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Stereoselective Synthesis of Spirooxindoles by Palladium-Catalyzed Decarboxylative Cyclization of γ-Methylidene-δ-valerolactones with Isatins

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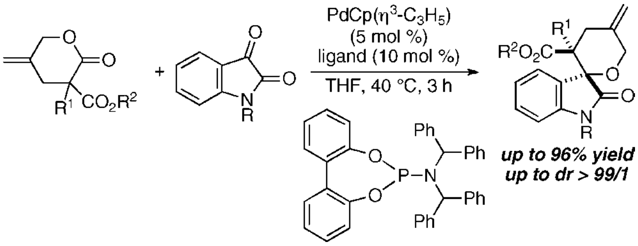
ABSTRACT



A new synthetic method of spirooxindole derivatives has been developed by way of a palladium-catalyzed decarboxylative cyclization of γ-methylidene-δ-valerolactones with isatins. By employing a newly prepared phosphoramidite ligand, the reaction proceeds smoothly with excellent diastereoselectivity. Preliminary results of its application to asymmetric catalysis using a chiral phosphoramidite ligand are also described.

Spirooxindoles are a class of compounds that can be found in many natural products and biologically active compounds,[1] and the development of synthetic methods for these compounds, including the ones with new substitution patterns, is therefore of high importance in organic chemistry. Although several efficient methods are available in the literature,[2,3] those with high stereoselectivity are still limited.[3] In this context, here we describe the development of a highly diastereoselective synthesis of spirooxindoles through palladium-catalyzed decarboxylative cyclization of γ-methylidene-δ-valerolactones[4] with isatins, including some preliminary results of its application to asymmetric catalysis.

Initially, we conducted a reaction of γ-methylidene-δ-valerolactone **1a** with *N*-methylisatin (**2a**) in the presence of 5 mol % of palladium catalyst in THF at 40 °C to examine

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[1] Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. and the references therein.

[2] For a review, see: (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. For recent examples, see: (b) Hilton, S. T.; Ho, T. C. T.; Pljevaljcic, G.; Jones, K. *Org. Lett.* **2000**, *2*, 2639. (c) Zhu, S.-L.; Ji, S.-J.; Zhang, Y. *Tetrahedron* **2007**, *63*, 9365.

[3] For examples: (a) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3186. (b) Malinakova, H. C.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 4083. (c) Lo, M. M.-C.; Neumann, C. S.; Nagayama, S.; Peristein, E. O.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 16077. (d) Overman, L. E.; Watson, D. A. *J. Org. Chem.* **2006**, *71*, 2587. (e) Hojo, D.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 5820.

[4] (a) Shintani, R.; Murakami, M.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12356. (b) Shintani, R.; Park, S.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 14866. (c) Shintani, R.; Park, S.; Shirozu, F.; Murakami, M.; Hayashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 16174. (d) Shintani, R.; Murakami, M.; Hayashi, T. *Org. Lett.* **2009**, *11*, 457. (e) Park, S.; Shintani, R.; Hayashi, T. *Chem. Lett.* **2009**, *38*, 204.

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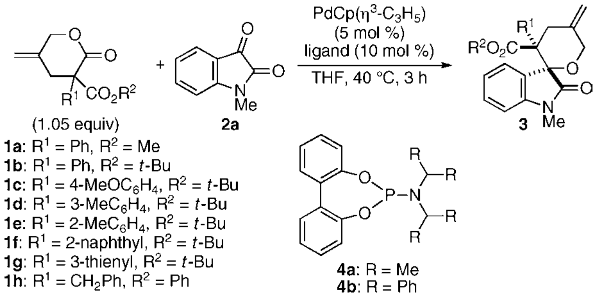
the effect of several known ligands (Table 1, entries 1−4). Among those tested, the reaction was best catalyzed by the use of phosphoramidite **4a**,[5] giving spirooxindole **3aa** in 94% yield with dr = 80/20 (entry 4). We subsequently found that the diastereoselectivity of **3aa** could be improved to 90/10 by using newly prepared phosphoramidite **4b** having a bis(diphenylmethyl)amino group on phosphorus (entry 5). By changing the ester group of **1a** from methyl to *tert*-butyl (**1b**), the diastereoselectivity was further improved to 97/3 with ligand **4b** (entry 6). Under these conditions, various α-(hetero)aryl-γ-methylidene-δ-valerolactones **1** efficiently undergo decarboxylative cyclization with **2a** in high yield with excellent diastereoselectivity (dr ≥ 95/5; entries 7−11). α-Alkyl lactones can also be successfully employed by adjusting the ester group to phenyl (entry 12) instead of methyl or *tert*-butyl, which results in less than 30% yield under otherwise the same conditions.

Table 1. Palladium-Catalyzed Decarboxylative [4 + 2] Cyclization of γ-Methylidene-δ-valerolactones **1** with *N*-Methylisatin (**2a**)

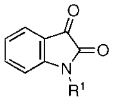
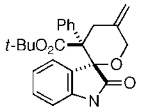
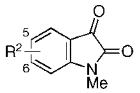
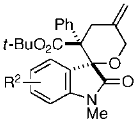
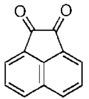
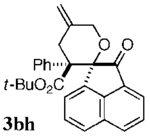
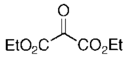
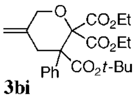


entry	1	ligand	product	yield (%)[a]	dr[b]
1	**1a**	PPh$_3$	**3aa**	77[c]	73/27
2	**1a**	P(O*i*-Pr)$_3$	**3aa**	82[c]	77/23
3[d]	**1a**	dppf	**3aa**	86[c]	77/23
4	**1a**	**4a**	**3aa**	94[c]	80/20
5	**1a**	**4b**	**3aa**	98[c]	90/10
6	**1b**	**4b**	**3ba**	96	97/3
7	**1c**	**4b**	**3ca**	84[e]	95/5
8	**1d**	**4b**	**3da**	94	97/3
9	**1e**	**4b**	**3ea**	70[e]	>99/1
10	**1f**	**4b**	**3fa**	93	97/3
11	**1g**	**4b**	**3ga**	96	98/2
12	**1h**	**4b**	**3ha**	76[e]	95/5

[a] Combined isolated yield of two diastereomers unless otherwise noted. [b] Determined by ^{1}H NMR of the crude material. [c] Determined by ^{1}H NMR against internal standard (*o*-xylene). [d] 5 mol % of ligand was used. [e] Isolated yield of the major diastereomer.

In addition to *N*-methylisatin (**2a**), *N*-benzyl- and *N*-methoxymethylisatins can be employed in the reaction with lactone **1b** as well, giving the corresponding spirooxindoles in high yield with excellent diastereoselectivity (dr ≥ 95/5; Table 2, entries 1 and 2). Isatins having various substituents on the benzene ring also undergo the present reaction with similar efficiency (dr ≥ 95/5; entries 3−6). The relative configuration of **3bf** (entry 5) was determined by X-ray crystallographic analysis as shown in Figure 1. The same mode of catalysis can be extended to other activated ketones. Thus, acenaphthenequinone (**2h**) and diethyl ketomalonate

Table 2. Palladium-Catalyzed Decarboxylative [4 + 2] Cyclization of γ-Methylidene-δ-valerolactone **1b** with Carbonyl Compounds **2**[a]

entry	2	3	yield (%)[b]	dr[c]
1	 **2b** (R^1 = CH$_2$Ph)	 **3bb** (R^1 = CH$_2$Ph)	93	95/5
2	**2c** (R^1 = CH$_2$OMe)	**3bc** (R^1 = CH$_2$OMe)	91	96/4
3	 **2d** (R^2 = 5-OMe)	 **3bd** (R^2 = 5-OMe)	93	98/2
4	**2e** (R^2 = 5-Me)	**3be** (R^2 = 5-Me)	94	98/2
5	**2f** (R^2 = 5-Br)	**3bf** (R^2 = 5-Br)	92	95/5
6	**2g** (R^2 = 6-Cl)	**3bg** (R^2 = 6-Cl)	94	95/5
7	 **2h**	 **3bh**	94	98/2
8[d]	 **2i**	 **3bi**	98	—

[a] Conditions: **1b** (0.21 mmol), **2** (0.20 mmol), PdCp(η^3-C$_3$H$_5$) (5 mol %), **4b** (10 mol %), THF (1.0 mL), 40 °C, 3 h. [b] Combined isolated yield of two diastereomers. [c] Determined by ^{1}H NMR of the crude material. [d] Ligand **4a** was used.

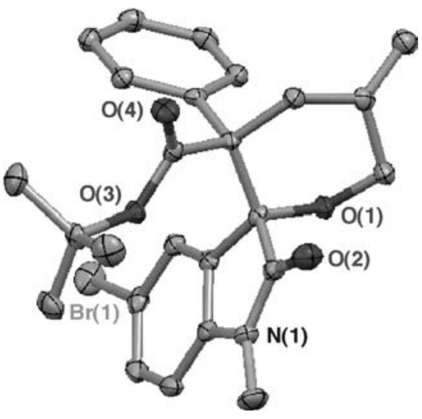


Figure 1. X-ray crystal structure of the major diastereomer of **3bf**.

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(5) Durán, J.; Moisés, G.; Castedo, L.; Mascareñas, J. L. *Org. Lett.* **2005**, *7*, 5693.

(**2i**) can be successfully used in the reaction with **1b** to give the decarboxylative cyclization products in high yield (entries 7 and 8).

A proposed catalytic cycle of the reaction of **1b** with **2a** is illustrated in Figure 2. Thus, oxidative addition of the allyl ester moiety of **1b** to palladium(0), followed by decarboxylation,[6,7] gives 1,4-zwitterionic species **A**. The anionic carbon of **A** then attacks the electrophilic carbon atom of **2a** to give intermediate **B**, which undergoes a ring closure through a nucleophilic attack of the oxygen atom to the π-allylpalladium moiety, leading to the formation of **3ba** along with regeneration of palladium(0).

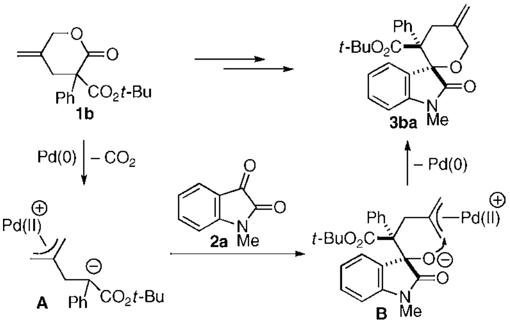
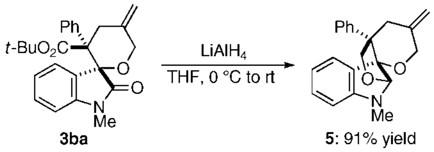


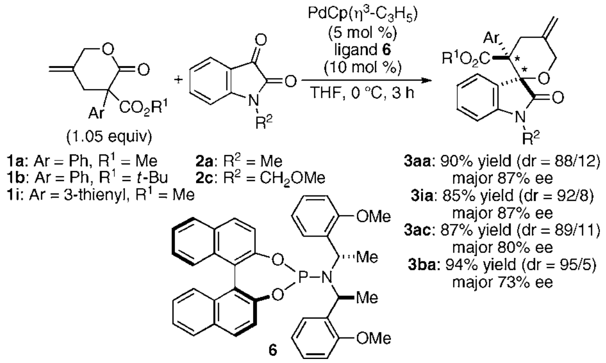
Figure 2. Proposed catalytic cycle for the palladium-catalyzed decarboxylative cyclization of **1b** with **2a**.

Spirooxindoles obtained by the present catalysis can be further derivatized to more complex structures. For example, treatment of compound **3ba** with $LiAlH_4$ in THF readily provides tetracyclic compound **5** with an *N*,*O*-acetal functionality in high yield (eq 1).



(1)

We have also begun to explore the development of asymmetric variant of this catalytic process to control the relative and absolute stereochemistry of the two contiguous quaternary stereocenters. By employing chiral phosphoramidite **6**[8] as a ligand, the reaction of lactone **1a** or **1i** with isatin **2a** or **2c** proceeds smoothly at 0 °C to give the corresponding spirooxindoles **3** with promising stereoselectivity (dr = 88/12 to 92/8, major 80−87% ee; eq 2). The use of lactone **1b** having a *tert*-butyl ester does improve the diastereoselectivity, but the enantioselectivity becomes somewhat lower under these conditions (dr = 95/5, 73% ee).



(2)

In summary, we have developed a palladium-catalyzed decarboxylative cyclization of γ-methylidene-δ-valerolactones with isatins to generate spirooxindoles under mild conditions. We have also described our preliminary results toward the development of an asymmetric variant. Future studies will focus on further improvement of the reaction conditions to achieve more efficient asymmetric catalysis.

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Supporting Information Available: Experimental procedures and compound characterization data and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[6] (a) Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199. (b) Tsuda, T.; Chuji, Y.; Nishi, S.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381. For reviews, see (c) Tunge, J. A.; Burger, E. C. *Eur. J. Org. Chem.* **2005**, 1715. (d) You, S.-L.; Dai, L.-X. *Angew. Chem., Int. Ed.* **2006**, *45*, 5246.

[7] For leading references, see: (a) Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 4113. (b) Rayabarapu, D. K.; Tunge, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13510. (c) Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 14860. (d) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180. (e) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924. (f) Patil, N. T.; Huo, Z.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 6991.

[8] (a) Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2426. (b) Alexakis, A.; Polet, D. *Org. Lett.* **2004**, *6*, 3529.