Homogeneous Catalysis

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Enantioselective Synthesis of 2,3-Dihydro-1*H*-benzo[*b*]azepines: Iridium-Catalyzed Tandem Allylic Vinylation/Amination Reaction**

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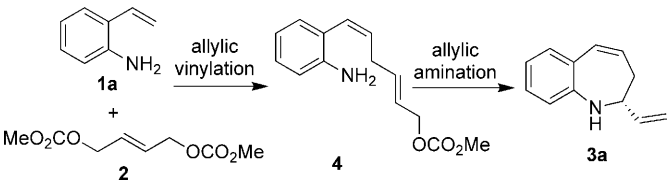
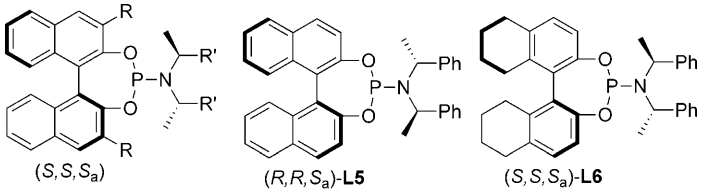
Significant efforts have been made to develop new methods for the preparation of benzannulated nitrogen heterocycles.[1] Among them, seven-membered ring benzazepines represent a particularly interesting class of heterocycles.[2] The 1-benzazepine moiety constitutes the core structure of numerous pharmacologically important compounds. Several members of this class have exhibited biological activity toward various targets such as enzymes, ion channels, and G-protein-coupled receptors (GPCRs).[3,4] Despite their interesting biological activities, 1-benzazepine derivatives have received little synthetic attention.[5] The asymmetric synthesis of 1-benzazepine derivatives is even more underexplored despite the importance of their related chiral compounds.[6] Therefore, the development of an efficient catalytic asymmetric synthesis of 1-benzazepine derivatives is a highly desirable yet challenging subject.

Pioneered by Helmchen and Hartwig, asymmetric iridium-catalyzed allylic substitution reactions have developed significantly in the past decade.[7–9] Particularly, Hartwig and co-workers have identified the cyclometalated iridium complex as the active catalyst.[10] With this catalytic system, we recently discovered an iridium-catalyzed allylic vinylation reaction of allylic carbonates with *ortho*-amino styrene derivatives.[11] This reaction provided a skipped *Z*,*E* diene instead of the amination product. On the basis of this result, we envisioned that 1-benzazepine motifs could be pursued by using an iridium-catalyzed tandem allylic vinylation/intramolecular allylic amination reaction (Scheme 1). Notably, Trost et al.[12] and Helmchen and co-workers[13] reported on the intramolecular asymmetric allylic amination reactions using palladium and iridium catalysts, respectively. Herein we report an efficient enantioselective synthesis of 1-benzazepine derivatives through an iridium-catalyzed tandem allylic vinylation/intramolecular allylic amination reaction.

We began our studies with a well-developed iridium catalytic system derived from [{Ir(cod)Cl}$_2$] (cod = 1,5-cyclooctadiene) and the phosphoramidite ligand **L1** (Figure 1).[10]



Scheme 1. Proposed tandem reaction for the synthesis of 1-benzazepine derivatives.



L1 R = H, R' = Ph
L2 R = H, R' = 2-naphthyl
L3 R = H, R' = 2-MeO-C_6H_4
L4 R = Ph, R' = Ph

Figure 1. Phosphoramidite ligands **L1**–**L6**.

In the presence of 4 mol% of [{Ir(cod)Cl}$_2$], 8 mol% of **L1**, and 2.2 equivalents of K_3PO_4, 2-vinylaniline (**1a**) reacted with (*E*)-but-2-ene-1,4-diyl dimethyl dicarbonate [(*E*)-**2**] in THF at 50 °C for 12 hours to give **3a** in 33% yield with 34% *ee* (Table 1, entry 1). The formation of **3a** indicates that the intramolecular allylic amination reaction proceeds faster than the allylic vinylation reaction. Examination of various bases such as Cs_2CO_3, DBU, KOAc, Et_3N, DIEA, and DABCO disclosed that DABCO was the optimal base, affording product **3a** in 73% yield with 92% *ee* (Table 1, entries 1–7). Increasing the substrate ratio of (*E*)-**2**/**1a** to 1.3:1 with 2.6 equivalents of DABCO led to an excellent yield (Table 1, entry 8). Varying the solvent (dioxane, toluene, CH_2Cl_2, DME, CH_3CN) and reaction temperature showed that the reaction in THF at 50 °C afforded the best result (Table 1, entries 9–15).

Under the conditions listed in entry 8, Table 1, different phosphoramidite ligands were evaluated, and the results are summarized in Table 2. Phosphoramidite ligands **L2** and **L3**, which have different substituents on the amine moiety, afforded the products in relatively low yields, albeit in with an excellent *ee* value in the case of ligand **L3** (Table 2, entries 1–3). Ligand **L4**, bearing aromatic substituents on the 3,3′-positions of the binaphthyl scaffold, was not effective for the reaction (Table 2, entry 4). The catalyst derived from **L5**, the diastereoisomer of **L1**, could catalyze the reaction but

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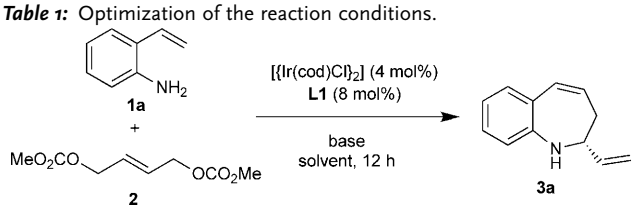
Table 1: Optimization of the reaction conditions.



Entry	**2** (equiv)	*T* [°C]	Solvent	Base[a]	Yield [%][b]	*ee* [%][c]
1	1.0	50	THF	K_3PO_4	33	34
2	1.0	50	THF	Cs_2CO_3	63	48
3	1.0	50	THF	DBU	trace	n.d.
4	1.0	50	THF	KOAc	trace	n.d.
5	1.0	50	THF	Et_3N	trace	n.d.
6	1.0	50	THF	DIEA	trace	n.d.
7	1.0	50	THF	DABCO	73	92
8	1.3	50	THF	DABCO	95	91
9	1.3	50	dioxane	DABCO	40	88
10	1.3	50	toluene	DABCO	trace	n.d.
11	1.3	reflux	CH_2Cl_2	DABCO	n.r.	n.d.
12	1.3	50	DME	DABCO	trace	n.d.
13	1.3	50	CH_3CN	DABCO	trace	n.d.
14	1.3	22	THF	DABCO	48	91
15	1.3	reflux	THF	DABCO	82	87

[a] Used 2.2 equiv for entries 1–7 and 2.6 equiv for entries 8–15. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis (Chiralcel OD-H column). DABCO = 1,4-diazabicyclo[2.2.2]octane, DME = dimethoxyehtane, DIEA = diisopropylethylamine, THF = tetrahydrofuran, n.d. = not determined, n.r. = no reaction.

Table 2: Screening of chiral ligands.[a]

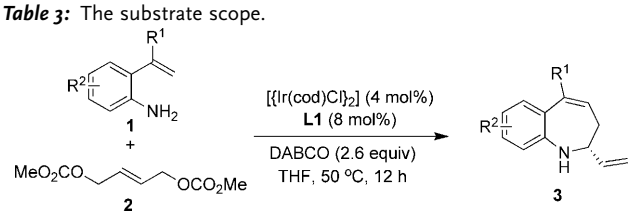
Entry	Ligand	Yield [%][b]	*ee* [%]
1	**L1**	95	91
2	**L2**	90	87
3	**L3**	78	92
4	**L4**	n.r.	n.d.
5	**L5**	26	20
6	**L6**	25	19

[a] Reaction conditions: as listed in entry 8, Table 1. [b] Yield of isolated product.

with decreased yield and enantioselectivity, indicating the importance of match of chiralities in (*S*,*S*,*Sa*)-**L1** (Table 2, entry 5). The catalyst derived from ligand **L6**, bearing the 8H-binol scaffold, catalyzed the reaction in 25% yield with 19% *ee* (Table 2, entry 6).

In the presence of 4 mol% of [{Ir(cod)Cl}$_2$], 8 mol% of **L1**, and 2.6 equivalents of DABCO in THF at 50°C, various 2-vinylanilines were examined as substrates. As summarized in Table 3, the reactions of 2-vinylaniline derivatives **1b**–**1d**, having electron-donating groups (5-MeO, 4-Me, and 5-Me) on the phenyl ring, gave the desired products in excellent yields with 91% *ee* (Table 3, entries 2–4). 2-Vinylaniline derivatives **1e**–**1f**, having electron-withdrawing groups (4-Cl, 5-Br), were well tolerated and furnished the 2,3-dihydro-1*H*-benzazepine products in good yields and excellent

Table 3: The substrate scope.



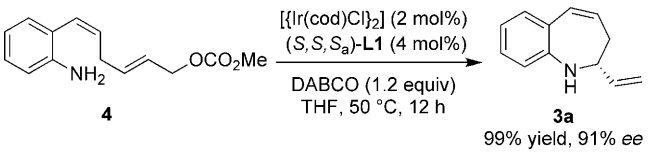
Entry	**1**, R^1, R^2	**3**, Yield [%][a]	*ee* [%]
1	**1a**, H, H	**3a**, 95	91
2	**1b**, H, 5-MeO	**3b**, 89	91
3	**1c**, H, 4-Me	**3c**, 86	91
4	**1d**, H, 5-Me	**3d**, 87	91
5	**1e**, H, 4-Cl	**3e**, 89	91
6	**1f**, H, 5-Br	**3f**, 75	90
7[b]	**1g**, H, 5-CF_3	**3g**, 49	87
8	**1h**, H, 4,5-Br,Br	**3h**, 10	87
9	**1i**, Me, H	**3i**, 92	94
10	**1j**, Me, 4-Br	**3j**, 74	91
11	**1k**, Me, 5-Cl	**3k**, 75	90
12	**1l**, Ph, 4-MeO	**3l**, 81	90
13	**1m**, Ph, 4-Br	**3m**, 14	91 (*R*)

[a] Yield of isolated product. [b] 8 mol% of [{Ir(cod)Cl}$_2$] and 16 mol% of (*S*,*S*,*Sa*)-**L1** were used.

enantioselectivities (Table 3, entries 5–6). Substrate **1g** having a strong electron-withdrawing group (5-CF_3) led to product **3g** in 49% yield and 87% *ee*, even with an increased catalyst loading (Table 3, entry 7). The unfavorable effect of the electron-withdrawing group was also observed for 4,5-dibromo-2-vinylaniline (**1h**; Table 3, entry 8). To our delight, the reaction of substrates **1i**–**1l** (R^1 = Me, or Ph) with (*E*)-**2** reacted smoothly to afford the desired products in good yields with excellent *ee* values (Table 3, entries 9–12).

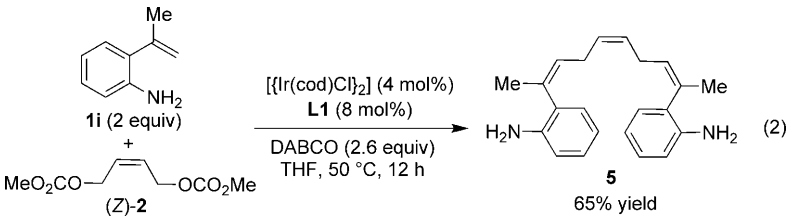
To determine the absolute configuration of the product, the enantiopure bromine-containing compound **3m** was obtained. An X-ray crystallographic analysis of enantiopure **3m** disclosed the absolute configuration as *R*.[14]

Notably, as evidence for the proposed reaction pathway (Scheme 1), the intermediate **4** could be isolated. When **4** was subjected to the same catalytic system, product **3a** was formed with an identical *ee* value [Eq. (1)]. This result suggests that **4** is the intermediate in the tandem process.



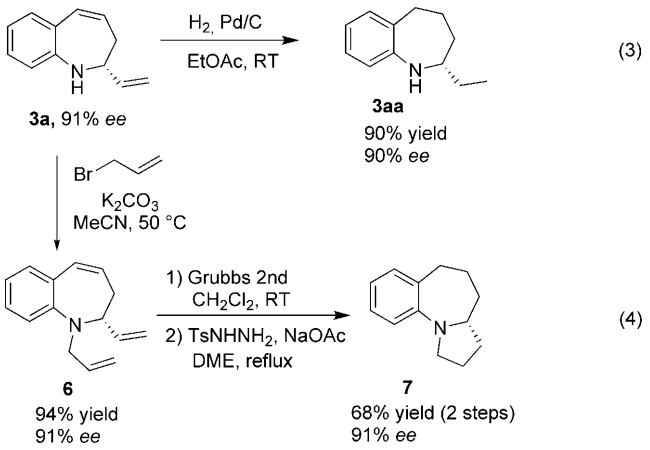
(1)

Interestingly, when (*Z*)-but-2-ene-1,4-diyl dimethyl dicarbonate [(*Z*)-**2**] was tested in the reaction with **1i**, the double vinylation product **5** was obtained instead of the cyclic compound [Eq. (2)].



(2)

The synthetic versatility of 2-vinyl-2,3-dihydro-1*H*-benzo[*b*]azepines has also been explored. Hydrogenation of **3a** afforded the secondary amine **3aa** in excellent yield (90%) without loss of optical purity [Eq. (3)].

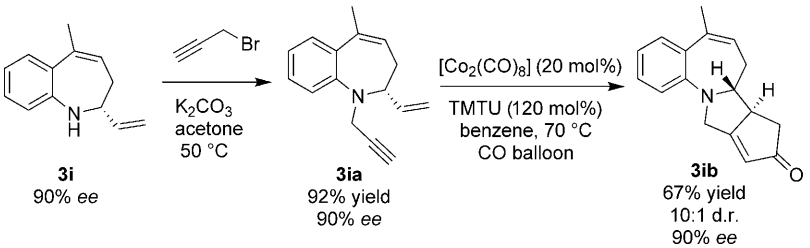


(3)

(4)

The fused tricyclic compound **7**[15] could also be readily synthesized from **3a**. Treatment of **3a** with allyl bromide led to **6** in 94% yield with 91% *ee*. The subsequent ring-closing metathesis[16] and hydrogenation[8e] afforded the tricyclic product **7** in 68% yield with 91% *ee* [Eq. (4)].

The C=C bond in the alkenyl substituent on the ring is a valuable functionality in some intramolecular cyclization reactions, such as the Pauson–Khand (PK) reaction.[17] 1,6-Enyne **3ia** was readily obtained in excellent yield by treating **3i** with 3-bromoprop-1-yne (92% yield, 90% *ee*). The subsequent PK reaction of **3ia** smoothly afforded the polycyclic compound **3ib** without loss of the optical purity [Eq. (5); TMTU = tetramethylthiourea].



(5)

In summary, we have found that [{Ir(cod)Cl}$_2$]/phosphoramidite efficiently catalyzes the tandem allylic vinylation and amination reaction of (*E*)-but-2-ene-1,4-diyl dimethyl dicarbonate with *ortho*-amino styrene derivatives, affording the 2,3-dihydro-1*H*-benzo[*b*]azepines with high enantioselectivity. The ready availability of the starting materials and the great importance of the enantiopure products make the current methodology particularly interesting in organic synthesis.

Experimental Section

General procedure for the iridium-catalyzed tandem allylic vinylation/amination reaction: A flame dried Schlenk tube was cooled to room temperature and filled with argon. [{Ir(cod)Cl}$_2$] (5.4 mg, 0.008 mmol), phosphoramidite ligand **L1** (8.6 mg, 0.016 mmol), THF (0.5 mL), and propylamine (0.5 mL) were then added to this flask. The reaction mixture was heated at 50 °C for 0.5 h, during which the color of the solution changed from orange to light yellow. Then the reaction mixture was cooled to room temperature, and the solvent was removed in vacuo. Styrene derivative **1** (0.20 mmol), (*E*)-but-2-ene-1,4-diyl dimethyl dicarbonate [(*E*)-**2**; 53.0 mg, 0.26 mmol], DABCO (58.2 mg, 0.52 mmol), and degassed THF (2 mL) were then added to the flask. The reaction mixture was stirred at 50 °C for 12 h. After the reaction was complete (monitored by TLC), the crude reaction mixture was filtered through celite and washed with EtOAc. The solvents were removed under reduced pressure, and the resulting residue was purified by silica gel column chromatography to afford the product **3**.

Full experimental details and characterization data are given in the Supporting Information.

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[14] CCDC 753353 ((*R*)-**3m**) 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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