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Chirality memory of α -methylene- π -allyl iridium species†

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Chirality is one of the most important types of steric information in nature. In addition to central chirality, axial chirality has been catching more and more attention from scientists. However, although much attention has recently been paid to the creation of axial chirality and the chirality transfer of allenes, no study has been disclosed as to the memory of such an axial chirality. The reason is very obvious: the chiral information is stored over three carbon atoms. Here, the first example of the memory of chirality (MOC) of allenes has been recorded, which was realized *via* an optically active alkylidene- π -allyl iridium intermediate, leading to a highly stereoselective electrophilic allenylation with amines. Specifically, we have established the transition metal-mediated highly stereoselective 2,3-allenylation of amines by using optically active 2,3-allenyl carbonates under the catalysis of a nonchiral iridium(III) complex. This method is compatible with sterically bulky and small substituents on both amines and 2,3-allenyl carbonates and furnishes the desired optically active products with a high efficiency of chirality transfer. Further mechanistic experiments reveal that the isomerization of the optically active alkylidene- π -allyl iridium intermediate is very slow.

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Introduction

Memory of chirality (MOC) is a topic of ever-lasting interest in the storage/transmission of steric information, chiral recognition, and asymmetric syntheses.¹ In addition to enolate chemistry,² some examples of transition-metal catalyzed stereospecific functionalizations of optically active allylic derivatives have been recorded.³ However, reports on the memory of chirality of α -alkylidene- π -allyl metallic species are very limited: the rapid racemization of such chiral intermediate *via* σ - π - σ -rearrangements has been reported by Tsukamoto (Scheme 1a).⁴ Herein, we wish to report the observation of an excellent memory of chirality (MOC) in the highly stereoselective reaction of optically active allenyl methyl carbonates with amines affording 2,3-allenyl amines in high ee *via* α -alkylidene- π -allyl iridium species (Scheme 1b).

Results

Optimization of reaction conditions

In the beginning, due to the importance of amines,⁵ we were studying the synthesis of racemic 2,3-allenyl amines. After trial and error, we observed some very attractive results with iridium-catalysis for the allenylation of benzylamine **2a** with racemic methyl dodeca-2,3-dienyl carbonate **1a**. With $[\text{Ir}(\text{COD})\text{Cl}]_2$ as the catalyst, a variety of phosphine ligands was screened. PPh_3 (Table

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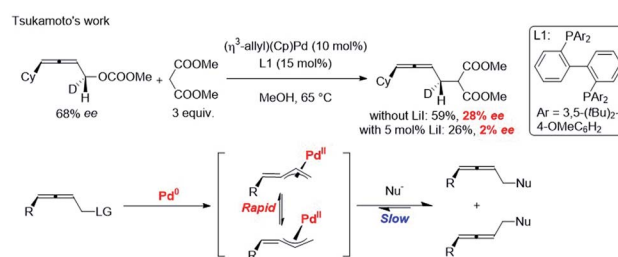
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a) Reaction of optically active α -alkylidene- π -allylic metallic species with racemization



b) Reaction of optically active α -alkylidene- π -allylic iridium species with MOC (This work)



Scheme 1 Reaction of optically active α -alkylidene- π -allylic metallic species.

Table 1 Screening of Ir catalyst^a

Entry	Ligand (mmol%)	Yield of 3aa ^b (%)	Yield of 4aa ^b (%)	Recovery of 1a ^b (%)
1	PPh ₃ (7)	13	1	85
2	dppm (3.5)	2	—	95
3	DPEphos (3.5)	2	—	99
4	P(OPh) ₃ (7)	1	—	96
5	dppe (3.5)	—	—	97
6	dppp (3.5)	—	—	99
7	dppf (3.5)	—	—	100
8	dppbe (3.5)	—	—	99
9	Xantphos (3.5)	—	—	100
10	BINAP (3.5)	—	—	99
11	Ir pre-catalyst A (3.5)	26	25	—

^a The reaction was conducted using **1a** (0.2 mmol) and BnNH₂ (0.3 mmol) in 0.4 mL of THF. ^b Determined by ¹H NMR analysis of the crude reaction mixture using 1,3,5-trimethylbenzene as an internal standard.

1, entry 1) afforded a 13% yield of **3aa**, 1% of bis-allenylation product **4aa**, and 85% recovery of **1a**. Further screening of other phosphine ligands led to poor results (Table 1, entries 2–10). To our delight, the utilization of a known cationic Ir(III) pre-catalyst **A** developed by Hartwig and co-workers⁶ yielded 26% of **3aa** and 25% of **4aa** with no recovery of **1a** (Table 1, entry 11).

Further optimization was focused on the selectivity of **3aa/4aa**. We firstly increased the amount of Ir pre-catalyst **A** to 7 mol%, but no improvement was observed (Table 2, entry 2). As

expected, the loading of benzylamine greatly affected the selectivity of **3aa/4aa**: the addition of 4 equiv. of benzylamine provided 41% of **3aa**, 6% of **4aa**, and 38% recovery of **1a** (Table 2, entry 7). By running the reaction at 50 °C, the yield was improved to 70% and no recovery of **1a** was detected (Table 2, entry 7). The reaction at a higher temperature resulted in an erosion of yield (Table 2, entry 8).

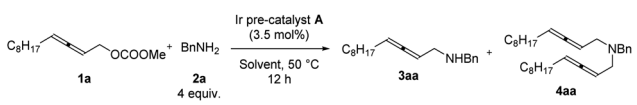
The reactions in other ethers (Table 3, entries 1–3) and chlorinated solvents (Table 3, entries 4 and 5) led to a lower

Table 2 Optimization of reaction conditions for Ir-catalyzed reaction of racemic allenyl carbonate **1a** with benzylamine **2a**^a

Entry	<i>n</i>	<i>T</i> /°C	Yield of 3aa ^b (%)	Yield of 4aa ^b (%)	Recovery of 1a ^b (%)
1	1.5	r.t.	26	25	—
2 ^c	1.5	r.t.	24	27	—
3	2	r.t.	35	28	—
4	4	r.t.	41	6	38
5 ^d	4	r.t.	45	7	45
6 ^d	4	40	64	8	11
7 ^d	4	50	70	8	—
8 ^d	4	60	65	9	—

^a The reaction was conducted using **1a** (0.2 mmol) in 0.4 mL of THF. ^b Determined by ¹H NMR analysis of the crude reaction mixture using 1,3,5-trimethylbenzene as an internal standard. ^c 7 mol% Ir pre-catalyst **A** was used. ^d The reaction was conducted using **1a** (0.2 mmol) in 1.0 mL of THF.



Table 3 Solvent effect^a


Entry	Solvent	Yield of 3aa ^b (%)	Yield of 4aa ^b (%)	Recovery of 1a ^b (%)
1	Ethyl ether	54	15	3
2	DME	64	10	—
3	MTBE	57	13	—
4	DCM	50	17	—
5	DCE	51	18	—
6	MeCN	50	18	—
7	DMF	35	21	—
8	DMSO	19	—	53
9	Toluene	70	9	—
10	THF	70	8	—
11 ^c	THF	71 ^d	9	—

^a The reaction was conducted using **1a** (0.2 mmol) and BnNH₂ (0.8 mmol) in 1.0 mL of THF. ^b Determined by ¹H NMR analysis of the crude reaction mixture using 1,3,5-trimethylbenzene as an internal standard. ^c The reaction was conducted using allene **1a** (1.0 mmol), BnNH₂ (4.0 mmol) in 5 mL of THF. ^d Isolated yield.

selectivity of **3aa/4aa**. Increasing the polarity of aprotic solvents displayed decreasing yields (Table 3, entries 6–8). Toluene provided a very similar yield and selectivity (Table 3, entry 9). Scaling the reaction up to 1.0 mmol furnished similar results with **3aa** isolated in a 71% yield together with 9% of the bis-allenylation product (Table 3, entries 10 and 11). Thus, **1a** (1 equiv.), **2a** (4 equiv.), and Ir pre-catalyst **A** (3.5 mol%) in THF at 50 °C was defined as the optimized reaction conditions for further study.

Allenylation of amines

With the optimal conditions in hand, diverse 2,3-allenyl carbonates and amines were investigated to demonstrate the scope of this reaction (Scheme 2). Terminal 2,3-allenyl carbonates showed slightly lower reactivities (products **3bb–3be**) (part I). 4-Mono-substituted 2,3-allenyl carbonates were then examined (part II): R¹ may be a 1°-alkyl group, such as n-C₈H₁₇ (**1a**), n-C₅H₁₁ (**1d**), n-C₆H₁₃ (**1t**), or a 2°-alkyl group, i-Pr (**1e**) and Cy (**1f**), smoothly affording products **3aa**, **3af**, **3ag**, **3ah**, **12**, **3tx**, **3dj**, **3dk**, **3el**, **3fm**, and **3fn** with the corresponding amines. Benzoxy (**1c**) and phenyl group (**1u**) were tolerated (products **3ci**, **3uy**, and **4uz**).

4-Aryl-2,3-allenyl carbonates were next exposed to the optimized reaction conditions (part III): 4-phenyl-2,3-allenyl carbonate **1g** furnished a similar result as compared with **1a** (product **3ga**). Substrates with a wide range of functional groups, such as *p*-Me (**1h**), *m*-OMe (**1i**), *p*-F (**1j**), *p*-Cl (**1k**), *p*-Br (**1l**), *p*-COOMe (**1v**), *p*-CF₃ (**1w**), and *p*-CN (**1x**), all exhibited a decent reactivity under the standard conditions (products **3hp**, **3im–3ir**, **3js**, **3kt**, **3lb**, **3vf**, **3wf**, and **3xr**). 2-Naphthyl (**1m**) and 3-thienyl (**1o**) were also accommodated to afford the target products **3mf**, **3mu**, **3ov**, and **3oa** in 61–90% yields; 3-furyl substituted allenyl carbonate **1p** turned out to be less reactive and reacted with *p*-methoxybenzylamine **2w** to yield product

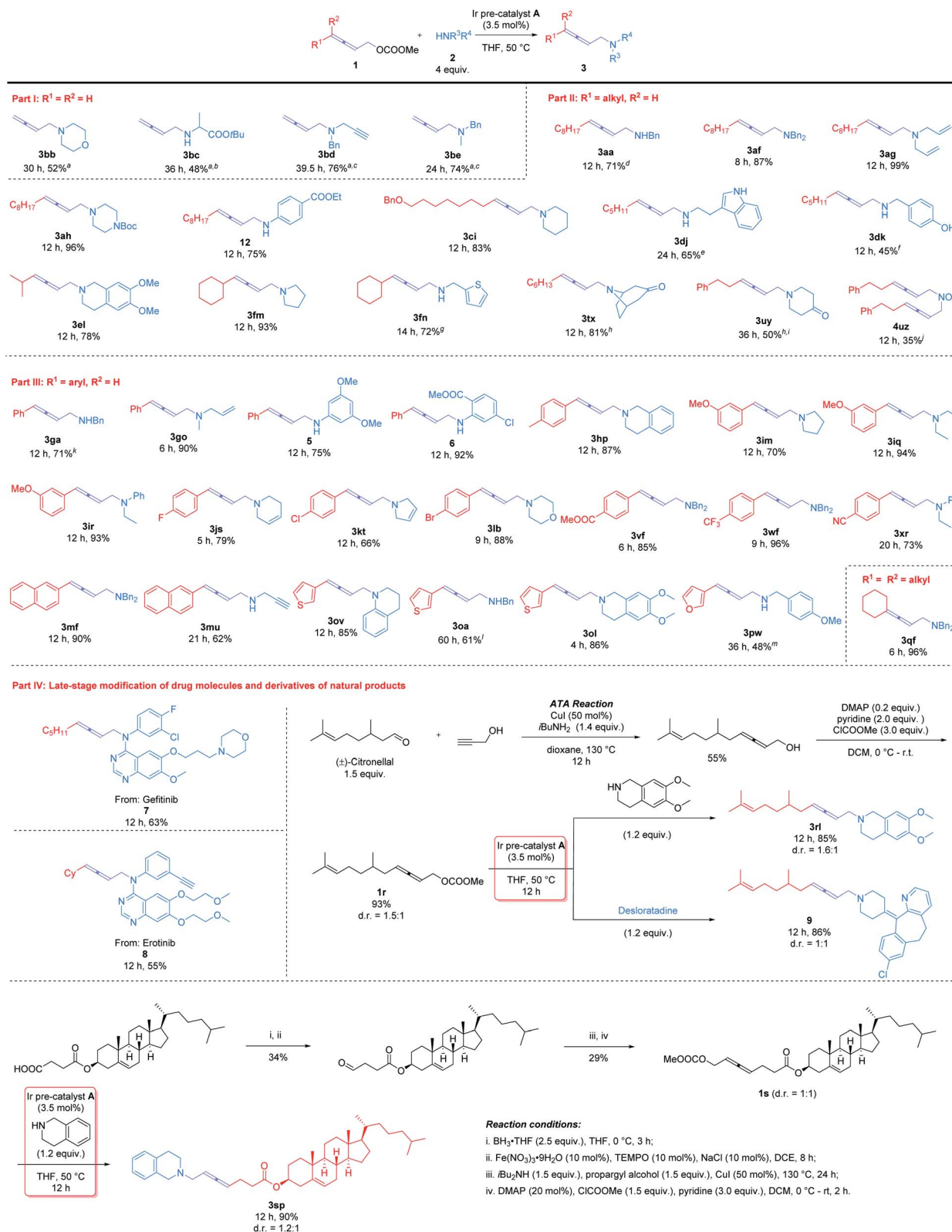
3pw in 48% isolated yield at 60 °C with 7 mol% Ir catalyst. 4,4-Disubstituted allenyl carbonate **1q** also worked to afford product **3qf**.

A wide range of amines were also tested. Acyclic amines bearing different alkyl (**2e**, **2o**, **2q**, and **2r**), phenyl (**12**, **5**, **6**, and **2r**), benzyl (**2a**, **2f**, **2k**, and **2w**), and synthetically useful functional groups, such as the allylic (**2g** and **2o**), propargyl (**2d** and **2u**) and ester (**2c**) groups, all furnished the corresponding products **3be**, **3go**, **3iq**, **12**, **5**, **6**, **3ir**, **3xr**, **3aa**, **3ga**, **3vf**, **3wf**, **3mf**, **3oa**, **3pw**, **3ag**, **3go**, **3bd**, **3mu**, and **3bc** in moderate to quantitative yields (48–99%). Tryptamine **2j**, which contains 3 potential reaction sites, was detected to be allenylated exclusively on the primary amino group as judged by ¹H NMR analysis of the crude product(s). Under standard reaction conditions, it is not necessary to protect the hydroxyl group (**2k**) to afford product **3dk**.

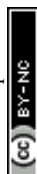
Cyclic amines act as widespread skeletons in drug molecules and natural products. Cyclic amines, such as morpholine **2b**, pyrrolidine **2m**, pyrroline **2t**, piperidine **2i**, piperazine **2h**, 1,2,3,6-tetrahydropyridine **2s**, tetrahydroisoquinoline (**2l** and **2p**), and tetrahydroquinoline **2v**, may all be modified with the allene unit furnishing the desired products **3bb**, **3lb**, **3fm**, **3im**, **3kt**, **3ci**, **3ah**, **3js**, **3el**, **3hp**, **3ol**, and **3ov** smoothly in 52–96% yields. Quaternary amine hydrochlorides exist widely in medical and pharmaceutical science due to their superior water solubility, absorption, and ease of formulation. Both nortropinone (**2x**) and 4-piperidinone (**2y**) furnished the desired products **3tx** and **3uy** in the presence of NaHCO₃. Hydroxylamine hydrochloride **2z** could also be allenylated, affording bis-allenylation product **4uz**.

In order to demonstrate the scope of the current Ir-catalyzed 2,3-allenylation reaction, we applied this strategy for the late-stage modification of drug molecules and derivatives of natural products (part IV). Two commercial drugs for cancer





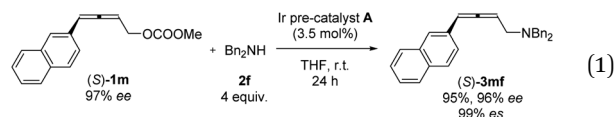
Scheme 2 Substrate scope of Ir-catalyzed 2,3-allenylation of amines. Standard conditions: Ir pre-catalyst A (3.5 mmol%), allene (1.0 mmol) and amine (4.0 mmol) in 5 mL of THF. ^a5.3 mol% Ir pre-catalyst A was used. ^b32% of **1b** was recovered. ^c10% of **1b** was recovered. ^d9% NMR yield of **4aa**. ^e5.3 mol% Ir pre-catalyst A was used and the reaction was conducted at 60 °C. ^f17% NMR yield of **4dk**. ^g7% NMR yield of **4fn**. ^hThe reaction was conducted using allene (1.0 mmol), amine·HCl (1.2 mmol), and NaHCO₃ (1.2 mmol) in 5 mL of THF. ⁱ7 mol% Ir pre-catalyst A was used. ^jThe reaction was conducted using allene (1.0 mmol), NH₂OH·HCl (4.0 mmol), and NaHCO₃ (4.0 mmol) in 5 mL of THF and 6% NMR yield of **3uz** was detected. ^k6% NMR yield of **4ga** was detected. ^l15% of **1o** was recovered and 3% NMR yield of **4oa** was detected. ^m7 mol% Ir pre-catalyst A was used and the reaction was conducted at 60 °C.



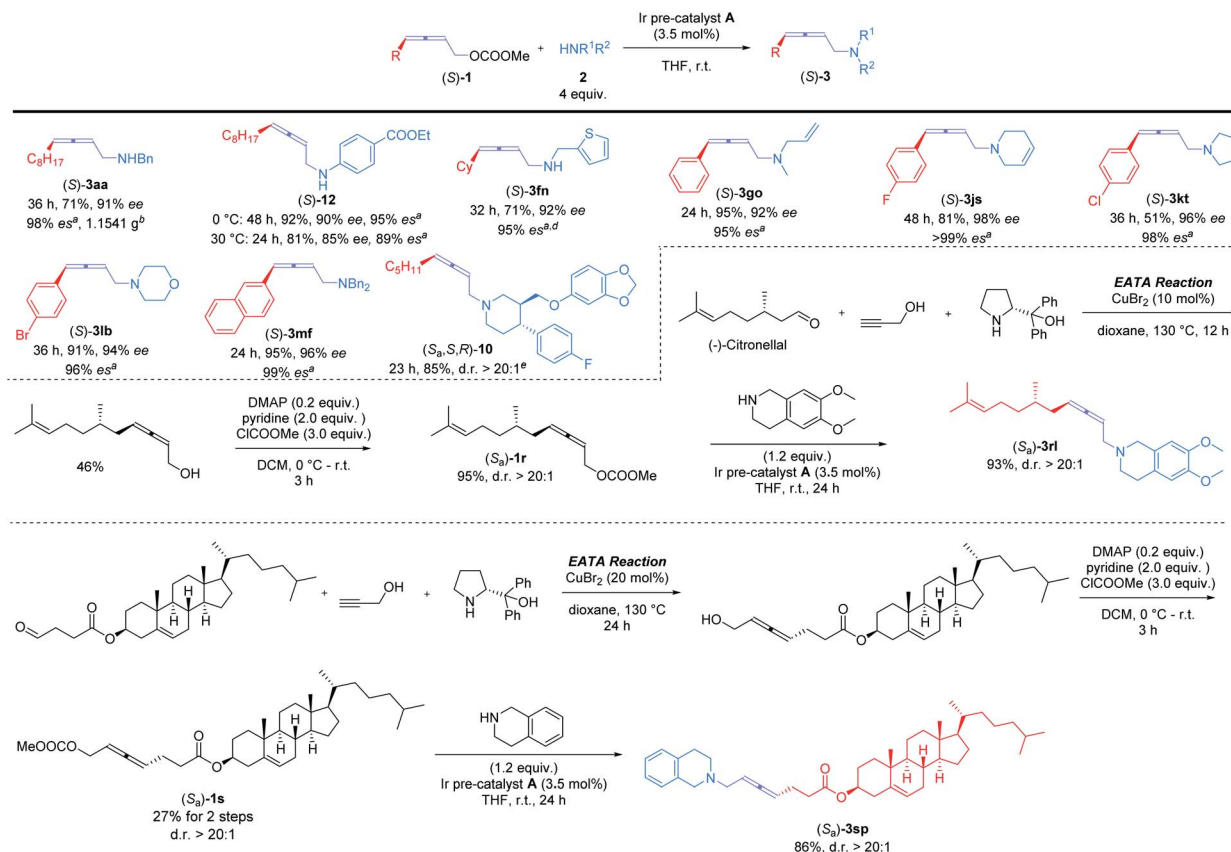
treatment, Gefitinib and Erlotinib,⁷ could be directly modified with an allene unit (products **7** and **8**). Furthermore, the ATA reaction⁸ of (\pm)-citronellal and cholesterol with propargyl alcohol conveniently gave the desired allenols, which were treated with chloroformate to afford the carbonates **1r** and **1s**. Subsequent Ir-catalyzed reactions with tetrahydroisoquinolines and desloratadine⁹ afforded 2,3-allenyl amines for **3rl**, **9**, and **3sp** with 85–90% yields.

Memory of chirality

Nowadays, optically active 2,3-allenols are readily available from the EATA reaction.¹⁰ Thus, after unveiling the scope of this protocol, we were anxious to investigate the memory of chirality by applying optically active 2,3-allenyl carbonates. Our first attempt was the reaction of (*S*)-**1m** with dibenzylamine **2f** at room temperature with 3.5 mol% Ir pre-catalyst **A** (eqn (1)). The target product could be obtained with 95% yield and an excellent efficiency of chirality transfer (99% es), *i.e.*, the axial chirality of the allene unit was passed to the axial chirality in the allenyl amines. To our knowledge, this is the first example of such transition metal-involved chirality memory.



Encouraged by this result, we further examined the scope of memory of chirality (Scheme 3). For 4-alkyl-substituted allenyl carbonate (*S*)-**1a**, reactions afforded (*S*)-**3aa** in 71% yield and 98% es on a gram-scale with benzylamine **2a** and (*S*)-**12** in 85% yield and 95% es with 4-ethoxycarbonyl aniline, respectively. The more sterically hindered (*S*)-**1f** yielded (*S*)-**3fn** in 95% es. Various 4-aryl-2,3-allenyl carbonates were next investigated: different substituents on benzene ring, including F ((*S*)-**1j**), Cl ((*S*)-**1k**), and Br ((*S*)-**1l**), were intact under the reaction conditions (products (*S*)-**3js**, (*S*)-**3kt**, and (*S*)-**3lb**). Different types of acyclic amines (**2a**, **2n**, **2o**, and **2f**) and cyclic amines (**2s**, **2t**, and **2b**) showed little influence on the yields and stereoselectivity. Paroxetine hydrochloride, a drug used against depression and social phobia,¹¹ could also be modified with optically active 2,3-allenyl carbonate ((*S*)-**1d**) efficiently to afford the desired product (*S_a*,*S_r*)-**10** in high es. Late-stage modification of optically active derivatives of natural products, (*S_a*)-



Scheme 3 Ir-catalyzed 2,3-allenylation of optically active 2,3-allenyl carbonates with amines. Reaction procedure: to a flame-dried Schlenk tube (25 mL) were added Ir pre-catalyst **A** (0.035 mmol)/THF (3 mL), amine (4.0 mmol)/THF (1 mL), and allene (1.0 mmol)/THF (1 mL) sequentially under an Ar atmosphere. The resulting mixture was stirred at r.t. ^aEnantioselectivity of the transformation based on the ee of the starting material. ^bThe reaction was conducted using allene (6.0 mmol) and amine (24.0 mmol) in 30 mL of THF at 40 °C with a 10% NMR yield of (*S,S*)-**4aa**. ^cThe reaction was conducted at 0 °C. ^d8% NMR yield of (*S,S*)-**4fn** was detected. ^eThe reaction was conducted using (*S*)-**1d** (1.0 mmol), paroxetine·HCl·½ H₂O (1.2 mmol), and NaHCO₃ (1.2 mmol) in 10 mL of THF.



1r) and cholesterol ((*S_a*)-**1s**), were sequentially performed, furnishing the corresponding products (*S_a*)-**3rl** and (*S_a*)-**3sp** smoothly in high yields and excellent d.r. (Scheme 3).

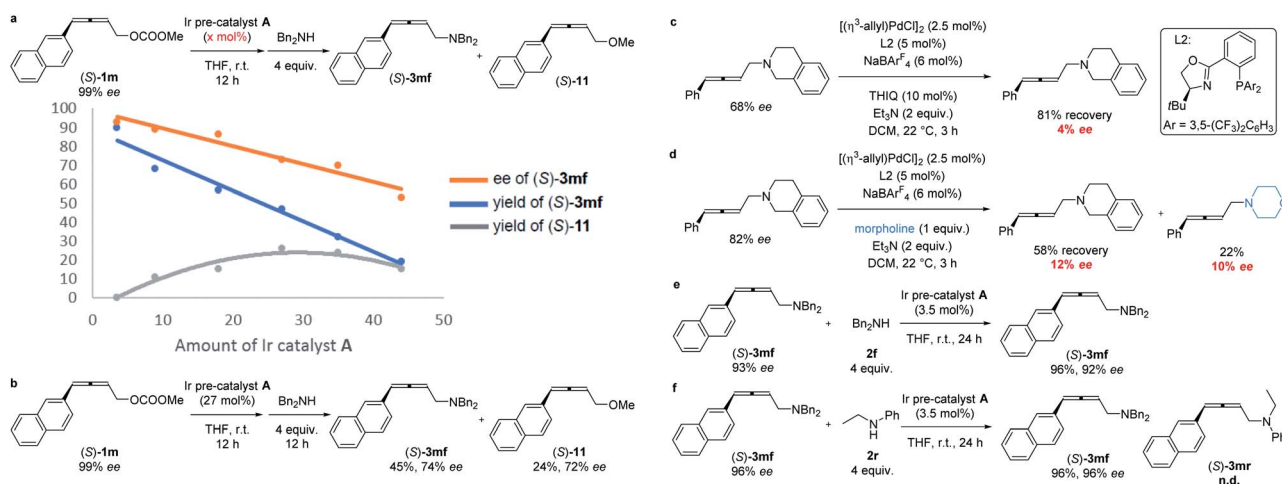
Mechanistic studies

The absolute configuration of (*S*)-**3mf** was confirmed by preparing this same product by following a known procedure.¹² To gain insight into the mechanism, a series of experiments was carried out.

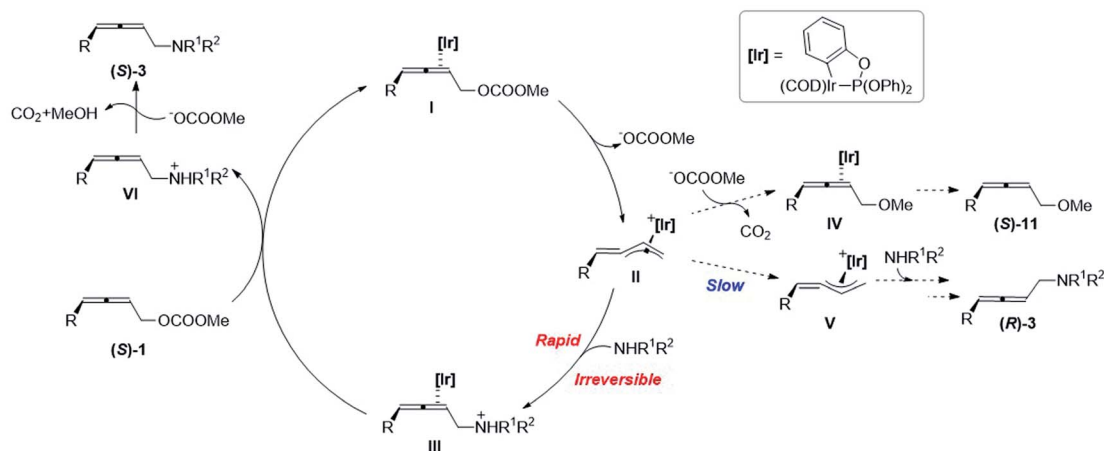
Firstly, we left a period of time for the racemization of the optically active alkylidene- π -allyl iridium intermediate as (*S*)-**1m** was treated with different amounts of Ir pre-catalyst **A** for as long as 12 h followed by the addition of the nucleophile dibenzylamine **2f**. As showed in Scheme 4a, the level of racemization is linear with the loading of the Ir pre-catalyst **A**. With the increased loading of the Ir pre-catalyst **A**, the

decarboxylation product, 2,3-allenyl methyl ether **11** was also generated with the same level of ee as compared to that of (*S*)-**3mf**. It is notable that the treatment of (*S*)-**1m** with 27% of pre-catalyst **A** for 12 h followed by the addition of dibenzylamine still formed (*S*)-**3mf** in 74% ee, which may be attributed to the much slower rate of racemization (Scheme 4b). Malcolmson *et al.*¹³ had reported that the rapid racemization of optically active 2,3-allenyl amine happened even in the presence of a chiral palladium catalyst (Scheme 4c and d). However, the treatment of the optically active product (*S*)-**3mf** under the standard reaction conditions did not lead to racemization (Scheme 4e). Moreover, no racemization of (*S*)-**3mf** or generation of (*S*)-**3mr** was observed in the scrambling experiment, indicating that the nucleophilic attack of amine is irreversible under the current Ir-catalyzed reaction conditions (Scheme 4f).

Based on the mechanistic experiments, a catalytic cycle is proposed as shown in Scheme 5. At first, the oxidative addition



Scheme 4 Mechanistic studies. The reaction procedure for the data in (a): to a flame-dried Schlenk tube were added Ir pre-catalyst **A** (*x* mol%)/THF (1.5 mL), and (*S*)-**1m** (0.5 mmol)/THF (0.5 mL) sequentially under an Ar atmosphere. The resulting mixture was stirred at room temperature for 12 h. Dibenzyl amine **2f** (2.0 mmol)/THF (0.5 mL) were then added sequentially under an Ar atmosphere. The resulting mixture was stirred at room temperature.



Scheme 5 Proposed catalytic cycle.

of Ir(I)- η^2 -(S)-**1** **I** leads to the formation of optically active alkylidene- π -allyl Ir(III) **II**, accompanied by the release of a carbonate anion. The chirality is memorized in this intermediate since the isomerization to form the allylic Ir intermediate **V** is very slow. The subsequent irreversible attack of amine results in the formation of Ir(I)- η^2 -2,3-allenyl aminylium ion **III**, which is much faster than the attack of methoxy in the carbonate anion after releasing carbon dioxide. The subsequent coordination of another (S)-**1** with Ir(I) in **III** regenerates **I** and releases the 2,3-allenyl ammonium ion **VI** to complete the catalytic cycle. With the aid of a carbonate anion, the final product (S)-**3** could be afforded by the deprotonation of **VI**, accompanied by the release of carbon dioxide and methanol.

Conclusions

In conclusion, although racemizations of the optically active alkylidene- π -allylic transition metal complexes are very common, leading to the erasure of the chiral information in the starting materials and have been extensively applied to the asymmetric syntheses of optically active allenes,¹⁴ we have recorded here the first example of chirality memory involving alkylidene- π -allylic transition metal species and developed a robust highly stereoselective approach for asymmetric allene synthesis. Such a chirality memory involving iridium will be critical for the storage and transmission of the axial chirality in optically active allenols, which are readily available from propargylic alcohols and aldehydes. Further studies with other nucleophiles in this area are being actively pursued in our laboratory.

Data availability

The ESI† include experimental details, specific rotation data, HPLC data, NMR data, MS data, IR data, elemental analysis data, and all the spectra.

Author contributions

S. M. directed the research and developed the concept of the reaction with Y. C., who also performed most of the experiments and prepared the ESI.† Y. Z., J. X., C. L., W. Z., C. H., G. W., A. Q., J. L., Q. L., H. W., P. W., H. X. and Y. Z., who also performed part of the experiments, contributed equally to this work. Y. C. and S. M. checked the experimental data. Y. C. and S. M. wrote the manuscript with contributions from the other authors.

Conflicts of interest

There are no conflicts to declare.

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References

- (a) T. Kawabata, K. Yahiro and K. Fuji, *J. Am. Chem. Soc.*, 1991, **113**, 9694; (b) K. Fuji and T. Kawabata, *Chem.-Eur. J.*, 1998, **4**, 373; (c) T. Kawabata, J. Chen, H. Suzuki and K. Fuji, *Synthesis*, 2005, **37**, 1368; (d) H. Zhao, D. C. Hsu and P. R. Carlier, *Synthesis*, 2005, **37**, 1; (e) D. Campolo, S. Gastaldi, C. Roussel, M. P. Bertrand and M. Nechab, *Chem. Soc. Rev.*, 2013, **42**, 8434; (f) S. Oliver and P. A. Evans, *Synthesis*, 2013, **45**, 3179; (g) V. Alezra and T. Kawabata, *Synthesis*, 2016, **48**, 2997; (h) C. S. Gloor, F. Dénès and P. Renaud, *Free Radical Res.*, 2016, **50**, S102; (i) K. Yamamoto, M. Kuriyama and O. Onomura, *Acc. Chem. Res.*, 2020, **53**, 105.
- (a) A. Mambrini, D. Gori, R. Guillot, C. Kouklovsky and V. Alezra, *Chem. Commun.*, 2018, **54**, 12742; (b) A. Mambrini, D. Gori, C. Kouklovsky, H. Kim, J. I. Yoshida and V. Alezra, *Eur. J. Org. Chem.*, 2018, **2018**, 6754; (c) V. Veeraswamy, G. Goswami, S. Mukherjee, K. Ghosh, M. L. Saha, A. Sengupta and M. K. Ghorai, *J. Org. Chem.*, 2018, **83**, 1106; (d) J. H. Kim, I. Kim, Y. Song, M. J. Kim and S. Kim, *Angew. Chem., Int. Ed.*, 2019, **58**, 11018; (e) S. Tan, F. Li, S. Park and S. Kim, *J. Org. Chem.*, 2019, **84**, 14436; (f) J. H. Kim, Y. Chung, H. Jeon, S. Lee and S. Kim, *Org. Lett.*, 2020, **22**, 3989.
- (a) J. L. Renaud, B. Demerseman, M. D. Mbaye and C. Bruneau, *Curr. Org. Chem.*, 2006, **10**, 115; (b) B. Breit and Y. Schmidt, *Chem. Rev.*, 2008, **108**, 2928; (c) S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard and B. L. Feringa, *Chem. Rev.*, 2008, **108**, 2824; (d) S. M. Pound and M. P. Watson, *Chem. Commun.*, 2018, **54**, 12286; (e) B. W. H. Turnbull and P. Andrew Evans, *J. Org. Chem.*, 2018, **83**, 11463; (f) M. B. Thoke and Q. Kang, *Synthesis*, 2019, **51**, 2585; (g) S. Akkarasamiyo, S. Ruchirawat, P. Ploypradith and J. S. M. Samec, *Synthesis*, 2020, **52**, 645; (h) H. S. Um, J. Min, T. An, J. Choi and C. Lee, *Org. Chem. Front.*, 2018, **5**, 2158; (i) Y. Sempere, J. L. Alfke, S. L. Rössler and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2019, **58**, 9537; (j) C. Casalta and S. Bouzbouz, *Org. Lett.*, 2020, **22**, 2359; (k) C. Chen, H. Wang, Y. Sun, J. Cui, J. Xie, Y. Shi, S. Yu, X. Hong and Z. Lu, *iScience*, 2020, **23**, 100985; (l) M. J. Tom and P. A. Evans, *J. Am. Chem. Soc.*, 2020, **142**, 11957.
- H. Tsukamoto, T. Konno, K. Ito and T. Doi, *Org. Lett.*, 2019, **21**, 6811.
- (a) J. D. Scott and R. M. Williams, *Chem. Rev.*, 2002, **102**, 1669; (b) A. L. Harvey, *Drug Discovery Today*, 2008, **13**, 894; (c) S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451; (d) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257.
- S. T. Madrahimov, Q. Li, A. Sharma and J. F. Hartwig, *J. Am. Chem. Soc.*, 2015, **137**, 14968.
- W. D. Travis, E. Brambilla, M. Noguchi, A. G. Nicholson, K. R. Geisinger, Y. Yatabe, D. G. Beer, C. A. Powell, G. J. Riely, P. E. Van Schil, K. Garg, J. H. M. Austin, H. Asamura, V. W. Rusch, F. R. Hirsch, G. Scagliotti,



- T. Mitsudomi, R. M. Huber, Y. Ishikawa, J. Jett, M. Sanchez-Céspedes, J.-P. Sculier, T. Takahashi, M. Tsuboi, J. Vansteenkiste, I. Wistuba, P.-C. Yang, D. Aberle, C. Brambilla, D. Flieder, W. Franklin, A. Gazdar, M. Gould, P. Hasleton, D. Henderson, B. Johnson, D. Johnson, K. Kerr, K. Kuriyama, J. S. Lee, V. A. Miller, I. Petersen, V. Roggli, R. Rosell, N. Saijo, E. Thunnissen, M. Tsao and D. Yankelewitz, *J. Thorac. Oncol.*, 2011, **6**, 244.
- 8 J. Kuang, H. Luo and S. Ma, *Adv. Synth. Catal.*, 2012, **354**, 933.
- 9 D. V. Wallace, M. S. Dykewicz, D. I. Bernstein, J. Blessing-Moore, L. Cox, D. A. Khan, D. M. Lang, R. A. Nicklas, J. Oppenheimer, J. M. Portnoy, C. C. Randolph, D. Schuller, S. L. Spector and S. A. Tilles, *J. Allergy Clin. Immunol.*, 2008, **122**, S1.
- 10 (a) X. Huang and S. Ma, *Acc. Chem. Res.*, 2019, **52**, 1301; (b) X. Huang, T. Cao, Y. Han, X. Jiang, W. Lin, J. Zhang and S. Ma, *Chem. Commun.*, 2015, **51**, 6956.
- 11 K. M. Bertelsen, K. Venkatakrishnan, L. L. Von Moltke, R. S. Obach and D. J. Greenblatt, *Drug Metab. Dispos.*, 2003, **31**, 289.
- 12 J. Ye, W. Fan and S. Ma, *Chem.-Eur. J.*, 2013, **19**, 716.
- 13 N. J. Adamson, H. Jeddi and S. J. Malcolmson, *J. Am. Chem. Soc.*, 2019, **141**, 8574.
- 14 (a) Y. Imada, K. Ueno, K. Kutsuwa and S.-I. Murahashi, *Chem. Lett.*, 2002, **31**, 140; (b) B. M. Trost, D. R. Fandrick and D. C. Dinh, *J. Am. Chem. Soc.*, 2005, **127**, 14186; (c) S. Song, J. Zhou, C. Fu and S. Ma, *Nat. Commun.*, 2019, **10**, 507; (d) F. Glatz, D. A. Petrone and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2020, **59**, 16404.

