Chiral Ferrocenyl P,N-Ligands for Palladium-Catalyzed Asymmetric Formal [3 + 2] Cycloaddition of Propargylic Esters with β-Ketoesters: Access to Functionalized Chiral 2,3-Dihydrofurans

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Supporting Information

ABSTRACT: A highly enantioselective palladium-catalyzed [3 + 2] cycloaddition of propargylic esters with β-ketoesters has been realized by employing a newly developed chiral ferrocene/benzimidazole-based P,N-ligand. This protocol features a good tolerance of functional groups in both propargylic esters and β-ketoesters, thereby delivering a variety of highly functionalized chiral 2,3-dihydrofurans bearing an exocyclic double bond at the 3-position in good yields and with high enantioselectivities (up to 98% ee).

2,3-Dihydrofurans are ubiquitous structural motifs in natural and synthetic products with wide-reaching biological activities, as well as useful synthetic intermediates for organic synthesis. Among many approaches toward their synthesis,7 the cycloaddition represents an attractive and powerful strategy, but catalytic asymmetric variants remain rare.3 Recently, we discovered a Cu-catalyzed asymmetric [3 + 2] cycloaddition of propargylic esters with β-ketoesters via Cu-allenylidene intermediates, leading to highly functionalized chiral 2-methylene-2,3-dihydrofurans (Scheme 1a).3 The success of this protocol, combined with the distinctive reaction pathway of propargylic esters with β-ketoesters observed under the catalysis of different transition metals,5,6 encouraged us to explore a new asymmetric process to access to a complementary set of enantioenriched 2,3-dihydrofurans, in particular those with an exocyclic double bond at the 3-position that remain unavailable with the known synthetic methods.3

In 1985, Tsuji and co-workers reported a palladium-catalyzed [3 + 2] cycloaddition of propargylic carbonates with β-ketoesters, leading to 3-alkylidene-2,3-dihydrofurans.7 The reaction proceeds via the π-propargylpalladium or allenyl-palladium intermediates, which are attacked consecutively by C- and O-nucleophilic atoms of β-ketoesters to give the cyclization product bearing an exocyclic double bond at the 3-position (Scheme 1b). Since this pioneering work, there have been several other studies of palladium-catalyzed cyclization of propargylic esters with bis-nucleophiles for the construction of structurally diverse carbon- and heterocyclic frameworks.8 However, the stereochemistry of this methodology is rarely investigated,9 and none has explored the possibility of accessing 3-alkylidene-2,3-dihydrofurans with control of the absolute stereochemistry. Given that the desired reactivity had been demonstrated, we believe that an appropriate chiral ligand would render this palladium-catalyzed asymmetric [3 + 2] cyclization enantioselective. However, the initial screening of the reaction with BINAP (L1), Trost’s ligand (L2), and PHOX (L3), the privileged ligands for palladium-catalyzed asymmetric allylic transformation,10 led to really disappointing performance (Table 1, entries 1−3), which clearly expresses the methodological difficulties. By the discovery of a novel chiral ferrocene/benzimidazole-based P,N-ligand, herein we described the first highly enantioselective palladium-catalyzed [3 + 2] cyclo-

Scheme 1. Catalytic Asymmetric [3 + 2] Cycloaddition of Propargylic Esters with β-Ketoesters

a: In our previous work with Cu catalyst to 2-methylene-2,3-dihydrofurans:

b: In this work with Pd catalyst to 3-methylene-2,3-dihydrofurans:

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addition of propargylic esters with β-ketoesters, which generated highly functionalized chiral 3-alkylidene-2,3-dihydrofurans in good chemical yields and with high enantioselectivities (up to 98% ee).

Our recent study disclosed that the presence of the additional N-atoms in chiral P,N-ligands could significantly promote the reaction performance in the Pd-catalyzed asymmetric transformations, which stimulated us to develop a series of novel and readily available chiral ferrocene/benzimidazole-based P,N-ligands for this cycloaddition. The reaction solvent: DMSO. The reaction solvent: toluene.

The reaction was carried out using 1a (0.3 mmol), 2a (0.33 mmol), [Pd] (0.015 mmol, 5 mol%), [L] (0.0165 mmol, 5.5 mol%), base (0.36 mmol, 1.2 equiv) in 3 mL of CH2Cl2 at room temperature for 20 h unless otherwise noted.


The reaction was carried out using 1a (0.3 mmol), 2a (0.33 mmol), Pd(OAc)2 (0.0075 mmol, 2.5 mol%), (R,S)-L4a (0.0165 mmol, 5.5 mol%), Cs2CO3 (0.36 mmol, 1.2 equiv) in 3 mL of toluene in a Schlenk tube at room temperature for 20 h. Yield of isolated product. Determined by chiral HPLC. The reaction was performed at 50 °C.

electron-donating and withdrawing groups at the para-position of the phenyl ring of β-ketoesters and gave the corresponding 2,3-dihydrofurans in high yields and with excellent enantioselectivities (entries 1–5). However, the substitution pattern of functionality on the phenyl ring showed a significant influence on the reactivity. Thus, both 4- and 3-Cl substituted β-ketoesters 1f and 1g gave the desired cycloadducts 3fa and 3ga in good yields and with high enantioselectivities (Table 2, entries 5 and 6), while no reaction was detected with the substrate 1h bearing a 2-Cl substituent under the same reaction conditions presumably due to the steric hindrance. Fortunately, the substrates 1h could be smoothly converted into the corresponding cycloadduct 3ha in 72% yield and with an ee value of 95% when the reaction was performed at 50 °C (entry 7). 2-Naphthyl-substituted substrate 1i turned out to be a suitable reaction partner, giving the cycloadduct 3ia in 91% yield and with 96% ee (entry 8). Heteroaromatic substrate 1j
also worked well, providing the cycloadduct 3ia in 88% yield and with 97% ee (entry 9). Remarkably, aliphatic β-ketoesters were well tolerated in this process, providing the corresponding cycloadducts 3ka and 3ia in slightly decreased yields and with high enantioselectivities (entries 10 and 11).

Having investigated the scope of β-ketoesters, we next examined the scope of this catalytic asymmetric [3 + 2] cycloaddition with regard to propargylic esters. The results in Table 3 indicated that a series of aromatic propargylic esters could be utilized to give 2,3-dihydrofurans in high yields and excellent enantioselectivities, irrespective of the electronic property and position of the functionality (entries 1–9). The use of a heteroaromatic substrate (2k) led to a decrease in the enantioselectivity to 83% ee (entry 10). However, the reaction did not well tolerate aliphatic and internal propargylic acetates, giving very low conversion. In these cases, the use of carbonates instead of acetates at an elevated reaction temperature (50 °C) was required (entries 11–13). For aromatic internal propargylic esters 2m, the reaction exclusively gave rise to the cycloadduct 3am bearing an E-exocyclic double bond in 88% yield and with 89% ee (entry 12). As for aliphatic internal propargylic esters 2n, minimal erosion of the product ratio (E/Z = 92/8) but an improved enantioselectivity (95% ee) for E-isomer was observed (entry 13). However, the aliphatic internal propargylic ester 2o (R = Bn, R′ = 'Bu) gave only very low conversion (entry 14). For the reaction between two aliphatic substrates 1k and 2l, a mixture of 2,3-dihydrofuran and its furan isomer was obtained. The absolute configuration of the cycloadduct was unambiguously determined by X-ray structure analysis of 3ej, to which an S-configuration was assigned.13

Based on the results, a plausible mechanism is proposed to explain the observed stereochemistry (Figure 1). The square-planar Pd-allyl intermediates give two possible orientations: M-type and W-type, in which the M-type (A) is favored due to the steric hindrance. The regioselective attack at the more congested x-allyl terminus according to the report by Larock14 and the trans-effect15 gives (S)-3aa as the major cycloadduct.

The practicality of the current methodology was demonstrated by a gram-scale synthesis, followed by the transformation of the cycloadduct 3aa into the lactone 516 (Scheme 2). The initial hydrogenation of 3aa predominantly generated the cis-diastereoisomer (S,S)-4 on the basis of the NOE experiment13 without any loss in enantioselectivity. (S,S)-4 was then converted into the corresponding lactone 5 by the formation of a new S-stereogenic center based on the NOE experiment.13

In conclusion, we have developed a highly enantioselective palladium-catalyzed [3 + 2] cycloaddition of propargylic esters with β-ketoesters, a process for the generation of highly functionalized chiral 2,3-dihydrofurans bearing an exocyclic double bond at the 3-position that remain unavailable with the known synthetic methods. The key to achieving high enantioselectivity of the reaction is the use of a new and readily available chiral ferrocene/benzimidazole-based P,N-ligand. The reaction tolerates a variety of substitution patterns in both reaction partners. In particular, internal propargylic esters also were found to be suitable substrates for this cycloaddition. Due to the generality of the method and mild conditions employed, we believe this method will see considerable use in both academic and industrial settings.

### Table 3. Substrate Scope of Propargylic Esters

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1, R2</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2b</td>
<td>94</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>2c</td>
<td>93</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>2d</td>
<td>82</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>2e</td>
<td>93</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>2f</td>
<td>91</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>2g</td>
<td>88</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>2h</td>
<td>88</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>2i</td>
<td>70</td>
<td>98</td>
</tr>
<tr>
<td>9</td>
<td>2j</td>
<td>86</td>
<td>95</td>
</tr>
<tr>
<td>10</td>
<td>2k</td>
<td>87</td>
<td>83</td>
</tr>
<tr>
<td>11−</td>
<td>2l</td>
<td>85</td>
<td>56</td>
</tr>
<tr>
<td>12−</td>
<td>2m</td>
<td>88</td>
<td>89</td>
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<tr>
<td>13−</td>
<td>2n</td>
<td>82</td>
<td>95</td>
</tr>
<tr>
<td>14−</td>
<td>2o</td>
<td>80−</td>
<td>56</td>
</tr>
</tbody>
</table>

“The reaction was carried out using 1a (0.3 mmol), 2 (0.33 mmol), Pd2(dba)2·CHCl3 (0.0075 mmol, 2.5 mol %), (R,S)-L4a (0.0165 mmol, 5.5 mol %), Cs2CO3 (0.36 mmol, 1.2 equiv) in 3 mL of toluene in a Schlenk tube at room temperature for 20 h. Yield of isolated product. Determined by chiral HPLC.”

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**Figure 1.** Proposed transition state for stereochemistry.

**Scheme 2. Synthetic Application**

Based on the results, a plausible mechanism is proposed to explain the observed stereochemistry (Figure 1). The square-planar Pd-allyl intermediates give two possible orientations: M-type and W-type, in which the M-type (A) is favored due to the steric hindrance. The regioselective attack at the more congested x-allyl terminus according to the report by Larock14 and the trans-effect15 gives (S)-3aa as the major cycloadduct.

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Experimental procedures and characterization data for all new compounds (PDF)
X-ray crystallographic data for L4a (CIF)
X-ray crystallographic data for (S)-3ej (CIF)

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Notes
The authors declare no competing financial interest.

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REFERENCES


