

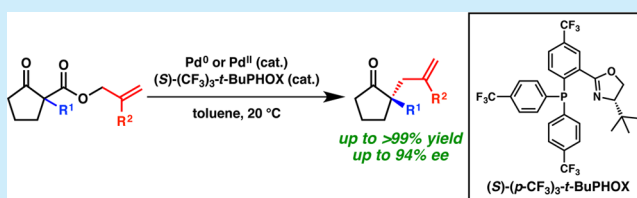
## Palladium-Catalyzed Enantioselective Decarboxylative Allylic Alkylation of Cyclopentanones

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## S Supporting Information

**ABSTRACT:** The first general method for the enantioselective construction of all-carbon quaternary centers on cyclopentanones by enantioselective palladium-catalyzed decarboxylative allylic alkylation is described. Employing the electronically modified (S)-(p-CF<sub>3</sub>)<sub>3</sub>-t-BuPHOX ligand,  $\alpha$ -quaternary cyclopentanones were isolated in yields up to >99% with ee's up to 94%. Additionally, in order to facilitate large-scale application of this method, a low catalyst loading protocol was employed, using as little as 0.15 mol % Pd, furnishing the product without any loss in ee.

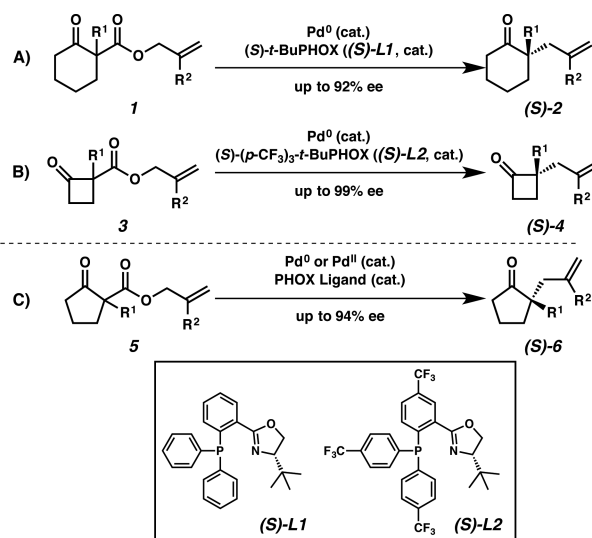


The efficient construction of all-carbon quaternary centers (Cq's) remains a challenge for the modern synthetic chemist.<sup>1</sup> The difficulty associated with forming Cq's arises from the inherent steric congestion during the C–C bond-forming event. Toward this end, our laboratory disclosed the first palladium-catalyzed enantioselective decarboxylative allylic alkylation for the construction of Cq's.<sup>2</sup> Over the past decade, we have continued to explore the breadth of our reaction manifold,<sup>3</sup> including the development of new ligands based on the original phosphinooxazoline (PHOX) scaffold.<sup>4</sup> Cyclic ketones generally represent the most explored class of substrates, from the initially reported cyclohexanones (Scheme 1A),<sup>2,5</sup> cycloheptanones,<sup>2,3d,5b,c</sup> and cyclooctanones<sup>2,3d,5b</sup> to the more recently disclosed and highly strained cyclobutanones (Scheme 1B).<sup>6</sup>

Contrastingly, cyclopentanones have typically performed worse than the corresponding 6-membered substrates, often furnishing the  $\alpha$ -Cq ketone products in comparatively reduced yields and enantiomeric excess (ee).<sup>3d</sup> Only a few examples with limited substrate scope exist for the formation of  $\alpha$ -Cq cyclopentanones by transition-metal-catalyzed enantioselective allylic alkylation.<sup>7</sup> However, cyclopentanes containing enantioenriched Cq's characterize a number of biologically pertinent and chemically fascinating natural products, including polycyclic terpenoids 7,<sup>8</sup> 8,<sup>9</sup> and 9<sup>10</sup> as well as alkaloids 10,<sup>11</sup> 11,<sup>11</sup> and 12<sup>12</sup> (Figure 1). As part of our continued efforts to extend the utility of our reaction methodology, we revisited the problematic cyclopentanone substrate class, striving to develop the first general method for the construction of  $\alpha$ -Cq cyclopentanones and 5-membered cyclic ketone substrates by transition metal-catalyzed enantioselective decarboxylative allylic alkylation (Scheme 1C).

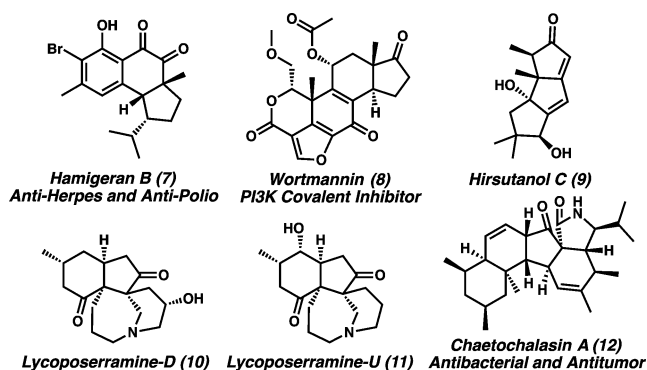
Initial reaction development employed *p*-Me-benzyl-substituted  $\beta$ -ketoester 13a, using catalytic Pd<sub>2</sub>(dba)<sub>3</sub> at 20 °C in

Scheme 1. Cyclic Ketone Substrates in Transition-Metal-Catalyzed Enantioselective Decarboxylative Allylic Alkylation



toluene in the presence of a chiral PHOX ligand, affording enantioenriched  $\alpha$ -Cq cyclopentanone 14a (Table 1).<sup>13,14</sup> Using the classic (S)-*t*-BuPHOX ligand ((S)-L1), cyclopentanone (S)-14a was provided in 87% ee (entry 1). Switching to the electron-deficient (S)-(p-CF<sub>3</sub>)<sub>3</sub>-*t*-BuPHOX ((S)-L2) furnished product (S)-14a in an improved 89% ee (entry 2). The recently disclosed, cost-effective alternative to L2, (R)-(p-CF<sub>3</sub>)<sub>3</sub>-*i*-PrPHOX<sup>Me2</sup> ((R)-L3), provided cyclic ketone (R)-14a in a decreased 83% ee (entry 3).<sup>4a</sup> Similarly to (R)-L3, geminally disubstituted

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**Figure 1.** Natural products characterized by cyclopentane rings containing chiral all-carbon quaternary centers (Cq's).

**Table 1.** PHOX Ligand Screen<sup>a</sup>

entry	R	$\beta$ -ketoester	product	ligand	ee (%) <sup>(b)</sup>
1	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> -	<b>13a</b>	( <i>S</i> )- <b>14a</b>	( <i>S</i> )- <b>L1</b>	87
2	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> -	<b>13a</b>	( <i>S</i> )- <b>14a</b>	( <i>S</i> )- <b>L2</b>	89
3	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> -	<b>13a</b>	( <i>S</i> )- <b>14a</b>	( <i>R</i> )- <b>L3</b>	83
4	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> -	<b>13a</b>	( <i>S</i> )- <b>14a</b>	( <i>S</i> )- <b>L4</b>	82
5	EtO <sub>2</sub> CCH <sub>2</sub> CH <sub>2</sub> -	<b>13b</b>	( <i>S</i> )- <b>14b</b>	( <i>S</i> )- <b>L1</b>	82
6	EtO <sub>2</sub> CCH <sub>2</sub> CH <sub>2</sub> -	<b>13b</b>	( <i>S</i> )- <b>14b</b>	( <i>S</i> )- <b>L2</b>	91
7	EtO <sub>2</sub> CCH <sub>2</sub> CH <sub>2</sub> -	<b>13b</b>	( <i>S</i> )- <b>14b</b>	( <i>R</i> )- <b>L3</b>	82
8	EtO <sub>2</sub> CCH <sub>2</sub> CH <sub>2</sub> -	<b>13b</b>	( <i>S</i> )- <b>14b</b>	( <i>S</i> )- <b>L4</b>	80

<sup>a</sup>Conditions:  $\beta$ -ketoester **13** (0.19 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (2.75 mol %), ligand (6.00 mol %), toluene (5.8 mL). <sup>b</sup>Measured by analytical chiral SFC.

valine-derived (*S*)-(*p*-CF<sub>3</sub>)<sub>2</sub>-*i*-PrPHOX<sup>Ph2</sup> ((*S*)-**L4**) afforded ketone (*S*)-**14a** with nearly equivalent ee (82%, entry 4). Switching to ester-substituted  $\beta$ -ketoester **13b**, we confirmed (*S*)-(*p*-CF<sub>3</sub>)<sub>3</sub>-*t*-BuPHOX ((*S*)-**L2**) was indeed the optimal ligand for the desired enantioselective decarboxylative allylic alkylation, providing enantioenriched  $\alpha$ -Cq cyclopentanone (*S*)-**14b** in 91% ee (entry 6). The remaining PHOX ligands (*S*)-**L1**, (*R*)-**L3**, and (*S*)-**L4** furnished the desired product (**14b**) in reduced ee's, ranging between 80% and 82% (entries 5, 7, and 8, respectively).

Having identified the optimal ligand for the enantioselective decarboxylative allylic alkylation, we next examined the solvent effect using  $\beta$ -ketoester **13b** (Table 2). Employing identical

**Table 2.** Solvent Effect on Enantiomeric Excess of Cyclopentanone Product (*S*)-**14b**<sup>a</sup>

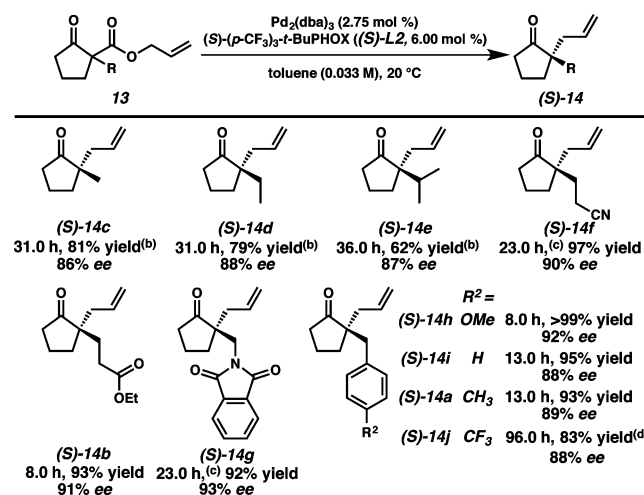
entry	solvent	time (h)	ee <sup>b</sup> (%)
1	toluene	8.0	91
2	2:1 hexane/toluene	8.0	88
3	MTBE	1.0	87
4	THF	1.0	81

<sup>a</sup>Conditions:  $\beta$ -ketoester **13b** (0.19 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (2.75 mol %), (*S*)-**L2** (6.00 mol %), toluene (5.8 mL). <sup>b</sup>Measured by analytical chiral SFC.

reaction conditions from our ligand screen, using toluene as the solvent, we isolated  $\alpha$ -Cq cyclopentanone (*S*)-**14b** in 91% ee, achieving complete consumption of starting material **13b** in 8.0 h (entry 1). Switching to the less polar solvent mixture 2:1 hexanes/toluene, which has previously provided increased ee's for other  $\alpha$ -Cq cyclic ketones constructed through palladium-catalyzed enantioselective decarboxylative allylic alkylation,<sup>15</sup> did not affect the reaction time but furnished ketone (*S*)-**14b** in a diminished 88% ee (entry 2). Changing to ethereal solvents (entries 3 and 4) drastically decreased the reaction time, facilitating the full consumption of  $\beta$ -ketoester **13b** in 1.0 h. While the use of MTBE (entry 3) afforded cyclopentanone (*S*)-**14b** in nearly identical ee to the mixed nonpolar solvent system (entry 2), switching to THF (entry 4) proved deleterious. Ultimately, the use of Pd<sub>2</sub>(dba)<sub>3</sub> (2.75 mol %) with (*S*)-(*p*-CF<sub>3</sub>)<sub>3</sub>-*t*-BuPHOX ((*S*)-**L2**, 6.00 mol %) in toluene (0.033 M in  $\beta$ -ketoester **13b**) at 20 °C proved optimal.

Subsequently, we explored the substrate scope of the enantioselective allylic alkylation of cyclopentanones. We found that our reaction manifold was tolerant of a variety of substitution at the  $\alpha$ -position of the cyclopentanone (Scheme 2).<sup>16</sup> Alkyl-substituted  $\alpha$ -Cq cyclopentanones (*S*)-**14c**, (*S*)-**14d**,

**Scheme 2.** Substrate Scope of Cyclopentanone Substitution in Enantioselective Allylic Alkylation<sup>a</sup>



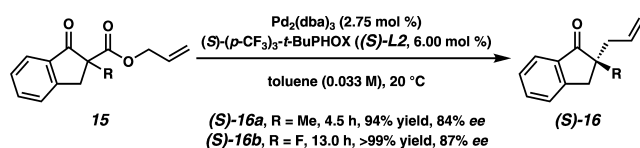
<sup>a</sup>Unless otherwise noted, all reported yields are isolated yields. Enantiomeric excess (ee) was determined by either analytical chiral SFC or HPLC. <sup>b</sup>Conditions:  $\beta$ -ketoester **13** (0.19 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (2.75 mol %), (*S*)-**L2** (6.00 mol %), toluene (5.8 mL). <sup>c</sup>Cyclopentanone product was volatile, resulting in a reduced isolated yield compared to other substrates. <sup>d</sup>Reaction performed at 0 °C. <sup>e</sup>Yield reported based on recovered  $\beta$ -ketoester starting material. Isolated yield was 56%.

and (*S*)-**14e** were each produced over reaction times greater than 30 h with ee's ranging from 86% to 88%, providing the more sterically congested cyclopentanone (*S*)-**14e** over a slightly longer reaction time.<sup>13</sup> Along with ester-substituted cyclopentanone (*S*)-**14b**, nitrile (*S*)-**14f** and phthalamide (*S*)-**14g** were both produced quite rapidly at 20 °C in excellent yield with good ee (2.5 h, 97% yield, 87% ee and 3.0 h, 93% yield, 88% ee, respectively). We found that we could increase the ee of these two products significantly by lowering the temperature without any deleterious effect on the yield, providing cyclopentanones (*S*)-**14f** and (*S*)-**14g** in an improved 90% ee and 93% ee, respectively, at 0 °C over 23.0 h. This result represents a dramatic

improvement in the formation of (S)-14g compared to our previously reported system, employing THF as the solvent with (S)-L1 as the ligand, which provided (S)-14g in only 67% yield with 48% ee.<sup>3d</sup> Comparatively, benzyl-substituted cyclopentanones proved to have a correlation between the electronics of the aryl substituent and the overall reaction time. Electron rich *p*-OMe-benzyl cyclopentanone (S)-14h was furnished in only 8.0 h, while the electron-neutral benzyl and *p*-Me-benzyl products ((S)-14i and (S)-14a) were each provided over a slightly extended reaction time (13.0 h). Contrastingly, the reaction producing electron poor *p*-CF<sub>3</sub>-benzyl-substituted (S)-14j failed to proceed to full conversion over 96.0 h, affording the product in a reduced 56% overall yield (83% yield based on recovered  $\beta$ -ketoester). Interestingly, despite the variable reaction times, the ee of the benzyl-substituted cyclopentanone products was largely consistent (88%–89% ee), with a slight boost for the electron-rich *p*-OMe-benzyl product ((S)-14h) to 92% ee.

Additionally, we found that indanones were competent substrates within our reaction manifold (Scheme 3).<sup>3d,5a,d,7g</sup>

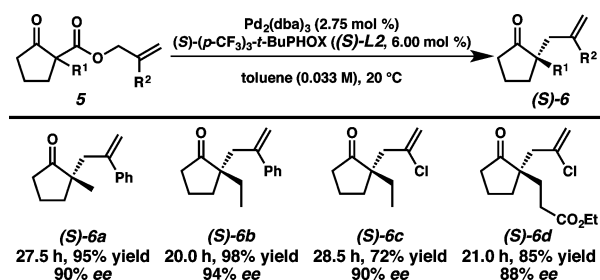
### Scheme 3. Enantioselective Allylic Alkylation of Indanone Substrates



Methyl-substituted indanone product (S)-16a was furnished over a greatly shortened 4.5 h compared to the methyl-substituted cyclopentanone product ((S)-14c, see Scheme 2). Additionally, bicycle (S)-16a was provided in 94% yield with 84% ee. Comparatively, the fluorinated analog (S)-16b was produced in an improved >99% yield and 87% ee, albeit over a longer reaction time (13.0 h).

Having investigated the tolerance of our reaction manifold to a variety of substitutions on the cyclopentanone ring, we next evaluated the potential to use 2-substituted allyl fragments in the enantioselective allylic alkylation of cyclopentanones (Scheme 4). Methyl- and ethyl-substituted cyclopentanone products (S)-6a and (S)-6b containing a 2-phenylallyl fragment were both produced in excellent yield and with 90% and 94% ee, respectively. Comparatively, cyclopentanones (S)-6c and (S)-6d, each containing a 2-chloroallyl fragment, were produced with

### Scheme 4. Enantioselective Allylic Alkylation of Cyclopentanone Substrates with 2-Substituted Allyl Fragments.<sup>a</sup>

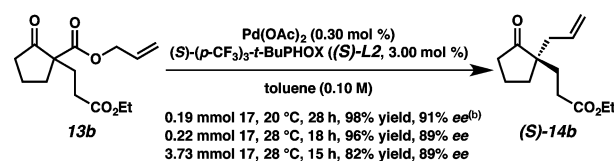


<sup>a</sup>All reported yields are isolated yields. Enantiomeric excess (ee) was determined by analytical chiral SFC. <sup>a</sup>Conditions:  $\beta$ -ketoester 5 (0.19 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (2.75 mol %), (S)-L2 (6.00 mol %), toluene (5.8 mL).

similar ee's in slightly reduced yield. Interestingly, each of the alkyl-substituted cyclopentanone products possessing a 2-substituted allyl fragment were produced over a shorter reaction time than the same substrates containing an unsubstituted allyl fragment (see Scheme 2).

Lastly, we examined the potential to apply our recently disclosed palladium(II) low catalyst loading protocol for enantioselective decarboxylative allylic alkylation to this new substrate class.<sup>17</sup> We discovered that on a small scale, ester-substituted cyclopentanone (S)-14b was provided in an identical 91% ee and an improved 98% yield at 20 °C using only 0.15 mol % palladium catalyst (Scheme 5) compared to our palladium(0)-

### Scheme 5. Low Catalyst Loading Palladium(II)-Mediated Enantioselective Allylic Alkylation<sup>a</sup>



<sup>a</sup>All reported yields are isolated yields. Enantiomeric excess (ee) was determined by analytical chiral SFC. <sup>b</sup>Pd(OAc)<sub>2</sub> (0.15 mol %), (S)-L2 (1.50 mol %) used.

mediated reaction conditions, which employ 5.50 mol % palladium (vide supra). Increasing the scale of the reaction slightly (0.22 mmol) as well as the temperature (28 °C) and catalyst loading (0.30 mol % Pd) furnished (S)-14b over a reduced 18 h in 96% yield with 89% ee. Using these reaction conditions and increasing the scale 17 times (3.73 mmol) provided (S)-14b with identical 89% ee, although in a slightly diminished 82% yield.

In conclusion, we have disclosed the first general method for the construction of  $\alpha$ -Cq cyclopentanones by enantioselective palladium-catalyzed decarboxylative allylic alkylation. The reaction manifold proved optimal when electron-deficient (S)-(p-CF<sub>3</sub>)<sub>3</sub>-t-BuPHOX ((S)-L2) was employed, providing a variety of substituted cyclopentanone products in up to near-quantitative yield and with up to 94% ee. Additionally, the enantioselective allylic alkylation was found to be tolerant of allyl fragments substituted at the 2-position. Use of low-catalyst loading, palladium(II)-mediated reaction conditions was successfully accomplished, facilitating the synthesis of  $\alpha$ -Cq cyclopentanones on increased scale in a cost-effective manner. Currently, our laboratory is pursuing further development of this technology through substrate scope extension and application in natural product synthesis.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02376.

Experimental details, characterization data, and NMR and IR spectra (PDF)

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### Author Contributions

<sup>†</sup>R.A.C. and S.A.L. contributed equally.



## Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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- (13) Absolute configuration of cyclopentanone (**S**)-**19** was determined by comparison of the optical rotation of the methyl ketone Wacker product to the known literature value; see: Thominiaux, C.; Roussé, S.; Desmaële, D.; d'Angelo, J.; Riche, C. *Tetrahedron: Asymmetry* **1999**, *10*, 2015–2021. The absolute configuration of all other products generated herein was assigned by analogy to the absolute configuration of (**S**)-**19**. For full details, see the [Supporting Information](#).
- (14) Additionally, silyl enol ether derivatives of cyclopentanones were found to be suitable enolate precursors for the formation of  $\alpha$ -Cq cyclopentanones under similar reaction conditions with an external allyl electrophile. See the [Supporting Information](#).
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- (16) Additionally,  $\alpha',\alpha'$ -disubstituted cyclopentanones were suitable substrates within the disclosed reaction manifold, albeit generally giving the  $\alpha$ -Cq cyclopentanone products in reduced yields and with slightly diminished ee.  $\beta,\beta$ -disubstituted cyclopentanones were not suitable substrates under the optimized conditions. See the [Supporting Information](#) for full details.
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