Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Open Access Article. Published on 03 August 2023. Downloaded on 12/6/2025 7:39:15 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

Check for updates

Cite this: *Org. Biomol. Chem.*, 2023, **21**, 6940

Enantioselective synthesis of 3-hydroxy- and 3-amino-3-alkynyl-2-oxindoles by the dimethylzinc-mediated addition of terminal alkynes to isatins and isatin-derived ketimines†

Elena Prieto, Jorge D. Martín, Javier Nieto * and Celia Andrés *

Received 27th June 2023,
Accepted 1st August 2023

DOI: 10.1039/d3ob01023f

rsc.li/obc

A common protocol for enantioselective alkynylation of isatins and isatin-derived ketimines using terminal alkynes and Me_2Zn in the presence of a catalytic amount of a chiral perhydro-1,3-benzoxazine with moderate to excellent enantioselectivity under mild reaction conditions is described. The additions to ketimines present a novel approach to chiral amines being derivatives of oxindoles. The reaction is broad in scope with respect to aryl- and alkyl-substituted terminal alkynes and isatin derivatives. In isatins, the alkynylation occurs at the *Si* face of the carbonyl group, whereas in the ketimine derivatives it occurs at the *Re* face of the imine.

Introduction

The 3-heteroatom-substituted oxindoles are an important class of compounds whose structure is present in a wide variety of natural and synthetic products that exhibit a wide range of interesting biological activities and pharmaceutical properties.[1] Studies of the structure–biological activity relationship have shown that their biological activities are significantly affected both by the configuration of the stereocentre in C-3 and by its substitution pattern.[2] Therefore, in recent years, the asymmetric synthesis of chiral 3-hydroxy and 3-aminooxindoles has become a hot topic in organic synthesis.[3,4]

Among the 2-oxindole derivatives, we are interested in the 3-hydroxy- and 3-amino-3-alkynyl-2-oxindole derivatives that can be prepared by alkynylation of isatins and isatin-derived ketimines, since some of these have been found to exhibit significant pharmacological activities (Fig. 1). For example, 3-(hex-1-yn-1-yl)-3-hydroxy-1-methylindolin-2-one (**I**) shows excellent biological activity in *Echinococcus multilocularis* metacestodes, which can cause severe liver problems,[5] 3-(cyclopropylethynyl)-3-hydroxy-1,5-dimethylindolin-2-one (**II**) is more active than efavirenz against HIV-1 replication[6] and 5-chloro-3-ethenyl-3-hydroxy-1-(prop-2-yn-1-yl)indolin-2-one (**III**) is a good inhibitor of the enzyme Akt kinase with potential anticancer activity.[7] In addition, 3-alkynyl-3-hydroxy-2-oxindoles and 3-alkynyl-3-amino-2-oxindoles are commonly used as versatile synthons in a wide variety of synthetic applications,[8] notably the preparation of biologically active spirooxindoles[9] and other heterocyclic derivatives (Fig. 2).[10]

Although there are different examples of alkynylations of isatins leading to racemic mixtures of products,[11] the asymmetric version of this reaction has only been studied recently. Different Cu(I) complexes have emerged as efficient catalysts for this transformation, as reported by Liu,[12] Guo[13] and Zhou[14] who employed Cu(I)/chiral guanidine, Cu(I)/chiral phosphine and Cu(I)/chiral aminophenol systems respectively. A Cu(II)/bisoxazoline complex has also been shown to be

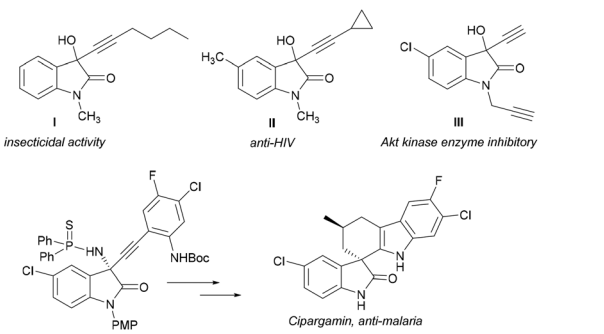


Fig. 1 Examples of bioactive 3-alkynyl-3-hydroxy-2-oxindoles and preparation of the antimalarial agent cipargamin from a chiral 3-alkynyl-3-amino-2-oxindole derivative.

Instituto CINQUIMA and Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Valladolid, Paseo de Belén, 7, 47011 Valladolid, Spain.
E-mail: franciscojavier.nieto@uva.es

†Electronic supplementary information (ESI) available: Experimental details, characterization data, NMR spectra data (^1H and ^{13}C) and chiral HPLC chromatograms for new synthesized compounds. CCDC 1872814 and 2097363. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3ob01023f

This journal is © The Royal Society of Chemistry 2023

Open Access Article. Published on 03 August 2023. Downloaded on 12/6/2025 7:39:15 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

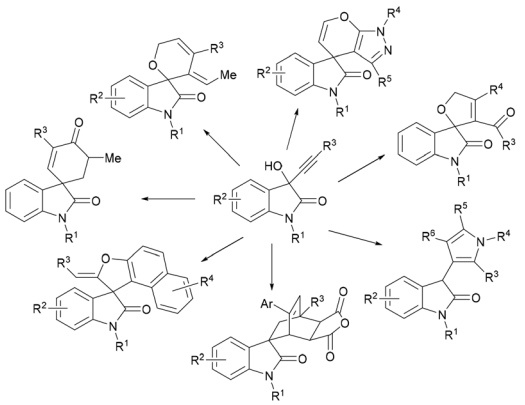


Fig. 2 Some representative examples of the preparation of spirooxindoles and other heterocyclic derivatives from chiral 3-alkynyl-3-hydroxy-2-oxindoles.

effective in the catalytic enantioselective addition of ynamides to isatins.[15] Alternatively, Maruoka has developed a competitive Ag(I)/chiral phase transfer catalytic system for the alkynylation of trityl-protected isatin derivatives,[16] and the Zhang group has developed the alkynylation of *N*-*p*-methoxybenzyl-protected isatins using a bifunctional Ag(I)/amidophosphine-urea catalyst.[17] In addition, Zn(II)/chiral hydroxyl oxazoline ligand and Co(II)/bisoxazolinephosphine catalytic systems have been successfully employed by Chen[18] and Li,[19] respectively. Zhao recently also developed a novel Zn/Co bimetallic catalysis system in the presence of a chiral bisphosphine with excellent results.[20]

Enantioselective alkynylation of isatin-derived ketimines has been much less explored, and to the best of our knowledge, there are only two examples of the catalytic enantioselective addition of terminal alkynes to isatin-derived ketimines. The Shibasaki group developed the addition of alkynylzinc derivatives to thiophosphinoyl ketimines catalysed by a mesitylcopper/bisphosphine complex[21] and applied this protocol to the enantioselective synthesis of the antimalarial agent cipargamin (Fig. 1),[9g] and the Liu group used a chiral Cu(I)/guaninide complex in the alkynylation of isatin-derived *N*-Boc ketimines.[22]

Despite much progress made to date, the development of new mild, and efficient catalytic systems for the enantioselective alkynylation of isatins and isatin-derived ketimines with a broad scope for both alkynes and isatins remains challenging and interesting, and to the best of our knowledge, a common method for both is not known.

In previous works, we have shown that conformationally restricted chiral perhydro-1,3-benzoxazines behave as excellent ligands in the enantioselective addition of organozinc derivatives to aldehydes and activated ketones, including the enantioselective alkynylation of α-keto esters and 1,2-diketones with alkynyl zinc derivatives,[23] and in this way, we envisioned their utilization as ligands for the enantioselective addition of alkynyl zinc reagents to isatin derivatives. These chiral perhydro-1,3-benzoxazines can be easily prepared in a few steps from (−)-8-aminomenthol.[23a,d,24]

Given the difference in structure and reactivity of substrates such as α-keto esters, α-diketones, isatins and isatin-derived ketimines, it is not usual to find the same chiral ligand that allows the alkynylation of all of them with a high enantioselectivity.

Results and discussion

Enantioselective alkynylation of isatins

Initially, asymmetric alkynylation of isatins with the *in situ* generated zinc acetylide from phenylacetylene and Me_2Zn was chosen as a reaction model to evaluate both the catalytic activity of a range of chiral perhydro-1,3-benzoxazines (**L1–6**) and the optimal substituent on the nitrogen of the isatin (Table 1).

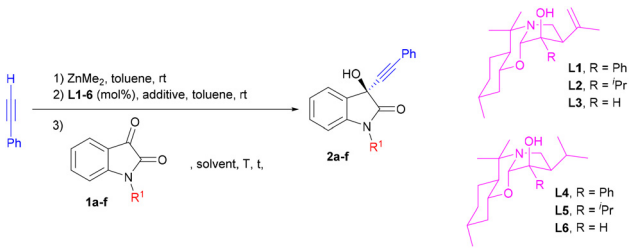
Alkynylation of *N*-methyl isatin **1a** in toluene at 0 °C in the presence of ligands **L1–6** (20 mol%) afforded **2a** in moderate enantioselectivity. The ligand **L2** led to the product in a good yield and with the best enantioselectivity (Table 1, entry 2). Then, we chose ligand **L2** to continue with the optimization of the reaction conditions, modifying the solvent, temperature, and N-protecting group at the isatin and using catalytic amounts of additives. On lowering the reaction temperature to −20 °C, the enantioselectivity improved to a good 91 : 9 er with a slightly decreased yield (entry 7), however, at −30 °C the reaction slows down and the enantioselectivity does not improve (entry 8). We also tested some previously reported additives,[25] such as Lewis acids, isopropanol and DiMPEG (entries 9–13), but they did not improve the enantioselectivity. With −20 °C as a suitable temperature, we tested different N-protecting groups (entries 14–18). The best result was found when *N*-2,6-dichlorobenzyl isatin **1c** was used, achieving the product in 72% with a 93 : 7 er (entry 14). No decrease in the enantiocontrol was observed when an electron-withdrawing acetyl group was used, and the product **2e** was obtained in a similar yield (entry 17), however, the *N*-tosyl isatin **1f** led to a moderate enantioselectivity and yield due to the formation of several by-products after only 3 h at −20 °C (entry 18). When the reaction of phenylacetylene with isatin **1c** was carried out using a 3 : 1 dichloromethane–toluene mixture as solvent, a significant improvement in both yield and enantioselectivity was observed (78%, er = 96 : 4, entry 19).

Finally, a considerable decrease in the chemical yield and enantioselectivity was observed when only 2 equivalents of the alkynylzinc reagent were employed or the ligand loading was reduced to 10 mol% (entries 20 and 21).

The absolute configuration of the newly formed stereogenic centre on **2a**, **2b** and **2d** was established as *R*. This configuration was assigned by comparing the sign of the optical rotation with literature data for the same compounds[12–14,16,18] and has been extended to all the other 3-hydroxy-3-alkynyloxindoles synthesized based on mechanistic analogy. On the other hand, the absolute configuration of the alkynylation product of **1e** was confirmed to be *R* by X-ray diffraction analysis of a single crystal of **2e**.

Open Access Article. Published on 03 August 2023. Downloaded on 12/6/2025 7:39:15 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

Table 1 Screening studies of the enantioselective addition of phenylacetylene to N-protected isatins **1a–f**[a]



Entry	Isatin, R	Ligand (mol %)	Additive (mol %)	Solvent	T (°C)	t (h)	Yield[b] (%)	er[c]
1	**1a**, CH_3	**L1** (20)	—	Toluene	0	20	**2a** (36)	76 : 24
2	**1a**, CH_3	**L2** (20)	—	Toluene	0	20	**2a** (79)	84 : 16
3	**1a**, CH_3	**L3** (20)	—	Toluene	0	20	**2a** (36)	72 : 28
4	**1a**, CH_3	**L4** (20)	—	Toluene	0	20	**2a** (55)	77 : 23
5	**1a**, CH_3	**L5** (20)	—	Toluene	0	20	**2a** (40)	73 : 27
6	**1a**, CH_3	**L6** (20)	—	Toluene	0	20	**2a** (38)	72 : 28
7	**1a**, CH_3	**L2** (20)	—	Toluene	−20	20	**2a** (72)	91 : 9
8	**1a**, CH_3	**L2** (20)	—	Toluene	−30	35	**2a** (60)	90 : 10
9	**1a**, CH_3	**L2** (20)	$B(OEt)_3$ (10)	Toluene	−20	12	**2a** (78)	86 : 14
10	**1a**, CH_3	**L2** (20)	DiMPEG (10)	Toluene	−20	20	**2a** (48)	87 : 13
11	**1a**, CH_3	**L2** (20)	iPrOH (10)	Toluene	−20	20	**2a** (52)	85 : 15
12	**1a**, CH_3	**L2** (20)	$Ti(OiPr)_4$ (10)	Toluene	−20	20	**2a** (64)	84 : 16
13	**1a**, CH_3	**L2** (20)	$B(OEt)_3$ (10)	Toluene	−40	45	**2a** (70)	86 : 14
14	**1b**, C_6H_5–CH_2	**L2** (20)	—	Toluene	−20	20	**2b** (68)	92 : 8
15	**1c**, 2,6-Cl_2–C_6H_3–CH_2	**L2** (20)	—	Toluene	−20	20	**2c** (72)	93 : 7
16	**1d**, $C(C_6H_5)_3$	**L2** (20)	—	Toluene	−20	24	**2d** (67)	92 : 8
17	**1e**, Ac	**L2** (20)	—	Toluene	−20	24	**2e** (68)	93 : 7
18	**1f**, Ts	**L2** (20)	—	Toluene	−20	3	**2f** (52)	83 : 17
19	**1c**, 2,6-Cl_2–C_6H_3–CH_2	**L2** (20)	—	CH_2Cl_2 : toluene 3 : 1	−20	22	**2c** (78)	96 : 4
20[d]	**1c**, 2,6-Cl_2–C_6H_3–CH_2	**L2** (20)	—	CH_2Cl_2 : toluene 3 : 1	−20	22	**2c** (50)	88 : 12
21	**1c**, 2,6-Cl_2–C_6H_3–CH_2	**L2** (10)	—	CH_2Cl_2 : toluene 3 : 1	−20	22	**2c** (60)	90 : 10

[a] Reaction conditions: 0.1 mmol of **1a–f**, 0.4 mmol of dimethylzinc and 0.4 mmol of phenylacetylene. [b] Yield of isolated product after purification by flash column chromatography. [c] Enantiomeric ratio determined by HPLC on a chiral stationary phase. [d] Only 0.2 mmol of dimethylzinc and 0.25 mmol of phenylacetylene were used.

With the optimized conditions in hand (entry 19 in Table 1), we proceeded to explore the scope of the reaction of *N*-2,6-dichlorobenzyl isatin **1c** with different terminal alkynes, as illustrated in Table 2.

To our satisfaction, a wide range of phenylacetylene derivatives bearing different electron-withdrawing and electron-donating substituents on the *ortho*, *meta* or *para* positions of the phenyl group were tolerated, giving the 3-alkynyl-3-hydroxy-2-oxindoles **3a–j** in a moderate to good yield and excellent enantioselectivity. When the reaction was carried out in the presence of aliphatic alkynes a decrease in yield and enantioselectivity was observed, particularly with the bulky *tert*-butyl derivative, which afforded the alcohol **3k** in a poor yield of 38% with moderate enantioselectivity (er = 92 : 8). An exception was the 4-bromobutyne which provided propargyl alcohol **3n** in a moderate chemical yield, but an excellent enantioselectivity (er = 99 : 1). Trimethylsilylacetylene also provided the corresponding tertiary alcohol **3o** with a good enantioselectivity of 95 : 5 er.

We next explored the scope of the reaction of phenylacetylene with isatins bearing different electron-withdrawing and electron-donating groups in the aromatic ring (Table 3). Pleasingly, substituents at position 5 did not have a remarkable influence in the enantiocontrol and the products **4a–f** were obtained in a moderate to good yield and excellent enantioselectivity. In addition, when 7-methyl-substituted isatin was employed, the propargylic alcohol **4g** was obtained in a competitive 77% and 95 : 5 er. Furthermore, good yields and excellent enantioselectivities were observed when *p*-tolylacetylene was reacted with 5-methoxy and 7-methyl-substituted isatins (products **4h** and **4j**, respectively), although a slight decrease in both yield and enantiocontrol was noted when using trimethylsilylacetylene with these isatins (products **4i** and **4k**).

Finally, to show the potential of our catalytic system we tested our ligand in the enantioselective synthesis of two pharmacologically active[5,6] compounds, **5a** and **5b**, derived from *N*-methylisatin (Scheme 1). Both chiral propargylic alcohols were obtained in a good yield under our optimized reaction conditions. Cyclopropinyl derivative **5a** was achieved with a high enantioselectivity, which was only moderate for compound **5b**.

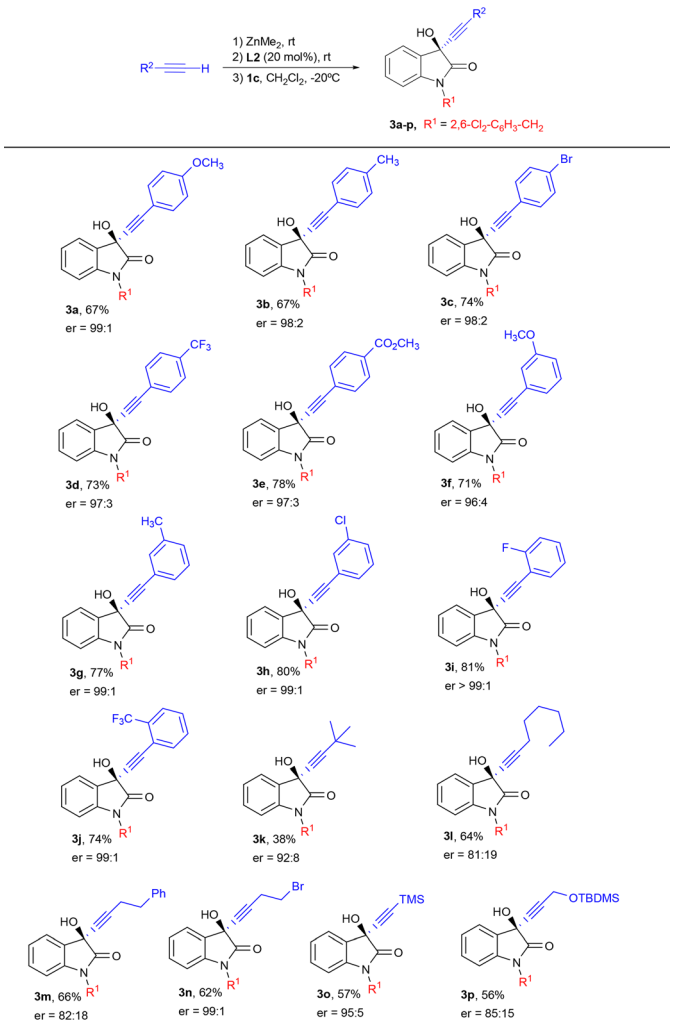
Enantioselective alkynylation of isatin-derived ketimines

The alkynylation of the isatin-derived *N*-phenyl ketimine **6a** with phenylacetylene was selected as the model reaction to

 This journal is © The Royal Society of Chemistry 2023

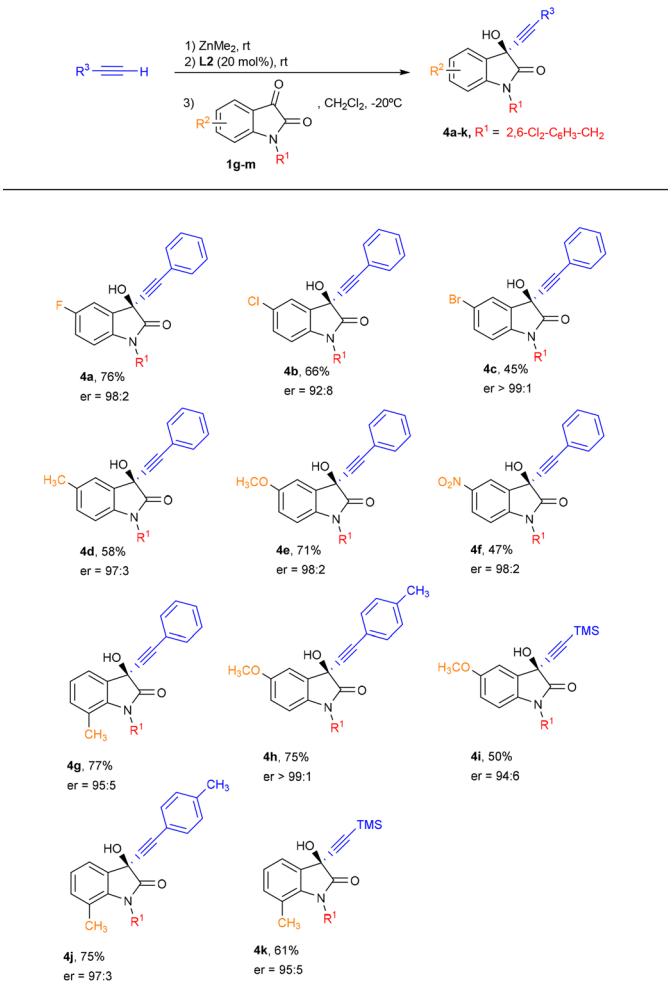
Open Access Article. Published on 03 August 2023. Downloaded on 12/6/2025 7:39:15 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

Table 2 Scope of the reaction of isatin **1c** with terminal alkynes[a]



[a] Reaction conditions. (1) 0.4 mmol of alkyne, 0.4 mmol of dimethylzinc, toluene, rt; (2) 0.02 mmol of **L2** toluene, rt; (3) 0.1 mmol of **1c**, dichloromethane, −20 °C, 22 h. Yield of isolated products after purification by flash column chromatography. Enantiomeric ratio determined by HPLC on a chiral stationary phase.

Table 3 Scope of the reaction of isatin derivatives **1g–m** with terminal alkynes[a]

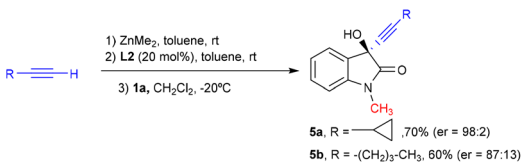


[a] Reaction conditions. (1) 0.4 mmol of alkyne, 0.4 mmol of dimethylzinc, toluene, rt; (2) 0.02 mmol of **L2** toluene, rt; (3) 0.1 mmol of **1g–m**, dichloromethane, −20 °C, 22 h. Yield of isolated products after purification by flash column chromatography. Enantiomeric ratio determined by HPLC on a chiral stationary phase.

optimize the reaction conditions. We first tested ligands **L1**, **L2**, **L4** and **L5** (20 mol%) using a mixture CH_2Cl_2 : toluene 2 : 1 as the solvent at room temperature, and the results are collected in Table 4.

In the presence of ligands **L1**, **L4** and **L5**, the reaction afforded amine **7a** in a high yield with moderate enantioselectivity (Table 4, entries 1, 3 and 4). Pleasingly, the product was achieved in a 92% yield and excellent enantioselectivity (99 : 1 er) when ligand **L2** was employed (Table 4, entry 2).

The reaction seemed to be sensitive to solvent conditions, as shown when the reaction was performed in a 1 : 2 CH_2Cl_2 : toluene mixture instead of a 2 : 1 one, both yield and enantiocontrol decreased (Table 4, entry 5). The reaction was also carried out using **L2** at 0 °C, but under these conditions product **7a** was obtained in a low yield after 60 hours (Table 4, entry 6). Thus, ligand **L2** in a mixture of toluene : CH_2Cl_2 1 : 2 at room temperature (Table 4, entry 2) was selected as the optimized condition for this catalytic system.

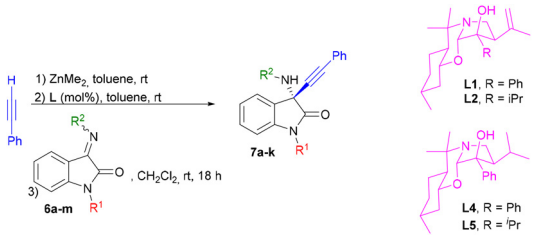


Scheme 1 Enantioselective synthesis of the pharmacologically interesting derivatives **5a–b**.

With the optimized condition in hand, we studied the effect of different aryl substituents R^2 at the imine position, as well as the influence of nitrogen protecting groups R^1 at the

Open Access Article. Published on 03 August 2023. Downloaded on 12/6/2025 7:39:15 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

Table 4 Optimization of the reaction conditions of the enantioselective addition of phenylacetylene to isatin-derived ketimines[a]



Entry	Ketimine	R^1	R^2	Ligand (mol %)	Yield[b] (%)	er[c]
1	**6a**	2,6-Cl_2–C_6H_3–CH_2	Ph	**L1** (20)	**7a** (89)	75 : 25
2	**6a**	2,6-Cl_2–C_6H_3–CH_2	Ph	**L2** (20)	**7a** (92)	99 : 1
3	**6a**	2,6-Cl_2–C_6H_3–CH_2	Ph	**L4** (20)	**7a** (92)	74 : 26
4	**6a**	2,6-Cl_2–C_6H_3–CH_2	Ph	**L5** (20)	**7a** (95)	79 : 21
5[d]	**6a**	2,6-Cl_2–C_6H_3–CH_2	Ph	**L2** (20)	**7a** (84)	90 : 10
6[e]	**6a**	2,6-Cl_2–C_6H_3–CH_2	Ph	**L2** (20)	**7a** (12)	98 : 2
7	**6b**	2,6-Cl_2–C_6H_3–CH_2	4-CF_3–C_6H_4	**L2** (20)	**7b** (95)	>99 : 1
8	**6c**	2,6-Cl_2–C_6H_3–CH_2	4-OCH_3–C_6H_4	**L2** (20)	**7c** (71)	>99 : 1
9	**6d**	2,6-Cl_2–C_6H_3–CH_2	2-OCH_3–C_6H_4	**L2** (20)	**7d** (85)	65 : 35
10	**6e**	2,6-Cl_2–C_6H_3–CH_2	2-CH_3–C_6H_4	**L2** (20)	**7e** (38)	95 : 5
11	**6f**	2,6-Cl_2–C_6H_3–CH_2	2,4,6-$(CH_3)_3$–C_6H_2	**L2** (20)	—	—
12	**6g**	2,6-Cl_2–C_6H_3–CH_2	3,5-Cl_2–C_6H_3	**L2** (20)	**7g** (98)	>99 : 1
13	**6h**	Bn	3,5-Cl_2–C_6H_3	**L2** (20)	**7h** (93)	94 : 6
14	**6i**	CH_3	3,5-Cl_2–C_6H_3	**L2** (20)	**7i** (90)	96 : 4
15	**6j**	MOM	3,5-Cl_2–C_6H_3	**L2** (20)	**7j** (93)	95 : 5
16	**6k**	CPh_3	3,5-Cl_2–C_6H_3	**L2** (20)	**7k** (95)	87 : 13
17	**6l**	Ac	3,5-Cl_2–C_6H_3	**L2** (20)	—	—
18	**6m**	H	3,5-Cl_2–C_6H_3	**L2** (20)	—	—
19	**6g**	2,6-Cl_2–C_6H_3–CH_2	3,5-Cl_2–C_6H_3	**L2** (10)	**7g** (65)	95 : 5
20[f]	**6g**	2,6-Cl_2–C_6H_3–CH_2	3,5-Cl_2–C_6H_3	**L2** (20)	**7g** (36)	—

[a] Unless specified, all the reactions were performed with phenylacetylene (0.4 mmol), dimethylzinc (0.4 mmol), **L** (0.02 mmol, 20 mol%) and **6a–m** (0.1 mmol) in a mixture of CH_2Cl_2 : toluene 2 : 1 (1.5 mL) at rt for 18 h. [b] Yield of isolated product after purification by flash column chromatography. [c] Enantiomeric ratio determined by HPLC on a chiral stationary phase. [d] A mixture of CH_2Cl_2 : toluene 1 : 2 was used as the solvent. [e] Performed at 0 °C for 60 h. [f] Only 0.2 mmol of dimethylzinc and 0.2 mmol of phenylacetylene were employed.

isatin moiety. Reactions of ketimines **6b** and **6g** bearing electron withdrawing substituents at the aromatic ring of the imine position proceeded with a full conversion to the desired product and excellent enantioselectivity (Table 4, entries 7 and 12). No detrimental effect on the enantiocontrol was observed when the *p*-anisidine derivative **6c** was tested although the chemical yield decreased to 71% (Table 4, entry 8). The reaction seemed to be sensitive to the steric effect of substituents in the *ortho* position of the aromatic ring, as shown in entries 9–11 in Table 4. Product **7e** bearing an *o*-toluidine moiety was achieved with a high enantioselectivity but only in a 38% yield and the use of the more sterically hindered mesityl group resulted in no conversion of the starting ketimine **6f** (Table 4, entries 10 and 11, respectively). In contrast, *o*-anisidine **6d** afforded the product **7d** in good yield, but the enantiomeric ratio was low, probably due to a different coordination between the zinc alkoxide catalyst and the 2-methoxyphenylimine derivative (Table 4, entry 9).

3,5-Dichloroaniline was chosen as the imine substituent in order to proceed with the evaluation of different protecting groups on the nitrogen of the isatin moiety, as collected in entries 13–18 in Table 4. Reactions between phenylacetylene and benzyl-, methyl- and methoxymethyl-protected substrates **6h**, **6i** and **6j** proceeded with a high chemical yield and good enantioselectivity (Table 4, entries 13–15). The use of the high sterically hindered trityl derivative **6k** did not affect product yield, but the enantioselectivity decreased slightly to er 87 : 13 (Table 4, entry 16). No product was obtained when the reaction was carried out using the unprotected imine **6m**, recovering the starting material after 18 hours of stirring at rt (Table 4, entry 18), nor with the acetyl derivative **6l**, which decomposed into several by-products (Table 4, entry 17).

Finally, when we tested the reaction between imine **6g** and phenylacetylene with a lower ligand charge (10 mol%) the catalytic system proved to be effective, but we observed a decrease in both product yield and enantioselectivity, obtaining **7g** in a 65% yield and 95 : 5 er (Table 4, entry 19). Unfortunately, using 2 equiv. of phenylacetylene and dimethylzinc instead of 4 equiv. resulted in a much slower reaction and poor chemical yield (Table 4, entry 20).

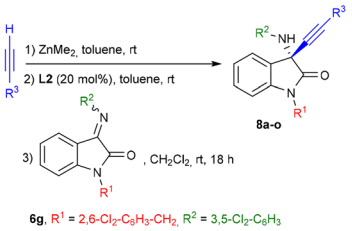
Since the 3,5-dichloroaniline moiety constitutes an important structural motif in many biologically active compounds,[26] 1-(2,6-dichlorobenzyl)-3-((3,5-dichlorophenyl)imino)indolin-2-one **6g** was selected to continue studying the scope of the reaction with terminal alkynes (Table 5).

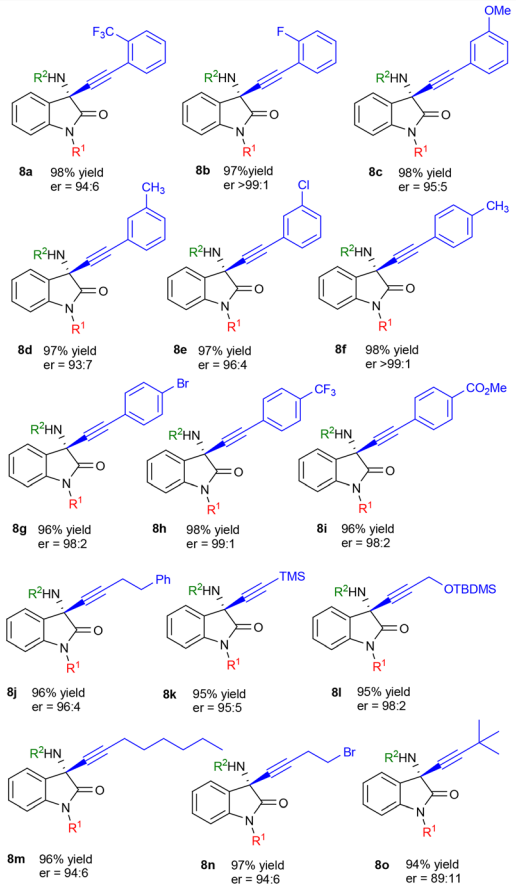
To our delight, our catalytic system again tolerated a wide range of terminal alkynes, including phenylacetylene deriva-

 This journal is © The Royal Society of Chemistry 2023

Open Access Article. Published on 03 August 2023. Downloaded on 12/6/2025 7:39:15 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

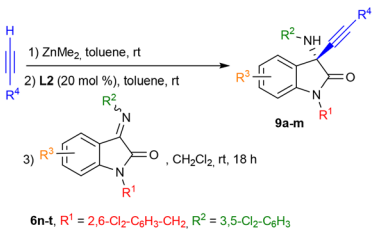
Table 5 Scope of the reaction of ketimine **5g** with terminal alkynes[a]

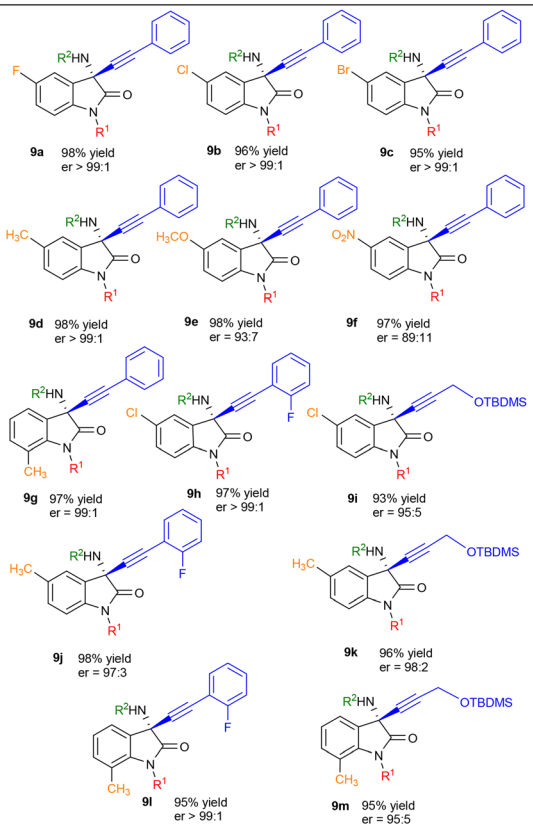




[a] Reaction conditions: (1) 0.4 mmol of alkyne, 0.4 mmol of dimethylzinc, toluene rt; (2) ligand **L2** 0.02 mmol (20 mol%), toluene, rt; (3) ketimine **1g** 0.1 mmol, CH_2Cl_2, rt 18 h. Isolated yields are given. The er values were determined by HPLC analysis on a chiral stationary phase.

Table 6 Scope of the reaction of terminal alkynes with isatin-derived ketimines bearing substituents at the aromatic ring of the isatin





Reaction conditions: (1) 0.4 mmol of alkyne, 0.4 mmol of dimethylzinc, toluene rt; (2) ligand **L2** 0.02 mmol (20 mol%), toluene, rt; (3) ketimine **5n–t** 0.1 mmol, CH_2Cl_2, rt, 18 h. Isolated yields are given. The er values were determined by HPLC analysis on a chiral stationary phase.

tives bearing electron-donating and electron-withdrawing substituents at different positions of the aromatic ring, and aliphatic alkynes. All the products **8a–o** were obtained with a high chemical yield and enantioselectivity, including propargylamines **8i**, **8k**, **8l** and **8n** derived from functionalized alkynes. Only the bulky 3,3-dimethylbut-1-yne led to propargylamine **8o** with a lower enantioselectivity.

We next explored the scope of the reaction of terminal alkynes with isatin-derived ketimines bearing electron-donating and electron-withdrawing substituents at the aromatic ring (Table 6). Again, the enantiocontrol seemed not to be influenced by the electronic effect of these substituents and the 3-amino-3-alkynyl-oxindoles **9a–m** were obtained in an excellent chemical yield and high enantioselectivity, with the exception of the nitro derivative **9f**, which was obtained with a moderate enantioselectivity (89 : 11 er).

To evaluate the synthetic potential of the catalyst, we tested the scalability of this method by carrying out the reaction on a gram scale. Under the optimized reaction conditions, 1.13 g (2.5 mmol) of **6g** reacted with phenylacetylene, giving a lower but still acceptable yield (1.18 g, 85% yield) of the desired product **6g** with an enantioselectivity of 98 : 2 er.

The absolute configuration of the newly formed stereogenic centre on **8c** was established by X-ray diffraction analysis and has been extended to all the other 3-amino-3-alkynyl-oxindoles **7a–k**, **8a–o**, and **9a–m** based on mechanistic analogy.

Open Access Article. Published on 03 August 2023. Downloaded on 12/6/2025 7:39:15 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

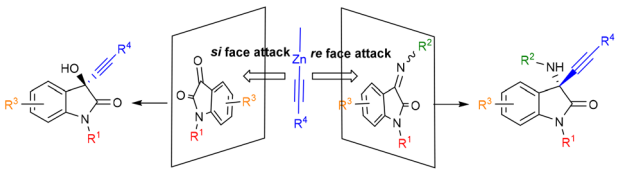


Fig. 3 Opposite facial selectivity in the enantioselective alkynylation of isatins and isatin-derived ketimines in the presence of **L2**.

Interestingly, a change in facial selectivity is observed in the alkynylation of the isatin-derived ketimines compared to that of isatins. In the isatins, the alkynylzinc derivative attacks the *Si* face of the carbonyl group, whereas in the isatin-derived ketimines the attack occurs on the *Re* face of the imine (Fig. 3).

A detailed mechanistic discussion is difficult at present due to the different coordination possibilities of the starting substrates in a bimetallic catalyst system, such as the one proposed by Noyori for the alkylation of carbonyl compounds with organozinc reagents in the presence of 1,2-aminoalcohols as chiral ligands.[27] In addition, the isatin imines exist as an equilibrium mixture of *E*/*Z* isomers,[28] further complicating the coordination possibilities. Further work to uncover the reaction mechanism and the application of these enantioselective reactions in other asymmetric transformations is in progress in our laboratories.

Conclusions

In summary, we have developed a common and efficient method for the preparation of chiral 3-hydroxy- and 3-amino-3-alkynyl-oxindoles *via* the Me_2Zn-mediated addition of terminal alkynes to isatins and isatin-derived ketimines using the same chiral ligand **L2**. A variety of isatins and ketimine derivatives bearing electron-withdrawing or electron-donating substituents on the aromatic ring and aromatic and aliphatic terminal alkynes were investigated, which gave rise to 1,2-addition products in excellent yields and high enantioselectivities. The process could be scaled up maintaining the same efficiency.

Experimental section

The experimental and analytical procedures are described in detail in the ESI.†

Author contributions

E. P. developed the catalytic enantioselective alkynylations of isatins and isatin-derived ketimines, conducted most of the experiments, analysed the results and wrote the original draft, J. D. M. performed part of the experiments of the enantioselective alkynylation of isatins. J. N. conceived, designed, and supervised the project, and prepared the manuscript. C. A. conceived, designed and supervised the project.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors thank Junta de Castilla y León (projects FEDER-VA115P17, and VA149G18) for financial support. The authors also thank Dr José M. Martín-Álvarez for his assistance in the determination of the X-ray structures.

Notes and references

1 (*a*) S. Peddibhotla, *Curr. Bioact. Compd.*, 2009, **5**, 20–38; (*b*) H.-p. Zhang, Y. Kamano, Y. Ichihara, H. Kizu, K. Komiyama, H. Itokawa and G. R. Pettit, *Tetrahedron*, 1995, **51**, 5523–5528; (*c*) S. Hibino and T. Choshi, *Nat. Prod. Rep.*, 2001, **18**, 66–87; (*d*) H. V. Erkizan, Y. Kong, M. Merchant, S. Schlottmann, J. S. Barber-Rotenberg, L. Yuan, O. D. Abaan, T.-h. Chou, S. Dakshanamurthy, M. L. Brown, A. Üren and J. A. Toretsky, *Nat. Med.*, 2009, **15**, 750–756; (*e*) M. Schönberger, C. Leggett, S. W. Kim and J. M. Hooker, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 3103–3106; (*f*) T. Emura, T. Esaki, K. Tachibana and M. Shimizu, *J. Org. Chem.*, 2006, **71**, 8559–8564; (*g*) M. Rottmann, C. McNamara, B. K. S. Yeung, M. C. S. Lee, B. Zou, B. Russell, P. Seitz, D. M. Plouffe, N. V. Dharia, J. Tan, S. B. Cohen, K. R. Spencer, G. E. González-Páez, S. B. Lakshminarayana, A. Goh, R. Suwanarusk, T. Jegla, E. K. Schmitt, H.-P. Beck, R. Brun, F. Nosten, L. Renia, V. Dartois, T. H. Keller, D. A. Fidock, E. A. Winzeler and T. T. Diagana, *Science*, 2010, **329**, 1175–1180; (*h*) Y. Khetmalis, M. Shivani, S. Murugesan and K. V. G. C. Sekhar, *Biomed. Pharmacother.*, 2021, **141**, 111842; (*i*) C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748–8758.

2 (*a*) P. Hewawasam, M. Erway, S. L. Moon, J. Knipe, H. Weiner, C. G. Boissard, D. J. Post-Munson, Q. Gao, S. Huang, V. K. Gribkoff and N. A. Meanwell, *J. Med. Chem.*, 2002, **45**, 1487–1499; (*b*) T. Tokunaga, W. E. Hume, T. Umezome, K. Okazaki, Y. Ueki, K. Kumagai, S. Hourai, J. Nagamine, H. Seki, M. Taiji, H. Noguchi and R. Nagata, *J. Med. Chem.*, 2001, **44**, 4641–4649; (*c*) J. S. Barber-Rotenberg, S. P. Selvanathan, Y. Kong, H. V. Erkizan, T. M. Snyder, S. P. Hong, C. L. Kobs, N. L. South, S. Summer, P. J. Monroe, M. Chruszcz, V. Dobrev, P. N. Tosso, L. J. Scher, W. Minor, M. L. Brown, S. J. Metallo, A. Üren and J. A. Toretsky, *Oncotarget*, 2012, **3**, 172–182; (*d*) J. Totobenazara, P. Bacalhau, A. A. San Juan, C. S. Marques, L. Fernandes, A. Goth, A. T. Caldeira, R. Martins and A. J. Burke, *ChemistrySelect*, 2016, **1**, 3580–3588.

3 (*a*) S. Mohammadi, R. Heiran, R. P. Herrera and E. Marqués-López, *ChemCatChem*, 2013, **5**, 2131–2148;

 This journal is © The Royal Society of Chemistry 2023

Open Access Article. Published on 03 August 2023. Downloaded on 12/6/2025 7:39:15 AM. This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

(*b*) P. Brandao and A. J. Burke, *Tetrahedron*, 2018, **74**, 4927–4957; (*c*) Z.-Y. Cao, F. Zhou and J. Zhou, *Acc. Chem. Res.*, 2018, **51**, 1443–1454; (*d*) A. Kumara and S. S. Chimni, *RSC Adv.*, 2012, **2**, 9748–9762; (*e*) B. Yu, H. Xing, D.-Q. Yu and H.-M. Liu, *Beilstein J. Org. Chem.*, 2016, **12**, 1000–1039; (*f*) G. Zhu, Y. Li, G. Bao, W. Sun, L. Huang, L. Hong and R. Wang, *ACS Catal.*, 2018, **8**, 1810–1816.

4 (*a*) J. Kaur and S. S. Chimni, *Org. Biomol. Chem.*, 2018, **16**, 3328–3347; (*b*) J. Kaur, S. S. Chimni, S. Mahajana and A. Kumar, *RSC Adv.*, 2015, **5**, 52481–52496; (*c*) P. Chauhan and S. S. Chimni, *Tetrahedron: Asymmetry*, 2013, **24**, 343–356; (*d*) J.-S. Yua, F. Zhoua, Y.-L. Liua and J. Zhou, *Synlett*, 2015, 2491–2504; (*e*) S. Hajra, S. S. Roy, A. Biswas and S. A. Saleh, *J. Org. Chem.*, 2018, **83**, 3633–3644.

5 M. E. Sarciron, P. Audin, I. Delabre, C. Gabrion, A. F. Petavy and J. Paris, *J. Pharm. Sci.*, 1993, **82**, 605–609.

6 (*a*) N. Boechat, W. B. Kover, V. Bongertz, M. M. Bastos, N. C. Romeiro, M. L. G. Azevedo and W. Wollinger, *Med. Chem.*, 2007, **3**, 533–542; (*b*) S. Chander, C.-R. Tang, A. Penta, P. Wang, D. P. Bhagwat, N. Vanthuyne, M. Albalat, P. Patel, S. Sankpal, Y.-T. Zheng and M. Sankaranarayanan, *Bioorg. Chem.*, 2018, **79**, 212–222.

7 P. S. Prathima, R. Bikshapathi, Y. Poornachandra, V. Himabindu, G. J. Kumar, N. Jagadeesh, C. G. Kumar and V. J. Rao, *Anti-Cancer Agents Med. Chem.*, 2017, **17**, 1963–1970.

8 (*a*) N. Kumarswamyreddy, M. Prakash, S. Jayakumar and V. Kesavan, *RSC Adv.*, 2015, **5**, 54316–54320; (*b*) K. Laxmikeshav, A. P. Sakla, S. Rasane, S. E. John and N. Shankaraiah, *ChemistrySelect*, 2020, **5**, 7004–7012; (*c*) S. Yaragorla, A. Pareek and R. Dada, *Adv. Synth. Catal.*, 2017, **359**, 3068–3075; (*d*) S. Yaragorla, R. Dada and A. Pareek, *ChemistrySelect*, 2018, **3**, 495–499; (*e*) S. Yaragorla, R. Dada, P. Rajesh and M. Sharma, *ACS Omega*, 2018, **3**, 2934–2946; (*f*) Y.-C. Lee, S. Patil, C. Golz, C. Strohmann, S. Ziegler, K. Kumar and H. A. Waldmann, *Nat. Commun.*, 2017, 14043; (*g*) D. Xie, X. Xu, S. Long, X.-Y. Tang and L. Wang, *J. Org. Chem.*, 2022, **87**, 7852–7863; (*h*) T. Khan, P. Rajesh, D. Arun and S. Yaragorla, *Org. Biomol. Chem.*, 2021, **19**, 10201–10209.

9 (*a*) N. Kumarswamyreddy and V. Kesavan, *Eur. J. Org. Chem.*, 2016, 5301–5308; (*b*) H. J. Roh, S. Y. Kim, B. K. Min and J. N. Kim, *Tetrahedron Lett.*, 2017, **58**, 21–24; (*c*) I. R. Siddiqui, Rahila, S. Shamim, P. Rai, Shireen, M. A. Waseem and A. A. H. Abumhdi, *Tetrahedron Lett.*, 2013, **54**, 6991–6994; (*d*) H. J. Roh, G. Kim, S. Cho, J. Y. Ryu, J. Lee and J. N. Kim, *Tetrahedron Lett.*, 2018, **59**, 1484–1488; (*e*) H. J. Roh, D. Y. Seo, J. Y. Ryu, J. Lee and J. N. Kim, *Tetrahedron Lett.*, 2017, **58**, 4094–4098; (*f*) Y.-W. Xu, L. Li and X.-P. Hu, *Org. Lett.*, 2020, **22**, 9534–9538; (*g*) H. Takada, N. Kumagai and M. Shibasaki, *Org. Lett.*, 2015, **17**, 4762–4765.

10 (*a*) B. Kalvacherla, S. Batthula, S. Balasubramanian and R. K. Palakodety, *Org. Lett.*, 2018, **20**, 3824–3828; (*b*) S. Yaragorla, R. Dada, G. Singh, A. Pareek, M. Rana and A. K. Sharma, *ChemistrySelect*, 2016, **1**, 6902–6906; (*c*) H. J. Roh, J. W. Lim, J. Y. Ryu, J. Lee and J. N. Kim, *Tetrahedron Lett.*, 2016, **57**, 4280–4283.

11 (*a*) M. Chouhan, K. R. Senwar, K. Kumar, R. Sharma and V. A. Nair, *Synthesis*, 2014, 195–202; (*b*) Z.-y. Wu, Z.-w. Zhang, L.-l. Ding, M. Xiang and S.-y. Luo, *Tetrahedron Lett.*, 2020, **61**, 15257711; (*c*) G. Chen, Y. Wang, S. Gao, H.-P. He, S.-L. Li, J.-X. Zhang, J. Ding and X.-J. Hao, *J. Heterocycl. Chem.*, 2009, **46**, 217–220; (*d*) V. K. Sing, A. Upadhyay and R. K. P. Singh, *Tetrahedron Lett.*, 2017, **58**, 156–158; (*e*) F. Lazreg, M. Lesieur, A. J. Samson and C. S. J. Cazin, *ChemCatChem*, 2016, **8**, 209–213; (*f*) B. Paplal, K. Sathish, S. Nagaraju and D. Kashinath, *Catal. Commun.*, 2020, **135**, 105874; (*g*) X.-P. Fu, L. Liu, D. Wang, Y.-J. Chen and C.-J. Li, *Green Chem.*, 2011, **13**, 549–553; (*h*) K. Dhara, A. Kapat, T. Ghosh and J. Dash, *Synthesis*, 2016, 4260–4268.

12 Q. Chen, Y. Tang, T. Huang, X. Liu, L. Lin and X. Feng, *Angew. Chem., Int. Ed.*, 2016, **55**, 5286–5289.

13 N. Xu, D.-W. Gu, J. Zi, X.-Y. Wu and X.-X. Guo, *Org. Lett.*, 2016, **18**, 2439–2442.

14 H. He, Z. Yang, Y. Chai, R. Wu, P. Cheng, J. Zhou and H. Zhou, *Org. Lett.*, 2021, **23**, 5739–5743.

15 M. Moskowitz and C. Wolf, *Angew. Chem., Int. Ed.*, 2019, **58**, 3402–3406.

16 S. Paria, H.-J. Lee and K. Maruoka, *ACS Catal.*, 2019, **9**, 2395–2399.

17 D. Jiang, P. Tang, Q. Tan, Z. Yang, L. He and M. Zhang, *Chem. – Eur. J.*, 2020, **26**, 15830–15834.

18 L. Chen, G. Huang, M. Liu, Z. Huang and F.-E. Chen, *Adv. Synth. Catal.*, 2018, **360**, 3497–3501.

19 J.-F. Chen and C. Li, *Org. Lett.*, 2020, **22**, 4686–4691.

20 R.-Z. Huang, Z.-C. Ma, Y. Huang and Y. Zhao, *J. Org. Chem.*, 2023, **88**, 7755–7763.

21 L. Yin, Y. Otsuka, H. Takada, S. Mouri, R. Yazaki, N. Kumagai and M. Shibasaki, *Org. Lett.*, 2013, **15**, 698–701.

22 Q. Chen, L. Xie, Z. Li, Y. Tang, P. Zhao, L. Lin, X. Feng and X. Liu, *Chem. Commun.*, 2018, **54**, 678–681.

23 (*a*) C. Andrés, R. Infante and J. Nieto, *Tetrahedron: Asymmetry*, 2010, **21**, 2230–2237; (*b*) R. Infante, J. Nieto and C. Andrés, *Org. Biomol. Chem.*, 2011, **9**, 6691–6699; (*c*) R. Infante, J. Nieto and C. Andrés, *Synthesis*, 2012, 1343–1348; (*d*) R. Infante, J. Nieto and C. Andrés, *Chem. – Eur. J.*, 2012, **18**, 4375–4379; (*e*) R. Infante, A. Gago, J. Nieto and C. Andrés, *Adv. Synth. Catal.*, 2012, **354**, 2797–2804; (*f*) R. Infante, J. M. Martín-Álvarez, C. Andrés and J. Nieto, *Org. Lett.*, 2017, **19**, 1516–1519; (*g*) E. Prieto, R. Infante, J. Nieto and C. Andrés, *Org. Biomol. Chem.*, 2021, **19**, 3859–3867.

24 C. Andrés, I. González, J. Nieto and C. D. Rosón, *Tetrahedron*, 2009, **65**, 9728–9736.

25 (*a*) E. M. Volgl, H. Gröger and M. Shibasaki, *Angew. Chem., Int. Ed.*, 1999, **38**, 1570–1577; (*b*) J. Rudolph, N. Hermanns and C. Bolm, *J. Org. Chem.*, 2004, **69**, 3997–4000; (*c*) J. Rudolph, M. Lormann, C. Bolm and S. Dahmen, *Adv. Synth. Catal.*, 2005, **347**, 1361–1368.

Open Access Article. Published on 03 August 2023. Downloaded on 12/6/2025 7:39:15 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

26 (*a*) J. Y. Lee, Y. S. Shin, S. Jeon, S. I. Lee, S. Noh, J.-E. Cho, M. S. Jang, S. Kim, J. H. Song, H. R. Kim and C. M. Park, *Bioorg. Med. Chem. Lett.*, 2021, **39**, 127885; (*b*) Y. Zhang, K. T. Zhao, S. G. Fox, J. Kim, D. R. Kirsch, R. J. Ferrante, R. I. Morimoto and R. B. Silverman, *J. Med. Chem.*, 2015, **58**, 5942–5949; (*c*) J.-P. Wu, J. Emeigh, D. A. Gao, D. R. Goldberg, D. Kuzmich, C. Miao, I. Potocki, K. C. Qian, R. J. Sorcek, D. D. Jeanfavre, K. Kishimoto, E. A. Mainolfi, G. Nabozny, Jr., C. Peng, P. Reilly, R. Rothlein, R. H. Sellati, J. R. Woska, Jr., S. Chen, J. A. Gunn, D. O'Brien, S. H. Norris and T. A. Kelly, *J. Med. Chem.*, 2004, **47**, 5356–5366; (*d*) A. C. Pappas and D. J. Fisher, *Pestic. Sci.*, 1979, **10**, 239–246.

27 (*a*) M. Yamakawa and R. Noyori, *J. Am. Chem. Soc.*, 1995, **117**, 6327–6335; (*b*) M. Yamakawa and R. Noyori, *Organometallics*, 1999, **18**, 128–133.

28 Q.-X. Guo, Y.-W. Liu, X.-C. Li, L.-Z. Zhong and Y.-G. Peng, *J. Org. Chem.*, 2012, **77**, 3589–3594.

This journal is © The Royal Society of Chemistry 2023