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Enantioselective Synthesis of 2-Substituted-1,5-Benzodiazepines through Domino Reaction of *o*-Phenylenediamine and Chalcone Derivatives

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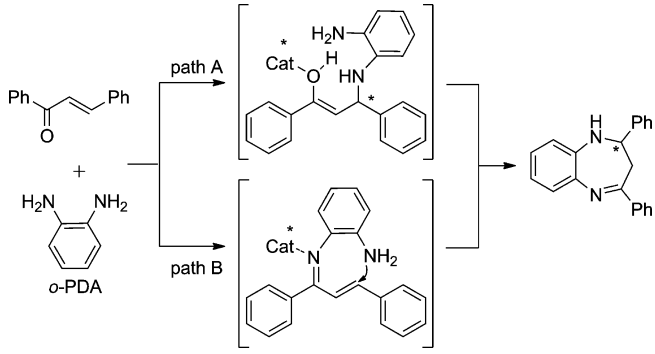
Chiral 2-substituted-1,5-benzodiazepine derivatives were synthesized for the first time from an enantioselective domino reaction involving *o*-phenylenediamine and 2′-hydroxychalcones. The titanium complex formed from chiral ligand **1a** derived from (*S*)-BINOL and L-prolineamide promoted the reaction and gave the products in good yields with up to 82 % *ee*.

Introduction

1,5-Benzodiazepines and their polycyclic derivatives are important classes of heterocycles with pharmacological activities, which are broadly used as analgesic, sedative, anticonvulsant, antianxiety, antidepressive, and hypnotic agents.[1] Recent medical research showed that 1,5-benzodiazepines could be extended to various diseases such as cancer, viral infection, and cardiovascular disorders.[2] Therefore, over the last decade benzodiazepines have been very appealing targets for synthetic purposes. One of the most efficient methods for their preparation is the domino reaction of *o*-phenylenediamine (*o*-PDA) with ketones,[3] α,β-unsaturated carbonyl compounds, or β-haloketones.[4] Catalysts such as $BF_3{\cdot}OEt_2$,[5] $NaBH_4$,[6] $Yb(OTf)_3$,[7] $Ga(OTf)_3$,[8] polyphosphoric acid,[9] nitrobenzoic acid,[10] multisite solid catalysts,[11] as well as ionic liquids,[12] and microwave irradiation assisted methods[13] have been employed to improve the yield under mild reaction conditions. Series of functionalized 1,5-benzodiazepine derivatives were obtained as racemates, whereas the enantioselective synthesis of these scaffolds has not been achieved.

The asymmetric domino reaction involving *o*-PDA and α,β-unsaturated carbonyl compounds and proceeding through an enantioselective aza-Michael reaction as the key process is a facile variant to achieve optically active 2,3-dihydro-2-substituted-1*H*-1,5-benzodiazepines (Scheme 1). Although attractive outcomes in enantioselective aza-Michael reaction[14] have been achieved in recent years, the related domino reaction for the asymmetric synthesis of 1,5-benzodiazepine derivatives seems more difficult due to low activity and poor differentiation of the two amine groups of *o*-PDA. Herein, we report the first enantioselective domino reaction to prepare chiral 2-substituted-1,5-benzodiazepines.



Scheme 1. Possible processes of the reaction between *o*-PDA and chalcone.

Results and Discussion

An initial attempt to react chalcone with *o*-PDA was disappointing, and no desired product was obtained with several kinds of chiral catalysts. We envisioned that the main issue would be the lack of synergy between the aza-Michael step and the ring-closing step to form the imine. If a chiral Lewis acid or amine facilitates the aza-Michael step, it would be unfavorable for the following cyclocondensation process (Scheme 1, path A). Likewise, if the ketimine is preferentially generated, steric hindrance would not benefit the activation of the α,β-unsaturated imine, therefore suppressing the intermolecular aza-Michael process (Scheme 1, path B). An alternative strategy to achieve asymmetric synthesis of chiral 2-substituted-1,5-benzodiazepines is to in-

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troduce a side functional group into the α,β-unsaturated ketone to improve its coordination and activation. 2′-Hydroxychalcone has been shown to be efficient in this seven-membered ring-formation reaction by Zhang and coworkers.[8] Then, we selected 2′-hydroxychalcone (**4a**) and *o*-PDA as the model substrates to realize the asymmetric transformation. After systematic investigation of the catalysts developed in our group [including *N*,*N*′-dioxide-Fe(acac)$_3$ and cinchona alkaloid–BINOL–Ti(O*i*Pr)$_4$ catalysts, see the Supporting Information for details], it showed that chiral titanium complexes of BINOL derivatives (Figure 1) could efficiently promote the asymmetric reaction.[15]

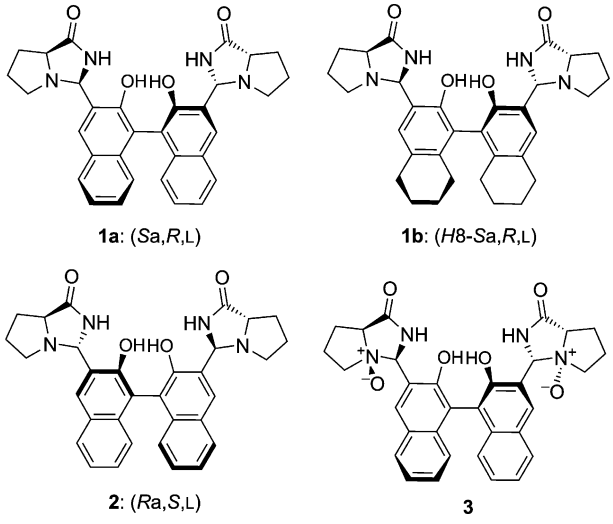
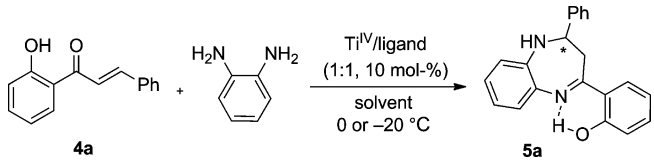


Figure 1. Chiral ligands used in the domino reaction.

Ti(O*i*Pr)$_4$ combined with chiral ligand **1a**, which was prepared from (*S*)-BINOL and L-prolineamide, could accelerate the domino reaction, and benzodiazepine **5a** was obtained in 88% yield with 47%*ee* at 0 °C in toluene (Table 1, Entry 1). When ligand **1b** derived from (*S*)-H$_8$-BINOL was employed, both the yield and the enantioselectivity dropped sharply (23% yield, 11%*ee*; Table 1, Entry 2). The results indicated that the dihedral angle of the axial biaryl group in the BINOL moiety was crucial for the outcome. Although diastereomeric ligand **2**, which is derived from (*R*)-BINOL and L-prolineamide, promoted the reaction with a suitable yield, the enantioselectivity decreased somewhat (90% yield, 35%*ee*; Table 1, Entry 3). Disappointingly, ligand **3**, the *N*-oxidation product of ligand **1a**, only gave racemic **5a** in moderate yield (Table 1, Entry 4). This poor results might be due to a change in the coordination model if an additional coordinated oxygen atom was introduced. The employment of chiral **1a** with TiCl$_4$ did not afford better results (Table 1, Entry 5 vs. 1). The screening of the solvents showed that the reaction proceeded well in THF, and the *ee* value was improved to 61% with the yield remaining nearly the same (Table 1, Entry 6). Other solvents such as Et$_2$O and *t*BuOMe decreased the yield of the reaction without improving the enantioselectivity (Table 1, Entries 7 & 8 vs. 6). The reactivity of the substrate was maintained in PhOMe, but the *ee* value decreased to 23% (Table 1, Entry 9). To further improve the enantioselectivity of the reaction, we attempted to perform the reaction at a lower temperature. If the temperature was dropped to –20 °C and the concentration of the reaction system was increased, the *ee* value could be raised to 73% but the yield decreased distinctly (Table 1, Entry 10). Additive tests showed that 5 Å molecular sieves increased the yield slightly, whereas the *ee* value was maintained (71% yield, 73%*ee*; Table 1, Entry 11).

Table 1. Optimization of the reaction conditions of the enantioselective domino reaction involving *o*-PDA and 2′-hydroxychalcone (**4a**).[a]



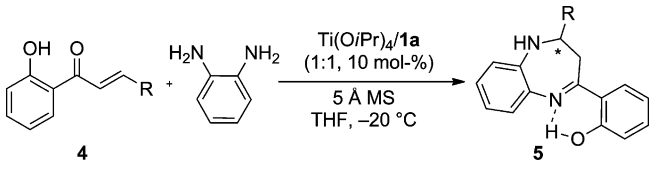
Entry	Ti^{IV}/ligand	Solvent	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	Ti(O*i*Pr)$_4$/**1a**	toluene	0	88	47
2	Ti(O*i*Pr)$_4$/**1b**	toluene	0	23	11
3	Ti(O*i*Pr)$_4$/**2**	toluene	0	90	35
4	Ti(O*i*Pr)$_4$/**3**	toluene	0	55	0
5	TiCl$_4$/**1a**	toluene	0	61	37
6	Ti(O*i*Pr)$_4$/**1a**	THF	0	85	61
7	Ti(O*i*Pr)$_4$/**1a**	Et$_2$O	0	59	47
8	Ti(O*i*Pr)$_4$/**1a**	*t*BuOMe	0	65	45
9	Ti(O*i*Pr)$_4$/**1a**	PhOMe	0	90	23
10[d]	Ti(O*i*Pr)$_4$/**1a**	THF	–20	60	73
11[d,e]	Ti(O*i*Pr)$_4$/**1a**	THF	–20	71	73

[a] Unless otherwise noted, reactions were carried out with *o*-PDA (0.1 mmol) and **4a** (0.1 mmol) in solvent (1.0 mL) at 0 °C for 72 h with the catalyst (Ti^{IV}/ligand = 1:1, 10 mol-%). [b] Isolated yield. [c] Determined by HPLC analysis. [d] Reactions were carried out in THF (0.5 mL) at –20 °C for 72 h. [e] 5 Å MS (20 mg) were added.

Under the optimal conditions (Table 1, Entry 11), the scope of 2′-hydroxychalcone derivatives was examined, and the results are shown in Table 2. The electronic nature of the substituent on the β-phenyl moiety had an obvious influence on the activity of the reaction. 2′-Hydroxychalcones with electron-withdrawing substituents, except for the *para*-nitro group, on the β-phenyl group showed higher yields than those with electron-donating substituents (Table 2, Entries 5–11 vs. 2–4). 3-Trifluoromethyl-substituted α,β-unsaturated ketone **4j** gave the best yield with moderate enantioselectivity (Table 2, Entry 10). Optically pure product **5j** was obtained through recrystallization, and its absolute configuration was confirmed to be *S* by X-ray analysis (Figure 2).[16] 2-Chloro-substituted **4g** afforded the corresponding 2-aryl-1,5-benzodiazepine in 93% yield with 82%*ee* (Table 2, Entry 7). However, 2-methoxy-substituted substrate **4d** yielded the product in only 23% yield with 69%*ee* (Table 2, Entry 4). Generally, moderate to excellent yields (up to 94%) with good enantioselectivities (up to 82%*ee*) were observed.

To evaluate the possible pathway of the domino reaction, comparative reactions of 2′-hydroxychalcone (**4a**) were carried out. No aza-Michael addition product was detected

Table 2. Substrate scope for the catalytic asymmetric domino reaction involving 2′-hydroxychalcones **4** and *o*-PDA.[a]



4 5

Entry	R	Product	Yield [%][b]	*ee* [%][c]
1	Ph (**4a**)	**5a**	71	73
2	2-MeC_6H_4 (**4b**)	**5b**	62	71
3	3-MeC_6H_4 (**4c**)	**5c**	73	73
4	2-$MeOC_6H_4$ (**4d**)	**5d**	23	69
5	4-ClC_6H_4 (**4e**)	**5e**	83	79
6	4-BrC_6H_4 (**4f**)	**5f**	93	78
7	2-ClC_6H_4 (**4g**)	**5g**	93	82
8	3-BrC_6H_4 (**4h**)	**5h**	74	65
9	3-ClC_6H_4 (**4i**)	**5i**	87	65
10	3-$CF_3C_6H_4$ (**4j**)	**5j**	94	67 (*S*)[d]
11	3-FC_6H_4 (**4k**)	**5k**	75	78
12	3-$NO_2C_6H_4$ (**4l**)	**5l**	66	59

[a] Unless otherwise noted, reactions were carried out with Ti(O*i*Pr)$_4$/**1a** (1:1, 10 mol-%), **4** (0.1 mmol), *o*-phenylenediamine (0.1 mmol), and 5 Å MS (20 mg) in THF (0.5 mL) at –20 °C for 72 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Determined by X-ray analysis.

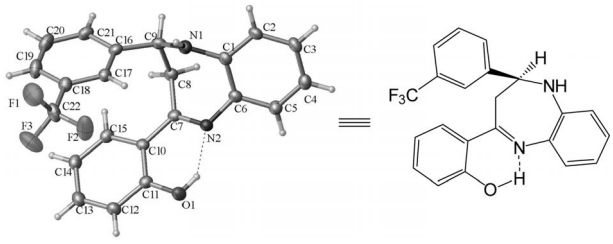
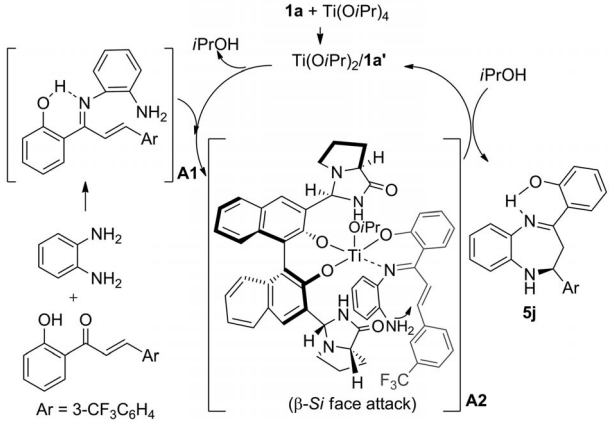


Figure 2. X-ray structure of product **5j**.

when **4a** was treated with anilines under the optimized reaction conditions. Considering the crucial role of the hydroxy group at the 2′-position of chalcone, we rationalized a possible catalytic cycle. As shown in Scheme 2, the α,β-unsaturated ketimine intermediate formed might be stabilized by an intramolecular hydrogen bond of the hydroxy group. In the presence of the chiral titanium complex, intermediate **A1** can coordinate to the metal with the oxygen atom of the hydroxy group and the nitrogen atom of the imine moiety to generate intermediate **A2**. In intermediate **A2**, the amino group prefers to attack the β-*Si* face of the C=C bond due to the fact that there is less steric hindrance between the aniline moiety and the neighboring pyrrolo[1,2-*c*]imidazol-1-one moiety of the ligand. Thus, (*S*)-**5j** is afforded and the chiral titanium complex is released.



Scheme 2. Proposed catalytic cycle.

Conclusions

In conclusion, we report the asymmetric synthesis of 2-aryl-1,5-benzodiazepine derivatives for the first time by using a chiral titanium complex with a ligand derived from (*S*)-BINOL and L-prolineamide. The 2′-hydroxy group of the α,β-unsaturated ketones was critical for both the reactivity and stereoinduction. Moderate to excellent yields and enantioselectivities were achieved. Further efforts will be dedicated to improve the enantioselectivity as well as the synthesis of chiral 2,3-disubstituted-1,5-benzodiazepines from the three-component reaction of ketones.

Experimental Section

Typical Procedure for the Asymmetric Domino Reaction of 2′-Hydroxychalcones and *o*-PDA: A mixture of ligand **2a** (3.4 mg, 0.01 mmol, 10 mol-%), Ti(O*i*Pr)$_4$ (1 M in THF, 10.0 μL, 0.01 mmol, 10 mol-%), *o*-PDA (10.8 mg, 0.10 mmol), and 5 Å MS (20 mg) was stirred in THF (0.5 mL) in a tube under a N_2 atmosphere at 25 °C for 0.5 h. Then, 2′-hydroxychalcone (**4a**; 22.4 mg, 0.10 mmol) was added at –20 °C, and the reaction system was stirred at this temperature for 72 h. The reaction was monitored by TLC and purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 20:1) to give pure product **5a** in 71% yield with 73%*ee*. The *ee* value was determined by chiral HPLC. HPLC (DAICEL CHIRALCEL AD-H column, 2-propanol/*n*-hexane = 20:80, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 11.68 (minor), 14.81 min (major). $[\alpha]_D^{28}$ = +61.4 (*c* = 0.214, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 15.28 (s, 1 H, O-H), 7.42–6.72 (m, 13 H, Ar-H), 5.22–5.17 (dd, *J* = 3.2, 8.8 Hz, 1 H, C-H), 3.85 (s, 1 H, C–NH–C), 3.35–3.31 (dd, *J* = 3.6, 14.0 Hz, 1 H, -CH_2), 3.09–3.03 (dd, *J* = 8.8, 13.6 Hz, 1 H, -CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.14, 162.63, 144.29, 139.09, 135.26, 132.86, 129.01, 128.38, 128.32, 128.07, 127.44, 125.91, 121.50, 120.74, 119.12, 118.34, 118.02, 69.99, 36.56 ppm.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H NMR and ^{13}C NMR spectra and HPLC chromatograms.

Acknowledgments

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[16] CCDC-831656 (for **5j**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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