

# Enantioselective Synthesis of 2,3-Disubstituted Indanones via Pd-Catalyzed Intramolecular Asymmetric Allylic Alkylation of Ketones

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## ABSTRACT



A Pd-catalyzed intramolecular asymmetric allylic alkylation (AAA) reaction with “hard” carbanions has been developed for the first time, affording 2,3-disubstituted indanones with high diastereo- and enantioselectivities. The transformation of these products into other core structures of natural products has been demonstrated.

2,3-Disubstituted indanones with two chiral centers are common subunits found in a variety of natural products and biologically active compounds.<sup>1</sup> Taiwaniaquinol B,<sup>2</sup>

nakiterpiosin,<sup>3</sup> and (+)-pauciflorol F<sup>4</sup> are examples. Such an indanone also served as the key precursor in the synthesis of a tetracyclic framework of tetrapetalone A<sup>5</sup> (Figure 1). Thus their synthesis has received a tremendous amount of attention from the synthetic community and many strategies have been developed to them.<sup>6</sup> However, the synthesis of 2,3-substituted indanones based on asymmetric catalysis is rare.<sup>7</sup> In the light of recent achievements in Pd-catalyzed asymmetric allylic alkylation (AAA),<sup>8</sup> we envisioned that chiral 2,3-substituted indanones could

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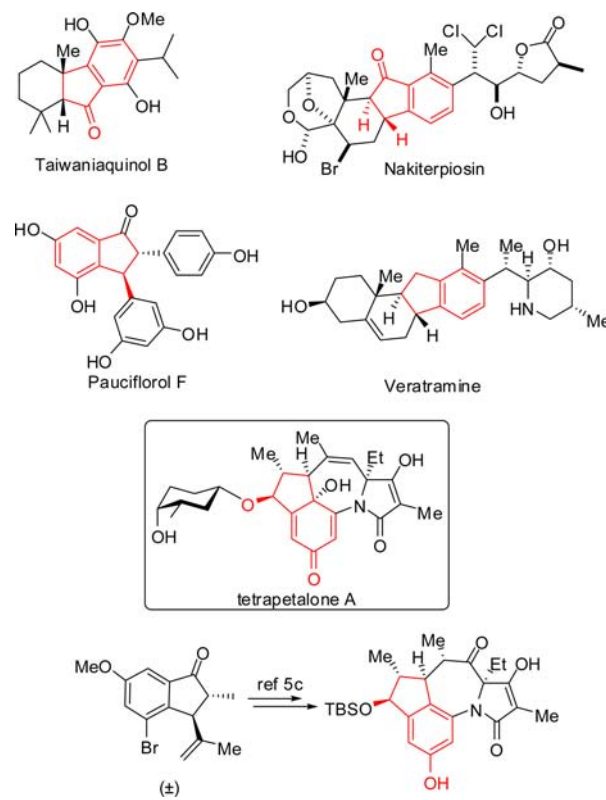
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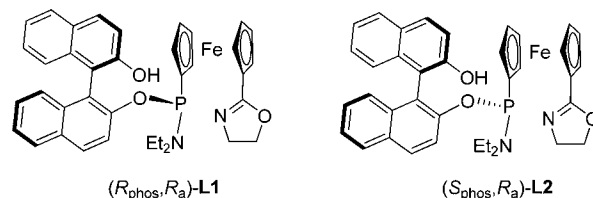
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potentially be generated via the Pd-catalyzed intramolecular AAA of ketones. While the synthesis of carbo- and heterocycles via an intramolecular Pd-catalyzed asymmetric allylic substitution has been well documented,<sup>9</sup> to the best of our knowledge, there are no reports on the use of “hard” carbanion nucleophiles in the intramolecular Pd-catalyzed asymmetric allylic substitution reaction, despite the fact that great progress has been made in the use of hard carbanions as nucleophiles in the Pd-catalyzed AAA reaction.<sup>10,11</sup> We have worked in the field of Pd-catalyzed AAA reactions for a couple of years<sup>11,12</sup> and have developed some hard carbanions as nucleophiles.<sup>11</sup> In this Letter, we disclose an enantioselective synthesis of 2,3-disubstituted indanones by an intramolecular Pd-catalyzed AAA with a hard carbanion

as nucleophile. The usefulness of the products has also been demonstrated.



**Figure 1.** Some natural products containing 2,3-disubstituted indanones substructure.



**Figure 2.** *P,N*-Ferrocene-based SIOCPhox ligands.

An initial test was the reaction of substrate **1a** in the presence of 2.5 mol % of  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$  and 5 mol % of (*R*<sub>phos</sub>, *R*<sub>a</sub>)-SIOCPhox **L1** in dimethoxyethane (DME), with LiHMDS as base, which provided the cyclic ether **2a** as the sole product in 82% yield. It was produced from *O*-alkylation of the ketone enolate generated in situ, which is an ambident nucleophile. It seems that *O*-alkylation is a more favorable process to form a 5-membered ether than 5-membered cyclic ketone formation.<sup>13</sup> Obviously the

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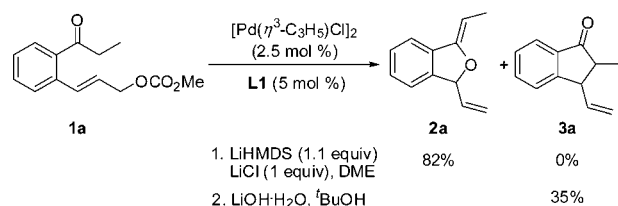
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issue of chemoselectivity was the first critical issue to be addressed in this Pd-catalyzed intramolecular AAA reaction. By trial and error, we found that when *tert*-butanol was the solvent with lithium hydroxide monohydrate as the base, formation of the *O*-alkylation product **2a** was efficiently suppressed, and the *C*-alkylation product **3a** was promoted, although the yield was only 35%, because of hydrolysis of the substrate **1a** (Scheme 1). These results encouraged us to study further the effect of the reaction parameters, including bases, solvents, and reaction temperature, on the reaction.

**Scheme 1.** Chemoselectivity of Pd-Catalyzed Intramolecular Reactions of **1a**



As shown in Table 1, the use of diethyl phosphate **1b**, a more stable substrate toward basic condition, and 10 mol % of tetrabutylammonium fluoride (TBAF) significantly increased the yield of product **3a** to 83% (entry 1). The reaction hardly proceeded in the presence of TBAF only without addition of LiOH·H<sub>2</sub>O (entry 2). The ee was higher with (*S*<sub>phos</sub>, *R*<sub>a</sub>)-SIOCPhox **L2** than with (*R*<sub>phos</sub>, *R*<sub>a</sub>)-SIOCPhox **L1** (Figure 2), although the yield was lower (entry 3 vs entry 1). With (*S*<sub>phos</sub>, *R*<sub>a</sub>)-SIOCPhox **L2** as ligand, the influence of the bases on the reaction was

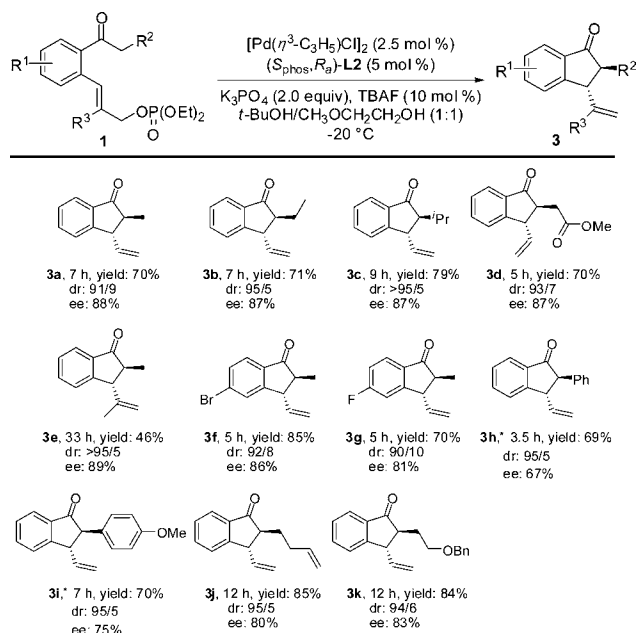
screened (entries 3–7). K<sub>3</sub>PO<sub>4</sub> was identified as the best among the bases screened in terms of both diastereo- and enantioselectivities (entry 7). The solvent effect is important on the enantioselectivity (entries 7–10). The reaction in 2-methoxyethanol provided the product **3a** in 80% yield, 87/13 *anti/syn* ratio, and 75% ee (entry 10). The ee value increased further to 82% by lowering the reaction temperature from rt to 0 °C, but the dr was lower (entry 11). Because the reaction in *tert*-butanol gave an excellent diastereoselectivity, we wondered if the use of mixed solvents of *tert*-butanol and 2-methoxyethanol could make both dr and ee higher. Pleasingly, the dr increased significantly from 84/16 to 93/7, whereas the enantioselectivity changed from 82 to 84%, when the reaction was run in 1:1 *tert*-butanol and 2-methoxyethanol (entry 12 vs entry 11). An increase of ee value to 88% was observed when the reaction was conducted at –20 °C (entry 13).

The substrate scope of the Pd-catalyzed intramolecular AAA of ketones **1** was investigated under the optimized reaction conditions (Figure 3). The reaction proceeded well in all cases, affording indanones **3** bearing two vicinal chiral centers in moderate-to-high yields with high diastereo- and enantioselectivities, the dr being 90/10 to >95/<5 with the ee value being 67–89%.  $\alpha$ -Substituents to the carbonyl group exerted little influence on the diastereo- and enantioselectivities of the reaction (**3a–3c**). Ketone **1** with an ester group was a suitable substrate for providing the product **3d** with excellent dr and ee. The reaction was compatible with a substrate **1** with a 1,2-disubstituted allylic group, affording the corresponding indanone **3e** in 95/5 dr and 89% ee albeit the yield being a little lower. The effect of halide substituents on the aryl group of substrates **1** on the reaction was examined. The dr of both products **3f** and **3g** was excellent, while the enantioselectivity was also

**Table 1.** Optimization of Reaction Conditions for Pd-Catalyzed Intramolecular AAA of Ketone **1b**<sup>a</sup>

entry	base	solvent	yield (%) <sup>b</sup>	<i>anti/syn</i> <sup>c</sup>	ee (%) <sup>d</sup>
1	LiOH·H <sub>2</sub> O	<i>t</i> BuOH	83	88/12	40
2	–	<i>t</i> BuOH	nr	–	–
3	LiOH·H <sub>2</sub> O	<i>t</i> BuOH	56	87/13	47
4	<i>t</i> BuOLi	<i>t</i> BuOH	80	89/11	44
5	KOH	<i>t</i> BuOH	58	69/31	16
6	K <sub>2</sub> CO <sub>3</sub>	<i>t</i> BuOH	70	94/6	18
7	K <sub>3</sub> PO <sub>4</sub>	<i>t</i> BuOH	81	92/8	44
8	K <sub>3</sub> PO <sub>4</sub>	<i>i</i> PrOH	87	87/13	47
9	K <sub>3</sub> PO <sub>4</sub>	MeOH	88	81/19	76
10	K <sub>3</sub> PO <sub>4</sub>	CH <sub>3</sub> OCH <sub>2</sub> CH <sub>2</sub> OH	80	87/13	75
11	K <sub>3</sub> PO <sub>4</sub> at 0 °C	CH <sub>3</sub> OCH <sub>2</sub> CH <sub>2</sub> OH	84	84/16	82
12	K <sub>3</sub> PO <sub>4</sub> at 0 °C	<i>t</i> BuOH/CH <sub>3</sub> OCH <sub>2</sub> CH <sub>2</sub> OH <sup>e</sup>	72	93/7	84
13	K <sub>3</sub> PO <sub>4</sub> at –20 °C	<i>t</i> BuOH/CH <sub>3</sub> OCH <sub>2</sub> CH <sub>2</sub> OH <sup>e</sup>	70	91/9	88

<sup>a</sup> Conditions: molar ratio **1b**/[Pd( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub>/L/base/TBAF = 100/2.5/5.0/200/10, 2.0 mL of solvent; entries 1 and 2: **L1** used as ligand; entries 3–13: **L2** used as ligand. <sup>b</sup> Isolated yield of **3a**. <sup>c</sup> Determined by <sup>1</sup>H NMR analysis. <sup>d</sup> Determined by chiral HPLC. <sup>e</sup> CH<sub>3</sub>OCH<sub>2</sub>CH<sub>2</sub>OH/*t*BuOH = 1/1.



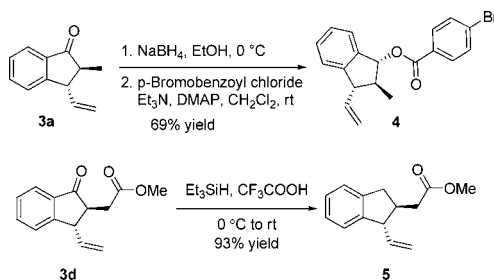
**Figure 3.** Substrate scope of Pd-catalyzed intramolecular AAA of ketones **1**. Conditions: Molar ratio  $1/[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2/(S_{\text{phos}}, R_a)\text{-L2}/\text{K}_3\text{PO}_4/\text{TBAF} = 100/2.5/5.0/200/10$ , 1.0 mL of  $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OH}$  and 1.0 mL of  $t\text{-BuOH}$ ; dr determined by  $^1\text{H}$  NMR; ee determined by chiral HPLC. Asterisk (\*) indicates  $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OH}/\text{DME}$  (1/1) used as solvent and tetrabutylammonium bromide (TBAB) used as additive.

high. The reaction also performed well for  $\alpha$ -aryl ketones **1**, providing the corresponding products in excellent dr and moderate enantioselectivity (**3h** and **3i**). Indanones **3j** and **3k** with multiple functional groups were also prepared with high yield and excellent diastereoselectivity.

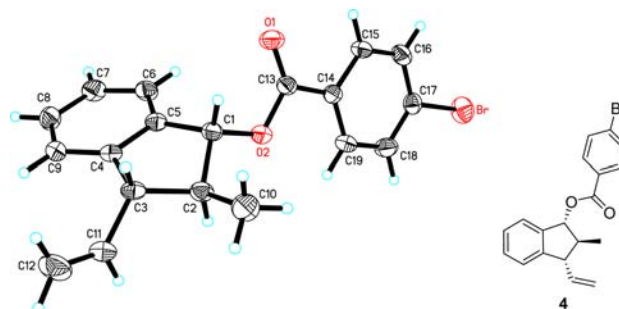
Optically active 2,3-disubstituted indanones were subjected to further modification. The reduction of product **3a** with  $\text{NaBH}_4$  followed by a protection of the hydroxyl group afforded a 2,3-dihydro-1*H*-indene **4** with three chiral centers, which possessed the core structure of tetrapetalone A (Scheme 2). The absolute configuration of product **4** was assigned as (1*R*,2*S*,3*S*) by X-ray analysis of its single crystal (Scheme 3). Accordingly, the absolute configuration of product **3a** was (2*S*,3*S*). The reduction of the carbonyl group of product **3d** into the methylene group was also feasible, as shown in Scheme 2. The resulting product **5** is an important subunit of the natural product veratramine.

In conclusion, we have achieved a Pd-catalyzed intramolecular AAA reaction with hard carbanions for the first

## Scheme 2. Transformations of Reaction Products



## Scheme 3. Determination of Absolute Configuration of Product 4



time, obtaining 2,3-disubstituted indanones with high diastereo- and enantioselectivities. The transformation of these products into other core structures of natural products was demonstrated. Further investigations on the intramolecular Pd-catalyzed AAA reaction with other substrates, and applications of the protocol in organic syntheses, are in progress.

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**Supporting Information Available.** Experimental procedure for synthesis of compounds **1**, spectra of compounds **1**, **3a–3k**, **4**, and **5**, X-ray analysis data of **4** in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.