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A Palladium-Catalyzed Asymmetric Allylic Alkylation Approach to α-Quaternary γ-Butyrolactones

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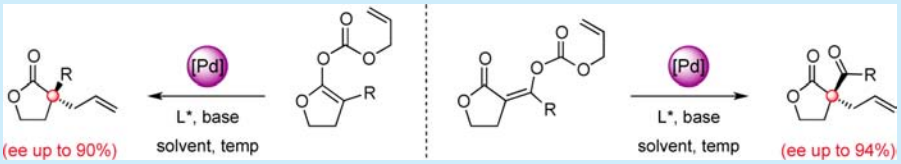
Supporting Information



ABSTRACT: The Pd-catalyzed asymmetric allylic alkylation (Pd-AAA) of enol carbonates derived from γ-butyrolactones is reported, affording the corresponding enantioenriched α,α′-disubstituted γ-butyrolactones in both high yields and high enantioselectivities (up to 94% ee). This method was eventually applied to the synthesis of chiral spirocyclic compounds.

The formation of stereochemically defined quaternary stereogenic centers remains a challenging task.[1] In this quest, the Pd-catalyzed Asymmetric Allylic Alkylation (Pd-AAA), also referred to as the Tsuji−Trost reaction, has proven particularly useful affording both high levels of enantioselectivity and broad functional group tolerance.[2] Moreover, since the first examples reported almost simultaneously by Stoltz,[3] Trost,[4] and Tunge[5] about a decade ago, this reaction has been successfully applied to a variety of prochiral substrates[6] and used as a key step in the synthesis of various natural products and pharmaceuticals.[7]

Our group has also contributed to this field by applying the Pd-AAA to cyclic dienol carbonates of type **I**. This allowed a straightforward and highly enantioselective access to chiral butenolides of type **II** bearing an all-carbon α-quaternary stereogenic center (Figure 1).[8] In addition to being highly enantioselective, this reaction also proved to be particularly regioselective, as the α-alkylation products were obtained preferentially over the γ-alkylation products, and this independently of the substitution pattern on the cyclic dienol carbonate precursor. Moreover, the resulting butenolides could be readily converted to the corresponding β-quaternary butyrolactones **IV** using a sequential DIBAL-reduction/PCC-mediated oxidation with no erosion of the enantioselectivity. Following these results, we became particularly interested in applying this key Pd-AAA process to cyclic enol carbonates of type **V** and **VII**, as it would allow a straightforward access to enantioenriched α-quaternary butyrolactones such as **VI** and **VIII**.

We initiate this study using cyclic enol carbonate **1a** as a model substrate. The latter was prepared in 33% overall yield starting from commercially available 2(5*H*)-furanone through a four-step sequence featuring a bromination, a Suzuki cross-coupling, a hydrogenation, and an *O*-acylation (see Supporting Information). The Pd-catalyzed asymmetric allylic alkylation of **1a** was then investigated by initially running the reactions in

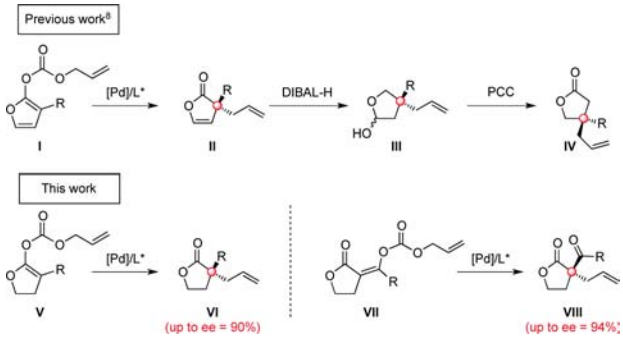


Figure 1. Stereoselective synthesis of α-quarternary butyrolactones via a palladium-catalyzed decarboxylative asymmetric allylic alkylation.

THF at 0 °C using a catalytic system consisting of $Pd_2(dba)_3$·$CHCl_3$ (5 mol %) and various chiral ligands (**L1**−**L9**, 10 mol %). The results are summarized in Table 1. As a general trend all the reactions afforded the desired α-quaternary butyrolactone **2a** in high yields, ranging from 83% to 99% (Table 1, entries 1−9). Interestingly, the use of axially dissymmetric C_2-chiral diphosphines such as (*S*)-BINAP (**L4**) (Table 1, entry 4) and mixed P/N ligands such as phosphine oxazolines (PHOX) (**L5**−**L6**) (Table 1, entries 5−6) induced lower levels of enantioselectivity compared to the chiral diphosphines **L1**−**L3** developed by Trost and co-workers (Table 1, entries 1−3), which were also found to be particularly effective for the Pd-AAA of cyclic dienol carbonates. Indeed the use of (*R*,*R*)-DACH phenyl **L1** provided butyrolactone **2a** in 98% yield and up to 77% ee (Table 1, entry 1). Encouraged by these preliminary results, we next examined the influence of the solvent. Interestingly, when performing the reaction in hexane

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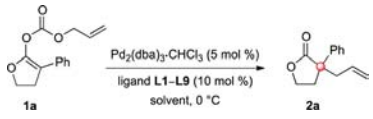
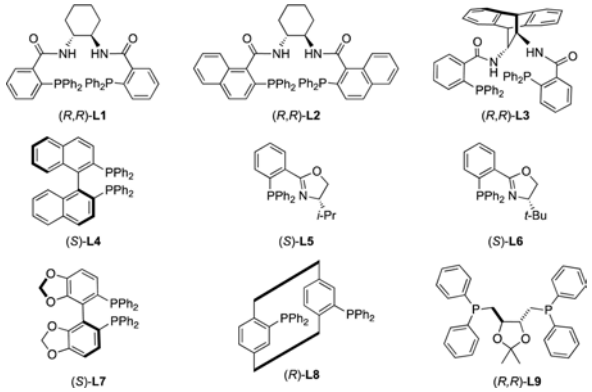
Table 1. Optimization of the Reaction Conditions[a]



	solvent	ligand	yield[b] (%)	ee[c,d] (%)
1	THF	(*R*,*R*)-**L1**	98	(+) 77
2	THF	(*R*,*R*)-**L2**	85	(+) 64
3	THF	(*R*,*R*)-**L3**	99	(+) 55
4	THF	(*S*)-**L4**	95	(−) 9
5	THF	(*S*)-**L5**	83	(+) 12
6	THF	(*S*)-**L6**	95	(+) 7
7	THF	(*S*)-**L7**	92	(−) 2
S	THF	(*S*)-**L8**	94	(+) 0
9	THF	(*R*,*R*)-**L9**	98	(+) 4
10	Hexane	(*R*,*R*)-**L1**	35	(+) 29
11	CH_3CN	(*R*,*R*)-**L1**	94	(+) 56
12	Toluene	(*R*,*R*)-**L1**	87	(+) 64
13	Et_2O	(*R*,*R*)-**L1**	97	(+) 65
14	DMF	(*R*,*R*)-**L1**	87	(+) 69
15	CH_2Cl_2	(*R*,*R*)-**L1**	72	(+) 70
16[e]	THF	(*R*,*R*)-**L1**	89	(+) 80

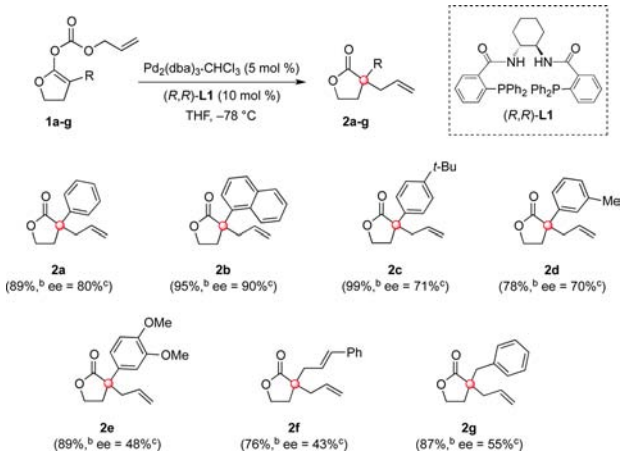
[a]All reactions were run on a 0.1 mmol scale. [b]Isolated yield. [c]determined by Supercritical Fluid Chromatography (SFC) analysis. [d]Sign assigned according to the optical rotation. [e]Reaction run at −78 °C.



under otherwise identical conditions, both the yield and ee decreased dramatically to 35% and 29% respectively (Table 1, entry 10). The use of other solvents such as CH_3CN, toluene, Et_2O, DMF, and CH_2Cl_2 led to good conversions, albeit with lower ee's (Table 1, entries 11−15). Finally, running the reaction in THF at −78 °C slightly improved the selectivity, as the corresponding butyrolactone **2a** was obtained in 80% ee (Table 1, entry 16).

After identifying the optimal reaction conditions [$Pd_2(dba)_3$·$CHCl_3$ (5 mol %), (*R*,*R*)-**L1** (10 mol %) in THF at −78 °C], we next examined the reaction scope by applying these conditions to various α-aryl (**2a**−**e**) and α-alkyl (**2f**−**g**) substituted enol carbonates. The results are summarized in Scheme 1. In general, the corresponding α,α-disubstituted-γ-butyrolactones were obtained in high yields ranging from 76% to 99%, and moderate to excellent enantioselectivities (up to 90% ee). More specifically, substrates bearing an electron-rich aromatic substituent (**2c**−**e**) or an alkyl group gave lower ee's (43% to 71%) than the substrates substituted by an extended aromatic system such as a naphthyl (**2b**), which offered up to 90% ee.

Scheme 1. Scope of the Reaction[a]

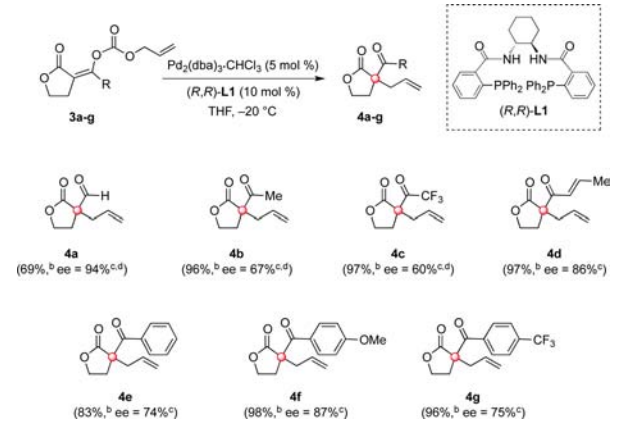


[a]All reactions were run on a 0.1 mmol scale. [b]Isolated yield. [c]Determined by Supercritical Fluid Chromatography (SFC) analysis.

In order to broaden the scope, we also applied the Pd-AAA to enol carbonates derived from α-acyl-γ-butyrolactones. The latter were prepared through a one-pot sequential *C*-acylation/*O*-acylation starting from commercially available γ-butyrolactone. Interestingly, when subjecting these newly synthesized allyl enol carbonates to our optimized Pd-AAA reaction conditions (Scheme 2), a sharp change in reactivity was observed. Indeed, these allyl enol carbonates appeared to be less reactive, which is not surprising considering that, during the AAA process, the negative charge generated is delocalized on both carbonyl groups. As a consequence, all the reactions were performed at −20 °C since no reaction was observed at −78 °C. Nonetheless, the desired α-quaternary γ-butyro-lactones were obtained in high yields ranging from 83% to 98% with good to excellent enantioselectivities; the best results were obtained with enol carbonate **3a** derived from the α-formyl-γ-butyrolactone, which reached 94% ee.

In an effort to further improve the method and also evaluate the influence of the base, we tested the Pd-AAA on a preformed enolate instead of the corresponding allyl enol carbonates

Scheme 2. Pd-AAA of Enol Carbonates Derived from α-Acyl-γ-butyrolactones[a]



[a]All reactions were run on a 0.1 mmol scale. [b]Isolated yield. [c]Determined by Supercritical Fluid Chromatography (SFC) analysis. [d]Determined after chemical derivatization.

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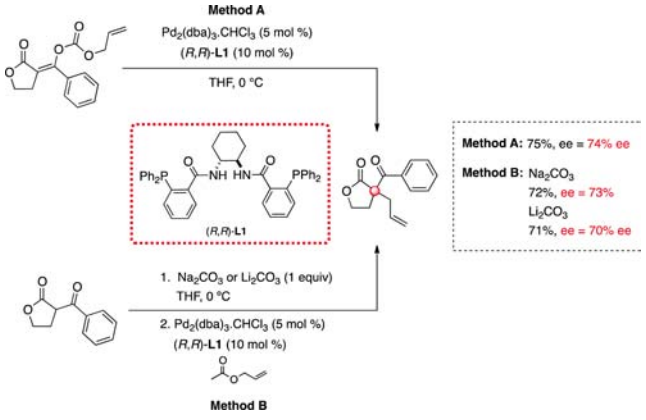
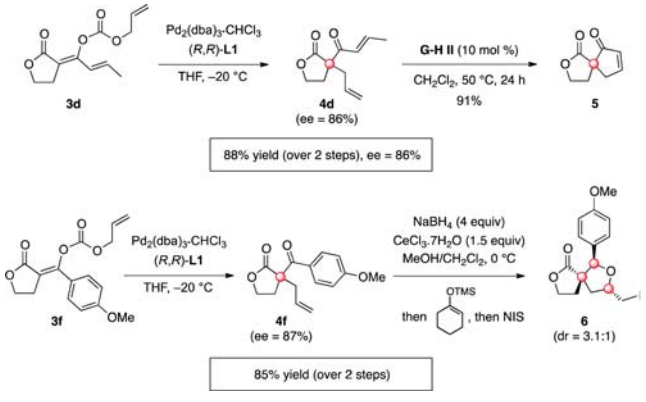
Scheme 3. Intramolecular vs Intermolecular Pd-AAA



(Scheme 3). Interestingly, both the yield and ee remained roughly unchanged whether the reaction was performed on the allyl enol carbonate or on the α-acyl-γ-butyrolactone using allyl acetate as the allyl donor. In addition, it is worth pointing out that the nature of the base did not influence the selectivity, as both Na_2CO_3 and Li_2CO_3 led to similar ee's. Nonetheless, this intermolecular approach appears much more appealing, as it does not require the synthesis of the allyl enol carbonate and can afford diversely substituted α-quaternary butyrolactones by simply changing the allyl donor.

Considering the importance of the spirocyclic motif, which is present in a number of natural products and pharmaceuticals,[9] we next decided to apply this Pd-AAA to the synthesis of γ-butyrolactone-derived spirocycles. Our first strategy relied on a sequential Pd-AAA/ring closing metathesis (see Supporting Information) and afforded the desired spirolactone **5** in 88% overall yield without any erosion of the ee (Scheme 4). Our second strategy involved a Luche reduction of an α,α-disubstituted-γ-butyrolactone followed by a subsequent iodocyclization. Under these conditions, the title spirocyclic compound **6** was obtained in 85% overall yield and with a 3.5:1 diastereoisomeric ratio.

Scheme 4. Synthesis of Enantioenriched Spirolactones



In summary, we have developed an extremely mild and particular efficient method for the enantioselective synthesis of γ-butyrolactones bearing an all-carbon α-quaternary stereogenic center starting from cyclic and exocyclic allyl enol carbonates. This Pd-AAA process was eventually used for the synthesis of chiral spirolactones, which were readily obtained in high yields and without any erosion of the enantioselectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02971.

Details of experimental procedures, ^{1}H and ^{13}C NMR spectra, Supercritical Fluid Chromatography (SFC) chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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