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Palladium-Catalyzed Asymmetric Direct Intermolecular Allylation of α-Aryl Cyclic Vinylogous Esters: Divergent Synthesis of (+)-Oxomaritidine and (−)-Mesembrine

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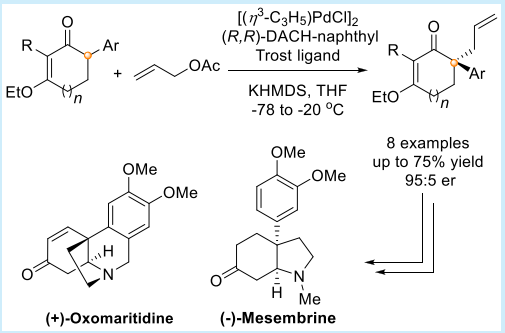
ABSTRACT: We demonstrate that α-aryl cyclic vinylogous esters are competent substrates in the direct intermolecular Pd-catalyzed asymmetric allylic alkylation, enabling a straightforward enantioselective synthesis of 6-allyl-6-aryl-3-ethoxycyclohex-2-en-1-ones, common motifs embedded in numerous structurally diverse natural products. As an initial demonstration of the utility of this protocol, the first catalytic enantioselective total synthesis of (+)-oxomaritidine and an improved five-step catalytic enantioselective synthesis of (−)-mesembrine have been completed divergently.



Catalytic asymmetric construction of all-carbon quaternary stereocenters is of great interest yet challenging in modern chemical synthesis. In particular, catalytic enantioselective approaches which are applicable to the total synthesis of natural products containing chiral all-carbon quaternary stereocenters remain more demanding.[1] Enantioenriched 6-alkyl-6-aryl-3-ethoxycyclohex-2-en-1-ones (**1**) represent a very attractive structural motif integrated into numerous structurally diverse natural products (Figure 1). Despite the importance of this structural motif, a general and straightforward method for its enantioselective synthesis has not yet been reported.[2]

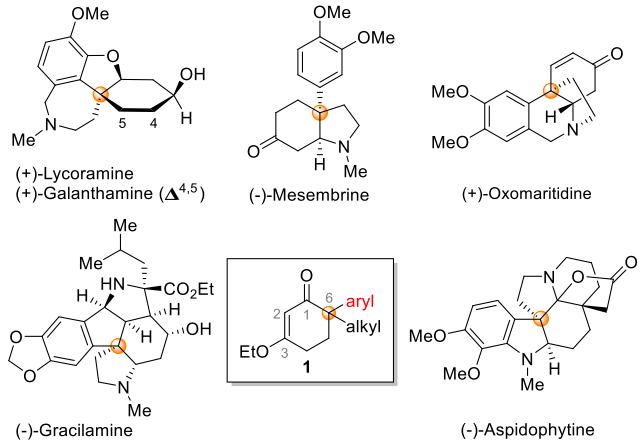


Figure 1. Chiral 6-alkyl-6-aryl-3-ethoxycyclohex-2-en-1-ones **1** and selected natural products.

Pd-catalyzed asymmetric allylic alkylation (Pd-AAA)[3] of α-aryl-monosubstituted cyclic vinylogous esters would be a direct and flexible method for the enantioselective construction of this important structural class. However, unlike α-monosubstituted cycloalkanones, α-monosubstituted cyclic vinylogous esters have proved to be a class of very challenging substrates in the direct intermolecular Pd-AAA.[4] In 2006, Trost and co-workers studied the direct intermolecular Pd-AAA of α-alkyl monosubstituted cyclic vinylogous esters **2** with their previously reported method of α-monosubstituted cyclohexenones[3d] by alkylating the kinetically generated enolates of **2**.[5] However, poor enantioselectivity (<30% ee) was obtained (Scheme 1a), despite numerous optimization attempts, highlighting the significant difference between cycloalkanones and cyclic vinylogous esters. Finally, they relied on a decarboxylative approach that delivered 6,6-dialkyl-3-alkoxycyclohex-2-en-1-ones with good enantioselectivity.[5,6] Since then, there have been no successful reports of the direct intermolecular Pd-AAA with α-monosubstituted cyclic vinylogous esters.

Given the importance and versatility of enantioenriched **1** and the lack of a general and direct method for its enantioselective synthesis, and promoted by our recent work in the Pd-catalyzed enantioselective allylation of vinylogous amides,[7] we revisited

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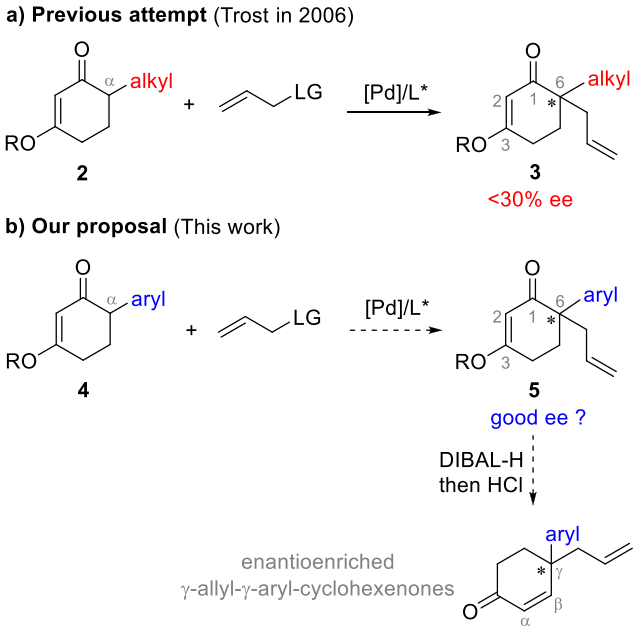
Scheme 1. Direct Intermolecular Pd-AAA of α-Monosubstituted Cyclic Vinylogous Esters (LG = Leaving Group)

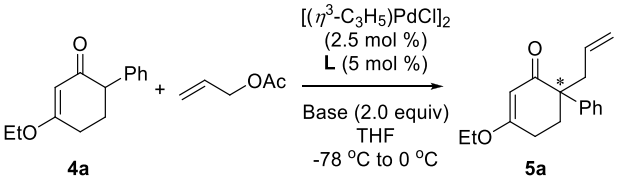


the longstanding unsolved direct intermolecular Pd-AAA of α-monosubstituted cyclic vinylogous ester substrates. We envisaged whether the difference between α-aryl- and α-alkyl-substitutents of cyclic vinylogous esters could result in the strikingly different facial discriminations, and if so, a direct enantioselective synthesis of **1** would be achieved. Furthermore, a Stork−Danheiser type transposition would convert **1** in one step to enantioenriched γ-allyl-γ-aryl-substituted cyclohexenones, a motif that also still poses a significant challenge in organic synthesis.[8] Herein, we report the realization of this strategy, and preliminary studies on the utility of enantioenriched **1** in divergent catalytic enantioselective total synthesis of (+)-oxomaritidine and (−)-mesembrine.[9]

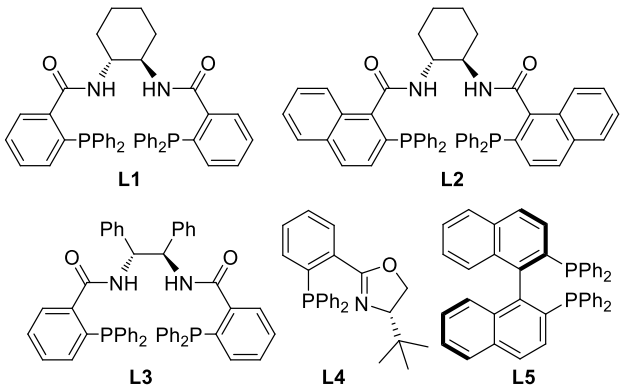
To test our hypothesis, we initiated our study with Pd-AAA of cyclic vinylogous ester **4a** to form enantioenriched **5a** (Table 1). When the reaction was performed in the presence of Trost ligand **L1** and NaHMDS as the base in THF, the desired product **5a** was obtained in 65% yield with 80.5:19.5 er (entry 1). To improve the enantioselectivity, various solvents were examined and no better results were obtained. Next, chiral ligands were screened. Among them, Trost ligand **L2** provided 91.5:8.5 er, albeit in a moderate yield of 57% (entry 2). Subsequent base screening indicated that the use of KHMDS can improve the chemical yield to 76% with the retention of enantioselectivity (entry 7). Decreasing the reaction temperature can further improve the enantioselectivity, and we ultimately determined that the designed reaction could afford **5a** in 71% yield with 94:6 er in the presence of **L2** as the chiral ligand and KHMDS as the base at −20 °C (entry 13; for details, see the Supporting Information).

With the optimized procedure in hand, we investigated the substrate scope of the direct intermolecular Pd-AAA of α-aryl cyclic vinylogous esters.[10] Pleasingly, various vinylogous esters **4** bearing electron-neutral, electron-rich, and electron-deficient aryl groups could be applied in the transformation to provide the desired 6-allyl-6-aryl-3-ethoxycyclohex-2-en-1-ones in good

Table 1. Selected Optimization Studies in the Pd-AAA of Vinylogous Ester 4a[a]



entry	L	base	yield (%)[b]	er[c]
1	**L1**	NaHMDS	65	80.5:19.5
2	**L2**	NaHMDS	57	91.5:8.5
3	**L3**	NaHMDS	41	56.5:43.5
4	**L4**	NaHMDS	33	66.5:33.5
5	**L5**	NaHMDS	41	50.5:49.5
6	**L2**	LiHMDS	68	89.5:10.5
7	**L2**	KHMDS	76	91:9
8	**L2**	NaH	59	84:16
9	**L2**	KH	54	85:15
10	**L2**	*t*-BuOK	15	87.5:12.5
11	**L2**	Cs_2CO_3	NR	-
12	**L2**	LDA	48	83:17
13[d]	**L2**	KHMDS	71	94:6
14[e]	**L2**	KHMDS	71	92.5:7.5



[a]Reaction conditions: **4a** (0.2 mmol, 1.0 equiv), allyl acetate (2.0 equiv), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (2.5 mol %), **L** (5 mol %) in THF (2.0 mL) at −78 to 0 °C. [b]Yield of isolated product **5a**. [c]Determined by chiral HPLC analysis. [d]−78 °C to −20 °C. [e]−78 °C to −30 °C.

yields and enantioselectivity (Scheme 2). The C2-methyl vinylogous ester **4g** was also tolerated well in this reaction, giving the desired product **5g** in 67% yield with 95:5 er. Moreover, the seven-membered vinylogous ester **4h** was also a suitable substrate for the direct intermolecular Pd-AAA,[11] which gave the corresponding allylated product **5h** in 64% yield with 90.5:9.5 er. The direct intermolecular Pd-AAA reaction of **4a** was performed on a 1 mmol scale, giving **5a** with comparative results (67% yield, 93.5:6.5 er). We tentatively made the following explanation about why this allylation having the aryl group displayed high er whereas the alkylated substrate reacted with low er: (1) the electronic property between the aryl group and the alkyl group is different; (2) the $\pi-\pi$ stacking interaction

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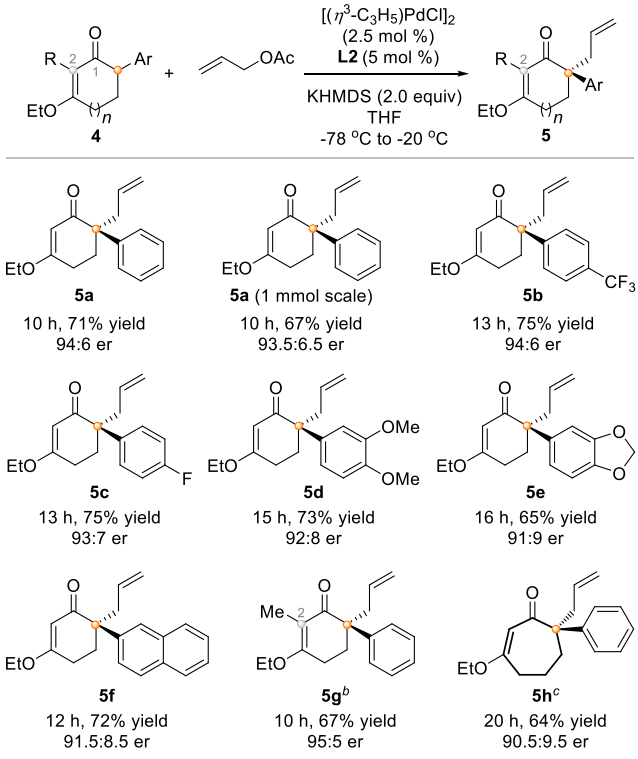
Scheme 2. Pd-Catalyzed AAA of α-Aryl Cyclic Vinylogous Esters[a]

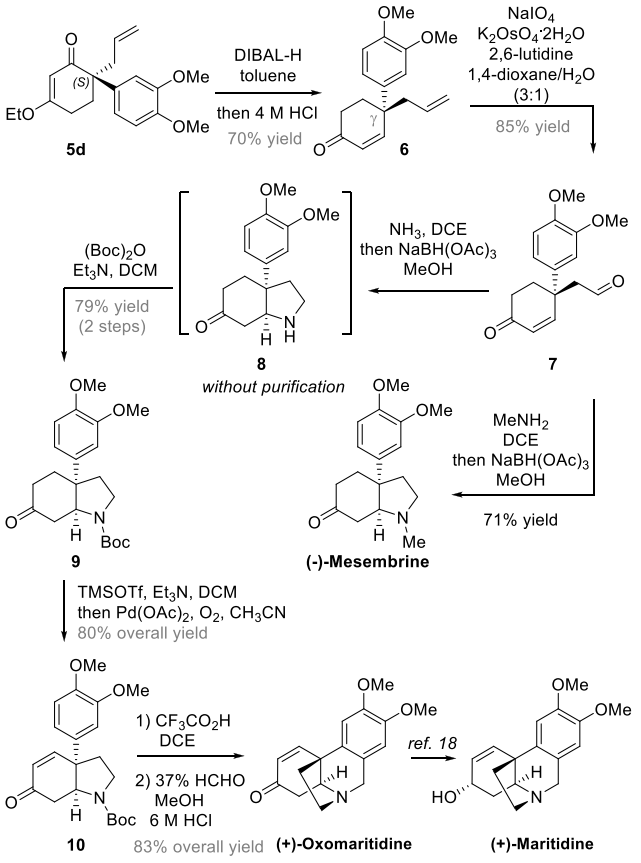


[a]Reaction conditions: **4** (0.2 mmol, 1.0 equiv), allyl acetate (2.0 equiv), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (2.5 mol %), **L2** (5 mol %) in THF (2.0 mL) at −78 °C to −20 °C. Yield of isolated product **5**. Er determined by chiral HPLC analysis. [b]DME (1,2-dimethoxyethane) as the solvent. [c]DME as solvent, at −78 °C to −40 °C.

between the aryl group and the chiral ligand might also be responsible for the high er in the allylation having the aryl group.

Having achieved the direct intermolecular Pd-AAA of α-aryl-substituted cyclic vinylogous esters, we preliminarily explored its utility in the enantioselective divergent natural product synthesis. One crinine-type *Amaryllidaceae* alkaloid (+)-oxomaritidine[12] and one *Sceletium* alkaloid (−)-mesembrine[13] were selected as our present synthetic targets. Crinine-type alkaloids, a large subclass (over 80 members) of the *Amaryllidaceae* alkaloid family, have attracted much attention from synthetic chemists due to their interesting bioactivities and diverse structures.[14] However, catalytic enantioselective synthesis remained rather limited,[15] and the *catalytic enantioselective total synthesis of oxomaritidine, to the best of our knowledge, has yet to be developed.*[16] One route for the enantioselective synthesis of (+)-oxomaritidine was developed as in Scheme 3. (*S*)-**5d**, obtained above, was treated with DIBAL-H to afford γ-allyl-γ-aryl-substituted cyclohexenone **6** on aqueous acidic workup in 70% yield.[17] Oxidative cleavage of the allyl group afforded the aldehyde **7**. **7** underwent intermolecular reductive amination to afford the *cis*-aryl hydroindole **9** on N-Boc-protection. **9** was transformed into the corresponding enone **10** via Saegusa oxidation.[18] The removal of the N-Boc group of **10** with trifluoroacetic acid followed by the Pictet−Spengler-type cyclization delivered (+)-oxomaritidine in 83% overall yield. Since oxomaritidine has been previously transformed into maritidine,[19] this also constitutes an enantioselective formal synthesis of (+)-maritidine. Divergently, from the common

Scheme 3. Concise, Divergent, and Enantioselective Total Syntheses of (+)-Oxomaritidine and (−)-Mesembrine



intermediate **7**, a reductive amination/cyclization cascade afforded (−)-mesembrine[20,21] in one step. This catalytic enantioselective total synthesis of mesembrine takes only five steps from commercially available starting materials.

In conclusion, a direct enantioselective synthesis of 6-allyl-6-aryl-3-ethooxycyclohex-2-en-1-ones, an important structural motif common in natural products chemistry, has been achieved through the development of the first direct intermolecular Pd-AAA of α-aryl-substituted cyclic vinylogous ester substrate class. Unlike α-alkyl-substituted cyclic vinylogous esters, α-aryl-substituted cyclic vinylogous esters underwent the direct intermolecular Pd-AAA with good enantioselectivity. Based on the preliminary exploration of this method, the first catalytic enantioselective total synthesis of *Amaryllidaceae* alkaloid (+)-oxomaritidine and a short, five-step catalytic enantioselective total synthesis of *Sceletium* alkaloid (−)-mesembrine were achieved divergently. The synthetic utility conferred by the α-aryl cyclic vinylogous ester substrate class is expected to find further applications in the enantioselective synthesis of other structurally diverse alkaloid natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04125.

Experimental procedures, analytical data, copies of NMR spectra for all new compounds and HPLC spectra for all chiral compounds (PDF)

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Author Contributions

†W.W. and J.D. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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