ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2023, 59, 12871

Received 6th September 2023,
Accepted 4th October 2023

DOI: 10.1039/d3cc04406h

rsc.li/chemcomm

Iridium-catalyzed asymmetric addition of imides to alkenes†

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Enantioselective addition of an imide N–H bond to alkenes was realized by use of a cationic iridium catalyst. Bulky diphosphine ligands such as DTBM-segphos, DTBM-MeO-biphep, and DTBM-binap were indispensable for the reaction. A variety of styrene derivatives, allylsilanes, and norbornene were good substrates to give the corresponding chiral adducts with high enantioselectivity.

Chiral amines are essential motifs that appear in pharmaceuticals, agrochemicals, and natural products.[1,2] In particular, chiral 1-arylethylamines exist as important pharmacophores and are known to exhibit bioactivities as shown in Fig. 1.[3] Therefore, much effort has been devoted to developing efficient methods for the synthesis of enantiopure 1-arylethylamines, and a variety of approaches such as nucleophilic addition to imines,[4] reductive amination,[5] hydrogenation of imine, enamine, and enamides,[6] and biocatalytic methods[7] have been developed.

Transition-metal-catalysed asymmetric intermolecular hydroamination, which is the addition of N–H bond across unsaturated bonds, is the most straightforward, effective, and atom-economical methods for preparing chiral amines from alkenes.[8] In this respect, Togni and co-workers reported the first enantioselective hydroamination of 2-norbornene with aniline catalysed by an iridium/diphosphine complex.[9] It was revealed that the presence of fluoride anion was necessary for reactivity and enantioselectivity. Afterward, Hartwig and co-workers reported iridium-catalyzed hydroamination of norbornene derivatives with a series of anilines using potassium bis(trimethylsilyl)amide (KHMDS) as a base, instead of the fluoride anion.[10] Thus far, several intermolecular enantioselective hydroamination of terminal alkenes,[11] alkynes,[12] allenes,[13] and dienes[14] have been developed.[15] 2-Aminopyridine derivatives have been often used as a nitrogen source in iridium-catalysed asymmetric hydroamination. Shibata and co-workers reported asymmetric hydroamination of styrene derivatives using C_3-TUNEPHOS as a chiral ligand, where the pyridyl group assisted the efficient oxidative addition of the N–H bond to iridium, providing the Markovnikov's adducts in moderate enantioselectivities (Scheme 1a).[16] Recently, Hartwig and co-workers demonstrated the enantioselective hydroamination of internal alkenes[17] or terminal alkenes[18] with 6-methyl-2-aminopyridine catalysed by iridium/(*R*)-TMS-SYNPHOS catalyst (Scheme 1b).

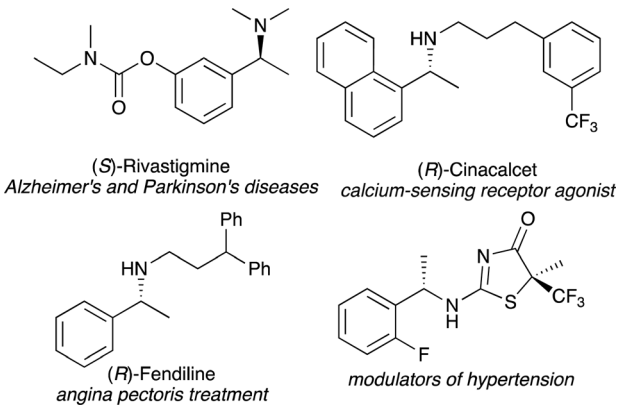

Fig. 1 Selected examples of 1-arylethylamine pharmaceuticals and bioactive compounds.

Phthalimide has been used to synthesize primary amines from alkyl halides in the Gabriel synthesis, where the intermediate *N*-alkylphthalimides are prepared by the substitution reaction.[19] To the best of our knowledge, enantioselective addition of phthalimide to alkenes for the synthesis of chiral *N*-alkylphthalimides has not been achieved to date. Here we report iridium-catalyzed enantioselective intermolecular hydroamination of alkenes with phthalimide derivatives. The bulky chiral diphosphine ligand enabled the addition of the N–H bond achieving high enantioselectivities. Not only styrene derivatives but also allylsilanes were suitable for the present catalytic system.

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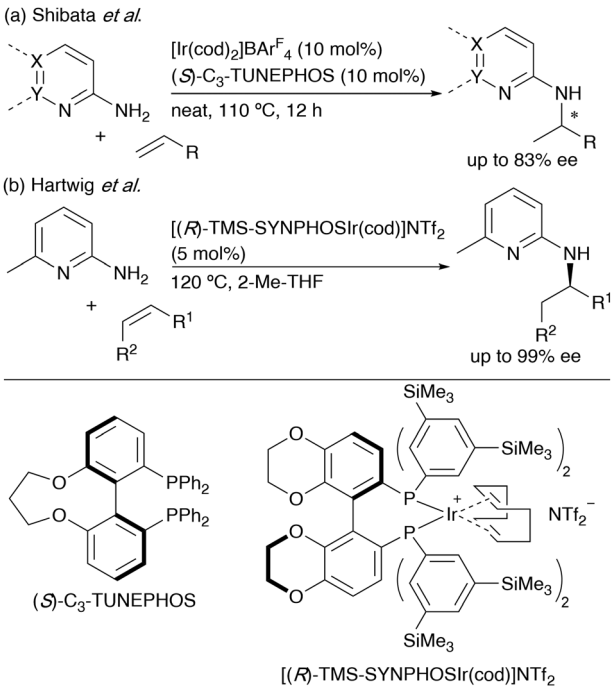
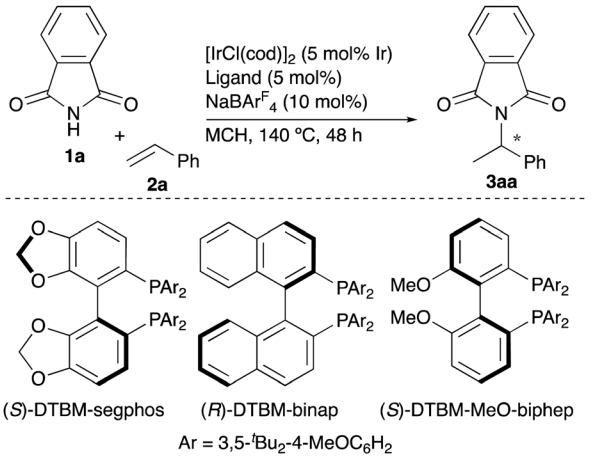
† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d3cc04406h



Scheme 1 Iridium-catalysed enantioselective hydroamination of alkenes with 2-aminopyridine derivatives.

Table 1 Ligand screening[a]



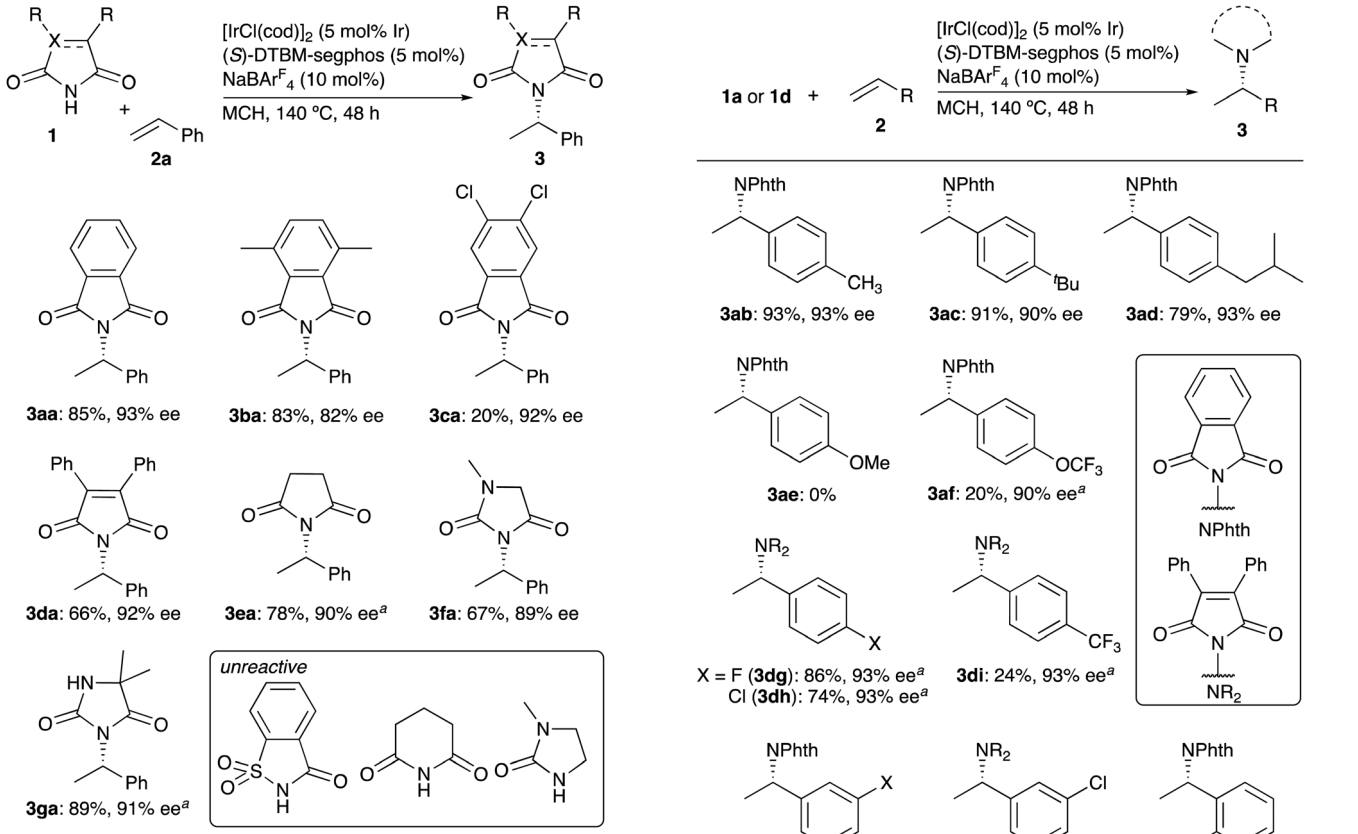
Entry	Ligand	Yield[b] (%)	Ee[c] (%)
1	(*S*)-DTBM-segphos	85	93
2	(*S*)-DTBM-MeO-biphep	85	89
3	(*R*)-DTBM-binap	92	84
4	(*S*)-segphos	0	—
5	(*R*)-binap	0	—
6[d]	(*S*)-DTBM-segphos	13	N.D[e]

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.30 mmol), $[IrCl(cod)]_2$ (5 mol% Ir), ligand (5 mol%), and $NaBAr^F_4$ (10 mol%) in MCH (0.4 mL) at 140 °C for 48 h. MCH: methylcyclohexane. [b] Isolated yields. [c] Determined by HPLC analysis with a chiral stationary phase column: Chiralpak ID. [d] With 5 mol% of $[Ir(cod)_2]BAr^F_4$ complex instead of $[IrCl(cod)]_2$ and $NaBAr^F_4$. [e] Not determined.

Treatment of phthalimide (**1a**) with styrene (**2a**, 3 equiv.) in the presence of a cationic iridium catalyst, which is generated from $[IrCl(cod)]_2$ (5 mol% Ir), (*S*)-DTBM-segphos (5 mol%), and $NaBAr^F_4$ (10 mol%) (cod = 1,5-cyclooctadiene, Ar^F = 3,5-$(CF_3)_2C_6H_3$) gave the addition product **3aa** in 85% yield with 93% ee (Table 1, entry 1).[20] The use of other bulky diphosphine ligands, such as (*S*)-MeO-DTBM-binphep and (*R*)-DTBM-binap, also promoted the reaction (entries 2 and 3), and smaller dihedral angle of the ligands was found to increase the enantioselectivity (dihedral angles: segphos (67.2°), MeO-biphep (72.3°), binap (86.2°)).[21] In sharp contrast, no addition products were formed by use of (*S*)-segphos or (*R*)-binap, which has diphenylphosphino groups (entries 4 and 5). The cationic iridium complex $[Ir(cod)_2]BAr^F_4$ as a catalyst precursor was less effective in catalysing the present reaction, thus giving **3aa** in 13% yield (entry 6). After optimizing reaction conditions, such as solvent, temperature, reaction time, and so on, we selected the reaction conditions shown in entry 1 of Table 1 (see Table S1 in ESI†). The absolute configuration of **3aa** obtained by use of (*S*)-DTBM-segphos was assigned to be *S*-(−) by correlation with the reported specific rotation values.[22]

Scheme 2 summarizes the results obtained for the addition of several imides to styrene. Not only substituted phthalimides (**1b** and **1c**) but also 3,4-diphenylmaleimide (**2d**) and succinimide (**2e**) underwent the hydroamination of styrene to give the corresponding products **3ba–3ea** with high enantioselectivities (82–92% ee). 1-Methylhydantoin (**2f**) and 5,5-dimethylhydantoin (**2g**) were also good substrates, giving **3fa** and **3ga** in high yields with high enantioselectivity. The present catalytic system could not be applied to the addition of saccharin, six-membered piperidine-2,6-dione, or 1-methylimidazolidin-2-one.

Under the catalysis of Ir^+/(*S*)-DTBM-segphos, *para*-alkyl substituted alkenes **2b–2d** effectively undergo the addition of phthalimide (**1a**) to give the corresponding adducts **3ab–3ad** in high yields and enantioselectivity (79–93% yield, 90–93% ee, Scheme 3). In contrast, the reaction with 4-methoxystyrene (**2e**) did not give the adduct **3ae** due to its intense polymerization in the presence of a cationic iridium complex.[23] *p*-Trifluoromethoxylstyrene (**2f**) participated in the reaction, but the yield of the adduct **3af** was still low (20% yield) due to the polymerization. In the reaction of styrenes **2g** (F), **2h** (Cl), and **2i** (CF_3), which are substituted with electron-withdrawing groups, 3,4-diphenylmaleimide (**1d**) exhibited the higher reactivity than phthalimide (**1a**), thus giving the corresponding adducts **3ag–3ai** (24–86% yields, 93% ee).[24] The reaction of *meta*-, *ortho*-, and multiply substituted styrenes **2j–2p** reacted with phthalimide (**1a**) or maleimide **2d** to give the adducts with high enantioselectivity (74–93% ee). To our delight, non-conjugated alkenes such as allylsilanes were applicable to the reaction. Thus, the reaction of trimethyl- (**2q**), diphenylmethy- (**2r**), and triphenyl-allylsilane (**2s**) proceeded to give the desired products **3aq–3as** with high enantioselectivity (80–86% ee). 2-Norbornene (**2t**) was also a good substrate to give *exo*-adduct **3at** in high yield with high enantioselectivity, even in a 1.0 mmol scale reaction of **1a** (94% yield, 96% ee). Unfortunately, however, the present catalytic system could

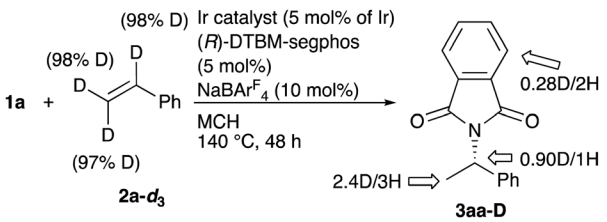


Scheme 2 Ir-catalysed asymmetric addition of an amide N–H bond to alkenes. Reaction conditions: **1** (0.10 mmol), **2a** (0.30 mmol), $[IrCl(cod)]_2$ (5 mol% Ir), (*S*)-DTBM-segphos (5 mol%), and $NaBAr^F_4$ (10 mol%) in MCH (0.4 mL) at 140 °C for 48 h. Isolated yields were shown. [a] 10 mol% of Ir, 10 mol% of (*S*)-DTBM-MeO-biphep, and 20 mol% of $NaBAr^F_4$ were used.

not be applied to the addition to simple alkenes such as 1-hexene, (*Z*)-3-octene, *cis*-stilbene, and indene.

To gain some insight into the reaction mechanism, stoichiometric reactions of **1a** with a cationic iridium complex were conducted. When the reaction of phthalimide (**1a**, 2 equiv.), $[IrCl(coe)]_2$ (1 equiv.), (*S*)-DTBM-segphos (1 equiv.), and $NaBAr^F_4$ (1 equiv.) in acetonitrile-d_3 was carried out at 80 °C for 15 min in an NMR tube, two major hydride resonances (77% and 14% yields determined by ^1H NMR using an internal standard) as well as three small resonances were observed. ^1H NMR of the major two hydride resonances showed a triplet at −18.0 ppm (J_{P-H} = 15 Hz) and a doublet of doublets at −20.0 ppm (J_{P-H} = 23, 14 Hz), implying that hydrogen atoms on Ir are located at the *cis*-position to the two phosphorous atoms. The result indicates that the cationic iridium coordinated with DTBM-segphos readily undergoes oxidative addition of phthalimide to give the hydride complexes. We also conducted a deuterium-labeling experiment (Scheme 4). The reaction of **1a** with deuterated styrene (**2a**-d_3) under the standard reaction conditions gave the corresponding product **3aa-D** in 40% yield, where H/D exchange was observed at both methine and methyl groups. The result indicates that the reversible insertion of the alkene moiety into the Ir–H occurs during the reaction,

Scheme 3 Scope of alkenes **2**. Reaction conditions: **1a** or **1d** (0.10 mmol), **2** (0.30 mmol), $[IrCl(cod)]_2$ (5 mol% Ir), (*S*)-DTBM-segphos (5 mol%), and $NaBAr^F_4$ (10 mol%) in MCH (0.4 mL) at 140 °C for 48 h. Isolated yields were shown. [a] 10 mol% of Ir, 10 mol% of (*S*)-DTBM-segphos, and 20 mol% of $NaBAr^F_4$ were used. [b] With 5 equiv. of **2q**. [c] At 120 °C. [d] 1.0 mmol scale.



Scheme 4 Deuterium-labelling experiment.

although the hydroamination products would be formed *via* aminometallation.[17,18]

In summary, we have developed the enantioselective addition of the N–H bond of phthalimide to alkenes. Diphosphine ligands possessing biaryl backbones with bulky aryl groups on the phosphorus atoms enabled smooth addition to give the adducts in high yield with high enantioselectivities. Styrene and allylsilane derivatives were good substrates to give the adducts with high enantioselectivities.

Kentaro Yamakawa: conceptualization; data curation; investigation; visualization; writing – original draft. Kana Sakamoto: conceptualization; data curation; funding acquisition; investigation; visualization; writing – review & editing. Takahiro Nishimura: conceptualization; data curation; funding acquisition; investigation; project administration; supervision; visualization; writing – review & editing.

This work was supported by JSPS KAKENHI Grant Number JP19H02721 and JP20J23499. K. S. thanks the JSPS for a research Fellowship for Young Scientists.

Conflicts of interest

There are no conflicts to declare.

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20 The cationic iridium complex [Ir((*S*)-DTBM-segphos)(cod)]$BAr^F{}_4$ was *in situ* prepared by mixing $[IrCl(cod)]_2$, (*S*)-DTBM-segphos, and $NaBAr^F{}_4$ in CH_2Cl_2. After removing CH_2Cl_2 under vacuum, substrates and the solvent were added. This procedure contributed the reproducibility of the reaction.
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22 See the ESI† for details.
23 The polymerization was separately confirmed in the reaction of **2e** in the presence of the cationic iridium catalyst without **1a**.
24 For example, the reaction of phthalimide (**1a**) with *p*-chlorostyrene (**2h**) gave the corresponding adduct **3ah** in 15% yield with 49% ee.

