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Sequential Ir-Catalyzed Allylation/2-aza-Cope Rearrangement Strategy for the Construction of Chiral Homoallylic Amines

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Summary of main observation and conclusion Sequential Ir-catalyzed asymmetric allylation/2-aza-Cope rearrangement of arylidene aminomalonates with allylic carbonates was successfully developed, and a variety of enantioenriched homoallylic amine derivatives were obtained in high yields with good chirality transfer and excellent *E/Z*-geometry control (up to 99% yield, 96% ee). Compared with previous dual catalytic system established for this transformation, the current mono metal catalytic system provides a simpler and more practical protocol employing the readily available starting materials.

Background and Originality Content

Chiral homoallylic amines and derivatives have been represented as an important class of privileged structural units, which are universally distributed in a number of nature products, drugs and biologically active molecules.[1] In addition, they can be served as versatile chiral building blocks and key intermediates in the field of asymmetric synthesis.[2] As a result, highly efficient synthesis of chiral homoallylic amines and derivatives is of particular interest. Extensive efforts have been made toward the construction of these scaffolds, and many synthetic strategies have been studied extensively and well-established.[2a-2b,3-6] Apart from the traditional reactions of imines with allyl metal reagents or metalloids under chiral substrate control or by the aid of chiral auxiliaries,[3] the asymmetric catalytic allylations of imines using [illegible] metal[4] or boron reagents[5] have been regarded as the important synthetic methodologies. However, allylic metal and boron reagents always required multi-step preparation and are generally sensitive to air or moisture, which enormously limited their wide application in organic synthesis. With chiral or achiral 2,1-disubstituted homoallylic amines as the starting materials, Kobayashi, Rueping, Wulff and Johnson documented chiral Brønsted acid-catalyzed 2-aza-Cope rearrangement for the construction of enantioenriched homoallylic amines.[7] Recently, an elegant Ir-catalyzed asymmetric allylation/2-aza-Cope rearrangement of sterically bulky N-fluorenyl imines to access chiral homoallylic amines was reported by Niu's group.[8] Based on the strategy of synergistic activation, our group developed dual Cu/Ir and PTC/Ir catalytic system to prepare a series of chiral homoallylic amines *via* a sequential allylation/2-aza-Cope rearrangement using the sterically bulky α-substituted aldimine esters as the nucleophiles, which provided the driving force for the ensuing 2-aza-Cope rearrangement through the release of the steric hindrance (Scheme 1a).[9] According to the mechanistic studies, we found that the stereoselectivity control of chiral copper catalyst is not indispensable to deliver the final homoallylic amines in the dual catalysis system followed by the subsequent acidic hydrolysis. The key role of copper complex is converting aldimine ester under basic condition to form more rigid and nucleophilic metallated azomethine ylide, which initiate the first asymmetric allylation[10] step as a nucleophile.[11] In order to make this method more economical and easy manipulation, it is important to develop a simple and efficient catalytic system to realize this transformation. We envisioned that the more active nucleophilic 2-azallyl carbanion could be readily generated under basic condition in the absence of copper complex through introducing an additional electron-withdrawing group at α-position of aldimine esters. Herein, we successfully developed a sequential Ir-catalyzed asymmetric allylation/2-aza-Cope rearrangement of easily available arylidene aminomalonates, affording various enantioenriched homoallylic amines and derivatives with well chirality transfer and excellent *E*/*Z*-geometry control (Scheme 1b).

Scheme 1 a) Dual Cu/Ir or PTC/Ir-catalyzed allylation/2-aza-Cope rearrangement; b) Mono metal-catalyzed allylation/2-aza-Cope rearrangement (This Work).

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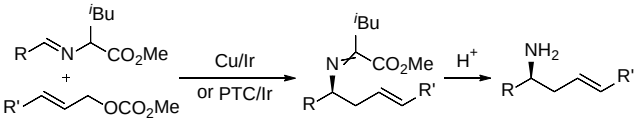
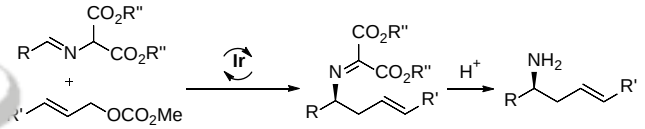
a) Previous work: cooperative dual Cu/Ir or PTC/Ir catalysis



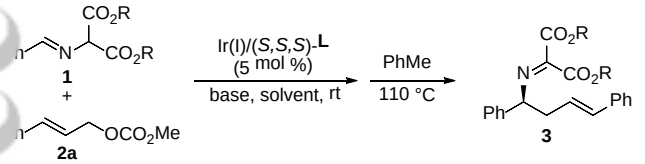
b) **This work**: mono metal-complex catalysis

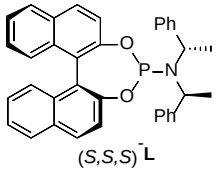


Results and Discussion

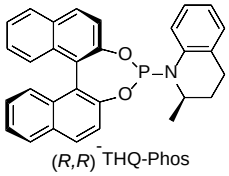
The initial study was began with diisopropyl benzylidene aminomalonate **1a** and methyl cinnamyl carbonate **2a** as model substrates with Ir(I)/(*S*,*S*,*S*)-**L** complex[12,13] (5 mol%) in CH_2Cl_2. The branched allylation product was obtained in good yield with excellent enantioselectivity (*vide infra*), then the desired homoallylic amine derivative **3aa** could be readily achieved in high yield with 96% ee through a stereospecific 2-aza-Cope rearrangement upon heating the allylation intermediate in toluene at 110 °C for 6 h (Table 1, entry 1). We found that base played an important role in Ir-catalyzed allylation step, and no allylation intermediate was observed in the absence of base (Table 1, entry 2). Subsequently, various bases such as Cs_2CO_3, NEt_3 and TMG, were inspected in this sequential process (Table 1, entries 3-5), and DBU was revealed as the best of choice in terms of yield and enantioselectivity. Variation of ester moiety in benzylidene aminomalonate was applied to further investigate the reactivity and enantioselectivity. Although the similar reactivity was observed with diethyl benzylidene aminomalonate **1b** as the nucleophilic precursor, the enantioselectivity is lower than that with diisopropyl benzylidene aminomalonate **1a** (Table 1, entry 7 *vs* entry 1). With the bulky di-*tert*-butyl benzylidene aminomalonate **1c** as the reaction partner, the corresponding product **3ca** was separated with 95% ee albeit with a little lower yield (Table 1, entry 8). With the chiral ligand (*R*,*R*)-THQ-Phos developed by You's group,[14] similar level of reactivity and enantioselectivity was observed (Table 1, entry 9).

Table 1 Optimization reaction conditions for sequential Ir-catalyzed allylation/2-aza-Cope rearrangement.[a]





(*S*,*S*,*S*)-**L**



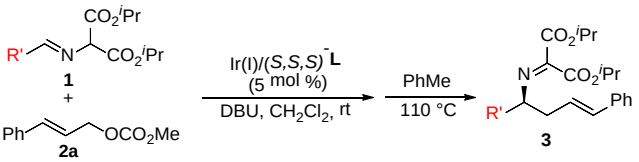
(*R*,*R*)-THQ-Phos

entry	R	base	solvent	**3**	yield (%)[b]	ee (%)[c]
1	^{i}Pr (**1a**)	DBU	CH_2Cl_2	**3aa**	90	96
2	^{i}Pr (**1a**)	-	CH_2Cl_2	**3aa**	NR	NA
3	^{i}Pr (**1a**)	Cs_2CO_3	CH_2Cl_2	**3aa**	87	93
4	^{i}Pr (**1a**)	Et_3N	CH_2Cl_2	**3aa**	92	92
5	^{i}Pr (**1a**)	TMG	CH_2Cl_2	**3aa**	88	96
6	^{i}Pr (**1a**)	DBU	PhMe	**3aa**	87	96
7	Et (**1b**)	DBU	CH_2Cl_2	**3ba**	95	90
8	^{t}Bu (**1c**)	DBU	CH_2Cl_2	**3ca**	80	95
9[d]	^{i}Pr (**1a**)	DBU	CH_2Cl_2	**3aa**	85	95

[a] All reactions were carried out with 0.30 mmol of **1** and 0.20 mmol of **2a** in 2 mL of solvent at room temperature within 12 h, then heated in PhMe at 110 °C for 6 h. DBU is 1,8-Diazabicyclo[5.4.0]undec-7-ene, TMG is 1,1,3,3-Tetramethylguanidine. NR = no reaction. NA = not available. [b] Yields refer to the isolated products after chromatographic purification. [c] The ee value was determined by HPLC analysis. [d] (*R*,*R*)-THQ-Phos was used instead of (*S*,*S*,*S*)-**L**.

With the optimized reaction conditions in hand, we made effort to investigate the substrate generality of this sequential Ir-catalyzed allylation/2-aza-Cope rearrangement. A wide range of diisopropyl arylidene aminomalonates were first examined, and these results were summarized in Table 2. These arylidene aminomalonates containing electron-donating (**1d-1g**, **1m**) or electron-withdrawing (**1h-1l**, **1n-1o**) substituents on the phenyl ring reacted with cinnamyl carbonate **2a** smoothly to give the corresponding homoallylic amine derivatives (**3da-3oa**) with moderate to high yields and excellent enantioselectivities (75%-95% yields, 89%-96% ee, Table 2, entries 1-12). We found that the substitution position on the phenyl ring has little effect on the reactivity and enantioselectivity, and comparable performance was still achieved for *ortho*-methyl and *ortho*-chloro-substituted aminomalonates (Table 2, entries 3 and 7). The fused 2-naphthylaldehyde-derived aminomalonate (**1p**) also worked well, affording the corresponding product (**3pa**) with 85% yield and 91% ee (Table 2, entry 13). Moreover, the heteroaromatic thiophene aldehyde-derived substrate (**1q**) was good reaction partner to provide the desired product (**3qa**) with 99% yield and 93% ee (Table 2, entry 14). However, alkyl aldehyde-derived aminomalonate was not compatible in this sequential process probably due to the less reactivity and fast decomposition of the imine ester.

Table 2 Substrate scope study of imines for sequential Ir-catalyzed allylation/2-aza-Cope rearrangement.[a]



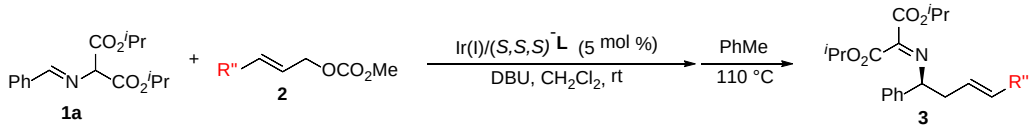
entry	R	**3**	yield (%)[b]	ee (%)[c]

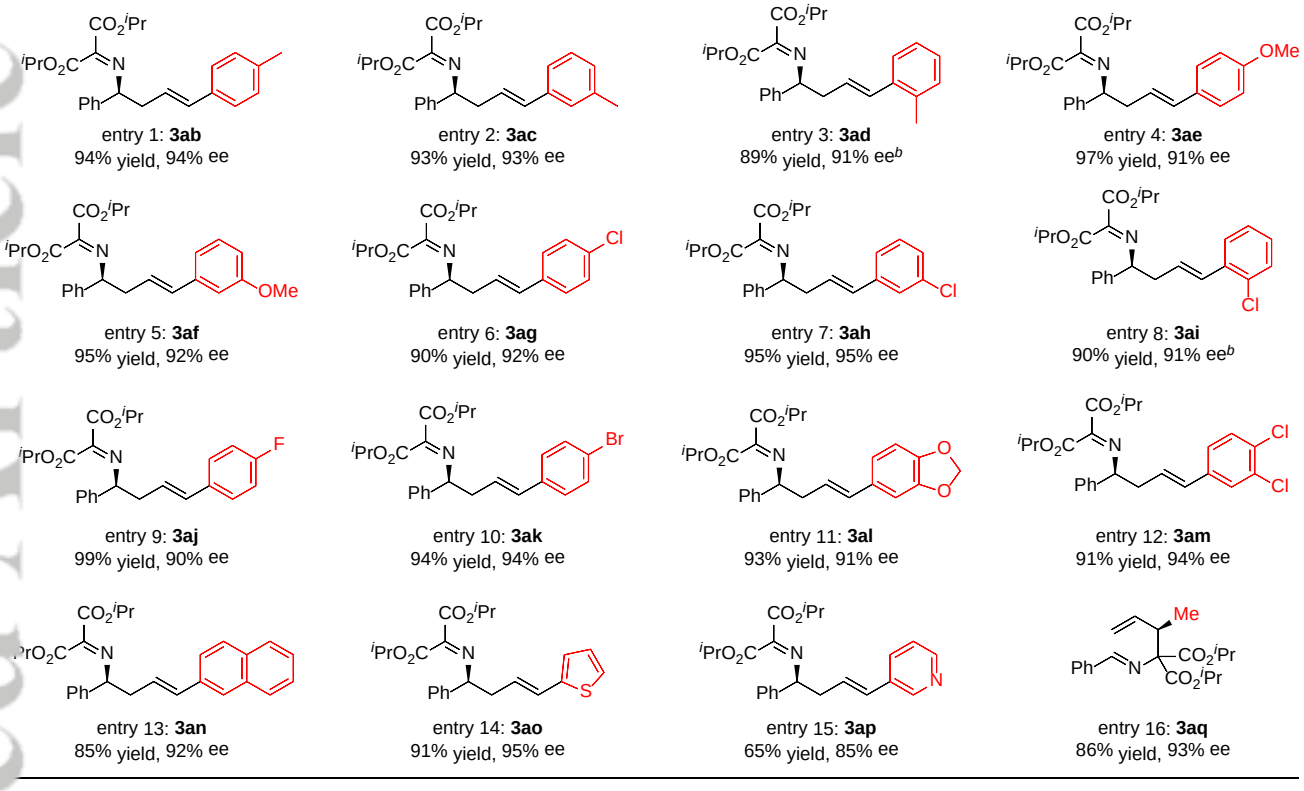
1	*p*-MeC_6H_4 (**1d**)	**3da**	80	95
2	*m*-MeC_6H_4 (**1e**)	**3ea**	95	93
3	*o*-MeC_6H_4 (**1f**)	**3fa**	76	89
4	*p*-$^tBuC_6H_4$ (**1g**)	**3ga**	94	93
5	*p*-ClC_6H_4 (**1h**)	**3ha**	80	94
6	*m*-ClC_6H_4 (**1i**)	**3ia**	75	94
7	*o*-ClC_6H_4 (**1j**)	**3ja**	77	90
8	*p*-FC_6H_4 (**1k**)	**3ka**	82	96
9	*p*-BrC_6H_4 (**1l**)	**3la**	80	90
10	3,5-$Me_2C_6H_3$ (**1m**)	**3ma**	90	92
11	2,4-$Cl_2C_6H_3$ (**1n**)	**3na**	87	90
12	*p*-$CF_3C_6H_4$ (**1o**)	**3oa**	91	92
13	2-napthyl (**1p**)	**3pa**	85	91
14	2-thiophenyl (**1q**)	**3qa**	99	93

[a] Unless otherwise noted, all reactions were carried out with 0.30 mmol of **1** and 0.20 mmol of **2a** in 2 mL of CH_2Cl_2 at room temperature within 12-16 h, then heated in PhMe at 110 °C for 6 h. [b] Yields refer to the isolated products after chromatographic purification. [c] The ee value was determined by HPLC analysis.

Encouraged by the excellent performance with respect to the nucleophilic partner, we turned our attention to exploring a variety of π-allyl precursors for further substrate scope study. As shown in Table 3, allyl carbonates bearing the substituted groups on the phenyl ring with diverse electronic properties and different positions were tolerated well in this sequential transformation, which led to various enantioenriched homoallylic amine derivatives (**3ab-3am**) in high yields and excellent enantioselectivities (89%-99% yields, 90%-95% ee, Table 3, entries 1-12). The *ortho*-methyl and chloro-substituted cinnamyl carbonates (**2d**, **2i**) with steric hindrance did not react efficiently to obtain the corresponding products with satisfied yields and enantioselectivities when using (*S*,*S*,*S*)-**L** as the chiral ligand. Fortunately, THQ-Phos ligand exhibited excellent asymmetric induction and catalytic activity for these *ortho*-substituted cinnamyl carbonates (Table 3, entries 3 and 8). 2-Naphthyl substituted allyl carbonate **2n** reacted smoothly to prepare product **3an** with 85% yield and 92% ee (Table 3, entry 13). To our delight, heteroaryl allyl carbonates (**2o** and **2p**) were well tolerated to deliver the expected products (**3ao-3ap**) in 65% yield with 85% ee and in 91% yield with 95% ee, respectively (Table 3, entries 14 and 15). When methyl crotyl carbonate was tested in this transformation, only the first allylation step occurred without further rearrangement probably due to the significantly reduced steric congestion, and the allylation product **3aq** was separated in 86% yield with 93% ee (Table 3, entry 16).

Table 3 Substrate scope study of allyl carbonates for sequential Ir-catalyzed allylation/2-aza-Cope rearrangement.[a]



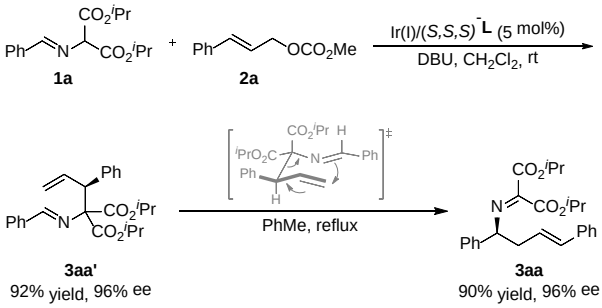


[a] Unless otherwise noted, all reactions were carried out with 0.30 mmol of **1a** and 0.20 mmol of **2** in 2 mL of CH_2Cl_2 at room temperature within 12-16 h, then heated in PhMe at 110 °C for 6 h. Yields refer to the isolated products after chromatographic purification. The ee value was determined by HPLC analysis. [b] (*R*,*R*)-THQ-Phos was used instead of (*S*,*S*,*S*)-**L**.

In order to reveal the stereochemical outcome of the current sequential Ir-catalyzed asymmetric allylation/2-aza-Cope rearrangement, the initial branch-selective allylation intermediate product **3aa'** was separated in 92% yield and 96% ee (Scheme 2). The absolute configuration of **3aa'** was deduced to be *S*-configuration based on the X-ray crystallography analysis of the corresponding *tert*-butyl analogue **3ca'**.[15] Therefore, the 2-aza-Cope rearrangement of (*S*)-**3aa'** occurred through six-membered chair-like transition state (Zimmerman-Traxler transition state[16]) to deliver the homoallylic amine (*S*)-**3aa** with well chirality transfer and excellent *E*/*Z*-geometry control.

To demonstrate the synthetic utility of this sequential protocol, gram-scale reaction of **1a** and **2a** was conducted under the optimized reaction condition to afford product **3aa** with 82% yield and 96% ee (Scheme 3, upside). Compound **3aa** was easily transformed to primary homoallylic amine **4** by treatment with hydroxylamine. The enantioenriched allylation intermediate **3aa'** obtained in the first step can be readily converted into compound **5** in good yield with maintained enantioselectivity (Scheme 3,

Scheme 2. Ir-catalyzed asymmetric allylation and proposed transition state for the ensuing 2-aza Cope rearrangement.



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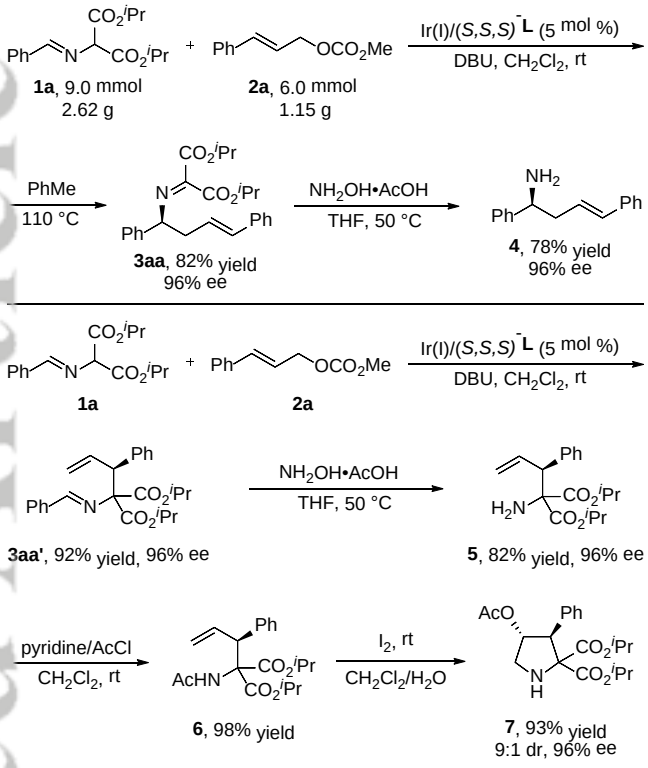
downside). Acetylation of **5** in the presence of pyridine furnished the compound **6**. Subsequently, I_2-promoted cyclization of **6** provided biologically important pyrrolidine **7** in high yield and high diastereoselectivity without erosion of enantioselectivity (93% yield, 9:1 dr, 96% ee).[17]

Scheme 3. Gram-scale synthesis and synthetic transformations.



Conclusions

In summary, we successfully developed a sequential Ir-catalyzed asymmetric allylation of readily available arylidene aminomalonates followed by a stereospecific 2-aza-Cope rearrangement, and a wide range of chiral homoallylic amines and derivatives could be obtained in high yield with good chirality transfer and excellent *E*/*Z*-geometry control. The sequential transformations can be performed at gram scale, and the branched allylation intermediate is readily converted into enantioenriched pyrrolidine derivative. Compared with our previously reported dual catalytic systems, the current protocol provides a simpler and more practical protocol to enantioenriched homoallylic amines.

Experimental

A flame dried Schlenk tube was cooled to rt and filled with N_2. To this flask were added $[Ir(COD)Cl]_2$ (0.005 mmol, 2.5 mol %), phosphoramidite ligand (*S,S,S*)-**L1** (0.01 mmol, 5 mol %), degassed THF (0.5 mL) and degassed *n*-propylamine (0.5 mL). The reaction mixture was heated at 50 °C for 30 min and then the volatile solvents were removed under vacuum to give a pale yellow solid. Then, DCM (2 mL), imines **1** (0.3 mmol, 1.5 equiv.), allylic carbonates **2** (0.2 mmol, 1 equiv.) and DBU (0.20 mmol) were added sequentially under N_2. The mixture was then stirred at rt for 12 h-16 h. Once allylic carbonate was consumed (monitored by TLC), the organic solvent was removed and the residue was purified by column chromatography to afford the desired allylation intermediate. The obtained intermediate was then dissolved in 2 mL toluene, sealed and stirred for 6 h at 110 °C. After removal of the solvent, the residue was purified by silica gel flash chromatography to afford the desired product **3**, which was then directly analyzed by HPLC to determine the enantiomeric excess.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2019xxxxx.

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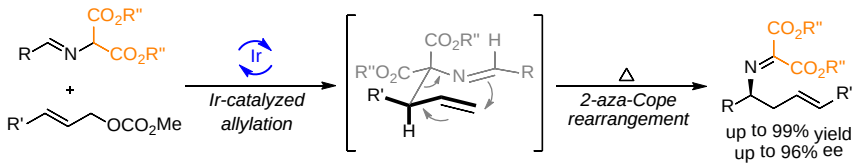

Ruo-Qing Wang,[a,§] Chong Shen,[a,§] Xiang Cheng,[a] Guo-Fei Wang,[a] Hai-Yan Tao,[a] Xiu-Qin Dong,*[a] and Chun-Jiang Wang*[a,b]

Sequential Ir-catalyzed asymmetric allylation/2-aza-Cope rearrangement of arylidene amino-malonates with allylic carbonates was successfully developed, and a variety of enantioenriched homoallylic amine derivatives were obtained in high yields with good chirality transfer and excellent *E/Z*-geometry control (up to 99% yield, 96% ee). Compared with previous dual catalytic system established for this transformation, the current mono metal catalytic system provides a simpler and more practical protocol employing the readily available starting materials.

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