Recently, a few catalytic asymmetric propargylations of imines were developed,[4,5] and these methods generated a stereocenter α to the nitrogen atom. Direct catalytic, enantioselective methods for the synthesis of homopropargyl amides with a stereocenter β to the amide remain to be developed.

We envisioned an alternative strategy to access chiral homopropargyl amides. If a suitable catalyst could be identified for the hydroalkynylation of enamides, we would be able to prepare homopropargyl amides directly from unfunctionalized terminal alkynes (Scheme 1). In addition, a chiral ligand might help to control the enantioselectivity in the hydroalkynylation event. However, the enantioselective hydroalkynylation of enamides faces substantial challenges. Alkene substrates for catalytic hydroalkynylation reactions are mostly limited to α,β-unsaturated compounds.[6,7] Recently, catalytic asymmetric hydroalkynylation of electron-neutral alkenes was developed, but the only applicable substrates are 1,3-dienes,[8] allenes,[9] and norbornene.[10,11] A catalytic hydroalkynylation of electron-rich alkenes remains undeveloped. Moreover, because the β-position of an enamide is more electron-rich than the α-position, a β-selective alkynylation process would require the catalyst to effectively overcome the intrinsic electronic requirement for the acetylide addition. Herein, we report the successful implementation of an enamide hydroalkynylation strategy for the synthesis of enantioenriched homopropargyl amides. A 1,2-bis(2,5-diphenylphospholano)ethane (Ph-BPE) ligated iridium complex catalyzes the hydroalkynylation of enamides and generates stereogenic homopropargyl amides at the β-carbon atom with complete regiocontrol and good to high enantioselectivity.



Scheme 1. Design of an enamide hydroalkynylation.

To evaluate the potential hydroalkynylation of an enamide, we chose to study the reaction of the *Z*-enamide **1a** and triisopropylsilylacetylene (Table 1). An N-benzoylenamide was used as the substrate because it is stable and readily accessible.[12] More importantly, the carbonyl group of the enamide might coordinate with the metal center to stabilize the alkylmetal intermediates.[13] We began by testing the combination of $[Ir(COD)_2]OTf$ and a series of chiral ligands as the catalyst. Bis(phosphine) ligands including Josiphos and Segphos did not show any activity (entries 1 and 2). Although a phospholanyl ligand based on ferrocene (**L1**) was not effective (entry 3), we observed 26% yield of the hydroalkynylation product with high enantioselectivity when Me-DuPhos was used as a ligand (entry 4). This result led us to investigate the structurally related BPE-Phos family. The substituents on the BPE ligands had a significant impact on the yield and enantioselectivity of the hydroalkynylation of enamides. The catalytic reaction did not occur with Me-BPE as a ligand (entry 5). However, 7% yield was obtained when *i*Pr-BPE was used (entry 6). A significantly improved yield was observed when the ligand was switched to Ph-BPE, and the enantioselectivity was also increased to 92% (entry 7). Further improvement of the yield was accomplished by using a preformed [Ir(COD)(Ph-BPE)]OTf complex as the catalyst (entry 8). This hydroalkynylation reaction occurred in a range of solvents including DCE, toluene, THF, and *t*BuOH, albeit in slightly lower yields, and high enantioselectivity was observed in all cases (entries 9–12).

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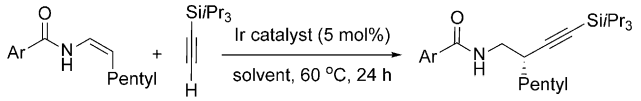
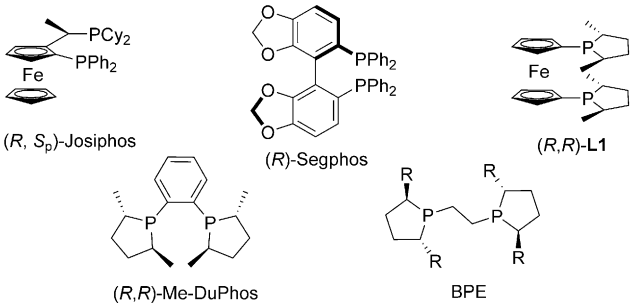
Table 1: Deveopment of an iridium-catalyzed hydroalkynylation.[a]



1a, Ar = 4-MeOC$_6$H$_4$ **2** **3a**



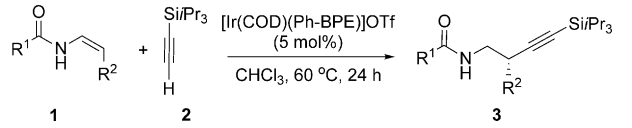
Entry	Catalyst	Solvent	Yield [%][b]	*ee* [%][c]
1	[Ir(COD)$_2$OTf]/(*R*,*S*$_p$)-Josiphos	$CHCl_3$	< 5	n.d.
2	[Ir(COD)$_2$OTf]/(*R*)-Segphos	$CHCl_3$	< 5	n.d.
3	[Ir(COD)$_2$OTf]/(*R*,*R*)-**L1**	$CHCl_3$	< 5	n.d.
4	[Ir(COD)$_2$OTf]/(*R*,*R*)-Me-DuPhos	$CHCl_3$	26	92
5	[Ir(COD)$_2$]OTf/(*R*,*R*)-Me-BPE	$CHCl_3$	< 5	n.d.
6	[Ir(COD)$_2$]OTf/(*S*,*S*)-*i*Pr-BPE	$CHCl_3$	7	75
7	[Ir(COD)$_2$]OTf/(*S*,*S*)-Ph-BPE	$CHCl_3$	54	92
8	[Ir(COD)((*S*,*S*)-Ph-BPE)]OTf	$CHCl_3$	69 (68)	92
9	[Ir(COD)((*S*,*S*)-Ph-BPE)]OTf	DCE	55	87
10	[Ir(COD)((*S*,*S*)-Ph-BPE)]OTf	toluene	40	92
11	[Ir(COD)((*S*,*S*)-Ph-BPE)]OTf	THF	33	91
12	[Ir(COD)((*S*,*S*)-Ph-BPE)]OTf	*t*BuOH	33	88

[a] Reaction conditions: **1a** (1.0 equiv), **2** (2.5 equiv), Ir catalyst (5.0 mol%), 60°C, 24 h. [b] Yields were determined by GC using *n*-dodecane as an internal standard. Yield of isolated product given within parentheses. [c] The *ee* values were determined by HPLC on a chiral stationary phase. cod = 1,5-cyclooctadiene, DCE = 1,2-dichloroethane, n.d. = not determined, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

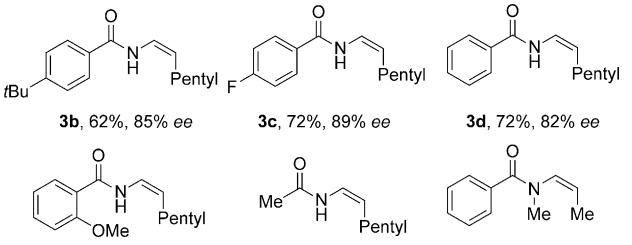
Reactions with a series of aryl- and alkyl-substituted enamides showed that the substituents on the amide had an influence on the yield and enantioselectivity of hydroalkynylation (**3b**–**g**; Table 2). The reaction with a phenyl-substituted enamide gave 72% yield and 82% *ee* (**3d**). Slightly increased enantioselectivities were obtained when the phenyl group contained either an electron-donating or electron-withdrawing substituent at its 4-position (**3b**,**c**). However, the yield and enantioselectivity were decreased with the enamide bearing an *ortho*-substituted phenyl group (**3e**). Hydroalkynylation of an N-acetyl enamide yielded much less product (**3f**) than that of a benzoyl enamide, probably as a result of their subtle difference in coordination with the iridium intermediate. A free NH group is important for reactivity, as no desired product was observed in the reaction with an N-methyl enamide (**3g**).

The yield and enantioselectivity of the hydroalkynylation reaction are highly dependent on the configuration of the enamide [Eq. (1)]. A lower yield was obtained when the reaction was conducted with an *E* enamide, and importantly, a reversal of enantioselectivity was observed. The switch in enantioselectivity from using the *Z* versus the *E* enamide

Table 2: Reactions with aryl- and alkyl-substituted enamides.[a]



1 **2** **3**

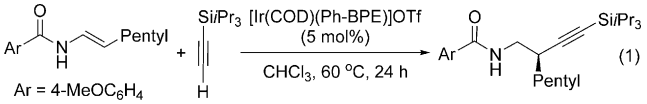


3b, 62%, 85% *ee* **3c**, 72%, 89% *ee* **3d**, 72%, 82% *ee*

3e, 36%, 66% *ee* **3f**, 21%, 67% *ee* **3g**, < 5%

[a] Reaction conditions: **1** (1.0 equiv), **2** (2.5 equiv), Ir catalyst (5.0 mol%), 60°C, 24 h. Yield is that of isolated product. The *ee* values were determined by HPLC on a chiral stationary phase.

indicates that the two substrates have the same mode of enantiofacial selection and that the olefin geometry does not play a major role in determining the facial selectivity of the hydroalkynylation.

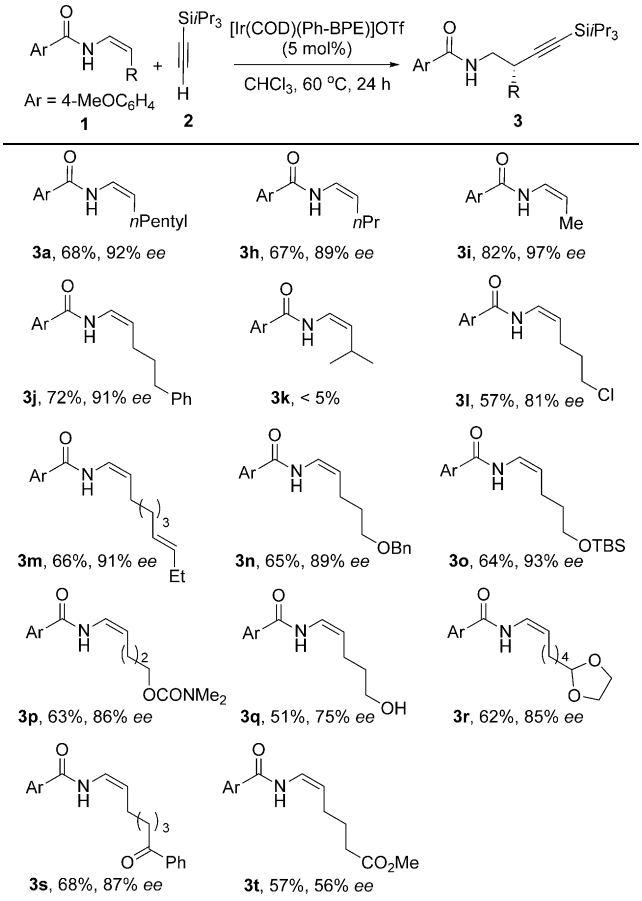


Ar = 4-MeOC$_6$H$_4$ (*E*)-**1a** **2** *ent*-**3a** 42%, 57% *ee* (1)

The scope of the iridium-catalyzed enantioselective hydroalkynylation of *Z* enamides is further demonstrated in Table 3. The reactions occurred with alkyl-substituted enamides in good yields and high enantioselectivity (**3h**–**j**). The catalyst is sensitive to the sterics of the substrate. For example, an isopropyl-substituted enamide did not undergo the hydroalkynylation (**3k**). An alkyl halide was compatible with the reaction conditions (**3l**), and chemoselective hydroalkynylation was observed with an enamide containing an internal alkene (**3m**). The double bond remained intact although it could undergo potential hydroalkynylation as well. Alcohols protected as a benzyl ether, silyl ether, and carbamate were also tolerated (**3n**–**p**). Even a free hydroxy group did not interfere with the hydroalkynylation process, and **3q** was obtained in 51% yield, but with a slightly lower *ee* value. Enamides with an acetal, ketone, and ester group underwent the hydroalkynylation smoothly (**3r**–**t**), thus furnishing valuable homopropargyl amides in good enantioselectivity except for the ester-containing product **3t**. As in many catalytic hydroalkynylation reactions, the alkynes are currently limited to silylacetylenes.[8–11] Aryl- and alkyl-substituted terminal alkynes did not react under the current reaction conditions because of fast oligomerization of these alkynes.

The catalytic hydroalkynylation can be conducted on larger scale. With 2.5 mol% of the catalyst, the hydroalkyny-

Table 3: Scope of iridium-catalyzed hydroalkynylation.[a]

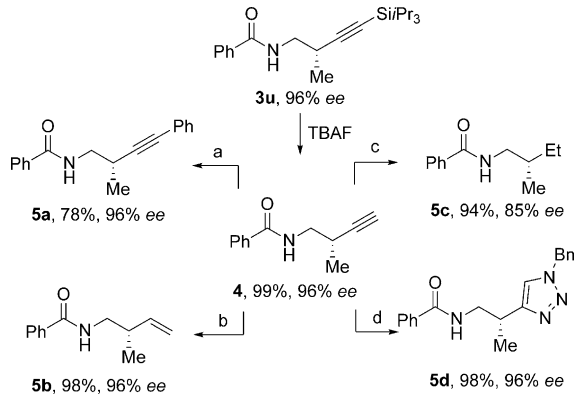


[a] Reaction conditions: **1** (1.0 equiv), **2** (2.5 equiv), Ir catalyst (5.0 mol%), 60°C, 24 h. Yield is that of isolated product. The *ee* values were determined by HPLC on a chiral stationary phase.

lation, on a 3.0 mmol scale, proceeded to completion and afforded **3u** in 87% yield and 96% *ee* [Eq. (2)].

(2)

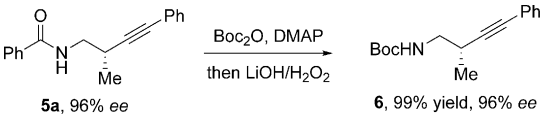
The alkyne group provided a useful handle for further functionalization of the hydroalkynylation product (Scheme 2).[14] Treatment of **3u** with TBAF resulted in the quantitative removal of the triisopropylsilyl group. The terminal alkyne in the homopropargyl amide could undergo a variety of transformations. For example, the alkyne **4** underwent a Sonogashira coupling to afford the aryl-substituted homopropargyl amide **5a** in 78% yield. Hydrogenation of **4** in the presence of Lindlar's catalyst generated the homoallyl amide **5b**, and complete hydrogenation of **4** provided the alkyl amide **5c** in high yield. The β-heteroaryl amide **5d** was formed in high yield through a copper-catalyzed click reaction. High enantioselectivity was maintained in the products during these transformations. The absolute configurations of the products were assigned based



Scheme 2. Synthetic transformation of homopropargyl amide. Reaction conditions: a) PhI, $[PdCl_2(PPh_3)_2]$, CuI, NEt_3/THF, 45°C. b) H_2, Lindlar's catalyst, MeOH, RT. c) H_2, Pd/C, MeOH, RT. d) BnN_3, $CuSO_4$, sodium ascorbate, RT.

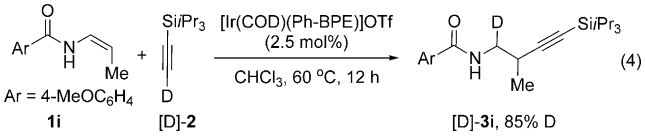
on the crystal structure of a brominated analogue of **5a** (see the Supporting Information).

The amide group of the products can be cleaved under mild reaction conditions. Activation of **5a** with Boc_2O and subsequent treatment with $LiOH/H_2O_2$ gave the product **6** in high yield [Eq. (3); Boc = tert-butoxycarbonyl, DMAP = 4-(*N*,*N*-dimethylamino)pyridine]. The Boc group in **6** was easily removed under acidic conditions to afford a free homopropargyl amine.



(3)

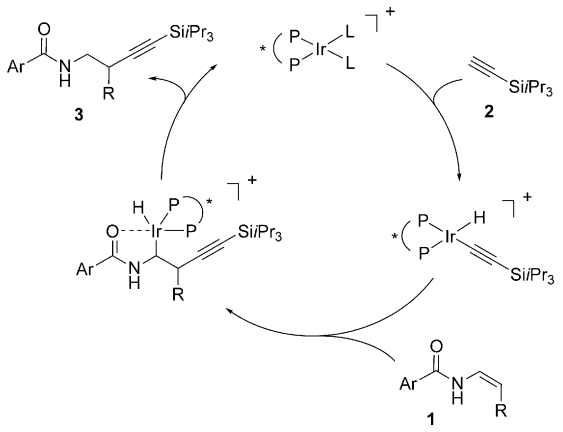
To gain insight into the mechanism, a deuterium-labelling experiment was conducted. In the product obtained from the hydroalkynylation with [D]-**2**, 85% of deuterium was incorporated at the α-position of the amide [Eq. (4)].



(4)

Based on these results, a proposed mechanism is shown in Scheme 3. Oxidative addition of silylacetylene generates an alkynyl iridium hydride intermediate. Coordination and subsequent migratory insertion of the enamide provides an alkyl iridium intermediate which is stabilized through coordination with the carbonyl group. Finally, reductive elimination of the iridium hydride gives the hydroalkynylation product and regenerates the iridium catalyst.

In summary, we have developed an iridium-catalyzed enantioselective hydroalkynylation of enamides. Previous methods for asymmetric hydroalkynylation are limited to electron-deficient alkenes such as α,β-unsaturated carbonyl



Scheme 3. Proposed mechanism.

compounds,[6] and electron-neutral alkenes such as allenes, 1,3-dienes, and norbornene.[8–10] We now have shown that an electron-rich enamide can undergo hydroalkynylation with high enantioselectivity. Although the β-position of an enamide is more electron rich than its α-position, the acetylide addition selectively occurs at the β-position. This method provides an alternative route for the synthesis of chiral homopropargyl amides. Further mechanistic studies to understand the regioselectivity and applications of this method to the synthesis of complex molecules are currently in progress.

Acknowledgments

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Keywords: alkynes · asymmetric catalysis · iridium · ligand design · synthetic methods

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