

Catalytic Asymmetric Synthesis of Quaternary Carbon Centers by Intramolecular Heck Reaction

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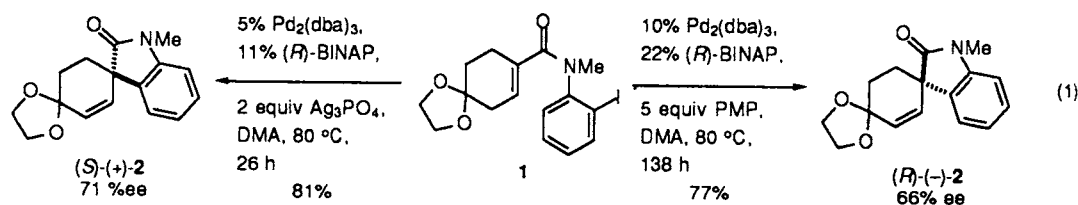
学 位 論 文 要 旨

Abstract: The effect of chiral diphosphine structure, method of catalyst generation, reaction solvent and HI scavenger on the formation of enantioenriched 3,3-disubstituted 2-oxindole **2** from asymmetric Heck cyclization of **1** was studied. Depending upon whether the HI scavenger was a silver salt or a basic tertiary amine, either enantiomer of **2** could be formed with good selectivity using the same enantiomer of BINAP. Using Pd-BINAP as catalyst, a variety of enantioenriched 3,3-disubstituted oxindoles, indolines and dihydrobenzofurans was prepared from (*E*)- α,β -unsaturated 2-haloaniline substrates. All cyclizations conducted in the presence of Ag₃PO₄ or 1,2,2,6,6-pentamethylpiperidine (PMP) afforded opposite enantiomers of the spirocyclic product. These studies demonstrate, for the first time, that asymmetric Heck reactions of halide substrates can proceed with useful levels of enantioselectivity without silver or thallium salts.

As the key reaction for the synthesis of physostigmine, the author investigated asymmetric Heck cyclization of (*E*)- and (*Z*)-butenilides **5** and discovered that the enantioselectivity highly depends on the geometry of the substrate. For (*Z*)-**5**, both of silver- and amine-promoted cyclizations predominantly gave (*R*)-enantiomer of aldehyde **7** and enantioselectivity over 90% is reproducibly realized in the amine-promoted cyclization. This method is highly promising to construct 2-oxindole **7** enantioselectively, which is an important intermediate for the synthesis of hexahydropyrrolo[2,3-*b*]indole skeleton of physostigmine and related alkaloids.

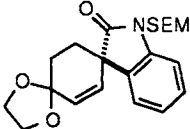
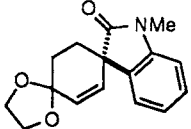
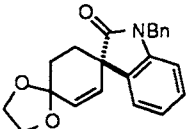
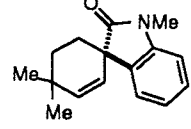
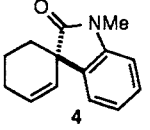
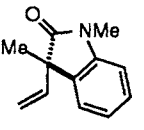
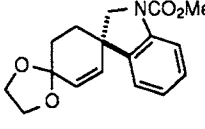
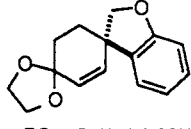
Most of naturally occurring compounds are optically active, and in many cases, each enantiomer shows variable potency of biological activities and sometimes has even completely different pharmacological features. Therefore, it is much important to synthesize such molecules in optically pure form. Recently, asymmetric syntheses using chiral transition metal catalysts have been developed, however few excellent methods yet exist for asymmetric carbon-carbon bond formation. Particularly underdeveloped is the asymmetric synthesis of quaternary carbon centers using chiral metal complexes.

The author expected that quaternary carbon center of spirooxindole **2** can be formed by asymmetric intramolecular Heck reaction. The effect of chiral diphosphine structure, method of catalyst generation, reaction solvent and HI scavenger on the formation of **2** from asymmetric Heck cyclization of **1** was studied. Depending upon whether the HI scavenger was a silver salt or basic tertiary amine, either enantiomer of **2** could be formed with good selectivity using the same enantiomer of BINAP (eq. 1).

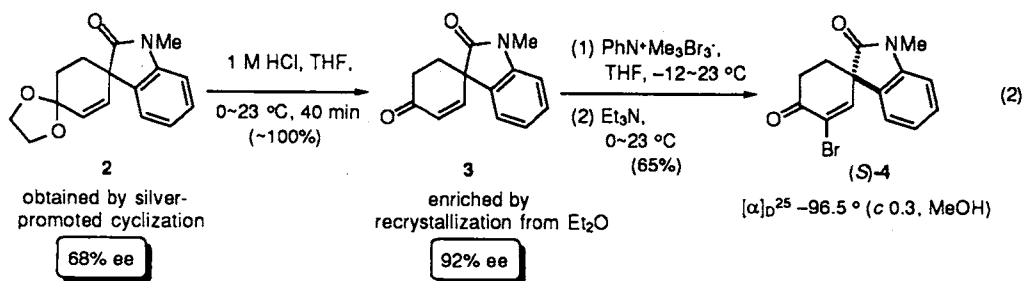


The scope of asymmetric Heck cyclizations of (*E*)- α,β -unsaturated 2-haloanilide substrates was surveyed. As the representative results summarized in Table 1, a variety of enantioenriched 3,3-disubstituted oxindole, indolines and dihydrobenzofurans was prepared using Pd-BINAP as catalyst. With all aniline substrates, opposite enantioselection was observed in Ag_3PO_4 - and 1,2,2,6,6-pentamethylpiperidine (PMP)-promoted cyclizations. These studies demonstrate, for the first time, that asymmetric Heck reactions of halide substrates can proceed with useful levels of enantioselectivity without silver or thallium salts.

Table 1. Asymmetric Synthesis of Either Spirocyclic Enantiomer from the Corresponding Aryl Iodide Using (*R*)-BINAP

 <p>Ag₃PO₄ - 76%, (<i>S</i>) 65 % ee PMP - 74%, (<i>R</i>) 75 % ee</p>	 <p>Ag₃PO₄ - 81%, (<i>S</i>) 71 % ee PMP - 77%, (<i>R</i>) 66 % ee</p>
 <p>Ag₃PO₄ - 91%, (<i>S</i>) 50 % ee PMP - 66%, (<i>R</i>) 55 % ee</p>	 <p>Ag₃PO₄ - 99%, (+) 72 % ee PMP - 89%, (-) 71 % ee</p>
 <p>Ag₃PO₄ - 74%, (<i>S</i>) 81 % ee PMP - 45%, (<i>R</i>) 95 % ee</p>	 <p>Ag₃PO₄ - 88%, (-) 63 % ee PMP - 91%, (+) 25 % ee</p>
 <p>Ag₃PO₄ - 90%, (+) 64 % ee PMP - 68%, (-) 8 % ee</p>	 <p>Ag₃PO₄ - 91%, (+) 55 % ee PMP - 66%, (-) 7 % ee</p>

The product (+)-**2** was hydrolyzed to the corresponding enone **3**, which could be purified to an ee of 92% by recrystallization from Et₂O and subsequently brominated to afford **4** (eq. 2). The α -bromoenone **4** was suitable for X-ray crystallographic analysis and its absolute configuration was determined. Absolute configurations of other cyclization products were assigned by direct chemical correlation with thus defined (*S*)-(+)-**2**.



The insertion step of the asymmetric Heck reactions in the presence of amine bases likely proceeds *via* the penta-coordinate complex **A** or a four-coordinate complex **B**. For high enantioselection, more rigid complex **B** is more likely than complex **A** with one phosphorus atom dissociated from palladium (Figure 1).

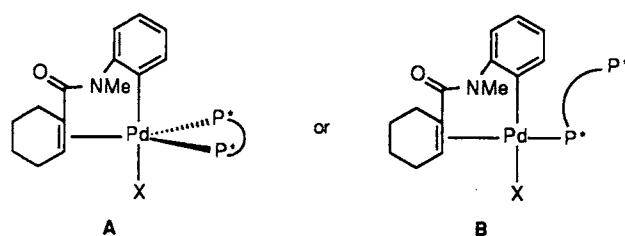


Figure 1

The author envisioned an application of the present asymmetric Heck reaction to construction of the critical quaternary carbon center of the hexahydropyrrolo[2,3-*b*]indole ring system of (-)-physostigmine (Figure 2).

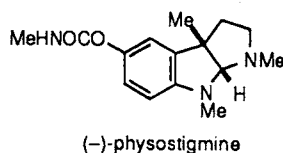


Figure 2

The investigation was focused on exploration of the asymmetric Heck reaction conditions to form enantiopure oxindole aldehyde **7** from (*E*)- and (*Z*)-substrates **5** (eq. 3). Cyclization of (*E*)-**5** in the presence of Ag₃PO₄ gave, after hydrolysis of the enoxysilane **6**, the *S* enantiomer of oxindole aldehyde **7**, while cyclization in the presence of PMP provided (*R*)-**6**, albeit both with low asymmetric induction (Table 2, entries 1 and 2). However, identical cyclization of (*Z*)-**5** proceeded with excellent enantioselection (95~96% and 81~85% in the presence of PMP and Ag₃PO₄, respectively), and both cyclizations provided the *R* enantiomer of oxindole aldehyde **7** (Table 2, entries 3 and 4). Considering the insertion proceeding preferentially *via* the

most stable cationic square planar complex having an approximate coplanar orientation of the alkene π and aryl-C σ bonds in the silver-promoted cyclization, predominant formation of *R* enantiomer from (*Z*)-substrate was rationalized by steric destabilizing interactions between (1) the β -TBDMSOCH₂-, (2) the twisted aryl ring of the substrate and *pseudo*-equatorial phenyl group of BINAP.

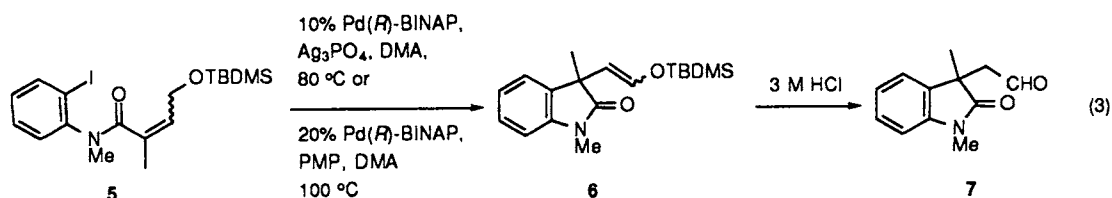


Table 2 Asymmetric Heck Cyclization of (*E*)- and (*Z*)-Butenanilides 5

entry	stereochem of 5	HI scavenger	6		oxindole aldehyde 7	
			<i>E</i> : <i>Z</i>	yield from 5, %	confign	ee, %
1	<i>E</i>	Ag ₃ PO ₄	-	80	<i>S</i>	45
2	<i>E</i>	PMP	77:23	91	<i>R</i>	45
3	<i>Z</i>	Ag ₃ PO ₄	-	77	<i>R</i>	81~85
4	<i>Z</i>	PMP	96:4	84~86 from (<i>E</i>)-6	<i>R</i>	95~96 from (<i>E</i>)-6

The present asymmetric Heck cyclization of (*Z*)-butenanilide **5** is a highly promising way to construct enantioselectively 2-oxindole aldehyde **7**, which is an important intermediate for the synthesis of physostigmine and related alkaloids.

In summary, the author discovered that the asymmetric Heck cyclization of (*E*)- α,β -unsaturated 2-haloanilides and related compounds with Pd-BINAP in the presence of silver salt (I) or tertiary amine reproducibly constructs 3,3-disubstituted oxindoles, indolines and dihydrobezofurans in good to excellent enantioselectivity. Particularly, that depending upon how HX is scavenged, either enantiomer of the Heck product can be formed using a single enantiomer of BINAP is indeed unprecedented. As the key reaction for the synthesis of physostigmine, the author investigated asymmetric Heck cyclization of (*E*)- and (*Z*)-butenanilides **5** and discovered that the enantioselectivity highly depends on the geometry of substrates **5**. For (*Z*)-**5**, both of silver- and amine-promoted cyclizations gave (*R*)-enantiomer for the first time and enantioselectivity over 90% is reproducibly realized in the amine-promoted cyclization. This method is highly promising to construct enantioselectively 2-oxindole **7**, which is an important intermediate for the synthesis of hexahydropyrrolo[2,3-*b*]indole skeleton of physostigmine and related alkaloids.

学位論文審査結果の要旨

医薬品等の生理活性化合物の合成における不斉合成の重要性は近年益々高まってきている。金属錯体を用いる触媒的不斉合成法が種々開拓されてきているが、C-C結合形成反応とりわけ不斉4級炭素の構築にはすぐれた方法は未だ少ない。申請者は、 α 、 β -不飽和ハロゲン化アニリドを基質として、分子内 Heck 反応を利用した3, 3-ジ置換オキシインドール誘導体の不斉合成を検討し、以下の新しい知見を得た。

1. 2-Iodo-*N*-(1, 4-dioxaspiro[4.5]dec-7-en-8-ylcarbonyl)-*N*-methylaniline から Pd-(*R*)-BINAP 触媒を用いる分子内 Heck 反応でオキシインドール体 1', 2'-dihydro-1'-methyl-2'-oxospiro[1, 4-dioxaspiro[4.5]dec-6-ene-8, 3'-3'-3'*H*-indole]の不斉合成を達成した。この際、HI-スカベンジャーとして Ag₃PO₄ 又は 1, 2, 2, 6, 6-pentamethylpiperidine(PMP)を使い分けることにより、それぞれ *S*(+)-体又は *R*(-)-体の両エナンチオマーが好収率、好光学収率で得られることを見出した。
2. 上記反応を各種 (*E*)- α 、 β -不飽和-2-ハロアニリド誘導体に適用し、4級不斉炭素を有する3, 3-ジ置換オキシインドール、インドリン及びジヒドロベンゾフラン誘導体の両エナンチオマーの不斉合成に成功した。
3. 2'-Iodo-*N*-methyl-(*Z*)-4-(*tert*-butyldimethylsilyloxy)-2-methyl-2-butenanilide に本不斉分子内 Heck 反応を適用し、Ag₃PO₄ 又は PMP いずれを用いても (*R*)-1, 2-dihydro-1, 3-dimethyl-2-oxo-3-(2-oxoethyl)-3 *H*-indole の高収率、高光学収率での不斉合成を達成した。
4. 上記成績体は (-)-physostigmine の重要合成中間体であり、ここに本アルカロイドの新規不斉合成ルートへの道を拓いた。

以上の成果は、分子内 Heck 反応を用いた3, 3-ジ置換オキシインドール体の両エナンチオマーの新しい触媒的不斉合成法を開拓したもので、不斉4級炭素の新しい構築法として着目され、不斉合成化学への寄与は大きく、医薬品を含む各種生理活性化合物の不斉合成に広い応用が期待されることから、本論文は博士(薬学)論文に値するものと判定した。