Enantioselective Palladium-Catalyzed [3C + 2C] and [4C + 3C] Intramolecular Cycloadditions of Alkylidenecyclopropanes

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ABSTRACT: We report a highly enantioselective [3C + 2C] intramolecular cycloadditions of alkylidenecyclopropanes (ACPs) and alkenes. The best results are obtained by using sterically demanding chiral phosphoramidite ligands derived from Vapol. Moreover, we also show that related, but less bulky phosphoramidites can also lead to very effective [4C + 3C] cycloadditions when dienes, instead of alkenes, are used as reacting partners. The reactions provide a practical, simple and selective access to optically active, synthetically appealing 5,5 and 5,7-bicyclic systems.

KEYWORDS: Alkylidenecyclopropane, enantioselective, cycloaddition, palladium, phosphoramidite, asymmetric

Many biologically relevant natural products exhibit complex polycyclic skeleton cores featuring five- to seven-membered carbocycles. Especially abundant are those exhibiting 5-5, 5-6 or 5-7 bicyclic scaffolds. One of the most attractive approaches to assemble these skeletons is based on cycloaddition processes, owing to their atom-economy and complexity-increase character. However, classical cycloadditions are limited to substrates that are appropriately matched from an electronic point of view. In this context, transition metal catalysis offers a very powerful alternative to promote annihilations of otherwise unreactive, non-activated precursors. Moreover, by incorporating chiral ligands at the metal center, it is possible to develop enantioselective variants and henceforth build enantiocyclic scaffolds.

While a number of highly enantioselective transition metal-catalyzed (TMC) cycloadditions have been developed in the last decades, it is quite remarkable that most examples so far reported involve intermolecular processes, typically leading to monocyclic products. Progress on intramolecular annihilations, which are more interesting from a constructive perspective, has clearly lagged behind. Indeed, enantioselective TMC intramolecular cycloadditions to give seven-membered carbocycles are limited to a handful of [5C + 2C] and [4C + 3C] processes, whereas intramolecular [3C + 2C] annihilations towards enantiocyclic cyclopentane cores are essentially unknown.

In recent years, we and others have developed several TMC cycloadditions using alkylidenecyclopropanes (ACPs) as three-carbon reaction partners (Figure 1a). The reactivity of ACPs arises from their ability to coordinate the metal complex and promote oxidative additions (via distal or proximal C–C bond activation) to give metallacyclobutane species that can further evolve via migratory insertions of diverse C–C unsaturated partners. Noteworthy, despite the synthetic power of these annihilations, highly enantioselective variants have not been reported. Herein, we present the first examples of a highly enantioselective Pd-catalyzed [3C + 2C] cycloaddition between ACPs and alkenes, as well as several examples of enantioselective [4C + 3C] annihilations of ACPs with 1,3-dienes (Figure 1b). The reactions allow the synthesis of either optically active bicyclo[3.3.0]octane or bicyclo[3.5.0]decene products, with excellent diastereoselectivities and good to excellent enantiomeric ratios. Given that the precursors are readily assembled, the strategies provide a rapid, practical, diastereo- and enantioselective entry to synthetically appealing cis-fused 5,5- and 5,7-bicyclic systems bearing up to three stereocenters. Also notably, challenging products with chiral quaternary carbon stereocenters at the ring fusion can be obtained with good e.r.’s.
At the outset, we selected the alk-5-enylidencyclopropane 1a to explore an enantioselective [3C + 2C] process. Based on the previously described racemic reaction, a Pd catalyst generated from Pd(II) (6 mol%) and phosphate ligands P(O)(OPr) or L1, 20 mol%, e.g. Table 1, entry 1, we analyzed chiral phosphoramidites, as they are electronically related π-acceptor ligands. As can be seen in entries 2 and 3, the use of Feringa’s phosphoramidite L2 led, after 8 h at 80 °C, to the quantitative formation of the single diastereomeric adduct 2a, but with low to moderate levels of asymmetric induction. The incorporation of phenyl rings at the Binol-ortho position of the ligand, allowed for a significant increase in the enantioselectivity. In particular, the use of L3, in its matched (S,R,R) configuration, led to 2a in 76% yield and 85:15 e.r. (entry 4). Most probably, the presence of these aryl groups reduces the flexibility around the palladium center, which allows a better transmission of the axial chirality of the ligand to the new stereogenic centers.

Table 1. Optimization of the enantioselective [3C + 2C] cycloaddition

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Pd] (x mol%)</th>
<th>L* (y mol%)</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Yield (%)</th>
<th>e.r. (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>Pd3(dba)3 (6)</td>
<td>L1 (20)</td>
<td>100</td>
<td>4</td>
<td>74</td>
<td>-</td>
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<tr>
<td>2</td>
<td>Pd3(dba)3 (6)</td>
<td>(S,R,R)-L2 (20)</td>
<td>80</td>
<td>8</td>
<td>99%</td>
<td>53:47</td>
</tr>
<tr>
<td>3</td>
<td>Pd3(dba)3 (6)</td>
<td>(R,R,R)-L2 (20)</td>
<td>80</td>
<td>8</td>
<td>99%</td>
<td>74:26</td>
</tr>
<tr>
<td>4</td>
<td>Pd3(dba)3 (6)</td>
<td>(S,R,R)-L3 (20)</td>
<td>80</td>
<td>8</td>
<td>76</td>
<td>85:15</td>
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Related phosphoramidites with different aryl groups at the ortho position did not provide further improvements in the e.r. However, with (S,R,R)-L4, which features a more rigid chiral backbone (Vaplo), we observed a slightly better selectivity (entry 6). Interestingly, screening of other Pd(0) sources revealed that the reaction could be significantly accelerated by using CpPd(π-cinnamyl) instead of Pd3(dba)3 (from 8 h to 2 h for completion), whereas the reaction yield was also improved up to 88% (entry 7). Using this Pd(0) source, the reaction could be carried out even at lower temperatures with a good yield; however, and contrary to common asymmetric protocols, the e.r. of the product significantly dropped down (entry 8). In line with this observation, increasing the temperature led to improvements on the enantioselectivity, reaching a maximum e.r. of 92 : 8 at 110 °C (entry 9). Importantly, the use of CpPd(π-cinnamyl) also allowed the palladium loading to be reduced from 12 to 5 mol% (6 mol% of ligand), without any significant deleterious effect in yield, rate or selectivity of the reaction, provided that the reaction milieu is carefully deoxygenated prior to heating. Alternatively, the use of a slight excess of ligand allows to elude the careful deoxygenation protocol (entries 10 and 11).

Having established an optimal protocol for the cycloaddition with a low catalyst loading, we tried to further optimize the enantioselectivity. Gratifyingly, the use of more congested ligands such as (S,R,R)-L5 and (S,R,R)-L6, featuring a bulkier amine counterpart (i.e. bis[1-naphthyl]ethyl amine), provided better enantioselectivities (entries 12, 13). In particular, the reaction using (S,R,R)-L6 produced 2a with an excellent 90% yield, complete diastereoselectivity and an excellent 96:4 e.r.

The scope of this catalytic process was then explored with other alkene-tethered ACPs (Table 2). The reaction tolerated ethyl malonate groups in the tether (2b, 97.3 e.r.) and the use of other ester groups at the alkene, like a bulky iso-propyl (2c, 95:5 e.r.). The reaction also works with substrates that bear heteroatoms in the connecting tether, thus products 2d-2f.
with nitrogen- and oxygen-based linkers, were obtained with good to complete diastereoselectivities, and only slightly lower e.r.’s (from 87:13 to 92:8). Importantly, the reaction also works with substrates like 1g or 1h to provide the corresponding adducts exhibiting carbon quaternary centers at the ring fusion, with very good yields and complete or excellent diastereoselectivities. Albeit the e.r. of 2g was moderate (72:28), the presence of a methyl in the ACP did not affect the enantioselectivity, so that 2h could be obtained with an e.r. of 96 : 4.

Table 2. Scope of the Pd-catalyzed [3C + 2C] cycloaddition

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<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
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1. [CO2Et]2
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A solution of [CO2Et]2 (10 mol%), (S,R,R)-L6 (10 mol%) and 1 in toluene was refluxed under argon for 6 h. Conversions > 99%, by H-NMR of the crude reaction mixture. E.r.’s determined by HPLC. Isolated yields of 2.

The synthetic potential of this type of 5,5-bicyclic systems was preliminary analyzed. For instance, product 2b could be transformed into the corresponding ketone in excellent yield, by using an standard ozonolysis (eq. 1, right), whereas treatment of this cycloadduct 2b or the related N-Tosyl or N-Benzyl derivatives 2d-2e with excess of LiAlH4 afforded the corresponding alcohols of type 4 in good yields (eq 1, left). Gratifyingly, the absolute stereochemistry of the adducts could be determined by X-ray crystallography analysis of two of these derivatives.

Mechanistically significant, the cis alkene precursor Z-1b can also engage in the cycloaddition, to give adducts 2b’ (51% yield, 92:8 e.r.) and 2b” (15% yield, e.r. not determined), a result consistent with a stereospecific annulation (Scheme 1). On these bases, and considering previous DFT calculations in related systems, the reaction likely involves palladacyclic intermediates of type II, which preserve the parent alkene geometry. Alternative paths via π-allyl Pd species of type III, which have also been shown to be energetically feasible by DFT computations, are less compatible with the observed stereoselectivity (Scheme 1).

At this point, we questioned whether these chiral Pd-catalysts might also promote asymmetric [4C + 3C] intramolecular cycloadditions between ACPs and dienes, since these reactions have also been proposed to proceed through analogous palladacyclic intermediates. The resulting 5,7-fused bicarbocyclic systems form the basic core of many biologically relevant sesquiterpenes; however, direct enantioselective approaches for their assembly are nearly unknown. Thus, we tested the reactivity of precursor 5a, which features an ACP tethered to a conjugated diene, with a terminally substituted carboxylic ester (Table 3). Compared to the [3 + 2] annulations, this is a more challenging process since, in addition to diastereo- and enantioselectivity, there are also regioselectivity issues, owing to the potential competitive formation of [3C + 2C] adducts of type 7. Indeed, as can be seen in Table 3, entry 1, when 5a was treated with PdPd(π-cinnamyl) (5 mol%) and (S,R,R)-L6 (10 mol%) under refluxing toluene, a 5 to 1 mixture of both the [4 + 3] adduct 6a and its [3 + 2] counterpart 7a was obtained. Moreover, the reaction took place with a moderate 56% conversion after 12 h, and an isolated 37% overall yield. Despite this low reactivity, the cycloheptene product 6a was obtained with complete diastereoselectivity and a remarkable e.r. of 94 : 6. Gratifyingly, by performing the reaction in a sealed tube at 150 ºC, we observed full conversion, a similar [4 + 3] / [3 + 2] ratio (5 : 1), and a better yield of 6a (75%, entry 2), which was now obtained with an excellent 96 : 4 e.r.

In an attempt to improve the conversion and further favor the formation of the [4 + 3] adduct 6a, we analyzed less bulky chiral phosphoramidites. Ligands like (S,R,R)-L4, which performed well in the [3 + 2] cycloaddition, provided better conversion at 110 ºC and equally good enantioselectivity, but did not improve the [4 + 3] / [3 + 2] ratios (6a : 7a = 3 : 1, entry 3). On the other hand, excellent selectivites in favor of the desired [4 + 3] adduct could be achieved with the very unhindered phosphoramidite (R,R)-L7; however, the enantioselectivity dropped (entry 4). An extensive analysis of structurally related unhindered phosphoramidites, Pd(0) sources and solvents, led us to identify the palladium catalyst derived from the Vanol-phosphoramidite ligand (S,R,R)-L8 as one leading to an optimal ratio in favor of the [4 + 3] adduct (6a : 7a = 10 : 1), provided that the cycloaddition is carried out in dioxane with Pd(dba)3 (81% yield, 95:5 e.r., entry 7). More significantly, the use of (S,R,R)-L2 instead of (S,R,R)-L8, under otherwise identical conditions, enables nearly complete selectivity in favor of 6a and similar e.r. (93:7, entry 8). Analysis of the diastereomeric ligand (R,R,R)-L2 allowed to confirm that the (S,R,R) configuration is a matched case, providing not only higher e.r., but also better [4 + 3] / [3 + 2] ratios (entry 9).

Table 3. Optimization of the enantioselective [4C + 3C] cycloaddition

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1. [CO2Et]2
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Scheme 1. Cycloaddition of Z-1b and proposed reaction intermediate.

A solution of [CpPd(π-cinnamyl)] (5 mol%), (S,R,R)-L6 (10 mol%) and 1 in toluene was refluxed under argon for 6 h. Conversions > 99%, by H-NMR of the crude reaction mixture. E.r.’s determined by HPLC. Isolated yields of 2.

Mechanistically significant, the cis alkene precursor Z-1b can also engage in the cycloaddition, to give adducts 2b’ (51% yield, 92:8 e.r.) and 2b” (15% yield, e.r. not determined), a result consistent with a stereospecific annulation (Scheme 1). On these bases, and considering previous DFT calculations in related systems, the reaction likely involves palladacyclic intermediates of type II, which preserve the parent alkene geometry. Alternative paths via π-allyl Pd species of type III, which have also been shown to be energetically feasible by DFT computations, are less compatible with the observed stereoselectivity (Scheme 1).
access to 5,7-bicarbocyclic systems bearing three stereogenic centers at the ring fusion, which could be obtained with 

ciclo[3.4.0]octane. Scope of the enantioselective Pd-catalyzed [4 + 3] cycloaddition

\[
Pd_2(dba)_3 / \text{(S,R,R)-L} \quad (\text{5 mol%})
\]

entry [Pd] (5%) L* (x mol%) solvent T (°C) t (h) 6a, 7a, 6a, 7a, %yield e.r.

1. CcPd(π-cyc.) (S,R,R)-L6 (10) tol. 110 12 5:1 37(56) 94:6
2. CcPd(π-cyc.) (S,R,R)-L6 (10) Tol. 150 6 5:1 75 66:4
4. CcPd(π-cyc.) (R,R)-L7 (10) tol. 110 4 19:1 86 85:15
5. CcPd(π-cyc.) (S,R,R)-L8 (10) tol. 110 12 3:1 68 94:6
6. CcPd(π-cyc.) (S,R,R)-L8 (10) dio. 101 5 10:1 45(70) 95:5
7. Pd2(dba)3 (S,R,R)-L8 (14) dio. 101 4 10:1 81 95:5

Conditions: A solution of [Pd] (5 mol%), L* (x mol%) and 5a in the indicated solvent was heated under argon at the indicated temperature. Conversion > 99%, unless otherwise noted. Ratio determined by 1H-NMR of the crude mixture. Isolated yields after column chromatography. Value of conversion under parenthesis. Determined by HPLC with chiral phases.

The enantioselective [4C + 3C] cycloaddition catalyzed by Pd2(dba)3 / (S,R,R)-L2 is not limited to the model substrate 5a. Related bicyclic systems such as 6b–6e could be readily obtained in good yields and moderate to excellent selectivities (Table 4). Particularly relevant is the synthesis of the bicyclo[3.4.0]octane 6b, containing a chiral carbon quaternary stereocenter at the ring fusion, which could be obtained with 97:3 e.r., whereas its counterpart 6c was obtained in good yield and 91:9 e.r. This represents the first enantioselective access to 5,7-bicarbocyclic systems bearing three stereogenic centers with one quaternary carbon at the ring fusion. Additionally, the reaction also tolerates heteroatoms in the connecting tether (5d, X = O), and also works with dienes lacking the ester activating group (5e, R1 = H), albeit the e.r.’s were lower.

Table 4. Scope of the enantioselective Pd-catalyzed [4 + 3] cycloaddition

In summary, we have developed the first highly enantioselective TMC cycloadditions involving ACPs, which further constitutes one of the very few enantioselective intramolecular cycloadditions leading to bicyclic systems containing five and seven-membered carbocycles. In particular, we identified two sets of conditions that allow the enantioselective assembly of bicyclo[3.3.0]octanes and bicyclo[5.3.0]decenes, featuring up to three stereogenic centers, including quaternary ones at the ring fusion. The demonstration that ACPs can engage in highly asymmetric annulations set the basis for further exploitation of these useful three-carbon synthons, and for devising synthetic applications.

ASSOCIATED CONTENT
Supporting Information
Full experimental procedures, optimization of the chiral catalysts and characterization of all new compounds, including 1H-, 13C-NMR spectra and chiral HPLC traces.

AUTHOR INFORMATION
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REFERENCES

ed Reaction of V inylcyclopropanes and


Preliminary asymmetric developments were included in refs. 8h, 8n and 8t. Only in an isolated case of a [3+2+1] cycloaddition, a high 89% ee was reported (ref. 8n).


(18) A preliminary exploration of these enantioselective [4 + 3] cycloadditions, with modest ee’s, was included in ref. 8h.
Dioxane, reflux

\[ \text{Pd}_2(\text{dba})_3 \] (cat) 
\[ \text{O} \text{O} \]
\[ \text{P} \text{N} \]
\[ \text{Ph} \text{Ph} \]
\[ \{4\text{C} + 3\text{C}\} \text{ up to } 97:3 \text{ e.r.} \]

Toluene, reflux

\[ \text{CpPd(} \text{p-cinnamyl)} \text{ (cat)} \]
\[ \{3\text{C} + 2\text{C}\} \text{ up to } 97:3 \text{ e.r.} \]