Asymmetric Catalysis

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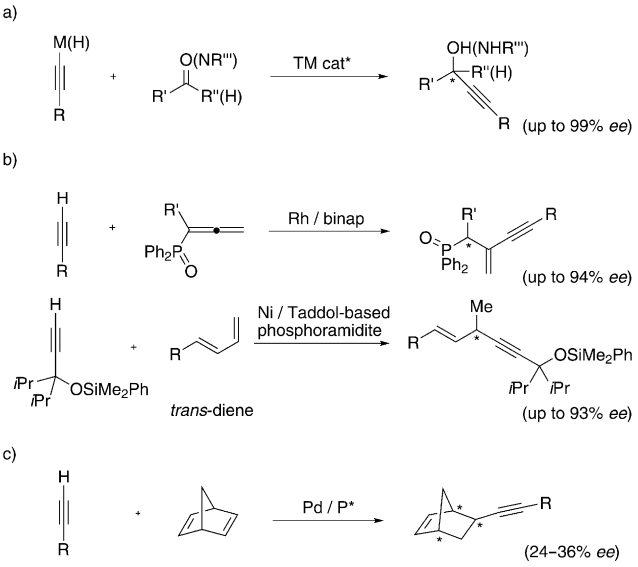
# Asymmetric Hydroalkynylation of Norbornadienes Promoted by Chiral Iridium Catalysts**

*Bao-Min Fan,* Qing-jing Yang, Jun Hu, Cai-ling Fan, Si-feng Li, Lu Yu, Chao Huang, Wing Wai Tsang, and Fuk Yee Kwong**

Chiral alkynes are structural motifs that frequently occur in agrochemically useful and pharmaceutically active compounds.[1] In particular, their versatile synthetic utility can be underlined by their use in a myriad of additional enantioselective/diastereoselective alkyne transformations.[1] Successful methods for preparing optically active alkynes are the nucleophilic alkynylation of aldehydes, ketones, imines, enones, and related compounds.[2] These reactions often require in situ generated metal acetylides (e.g. Stephen–Castro reagent) as key intermediates. Certainly, this C–H addition across a carbonyl moiety has been successful in the area of enantioselective catalysis (Scheme 1 a).[2a]

Despite notable achievements in carbonyl hydroalkynylation, the hydroalkynylation of nonpolar or unfunctionalized C=C bonds remains difficult. Recently, chemists employed transition-metal complexes to catalyze the reaction between terminal alkynes and allenes,[3] 1,3-dienes,[4] cyclopropenes,[5] norbornadienes,[6] and vinylarenes.[7] Enantioselective versions of these reactions remain underdeveloped. The scope of the asymmetric hydroalkynylation of unfunctionalized C=C bonds is still significantly limited. In 2008, Hayashi and coworkers disclosed the first rhodium-catalyzed enantioselective hydroalkynylation of allenes (Scheme 1 b).[8] It was found that the allene moiety had to contain the coordinating diphenylphosphinyl group ($P(O)Ph_2$). In 2010, Shirakura and Suginome pioneered the nickel-catalyzed enantioselective addition of the C–H bond of a terminal alkyne across a 1,3-diene (Scheme 1 b).[9] The *trans* diene was demonstrated to be crucial for obtaining high enantioselectivity (up to 93% *ee*) and reactivity. The *cis*-diene analogue afforded only 18% *ee* together with undesirable alkyne dimerization products. Moreover, another limiting factor is that the alkyne




***Scheme 1.*** Recent progress in asymmetric hydroalkynylation. a) Extensive examples of successful asymmetric hydroalkynylations of C=O and related compounds. b) The limited scope of recent asymmetric hydroalkynylations of C=C bonds using unique alkenes(allenes) or specific alkynes. c) Some examples of asymmetric hydroalkynylations of nonpolar C=C bonds using common alkynes.

moiety must contain the unique α-siloxy-*sec*-alkyl group on the alkynyl carbon atom to make this asymmetric reaction viable. In fact, apart from the tailor-made alkene/allene and the alkyne moieties having certain heteroatom-coordinating abilities, there has been only one report on the enantioselective hydroalkynylation reaction of nonpolar alkenes, and it showed poor enantioselectivities (Scheme 1 c).[10] Thus, development of an effective reaction system for this transformation is in significant demand. Indeed, it is highly challenging to establish catalytic systems which are able to handle relatively less coordinating alkenes or alkynes in the asymmetric hydroalkynylation reactions for generating highly enantioenriched alkynes. In continuing our research focus on alkene and alkyne coupling reactions,[11] we report herein the first successful asymmetric hydroalkynylation of norbornadienes with high to excellent enantioselectivities (up to 97% *ee*).

We started to investigate the prototypical hydroalkynylation by using norbornadiene and aromatic alkynes as the benchmark substrates. A series of commercially available chiral phosphine ligands were examined for the feasibility of the iridium-catalyzed asymmetric addition of the C–H of an alkyne across the C=C bond (Table 1). Control experiments revealed that a reaction did not occur in the absence of

[*] Prof. Dr. B.-M. Fan, Q.-J. Yang, J. Hu, C.-L. Fan, S.-F. Li, L. Yu, Dr. C. Huang
Key Laboratory of Chemistry in Ethnic Medicinal Resources
State Ethnic Affairs Commission & Ministry of Education
Yunnan University of Nationalities, Kunming, 650500 (China)
E-mail: adams.bmf@hotmail.com
W. W. Tsang, Prof. Dr. F. Y. Kwong
State Key Laboratory of Chirosciences
Department of Applied Biology and Chemical Technology
The Hong Kong Polytechnic University
Hung Hom, Hong Kong (Hong Kong)
E-mail: bcfyk@inet.polyu.edu.hk

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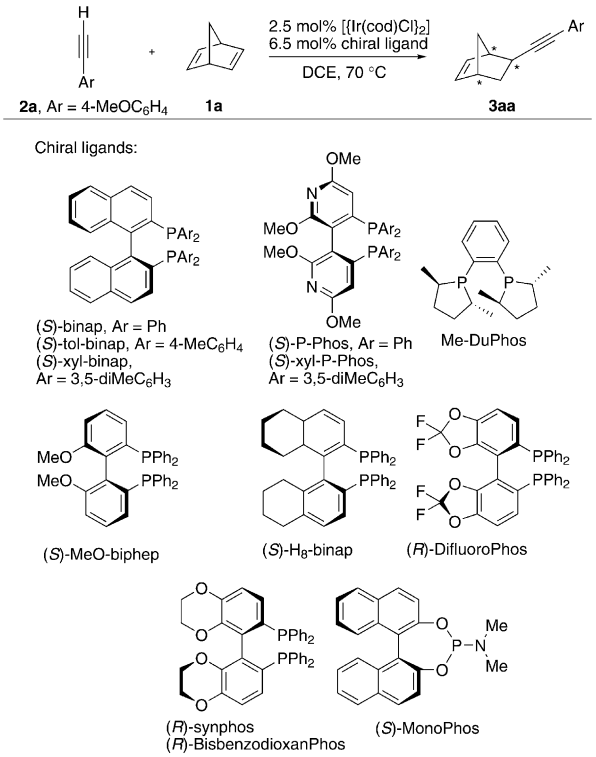
***Table 1:*** Ligand screening of iridium-catalyzed asymmetric hydroalkynylation of norbornadiene.[a]




| Entry | Chiral ligand | *t* [h] | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|
| 1 | – | 8 | 0 | – |
| 2 | (±)-binap | 4 | 87 | – |
| 3 | (*S*)-binap | 4 | 77 | 70 |
| 4 | (*S*)-tol-binap | 4 | 70 | 72 |
| 5 | (*S*)-xyl-binap | 4 | 33 | 54 |
| 6 | (*S*)-P-Phos | 4 | 79 | 74 |
| 7 | (*S*)-xyl-P-Phos | 4 | 70 | 80 |
| 8 | (*S*)-$H_8$-binap | 4 | 65 | 66 |
| 9 | (*S*)-MeO-biphep | 4 | 76 | 80 |
| 10 | (*R*)-DifluoroPhos | 4 | 76 | 75 |
| 11 | (*R*)-synphos | 4 | 85 | 84 |

[a] Reaction conditions: **2a** (0.4 mmol), **2a**/**1a**/[{Ir(cod)Cl}$_2$]/ligand (1:2:0.025:0.065), in DCE (2 mL) at 70 °C under $N_2$ for indicated period of time. [b] Yield of isolated product after column chromatography. [c] The *ee* values were determined by HPLC using the chiral stationary phase Chiralcel OJ-H. cod = 1,5-cyclooctadiene, DCE = 1,2-dichloroethane.

ligands (entry 1), and the reaction was promoted by utilizing a diphosphine (entry 2). Encouraged by this initial result, the enantioselective version of this reaction was then probed. The commonly used state-of-the-art binap ligands were found satisfactory (entries 3–5). Interestingly, the sterically more demanding (*S*)-xyl-binap provided a poor stereochemical outcome for this reaction (entry 3 versus 5).[12] The heterobiarylphosphine P-Phos[13] family gave both good product yield and enantioselectivity (entries 6 and 7). Surprisingly in these trials, the more sterically congested xyl-P-Phos ligand offered higher enantioselectivity than its parent P-Phos ligand, a result which is in contrast to that of the binap class of ligands. These results indicated that this hydroalkynylation is highly sensitive to the steric bulk of the ligand. The larger dihedral angle of $H_8$-binap was not beneficial (entry 3 versus 8). Among other axially chiral ligands examined, synphos[14] (also named as BisbenzodioxanPhos independently)[15] gave the best results (entries 9–11). The phospholane-type DuPhos and monodentate (*S*)-MonoPhos were ineffective for this reaction.

A series of screening experiments were performed for the optimization of the reaction parameters (Table 2). [Ir(cod)acac] showed good product enantioselectivity but poor

***Table 2:*** Optimization of the reaction conditions.[a]

| Entry | Ir precursor | *T* [°C] | Solvent | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | [Ir(cod)acac] | 70 | DCE | 35 | 83 |
| 2 | [Cp*$IrCl_2$] | 70 | DCE | 36 | 3 |
| 3 | [{Ir(cod)Cl}$_2$]/$AgBF_4$ | 70 | DCE | trace | – |
| 4 | [{Ir(cod)Cl}$_2$] | 70 | DCE | 85 | 84 |
| 5 | [{Ir(cod)Cl}$_2$] | 70 | THF | 86 | 79 |
| 6 | [{Ir(cod)Cl}$_2$] | 70 | DME | 84 | 80 |
| 7 | [{Ir(cod)Cl}$_2$] | 70 | toluene | 84 | 76 |
| 8 | [{Ir(cod)Cl}$_2$] | 70 | MeOH | trace | – |
| 9 | [{Ir(cod)Cl}$_2$] | 70 | 1,4-dioxane | 38 | 74 |
| 10 | [{Ir(cod)Cl}$_2$] | 70 | *i*PrOH | 32 | 76 |
| 11[d] | [{Ir(cod)Cl}$_2$] | 90 | DCE | 81 | 84 |
| 12[e] | [{Ir(cod)Cl}$_2$] | 50 | DCE | 80 | 82 |
| 13[f] | [{Ir(cod)Cl}$_2$] | RT | DCE | 50 | 68 |

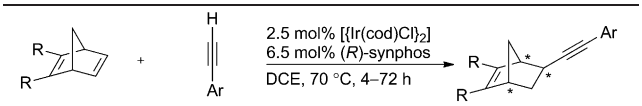
[a] Reaction conditions: **2a** (0.4 mmol), **2a**/**1a**/Ir/(*R*)-synphos (1:2:0.05:0.065), in solvent (2 mL) at 70 °C under $N_2$ for indicated period of time. [b] Yield of isolated product. [c] The *ee* values were determined by HPLC using the chiral stationary phase Chiralcel OJ-H. [d] Run for 3 h. [e] Run for 24 h. [f] Run for 40 h. acac = acetylacetonate, Cp* = $C_5Me_5$, DME = 1,2-dimethoxyethane, THF = tetrahydrofuran.

product yield (entry 1). A cyclopentadienyl iridium complex did not effectively facilitate the stereoinduction (entry 2), and a cationic iridium precursor did not promote this reaction (entry 3). Yet, with [{Ir(cod)Cl}$_2$] the reaction proceeded smoothly (entry 4). Commonly used organic solvents were also surveyed. DCE, THF, DME, and toluene provided good yields and *ee* values (entries 4–7), whereas MeOH was found to be inferior in this catalysis (entry 8). 1,4-Dioxane and *i*PrOH gave good *ee* values but poor product yields (entries 9 and 10). Increasing the reaction temperature did not deteriorate the enantioselectivity (entry 11), and a lower reaction temperature required an extended reaction time (entries 12 and 13).

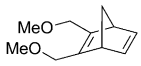
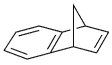
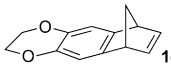
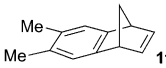
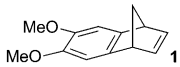
To test the effectiveness of the newly developed catalytic system, a variety of substituted norbornadienes were examined under the optimized reaction conditions (Table 3). Both dialkyl-substituted norbornadienes and benzonorbornadienes were applicable substrates. Notably, these reaction conditions were tolerated by a bromo substituent (entry 7). This functional-group compatibility potentially offers the opportunity for additional functionalization of the chiral alkyne product by using well-established cross-coupling protocols.[16] Some nonconjugate electronic effects of the alkene moiety on the product enantioselectivity were observed (entries 3, 6–8).[17] Electron-donating groups on the benzonorbornadiene provided a better stereochemical outcome,[18] possibly because of

***Table 3:*** Iridium-catalyzed asymmetric hydroalkynylation of different norbornadienes.[a]

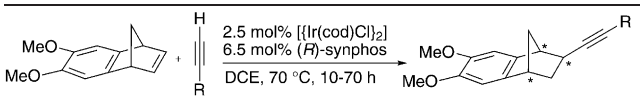



**1** **2a**: Ar = 4-MeOC$_6$H$_4$ **3**

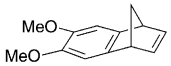
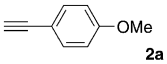
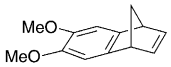
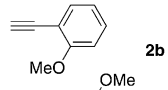
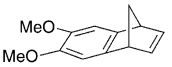
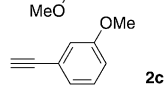
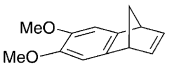
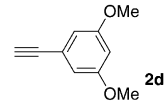
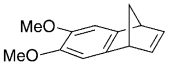
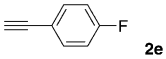
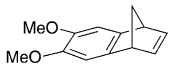
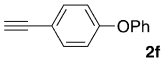
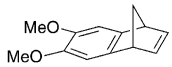
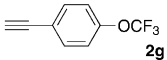
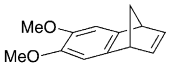
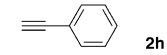
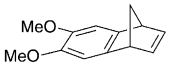
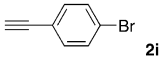
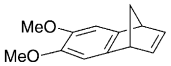
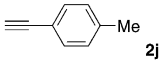
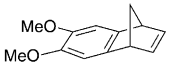
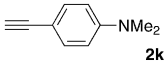
| Entry | Norbornadiene | Alkyne | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|
| 1 |  **1a** |  | 85 | 84[d] |
| 2 |  **1b** |  | 60 | 81 |
| 3 |  **1c** |  | 55 | 86 |
| 4 |  **1d** |  | 63 | 91 |
| 5 |  **1e** |  | 84 | 90 |
| 6 |  **1f** |  | 80 | 93 |
| 7 |  **1g** |  | 63 | 86 |
| 8 |  **1h** |  | 73 | 95 |

[a] Reaction conditions: **2a** (0.4 mmol), **2a**/**1**/Ir/(*R*)-synphos (1:2:0.05:0.065), in DCE (2 mL) at 70 °C under $N_2$ (see the Supporting Information for the reaction times). [b] Yield of the isolated products. [c] The *ee* values were determined by HPLC using the chiral stationary phases Chiralcel OJ-H, OD-H, AD-H, and AS-H. [d] Used **1a** (0.8 mmol), **1a**/**2a**/Ir/(*R*)-synphos (2:1:0.05:0.065). TMS = trimethylsilyl.

***Table 4:*** Iridium-catalyzed asymmetric hydroalkynylation of dimethoxybenzonorbornadienes using various alkynes.[a]




**1h** **2** **3**

| Entry | Norbornadiene | Alkyne | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|
| 1 |  |  **2a** | 73 | 95 |
| 2 |  |  **2b** | 91 | 93 |
| 3 |  |  **2c** | 72 | 91 |
| 4 |  |  **2d** | 70 | 92 |
| 5 |  |  **2e** | 73 | 90 |
| 6 |  |  **2f** | 75 | 93 |
| 7 |  |  **2g** | 46 | 90 |
| 8 |  |  **2h** | 89 | 91 |
| 9 |  |  **2i** | 67 | 94 |
| 10 |  |  **2j** | 88 | 93 |
| 11 |  |  **2k** | 83 | 97 |
| 12 |  |  **2l** | 54 | 94 |
| 13 |  |  **2m** | 65 | 93 |
| 14 |  |  **2n** | 92 | 86 |
| 15 |  |  **2o** | 57 | 86 |

[a] Reaction conditions: **1h** (0.2 mmol), **1h**/**2**/Ir/(*R*)-synphos (1:1.4:0.05:0.065), in DCE (2 mL) at 70 °C under $N_2$ (see the Supporting Information for reaction times). [b] Yield of the isolated product. [c] The *ee* values were determined by HPLC using the chiral stationary phases Chiralcel OD-H, AS-H, and AD-H.

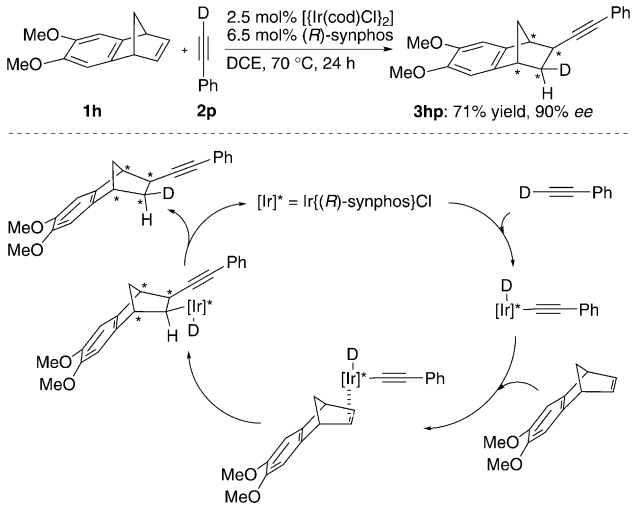
a more favorable coordination of C=C to the chiral iridium center (entries 6 and 8).

In addition to the alkene moiety investigated, a series of alkynes were also tested (Table 4). A sterically hindered aromatic alkyne provided a good yield and *ee* value (entry 2). Alkynes having different substituents were applicable substrates (entries 3–11). In particular, hydroxy and free amino groups were found to be compatible under these reaction conditions (entries 12 and 13). Indeed, the $NH_2$ group can be additionally modified, for example, by the Buchwald–Hartwig amination reaction. The TMS-substituted alkyne reacted smoothly to give a good product yield (entry 14). Thus, the chiral alkyne product can undergo desilylation to generate a terminal alkyne for a subsequent Sonogashira coupling reaction.[19] An alkyl-substituted alkyne furnished product with good enantioselectivity (entry 15).

To elucidate the hydroalkynylation mechanism, a preliminary deuterium-labeling experiment was carried out (Scheme 2). The terminal alkyne is proposed to undergo oxidative addition to the $Ir^I$ complex. The alkene moiety then coordinates to the chiral $Ir^{III}$ complex and the phenyl acetylide undergoes migratory insertion to the alkenyl moiety in an *exo* manner. Reductive elimination of the iridium deuteride and norbornyl scaffold gives the desired product.

In summary, we have succeeded in showing the first iridium-catalyzed asymmetric hydroalkynylation across a non-




***Scheme 2.*** Deuterium-labeling experiment and proposed mechanism.

polar alkene with good to excellent enantioselectivity (up to 97% *ee*). Previous findings showed that special groups adjacent to the alkene (allene), or a unique alkyne structure were necessary for achieving high product enantioselectivity. Here, a broader substrate scope is presented on either the alkene/allene or alkyne moieties. Particularly noteworthy is that this iridium/synphos catalyst system exhibits good functional-group compatibility, as $NH_2$, OH, Br, F, and TMS groups remain intact during the course of the reaction. Given the attractive feature of using non-prefuctionalized alkenes/alkynes and the good functional-group tolerance, we anticipate that this enantioselective transformation will be useful for accessing chiral alkynes in asymmetric organic synthesis. Additional detailed mechanistic studies of this catalysis are currently in progress.

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