Palladium-catalyzed three-component tandem cyclization of buta-2,3-dien-1-ol, aryl iodides, and imines: an efficient protocol for the synthesis of oxazolidine derivatives†

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An efficient three-component tandem cyclization reaction for the synthesis of highly substituted oxazolidines was achieved through the Pd0-catalyzed cyclization of buta-2,3-dien-1-ol with aryl iodides and imines. A range of R1 and R2 functional groups is well-tolerated while affording cyclization products in moderate yields and with moderate to high diastereoselectivities.

Introduction

Multifunctional heterocyclic compounds play an essential role in organic and medicinal chemistry, as well as in drug discovery. Notably, nearly 70% of marketed drugs contain heterocycles. Oxazolidine rings are common pharmacophores that comprise potent antitumor tetrahydroisoquinoline-based natural products including quinocarcin (Fig. 1, I) and tetrazomine (Fig. 1, II). In addition, chiral oxazolidines are used as chiral auxiliaries (Fig. 1, III) and chiral ligands (Fig. 1, IV) in a variety of asymmetric transformations. Oxazolidines are also commonly utilized as prodrugs for improving the pharmacokinetic profile of certain β-amino alcohol pharmacophores.

For instance, the anticancer drug doxorubicin (Fig. 1, V) could be transformed into the oxazolidine prodrug VI to increase tumor response and minimize side effects, especially the treatment-limiting cardiotoxicity associated with doxorubicin therapy. Accordingly, the development of new methodologies for the synthesis of oxazolidines has garnered considerable attention.

Recently, Yoon et al. developed an efficient method for synthesizing oxazolidines through the iron- or copper-catalyzed aminohydroxylation of olefins (Scheme 1, Eq (1)). Jarvo further demonstrated the stereoselective and stereospecific syntheses of oxazolidines using catalysts with differing rates of allylmetal isomerization (Scheme 1, Eq (2)). Zhang investigated the [3 + 2] cycloaddition of azomethine ylides with carbonyl compounds for the synthesis of oxazolidines (Scheme 1, Eq (3)). More...
recently, Zhang explored a new organocatalytic strategy to synthesize oxazolidines through the Pd-catalyzed asymmetric decarboxylative cycloaddition of vinyl epoxides (VECs) with imines in the presence of chiral ligands (Scheme 1, Eq (4)). Therefore, the development of operationally simple and efficient synthetic approaches towards oxazolidines using readily available and stable starting materials is desired.

Multi-component reactions (MCRs) involving domino processes have emerged as powerful tools for the synthesis of molecules, including heterocyclic compounds, with efficiency, atom-economy, and diversity from simple substrates. In addition, functionalized allenes have been shown to be efficient starting materials for the synthesis of potentially useful carbones and heterocycles. Inspired by the synthesis of 1,3-oxazolidines from the cycloaddition of imines and vinyl epoxides (Scheme 1, Eq (4)), we hypothesized that other substrates, such as terminal β-allenols instead of vinyl epoxides or VECs, could be involved in the Pd0-catalyzed reaction of organic halides and imines without the necessity of a chiral ligand, which would allow for the formation of oxazolidine derivatives (Scheme 1, Eq (5)). Towards that end, we developed a novel and efficient route towards 1,3-oxazolidines via the cycloaddition of buta-2,3-dien-1-ol (1a) with aryl iodides and imines by varying the reaction conditions.

Results and discussion

Based on literature precedent, we set out to test the model reaction of buta-2,3-dien-1-ol (1a) with iodobenzene (2a) and imine (3a) in the presence of 5 mol% of [Pd(PPh3)4] at 80 °C, as shown in Table 1. The reaction in THF with K2CO3 as the base afforded oxazolidine 4aa in 23% yield with a dr of 3 : 1 (Table 1, entry 1). In order to improve the yield and stereoselectivity, different bases, solvents, and additives were tested. Among the tested bases, CsF and Cs2CO3 resulted in higher efficiencies with 50% and 38% yields, respectively (Table 1, entries 4–5), while Na2CO3 only gave the product in a trace yield (Table 1, entry 3). Polar solvents such as DMSO and DMF resulted in moderate stereoselectivity with a >25 : 1 dr (Table 1, entries 9 and 11). Less polar solvents such as toluene decreased the diastereoselectivity to 8 : 1 and resulted in an 18% yield (Table 1, entry 7). When the reaction was conducted in dioxane, 4aa was obtained in 50% yield with a >30 : 1 dr (Table 1, entry 10).

Next, the reaction temperature was examined. Upon lowering the temperature to 40 °C, the conversion dramatically dropped to only 10%, even when the reaction time was extended to 48 h. Higher temperatures (100 °C) accelerated the reaction rate without any increase in the yield (Table 1, entries 10 and 15). On the basis of previous studies, various additives were tested (Table 1, entries 12–13). Among them, the phase-transfer catalyst n-Bu4NBr had no dramatic effect on the stereoselectivity. The Lewis acid Cu(OTf)2 did not improve the yields, but the cis/trans ratio decreased to 10 : 1. An increase in the molar amount of imine 3a from 1.2 to 3.0 equiv. also gave a similar result (Table 1, entries 1 vs. 2, 15 vs. 16). Higher palladium concentrations (from 5 mol% to 50 mol%) was tried in order to improve the yield, but the yield did not increase (Table 1, entry 17). Overall, the best results were obtained when 3.0 equiv. of

![Table 1](image)

| Entry | Base | Additive | Solvent | Temp (°C) | Time (h) | Yield (%) | dr (cis/trans) |
|-------|------|----------|---------|-----------|----------|-----------|---------------|
| 1     | K2CO3| —        | THF     | Reflux    | 15       | 23        | 3 : 1         |
| 2     | K2CO3| —        | THF     | Reflux    | 15       | 25        | 3 : 1         |
| 3     | NaN2CO3| —       | THF     | Reflux    | 15       | Trace     | —             |
| 4     | Cs2CO3| —        | THF     | Reflux    | 12       | 38        | 10 : 1        |
| 5     | CsF  | —        | THF     | Reflux    | 10       | 50        | 15 : 1        |
| 6     | CsF  | —        | CH3CN   | Reflux    | 10       | 48        | 20 : 1        |
| 7     | CsF  | —        | Toluene | 80        | 10       | 18        | 8 : 1         |
| 8     | Cs2CO3| —       | Dioxane | 80        | 12       | 41        | >30 : 1       |
| 9     | CsF  | —        | DMSO    | 80        | 12       | 43        | 25 : 1        |
| 10    | CsF  | —        | Dioxane | 80        | 10       | 50        | >30 : 1       |
| 11    | CsF  | —        | DMF     | 80        | 10       | 45        | 25 : 1        |
| 12    | CsF  | A        | Dioxane | 80        | 10       | 48        | >30 : 1       |
| 13    | CsF  | B        | Dioxane | 80        | 10       | 50        | 10 : 1        |
| 14    | CsF  | —        | Dioxane | 40        | 10       | 48        | —             |
| 15    | CsF  | —        | Dioxane | 100       | 8        | 45        | >30 : 1       |
| 16    | CsF  | —        | Dioxane | 80        | 10       | 49        | >30 : 1       |
| 17    | CsF  | —        | Dioxane | 80        | 10       | 49        | >30 : 1       |

*a Reaction conditions: under a N2 atmosphere, 1a (0.35 mmol, 1 equiv.), 2a (0.42 mmol, 1.2 equiv.), 3a (0.42 mmol, 1.2 equiv.), [Pd(PPh3)4] (0.018 mmol, 5 mol%), base (1 mmol, 3 equiv.), solvent (3.0 mL). *d Determined by 1H NMR. *c = n-Bu4NBr (5 mol%), B = Cu(OTf)2 (5 mol%). *f Imine 3a (3.0 equiv.) was used. / [Pd(PPh3)4] (20 mol% or 50 mol%) was used.
CsF was used as the base in the presence of 5 mol% [Pd(PPh₃)₄] in dioxane at 80 °C.

Under the optimized reaction conditions, the scope and limitations of the transformation were evaluated for the reaction of 1a with various imines 3; the results are listed in Table 2. Tandem reactions with imines derived from arylaldehydes with different steric and electronic features proceeded smoothly to afford the corresponding oxazolidines 4 in moderate yields and diastereoselectivities (Table 2, entries 1–14). The position of the substituents on the aryl ring affected the reactivity. For example, p-fluorophenyl-substituted 3f afforded the desired cycloaddition product 4af in 48% yield with a dr of 10 : 1 under the optimized conditions (Table 2, entry 6). In contrast, o-fluorophenyl-substituted 3g exhibited a decreased conversion with low diastereoselectivity, indicating that o-substitution on the aryl ring is unfavorable (Table 2, entry 7). The reaction efficiency and diastereomeric ratio decreased dramatically when multiple-halogen atoms were present on the aryl ring, implying that stereospecific blockade groups have a negative effect on the cycloaddition reaction (Table 2, entries 10 and 11). Imines 3l and 3m, derived from 2-formylthiofururan and furfural, were also suitable substrates for the cycloaddition and furnished the corresponding oxazolidines in 47% and 43% yields, respectively (Table 2, entries 12–13). However, imine 3o (R¹ = 2-pyryrol) gave the product 4ao in only a trace yield, indicating that it was significantly less reactive than 3l (R¹ = 2-thienyl) and 3m (R¹ = 2-furyl). Gratifyingly, (E)-N-mesy imine 3n was a viable substrate in this transformation, affording the product in 45% isolated yield under the standard conditions. When using imines 3p with phenyl or p-methoxy phenyl groups at nitrogen, the target product was not detected, which suggesting that imines with electron-withdrawing groups at nitrogen was necessary in this reaction. The structures and relative stereochemistries of the products were established by X-ray crystallography analysis of 4aa as the 2,4-cis-isomer (Fig. 2), and those of the other products were assigned by analogy.

After the successful cycloaddition of 1a and iodobenzene 2a with various imines, we subsequently turned our attention toward the cycloaddition of 1a and (E)-N-benzylidenemethanesulfonamide 3a with various aryl iodides; the results are summarized in Table 3. In general, aryl iodides bearing electron-withdrawing (Table 3, entries 4–5) or electron-donating groups (Table 3, entries 2–3) afforded the corresponding oxazolidines in moderate yields and diastereoselectivities under identical conditions. Furthermore, the incorporation of multiple-halogen or strong EWGs on the phenyl ring decreased the

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**Table 2** The Pd²-catalyzed three-component tandem cyclization reaction of 1a, iodobenzene 2a, and different imines

| Entry | 3 | 4 Yield (%) | dr (cis/ trans) |
|-------|---|-------------|-----------------|
| 1     | 3a (R¹ = Ph) | 4aa 50 | >30 : 1 |
| 2     | 3b (R¹ = p-MeC₆H₄) | 4ab 55 | 15 : 1 |
| 3     | 3c (R¹ = p-MeO₂CC₆H₄) | 4ac 52 | >30 : 1 |
| 4     | 3d (R¹ = m-MeC₆H₄) | 4ad 45 | 10 : 1 |
| 5     | 3e (R¹ = p-ClC₆H₄) | 4ae 51 | 8 : 1 |
| 6     | 3f (R¹ = p-FC₆H₄) | 4af 48 | 10 : 1 |
| 7     | 3g (R¹ = o-FC₆H₄) | 4ag 30 | 3 : 1 |
| 8     | 3h (R¹ = o-C₆H₄) | 4ah 28 | 5 : 1 |
| 9     | 3i (R¹ = p-BrC₆H₄) | 4ai 54 | 4 : 1 |
| 10    | 3j (R¹ = 2,4-(F)₂C₆H₄) | 4aj 25 | 3 : 1 |
| 11    | 3k (R¹ = 2,4-(F)₂C₆H₄) | 4ak 18 | 2 : 1 |
| 12    | 3l (R¹ = 2-thienyl) | 4al 47 | 4 : 1 |
| 13    | 3m (R¹ = 2-furyl) | 4am 43 | 2 : 1 |
| 14    | 3n (R¹ = Ph) | 4an 45 | 4 : 1 |
| 15    | 3o (R¹ = 2-pyryrol) | 4ao Trace | — |
| 16    | 3p (R¹ = Ph) | 4ap Trace | — |

* Reaction conditions: under a N₂ atmosphere, 1a (0.35 mmol, 1 equiv.), 2a (0.42 mmol, 1.2 equiv.), 3a (0.42 mmol, 1.2 equiv.), [Pd(PPh₃)₄] (0.018 mmol, 5 mol%), CsF (1 mmol, 3 equiv.), dioxane (3.0 mL). * Isolated yield. * Determined by H NMR. The absolute configuration of 4aa was determined by X-ray crystallography (see Fig. 2); those of the other products were assigned by analogy. * 3n = (E)-N-benzylidenemethanesulfonamide. * 3p = (E)-N,N-diphenylmethanimine or (E)-N-(4-methoxyphenyl)-1-phenylmethanimine.

**Table 3** The Pd²-catalyzed three-component tandem cyclization reaction of 1a, imine 3a, and different aryl iodides

| Entry | 2 | 3 | 4 Yield (%) | dr (cis/ trans) |
|-------|---|---|-------------|-----------------|
| 1     | 2a (R² = Ph) | 4aa 50 | >30 : 1 |
| 2     | 2b (R² = p-MeC₆H₄) | 4ba 55 | 11 : 1 |
| 3     | 2c (R² = p-MeO₂CC₆H₄) | 4ca 53 | 10 : 1 |
| 4     | 2d (R² = p-MeO₂CC₆H₄) | 4da 40 | 10 : 1 |
| 5     | 2e (R² = p-NO₂C₆H₄) | 4ea 38 | 12 : 1 |
| 6     | 2f (R² = p-FC₆H₄) | 4fa 46 | 16 : 1 |
| 7     | 2g (R² = 2,4-(F)₂C₆H₄) | 4ga 33 | >30 : 1 |
| 8     | 2h (R² = 3,4-(F)₂C₆H₄) | 4ha 28 | >30 : 1 |
| 9     | 2i (R² = 2-thienyl) | 4ia 43 | 22 : 1 |
| 10    | 2j | 4ja Trace | — |

* Reaction conditions: under a N₂ atmosphere, 1a (0.35 mmol, 1 equiv.), 2a (0.42 mmol, 1.2 equiv.), 3a (0.42 mmol, 1.2 equiv.), [Pd(PPh₃)₄] (0.018 mmol, 5 mol%), CsF (1 mmol, 3 equiv.), dioxane (3.0 mL). * Isolated yield. * Determined by H NMR. * 2j = phenyl bromide or phenyl chloride.
reaction efficiency, which suggested that the electron density of the phenyl ring played a role in the reaction efficiency (Table 3, entries 4–5, 7–8, 28–40%). Notably, when a heteroaryl iodide was employed as a substrate (Table 3, entry 9, 43%), the product yield was slightly affected, which was attributed to the electronic property of the thiophene ring. In order to investigate the limitations of aryl halides with different carbon–halogen bonds, phenyl bromide and phenyl chloride were tested. As presented in Table 3 (entries 10 vs. 1), only the carbon–iodine bond was cleaved, suggesting that aryl iodides resulted in higher efficiencies. Interestingly, compounds 4aa–4ia (dr > 10:1) in Table 3 gave a higher diastereomeric ratio than compounds 4ad–4an (dr = 2:1–10:1) in Table 2, which indicated that R² has a more general substrate scope.

Based on previous studies, a plausible mechanism for the cross-coupling reaction is proposed in Scheme 2. The carbopalladation of PhPdI, which is formed in situ from the oxidative addition of Pd⁰ to iodobenzene, with buta-2,3-dien-1-ol (1a) at the center carbon atom forms the π-allylic palladium complex B. Subsequent nucleophilic attack of the oxygen nucleophile of B on the imines 3 leads to the intermediate C. Finally, the resulting intermediate C undergoes an intramolecular nucleophilic attack on the inner π-allylic carbon atom to produce the cyclized products 4, along with the regeneration of the Pd⁰ catalyst D.

Conclusions

In conclusion, we have developed an efficient Pd⁰-catalyzed MCR for the synthesis of polysubstituted oxazolidine derivatives from buta-2,3-dien-1-ol, aryl iodides, and imines. Because of the three-component reaction concept, this cyclization could provide multiple points for diversity with excellent diastereoselectivity. As all three building blocks are readily available, this study will advance the transition-metal-catalyzed chemistry of allenes. Further studies regarding the scope and synthetic applications of this reaction are being pursued in our laboratory and will be reported in due course.

Acknowledgements

We are grateful for the financial support from the Program for Innovative Research Team of the Ministry of Education and Program for Liaoning Innovative Research Team in University (IRT1073).

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