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Pd-Catalyzed Asymmetric Synthesis of 3,4-Dihydroisoquinolinones From *N*-Ts-Benzamides and 1,3-Dienes

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Chiral 3,4-dihydroisoquinolinones are important skeletons often found in various naturally occurring and bioactive compounds (Figure 1).[1] Therefore, their efficient and stereoselective synthesis is highly desirable.

Transition metal-catalyzed annulative coupling reaction for the synthesis of various heterocyclic compounds has been extensively studied as a powerful synthetic tool, giving considerable advantages over traditional synthetic methods.[2] In this context, various transition metal-catalyzed synthetic methods to access 3,4-dihydroisoquinolinones have been developed, which involve direct intermolecular oxidative annulation between benzamides and alkenes through both C─C and C─N bond formation.[3] Despite significant advances, asymmetric synthesis of such compounds from these readily available starting materials remains a challenging task and still in demand (Scheme 1(a)).[4] While most of these reactions were promoted by costly Rh complexes, the use of relatively inexpensive and common Pd catalysts is challenging, leading to the formation of undesired products such as 2-alkenylated benzamides or isoindolin-1-ones due to the competitive β-hydride elimination followed by intramolecular cyclization.[5] Booker-Milburn and co-workers successfully developed a Pd-catalyzed protocol by using *N*-methoxybenzamides and 1,3-dienes, which involves a palladacycle (**I**) through C─H activation and relatively more stable π-allyl Pd intermediate (**II**).[6] However, limitations such as low-to-moderate yields (3–64%) and limited substrate scope (only R = ester) still remain.

In light of our recent success in Pd-catalyzed regio- and stereoselective synthesis of (*E*)-3-arylmethyleneisoindolin-1-ones from *N*-Ts-benzamides and alkenes,[5] and on the basis of literature on various C(sp^2)─H functionalization reactions with assistance of the *N*-tosylcarboxamide group as a directing group,[5,6b] we reasoned that a carefully selected catalytic system would promote an asymmetric oxidative annulation of *N*-Ts-benzamides with 1,3-dienes, leading to chiral 3,4-dihydroisoquinolinones. Considering that the prior related reactions proceeded only under ligand-free conditions at high temperature (≥90 °C),[6] finding a suitable chiral ligand and reaction conditions is critical for the success of this asymmetric reaction.

As part of our continued interest in annulative coupling reactions,[5] we herein report a Pd(II)-catalyzed asymmetric oxidative annulation of *N*-Ts-benzamides with 1,3-dienes using a chiral pyridine-oxazoline (PyOX)-type ligand for the regio- and stereoselective synthesis of chiral 3,4-dihydroisoquinolinones (Scheme 1(b)). During our investigations on this project, Gong[7a] and Yang[7b] independently reported a closely related Pd(II)-catalyzed asymmetric reaction of benzamides with 1,3-dienes: In sharp contrast to our results, however, the use of only electron-

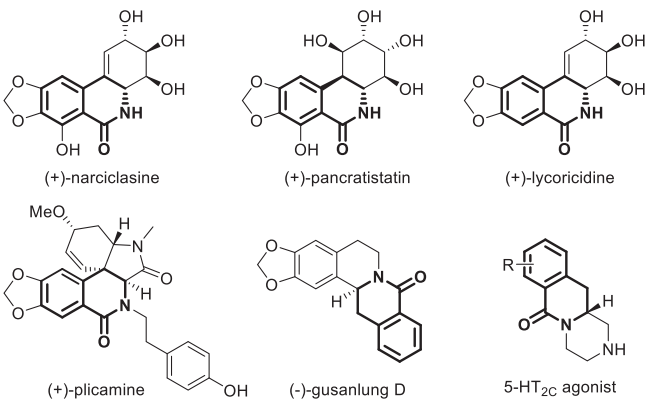

Figure 1. Bioactive molecules containing chiral 3,4-dihydroisoquinolinone scaffold.

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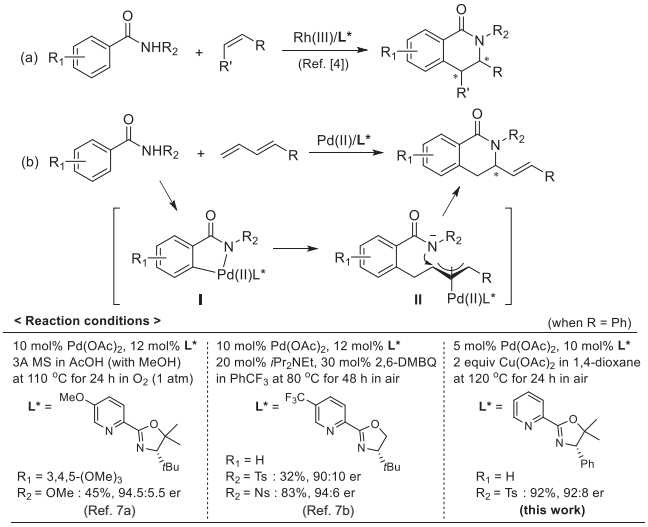
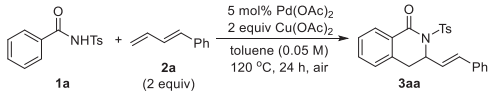


Scheme 1. Transition-metal-catalyzed asymmetric synthesis of chiral 3,4-dihydroisoquinolinones.

Table 1. Optimization studies for the synthesis of 3,4-dihydroisoquinolinones.



Entry	Variation from the standard conditions	Yield (%)[a]
1	None	(90)
2	1,4-Dioxane instead of toluene	(93)
3	$ClCH_2CH_2Cl$, EtOH, MeCN, DMF, DMSO instead of toluene	0-(37)
4	At 100°C	39
5	$PdCl_2$, $PdCl_2(MeCN)_2$, $[Pd(allyl)Cl]_2$, $Pd(PPh_3)_4$ instead of $Pd(OAc)_2$	27–49
6	$Pd(O_2CCF_3)_2$, $PdCl_2(PhCN)_2$, $PdCl_2(PPh_3)_2$, $Pd(dba)_3$, $PdCl_2(dppf)\cdot CH_2Cl_2$ instead of $Pd(OAc)_2$	62–85
7	CuX (X=Cl, Br, I) instead of $Cu(OAc)_2$	5–19
8	CuX_2 (X=Cl, Br, OTf) instead of $Cu(OAc)_2$	0
9	$Cu(OAc)_2\cdot H_2O$ instead of $Cu(OAc)_2$	56
10	Ag_2CO_3, AgOAc, Ag_2O, *t*BuOOH, $(tBuO)_2$, BQ, Oxone, $K_2S_2O_8$, TEMPO, Selectfluor, $PhI(OAc)_2$ instead of $Cu(OAc)_2$	0–16
11	40 mol % $Cu(OAc)_2$	56

[a] Determined by ^1H NMR. Values in parentheses indicate isolated yields.

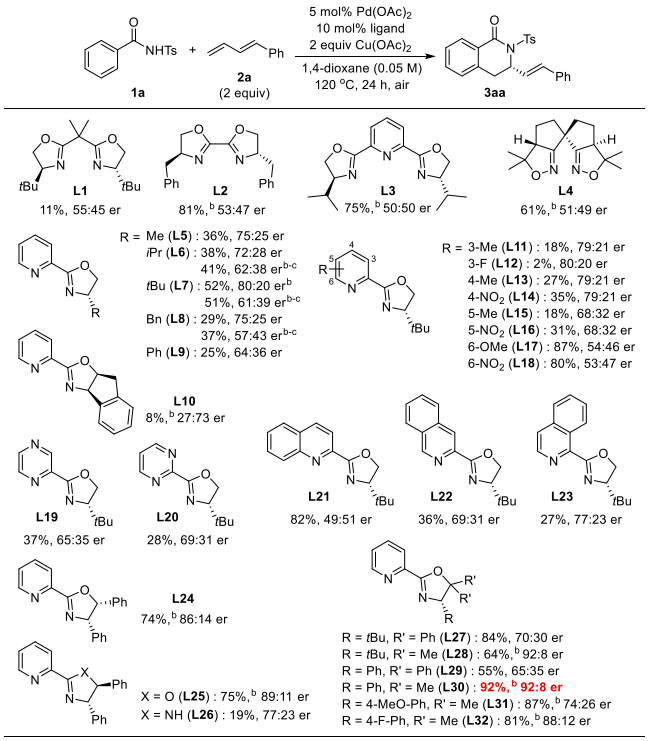
rich benzamides in acid solvent and oxygen gas,[7a] or base additive and long reactions[7b] were required to result in still low-to-moderate chemical yields of the products with moderate to good stereoselectivities.

In light of our recent success in the Pd-catalyzed oxidative annulation reaction of *N*-Ts-benzamides and alkenes,[5] we began our studies on the proposed reaction using **1a** and **2a** as the substrates without a ligand (Table 1). After examination of the reaction parameters (*e.g.*, Pd complexes, oxidants, solvents), a reaction system consisting of $Pd(OAc)_2$ and $Cu(OAc)_2$ as a catalyst and oxidant, respectively, in toluene or 1,4-dioxane in air was found to be the optimal reaction conditions to afford **3aa** in high yields with complete regioselectivity (entries 1–2).

Next, we extended our investigation to a variety of chiral ligands, which have been widely used in Pd-catalyzed asymmetric transformations (Table 2).[8] Among various bi- and tridentate nitrogen and phosphorus ligands examined, pyridine-oxazoline (PyOX) derivatives proved to be superior to the others, such as chiral amino acid, BINAP, phosphoramidite, phosphinooxazoline, bis(oxazoline) (**L1**–**L2**), pyridinebis(oxazoline) (**L3**), and spiro bis(isoxazoline) (**L4**) type ligands.

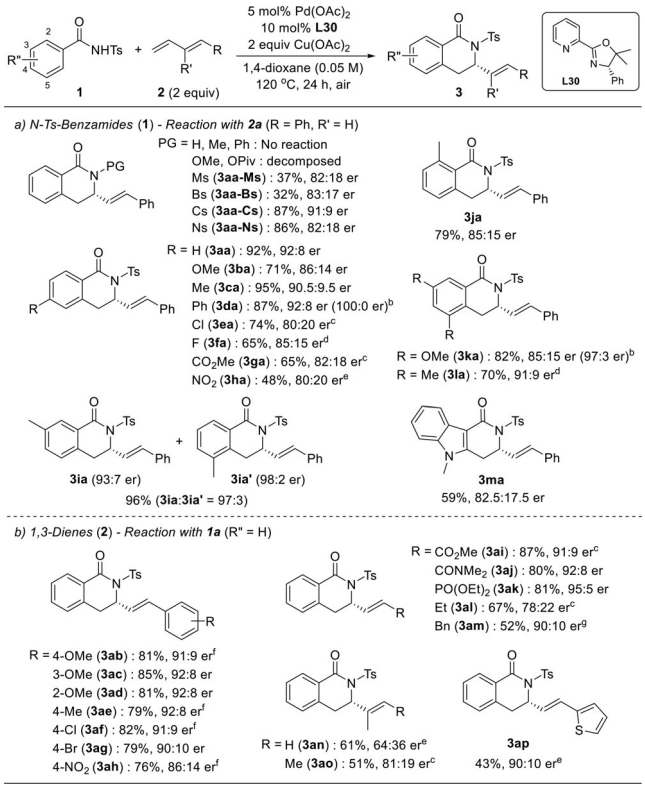
The evaluation of various chiral PyOX ligands showed that *t*Bu-substituted oxazoline-containing **L7** gave the highest yield and enantioselectivity among **L5**-**L10**, while the

Table 2. Screening of chiral ligands for asymmetric reaction.



[a] Determined by ^{1}H NMR. Enantiomeric ratio (er) was determined by HPLC analysis.
[b] Isolated yields.
[c] In toluene.

Table 3. Substrate scope.[a]



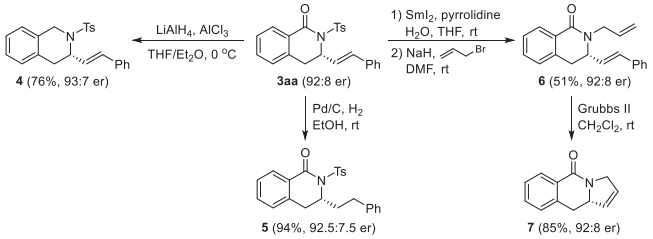
[a] Isolated yields were provided. Enantiomeric ratio (er) was determined by HPLC analysis.
[b] After recrystallization.
[c] Using 10 mol % $Pd(OAc)_2$ and 20 mol % **L30**.
[d] Using 15 mol % $Pd(OAc)_2$ and 30 mol % **L30**.
[e] Using 20 mol % $Pd(OAc)_2$ and 40 mol % **L30**.
[f] Using 7.5 mol% $Pd(OAc)_2$ and 15 mol% **L30**.
[g] Using 25 mol % $Pd(OAc)_2$ and 50 mol% **L30**.

substituents on the pyridine moiety (**L11**–**L23**) did not give any beneficial effect. Interestingly, switching a solvent from 1,4-dioxane to toluene led to diminished enantioselectivities, albeit in comparable yields (**L6**–**L8**). Further examination of the substituent effect of the oxazoline moiety revealed that an additional *gem*-dimethyl moiety resulted in significant increases of both yield and enantioselectivity (**L28** vs. **L7** and **L30** vs. **L9**). The best results (92%, 92:8 er) were obtained with **L30**, which was efficient for one-pot domino C–H functionalization and the asymmetric allylation sequence, rendering the latter with high stereocontrol.

With the establishment of a viable catalytic system, we set out to explore the scope of this process. First, the effect of different *N*-PGs was examined (Table 3). Only sulfonyl group was effective, while decomposition or no reaction occurred with other protecting groups. Among various sulfonyl groups examined, the Ts group was revealed as the protecting group of choice for this transformation.

In general, a variety of *N*-Ts-benzamides (**1**) were well tolerated regardless of substituent position (**3aa**–**3la**), while strongly electron-withdrawing substituents, such as NO_2 (**3ha**), resulted in relatively lower yields of the desired products with moderate enantioselectivity. Indole-3-caboxamide derivative was also a suitable substrate for the formation of the chiral fused tricyclic 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-1-one (**3ma**).

Subsequently, we examined the reaction of various 1,3-dienes with **1a**. A wide range of 1-aryl-1,3-dienes underwent the reaction smoothly to afford the corresponding chiral 3,4-dihydroisoquinolinones (**3ab**–**3ah**) in good yields with moderate-to-high enantioselectivities, regardless of their electronic properties and the positions of their substituents. Activated 1,3-dienes containing an electron-withdrawing group (*e.g.*, esters, amides, and phosphonates) were also good substrates for this reaction, affording the corresponding products (**3ai**–**3ak**) with high yields and enantioselectivities. Reactions with alkyl- and heteroaryl-substituted 1,3-dienes proceeded uneventfully to afford **3al**–**3ao** and **3ap**, respectively, with moderate-to-good enantioselectivities, while isoprene resulted in much lower enantioselectivity (**3an**). Notably, this process can tolerate



Scheme 2. Synthetic application.

various functional groups such as halogen, ester, amide, phosphonate, and nitro groups.

To highlight the synthetic utility of this transformation, further transformation of the chiral 3,4-dihydroisoquinolinones obtained from this process was undertaken (Scheme 2). The amide carbonyl group and the alkene moiety in **3aa** could be selectively reduced to afford **4** and **5**, respectively, in good yields without loss of the optical purity. Smooth removal of the *N*-Ts group led to NH-free 3,4-dihydroisoquinolinones, which could be transformed into **6** by allylation. Then, a metathesis reaction of **6** was carried out to form a chiral tricyclic heterocycle, dihydropyrrolo[1,2-*b*]isoquinolin-5(3*H*)-one **7** without any racemization.

In summary, we have developed a Pd(II)-catalyzed asymmetric synthesis of 3,4-dihydroisoquinolinones through a one-pot C─C and C─N bonds formation between *N*-Ts-benzamides and 1,3-dienes using a chiral PyOX-type ligand. This protocol features regio- and stereoselective synthesis of chiral 3,4-dihydroisoquinolinones from readily available starting materials, mild neutral reaction conditions in air, broad substrate scope, and good functional group tolerance. Further elaboration of the resulting 3,4-dihydroisoquinolinone products provided access to diverse chiral *N*-heterocycles.

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Supporting Information. Additional supporting information may be found online in the Supporting Information section at the end of the article.

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