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## An Efficient Protocol for the Palladium-catalyzed Asymmetric Decarboxylative Allylic Alkylation Using Low Palladium Concentrations and a Palladium(II) Precatalyst

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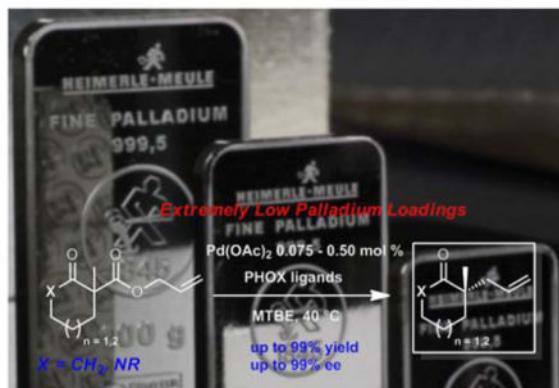
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### Abstract

Enantioselective catalytic allylic alkylation for the synthesis of 2-alkyl-2-allylcycloalkanones and 3,3-disubstituted pyrrolidinones, piperidinones and piperazinones has been previously reported by our laboratory. The efficient construction of chiral all-carbon quaternary centers by allylic alkylation was previously achieved with a catalyst derived *in situ* from zero valent palladium sources and chiral phosphinooxazoline (PHOX) ligands. We now report an improved reaction protocol with broad applicability among different substrate classes in industry-compatible reaction media using loadings of palladium(II) acetate as low as 0.075 mol % and the readily available chiral PHOX ligands. The novel and highly efficient procedure enables facile scale-up of the reaction in an economical and sustainable fashion.

### Graphical Abstract



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Dedicated to Professor Stephen L. Buchwald on the occasion of his 60<sup>th</sup> birthday.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.201500253>.

## Keywords

asymmetric catalysis; allylic alkylation; palladium; quaternary center; scale-up

The catalytic enantioselective construction of all-carbon quaternary centers represents a considerable challenge in synthetic organic chemistry.<sup>[1,2]</sup> A new carbon–carbon bond must be formed in the face of significant steric hindrance to accomplish this goal.

Synthetic methods for the generation of quaternary stereocenters are extremely desirable given their prevalence in a broad variety of biologically active natural products.<sup>[2]</sup> Despite their importance, the number of highly enantioselective transformations that construct quaternary stereocenters under mild reaction conditions is limited. The palladium-catalyzed decarboxylative asymmetric allylic alkylation is a powerful and reliable approach to bridge this gap.<sup>[3]</sup>

This class of reactions was developed in the 1980s by Tsuji and co-workers, employing various substrates, such as allyl enol carbonates<sup>[4]</sup> or  $\beta$ -ketoesters.<sup>[5]</sup> Over the past decade our group has made significant contributions to this field; our initial efforts resulted in the first catalytic enantioselective Tsuji allylic alkylation of simple alkanone derivatives in 2004.<sup>[6]</sup> We have since expanded the scope of this transformation considerably,<sup>[7]</sup> and elucidated the catalytic cycle through mechanistic investigations.<sup>[8]</sup> Numerous applications of this technology in the field of natural product synthesis have been demonstrated by our group<sup>[9]</sup> and others,<sup>[10]</sup> highlighting the power and broad applicability of this reaction.

Despite the importance of palladium-catalyzed decarboxylative asymmetric alkylation in total synthesis, its application on an industrial scale is hampered by the need for high catalyst loadings (5.0–10.0 mol %). The high cost of palladium significantly increases the cost of each reaction. Furthermore, high catalyst loadings also increase the risk of poisoning downstream chemistry or contaminating active pharmaceutical ingredients.<sup>[11]</sup>

These drawbacks have prevented application of the enantioselective allylic alkylation on a larger scale. The application of transition metal catalysis to industry-scale synthesis requires transformations that are safe, robust, cost-effective, and scalable.<sup>[12]</sup>

Consequently, there remains a significant need to develop new reaction protocols that employ lower catalyst concentrations and hence facilitate the scale-up of such transformations. Consequently, we began to question the existing protocols and reinvestigated critical reaction parameters such as the palladium source, catalyst loading, solvent and temperature, with respect to the scalability of our reaction and its compatibility with industry requirements.

We first turned our attention to the palladium source in an effort to replace the oxygen-sensitive  $\text{Pd}_2(\text{dba})_3$  used in our original conditions. Therefore, the original catalytic enantioconvergent decarboxylative allylic alkylation of allyl 1-methyl-2-oxocyclohexanecarboxylate (**1a**) was chosen as a model reaction (Scheme 1).<sup>[13]</sup>

The catalytic cycle of the allylic alkylation operates starting from a zero valent palladium source and is believed to involve a palladium (0/II) redox cycle.<sup>[8]</sup>

While utilization of Pd<sub>2</sub>(dba)<sub>3</sub> renders *in situ* reduction of the catalyst obsolete, its application is not only hampered by increased sensitivity to oxygen, but also the dibenzylideneacetone ligand is challenging to separate from non-polar reaction products.

In their original reports Tsuji and co-workers performed the allylic alkylation reactions in the presence of Pd(OAc)<sub>2</sub> and PPh<sub>3</sub>.<sup>[4,5a]</sup> We adopted this strategy and started screening a variety of Pd(II) sources in combination with the chiral phosphinooxazoline ligands (*S*)-*t*-BuPHOX **3**<sup>[14]</sup> and (*S*)-(CF<sub>3</sub>)<sub>3</sub>-*t*-BuPHOX **4** (Figure 1).<sup>[15]</sup>

When comparing Pd(OAc)<sub>2</sub> and Pd<sub>2</sub>(dba)<sub>3</sub> at 1.0 mol % palladium in combination with a tenfold excess of PHOX ligands **3** or **4** respectively, in TBME at 80 °C we were pleased to find that both palladium sources exhibited comparable catalytic performance (Table 1, entries 1–4). At lower palladium concentrations, however, Pd(OAc)<sub>2</sub> was clearly superior, delivering quantitative yields and good enantioselectivity at only 0.10 mol % Pd (Table 1, entries 5 and 6). When 0.10 mol % Pd<sub>2</sub>(dba)<sub>3</sub> was used to form the catalyst, a dramatic decrease in yields was observed (Table 1, entries 7 and 8).

We then became interested to see if other palladium(II) sources were equally suited to catalyze the decarboxylative allylic alkylation. Consequently, a total of eight different commercially available Pd(II) precursors were examined in our model reaction in the presence of ligand **3**.<sup>[16]</sup> While with Pd(OAc)<sub>2</sub> a quantitative yield for the desired allylic alkylation product was obtained, none of the other palladium(II) sources promoted any conversion of the substrate. We reason that the limited solubility of these palladium salts in TBME likely prevented catalysis.

Limited to Pd(OAc)<sub>2</sub> as the only viable palladium precursor, we turned our attention to minimizing the catalyst loading. A screening of six different catalyst loadings, ranging from 0.05 mol % to 1.0 mol %, was performed (Table 2). All reactions were conducted in the presence of a tenfold excess of ligand with respect to palladium, in TBME at 40 °C.<sup>[18]</sup>

Under these reaction conditions, palladium loadings as low as 0.10 mol % were sufficient to deliver the desired allylic alkylation product in 90% yield and with high enantioselectivity (Table 2, entry 5). To obtain a quantitative yield of ketone **2a**, the catalyst loading was increased to 0.15 mol % of Pd(OAc)<sub>2</sub> (Table 2, entry 4). Enantioselective allylic alkylation reactions are typically performed in solvents such as THF,<sup>[6,19]</sup> DCM,<sup>[19b,c]</sup> dioxane<sup>[2,20]</sup> or diethylether.<sup>[13]</sup> While these solvents are common for academic laboratory scale, their use prohibits conducting the reaction in an industrial setting.<sup>[21]</sup> We sought to overcome this limitation and performed a solvent screening with a total of ten different solvents that are considered to be safe, sustainable and cost-efficient (Table 3).<sup>[21,22]</sup>

Conversion of allyl 1-methyl-2-oxocyclohexane-carboxylate (**1a**) in TBME resulted in a high yield and good enantioselectivity (Table 3, entry 1). When the reaction was performed in various alkyl acetates the yields dropped dramatically, to 12%, 28% and 17% respectively (Table 3, entries 2, 4 and 5). Similarly low yields were observed for reactions performed in

acetonitrile, dimethylacetamide, 2-Me-THF, and acetone (Table 3, entries 3, 6, 8 and 10). Moderate conversion was found when the reaction was performed in toluene (Table 3, entry 7). Consequently, all further experiments were carried out in TBME.

At this point, we considered that the palladium concentration could be lowered further by performing the reaction at higher temperatures, and we were interested in the influence of increased reaction temperature on stereoselectivity. All experiments were performed in TBME with a tenfold excess of ligand **3** (Table 4). A palladium loading as low as 0.075 mol % afforded ketone **2a** in 99% yield when the reaction was performed at 80 °C, which corresponds to a turnover number of 1320 for the *in situ* formed catalyst. Nevertheless, a slightly lower enantioselectivity of 84% was observed in this case (Table 4, entry 1). At 60 °C and 40 °C, palladium loadings of 0.10 and 0.125 mol % respectively were sufficient to deliver the desired product in quantitative yield and retain high enantioselectivity (Table 4, entries 2 and 3).

We then applied the protocol to the 10 and 20 mmol scale synthesis of alpha-quaternary ketones **2a** and **2b** (Table 5). Both reactions were performed in TBME with a tenfold excess of ligand **3**. Cyclohexanone **1a** was converted on a 10.0 mmol scale (1.96 g) in the presence of 0.15 mol % (3.37 mg) of Pd(OAc)<sub>2</sub> at 60 °C. The corresponding product **2a** was isolated by distillation in excellent yield and high enantioselectivity (Table 5, entry 1). Similarly, tetralone substrate **1b** was subjected to enantioselective allylic alkylation conditions at 40 °C on a 20 mmol scale (4.89 g). The desired product **2b** was purified by flash chromatography and isolated in 95% yield and 88% ee (Table 5, entry 2).

Satisfied with the scalability of our new allylic alkylation conditions, we turned our attention to reducing the ligand loading. A series of six experiments, employing different quantities of ligand, from 0.20 mol % to 1.0 mol %, in the presence of 0.10 mol % Pd(OAc)<sub>2</sub> was performed (Table 6).

A ligand loading of 0.40 mol %, which corresponds to a 4-fold excess of ligand with respect to palladium, was sufficient to provide the desired product in quantitative yield and high enantioselectivity (Table 6, entry 4). Only at a loading of 0.20 mol % of ligand **3** a slight decrease in enantioselectivity was observed (Table 6, entry 5).

Finally, we investigated the influence of concentration on reactivity. A brief study across five different substrate concentrations was executed (Table 7).

We were pleased to find that the decarboxylative alkylation reaction could be performed in high concentrations of up to 0.40 M without any negative impact on yield or enantiomeric excess (Table 7, entry 1). When the reaction was performed at higher dilution (0.033 M) a slight decrease in yield and optical purity was observed (Table 7, entry 5).

After optimizing all critical reaction parameters for the conversion of cyclohexanone substrate **1a** we sought to investigate the substrate scope of this novel protocol. In particular the decarboxylative allylic alkylation of lactams is important, given the prevalence of quaternary *N*-heterocycles in biologically active alkaloids and their potential importance in pharmaceutical agents.<sup>[23]</sup> Initial experiments suggested that higher palladium loadings were

required for the decarboxylative allylic alkylation of piperidinones. Consequently, a brief study was performed to determine the minimal palladium loading needed to efficiently catalyze the reaction (Table 8). The electron-poor ligand (*S*)-(CF<sub>3</sub>)<sub>3</sub>-*t*-BuPHOX **4** was applied in the presence of varying amounts of Pd(OAc)<sub>2</sub> in TBME at 60 °C.<sup>[23]</sup>

At 0.10 mol % of Pd(OAc)<sub>2</sub> the desired product was obtained in only 77% yield and a reduced enantioselectivity of 84% ee. (Table 8, entry 3) Nevertheless, a catalyst concentration of only 0.30 mol % was sufficient to render the chiral lactam **6a** in 85% yield and 97% ee (Table 8, entry 2). Compared to the original report, in which 5.0 mol % of Pd<sub>2</sub>(dba)<sub>3</sub> were applied, this constitutes a more than thirtyfold decrease in palladium loading.

To demonstrate the broad applicability of this novel protocol, a total of ten compounds were subjected to the improved reaction parameters (Table 9). Asymmetric allylic alkylation to generate products **2a**, **2b** and **6a** was discussed previously in detail (Table 9, entries 1–3). Allylmethylpiperidinone **6b** and allylfluoropiperidinone **6d** were synthesized in a similar fashion. Yields of 81% and 80% respectively, and enantioselectivities of up to 99% could be obtained (Table 9, entry 4 and 6). In the latter case, a catalyst loading as low as 0.125 mol % was sufficient to yield the product in near to perfect enantioselectivity. Despite the 80-fold reduction in palladium loading compared to the original procedure, no erosion of enantioselectivity was observed (Table 9, entry 6).

Gratifyingly, the novel allylic alkylation protocol could be applied to seven-membered rings as well; however, despite a near quantitative yield only reduced enantiomeric excess of 70% was observed for ketone **2c** (Table 9, entry 7). Nevertheless, seven-membered caprolactam **6e** was isolated in 95% yield and high enantioselectivity (Table 9, entry 8). Notably, despite the dilution, cyclohexylketal **2d** was generated in 79% yield and good enantioselectivity through intermolecular allylic alkylation of the corresponding silyl enol ether and allyl methanesulfonate (Table 9, entry 9).

Finally, cyclohexanedione **2e**, which is a critical intermediate in the synthesis of (–)-cyanthiwigin F,<sup>[9b]</sup> could be accessed through double enantioselective allylic alkylation of the bis(β-ketoester) **1e** in excellent yield and near perfect enantioselectivity using only 0.25 mol % palladium. This corresponds to 5% of the palladium loading used in the original protocol. Despite the considerable reduction in catalyst concentration the yield for this reaction was improved to 97% (Table 9, entry 10).

In conclusion, we have reported a novel and highly efficient protocol for the decarboxylative enantioselective allylic alkylation using palladium acetate and loadings below 0.50 mol %. For simple quaternary ketone products metal loadings as low as 0.075 mol % effectively catalyzed the reaction and generated the desired products in high yields and enantioselectivities. Thereby, turnover numbers (TON) of up to 1320 could be reached. We envision that the key for high TON in this system involves the lack of dba in the reaction mixture, which would likely result in trapped Pd(0)-olefin species that lie outside of the catalytic cycle.<sup>[8b]</sup> Furthermore, a variety of critical reaction parameters such as temperature, concentration, ligand stoichiometry and choice of solvent were optimized to

increase the scalability and lower the cost basis for palladium-catalyzed allylic alkylation reactions. The method is broadly applicable among a variety of substrate classes for both inter- and intramolecular allylic alkylations, and is tolerant of most functional groups because of the neutral reaction conditions and modest reaction temperatures. We anticipate these advances will promote the continued use of palladium-catalyzed allylic alkylation reactions as means of installing quaternary stereocenters in multi-step syntheses in academic laboratories, and hope to see these reactions used to synthesize valuable molecules in the chemical and pharmaceutical industries.

## Experimental Section

### General Procedure

In a nitrogen-filled glove box, a stock solution of Pd(OAc)<sub>2</sub> (1.1 mg, 4.9 μmol, in 20 mL TBME) was prepared in a 20 mL scintillation vial. In a separate 1-dram vial, (*S*)-*t*-BuPHOX (1.9 mg, 4.9 μmol) was dissolved in TBME (1 mL). To a 2-dram vial equipped with a magnetic stirbar, 1.02 mL of the Pd(OAc)<sub>2</sub> solution was added (56 μg, 0.25 μmol, 0.125 mol %) followed by 0.51 mL of the (*S*)-*t*-BuPHOX solution (0.97 mg, 2.5 μmol, 1.25 mol %). This mixture was stirred at ambient temperature (28 °C) in the glove box for 30–40 min. Substrate (0.20 mmol, 1.0 equiv) was taken up in TBME (0.5 mL) and added to the stirring catalyst solution. In reactions analyzed by GC, tridecane (24 μL, 0.1 mmol, 0.5 equiv) was added. The reaction was sealed with a Teflon-lined cap, removed from the glove box and stirred at the indicated temperature for the indicated duration of time. At this point, the reaction was analyzed by GC, or passed through a silica plug, concentrated in vacuo, and purified by distillation or column chromatography.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

We wish to thank the NIH-NIGMS (R01GM080269), Amgen, AbbVie, Boehringer Ingelheim, and Caltech for financial support. This material is based upon work supported by the German National Academy of Sciences Leopoldina under Grant No. LPDS 2011-12 (fellowship to A.N.M.). D.C.D. is grateful for financial support from the National Science Foundation (Predoctoral Research Fellowship, No. DGE-1144469). We also wish to thank the National Cancer Institute of the National Institutes of Health under Award Number F31CA174359 (fellowship to R. A. C.), and the Swiss National Science Foundation (SNSF, fellowship for M. L.). Y.N. thanks Toray Industries, Inc. for a postdoctoral fellowship. Dr. Scott Virgil is acknowledged for assistance with instrumentation. Dr. John A. Enquist and Dr. Nathaniel H. Sherden are acknowledged for preliminary experimental work related to these results. Dr. Douglas C. Behenna is acknowledged for insightful discussions.

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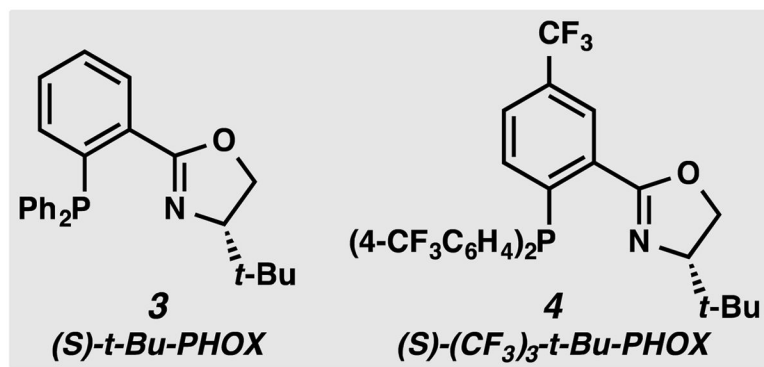
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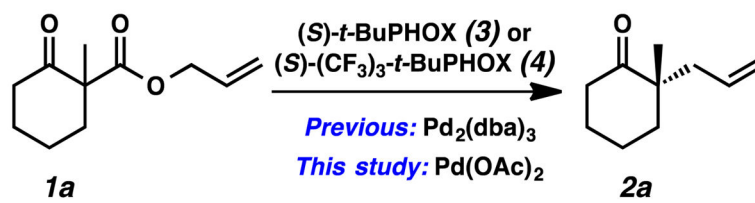
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16. Palladium(II) sources applied in screening: Pd(OAc)<sub>2</sub>, PdCl<sub>2</sub>, Pd(PhCN)<sub>2</sub>Cl<sub>2</sub>, Pd(CH<sub>3</sub>CN)<sub>2</sub>Cl<sub>2</sub>, PdBr<sub>2</sub>, Pd(acac)<sub>2</sub>, [Pd(allyl)Cl]<sub>2</sub>, Pd(TFA)<sub>2</sub>.
17. See supporting information.
18. The high-excess of ligand was chosen to facilitate formation of the active catalyst through *in situ* reduction of Pd(OAc)<sub>2</sub>. We reasoned that the PHOX ligand hereby acts as the reductive agent.
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24. Previous experiments have demonstrated that (*S*)-(CF<sub>3</sub>)<sub>3</sub>-*t*BuPHOX was superior for the transformation of N-heterocyclic substrates. For more details see reference 23.





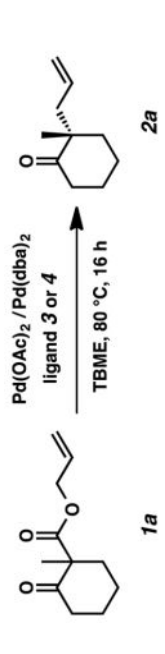
**Figure 1.**  
Chiral phosphinooxazoline ligands applied in this investigation.

**Scheme 1.**

Pd-catalyzed enantioconvergent de-carboxylative allylic alkylation.

Table 1

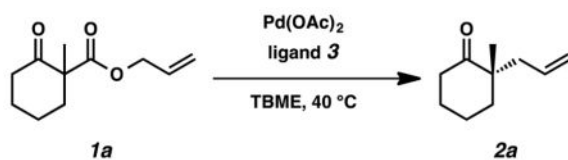
Comparison between palladium precursors in different oxidation states.



Entry	Ligand [mmol]	Pd source [mol%]	Yield [%] <sup>a)</sup>	ee [%] <sup>b)</sup>
1	3	10.0 Pd(OAc) <sub>2</sub>	1.0 99	86
2	4	10.0 Pd(OAc) <sub>2</sub>	1.0 99	82
3	3	10.0 Pd <sub>2</sub> (dba) <sub>3</sub>	1.0 99	84
4	4	10.0 Pd <sub>2</sub> (dba) <sub>3</sub>	1.0 90	82
5	3	1.0 Pd(OAc) <sub>2</sub>	0.1 99	79
6	4	1.0 Pd(OAc) <sub>2</sub>	0.1 99	83
7	3	1.0 Pd <sub>2</sub> (dba) <sub>3</sub>	0.1 12	n.d.
8	4	1.0 Pd <sub>2</sub> (dba) <sub>3</sub>	0.1 14	n.d.

<sup>a)</sup> GC yield relative to an internal standard (tridecane).

<sup>b)</sup> Enantiomeric excess measured by chiral GC.<sup>[17]</sup>

**Table 2**Optimization of the Pd(OAc)<sub>2</sub> loading for the decarboxylative allylic alkylation.

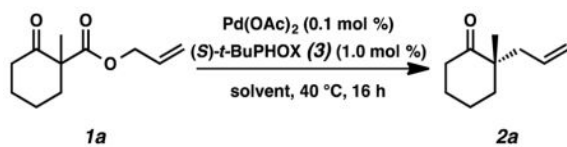
Entry	Pd [mol %]	<b>3</b> [mol %]	Yield [%] <sup>a)</sup>	ee [%] <sup>b)</sup>
1	1.00	10.0	99	90
2	0.50	5.0	99	90
3	0.25	2.50	99	90
4	0.15	1.50	99	89
5	0.10	1.0	90	89
6	0.05	0.50	10	89

<sup>a)</sup> GC yield relative to an internal standard (tridecane).

<sup>b)</sup> Enantiomeric excess measured by chiral GC.<sup>[17]</sup>

Table 3

Optimization of the reaction medium.



Entry	solvent	Yield [%] <sup>a)</sup>	ee [%] <sup>b)</sup>
1	TBME	88	89
2	EtOAc	12 <sup>c)</sup>	74
3	Acetonitrile	trace	-
4	Isopropyl acetate	28	64
5	Isobutyl acetate	17	-
6	Dimethylacetamide	trace	-
7	Toluene	52	80
8	2-Me-THF	21	89
9	<i>t</i> -AmylOH	- <sup>c)</sup>	-
10	Acetone	12 <sup>c)</sup>	47

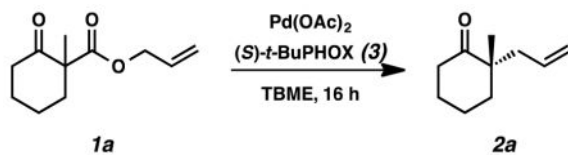
<sup>a)</sup>GC yield relative to an internal standard (tridecane).

<sup>b)</sup>Enantiomeric excess measured by chiral GC.

<sup>c)</sup>Reaction performed at 60 °C.[17]

**Table 4**

Optimization of the palladium loading for the decarboxylative allylic alkylation at various temperatures.



Entry	Pd [mol %]	T [°C]	Yield [%] <sup>a)</sup>	ee [%] <sup>b)</sup>
1	0.075	80	99	84
2	0.10	60	99	88
3	0.125	40	99	89

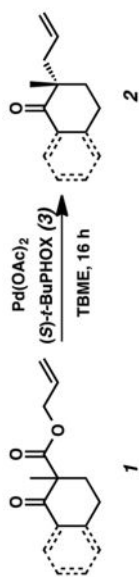
<sup>a)</sup>GC yield relative to an internal standard (tridecane).

<sup>b)</sup>Enantiomeric excess measured by chiral GC.<sup>[17]</sup>



Table 5

Scale-up experiments.



Entry	Substrate	Scale [mol]	T [°C]	Pd [mol %]	Yield [%]	ee [%]
1	Cyclohex anone <b>1a</b>	0.01	60	0.150	95 <sup>a)</sup>	89 <sup>c)</sup>
2	Tetralone <b>1b</b>	0.02	40	0.125	95 <sup>b)</sup>	88 <sup>d)</sup>

<sup>a)</sup> Isolated yield, purification by distillation.

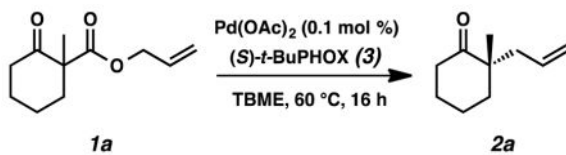
<sup>b)</sup> Isolated yield, purification by flash chromatography.

<sup>c)</sup> Enantiomeric excess measured by chiral GC.

<sup>d)</sup> Enantiomeric excess measured by chiral SFC. [17]

**Table 6**

Optimization of the ligand loading for the decarboxylative allylic alkylation.



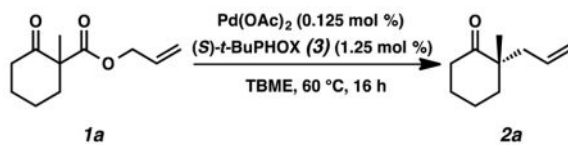
Entry	Ligand 3 [mol %]	Yield [%] <sup>a)</sup>	ee [%] <sup>b)</sup>
1	1.00	99	88
2	0.80	99	89
3	0.60	99	88
4	0.40	99	88
5	0.20	99	86

<sup>a)</sup>GC yield relative to an internal standard (tridecane).

<sup>b)</sup>Enantiomeric excess measured by chiral GC.<sup>[17]</sup>

**Table 7**

Optimization of the reaction concentration.



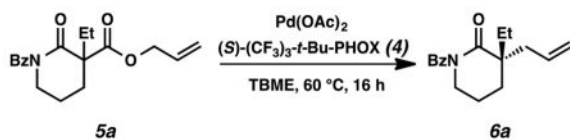
Entry	concentration [M]	Yield [%] <sup>a)</sup>	ee [%] <sup>b)</sup>
1	0.40	99	88
2	0.20	99	88
3	0.10	99	89
4	0.05	99	89
5	0.033	91	87

<sup>a)</sup>GC yield relative to an internal standard (tridecane)

<sup>b)</sup>Enantiomeric excess measured by chiral GC.<sup>[17]</sup>

**Table 8**

Optimization of the palladium loading for the decarboxylative allylic alkylation of lactams.



Entry	Pd [mol %]	4 [mol %]	Yield [%] <sup>a)</sup>	ee [%] <sup>b)</sup>
1	0.50	5.0	87	96
2	0.30	3.0	85	97
3	0.10	1.0	77	84

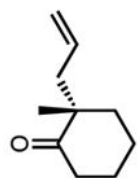
<sup>a)</sup> GC yield relative to an internal standard (tridecane).

<sup>b)</sup> Enantiomeric excess measured by HPLC.<sup>[17]</sup>

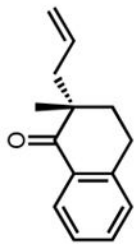
Table 9

Scope of the decarboxylative allylic alkylation.<sup>a)</sup>

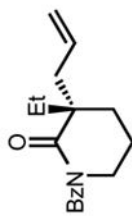
Entry	Protocol	Pd [mol %]	Yield [%]	ee [%]
1	old	5.00	89	88
	new	0.125	99 <i>b)</i>	89
2	old	8.00	97	92
	new	0.125	85 <i>b)</i>	89
3	old	10.0	97	99
	new	0.30	85 <i>f)</i>	97
4	old	10.0	85	99
	new	0.50	81 <i>f)</i>	95
5	old	10.0	91	94
	new	0.125	99 <i>f)</i>	88



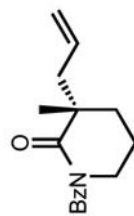
2a



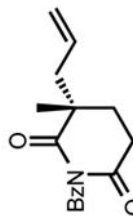
2b



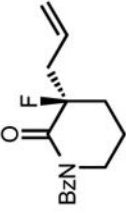
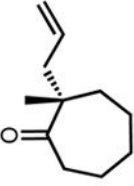
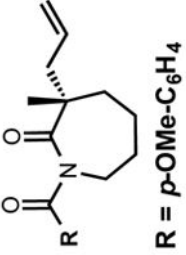
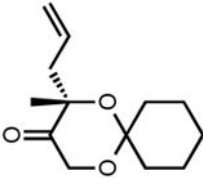
6a



6b



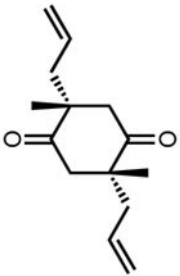
6c

Entry	Protocol	Pd [mol %]	Yield [%]	ee [%]
6		old	89	99
		new	80 <sup>f</sup>	99
7		old	83	87
		new	97 <sup>e,f</sup>	70
8		old	83	93
		new	95 <sup>f</sup>	90
9		old	-	-
		new	79 <sup>c,e,f</sup>	90



Entry	Protocol	Pd [mol %]	Yield [%]	ee [%]
10	old	5.00	78	99
	new	0.25	97 <sup>d), e), f), h)</sup>	99 <sup>g)</sup>



**2e**

a) Conditions: Reactions were performed according to the “general procedure” in TBME at 60 °C with a tenfold excess of ligand **3** with respect to Pd.

b) Temperature: 40 °C.

c) Temperature: 32 °C.

d) Temperature: 27 °C.

e) Reaction performed in toluene.

f) Ligand **4** was used.

g) Diketone **2e** was obtained in 4.85:1.00 d.r.

h) Isolated yield. GC yield relative to an internal standard (tridecane). Enantiomeric excess measured by chiral GC, HPLC or SFC. [17]