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Catalytic synthesis of chiral spirocyclic ketones was accomplished via the Pd-catalyzed intramolecular C-arylation of C-substituted cyclic ketones. The obtained spirocyclic ketone could be converted into a bifunctional organocatalyst.

The spirobicyclic framework is frequently found in natural products and biologically active compounds. In the last two decades, chiral ligands and organocatalysts with a spiro skeleton have received considerable attention in asymmetric catalysis because of their unique structural properties and high asymmetric induction efficiency. However, enantioselective synthesis of optically pure spirobicyclic compounds remains a formidable task because the chiral catalysts must control not only the enantiodiscrimination but also the formation of the quaternary carbon center. Efficient synthesis of chiral spirobicycles with multiple functional groups is more challenging and attractive in organic asymmetric synthesis. Herein, we report the facile synthesis of chiral spirobicycles through the Pd-catalyzed intramolecular α-arylation of α-substituted cyclic ketones. The combination of Pd(OAc)2, (S,R)-Josiphos and K2CO3 in 1,2-dimethoxyethane (DME) at 90 °C was effective for the α-arylation of ketones. The functionalized spiro compound 2a could be converted into the chiral acid–base organocatalyst.

**Table 1** Screening of chiral ligands.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>(R)-SDP</td>
<td>24</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>(S)-SDP</td>
<td>24</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>1c</td>
<td>(R)-DIOP</td>
<td>24</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>1d</td>
<td>(S)-DIOP</td>
<td>24</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>1e</td>
<td>(R,R)-DIOP</td>
<td>24</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>1f</td>
<td>(S,S)-DIOP</td>
<td>24</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>1g</td>
<td>(S,R)-Josiphos</td>
<td>24</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>1h</td>
<td>(S,R)-Josiphos</td>
<td>24</td>
<td>95</td>
<td></td>
</tr>
</tbody>
</table>

*Reaction conditions: 1Pd(OAc)2/chiral ligand = 1/0.1/0.01, K2CO3 (2 eq), toluene (0.2 M). 1R)-arylation of carbonyl units is still ongoing. 1Chiralpak IA. 1PdCl2(PPh3)2 (10 mol %) was used. 1NaO-Bu (3 eq) and L1 (22 mol %) were used.*

**Fig. 1** Enantioselective Pd-catalyzed intramolecular α-arylation of α-substituted cyclic ketones 1.
In 1997, Muratake and Natsume reported racemic synthesis of spirocyclic ketones 1 via Pd-catalyzed intramolecular α-arylation of cyclic ketones. We became interested in a DYKAT for spirocyclic ketones 2 because the OMe group on the aromatic ring could be readily transformed to a Brønsted acid region. Although the steric hindrance of multiple substituents on the aromatic ring may prevent the formation of the spiro skeleton, desired racemic 2a was found in 88% yield under the reported conditions. Next we focused on searching for an appropriate chiral ligand to construct 2a with high optical purity. The use of BINAP, SDP, t-Pr-PHOX, or N-heterocyclic carbene ligand L1 provided desired spiro[4,4]nonalone 2a in moderate-to-good yields (42–75%) with low enantioselectivities (up to 18% ee) (entries 1–5). The reaction with (R,R)-DIOP afforded 2a in 85% yield as a racemic mixture (entry 6). The ee values of 2a increased when P-chiral ligands such as DuanPhos (61% ee, entry 7) and BenzP* (46% ee, entry 8) were used. Among the chiral ligands tested, only the Josiphos ligand, which contains a ferrocene unit, produced high enantioselectivity (83% ee, entry 9). Substrate 1a (X = I) failed to provide high enantioselectivity of spiro[4,4]nonalone 2a (entry 10). The optimal result for 2a (82% yield, 83% ee) was obtained when the reaction of 1a was performed in MeOH at 90 °C in the presence of K2CO3 as a base (Scheme 1).

**Scheme 1** Substrate scope of Pd-catalyzed intramolecular α-arylation of α-substituted cyclic ketones 1.

![Scheme 1 Diagram](Image)

The substrate scope is shown in Scheme 1. During our investigation of the substituent effect on the aromatic ring in racemic 1a–1g, we found that the benzyl group (1d: R = OBn) led to the best outcome; spiro[4,4]nonalone 2d was obtained in quantitative yield with 83% ee. Substrates 1f, which contained no alkoxy groups, gave spiro[4,4]nonalones 2f with lower enantioselectivity (21% ee); thus alkoxy substituents on the aromatic ring play an important role in the enantiodiscrimination that produces the chiral spiro[4,4]nonalone skeleton. The present transformation constructed of spiro[4,5], [4,6], and [5,5]alkanones 2h–2l in up to 61% ee. The absolute configuration of spirocyclic ketone 2d was assigned as S by X-ray analysis of deprotected product 3 (Scheme 2).

**Scheme 2** Determination of absolute configuration of the spirocyclic ketone.

2d 83% ee
1) Pd/C, H2
2) recrystallization

![ORTEP drawing of 3](Image)

To demonstrate the potential utility of the spiro compounds, 2a was transformed to chiral spiro-type organocatalyst 6. As shown in Scheme 3, 2a (83% ee) underwent trilaftion and photophosphination to give 4 with 66% yields in two steps. After demethylations of 4, recrystallization of 5 (83% ee) produced optically pure 5 in 60% yield. Finally, reduction of phosphine 5 afforded desired acid–base organocatalyst 6 in 92% yield. To evaluate the catalytic activity of our spiro-type organocatalyst, we used (S)-6 for the enantioselective aza-Morita–Baylis–Hillman (aza-MBH) reaction, which is an atom-economical C–C bond-forming reaction. Preliminary results showed that spiro-type organocatalyst 6 promoted the aza-MBH reaction of 7 with 8 to afford adduct 9 in 71% yield with 54% ee.

**Scheme 3** Preparation of acid–base organocatalyst 6 and its application to the aza-MBH reaction.

(S)-2a 83% ee
1) 2,6-lutidine, Tf2O
2) Pd(OAc)2, dipp, IPr, Pd(OAc)2, dippPh3
3) recrystallization

![Scheme 3 Diagram](Image)

**Conclusions**
We have developed the catalytic and enantioselective synthesis of spirocyclic ketones 2 through the Pd-catalyzed intramolecular α-arylation of α-substituted cyclic ketones 1. Investigation into the reaction mechanism as well as the development of new spiro-type ligands and organocatalysts from 2 is currently underway.

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Notes and references

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6. For recent reviews on asymmetric MBH reaction, see ESI. Screening of other reaction conditions, see ESI. The reaction of 11 using the Pd-Josiphos gave 21 in 59% yield with 3% ee.

7. Crystallographic data (S)-3 for structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CDD No. 1023163. Copies of this information may be obtained for free of charge from The Director, CDDC, 12 Union Road, Cambridge, CB21 6EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).