Organic LETTERS

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Palladium-Catalyzed Enantioselective Decarboxylative Allylic Alkylation of Cyclopentanones

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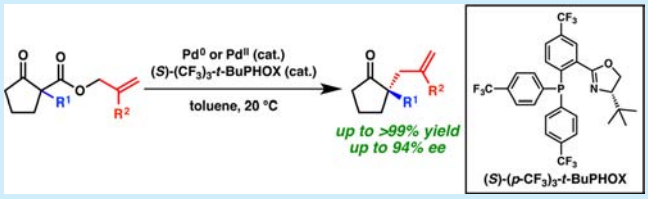
Supporting Information

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_3)$_3$-*t*-BuPHOX ligand, α-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.

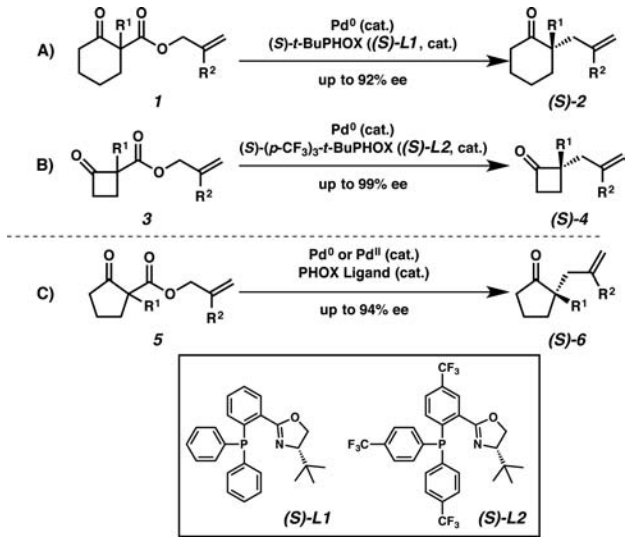


The efficient construction of all-carbon quaternary centers (Cq's) remains a challenge for the modern synthetic chemist.[1] The difficulty associated with forming Cq's arises from the inherent steric congestion during the C−C bond-forming event. Toward this end, our laboratory disclosed the first palladium-catalyzed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

Contrastingly, cyclopentanones have typically performed worse than the corresponding 6-membered substrates, often furnishing the α-Cq ketone products in comparatively reduced yields and enantiomeric excess (ee).[3d] Only a few examples with limited substrate scope exist for the formation of α-Cq cyclopentanones by transition-metal-catalyzed enantioselective allylic alkylation.[7] However, cyclopentanes containing enantioenriched Cq's characterize a number of biologically pertinent and chemically fascinating natural products, including polycyclic terpenoids **7**,[8] **8**,[9] and **9**[10] as well as alkaloids **10**,[11] **11**,[11] and **12**[12] (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 α-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 β-ketoester **13a**, using catalytic $Pd_2(dba)_3$ at 20 °C in toluene in the presence of a chiral PHOX ligand, affording enantioenriched α-Cq cyclopentanone **14a** (Table 1).[13,14] 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_3)$_3$-*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_3)$_3$-*i*-PrPHOX^{Me2} ((***R***)-**L3**), provided cyclic ketone (***R***)-**14a** in a decreased 83% ee (entry 3).[4a] Similarly to (***R***)-**L3**, geminally disubstituted

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



Received: August 17, 2015
Published: October 26, 2015

DOI: 10.1021/acs.orglett.5b02376
Org. Lett. 2015, 17, 5160−5163

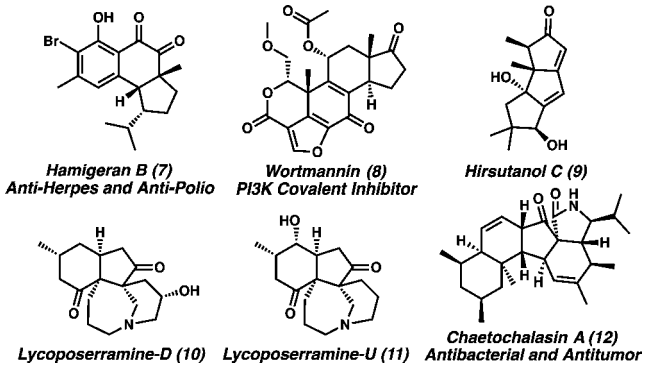
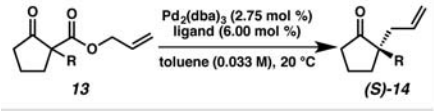
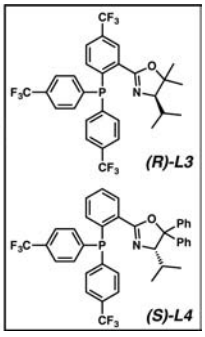


Figure 1. Natural products characterized by cyclopentane rings containing chiral all-carbon quaternary centers (Cq's).

Table 1. PHOX Ligand Screen[a]





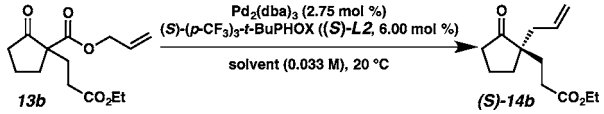
entry	R	β-Ketoester	product	ligand	ee (%)[b]
1	*p*-Me-$C_6H_4CH_2$–	**13a**	**(*S*)-14a**	**(*S*)-L1**	87
2	*p*-Me-$C_6H_4CH_2$–	**13a**	**(*S*)-14a**	**(*S*)-L2**	89
3	*p*-Me-$C_6H_4CH_2$–	**13a**	**(*S*)-14a**	**(*R*)-L3**	83
4	*p*-Me-$C_6H_4CH_2$–	**13a**	**(*S*)-14a**	**(*S*)-L4**	82
5	$EtO_2CCH_2CH_2$–	**13b**	**(*S*)-14b**	**(*S*)-L1**	82
6	$EtO_2CCH_2CH_2$–	**13b**	**(*S*)-14b**	**(*S*)-L2**	91
7	$EtO_2CCH_2CH_2$–	**13b**	**(*S*)-14b**	**(*R*)-L3**	82
8	$EtO_2CCH_2CH_2$–	**13b**	**(*S*)-14b**	**(*S*)-L4**	80

[a]Conditions: β-ketoester **13** (0.19 mmol), $Pd_2(dba)_3$ (2.75 mol %), ligand (6.00 mol %), toluene (5.8 mL). [b]Measured by analytical chiral SFC.

valine-derived (*S*)-(*p*-CF_3)$_2$-*i*-PrPHOX^{Ph2} ((**S**)-**L4**) afforded ketone (**S**)-**14a** with nearly equivalent ee (82%, entry 4). Switching to ester-substituted β-ketoester **13b**, we confirmed (*S*)-(*p*-CF_3)$_3$-*t*-BuPHOX ((**S**)-**L2**) was indeed the optimal ligand for the desired enantioselective decarboxylative allylic alkylation, providing enantioenriched α-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 β-ketoester **13b** (Table 2). Employing identical

Table 2. Solvent Effect on Enantiomeric Excess of Cyclopentanone Product (*S*)-14b[a]



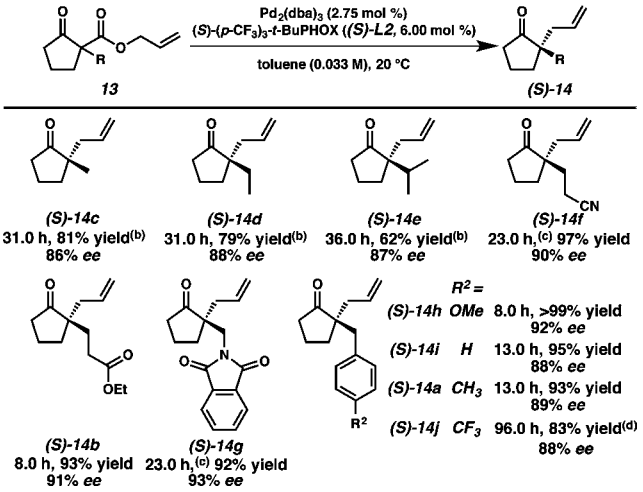
entry	solvent	time (h)	ee[b] (%)
1	toluene	8.0	91
2	2:1 hexane/toluene	8.0	88
3	MTBE	1.0	87
4	THF	1.0	81

[a]Conditions: β-ketoester **13b** (0.19 mmol), $Pd_2(dba)_3$ (2.75 mol %), (**S**)-**L2** (6.00 mol %), toluene (5.8 mL). [b]Measured by analytical chiral SFC.

reaction conditions from our ligand screen, using toluene as the solvent, we isolated α-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 α-Cq cyclic ketones constructed through palladium-catalyzed enantioselective decarboxylative allylic alkylation,[15] 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 β-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 $Pd_2(dba)_3$ (2.75 mol %) with (*S*)-(*p*-CF_3)$_3$-*t*-BuPHOX ((**S**)-**L2**, 6.00 mol %) in toluene (0.033 M in β-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 α-position of the cyclopentanone (Scheme 2).[16] Alkyl-substituted α-Cq cyclopentanones (**S**)-**14c**, (**S**)-**14d**,

Scheme 2. Substrate Scope of Cyclopentanone Substitution in Enantioselective Allylic Alkylation[a]



[a]Unless otherwise noted, all reported yields are isolated yields. Enantiomeric excess (ee) was determined by either analytical chiral SFC or HPLC. [a]Conditions: β-ketoester **13** (0.19 mmol), $Pd_2(dba)_3$ (2.75 mol %), (**S**)-**L2** (6.00 mol %), toluene (5.8 mL). [b]Cyclopentanone product was volatile, resulting in a reduced isolated yield compared to other substrates. [c]Reaction performed at 0 °C. [d]Yield reported based on recovered β-ketoester starting material. Isolated yield was 56%.

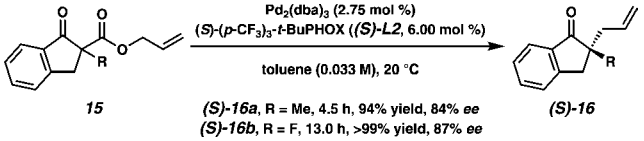
and (**S**)-**14e** were each produced over reaction times greater than 30 h with ee's ranging from 86% to 88%, providing the more sterically congested cyclopentanone (**S**)-**14e** over a slightly longer reaction time.[13] Along with ester-substituted cyclopentanone (**S**)-**14b**, nitrile (**S**)-**14f** 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

DOI: 10.1021/acs.orglett.5b02376
Org. Lett. 2015, 17, 5160−5163

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.[3d] 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_3-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 *β*-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).[3d,5a,d,7g]

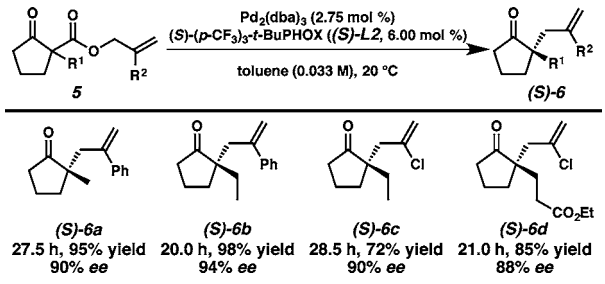
Scheme 3. Enantioselective Allylic Alkylation of Indanone Substrates



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.[a]

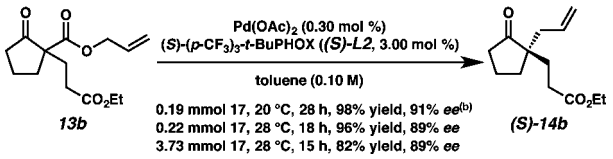


[a]All reported yields are isolated yields. Enantiomeric excess (ee) was determined by analytical chiral SFC. [a]Conditions: *β*-ketoester **5** (0.19 mmol), $Pd_2(dba)_3$ (2.75 mol %), (*S*)-**L2** (6.00 mol %), toluene (5.8 mL).

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.[17] 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[a]



[a]All reported yields are isolated yields. Enantiomeric excess (ee) was determined by analytical chiral SFC. [b]$Pd(OAc)_2$ (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 *α*-Cq cyclopentanones by enantioselective palladium-catalyzed decarboxylative allylic alkylation. The reaction manifold proved optimal when electron-deficient (*S*)-(*p*-CF_3)$_3$-*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 *α*-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

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DOI: 10.1021/acs.orglett.5b02376
Org. Lett. 2015, 17, 5160−5163

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the NIH-NIGMS (R01GM080269 and postdoctoral fellowship F32GM073332 to A.M.H.), Amgen, the Gordon and Betty Moore Foundation, and Caltech for financial support. R.A.C. gratefully acknowledges the support of this work provided by a predoctoral fellowship from the National Cancer Institute of the National Institutes of Health under Award No. F31A17435. Additionally, we thank Eli Lilly (predoctoral fellowship to J.T.M.) and the Fannie and John Hertz Foundation (predoctoral fellowship to D.C.B.).

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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 α-Cq cyclopentanones under similar reaction conditions with an external allyl electrophile. See the Supporting Information.

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(16) Additionally, α',α'-disubstituted cyclopentanones were suitable substrates within the disclosed reaction manifold, albeit generally giving the α-Cq cyclopentanone products in reduced yields and with slightly diminished ee. β,β-disubstituted cyclopentanones were not suitable substrates under the optimized conditions. See the Supporting Information for full details.

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DOI: 10.1021/acs.orglett.5b02376
Org. Lett. 2015, 17, 5160−5163