

# Catalytic asymmetric Nakamura reaction by gold(I)/chiral N,N-dioxide-indium(III) synergistic catalysis

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## Article

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# Abstract

Intermolecular addition of enols and enolates to unactivated alkynes was proved to be a simple and powerful method for carbon-carbon bond formation. Up to date, a catalytic asymmetric version of alkyne with 1,3-dicarbonyl compound has not been realized. Herein, we achieve the first catalytic asymmetric intermolecular addition of 1,3-dicarbonyl compounds to unactivated 1-alkynes. A range of  $\beta$ -ketoamides with a cyclic all-carbon quaternary center and acyclic quaternary center with a fluorine substituent were synthesized in excellent yields with good enantioselectivities attributing to the synergistic activation of chiral  $N,N'$ -dioxide-indium(III) Lewis acid and achiral gold(I)  $\pi$ -acid. Besides, a possible catalytic cycle and transition state models were proposed to illustrate the origin of process based on the experimental investigations.

## Introduction

The addition of carbonyl compounds without prior enolate formation to unactivated alkynes is an attractive and atom economical method for carbon-carbon bond formation<sup>1</sup>. It results in the introduction of a vinyl substituent to vicinal position of carbonyl groups, possessing an important role in organic synthesis of natural products and drugs<sup>2-5</sup>. The intramolecular type, which is known as the Conia-ene reaction, generating cycloalkene derivatives, has achieved significant progress. Besides the well-developed non-enantioselective systems<sup>6-11</sup>, catalytic asymmetric Conia-ene reactions already be realized by synergistic hard/soft Lewis acid catalysts (e.g., Pd/Yb, Yb/Zn, Ag/La, Ag/Fe)<sup>12-15</sup>, Lewis basic amine/Lewis acid catalysts (e.g., Cu, Ag-based)<sup>16-19</sup> and Brønsted basic amine/Lewis acid catalyst ( $B(C_6F_5)_3/Zn/PMP$ )<sup>20</sup>. In contrast, the intermolecular reaction of 1,3-dicarbonyl compounds to unactivated 1-alkynes (Nakamura reaction) was less developed. Such a process is unviable because of the unfavorable thermodynamics that there is a high-lying LUMO of an unactivated alkyne compared to the HOMO of 1,3-dicarbonyl compounds<sup>21-22</sup>. In 2003, Nakamura and co-workers documented an indium-catalyzed addition of 1,3-dicarbonyl compounds to unactivated 1-alkynes<sup>23</sup>, providing an efficient synthetic route to form 2-alkenyl-1,3-dicarbonyl compounds from abundant carbon alkynes sources. After that, In(III)<sup>24-28</sup>, Re(I)<sup>29-31</sup>, Ir(I)<sup>32</sup>, Pd(0)<sup>33</sup>, Co(II)<sup>34</sup>, Mn(I)<sup>35-36</sup>, Ru(I)-(III)<sup>37-39</sup> catalytic systems were discovered, all of which were racemic reports except only one example using substrates with chiral auxiliary<sup>40</sup>. All the above reports, the dicarbonyl compounds and alkynes need to be activated simultaneously. Beyond that, the Shi group reported a synergistic Au(I)/Ga(III) catalysis in Nakamura reaction<sup>41</sup>, in which Au(I) activated the alkynes whereas Ga(III) enhanced the acidity of the 1,3-dicarbonyl compounds<sup>42</sup>, affording racemic 2-alkenyl-1,3-dicarbonyl products. Generally, all the Nakamura reactions were still limited to racemic examples. Therefore, developing an efficient catalytic system to realize the asymmetric version of the Nakamura reaction is challenging but highly desirable.

Bimetallic catalysis is also promising in asymmetric catalysis<sup>43-45</sup>. However, one of the perceived challenges is that two distinct metals might competitively coordinate with the ligand, as well as potentially affect each other's catalytic cycles. Recently, chiral  $N,N'$ -dioxides/hard Lewis acid complexes

developed by our group were found to be good partners with soft metals<sup>46-50</sup> in relay catalysis systems. We envisioned that *N,N'*-dioxide/Lewis acid complex could also be applied to synergistic catalyst system. Herein, we report our efforts in developing a gold(I)/chiral *N,N'*-dioxide-indium(III) synergistic catalyst system to realize the catalytic asymmetric Nakamura reaction.

## Results

Indanone-derived  $\beta$ -ketoamide **1a** and phenylacetylene **2a** were selected as the model substrates to conduct our research. Firstly, several cooperative catalytic systems, which showed good ability in catalytic enantioselective Conia-ene reaction, including Pd(II)/Yb(III) dual catalyst system, Zn(II)/Yb(III) catalyst system and amine–silver, were investigated<sup>13,16,19</sup>. But all of them gave only trace amount of product without enantioselectivities even rising the reaction temperature to 70 °C (Table 1, entries 1–3). Then chiral *N,N'*-dioxide ligand-metal complexes were chosen as the activators of ketoamides, in connection with AuCl·PPh<sub>3</sub>/AgOTf for the activation of 1-alkyne. Firstly, Sc(OTf)<sub>3</sub> was used to coordinate with chiral *N,N'*-dioxide **L-PiEt<sub>2</sub>** to promote the reaction under air atmosphere, the byproduct **3bb** was obtained as the main product along with the desired product **3aa** in 11% yield with 60:40 e.r. (entry 4). Further research showed that the reaction could possess efficiency in an absolute anaerobic condition, delivering the product **3aa** in 92% yield with 60:40 e.r. (entry 5). Then Ga(OTf)<sub>3</sub> which showed efficient catalytic activity in Shi's report<sup>41</sup> was used to coordinate with chiral *N,N'*-dioxide **L-PiEt<sub>2</sub>** to promote the reaction, however, only trace of product **3aa** was obtained (entry 6). To our delight, In(OTf)<sub>3</sub> could improve the reaction activity greatly and deliver the desired product with 62:38 e.r. (entry 7). To improve the enantioselectivity, other conditions were carefully studied. Changing the *N,N'*-dioxide ligand to **L-PiEt<sub>2</sub>Me**, which has ethyl groups at *ortho*-positions and methyl group at *para*-position of aniline, the yield could be improved to 99% with 63:37 e.r. (entry 8). Moreover, the addition of trace amount of H<sub>2</sub>O (entry 9) and increasing the amount of ligand **L-PiEt<sub>2</sub>Me** (entry 10) benefited the improvement of the enantioselectivity. Further exploration showed that the solvent had a great influence on the reaction, when *para*-xylene was used as solvent, the desired product was isolated in 98% yield with 90:10 e.r. (entry 11). The enantioselectivity enhanced into 94.5:5.5 e.r. after the concentration of **1a** reduced to 0.067 mol/L by enhancing the amount of solvent (entry 12). The steric hindrance of the ligands on [Au] catalyst was another key factor. Changing the AuCl·PPh<sub>3</sub> into more sterically hindered XPhosAu(TA)OTf, only trace product could be obtained (entry 13). In comparison, other indium catalysts of the typical chiral ligands such as Pybox **L3**, Box **L2**, or CPA organocatalyst were used, the product **3aa** was obtained in extremely low yield with poor enantioselectivity (entries 14–16).

With the optimized reaction conditions in hand (Table 1, entry 12), the substrate scope was then evaluated (Fig. 2). A variety of ketoamides **1** derived from 1-indanones with different substituents were tested. Substrates with electron-donating groups exhibited excellent yields and enantioselectivities (**3ba–3ea**) at 50 °C. Substrate **1f** bearing an electron-withdrawing group transformed to the desired product **3fa** in 98% yield with 85:15 e.r. at higher temperature (60 °C). With respect to 1-alkynes **2**, when the substituents at the aromatic ring of the phenylacetylenes varied, both steric hindrance and electronic

properties had little effect on the reaction (**3ab–3ai**). However, substrate 1,4-diethynylbenzene **2j** just delivered the product **3aj** in moderate yield with excellent enantioselectivity. It might be caused by the competitive coordination of the alkyne-bearing product with AuOTf•PPh<sub>3</sub>. The thienyl-substituted alkynes (**2k** and **2l**) were also suitable. Various aliphatic 1-alkynes (**2m–2q**) could also be transformed to the desired products in moderate to brilliant yields with good enantioselectivities (**3am–3aq**). Importantly, the methodology was applicable to the alkyl-alkyne derived from saccharide **2r**. Next, ring structure of ketoamides was studied. The substrate **1h** derived from 1-tetralone got good results (**3ha–3hl**), while **1i** derived from 1-benzosuberone gave much lower yield and e.r.. It might be caused by steric hindrance between methylene of substrate **1i** with AuOTf•PPh<sub>3</sub>-activated **2a**. Meanwhile, aliphatic substrate **1j** was also tolerated, affording the product **3ja** in moderate yield with good enantioselectivity. The absolute configuration of **3ae** was determined to be *R* by X-ray crystallographic analysis and the absolute configurations of **3aa–3ac** and **3ag–3ah** were determined to be *R* by comparison of the CD spectra with that of **3ae**.

For acyclic β-ketoamide **3a**, which without other substituent on α-position transformed to thermodynamically stable achiral α,β-conjugated carbonyl product **4aa** through olefin isomerization (Fig. 3). When acyclic β-ketoamides **3b–3e** which bearing methyl, phenyl, benzyl or chlorine group on the α-position were used as the nucleophiles, the corresponding products could not be observed due to steric hindrance of substituents. Therefore, α-fluoro substituted **3f** with smaller steric hindrance and stronger acidity of α-proton was evaluated (Fig. 4). Moderate yields with good e.r. could be obtained after adjusting the ligand to L-PiEt<sub>2</sub>, increasing the reaction temperature and prolonging the reaction time. Electron-donating or electron-withdrawing substituents on the *para*-position of phenyl ring were tolerated well. Generally, the 1-alkynes **2** with an electron-donating substituent led to better yields than the ones with electron-withdrawing substituents. Compared with the phenylacetylene, the more electron-rich aromatic alkynes like **2l** and **2s** showed better reactivities (**4fl** and **4fs**). When aliphatic 1-alkynes **2m** and **2n** were applied to the reaction, the products were delivered in moderate yields with good e.r. values.

To evaluate the synthetic potential of the catalytic system, a gram-scale synthesis of the product **3aa** was carried out (Fig. 5). Under the optimized conditions, 3.5 mmol of **1a** and 7.0 mmol of **2a** reacted smoothly, delivering 1.14 g (98% yield) of **3aa** without any erosion of the enantioselectivity. The reduction of carbonyl group of **3aa** using LiAlH<sub>4</sub> provided secondary alcohol product **5aa** in 90% yield with 92:8 d.r. and 94.5:5.5 e.r.. The absolute configuration of the major isomer was confirmed to be (1*S*, 2*R*) by X-ray crystal analysis, and the stereo-arrangement at the quaternary carbon center is consistent with that of **3ae**. Besides, the epoxidation of **3aa** in the presence of *m*-CPBA afforded the epoxide derivative **6aa** in 98% yield with 90:10 d.r. and 94.5:5.5 e.r. (Fig. 5).

Next, the reaction mechanism was investigated (Fig. 6). Some control experiments were carried out (Fig. 6a). In the absence of AuCl•PPh<sub>3</sub>/AgOTf or In(OTf)<sub>3</sub>/L-PiEt<sub>2</sub>Me, only trace amount of the product **3aa** was detected, which indicates that the two catalysts work cooperatively. *N,N'*-dioxide/In(OTf)<sub>3</sub> crystal structure obtained in our previous study<sup>48</sup> showed that a OH-bridged dinuclear indium complex forms in

the presence of H<sub>2</sub>O, in which *N,N'*-dioxide coordinates to In(III) in a tetradentate manner. Nevertheless, the investigation of relationship between the e.e. value of **L-PiEt<sub>2</sub>Me** and that of **3aa** showed a clear linear effect (Fig. 6b), implying that the active catalytic species is likely to be the mixture of In(OTf)<sub>3</sub> and **L-PiEt<sub>2</sub>Me** in a 1:1 ratio. The OH anion generated from the water in situ preparation of the chiral indium catalyst might act as a base to accelerate the enolization of 1,3-dicarbonyl compounds. In addition, the M<sup>+</sup> peak (Found: 561.1058), which corresponded to a 1:1 complex **C** of [Au·PPh<sub>3</sub>]<sup>+</sup> and phenylacetylene **2a**, was detected by ESI-TOF analysis in the positive-ion mode. The mixture of **L-PiEt<sub>2</sub>Me**, In(OTf)<sub>3</sub>, and **1a** (1:1:1) in *p*-xylene displaying an ion at *m/z* 1114.4025 ([**L-PiEt<sub>2</sub>Me**+In<sup>3+</sup>+OTf<sup>-</sup>+**1a**-H<sup>+</sup>]) *m/z* calcd 1114.4036) suggested that enolized **1a** coordinate to the catalyst in a 1:1 molecular ratio (Fig. 6c), which is consistent with our non-linear effect.

Based on above analysis and previous work, a catalytic cycle with a possible transition state is proposed. As illustrated in Fig. 7, in In(OTf)<sub>3</sub>/**L-PiEt<sub>2</sub>Me** cycle, initially, the tetradentate **L-PiEt<sub>2</sub>Me** coordinates to In<sup>III</sup> to form a six-coordinate octahedral geometry complex **A'** and dimer **A**. When ketoamide **1a** was added, the basic anion of the catalytic species accelerates the deprotonation process, and the enol ion of **1a** coordinates tightly to chiral indium(III) center through two oxygens to form the carbanion nucleophile intermediate **B**. On the other hand, as for [Au] cycle, the [Au]OTf which is the more reactive species would bind to the π-bond of 1-alkyne **2** in an unsymmetrical fashion to form species **C**. The intermediate **C** then reacts with the complex **B** to form the Au/In stabilized reactive intermediate **TS** which is the origin of the stereoselectivity. Due to the steric hindrance of [Au] unit with the amide moiety of the ligand **L-PiEt<sub>2</sub>Me**, cat<sup>1</sup> activated π-bond of **2a** approaches preferably from the *Re*-face to undergo an energetically favorable C–C bond forming reaction, forming the complex **D** with *R* absolute configuration at the newly formed stereogenic center. Subsequent protonation of **D** gives the desired product **3** and releases the two catalysts.

In summary, we have successfully realized an efficient catalytic asymmetric Nakamura reaction of cyclic and acyclic 1,3-dicarbonyl compounds with unactivated 1-alkynes by developing a bimetallic synergistic catalysis. The combination of π-acid gold(I)/chiral *N,N'*-dioxide-indium(III) complex enabled the activation of alkyne and the efficiency and stereoselectivity of nucleophile. Various β-ketoamide derivatives with a cyclic all-carbon quaternary center and acyclic quaternary center with a fluorine substituent were obtained in moderate to excellent yields with brilliant enantioselective ratios under mild conditions. A possible catalytic cycle with a transition-state model was proposed to elucidate the process of the reaction and origin of chiral induction. Further studies on hetero bimetallic synergistic or relay catalysis are underway in our laboratory.

## Methods

Full experimental details and the characterization of compounds can be found in the Supplementary Methods.

**Typical procedure for cyclic 1,3-dicarbonyl compounds involved in catalytic asymmetric reaction.** A mixture of AuCl•PPh<sub>3</sub> (5 mol%, 2.5 mg), AgOTf (5 mol%, 1.3 mg), In(OTf)<sub>3</sub> (10 mol%, 5.6 mg), L-PiEt<sub>2</sub>Me (12 mol%, 7.4 mg) and the *N*-(tert-butyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxamide **1a** (0.10 mmol) were added to a test tube under N<sub>2</sub> atmosphere. Then, anhydrous *para*-xylene (1.5 mL) was added and the mixture was stirred at 30 °C for 30 minutes. Subsequently, H<sub>2</sub>O (1.1 equiv, 2.0 μL) was added under stirring at 30 °C. Five minutes later, phenylacetylene **2a** (2.0 equiv, 22 μL) was added at 50 °C, and the reaction mixture continued stirring at 50 °C for the indicated time. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 15:1, v/v) to afford the desired product **3aa** (98% yield, 94.5:5.5 e.r.).

**Typical procedure for acyclic 1,3-dicarbonyl compounds involved in catalytic asymmetric reaction.** A mixture of AuCl•PPh<sub>3</sub> (5 mol%, 2.5 mg), AgOTf (5 mol%, 1.3 mg), In(OTf)<sub>3</sub> (10 mol%, 5.6 mg), L-PiEt<sub>2</sub> (12 mol%, 7.4 mg) and the *N*-(tert-butyl)-2-fluoro-3-oxo-3-phenylpropanamide **3f** (0.10 mmol) were added to a test tube under N<sub>2</sub> atmosphere. Then, anhydrous *para*-xylene (1.5 mL) was added and the mixture was stirred at 30 °C for 30 minutes. Subsequently, H<sub>2</sub>O (1.1 equiv, 2.0 μL) was added under stirring at 30 °C. Five minutes later, phenylacetylene **2a** (3.0 equiv, 33 μL) was added at 70 °C, and the reaction mixture continued stirring at 70 °C for the 120 h. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 6:1, v/v) to afford the desired product.

## Declarations

### Data availability

The X-ray crystallographic coordinates for structures **3ae** and **5aa** reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers 1964558 and 1989114. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif). All other data is available from the corresponding author upon reasonable request.

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### Author contributions

X.Y.H performed the experiments. X.X.T repeated data. X.Y.Z participated in the discussion. X.M.F. and L.L.L. supervised the project. X.M.F., L.L.L., X.Y.H co-wrote the manuscript.

### Competing financial interests

The authors declare no competing interests.

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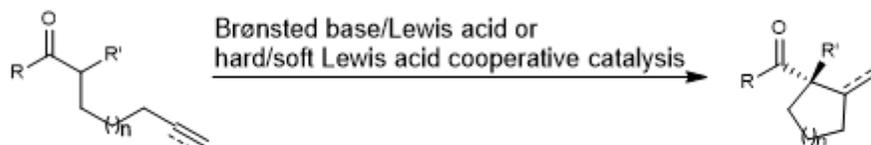
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## Table

Due to technical limitations, full-text HTML conversion of Table 1 could not be completed. However, the table can be downloaded and accessed in the Supplementary Files.

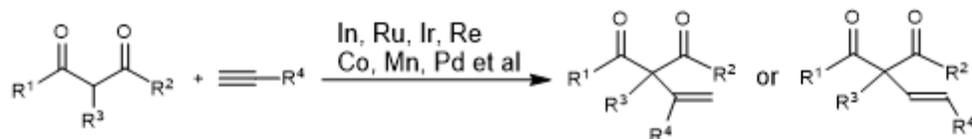
## Figures

a) Catalytic asymmetric Conia-ene reaction (intramolecular, cyclised products):



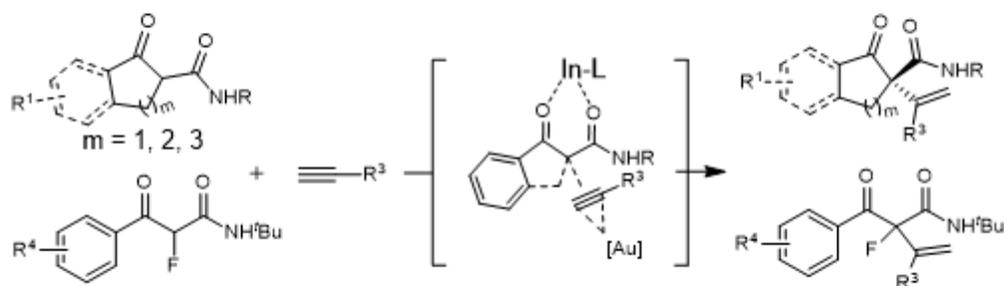
by Toste, Shibasaki, Dixon, Shibata, White

b) Nakamura reaction (intermolecular, chain products):



**Current development:** mostly non-enantioselective examples, racemic products  
one chiral auxiliary, no catalytic asymmetric example

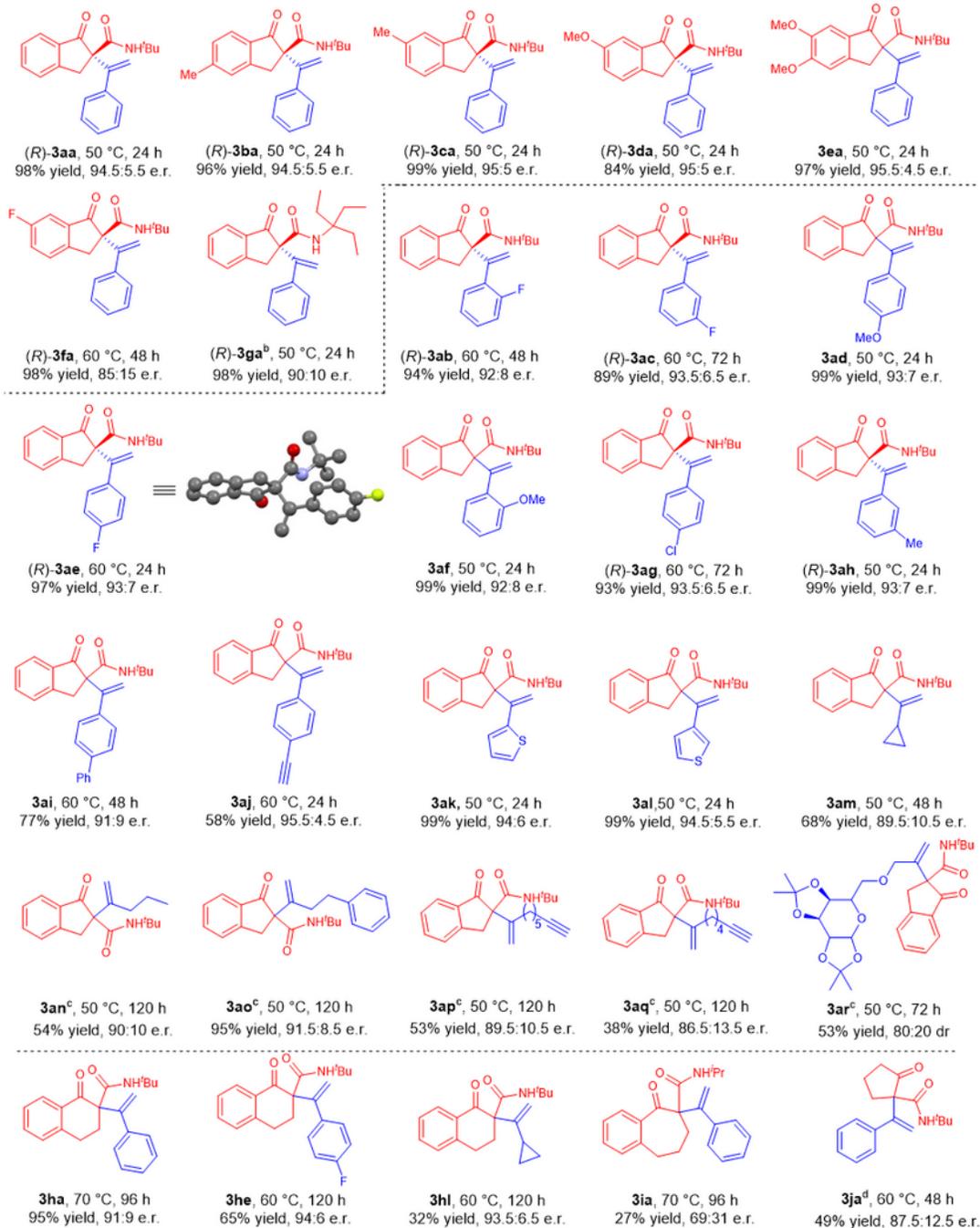
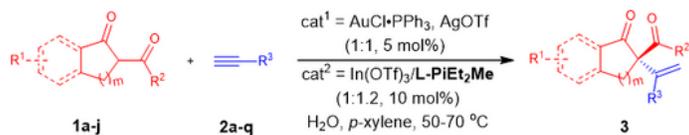
**This work:**



- ◆ First catalytic asymmetric Nakamura reaction
- ◆ Chiral 2-alkenyl-carbonyl compounds with a chiral all-carbon quaternary center or acyclic centre with a fluorine substituent
- ◆ High enantioselectivity

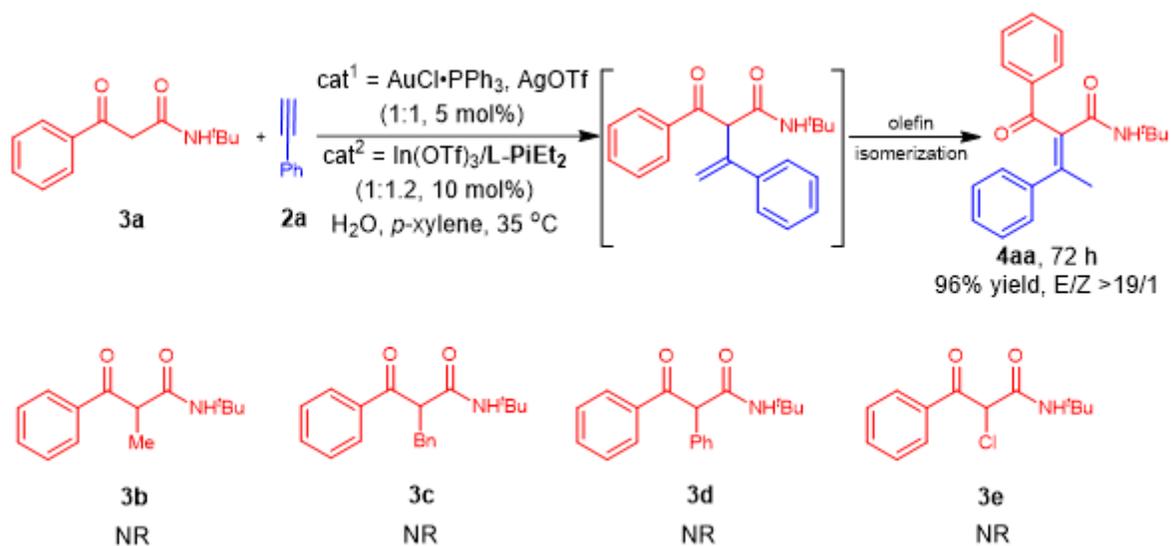
**Figure 1**

The catalytic asymmetric addition of of 1,3-dicarbonyl compounds to alkynes.



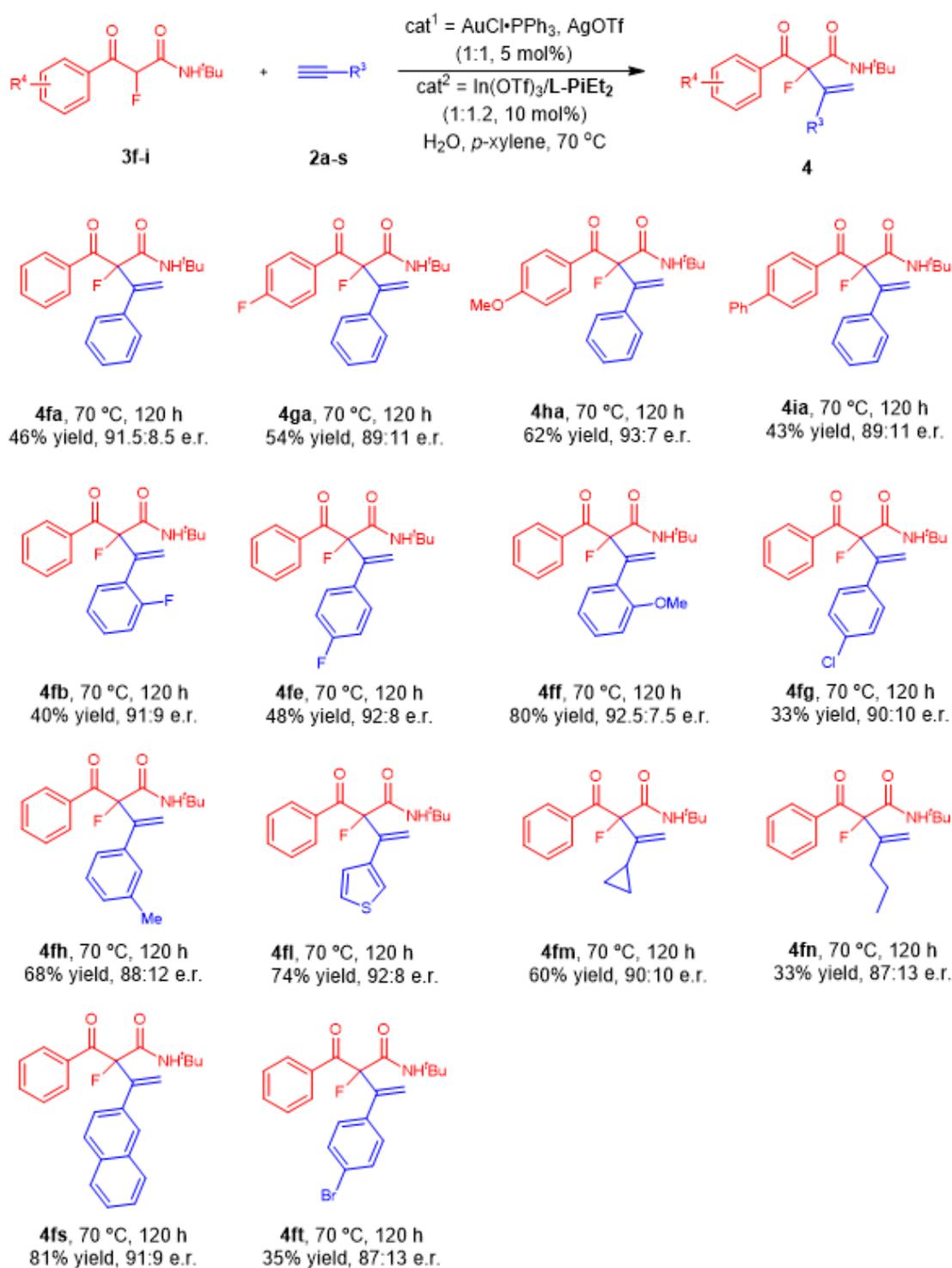
**Figure 2**

Substrate scope - Unless otherwise noted, all reactions were carried out, AuCl•PPh<sub>3</sub>/AgOTf (1:1, 5 mol%), In(OTf)<sub>3</sub>/L-PiEt<sub>2</sub>Me (1:1.2, 10 mol%), 1 (0.10 mmol) and 2 (2.0 equiv), H<sub>2</sub>O (2 μL) as additive in p-xylene (1.5 mL) at 50–70 °C for 24–120 h. Isolated yields. The e.r. values were determined by HPLC analysis on chiral column. b L-PiEt<sub>2</sub> was used as ligand. c 3.0 equiv of 2 was used. d L-PiMe<sub>3</sub> was used as ligand.



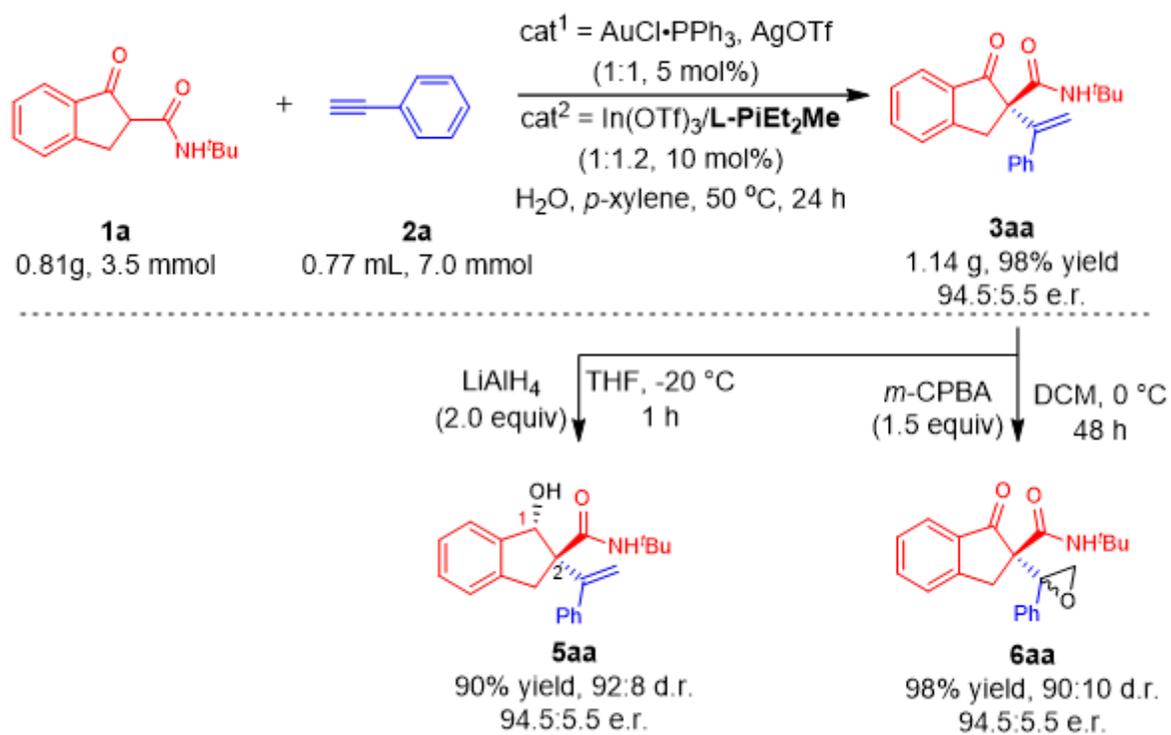
**Figure 3**

Scope limitation - Unless otherwise noted, all reactions were carried out, AuCl•PPh<sub>3</sub>/AgOTf (1:1, 5 mol%), In(OTf)<sub>3</sub>/L-PiEt<sub>2</sub> (1:1.2, 10 mol%), 3 (0.10 mmol) and 2a (3.0 equiv), H<sub>2</sub>O (2 μL) as additive in p-xylene (1.5 mL) at 70 °C for 120 h.



**Figure 4**

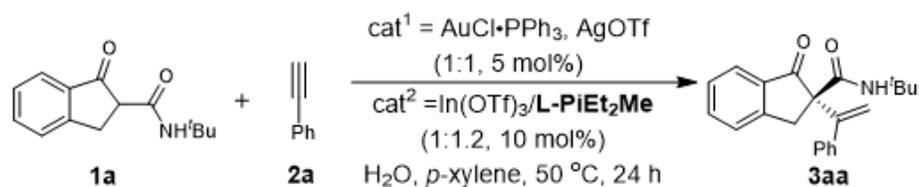
Substrate scope - Unless otherwise noted, all reactions were carried out, AuCl·PPh<sub>3</sub>/AgOTf (1:1, 5 mol%), In(OTf)<sub>3</sub>/L-PiEt<sub>2</sub> (1:1.2, 10 mol%), 1 (0.10 mmol) and 2 (3.0 equiv), H<sub>2</sub>O (2 μL) as additive in p-xylene (1.5 mL) at 50-70 °C for 72-120 h.



**Figure 5**

Gram-scale synthesis and transformation of the product 3aa.

(a) Control experiments

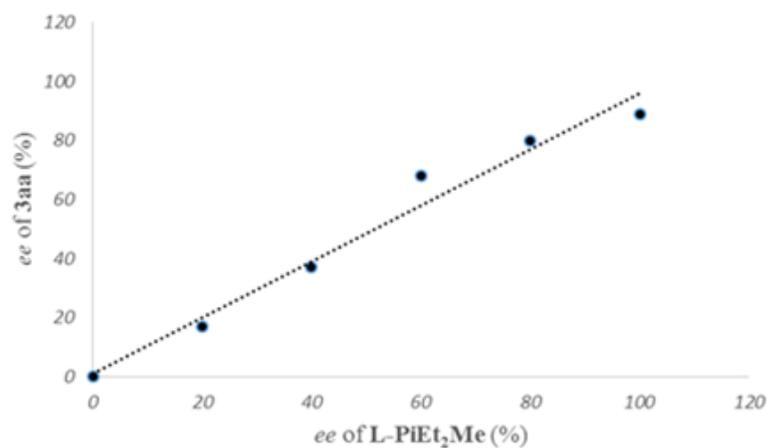


variation from optimized conditions

without AuCl•PPh<sub>3</sub>, AgOTf trace

without In(OTf)<sub>3</sub>/L-PiEt<sub>2</sub>Me trace

(b) Investigation of the non-linear effect



(c) ESI-TOF analysis

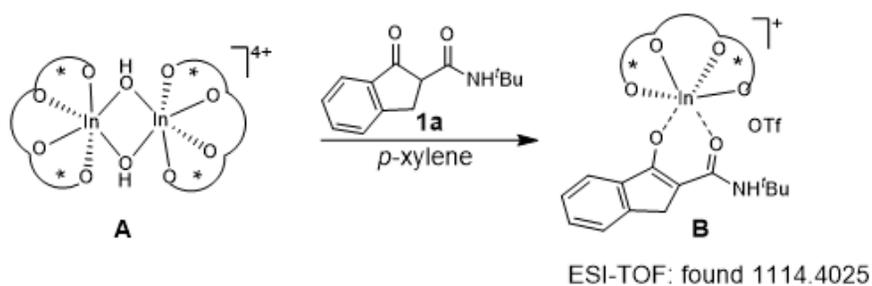
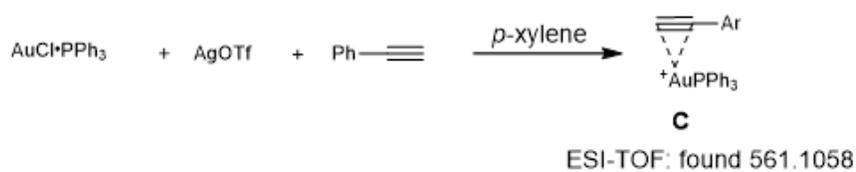


Figure 6

Mechanism investigation.

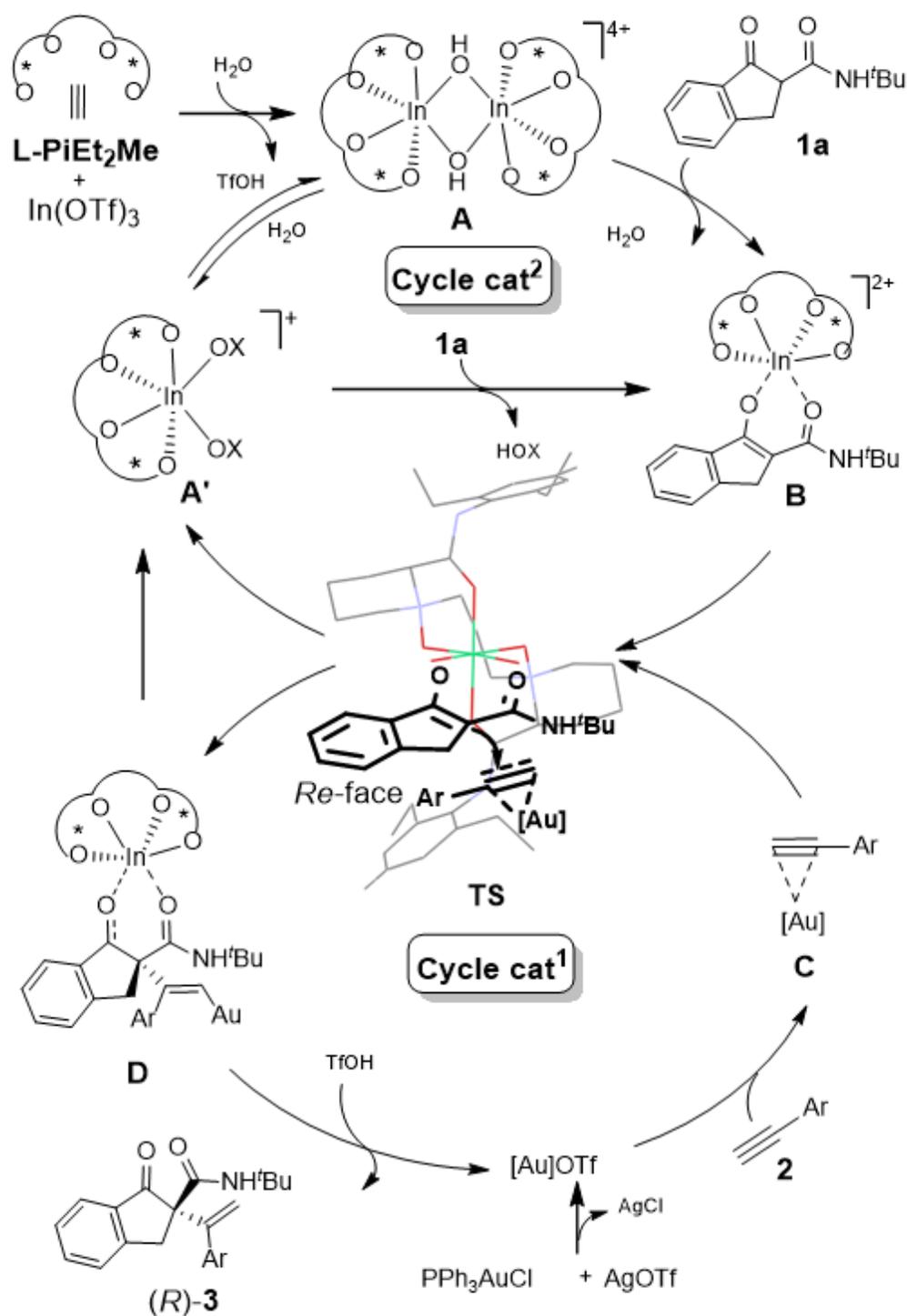


Figure 7

Proposed catalytic cycle and transition-state model.

## Supplementary Files

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- [supplement3.docx](#)