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Palladium-Catalyzed Enantioselective Ene and Aldol Reactions with Isatins, Keto Esters, and Diketones: Reliable Approach to Chiral Tertiary Alcohols

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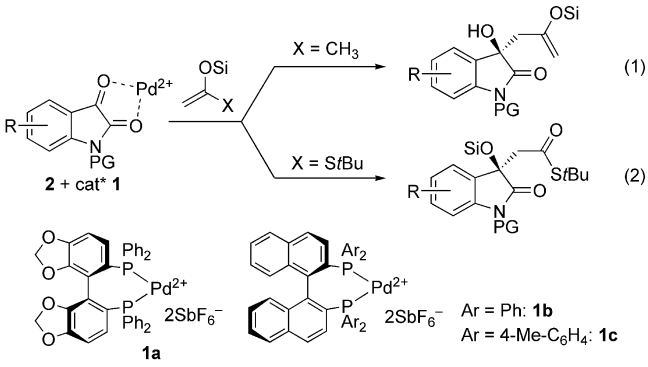
Chiral dicationic Pd-complex-catalyzed enantioselective ene and aldol reactions with various isatin derivatives are shown to produce the corresponding 3-hydroxy-2-oxindole products in good yields with high enantioselectivities. These catalytic processes are effective not only with isatins but also with keto esters and diketones derivatives. Even with unprotected isatin, high yields and enantioselectivities were obtained to produce convolutamydine A as a naturally occurring compound. Sequentially, α-oxidation by *m*-CPBA and α-fluorination by selectfluor of the ene product could be achieved to give the corresponding α-hydroxy and α-fluoro ketones, respectively.

Introduction

3-Substituted 3-hydroxy-2-oxindole derivatives are important synthetic intermediates for a variety of biologically active alkaloids.[1] In recent years, these enantiomerically enriched compounds have attracted much attention to directly synthesize their chiral backbones by asymmetric catalysts.[2,3] In order to efficiently construct and sequentially functionalize their carbon skeletons, we focused our attention on aldol[4,5] and ene[6,7] reactions with readily available isatin derivatives[8] using chiral Lewis acid catalysts. These catalytic asymmetric reactions with ketones are efficient carbon–carbon bond-forming processes that give highly enantiomerically enriched tertiary alcohols; acetone silyl enol ether (X = CH_3) as a nucleophile is expected to produce the corresponding ene products through a prototropic pathway of the allylic proton (Scheme 1, Equation 1).[7a,7c–7e] On the other hand, trimethylsilyl ketene thioacetal (X = S*t*Bu) would lead to the aldol products by silatropic approach (Scheme 1, Equation 2).[7b]

To produce highly functionalized α-hydroxy carbonyl compounds, our laboratory has strived to develop an asymmetric ene reaction with glyoxylate as an aldehyde or α-keto ester as a ketone by using chiral Ti[7a,7b] or Pd catalysts.[7e,9] In particular, chiral Pd complexes are air- and moisture-stable Lewis acid catalysts,[7e,10] which are easily synthesized, handled, and catalytically very active with high yield and enantioselectivity. In this paper, we present a chiral palladium-complex-based catalyst system for the highly enantioselective aldol and ene reactions with a variety of isatin derivatives. The catalytic asymmetric aldol reactions are also applicable to keto esters and diketones under similar conditions.



Scheme 1. Prototropic ene and silatropic aldol reactions.

Results and Discussion

The key features of the ene reaction optimized are summarized in Table 1. At the outset, the prototropic ene reactions were investigated with isopropenyloxy(triisopropyl)-silane (**3a**) and *N*-benzyl-protected isatins **2a**–**j** in the presence of chiral dication Pd complex **1a** bearing (*R*)-SEGPHOS. The Pd complex was simply activated by the addition of $AgSbF_6$ to the corresponding neutral dichloride complex.[9,10] Indeed, the reaction of **2a** with **3a** could be catalyzed by treatment of **1a** to give a high level of enantioselectivity (97%*ee*; Table 1, Entry 1). Even the use of sterically more demanding **2d** (R^1 = Br) led to almost enantiopure product **4d** in spite of a slightly lower yield (72%, >99%*ee*; Table 1, Entry 4). Complex **1a** also facilitated the reactions with Br- or Cl-substituted isatins **2b**, **2c** and **2e** in other positions to afford high yields and enantioselectivities

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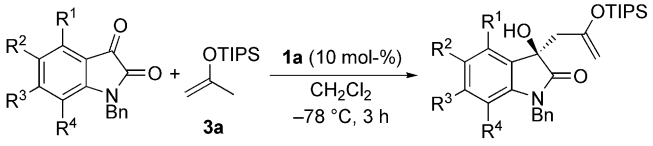
(84–93%, 94–95%*ee*; Table 1, Entries 2, 3, and 5). In the cases of 5-substituted (R^2) isatins **2f** and **2g** with electron-donating substituents, high enantioselectivities were maintained (95 and 98%*ee*), but **2h** and **2i** with electron-withdrawing substituents gave modestly decreased enantioselectivities (80 and 88%*ee*; Table 1, Entries 6–9). In contrast, the reaction with isatin **2j** bearing an electron-withdrawing 4,6-dibromo substituent was found to proceed in high yield with almost complete enantioselectivity (96%, >99%*ee*; Table 1, Entry 10).

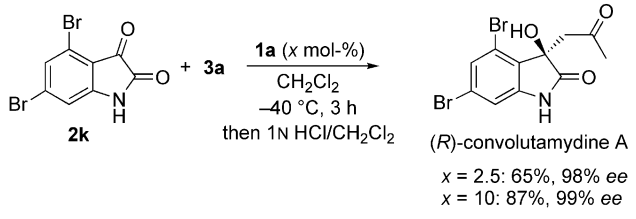
Table 1. Catalytic enantioselective ene reaction with various isatin derivatives.



Entry	Comp.	R^1	R^2	R^3	R^4	Yield [%][b]	*ee* [%][c]
1[a]	**2a**	H	H	H	H	87	97
2	**2b**	H	H	Br	H	93	95
3	**2c**	H	H	Cl	H	84	94
4	**2d**	Br	H	H	H	72	>99
5	**2e**	H	H	H	Br	87	94
6	**2f**	H	OMe	H	H	88	95
7	**2g**	H	Me	H	H	96	98
8	**2h**	H	NO_2	H	H	97	80
9	**2i**	H	Br	H	H	98	88
10	**2j**	Br	H	Br	H	96	>99

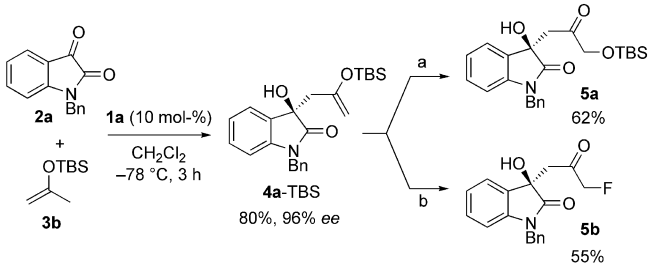
[a] Reaction time was 24 h. [b] Isolated yield after desilylation to the corresponding β-hydroxy ketone. [c] Enantiomeric excess was determined by chiral HPLC analysis after desilylation to the corresponding β-hydroxy ketone.

Even with unprotected **2k**, high enantioselectivity was obtained in the presence of 2.5 or 10 mol-% of the Pd complex at high temperature (98–99%*ee*, Scheme 2). The ene product was treated with 1 N HCl/CH_2Cl_2 at room temperature to produce convolutamydine A[11] as a natural compound, which exhibits a potent inhibitory activity on the differentiation of HL-60 human promyelocytic leukemia cells at 0.1–25 μg/mL, in good yield. The absolute configuration at the newly created center was determined to be *R* by comparing the optical rotation data given in the literature.[11]



Scheme 2. Enantioselective synthesis of (*R*)-convolutamydine A.

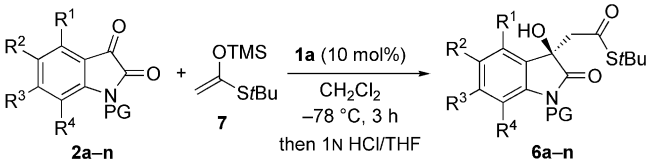
The same method could be applied to the reaction of isatin **2a** with **3b** bearing TBS instead of TIPS to obtain the more reactive ene product **4a**-TBS (96%*ee*), which is the key structure featured in important natural alkaloids (Scheme 3). α-Oxidation of **4a**-TBS with *m*-CPBA or α-fluorination with selectfluor could be achieved to give the corresponding product **5a** or **5b** in 62 or 55% yield, respectively.[7c–7e]



Scheme 3. Reactions via the ene reaction. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, 0 °C, 1 h; b) selectfluor, CH_3CN, 0 °C, 12 h.

With these successes in terms of the high yield and enantioselectivity in the catalytic ene reactions, we then examined the aldol reaction[12] with isatin derivatives **2** and trimethylsilyl ketene thioacetal **7**; Table 2 summarizes the representative results. Under the optimized conditions for the ene reaction, reactions of isatins **2a**–**c** with or without electron-withdrawing Br and Cl substituents in the *meta* position of the amide proceeded in 81–89% yield to afford aldol products **6a**–**c** in good-to-excellent enantioselectivities after desilylation by treatment with 1 N HCl/THF (85 to >99%*ee*; Table 2, Entries 1–3). In sharp contrast to the ene reactions, the aldol reactions are sensitive to both electronic and steric effects of the substituents of isatins; aldol reactions with isatins **2e**, **2h**, and **2i** bearing electron-withdrawing substituents in the *ortho* or *para* positions of the amide did not produce the corresponding aldol products (Table 2, Entries 5, 8, and 9). It is highly likely that a decrease in electron density of the amide oxygen prevents the

Table 2. Catalytic enantioselective aldol reaction with various isatin derivatives.

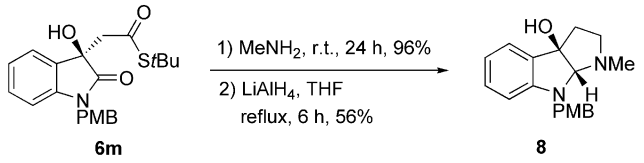


Entry	Comp.	R^1	R^2	R^3	R^4	PG	Yield [%][b]	*ee* [%][c]
1	**2a**	H	H	H	H	Bn	89	>99
2	**2b**	H	H	Br	H	Bn	87	89
3	**2c**	H	H	Cl	H	Bn	81	85
4[a]	**2d**	Br	H	H	H	Bn	trace	–
5[a]	**2e**	H	H	H	Br	Bn	trace	–
6	**2f**	H	OMe	H	H	Bn	98	99
7	**2g**	H	Me	H	H	Bn	92	99
8[a]	**2h**	H	NO_2	H	H	Bn	0	–
9[a]	**2i**	H	Br	H	H	Bn	trace	–
10	**2j**	Br	H	Br	H	Bn	40	0
11[a]	**2l**	H	H	H	H	H	0	–
12	**2m**	H	H	H	H	PMB	>99	99
13[a]	**2n**	H	H	H	H	Boc	0	–

[a] At –20 °C for 24 h. [b] Isolated yield. [c] Enantiomeric excess was determined by chiral HPLC analysis.

chelation of isatins to palladium. Therefore, high-to-excellent yields and enantioselectivities were obtained in the case of **2f** and **2g** with electron-donating MeO and Me substituents (98%, 99%*ee* and 92%, 99%*ee*; Table 2, Entries 6 and 7). The reactions with 4-substituted (R^1) isatins **2d** and **2j** gave low reactivity due to steric hindrance (Table 2, Entries 4 and 10). Introduction of a Bn protecting group led not only to an enhancement in reactivity but also to high enantioselectivity (Table 2, Entry 1 vs. 11 and 13). *N*-PMB-protected isatin **2m** was also applicable under the same conditions to give excellent results (Table 2, Entry 12).

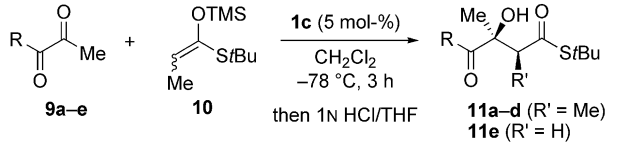
The aldol product can be converted into carbon skeletons found in valuable natural products (Scheme 4). For example, treatment of aldol product **6m** (99%*ee*) with $MeNH_2$ in methanol followed by $LiAlH_4$ afforded the corresponding alkaloid, *N*-protected alline **8**.[1d,1e,13]



Scheme 4. Transformation into natural alkaloid structure.

On the hypothesis that the bidentate coordination of isatin derivatives to the palladium center was significantly important not only to induce a high level of enantioselectivity but also to increase the reactivity, we employed keto esters **9a** and **9e** and diketones **9b–d** with a similar dicarbonyl backbone (Table 3).[5] Reaction of ketene thioacetal **10** (*Z*/*E* = 97:3) with **9a** efficiently afforded desired aldol product **11a** in good diastereoselectivity (*syn*/*anti* = 95:5) with excellent enantioselectivity (>99%*ee*; Table 3, Entry 1). In contrast, **10** (*Z*/*E* = 10:90) also produced *syn*-**11a** as a major product but in lower yield and enantioselectivity (37%, 12%*ee*; Table 3, Entry 2). The use of 1 mol-% of the Pd complex was sufficient to promote the reaction with 98%*ee*, although a longer reaction time was required (Table 3, Entry 3). Additionally, dimethyl diketone **9b** afforded desymmetrized product **11b** in almost complete diastereo- and enantioselectivity (*syn*/*anti* >99:1, >99%*ee*; Table 3, Entry 4). The aldol products on the methyl ketone position were only obtained with unsymmetrical diketones **9c** and **9d**, leading to almost complete diastereo- and enantioselectivity in good yields (Table 3, Entries 5 and 6). The reaction of ethyl pyruvate **9e** with **7** also proceeded to give high yield and enantioselectivity (86%, 99%*ee*; Table 3, Entry 7).

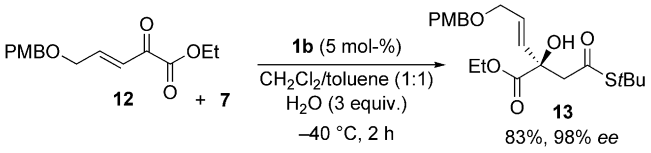
Table 3. Aldol reaction with pyruvates or diketones.



Entry	Comp.	R	**10** (*Z*/*E*)	**11** (*syn*/*anti*)	Yield [%][d]	*ee* [%][e]
1	**9a**	OMe	97:3	95:5	81	>99
2	**9a**	OMe	10:90	72:28	37	12
3[a]	**9a**	OMe	97:3	95:5	65	98
4	**9b**	Me	97:3	>99:1	95	>99
5	**9c**	Et	97:3	>99:1	87	>99
6	**9d**	*n*Bu	97:3	>99:1	93	99
7[b]	**9e**	OEt	–[c]	–	86	99

[a] Reaction time was 48 h with 1 mol-% of Pd catalyst. [b] Reaction time was 30 min. [c] Trimethylsilyl ketene thioacetal **7** was used instead of **10**. [d] Isolated yield. [e] Enantiomeric excess of *syn* product was determined by chiral HPLC analysis.

To explore the applicability of another electrophile, the aldol reaction in the presence of complex **1b** and 3 equiv. of water as an additive[14] was tested using α,β-unsaturated keto ester **12** with **7** (Scheme 5). Significantly, the corresponding aldol product **13** was produced in almost complete chemoselectivity and high enantioselectivity (83%, 98%*ee*).



Scheme 5. 1,2-Aldol reaction of α,β-unsaturated keto ester.

Conclusions

We have succeeded in the development of chiral dicationic Pd-catalyzed enantioselective ene and aldol reactions, which construct highly optically active tertiary alcohols. The catalytic process is effective with a wide range of substrates such as isatins, keto esters, and diketone derivatives. Further investigations of this reaction are currently in progress to construct more sterically demanding skeletons.

Experimental Section

Typical Procedure for the Catalytic Enantioselective Ene Reaction: To a solution of $PdCl_2$[(*R*)-SEGPHOS] (7.9 mg, 0.01 mmol) in CH_2Cl_2 (2 mL) was added $AgSbF_6$ (7.6 mg, 0.022 mmol) at room temperature. After stirring for 30 min at room temperature, to the mixture was added 1-benzyl isatin **2a** (23.8 mg, 0.1 mmol) in CH_2Cl_2 (1 mL); silyl enol ether **3a** (42.9 mg, 0.2 mmol) was then added at –78 °C. The reaction mixture was stirred at –78 °C for 24 h. The reaction solution was passed through a silica-gel short column (hexane/AcOEt, 1:1) and evaporated under reduced pressure. To the solution of ene product **4a** in CH_2Cl_2 (0.5 mL) was added 1 N HCl/MeOH (2–3 drops). After stirring for 15 min at room temperature, the mixture was directly loaded onto a silica-gel column (hexane/AcOEt, 2:1) to give the corresponding β-hydroxy ketone (87% yield, 97%*ee*; Table 1, Entry 1).

Typical Procedure for the Catalytic Enantioselective Aldol Reaction: To a solution of $PdCl_2$[(*R*)-SEGPHOS] (7.9 mg, 0.01 mmol) in CH_2Cl_2 (2 mL) was added $AgSbF_6$ (7.6 mg, 0.022 mmol) at room temperature. After stirring for 30 min at room temperature, to the mixture was added 1-benzyl isatin **2a** (23.8 mg, 0.1 mmol) in CH_2Cl_2 (1 mL); trimethylsilyl ketene thioacetal **7** (51.1 mg, 0.25 mmol) was then added at –78 °C. The reaction mixture was stirred at –78 °C for 3 h. The reaction solution was passed through

a silica-gel short column (hexane/AcOEt, 1:1) and evaporated under reduced pressure. To a solution of the crude in THF (5 mL) was added 1 N HCl (1 mL). After stirring for 2 h at room temperature, the mixture was poured into a solution of Et_2O (10 mL) and H_2O (5 mL). The organic layer was washed with sat. aq. $NaHCO_3$ and brine and dried with anhydrous Na_2SO_4. Purification by silica-gel chromatography (hexane/AcOEt, 4:1) gave aldol product **6a** (89% yield, >99%*ee*; Table 2, Entry 1).

Supporting Information (see footnote on the first page of this article): Experimental procedures and spectroscopic data for the ene and aldol products.

Acknowledgments

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