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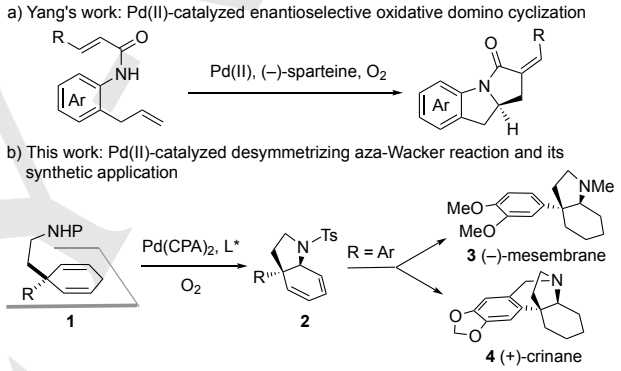
Palladium-Catalyzed Enantioselective Desymmetrizing Aza-Wacker Reaction: Development and Application to the Total Synthesis of (–)-Mesembrane and (+)-Crinane

Xu Bao, Qian Wang, Jieping Zhu*

Abstract: *We report in this paper an unprecedented catalytic enantioselective desymmetrizing aza-Wacker reaction. In the presence of a catalytic amount of newly developed Pd(CPA)$_2$(MeCN)$_2$ catalyst (CPA stands for chiral phosphoric acid), a pyrox ligand and molecular oxygen, cyclization of properly functionalized prochiral 3,3-disubstituted cyclohexa-1,4-dienes afforded enantioenriched cis-3a-substituted-tetrahydroindoles in good yields with excellent enantioselectivities. A cooperative effect between the phosphoric acid and the pyrox ligand ensured the efficient transformation. This reaction was tailor-made for Amaryllidaceae and Sceletium alkaloids as illustrated by its application in the development of the concise and divergent total synthesis of (–)-mesembrane and (+)-crinane*.

The Pd(II)-catalyzed Wacker reaction has found widespread application in the synthesis of natural products and designed bioactive compounds.[1] The asymmetric Wacker-type cyclization involving a key stereocenter-generating oxypalladation step has also been successfully developed for the synthesis of chiral non-racemic oxaheterocycles.[2,3] On the other hand, the development of oxidative enantioselective intramolecular aza-Wacker type reaction remained inherently more challenging and only few examples have been reported in the literature.[4-6] Yang and co-workers reported in 2006 the first examples of Pd(II)/(–)-sparteine catalyzed oxidative domino cyclization of 2-allyl-acrylanilides (Scheme 1a).[5] Other groups have subsequently reported different catalytic conditions for the oxidative enantioselective cyclization of *N*-acyl or *N*-tosyl aminoalkenes.[6]

The difficulties associated with the development of oxidative aza-Wacker reaction are due to a) the reversibility of the aminopalladation step;[7] b) the competing *syn*- and *anti*-aminopalladation processes;[8] and c) the limited choice of chiral ligands. Most of the phosphine-based ligands are in fact incompatible with the oxidative conditions. In connection with our research program dealing with the Pd(0)-catalyzed enantioselective difunctionalization of alkenes,[9] we became interested in addressing this challenging topic. In designing such a transformation, we paid particular attention on its potential application in natural product synthesis.[10] Landais and co-workers have reported a Pd(II)-catalyzed aza-Wacker reaction of 3,3-disubstituted cyclohexa-1,4-dienes.[11] However, the catalytic enantioselective version has remained unknown. We report herein a Pd(CPA)$_2$(MeCN)$_2$/pyrox-catalyzed enantioselective desymmetrizing aza-Wacker reaction of cyclohexa-1,4-dienes **1** for the synthesis of enantioenriched *cis*-3a-substituted tetrahydroindoles.[12] A cooperative effect between chiral phosphoric acid (CPA) and chiral pyrox ligand is key to the development of this enantioselective transformation.[6g] Divergent total synthesis of (–)-mesembrane and (+)-crinane, representative structures of Amaryllidaceae and *Sceletium* alkaloids,[13] featuring this reaction as a key step will also be documented.



Scheme 1. Enantioselective aza-Wacker reaction.

3-Phenyl-3-[2-(4-tolylsulfonyl)]aminoethyl-cyclohexa-1,4-diene (**1a**) was chosen as a test substrate.[14] Heating a toluene solution of **1a** in the presence of Pd(OAc)$_2$, pyridine, Na_2CO_3 under O_2 atmosphere afforded indeed **2a** in 65% yield (entry 1, Table 1).[11] However, the same reaction using (–)-sparteine as ligand provided **2a** in only 8% yield (entry 2). We therefore turned our attention to the chiral quinox and pyrox type ligands[15] using a more electrophilic Pd(TFA)$_2$ as a Pd(II) source (Figure 1). The results are summarized in Table 1. In quinox series, **L4** derived from (1*R*,2*S*)-1-amino-2-indanol was a superior ligand than those (**L1**-**L3**) derived from the acyclic amino alcohols in terms of product *ee* (entries 7 vs 3-6). The same trend was observed in the pyrox series with **L7** being a better ligand than **L5** and **L6** (entries 10 vs 8, 9). Tuning the electronic and steric properties of **L7** led to the decrease of both the yield and the *ee* of the product (**L8**-**L10**, entries 11-13). Unfortunately, varying the solvents and the bases failed to increase the synthetic efficiency of this transformation. Adding molecular sieves (MS) to the reaction mixture decreased the yield of **2a** (entries 14-16).[16] However, the enantioselectivity was significantly increased when 5 Å MS were added into the reaction mixture (entry 16).

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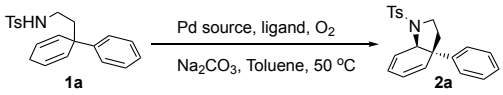
Table 1. Optimization of the reaction conditions.[a]



1a 2a

entry	Pd salt	ligand	additive	yield (%)[b]	*ee* (%)[c]
1[d]	$Pd(OAc)_2$	pyridine	---	65	---
2	$Pd(OAc)_2$	(–)-sparteine	---	8	---
3	$Pd(OAc)_2$	**L1**	---	27	9
4	$Pd(TFA)_2$	**L1**	---	trace	-20
5	$Pd(TFA)_2$	**L2**	---	9	3
6	$Pd(TFA)_2$	**L3**	---	9	16
7	$Pd(TFA)_2$	**L4**	---	16	51
8	$Pd(TFA)_2$	**L5**	---	13	40
9	$Pd(TFA)_2$	**L6**	---	25	59
10	$Pd(TFA)_2$	**L7**	---	41	70
11	$Pd(TFA)_2$	**L8**	---	27	62
12	$Pd(TFA)_2$	**L9**	---	23	56
13	$Pd(TFA)_2$	**L10**	---	18	52
14	$Pd(TFA)_2$	**L7**	3 Å MS[e]	23	70
15	$Pd(TFA)_2$	**L7**	4 Å MS	24	75
16	$Pd(TFA)_2$	**L7**	5 Å MS	22	81

[a] **1a** (0.1 mmol), PdX_2 (0.01 mmol), ligand (0.02 mmol), Na_2CO_3 (0.2 mmol), O_2, toluene (2.0 mL), 50 °C. [b] Yields refer to the isolated products. [c] Determined by SFC analysis on a chiral stationary phase. [d] Performed at 80 °C. [e] MS = molecular sieves (70.0 mg).

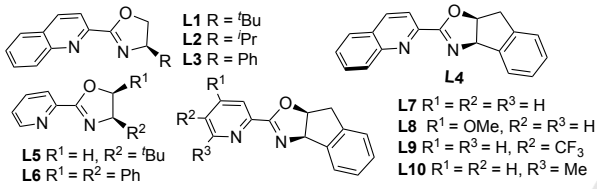
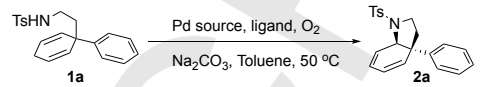


Figure 1. Structures of quinox and pyrox surveyed.

The aforementioned results were far from satisfactory, we set out to examine the cooperative effects between the chiral pyrox ligand **L7** and acid additives.[17] Adding (*R*)-mandelic acid or (*S*)-*N*-Boc phenylalanine to the above optimized conditions [$Pd(TFA)_2$, **L7**, Na_2CO_3, O_2, 5 Å MS, toluene, 50 °C] shut down the reaction (entries 1 and 2, Table 2).[18,19] Chiral phosphoric acids having a bulky substituent at the C3, C3' positions [(*R*)-CPA **1**, **4** and **5**, Figure 2] exerted also a deleterious effect on the reaction outcome (entries 3-5).[20,21] However, addition of the less hindered CPAs [(*R*)-CPA **2**, **3**] increased slightly the yield and *ee* of the product **2a** (entries 6-7). Interestingly, adding (*S*)-CPA **3** to the reaction mixture led to the product with diminished yield and *ee*, while adding achiral biphenol-derived phosphoric acid (PA **6**) increased slightly the yield of **2a** (entry 9, Table 2, vs entry 16, Table 1). The pronounced counterion effect led us to assume that trifluoroacetic acid (TFA) present in the reaction mixture might also impact the reaction outcome. We therefore synthesized Pd[(*R*)-CPA **3**]$_2$$(MeCN)_2$ and Pd[(*R*)-CPA **7**]$_2$$(MeCN)_2$ complexes following literature procedures.[21a,22] Gratefully, both pre-catalysts displayed superior reactivity than the in situ combination of $Pd(TFA)_2$ and CPA (entries 10, 11). Using Pd[(*R*)-CPA **7**]$_2$$MeCN_2$ as catalyst, compound **2a** was isolated in 63% yield with 93% *ee*. It is important to stress that the cyclization of **1a** catalyzed by Pd[(*R*)-CPA **7**]$_2$$MeCN_2$ alone afforded the product **2a** in a low yield and *ee* (entry 12). Furthermore, cyclization of **1a** catalyzed by Pd[(*R*)-CPA **7**]$_2$$(MeCN)_2$ and *ent*-**L7** furnished *ent*-**2a** in only 16% yield with 72% *ee*. These results indicated a strong cooperative effect between the CPA and the pyrox ligand. The pyrox ligand determined the sense of the enantioselectivity, whereas the presence of CPA-**7** increased not only the enantioselectivity of the reaction but also the yield of the product. While Pd[(*R*)-CPA **7**]$_2$$(MeCN)_2$ was isolable and was spectroscopically characterized (Supporting information), all attempts to isolate and characterize the Pd-CPA-pyrox ternary complex failed.

Table 2. Effects of the chiral acids on the reaction outcome.[a]



1a 2a

entry	acids[b]	yield (%)[c]	*ee* (%)[d]
1	(*R*)-mandelic acid	trace	---
2	(S)-*N*-Boc-Phe	trace	---
3	(*R*)-CPA **1**	7	56
4	(*R*)-CPSA **4**	trace	---
5	(*R*)-CPA **5**	9	16
6	(*R*)-CPA **2**	33	84
7	(*R*)-CPA **3**	31	88
8	(*S*)-CPA **3**	23	80
9	PA **6**	48	84
10	Pd[(*R*)-CPA **3**]$_2$$(MeCN)_2$[e]	32	94
11	Pd[(*R*)-CPA **7**]$_2$$(MeCN)_2$[e]	63	93
12	Pd[(*R*)-CPA **7**]$_2$$(MeCN)_2$[f]	10	3

[a] **1a** (0.1 mmol), $Pd(TFA)_2$ (0.01 mmol), **L7** (0.02 mmol), Na_2CO_3 (0.2 mmol), O_2, 5 Å MS (70.0 mg), toluene (2.0 mL), 50 °C. [b] Acid (0.02 mmol). [c] Yields refer to the isolated products. [d] Determined by SFC analysis on a chiral stationary phase. [e] Catalyst loading (0.01 mmol). [f] Without ligand **L7**. Abbrev. CPA = Chiral Phosphoric Acid.

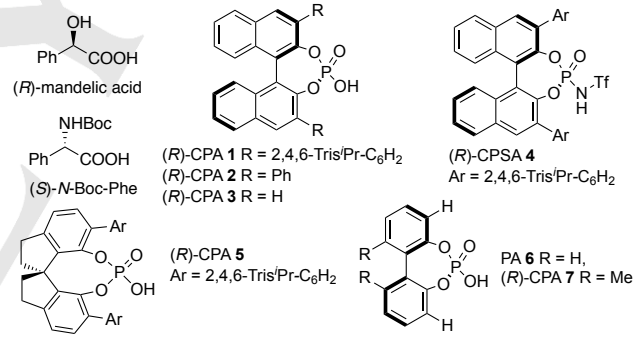


Figure 2. Structures of the carboxylic acids and phosphoric acids surveyed.

With the optimum conditions in hand, the scope of this catalytic enantioselective aza-Wacker reaction was next explored (Scheme 2). The products with different C3a-aromatic substituents were obtained in good yields with excellent *ees* (**2a**-**2j**). As expected, the aryl bromide was stable under these mild Pd(II)-catalyzed reaction conditions (**2e**), so were the standard hydroxyl and amino protective groups (OTBS, OBn, OAc and phthalimide). The tetrahydroindoles substituted by a functionalized alkyl group at C3a position were also accessible (**2k**-**2o**), albeit with slightly reduced enantiomeric excesses. Importantly, the C3a-unsubstituted tetrahydroindole **2p** can also be synthesized with excellent *ee*. Although the yield of **2p** was moderate, we noted that the corresponding indoline, the oxidized derivative, was not detected. Finally, the substrate bearing an easily removable *N*-(4-nitro)phenylsulfonamide function cyclized to afford **2q** in 61% yield with 93% *ee*. The absolute configuration of **2a** (3a*S*, 7a*R*) was determined by *X*-ray crystallographic analysis and that of the others were assigned accordingly.

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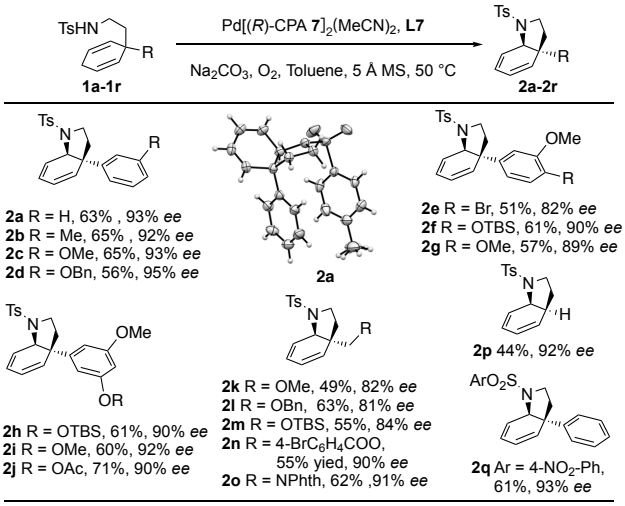
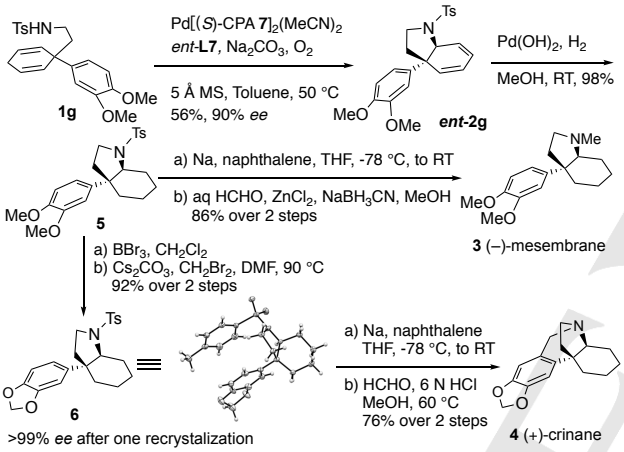


Scheme 2. Scope of desymmetrizing aza-Wacker reaction.



Scheme 3. Divergent synthesis of (–)-mesembrane and (+)-crinane.

The *cis*-3a-aryloctahydroindole possessing an all carbon quaternary stereocenter is a key structural motif found in Amaryllidaceae and *Sceletium* alkaloids.[13] These natural products attracted considerable attention over the years due to their diverse structures and potent bioactivities. Although elegant synthetic routes have been developed, catalytic enantioselective synthesis remained rare.[23] Since both enantiomers of some members of these families of natural products exist in nature, the development of catalytic enantioselective approach is particularly appealing. The asymmetric aza-Wacker reaction developed in this study is indeed tailor-made for these alkaloids as illustrated by the realization of divergent synthesis of (–)-mesembrane (**3**)[24] and (+)-crinane (**4**),[25] the latter being a basic framework for Amaryllidaceae (Scheme 3). Treatment of **1g** with Pd[(*S*)-CPA **7**]$_2$(MeCN)$_2$ and ligand *ent*-**L7** under otherwise standard conditions furnished *ent*-**2g** (56%, 90% *ee*). Hydrogenation of *ent*-**2g** in the presence of Pearlman's catalyst provided **5** in 98% yield. Removal of *N*-Ts followed by reductive *N*-methylation with aqueous formaldehyde furnished (–)-mesembrane (**3**) in 86% overall yield {[α]$^{25}_D$ – 13.8 (*c* 1.2, MeOH); lit.[24a] [α]$^{20}_D$ – 14.6 (*c* 1.0, MeOH)}. On the other hand, demethylation of **5** (BBr_3, CH_2Cl_2) followed by methylenation of the resulting catechol furnished **6** in 92% yield with 92% *ee*. The *ee* of **6** was upgraded to > 99% by a simple recrystallization and its absolute configuration was unambiguously determined by X-ray crystallographic analysis. Removal of the *N*-Ts group followed by the Pictet-Spengler reaction converted **6** to (+)-crinane (**4**) in 76% yield over 2 steps {[α]$^{25}_D$ + 8.2 (*c* 1.0, $CHCl_3$); lit.[25c] [α]$^{20}_D$ + 7.01 (*c* 1.0, $CHCl_3$). The spectroscopic data of the synthetic (–)-mesembrane (**3**) and (+)-crinane (**4**) are identical with those reported for the natural products.

In summary, we reported a catalytic enantioselective desymmetrizing aza-Wacker reaction. In the presence of a catalytic amount of newly developed chiral Pd(CPA)$_2$(MeCN)$_2$ complex, a pyrox ligand and molecular oxygen, cyclization of functionalized prochiral 3,3-disubstituted cyclohexa-1,4-dienes afforded enantioenriched *cis*-3a-substituted tetrahydroindoles in good yields with excellent enantioselectivities. A cooperative effect between the chiral pyrox ligand and the phosphoric acid increased both the yield and the *ee* of the product. Specifically, the pyrox ligand determined the sense of enantioselectivity, while the matched chiral phosphoric acid increased synergistically both the *ee* and the yield of the product. Application of this reaction allowed us to develop the concise and divergent total synthesis of (–)-mesembrane and (+)-crinane.

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Keywords: Aza-Wacker • asymmetric synthesis • palladium • chiral Brønsted acid • cooperative effect • alkaloids

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Entry for the Table of Contents (Please choose one layout)

Layout 1:

Asymmetric Synthesis

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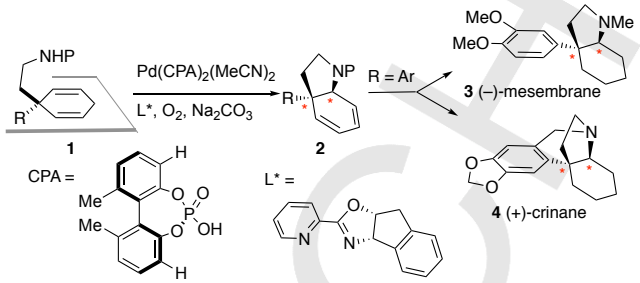
Palladium-Catalyzed Enantioselective Desymmetrizing Aza-Wacker Reaction: Development and Application to the Total Synthesis of (–)-Mesembrane and (+)-Crinane



Be cooperative: *In the catalytic enantioselective cyclization of **1** to **2**, the pyrox ligand determined the sense of enantioselectivity, while the matched chiral phosphoric acid increased synergistically both the ee and the yield of the product. A concise and divergent total synthesis of (–)-mesembrane and (+)-crinane was subsequently developed.*