Tandem Cyclization/Hydroarylation of $\alpha,\omega$-Dienes Triggered by Scandium-Catalyzed C–H Activation

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Supporting Information

ABSTRACT: A highly regio- and diastereoselective cyclization/hydroarylation reaction of 1,5- and 1,6-dienes with aromatic ethers and tertiary anilines was established by a cationic 2-picoline-tethered-half-sandwich scandium alkyl catalyst, which constitutes a process for producing a diverse array of cis-1,3-disubstituted arylated and trans-1,2-disubstituted benzylated methylcyclopentane derivatives in one step with 100% atom-efficiency. Furthermore, a mechanism involving a scandium-catalyzed aromatic ortho-C–H activation and alkene-insertion cascade was also proposed.

KEYWORDS: ring-closure, C–H activation, dienes, hydroarylation, rare earths

The exploration of new annulation methods continues to be a highly active area of research because of the prevalence of carbocyclic units in biologically relevant molecules. In this regard, catalytic cyclization of $\alpha,\omega$-dienes represents a powerful conversion of simple, readily accessible substrates into versatile carbocyclic skeletons. Besides the formation of carbocyclic alkenes via cycloisomerization, diene cyclization combined with various transformations such as silylation, boration, and carbometalation also produces functionalized carbocycles for further elaboration. With the increasing progress in C–H functionalization, especially in C–H addition to monoalkenes, and its extensive recognition as a step- and atom-economical synthesis strategy, a cascade C–H addition sequence into dienes would, in principle, also allows one-step construction of C-substituted carbocyclic derivatives. However, such a C–H-activation-mediated cyclization of dienes has been hardly achieved at the current time. Transition metals such as Rh and Ni have been reported to catalyze C–H transformation toward dienes, but in most cases, they preferred to furnish linear adducts rather than cyclization products.

We recently studied a class of mono(phosphinoamide) rare-earth dialkyl complexes and found that cationic scandium alkyl species such as [N–P–Sc]$^+$ could effectively facilitate a cascade addition of pyridine ortho-C–H across 1,5-dienes to form 2-(3-methylcyclopentyl)pyridines with a distinctive cis-geometry. The success of this transformation may be ascribed to the high activity of cationic scandium catalyst for C–H activation as well as for diene cyclization. Relevantly, cationic half-sandwich scandium alkyl [Cp*$^*$-Sc]$^+$ was also reported to be active for hydrothiomethylative cyclization of 1,5-dienes catalytically. To our knowledge, none of previous works were reported to catalyze hydroarylative cyclization of dienes, especially for 1,6-dienes. As an extension of our work in this field, herein we report a highly regio- and diastereoselective and scandium-catalyzed hydroarylative cyclization of 1,5- and 1,6-dienes with aromatic ethers and tertiary anilines. A broad range of substrates were subjected to a novel cationic 2-picoline-tethered-half-sandwich scandium catalyst [Cp*$^*$-Sc]$^+$, yielding a variety of cis-1,3-disubstituted arylated and trans-1,2-disubstituted benzylated methyl-cyclopentane derivatives via a one-step process with noticeable efficiency.

Our project began with the exploration of C–H alkylation of anisole (1a) toward 1,5-hexadiene (2a) by employing various rare-earth complexes in conjunction with equimolar borate compound [Ph$_3$C][B(C$_6$F$_5$)$_4$] for optimization (see Table 1). After the reaction proceeded at 70 °C for 1 h in chlorobenzene (C$_6$H$_5$Cl), phosphinoanido-bridged scandium complex N–P–Sc delivered the cyclization product of 3aa in 8% yield (Table 1, entry 1), and the extension of reaction time (for 36 h) or elevation of reaction temperature (at 100 °C) failed to increase the yield of 3aa significantly. Likewise, the reported half-sandwich scandium complex Cp*$^*$-Sc was also proved to be less effective (Table 1, entry 2). Fortunately, the

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Table 1. Optimization of Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Ln]</th>
<th>[B]</th>
<th>Yield (%)†</th>
<th>cis/trans*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N−P−Sc</td>
<td>[Ph₃C][B(C₆F₅)₄]</td>
<td>8 (6)</td>
<td>98:2</td>
</tr>
<tr>
<td>2</td>
<td>Cp⁶⁻⁻⁴⁻Sc</td>
<td>[Ph₃C][B(C₆F₅)₄]</td>
<td>9 (7)</td>
<td>92:8</td>
</tr>
<tr>
<td>3</td>
<td>Cp⁶⁻⁻⁴⁻Sc</td>
<td>[Ph₃C][B(C₆F₅)₄]</td>
<td>88 (84)</td>
<td>75:25</td>
</tr>
<tr>
<td>4</td>
<td>Cp⁶⁻⁻⁴⁻Sc</td>
<td>[Ph₃C][B(C₆F₅)₄]</td>
<td>97 (92)</td>
<td>&gt;98:2</td>
</tr>
<tr>
<td>5</td>
<td>Cp⁶⁻⁻⁴⁻Sc</td>
<td>[Ph₃C][B(C₆F₅)₄]</td>
<td>15 (13)</td>
<td>80:20</td>
</tr>
<tr>
<td>6</td>
<td>Cp⁶⁻⁻⁴⁻Sc</td>
<td>[Ph₃C][B(C₆F₅)₄]</td>
<td>96 (94)</td>
<td>&gt;98:2</td>
</tr>
<tr>
<td>7</td>
<td>Cp⁶⁻⁻⁴⁻Sc</td>
<td>[Ph₃C][B(C₆F₅)₄]</td>
<td>1 (—)</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>Cp⁶⁻⁻⁴⁻Sc</td>
<td>[Ph₃C][B(C₆F₅)₄]</td>
<td>94 (96)</td>
<td>&gt;98:2</td>
</tr>
</tbody>
</table>

†Reaction conditions: 1a (1.0 mmol), 2a (1.5 mmol), [Ln] (2.0 mol %), [Ph₃C][B(C₆F₅)₄] (2.0 mol %), at 70 °C, 1 h, in C₆H₅Cl (2.0 mL). †GC yield, isolated yield was in parentheses. †Stereoselectivity was determined by ‘H NMR spectrum. †In toluene (2.0 mL). †In benzene (2.0 mL).

With these results in hand, various aromatic ethers were subsequently scrutinized with 2a as a partner (see Table 2). In the case of 2-substituted anisoles, substituents such as Me, Bu, allyl, Ph, and even halogens were well-tolerated, leading to high yields of alkylation products 3ba–3ia with excellent cis-selectivity (77–97% yield, >97 cis). For 3-substituted anisoles that have two different ortho-C–H bonds, 3-methylandisole provided a regioisomeric mixture of cis-3ja and cis-3ja' (90% combined yield, >98 cis), while 3-phenylanisole or 3-Cl(Br)-anisole produced a single regioisomer (see 3ka–3ma, Table 2). This is probably due to the electronic effect of different substituents. 1,4-Benzodioxane, bearing two O-directing groups, quantitatively offered dialkylation product cis-3na through a bis-C–H functionalization (90% yield, >97 cis). Noticeably, coupling with cis-cyclization of 2a, the C–H alkylation of 1,4-benzoxathian (1o) or N-methylbenzoximorpholine (1p) also occurred exactly at ortho-position of O rather than S or N atom, implying the stronger oxophilicity of metal center of catalyst (see 3oa–3pa, Table 2). It was noteworthy that the C–S bond of 1o survived intact over the course of C–H activation. Upon replacing methyl unit at O atom in 1a with phenyl or ethyl group, ortho-C–H alkylation followed by the cis-cyclization of 2a also proceeds well (see 3qa–3ra, Table 2).

The scope of C–H substrate was then expanded to include tertiary anilines (See Table 3). Typically, with N,N-dimethylaniline (1s), trapping the cyclization of 2a (1.5 equiv) at 70 °C
for 1h resulted in the formation of ortho-(3-methyl-cyclopropyl)aniline (3sa) as a single cis-isomer along with minor bis-C−H alkylation byproduct. To avoid over alkylation, the reaction was optimized at 50 °C with the use of 1.1 equiv of 2a, in which cis-3sa was isolated in 87% yield. Under these new conditions, a range of N,N-dimethylanilines were examined and good results were obtained as well (see 3ta-3aaa, Table 3). Notably, N-ethyl-N-methylaniline (1ab), N-methyl-1,2,3,4-tetrahydroquinoline (1ac), and 1-phenyl-propyl-line (1ad) could also be successfully ortho-C−H alkylated in a similar manner (see 3aba-3ada, Table 3). The cis-geometry of 3ta was unambiguously confirmed by X-ray crystallographic analysis of its HPF₆ salt.

Next, we checked the cyclization of various 1,5-dienes with N,N,4-trimethylaniline (1t) as C−H partner at 50 °C in C₆H₅Cl with 4.0 mol % catalyst loading (see Table 4). Similar to 2a, the reaction of substituted 1,5-dienes also performed well and was found highly selective without the contamination of linear adducts. Usually, the initial 2,1-addition of Sc/C−H bond prefers to occur at a less hindered alkene, and followed by intramolecular cis-cyclization to produce arylated 3-methyl-cyclopentane derivatives. Thus, 2-methyl-1,5-hexadiene (2b) afforded the expected racemic carbocyclic product 3tb in 94% yield. E/Z-hepta-1,5-diene was converted to carbocycle 3tc in 95% yield and with 67% cis-selectivity. To our surprise, racemic-2-methyl-4-phenyl-1,5-diene (2d) was cyclized to diastereoisomer 3td containing 63% cis-isomer. The excess of cis-3td presumably arises from minimizing the steric repulsion between catalyst and substituents of 2d in the second insertion event. 1,5-Dienes 2e and 2f, bearing a bulky cycloalkane unit, were also found suitable for this annulation, affording 100% cis-fused bicyclo[3,3,0] and bicycle[4,3,0] products 3te and 3tf in 96% and 70% yields, respectively. The cyclization of 3-phenyl-1,5-diene (2g) and 3-methyl-3-phenyl-1,5-diene (2h) were also proved efficient, affording diastereomeric products 3tg and 3th, quantitatively.

As indicated in Table 5, a series of 1,6-dienes were then evaluated using this annulation protocol. Unlike the reported Ti (or Y)-catalyzed cyclization/functionlization of 1,6-dienes that usually yields the expected cyclohexane motifs, the hydroarylation-cyclization of 1,6-dienes using this scandium catalyst, surprisingly, produce unusual 1,2-disubstituted benzylated methylcyclopentane derivatives as major products. Furthermore, the cyclization reaction proceeded with extremely high trans-selectivity. The X-ray diffraction analysis of crystal 4sl clearly highlights its trans-geometry. In this way, cyclizations of hepta-1,6-diene (2i), 4-phenyl-1,6-diene (2j), sterically hindered 1,6-dienes (2k-2n), and even dialkylsilanes (2o-2r) with 1t were all well achieved (see 4it-4tr 42−95% yield, > 98 trans). As was the case for Pd-catalyzed hydrosilyative cyclization of 1,6-dienes, the current ring-closing pattern maybe stem from a cascade 1,2- and 2,1-insertion of alkene sequence.

To further assess this annulation protocol, spirobicyclization of trienes were probed with 1t as a C−H partner. Under the optimized conditions, trienes 2s and 2t underwent a sequential cyclization to give expected arylated spiro[4.4]nonane 3ts and benzylated spiro[4.5]decane 4tt in 88% and 94% yields upon isolation (see Scheme 1).

To get some mechanistic insight into this annulation protocol, deuterium-labeling experiments were conducted, as shown in Scheme 2. The ortho-D of aniline 1s-D₃ was transferred to the methyl group of carbocycle in 3sa-D₃ or 4so-D₅, which implies an amino-directing C−H bond cleavage.
the high cycloselectivity of this catalysis. The diastereoselective alkene 2,1-insertion of 2a or alkene 1,2-insertion of 2o into Sc–Ph bond forms alkylscandium olefin B or D, followed by rapid intramolecular 2,1-insertion of remained alkene into Sc–C bond in B or D to form cyclopentylmethylscandium C or E (cyclization). Upon activating ortho-C–H of another 1s, C or E regenerates A while liberating cis-3sa or trans-4so.

In summary, we have realized the first example of hydroarylation cyclization of 1,5- and 1,6-dienes with aromatic ethers and tertiary anilines as C–H partners using CpSc in combination with [Ph3C][B(C6F5)4] as catalyst and proposed the possible reaction mechanism. The reaction is a green process and generally proceeds under mild conditions to yield a variety of cis,1,3-disubstituted arylated and trans,1,2-disubstituted benzylated methylcyclopentanone derivatives containing monocyclic, bicyclic, spirocyclic, and heterocyclic skeletons in one step with high regio- and diastereoselectivity. The simple starting materials, broad scope of substrates, 100% atom-economy, unusual stereoselectivity, and ring-closing pattern may enable this reaction highly valuable in view of the wealth of biologically active and naturally occurring carbocycles. Further study on asymmetric version of this methodology using chiral rare-earth catalysts is in progress.

**ASSOCIATED CONTENT**

† Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b04713.

Experiment detail and NMR data (PDF)

X-ray data (CIF)

X-ray data (CIF)

X-ray data (CIF)

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**Notes**

The authors declare no competing financial interest.

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**REFERENCES**


(12) For the synthesis and characterization of rare-earth complexes CpxSenSc and CpxSenLn (Ln = Sc, Y, and Lu), see Supporting Information.

(13) For details of preparation and X-ray crystallography study of compounds cis-3ta-HPF6 (CCDC 1880298) and trans-4ta (CCDC 1880297), see Supporting Information, Figure S2.
None of acyclic byproducts were observed in all cases, and a small amount of 1,3-disubstituted arylated methylcyclohexanes were also formed in the cyclization/hydroarylation reactions of 1,6-dienes \(2i, 2j\) with \(1t\). See Supporting Information.

The formation of intermediate \(A\) was validated by \(^1\)H NMR spectrum through the reaction in situ of \(\text{Cp}^\beta\text{Sc}\) with \([\text{PhNHMe}_2][\text{B}(\text{C}_6\text{F}_5)_4]\) in \(\text{C}_6\text{D}_5\text{Cl}\). See Supporting Information.