Ligand-dependent, palladium-catalyzed stereodivergent synthesis of chiral tetrahydroquinolines†

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The most fundamental tasks in asymmetric synthesis are the development of fully stereodivergent strategies to access the full complement of stereoisomers of products bearing multiple stereocenters. Although great progress has been made in the past few decades, developing general and practical strategies that allow selective generation of any diastereomer of a reaction product bearing multiple stereocentres through switching distinct chiral catalysts is a significant challenge. Here, attaining precise switching of the product stereocentres, we develop a novel P-chirogenic ligand, i.e. YuePhos, which can be easily derived from inexpensive and commercially available starting materials in four chemical operations. Through switching of three chiral ligands, an unprecedented ligand-dependent diastereodivergent Pd-catalyzed asymmetric intermolecular [4 + 2] cycloaddition reaction of vinyl benzoxazinanone with α-arylidene succinimides was developed. This novel method provides an efficient route for the stereodivergent synthesis of six stereoisomers of pyrrolidines bearing up to three adjacent stereocentres (one quaternary center). Despite the anticipated challenges associated with controlling stereoselectivity in such a complex system, the products are obtained in enantiomeric excesses ranging up to 98% ee. In addition, the synthetic utilities of optically active hexahydrocarbazoles are also shown.

The chirality of a biologically active molecule can alter its physiological properties. Therefore, highly efficient access to and fully characterizing all possible stereoisomers of a chiral molecule is one of the fundamental challenges in organic synthesis, drug discovery and development processes. However, most asymmetric catalytic transformations afford products enantioselectively and diastereoselectively and only form one of the stereoisomers containing multiple stereocenters. Stereodivergent access to all possible stereoisomers of the products is incredibly difficult because diastereomeric preference is largely dominated by the inherent structural and stereoelectronic characteristics of substrates, while absolute conformation can be dictated by the choice of the chiral catalyst.1 In 2013, Carreira and co-workers addressed this limitation by introducing the concept of stereodivergent dual-catalytic synthesis, reporting the allylation of aldehydes in a diastereodivergent fashion by the synergistic reactivity of iridium and amine catalysts under acidic conditions.2 Soon after, Carreira,3 Zhang,4 Hartwig,5 Dong,6 Wang,7 Zi,8 Lee,9 and other groups10 reported using an appropriate combination of dual chiral catalysts in a series of elegant studies (Scheme 1A). Recently, chemists found, in some cases, that tuning non-chiral parameters, including solvents or additives, also controlled the stereoechemical outcomes through subtle perturbation of the key diastereomeric transition states.11 In 2018, You and co-workers reported a solvent-controlled palladium-catalyzed enantioselective dearomative formal [3 + 2] cycloaddition, affording stereodivergent synthesis of two diastereomeric tetrahydrofuranoindoles.12 However, a rapid and predictable way to access complete stereoisomers of products bearing multiple stereocentres (for example, three contiguous stereocentres) remains an unsolved challenge through switching of ligands. To the best of our knowledge, only two successful examples were reported by Buchwald and Zhang, in which eight stereoisomers were obtained through tuning catalysts and reactive substrates (Scheme 1B).13,14

In metal-catalyzed reactions, ligands can manipulate the reactivity and selectivity by affecting the steric and electronic properties of metal catalysts. Therefore, the design and development of new ligands to improve the utility, activity and selectivity of their related metal catalysts are greatly desired by organic chemists. Recently, our groups have synthesized a new and promising class of P-chiral ligands ZD-Phos (including Gaphos and Jiaphos), and their conformational rigidity and chemical robustness have endowed the structure and its
variants with outstanding activity and selectivity as well as excellent stereoccontrol features essential to asymmetric cycloaddition reactions. Inspired by these advances, we are interested in continuing the development of $P$-chiral ligands with new structural motifs in the search for new reactivity and selectivity to tackle current synthetic challenges. More recently, Sadphos has emerged as another superior chiral skeleton, owing to the pioneering contributions by Zhang. Thus its aminophosphine scaffold is envisaged to be introduced into our 1-phosphanorbornene framework (ZD-Phos). We aim to combine the advantages of the aforementioned two types of chiral motifs, thus developing a novel $P,P$-bidentate ligand. Thus the novel $P$-chiral ligands, called Yuephos, may show unique stereoselectivity in a metal-catalyzed asymmetric cycloaddition reaction (Fig. 1).

Scheme 1 Strategy for stereodivergent synthesis of different stereoisomers.

Table 1 Optimization of reaction conditions

| Entry | Ligands | Solvent | Yield (%) | dr (3a : 4a) | ee (%) |
|-------|---------|---------|-----------|-------------|--------|
| 1     | Yue-1   | EA      | 69        | >20 : 1     | 96 (S, R, S) |
| 2     | Yue-1'  | EA      | 64        | 4 : 1       | 33 (S, R, S) |
| 3     | Yue-2   | EA      | 73        | >20 : 1     | 95 (S, R, S) |
| 4     | Yue-3   | EA      | 60        | 6 : 1       | 80 (S, R, S) |
| 5     | Yue-4   | EA      | 44        | 3 : 1       | 85 (S, R, S) |
| 6     | Yue-5   | EA      | 62        | 14 : 1      | 90 (S, R, S) |
| 7     | L1      | EA      | 31        | >20 : 1     | 14 (S, R, S) |
| 8     | L2      | EA      | 42        | >20 : 1     | 73 (S, R, S) |
| 9     | L3      | EA      | —         | —           | —      |
| 10    | L4      | EA      | 64        | 1 : 15      | 77 (S, S, S) |
| 11    | L4      | DCM     | 89        | <1 : 20     | 87 (S, S, S) |
| 12    | L4      | DCM     | 89        | <1 : 20     | 86 (S, S, S) |
| 13    | L4      | DCM     | 87        | <1 : 20     | 88 (S, S, S) |
| 14    | L4      | DCM     | 85        | <1 : 20     | 92 (S, S, S) |

$^a$ Unless otherwise stated, reactions were performed with 1a (60 mg, 0.2 mmol) and 2a (26 mg, 0.1 mmol), in 1.0 mL of solvent at 15 °C for 72 h, and EA = ethyl acetate; DCM = dichloromethane. $^b$ Isolated yield after chromatography. $^c$ The diastereomeric ratios were determined by column chromatography. $^d$ Determined by HPLC analysis. $^e$ L4 (10 mol%) was used, Cs2CO3 (2.0 equiv.). $^f$ Reaction temperature: 0 °C. $^g$ Reaction temperature: −10 °C. $^h$ Reaction temperature: −20 °C.
The synthesis of all stereoisomers of fully substituted tetrahydroquinolines has been an important and challenging task in organic synthesis. However, to date, full control of absolute and relative stereochemical configuration of these molecules has remained an unmet synthetic challenge. Considering the potentiality of fully substituted chiral tetrahydroquinolines in drug discovery and stereodivergent synthesis, we envisioned that using our new palladium/ZD-Phos catalytic system may offer an efficient strategy for overcoming the challenges related to regio-, enantio-, and diastereo-selectivity. Herein, we report our studies on the unexplored stereodivergent synthesis of fully substituted tetrahydroquinolines through ligand-controlled, metal-catalyzed asymmetric annulation. Six possible stereoisomers bearing two tertiary and one quaternary stereocenters were easily synthesized in good yields with high enantio- and diastereo-selectivities from the same starting materials (Scheme 1C).

The new bisphosphorus ligands we report herein can be easily synthesized by a two-pot method with good yields (Scheme 2). Starting from the corresponding aldehyde and commercially available chiral amine, one-pot sequential reaction gave diastereomers Y1 and Y1 with 1 : 1 dr, which could be straightforwardly separated by column chromatography. The subsequent reduction using Raney Ni produced the final Yuephos in good yields. The absolute configuration of Yue1' was established by single crystal X-ray diffraction. Importantly, the ligands Yuephos can remain stable in air and moisture for more than one year.

With new Yuephos ligands in hand, we began our study by choosing vinyl benzoxazinanone 1a with z-phenylidene succinimide 2a as the model substrate, combined with the Pd2dba3·CHCl3/L complex as the catalyst. Details of [Pd] source and solvent screening can be found in the ESI (Table S1 and S2†). Notably, using Pd2dba3·CHCl3/Yuephos as the catalyst in ethyl acetate, the reaction proceeded smoothly, affording the desired product 3a in 69% yield with 96% ee and >20 : 1 dr (entry 1). It should be noted that Yuephos ligands were found to be efficient for this reaction, and the product 3a was obtained in good enantioselectivity with seemingly irregular yields and

Table 2  Scope of the substrates for the synthesis of (S, R, S)-3a

| Substrate | Product 3a | Yield (%) | ee (%) | dr |
|-----------|------------|----------|--------|----|
| 1a        | 3a         | 69       | 96     | 20 : 1 |

*a Reaction conditions: see Table 1, entry 1. The yield is isolated yield. The reaction was performed for 72 h.

Table 3  Scope of the substrates for the synthesis of (S, S, S)-4a

| Substrate | Product 4a | Yield (%) | ee (%) | dr |
|-----------|------------|----------|--------|----|
| 1a        | 4a         | 85       | 99     | 45 : 1 |

| Substrate | Product 4a | Yield (%) | ee (%) | dr |
|-----------|------------|----------|--------|----|
| 1a        | 4a         | 85       | 99     | 45 : 1 |

*b Reaction temperature: −30 °C.
diastereoselectivities (entries 2–6). Trost’s ligand (L1) and chiral diphosphine ligand (L2) promoted the reaction with good diastereoselectivity but in a low yield and poor enantioselectivity (entries 7–8). However, (R)-SegPhos (L3) failed to afford the desired product (entry 9). To our surprise, when the phosphoramidite ligand (L4) was used, the diastereoselectivity was reversed compared to that in Yuephos (entry 10). Thus, a diastereodivergent phenomenon induced by the chiral ligand was discovered. To further improve the yield and selectivity, various solvents and [Pd] sources were screened (Table S3 and S4 in the Supporting Information). Interestingly, (4-MeC₆H₄, 3-MeOC₆H₄, 2-MeC₆H₄, 4-FC₆H₄, 3-FC₆H₄, and 4-ClC₆H₄) were selected as the substrate giving the corresponding products 3o with well-controlled stereoselectivity (1:20–1 dr, 85% ee) (Table 2, 3o).

The reaction could be extended to α-arylidene succinimides containing different N-protected groups (such as 4-ClC₆H₄, 4-MeC₆H₄, and 3,4-Me₂C₆H₃), which provided the products with high levels of stereoselectivity (Table 2, 3p–3r). The absolute configuration (S, R, S) of 3c was unambiguously assigned by single-crystal X-ray analysis.

Compared with the Pd/Yue-1 complex, the reaction, using the Pd/L4 complex as the catalyst, proceeded smoothly to produce the diastereoisomer 4. As outlined in Table 3, most of these [4 + 2] cycloaddition reactions proceeded well, giving the corresponding (S, S, S) products in 42–92% yields with dr values ranging from 9:1 to >20:1 and ee values of up to 98%. Of particular note, (S, S, S)-4 and (S, R, S)-3 could be accessed with comparably high selectivities when using substrates containing H, 6-Me and 6-Br groups on benzene rings (Table 3, 4a–4c). Furthermore, the groups on N1 of vinyl benzoxazinanones have no apparent influence on the yield and stereoselectivity (Table 3, 4a vs. 4f). Substrates bearing either an electron-donating group (4-Me, 4-MeO, 3-MeO, 2-MeO, 4-ET, and 3,4-OE₂) or electron-withdrawing group (4-NO₂, 4-CN, 4-CF₃, 4-F, 4-Cl, and 3-Cl) on aryl rings provided 4 with good to excellent yields (56–87%), good diastereoselectivity (10:1 to >20:1 dr), and good to excellent enantioselectivity (84–97% ee) (Table 3, 4g–4l). In addition, naphthyl and thienyl-substituted α-arylidene succinimides 2s and 2t reacted with 1a to give 4s and 4t in...
Conclusions

In summary, we developed new P-chiral ligands Yuephos, which showed good performance for highly enantioenriched synthesis of tetrahydroquinolines. This protocol assembled three contiguous stereocentres (one quaternary centre), using vinyl benzoazinanones and α-arylidene succinimide substrates, in a highly selective, palladium-catalysed [4 + 2] cycloaddition reaction. Essential to our approach was highly effective ligand control, and by switching appropriate ligands, six diastereomers could be obtained with high diastereo- and enantioselectivity in most cases. This method represents a rare example of the stereodivergent synthesis of spiro compounds from the same set of starting materials. We believed that this work might be generally applicable to the development of other enantio- and diastereo-divergent cycloaddition reactions.

Data availability

Full experimental and characterization data is available in the ESI.

Author contributions

Z. D. and E.-Q. L. directed the project. Y. W. performed the experiments and analyzed the data.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

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