Natural product inspired chiral ligand design: Aloperine induced asymmetric hydroarylation of ketimines under Pd catalysed conditions

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Abstract: A naturally occurring alkaloid aloperine was utilized as a core chiral skeleton for the development of new ligands. Using these chiral 1,3-diamine ligands, a Pd catalysed asymmetric hydroarylation of ketimines was reported. A range of chiral sulfonfyl amides were prepared in high yields and enantioselectivities. The stereoselectivity and structure relationships of aloperine has been studied by the introduction of various substituents. These discoveries would provide a new future development for natural product inspired chiral ligand design and developments.

Mother nature prepares molecules in great complexity with both constitutional and dimensional information.1 Among vast varieties of natural products, alkaloids are one of the most abundant and well-studied classes of chemical entities which have been very well explored in medicinal chemistry. The key feature of these natural products is the heteroatom. Therefore, these amines or amides have also been considered as catalysts in molecular engineering.2 Typical examples including cinchona alkaloids, sparteine family, brucine analogues have attracted great attention in the past few decades due to their unique structures. As shown in Fig. 1, cinchona alkaloid L1, has shown a flat quinoline jointed with a chiral amino alcohol moiety which had been widely used in organocatalysis as well as metallocatalysis, is commonly recognized as one of the privileged chiral catalyst/ligand.3 Numerous asymmetric transformations including reduction,
oxidation, addition, cyclization and substitution reactions have been systematically studied using readily available or functionally modified cinchona alkaloids.\(^4\)

Sparteine L\(_2\), an alkaloid having a tetracyclic ring system with quinolizidine and bispidine hybrid in an elegant butterfly shape, has also been utilized as a chiral inducing reagent in the past few decades. More interestingly, after over 10 years’ shortage, currently both enantiomers (\(\text{--}\))-sparteine and (+)-sparteine are available in the market. Before 2010, (\(\text{--}\))-sparteine was beautifully demonstrated as a powerful ligand in organolithium chemistry.\(^5\) More recently, both (+)-sparteine and (\(\text{--}\))-sparteine were utilized and transition metal involved Negishi type of coupling reactions were also developed.\(^6\) Catalysis using sparteine with transition metals such as Ni,\(^7\) Cu,\(^8\) Zn\(^9\) and Pd\(^10\) were also studied briefly comparing to large number of examples shown in carbanion chemistry.

Brucine L\(_3\), belonging to the \textit{Strychnos} alkaloids, structurally complicated with six fused heterocyclic ring systems, has been used as chiral resolving agents and ligands for decades.\(^11\) Within brucine family, the corresponding diol makes wider applications in asymmetric synthesis, such as cycloaddition reactions, aldol-type addition reactions, and Friedel–Crafts alkylation reactions.\(^12\)

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\[\text{Aloperine L}\(_4\), belonging to lupinine alkaloids family, was isolated from \textit{Sophora alopecuroides} L, which has shown various pharmacological activities with potential treatments for skin hypersensitivity, tumor and inflammatory disorders.}\]^13\]

\[\text{The total synthesis of this interesting consecutive multi-cyclic chiral diamine had been demonstrated by Overman in 1999 and by Passarella/Riva in 2004.}\]^14\]

\[\text{The bridged chiral diamine however had never been considered and used in organic synthesis.}\]
Looking at the molecular skeleton, aloperine shares a similar bridged tetracyclic structure with (+)-sparteine L2. These may provide this natural product skeleton an opportunity as a chiral ligand in asymmetric synthesis. With our continuous interests in the construction and utilization of heterocycles, we herein report the first asymmetric synthesis employing natural product aloperine and derivatives.

As chiral diamine ligands, (–)-sparteine L6 and (+)-sparteine L2 both are commercially available have been well studied in asymmetric synthesis (Fig. 2). N-Me (–)-sparteine surrogates L5 and L7 have been prepared through total synthesis by Lesma and Silvani. In deprotonation substitutions reactions of N-Boc pyrrolidine, diamine L7 had shown excellent asymmetric induction (94% ee) similar to (–)-sparteine (97% ee) while L5 only gave the product in 31% yield with disappointing 21% ee. Simultaneously, O’Brien reported a semi-synthesis for accessing (+)-sparteine surrogate L8, L9 with similar observation. With experimental results and computational studies by Kozlowski, O’Brien and Breuning, the stereogenic centre in the chiral quinolizidine predominantly contribute to the stereocontrol in asymmetric induction. Very similar to (+)-sparteine surrogate L8, natural product aloperine L4 with quinolizidine ring D configuration identical to (+)-sparteine surrogate L8 may provide low enantioselectivity when using in asymmetric synthesis. Also in the molecule, both chiral amines are involved in the reaction with a secondary amine and a tertiary amine. Shifting stereocontrol may provide good asymmetric induction if the secondary amine could be the key coordinator. Therefore, we propose to tune the binding affinity by the introduction of substituents modulate the N coordination electronically and sterically.
To prove the concept, a number of substituted-aloperine derivatives were prepared straightforwardly in good yields. As shown in Fig. 3, aloperines L10–L14 were successfully obtained and are ready for the evaluation in asymmetric transformations.

With aloperine and the derivatives in hands, we commenced our studies with the reaction of arylboronic acids and cyclic sulfonyl-ketimines under palladium catalysed conditions at 90 °C in trifluoroethanol. These type of transformations have been studied with both Rh and Pd catalysts. Privileged chiral ligands such as Pyrox, BINAP and Phox have been evaluated. In our research, a number of common chiral ligands were tested under the reaction conditions. When reaction was treated with commercially available (S)-BINAP L15 as ligand, the corresponding product sulfonamide 3a was isolated in good yield and enantioselectivity (86%, 8:92 er as shown in Scheme 1). Using cinchona alkaloid quinine L1, the desired product was obtained in low yield and nearly none enantioselectivity. (+)-Sparteine L2 was also tested under the conditions, the
reaction proceeded smoothly to give the product with 92% yield and 93:7 er with R-configuration. Matrine L16, one of the lupanine alkaloids in *Sophora alopecuroides* L\(^{22}\) was also employed as ligand under our condition, the product was isolated in good yield but low enantioselectivity (80% yield, 58:42 er). Interestingly, aloperine L4 has shown good potential in this transformation with product produced in 86% yield and 71:29 er, the stereocontrol seemed to be under both N atoms. While aloperines L10 and L11 bearing electronically withdrawing groups have shown poor stereoselectivity as the N atom on the quinolizidine ring predominantly contributed to the stereoselectivity outcome. Ally group protected aloperine L12 has shown good enhancement on the enantioselectivity comparing to the corresponding NH aloperine. As expected, N-butyl derivative was an excellent ligand under the conditions providing the product with excellent yield and enantioselectivity (99%, 99:1 er, R-configuration). The N-benzyl aloperine L14, similar to N-Bu aloperine L13, gave the same product in 99% yield and 97:3 er. As expected in our proposal, substituents with electron-withdrawing effect providing reactions with low yields and disappointing enantioselectivity, on the other hand, aloperines with N-electron donating groups are good ligands in this type of reactions.

**Scheme 1** Screening of chiral ligands. Reaction conditions: sulfonyl-ketimines 1a (0.2 mmol), phenylboronic acid 2a (0.8 mmol), Pd(TFA)\(_2\) (5 mol%), L (20 mol%), TFE (1 mL), 90 °C, 12–24 h.

Different temperatures, catalyst/ligand ratios and solvent were screened based on the basic conditions. Low reaction temperature caused the low conversion therefore, decrease in yields (entries 1–3, table 1). And lower ligands loading
didn’t influence the reaction in yields but slightly in enantioselectivity (entries 3–5, table 1). Reactions in the solvents of DCE and dioxane provided good enantioselectivities but low yields (entries 6 and 7, table 1) while ethanol and water were moderate solvents for the reaction (entries 8 and 9, table 1). The polar aprotic DMF was failed to form the product in the reaction, this might be caused by the strong coordinating effect of DMF molecules.

**Table 1. Condition Screening.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>T (°C)</th>
<th>Solvent</th>
<th>Cat.:L11&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield</th>
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<tr>
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<td>TFE</td>
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<td>89</td>
<td>99:1</td>
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<tr>
<td>3</td>
<td>90</td>
<td>TFE</td>
<td>5:20</td>
<td>99</td>
<td>99:1</td>
</tr>
<tr>
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<td><strong>90</strong></td>
<td><strong>TFE</strong></td>
<td><strong>5:10</strong></td>
<td><strong>99</strong></td>
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<tr>
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<td>97</td>
<td>95:5</td>
</tr>
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<td>20</td>
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<td>75</td>
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<td>DMF</td>
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<td>-</td>
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<tr>
<td>11</td>
<td>90</td>
<td>TFE</td>
<td>1:2</td>
<td>36</td>
<td>93:7</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conditions: sulfonyl-ketimines 1a (0.2 mmol), phenylboronic acid 2a (0.8 mmol), Pd(TFA)<sub>2</sub> (1–5 mol%), L13 (2–20 mol%), TFE (1 mL), 50–90 °C, 12 h.  
<sup>b</sup> the ratio of catalyst and ligand.

With the optimized reaction conditions in hand, arylboronic acids bearing substituents with different electronic and steric characteristics were employed to test the reaction scope, and all the tested arylboronic acids worked well furnishing the products 3a–3m in good to excellent yields (72–99%) with good to high ers (96:4–99.5:0.5 ers). Generally, electronic effects influenced the yields
other than enantioselectivities (3e, 3f, 3h) while bulky substituents were well tolerated (3l, 3m).

**Scheme 2** Substrates scope of boronic acids. Reaction conditions: sulfonyl-ketimines 1a (0.2 mmol), phenylboronic acid 2 (0.8 mmol), Pd(TFA)$_2$ (5 mol%), L13 (10 mol%), TFE (1 mL), 90 °C, 12–24 h.

Next, we examined the substrates with substituents on the cyclic sulfonyl-ketimines. Reactions with both electron rich and electron deficient substituents all gave the corresponding products 3n-3w in excellent yields and enantioselectivity.
Scheme 3 Substrates scope of cyclic sulfonyl-ketimines. Reaction conditions: sulfonyl-ketimines 1 (0.2 mmol), phenylboronic acid 2 (0.8 mmol), Pd(TFA)$_2$ (5 mol%), L13 (10 mol%), TFE (1 mL), 90 °C, 12–24 h.

Gram scale reaction was also carried out. We were pleased to find that this reaction was very robust and chiral sulfonamide 3a was prepared in 1.65 grams with 95% yield and 99:1 enantiomeric ratio (eq. 1, Scheme 4). The ring opening of the sulfonyl amide product 3a with LiAlH$_4$ was also accomplished, and the phenolic amine 4 was formed in 82% yield with slight enantiomeric purity loss. The chiral hydroxyl amine 4 could be potentially utilized also as chiral ligand according to the literature precidents.\(^{23}\)

Scheme 4 Gram scale reaction and ring opening reaction.
In conclusion, we have developed the first application of lupinine alkaloid aloperine in asymmetric synthesis incorporated with palladium catalyst. The different binding affinity of palladium catalyst to the two N atoms in the diamine ligands may determine the chiral induction in the reaction, and a range of sulfonyl amides were successfully synthesized in good yields and enantioselectivities. The detailed mechanistic study is still ongoing.

**Conflicts of interest**

There are no conflicts to declare.

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**Notes and references**


