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# Diastereodivergent cis- and trans-fused [4 + 2] annulations of cyclic 1,3-dienes and 1-azadienes via ligand-controlled palladium catalysis $\dagger$ 

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#### Abstract

Despite the blossoming of reports of diastereodivergent synthesis over the past years, switchable control of the stereochemistry of the bridgehead atoms of the fused frameworks has been significantly underdeveloped. Here we disclose the ability of $\mathrm{Pd}^{0}-\pi$-Lewis base catalysis to finely reverse the concerted inverse-electron-demand aza-Diels-Alder cycloaddition reaction between cyclic 1,3-dienes and aurone-derived 1-azadienes. In contrast, the in situ-formed HOMO-energy-increased $\mathrm{Pd}^{0}-\eta^{2}$ complexes of cyclic 1,3-dienes underwent a cascade vinylogous Michael addition/allylic amination process with 1-azadienes. Moreover, judicious selection of chiral ligands allowed for switchable diastereodivergent $[4+2]$ annulations to be accomplished, resulting in the construction of both cis- and trans-fused tetrahydropyridine architectures in high yields with moderate to excellent stereoselectivity levels. A variety of acyclic 1,3-dienes and 1-heterodienes were also applied, and furnished a structural diversity of enantioenriched frameworks.


## Introduction

As different stereoisomers usually display distinct biological activities, precise construction of multiple optically active isomers has always been an attractive but challenging task in organic chemistry and the drug discovery field. ${ }^{1}$ Diastereodivergent synthesis, which enables producing diverse diastereomers from the same set of starting materials just by varying reaction conditions, has emerged as a flourishing area owing to its high efficiency and great versatility. ${ }^{2}$ Several strategies, including tuning the catalysts, ${ }^{3}$ ligands, ${ }^{4}$ solvents ${ }^{5}$ and additives, ${ }^{6}$ etc, ${ }^{7}$ have demonstrated to be useful for furnishing divergently many diastereomers with linear and cyclic structures. However, there have been few well-developed studies showing an ability to switch the stereochemistry of the bridgehead atoms in fused structures, and only a few examples have

[^0]been uncovered for constructing both cis- and trans-fused bicyclic or polycyclic frameworks (Scheme 1a). ${ }^{8}$

The application of cyclic alkenes as dienophile partners in a Diels-Alder cycloaddition reaction provides a very straightforward strategy to access fused skeletons; however, cis-fused products are usually obtained due to the inherent concerted

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Scheme 1 Diastereodivergent construction of cis- and trans-fused cyclic frameworks. (a) Diastereodivergent synthesis of various frameworks. (b) Uncatalysed inverse-electron-demand aza-Diels-Alder reaction. (c) Diastereodivergent $[4+2]$ annulations enabled by $\mathrm{Pd}^{0}-\pi$ Lewis base catalysis.

Table 1 Optimisation of catalytic conditions for diastereodivergent [4 +2 ] annulations ${ }^{a}$

${ }^{a}$ Unless noted otherwise, reactions were carried out with $\mathbf{1 a}(0.1 \mathrm{mmol})$, $2 \mathbf{a}(0.05 \mathrm{mmol}), \mathrm{Pd}_{2}(\mathrm{dba})_{3}(5 \mathrm{~mol} \%), \mathbf{L}(20 \mathrm{~mol} \%)$ in toluene $(0.5 \mathrm{~mL})$ at $60^{\circ} \mathrm{C}$ for 36 h under Ar. ${ }^{b}$ Yield of the isolated product. ${ }^{c}$ The ratio of $4 \mathrm{a} /$ $\mathbf{5 a}$, determined from ${ }^{1} \mathrm{H}$ NMR analysis of crude products. ${ }^{d}$ Determined from HPLC analysis on a chiral stationary phase. ${ }^{e} \mathbf{L} 7$ (10 mol\%). ${ }^{f}$ With $\mathrm{Pd}_{2}(\mathrm{dba})_{3}(2.5 \mathrm{~mol} \%) .{ }^{g}$ With $\mathbf{L 1 0}(10 \mathrm{~mol} \%) .{ }^{h}$ At $50^{\circ} \mathrm{C}$, for 72 h .
reaction mechanism. ${ }^{9}$ As illustrated in Scheme 1b, exclusive endo-selectivity was observed in the uncatalysed inverse-electron-demand Diels-Alder reaction between 1,3-cyclohexadiene 1a and aurone-derived 1-azadiene 2a, ${ }^{\mathbf{1 0}}$ resulting in the formation of cis-fused polycyclic product 3a in a moderate yield after heating the reaction mixture at $80{ }^{\circ} \mathrm{C}$ for 36 h . Recently, our group demonstrated that $\mathrm{Pd}^{0}$ could act as a $\pi$ Lewis base catalyst to increase the highest occupied molecular orbital (HOMO) energy of linear 1,3-dienes through $\eta^{2}$-coordination, thus promoting asymmetric Friedel-Crafts-type vinylogous addition to $N$-sulfonylimines enantioselectively. ${ }^{11}$ We envisaged that the $\operatorname{Pd}^{0}-\pi$-Lewis base catalysis would facilitate the asymmetric assembly of 1,3-cyclohexadiene 1a and 1-azadiene 2 a by generating the high-HOMO-energy complex I. The reaction of $\mathbf{1 a}$ with 1 -azadiene $2 \mathbf{a}$ indeed was promoted at a lower temperature $\left(60^{\circ} \mathrm{C}\right)$ in the presence of catalytic amounts of $\mathrm{Pd}\left(\mathrm{PPh}_{3}\right)_{4}$; intriguingly, endo-cis-3a was produced in a low
yield, whereas diastereomeric exo-cis cycloadduct 4a and unexpected trans-5a were predominantly produced (from ${ }^{1} \mathrm{H}$ NMR analysis). ${ }^{12}$ These experimental results suggested that $\mathrm{Pd}^{0}$ might render 1,3-cyclohexadiene 1a more nucleophilic upon $\pi$-Lewis base activation, which would reverse the synergistic cycloaddition to a cascade vinylogous Michael addition and diastereodivergent allylic amination process with 1 -azadiene $2 \mathbf{2 a}$, as proposed in Scheme 1c. In the current work, we carried out a detailed study of the diastereodivergent and asymmetric [4 + 2] annulations between cyclic 1,3-dienes and 1 -azadienes via ligand-controlled Pd catalysis. These annulations furnished both cis- and trans-fused tetrahydro-pyridine frameworks, structures having potential biological relevance, in a switchable and enantioenriched manner. ${ }^{13}$

## Results and discussion

Optimisation of conditions for the diastereodivergent [4+2] annulation reaction

As discussed above, using $\operatorname{Pd}\left(\mathrm{PPh}_{3}\right)_{4}$ successfully changed the reaction pathway of the reaction of 1,3-cyclohexadiene 1a with 1-azadiene 2 a from a concerted Diels-Alder process into a stepwise tandem vinylogous Michael addition/allylic amination sequence, making the potential diastereodivergent construction of both cis- and trans-fused cycloadducts possible when properly tuning the catalytic conditions. A series of chiral ligands in combination with $\operatorname{Pd}_{2}(\mathrm{dba})_{3}$ were investigated in order to realise the diastereo-divergent [4 + 2] annulations asymmetrically. While commonly used $S$-BINAP L1 and Trost's ligand $\mathbf{L} 2$ failed to promote the conversions at $60^{\circ} \mathrm{C}$ (Table 1, entries 1 and 2), using TADDOL-derived phosphoramidite ligand L3 pleasingly provided chiral exo-4a in moderate yield and enantioselectivity with complete diastereocontrol (entry 3). Other types of phosphoramidite ligands, namely $\mathbf{L 4} \mathbf{- L} \mathbf{7}$, derived from different chiral backbones were also screened (entries 47), and 4 a was finally obtained as a single diastereomer in outstanding yield and enantioselectivity by using a SPINOLbased ligand L7 (entry 7). ${ }^{14}$ High catalytic efficiency was still observed with lower ligand loadings (entry 8), but the yield was decreased significantly with $5 \mathrm{~mol} \%$ palladium (entry 9). In order to switch the diastereoselectivity, more chiral ligands were investigated. While Tang's chiral P-based ligand L8 and 1,2-aminoalcohol-derived ligand $\mathbf{L} 9$ delivered the products as diastereomeric mixtures (entries 10 and 11), ${ }^{15,16}$ employing commercially available $(R, R)$-Me-DuPhos monoxide L10 led to exclusive formation of trans-5a in an excellent yield with good enantiocontrol (entry 12). In order to further improve the enantioselectivity for $\mathbf{5 a}$, more reaction parameters involving ligands, solvents, additives and temperature were evaluated, but inferior results were generally observed (entries 13-21)..$^{17,18}$

## Substrate scope and limitations

With the optimised catalytic conditions in hand, we first investigated the substrate scope and limitations for asymmetric synthesis of cis-fused diastereomers 4 under the catalysis of $\mathrm{Pd}_{2}(\mathrm{dba})_{3}$ and ligand $\mathbf{L} 7$. As summarised in Scheme 2a, an array

(a) Substrate scope for constructing cis-diastereomers 4

4a $\mathrm{R}^{3}=\mathrm{Ph}, 95 \%, 98 \%$ ee
(1.0 mmol: $92 \%, 98 \%$ ee)
$4 b \mathrm{R}^{3}=3-\mathrm{MeOC}_{6} \mathrm{H}_{4}, 91 \%, 98 \%$ ee
$4 \mathrm{CR}^{3}=4-\mathrm{MeC}_{6} \mathrm{H}_{4}, 90 \%, 97 \%$ ee
$4 \mathrm{~d}^{3}=4-\mathrm{RC}_{6} \mathrm{H}_{4}, 99 \%, 98 \%$ ee
$4 e \mathrm{R}^{3}=2-\mathrm{Naphthyl}^{3}, 88 \%, 97 \%$ ee
$4 f \mathrm{R}^{3}=2$-Thienyl, $96 \%, 97 \%$ ee
$4 \mathrm{~g} \mathrm{R}^{3}=t$-Bu, $92 \%, 98 \%$ ee

$4 h R^{2}=M e, 99 \%, 94 \%$ ee $4 i R^{2}=C I, 98 \%, 93 \%$ ee


4j $89 \%, 97 \%$ ee


(b) Substrate scope for constructing trans-diastereomers 5
$\begin{aligned} \text { 5a } R^{3}= & \text { Ph, } 86 \%, 82 \% \text { ee } \\ \text { 5b } R^{3}= & 3-\mathrm{MeOC}_{6} \mathrm{H}_{4}, 74 \%, 77 \% \text { ee } \\ 5 \text { c } \mathrm{R}^{3}= & 4-\mathrm{MeC}_{6} \mathrm{H}_{4}, 88 \%, 82 \% \text { ee } \\ 5 \mathrm{~d} \mathrm{R}^{3}= & 4-\mathrm{FC}_{6} \mathrm{H}_{4}, 83 \%, 79 \% \text { ee } \\ & \quad \text { (Recryst. } 42 \%, 91 \% \text { ee) } \\ 5 e R^{3}= & 2-\text { Naphthyl, } 85 \%, 88 \% \% \text { ee } \\ \text { 5f } \mathrm{R}^{3}= & 2-\text { Thienyl, } 86 \%, 83 \% \text { ee }\end{aligned}$

$\mathbf{5 g} \mathrm{R}^{2}=\mathrm{Me}, 87 \%, 85 \%$ ee (Recryst. 42\%, 97\% ee) 5h $\mathrm{R}^{2}=\mathrm{Cl}, 85 \%, 87 \%$ ee (Recryst. $56 \%, 98 \%$ ee)


5i $81 \%, 70 \%$ ee
 (at $80^{\circ} \mathrm{C}$ )

1c $\quad$ 1d
messy reaction




Scheme 2 Substrate scope and limitations of diastereodivergent [ $4+2$ ] annulations. Unless noted otherwise, reactions were carried out with 1 ( $0.2 \mathrm{mmol}, 2.0$ equiv.), 1 -azadiene $2\left(0.1 \mathrm{mmol}, 1.0\right.$ equiv.), $\mathrm{Pd}_{2}(\mathrm{dba})_{3}(5 \mathrm{~mol} \%)$, and $\mathrm{L} 7(10 \mathrm{~mol} \%)$ or $\mathrm{L} 10(20 \mathrm{~mol} \%)$ in toluene ( 1.0 mL ) at $60{ }^{\circ} \mathrm{C}$ for 48 h under Ar .




Scheme 3 Investigation of more cyclic dienes or polyenes. (a) Reactions of cycloheptadiene 6. (b) Reactions of cycloheptatriene 10. (c) Reactions of cyclopentadiene 13.
(a)







Scheme 4 Investigation of linear 1,3-dienes and 1-heterodienes. (a) Assembly of linear 1,3-diene and 1-azadiene 2a. (b) Investigation of linear electron-deficient heterodienes.
of $N$-tosyl 1-azadienes 2 bearing diverse aryl, heteroaryl, and even tert-butyl groups underwent the [4+2] annulations with 1,3-cyclohexadiene 1a smoothly, affording the expected products $\mathbf{4 b} \mathbf{- 4} \mathbf{g}$ with excellent yields and stereoselectivity, even on a 1.0 mmol scale (for product 4a). In addition, varying the substituents on the benzofuran ring and $N$-protecting group had minimal effect on the reactivity and stereoselectivity, as comparably good results were attained for products $\mathbf{4 h} \mathbf{4 j}$. Moreover, diene partner 1b bearing a $2-n$-butyl group was also applicable, having reacted to form enantioenriched product $\mathbf{4 k}$ in a moderate yield, whereas complex reaction profiles were observed with 2-phenyl-1,3-cyclohexadiene 1c and 1-n-butyl-1,3cyclohexadiene $\mathbf{1 d}$.

The substrate scope for the synthesis of trans-fused diastereomers 5 was investigated next. As outlined in Scheme 2b, this synthesis was observed to be relatively inefficient when $\mathrm{Pd}_{2}(\mathrm{dba})_{3}$ in combination with $\mathbf{L 1 0}$ was used as the catalyst. The trans-fused products $\mathbf{5 b} \mathbf{b} \mathbf{5 i}$ were generally obtained in good yields and enantioselectivity but with exclusive
diastereoselectivity, whereas a significantly decreased yield and enantiocontrol were observed for alkyl-substituted product $\mathbf{5 j}$. And the alkyl-substituted 1-azadiene 2 g was not reactive. It should be noted that the optical purity levels of some products, such as $\mathbf{5 d}, \mathbf{5 g}$ and $\mathbf{5 h}$, could be readily improved by subjecting them to simple recrystallisation (Scheme 2b, data in parentheses). Moreover, ent-4a and ent-5a could be effectively furnished by using the combination of $\mathrm{Pd}_{2}(\mathrm{dba})_{3}$ with complementary ligands ent-L7 and ent-L10, respectively; thus four diastereomers could be smoothly produced just by tuning the ligands, demonstrating the versatility of the current method.

Additional types of cyclic dienes and even polyenes were investigated. As illustrated in Scheme 3a, 1,3-cycloheptadiene 6 could be successfully applied to diastereodivergent [4 + 2] annulations with 1 -azadiene 2a to produce cis-product 7 and trans-product 8 in moderate to good yields and stereoselectivity, by employing ligands $\mathbf{L 1 2}$ and L10, respectively. Interestingly, a $\beta$-H elimination, rather than $N$-allylic alkylation, occurred to
give adduct 9 in a moderate yield with fair enantioselectivity, when using TADDOL-derived phosphoramidite ligand $\mathbf{L 3}$; this result provided further support for the involvement of a stepwise process in the observed [4+2] reaction. Additionally, cisfused cycloadduct $\mathbf{1 1}$ was obtained from cycloheptatriene $\mathbf{1 0}$ and 1-azadiene 2 with excellent enantioselectivity and moderate diastereoselectivity when using $\mathrm{Pd} / \mathrm{L} 13$ as the catalyst, whereas $\beta$-H elimination product 12 was delivered with moderate results when using Pd/L14 (Scheme 3b). Furthermore, the assemblies of cyclopentadiene 13 and 1-azadienes 2 occurred successfully when $\mathrm{Pd} / \mathrm{L} 7$ was used as the catalyst, and exo-selective cycloadducts 14a-14c were furnished with high enantioselectivity and moderate diastereoselectivity (Scheme 3c).

The current catalytic strategy could be further expanded to acyclic dienes, further enriching the structural diversity of the frameworks constructed. As depicted in Scheme 4a, diastereodivergent $[4+2]$ annulations between linear terminal 1,3diene 15 and 1 -azadiene $2 a$ could be similarly realised via ligand-controlled palladium catalysis. Both exo- and endoselective cycloadducts 16 and 17 were efficiently constructed when using ligands L4 and L15, respectively, albeit with moderate enantioselectivity. Internal diene 18 exhibited higher reactivity with 1-azadiene 2 a when using $\mathrm{Pd} / \mathbf{L 1 0}$ as the catalyst, providing the exo-cycloadduct 19 in excellent yield and stereoselectivity, along with an inseparable regioisomer 20. Nevertheless, a chemoselective intramolecular iodoetherification of 19 was further carried out to generate tetracyclic product 21 with exclusive diastereocontrol. Apart from cyclic 1-azadienes 2 , linear 2-N-tosyliminoacrylate 22 and 1-oxadiene 24 were also reliable partners in the assemblies with linear 1,3-dienes, ${ }^{11 e}$ furnishing tetrahydropyridine product 23 and dihydropyran 25 , respectively, with moderate results. These experiments well verified the general compatibility of the $\pi$-Lewis base catalysis of $\mathrm{Pd}^{0}$ complexes for activating diene substrates, though some improvements remain to be made.

## Conclusions

Taking advantage of the unique vinylogous activation feature of $\operatorname{Pd}^{0}-\pi$-Lewis base catalysis, we successfully reversed the process of the concerted and endo-selective hetero-Diels-Alder cycloaddition reaction between cyclic 1,3-diene and electron-deficient aurone-derived cyclic 1-azadienes into a stepwise cascade vinylogous Michael addition/allylic amination sequence. As a result, the formal exo-selective and cis-fused [4+2] annulation products with polycyclic architectures were efficiently constructed with moderate to excellent enantioselectivity and diastereoselectivity levels by using a chiral SPINOL-derived phosphoramidite ligand. Moreover, the switchable diastereodivergent synthesis of challenging trans-fused [4+2] frameworks was also successfully accomplished by employing commercially available ( $R, R$ )-Me-DuPhos monoxide ligand. In addition, the current $\mathrm{Pd}^{0}-\pi$-Lewis base catalysis was applicable to the assemblies for a variety of acyclic 1,3-dienes and 1-heterodienes, further enriching the structural diversity and versatility of relevant cycloadducts.

## Data availability

The data that support the findings of this study are available in the ESI $\dagger$ or on request from the corresponding author.

## Author contributions

All authors contributed to the writing of the manuscript and have given approval to the final version of the manuscript.

## Conflicts of interest

There are no conflicts to declare.

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17 For more condition screenings, see the ESI $\dagger$
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