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Stereodivergent synthesis *via* iridium-catalyzed asymmetric double allylic alkylation of cyanoacetate†

Chong Shen,^a Xiang Cheng,^a Liang Wei,^{ID a} Ruo-Qing Wang^a
and Chun-Jiang Wang^{ID *ab}

Methods that enable the rapid construction of multiple C–C bonds using a single catalyst with high diastereo- and enantio-control are particularly valuable in organic synthesis. Here, we report an Ir-catalyzed double allylic alkylation reaction in which bisnucleophilic cyanoacetate reacted successively with electrophilic π -allyl-Ir species, producing various *pseudo*-C₂-symmetrical cyanoacetate derivatives in high yield with excellent stereocontrol. More challenging sequential allylic alkylation/allylic alkylation with two distinct allylic carbonates that can deliver the corresponding products bearing three contiguous tertiary–quaternary–tertiary stereocenters was also developed by using a modified catalytic system, which is revealed to be associated with the *quasi*-dynamic kinetic resolution of the initially formed diastereomeric monoallylation intermediates. Notably, stereodivergence for this sequential process depending on a single iridium catalyst was successfully realized, and up to six stereoisomers could be predictably prepared by combining the appropriate enantiomer of the chiral ligand for the iridium catalyst and adjusting the adding sequence of two distinct allylic precursors.

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Introduction

The physiological or pharmacological properties of chiral compounds mainly depend on the interactions between such molecules and chiral environments created by enzymes/receptors in biological systems.¹ Hence, for biologically important compounds bearing multiple stereogenic centers, developing selective access to different enantio- and diastereomers to evaluate the corresponding biological activity is of great practical importance for pharmaceutical applications.² Although the efficacy of asymmetric catalysis has been thoroughly demonstrated for the construction of a tremendous amount of chiral skeletons, stereodivergent synthesis of as many as possible stereoisomers from the same starting material remains extremely challenging.³ For a given asymmetric transformation, while enantiodivergence could be realized through employing an enantiomeric pair of the chiral catalyst, controlling the relative configuration of the product to produce individual diastereomers is much more difficult. Specifically, one typical

diastereomer is usually inherently preferred and the complementary diastereomer(s) cannot be effectively constructed *via* the same strategy.⁴ To overcome the diastereoselective bias in the chiral induction process, diverse methodologies, such as the modulation of the structure of the catalyst and substrate, changing the reaction conditions (solvent, temperature, pressure, and additives) or using an entirely different catalytic system, have been developed in the past twenty years.^{5,6} Despite many important advances, serendipity is the most important factor in these findings and such strategies cannot be readily extended to the development of other stereodivergent transformations.

In comparison, the recently developed stereodivergent synthesis that can predictably induce stereodivergence has demonstrated to be a superior strategic alternative to traditional methods (Scheme 1) since the groundbreaking research work of Carreira in 2013.^{7,8} Two conceptually distinct methodologies have been disclosed for stereodivergent synthesis: dual catalysis involves the simultaneous activation of prochiral nucleophiles and allylic carbonates/alkynes with a synergistic catalytic system, exerting full control over the absolute/relative configuration in the coupling step (Scheme 1a);^{7,9} and single catalysis allows the use of a single catalyst to introduce multiple stereogenic centers sequentially in a multistep transformation (Scheme 1b).^{10,11} Numerous elegant studies have been reported in the field of stereodivergent synthesis *via* dual catalysis for the construction of biologically important chiral molecules.^{7–9} In sharp contrast, several daunting challenges such as the need for

^aEngineering Research Center of Organosilicon Compounds & Materials, Ministry of Education, College of Chemistry and Molecular Sciences, Wuhan University, Wuhan, 430072, China. E-mail: cjwang@whu.edu.cn

^bState Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Shanghai, 230021, China

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Scheme 1 Two conceptually distinct stereodivergent syntheses with dual catalysis (a) and single catalysis (b).

a multitasking catalyst and the potential matched/mismatched effects between the substrate and catalyst resulted in the applications of single catalysis in stereodivergent synthesis being largely unexplored. In 2016, Buchwald *et al.* developed the first example of a sequential reduction/hydroamination of enals/enones catalyzed by a chiral copper hydride catalyst for the stereodivergent synthesis of 1,3-aminoalcohols.¹⁰ Recently, Trost *et al.* developed a bimetallic Zn–ProPhenol-catalyzed enantioselective Mannich/aldol-type reaction of branched aldehydes, allowing the preparation of four stereoisomers of the corresponding 1,3-aminoalcohols.¹¹ Nonetheless, stereodivergent synthesis of highly functionalized and diversified

chiral scaffolds with single catalysis is still in its infancy and remains significantly challenging.

Iridium-catalyzed enantioselective allylic alkylation is a powerful methodology for carbon–carbon and carbon–heteroatom bond formation and constitutes great contributions in the field of stereodivergent synthesis *via* dual catalysis (Scheme 2a).¹² To date, most of the investigations focus on the incorporation of one allyl moiety into diverse nucleophiles with high branched selectivity. We anticipated that an Ir-catalyzed sequential allylic alkylation/allylic alkylation of one-site C-based bisnucleophilic reagents would provide a rapid access to complex structures with multiple stereogenic centers and functional groups that can be easily manipulated in downstream transformations. In addition, the use of an enantiomeric pair of the chiral iridium catalyst for each allylation step might permit the stereodivergent construction of the target products. However, such a process has only been sporadically realized by using bisnucleophiles with minimum steric hindrance such as Na₂S and NH₃,¹³ and the double allylation of prochiral bisnucleophiles remains undeveloped due to the inherent steric repulsion in the formation of an acyclic quaternary stereogenic center.¹⁴ Furthermore, it is unpredictable how the matched/mismatched effects of the chiral intermediate formed in the first allylation step with a chiral π -allyl-Ir complex facilitate/deteriorate the catalytic efficiency and the stereoselective control in the second step. Herein, we successfully alleviate these problems by presenting a single iridium-catalyzed stereodivergent synthesis of highly functionalized cyanoacetate bearing two tertiary and one all-carbon quaternary stereogenic centers, and the *quasi*-dynamic kinetic resolution¹⁵ of the



Scheme 2 Ir-catalyzed double-asymmetric allylic alkylation ((a) previous work) and stereodivergent double allylation ((b) this work).



monoallylated intermediate made the designed sequential allylic alkylation/allylic alkylation process highly diastereoselective. More importantly, up to six stereoisomers of the corresponding products could be efficiently obtained in high regio-, diastereo- and enantio-selectivity (Scheme 2b).

Results and discussion

In initial attempts to implement the proposed allylic alkylation/allylic alkylation sequence, we first evaluated the reaction of glycine-derived imine ester¹⁶ **2** with 2.2 equivalents of methyl cinnamyl carbonate **1a**. A synergistic Cu/Ir system which has proved to be efficient for stereodivergent allylation in our previous work^{9f} was utilized; however, none of the desired bisallylation product **6** could be detected. Instead, the reaction finished exclusively in the first allylation step, providing the corresponding **4** in 85% yield with poor diastereoselectivity (Table 1, entry 1). The variation of reaction parameters including increasing the reaction temperature or using stronger bases was unable to promote the generation of **6**. We speculated that the unfavorable steric congestion completely suppressed the second allylation step and a suitable bisnucleophile with sufficient nucleophilicity and less steric hindrance would be the linchpin for the design process. To verify this hypothesis, various potential bisnucleophiles were subjected to reaction with **1a**. Delightfully, when cyanoacetate **3** was selected as the reactant, the reaction proceeded smoothly using a single Ir(i)/(*R,R,R*)-**L2** catalyst along with triethylamine as the base, affording the bisallylation product **7a** in good yield with a 4 : 1 ratio of di/mono, 10 : 1 dr and 98% ee (entry 2). Switching the base to Cs₂CO₃ further advanced the catalytic efficiency, leading to full conversion of starting materials to desired **7a** quantitatively as an exclusive diastereomer (>20 : 1 dr) with maintained enantioselectivity (entry 3).

With reaction conditions for double allylic alkylation of cyanoacetate established, we first examined the substrate scope of this transformation (Table 2). A range of *para*- and *meta*-substituted cinnamyl carbonates bearing diverse functional groups were efficient Ir- π -allyl precursors, providing the desired

bisallylated cyanoacetate derivatives **7a–n** in high yield with excellent stereoselectivity (entries 1–14). *Ortho*-substituted cinnamyl carbonate was not a viable substrate, which is a known issue associated with Feringa-type ligands in Ir-catalyzed allylic alkylation reactions.¹² 2-Naphthyl allylic carbonate **1o** also reacted successfully with **3** to produce **7o** in 97% yield with >20 : 1 dr and 99% ee. A moderate yield and diastereoselectivity were observed for bulky 1-naphthyl substituted **1p** under the standard conditions due to the disfavored steric congestion. Using You's (*S,S*)-Me-THQphos¹⁷ as the chiral ligand instead of (*R,R,R*)-**L2** effectively improved the catalytic efficacy, giving **7p** in 81% yield with exclusive diastereoselectivity (>20 : 1 dr) and excellent enantioselectivity (>99% ee). In addition, the iridium catalysis showed a comparable level of stereoselectivity towards allylic carbonates bearing heteroaromatic groups, and the corresponding products **7q** and **7r** were achieved in >20 : 1 dr and 99% ee albeit with a moderate yield. Furthermore, the current system could be further extended to less reactive crotyl carbonate **1s**, affording **7s** in 72% yield with 7 : 1 dr and 95% ee. Switching the iridium precursor to [Ir(DBCOT)Cl]₂ significantly enhanced the reactivity and diastereoselectivity. The absolute configuration of *ent*-**7j** using Ir(i)/(*S,S,S*)-**L2** as the catalyst was unambiguously determined to be (*S,S*) by X-ray crystallographic analysis (CCDC 2096475†).

Having developed an efficient method to produce cyanoacetate derivatives bearing two identical allyl moieties, we attempted to further investigate the more challenging double allylic alkylation using different allylic carbonates for each step (Scheme 3). 4-Bromo-substituted cinnamyl carbonate **1d** and 2-naphthyl allyl carbonate **1o** were selected as the representative allyl precursors to react sequentially with cyanoacetate **3**. We anticipated that the selective interruption of the reaction process to avoid the above-mentioned *gem*-allylation is key to realizing the designed process. Based on this surmise, we first tested the reaction of **3** with 1 equivalent of **1d** under the standard conditions except for changing the base to weaker basic Et₃N. Indeed, the mono-allylation product could be isolated in 47% yield. The same catalytic system further initiated the following allylic alkylation with 1 equivalent of **1o** and thus

Table 1 Initial test to find an appropriate bisnucleophile to facilitate double allylic alkylation

1a

(**2**, R = N=CHPh; **3**, R = CN)

Cat.

Et₃N, CH₂Cl₂, 25 °C

[**4**, R = N=CHPh; **5**, R = CN]

1a, Cat.

Et₃N, CH₂Cl₂, 25 °C

[**6**, R = N=CHPh; **7a**, R = CN]

(*S,S_p*)-**L1**

(*S,S,S*)-**L2**

Entry ^a	cat.	di/mono	yield (%)	dr	ee (%)
1	Cu/ L1 + Ir/ L2	0:100 (6/4)	4 , 85	4 , 1:1	-
2	Ir/ L2	4:1 (7a/5)	7a , 75	7a , 10:1	7a , 98
3^b	Ir/ L2	100:0 (7a/5)	7a , 97	7a , >20:1	7a , 99

^a All reactions were carried out with 0.44 mmol of **1a** and 0.20 mmol of **2** or **3** in 2 mL of CH₂Cl₂. ^b Cs₂CO₃ was used as the base instead of Et₃N.



Table 2 Substrate scope for Ir-catalyzed asymmetric double allylic alkylation of cyanoacetate^a

^a All reactions were carried out with 0.2 mmol of **3** and 0.44 mmol of **1** in 2 mL of DCM. Yields refer to isolated yields. ee was determined by chiral HPLC analysis. ^b (*S,S*)-Me-THQphos was used as the chiral ligand. ^c [Ir(DBCOT)Cl]₂ was used as the catalyst precursor.



Scheme 3 Initial test for sequential allylic alkylation with two different allyl carbonates.



converted the isolated mono-allylation intermediate into the desired bisallylation cyanoacetate (*R,R,R*)-**8A** bearing three contiguous tertiary–quaternary–tertiary stereogenic centers in 92% yield. However, a mixture of inseparable diastereomers with a 1 : 0.25 : 0.1 : 0.08 diastereomeric ratio was detected through NMR analysis. We reasoned the unsatisfactory overall yield and diastereoselectivity to be as a result of (1) incomplete suppression of double allylation in the first step; (2) insufficient stereocontrol over the allyl stereogenic center by the Ir(I)/(*R,R,R*)-**L2** complex under slightly modified reaction conditions; (3) the mutual effects of substrate- and catalyst-controlled chiral induction on the quaternary stereogenic center in the second allylation step.

To validate our conjecture, the stereocontrol efficacy of iridium catalysis for the first allylation step was then systematically investigated (Table 3). We first isolated the mixture of diastereomeric monoallylation intermediates **5d** in 47% yield with an unsatisfactory diastereoselectivity (1.1 : 1 dr), which was caused by the easy epimerization of the tertiary stereogenic center at the α -position of compound **5d** under basic conditions. Furthermore, the enantioselectivity of the allyl stereogenic center was determined to be 90% ee by transforming **5d** into nitrile **9** through a LiCl-promoted Krapcho reaction (entry 1).¹⁸ An imperfect chiral induction by the Ir(I)/(*R,R,R*)-**L2** catalyst in the first allylation step would dramatically deteriorate the diastereoselectivity in the sequential process, and thus we set out to re-optimize the reaction conditions for this monoallylation reaction aiming to improve the chemical yield and enantioselectivity (see the ESI† for details). After screening various solvents and chiral phosphoramidite ligands, a moderate yield with a slightly higher enantioselectivity (93% ee for **9**) was obtained using Ir(I)/(*R,R,R*)-**L3** as the catalyst in THF at room temperature (entry 2). Replacing the base with DABCO and using two equivalents of **3** slightly enhanced the reactivity, giving compound **5d** in 56% yield (entry 3). Further variation of the reaction temperature indicated that a lower

temperature was beneficial to the current transformation, leading to a significant improvement in terms of both yield and enantioselectivity (entry 4). To conclude, the [Ir(cod)Cl]₂/(*R,R,R*)-**L3**/DABCO/THF system was chosen for the first allylic alkylation step. Additionally, the subsequent optimization of the second step identified the [Ir(cod)Cl]₂/(*R,R,R*)-**L3**/Cs₂CO₃/DCM system to be optimal (see the ESI† for details).

With the modified reaction conditions for the sequential double allylic alkylation in hand, we were particularly interested in advancing this method to stereodivergently assemble the stereoisomers of the cyanoacetate derivatives (Scheme 4). As described above, we have prepared (*R,R,R*)-**8A** by using Ir(I)/(*R,R,R*)-**L3** as the chiral catalyst for both steps (Scheme 4h). The enantiomeric (*S,S,S*)-**8A** could be easily obtained *via* the use of the (*S,S,S*)-**L3** ligand for the iridium catalyst (Scheme 4e). To prepare (*R,S,S*)-**8A**, we developed a modified protocol involving one chiral ligand switch in the sequential double allylation, that is, cyanoacetate **3** was first monoallylated with *para*-bromo cinnamyl carbonate **1d** using (*S,S,S*)-**L3** as the ligand, and the resultant α -monoallylation intermediate was isolated and then subjected to the second allylation conditions with 2-naphthyl allylic carbonate **1o** catalyzed by Ir(I)/(*R,R,R*)-**L3** (Scheme 4f). (*S,R,R*)-**8A** was then constructed efficiently by employing the same ligand-switch strategy except for using (*R,R,R*)-**L3** and (*S,S,S*)-**L3** as the chiral ligand for each step, respectively (Scheme 4g). Moreover, reversing the adding sequence of **1d**/**1o** along with the utilization of the same chiral ligand (*S,S,S*)-**L3** or (*R,R,R*)-**L3** for two sequential allylations could afford enantiomeric (*S,R,S*)-**8A** (X-ray, CCDC 2096476†) or (*R,S,R*)-**8A**, respectively, which are the opposite enantiomers of each other (Scheme 4a and d). Interestingly, combining the reversed adding sequence with the ligand-switch strategy as shown in Scheme 4b and c led to the generation of (*S,R,R*)-**8A** and (*R,S,S*)-**8A**, respectively, which could also be obtained with the protocol shown in Scheme 4g and f. Ultimately, by pairwise selection of the enantiomeric ligand and adding sequence of two distinct

Table 3 Re-optimization of the reaction parameters for monoallylation

Entry ^a	L/solvent/base	yield of 5d (%) ^b	ee of 9 (%) ^c
1	L2 /DCM/Et ₃ N	47	90
2	L3 /THF/Et ₃ N	48	93
3	L3 /THF/DABCO	56	94
4 ^d	L3 /THF/DABCO	68	99

^a All the reactions were carried out with 0.2 mmol of **3** and 0.1 mmol of **1d** in 2 mL of solvent. ^b Isolated yield. ^c Determined by HPLC analysis. ^d The reaction was performed at 0 °C.





Scheme 4 Stereodivergent synthesis of six accessible stereoisomers using an appropriate enantiomer of the chiral ligand for the iridium catalyst and adding sequence of two different allylic carbonates.

allylic carbonates, six of all eight stereoisomers of bisallylated cyanoacetate **8A** were predictably constructed in good overall yields (around 60%) with excellent stereoselectivities. The generality of the current stereodivergent synthesis *via* the single catalysis strategy was further extended to the preparation of six stereoisomers of **8B** (from **3, 1d** and **1n**) and **8C** (from **3, 1n** and **1o**) in synthetically useful yield with comparable levels of stereoselectivities.

Based on the experimental results, a plausible reaction pathway and transition states were proposed to rationalize the origin of the stereochemical outcome. As depicted in Scheme 5, Ir(I)/(S,S,S)-L3-catalyzed monoallylation with **1o** would produce

a mixture of diastereomeric *syn*-(2*R*,3*R*)-**5o** (in which the bulky substituents, Ar and CO₂tBu groups, reside in a *syn*-fashion) and *anti*-(2*S*,3*R*)-**5o** (in which the bulky substituents, Ar and CO₂tBu groups, reside in an *anti*-fashion), both of which could be readily interconverted under basic conditions through the enol form (*S*)-**10** due to the strong α -H acidity of **5o**. When using the Ir(I)/(S,S,S)-L3 complex as the chiral catalyst in the second step, both *syn*-(2*R*,3*R*)-**5o** and *anti*-(2*S*,3*R*)-**5o** were diastereomergently converted into the corresponding *syn-anti*-(*S*,*R*,*S*)-**8A** in a *quasi*-dynamic kinetic resolution (*quasi*-DKR) manner *via* the attack of the *Si*-face of the nucleophilic (*S*)-**10** to the *Re*-face of the electrophilic (*R*)-(S,S,S)- π -allyl-Ir species.^{19a,b}



Scheme 5 The rationale of the stereochemical outcome of stereodivergent synthesis.

Consequently, in the second carbon–carbon bond-forming step, the newly generated allylic stereogenic center had (*S*)-configuration (catalyst-control), and the original labile tertiary stereocenter in **5o** was transformed into a stable non-epimerized quaternary stereogenic center as (*R*)-configuration (substrate-control) (Scheme 5a). We reasoned that the energy-favored transition state **TS-1** dominated the generation of the relative *syn*-configuration between the first allylic tertiary stereocenter and the quaternary stereocenter. When using the Ir(I)/(*R,R,R*)-L3 complex as the chiral catalyst in the second step, the corresponding diastereomer *syn-syn*-(*S,R,R*)-**8A** was obtained in a similar *quasi*-DKR manner *via* the attack of the *Si*-face of (*S*)-**10** to the *Si*-face of (*S*)-(*R,R,R*)- π -allyl-Ir species,^{19c,d} in which the relative configuration between the first allylic tertiary stereocenter and the quaternary stereocenter also maintained as the observed *syn*-configuration (Scheme 5b). Similarly, the stereochemical outcome of *syn-syn*-(*R,S,S*)-**8A** and *syn-anti*-(*R,S,R*)-**8A**

generated from the manipulation procedures shown in Scheme 5c and d, respectively, could also be rationalized as a result of *quasi*-DKR of (*2R,3S*)-**5** and (*2S,3S*)-**5** *via* the transition state **TS-2**. In addition, the stereochemical outcomes of *syn-anti*-(*S,S,S*)-**8A**, *syn-syn*-(*R,S,S*)-**8A**, *syn-syn*-(*S,R,R*)-**8A**, and *syn-anti*-(*R,R,R*)-**8A**, which were obtained as shown in Scheme 4e–h using a reversed adding sequence of the two allylic carbonates, can be explained similarly (not shown in Scheme 5). Notably, the protocols in Scheme 4b/g and 4c/f provided the same stereoisomers *syn-syn*-(*S,R,R*)-**8A** and *syn-syn*-(*R,S,S*)-**8A**, respectively. The reaction model and the related plausible transition states shown in Scheme 5 also revealed that two additional isomers *anti-anti*-(*S,S,R*)-**8A** and *anti-anti*-(*R,R,S*)-**8A** cannot be generated *via* the current methodology probably due to the kinetically disfavored *anti-anti*-configuration, which is consistent with the experimental results.



Scheme 6 Preparation of *meso*-(*S,S,R*)-**7d** using the sequential double allylation protocol.



Scheme 7 Gram scale preparation of (S,S)-**7n** (a) and synthetic transformations (b).

According to the experimental results and rationale shown in Scheme 5b and c, we envisioned that a *meso*-bisallylation compound could be prepared through a sequential double allylation process in which two enantiomeric chiral ligands were respectively used in the first and the second allylation reaction with the same allylic carbonate as the π -allyl-Ir precursor. As expected, starting from cyanoacetate **3**, the relay Ir(I)/(S,S,S)-**L3** and Ir(I)/(R,R,R)-**L3** catalyzed double allylic alkylation with allylic carbonate **1d** produced *syn-syn*-selective *meso*-(S,S,R)-**7d** (X-ray, CCDC 2096474[†]) in 86% yield with exclusive diastereoselectivity (>20 : 1 dr), and no *anti-anti*-selective *meso*-isomer (S,r,R)-**7d** was observed (Scheme 6), which is fully consistent with the above analysis (Scheme 5b and c).

Next, gram-scale double allylic alkylation of **3** (3.0 mmol, 0.42 g) with **1n** (6.0 mmol, 1.57 g) catalyzed by the 5 mol% of Ir(I)/(S,S,S)-**L2** complex was conducted to show the practicability of the current method, and the desired product (S,S)-**7n** could be isolated in high yield with excellent yield and stereoselectivity (1.38 g, 90% yield, >20 : 1 dr and 99% ee) (Scheme 7a). The presence of multiple synthetically useful functional groups in bisallylated cyanoacetate enabled rapid access to a variety of highly functionalized complex molecules. As summarized in Scheme 7b, (S,S)-**7** could be converted to diverse enantioenriched building blocks **11–14** under standard chemistry. The hydrolysis of (S,S)-**7n** by TFA provided α -cyano carboxylic acid **11** in 81% yield, which could then be stereospecifically transformed into γ -butyrolactone derivative **12** in

57% yield with >20 : 1 dr and 99% ee through I₂-promoted lactonization. The absolute configuration of **12** was determined by X-ray analysis (CCDC 2096478[†]). Nitrile **13** was efficiently generated from **7n** via a Krapcho reaction in good yield with excellent stereoselectivity. In addition, the [Ir(COD)Cl]₂/DPPM catalyzed double hydroboration of (S,S)-**7o** successfully delivered the desired boronate **14**.

Conclusions

In conclusion, we have presented a highly efficient sequential allylic alkylation/allylic alkylation of cyanoacetate empowered by single iridium catalysis. Using an identical allylic carbonate as the electrophile in succession, a range of *pseudo-C*₂-symmetrical bisallylated cyanoacetates were constructed in high yield with excellent diastereo- and enantio-selectivity. The careful investigation and analysis of double allylic alkylation using two different allyl carbonates further demonstrated the single iridium catalysis in stereodivergent synthesis. By combining the appropriate enantiomer of the chiral ligand for the iridium catalyst with adjusting the adding sequence of two distinct allylic precursors, we were able to predictably prepare six of all eight stereoisomers of the corresponding products containing three contiguous tertiary–quaternary–tertiary stereocenters in good yield with excellent stereoselective control. In addition, a *quasi*-dynamic kinetic resolution process of the initially formed diastereomeric monoallylation intermediates was also clearly



revealed in the ensuing allylic alkylation step. Further investigations on the stereodivergent synthesis *via* single iridium catalysis, as well as the synthetic applications of this method to high-value molecules, are ongoing in our laboratory.

Data availability

All experimental and characterization data in this manuscript are available in the ESI.† Crystallographic data for compound (*S,S*)-**7j**, (*S,R,S*)-**8A**, *meso*-(*S,s,R*)-**7d**, (*3S,4S,5R*)-**12** have been deposited at the CCDC 2096474-2096476 and 2096478, respectively.

Author contributions

C.-J. W. conceived and designed the research. C. S., X. C., and R.-Q. W. performed the research. C.-J. W., L. W., and C. S. co-wrote the paper. All authors analysed the data, discussed the results, and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

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