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Enantioselective Synthesis of 3-Azabicyclo[4.1.0]heptenes and 3-Azabicyclo[3.2.0]heptenes by Ir-Catalyzed Asymmetric Allylic Amination of *N*-Tosyl Propynylamine and Pt-Catalyzed Cycloisomerization

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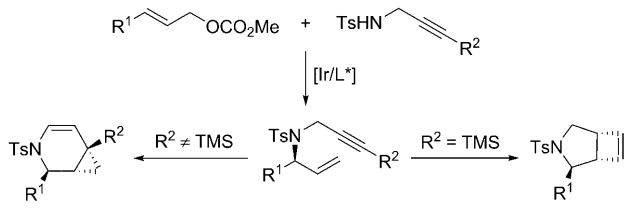
3-Azabicyclo[4.1.0]heptane and 3-azabicyclo[3.2.0]heptane frameworks exist as two important skeletons for many biologically interesting compounds (Scheme 1).[1] Development



Scheme 1. Synthesis of 3-azabicyclo[4.1.0]heptene and 3-azabicyclo-[3.2.0]heptene derivatives. TMS = trimethylsilyl, Ts = tosyl.

of efficient syntheses, particularly enantioselective syntheses, towards these two scaffolds has been an intense subject in organic synthesis.[2] Over the past several decades, 1,6-enynes were recognized as the key intermediates for structurally diverse polycyclic compounds through transition-metal-catalyzed cycloisomerization reactions.[3] Construction of the 3-azabicyclo[4.1.0]heptane skeleton by transition-metal catalyzed cycloisomerization of substituted *N*-allylpropynylamines has been documented in the literature,[4] whereas their catalytic asymmetric studies are less explored, with only handful examples to date.[5] In addition, the efficient synthesis of 3-azabicyclo[3.2.0]heptanes by cycloisomerization is limited with only one recent report in which amide-tethered 1,6-enynes were used with the aid of an Au^I catalyst to afford bicyclo[3.2.0]hept-6-enes.[6] To the best of our knowledge, their asymmetric version is still unknown.

Ir-catalyzed asymmetric allylic amination reactions have been studied extensively in the past decade.[7,8] Recently, studies by Hartwig et al. and Helmchen et al. demonstrated the cyclometallated iridium as the active catalytic species.[9] With this catalytic system, we envisaged that the use of propargyl amines would afford the enantioenriched substituted *N*-allylpropynylamines (Scheme 1). Although this seems a straightforward synthesis, there is no direct utilization of propargyl nucleophiles in Ir-catalyzed allylic substitution reactions.[10] Notably, Ueno and Hartwig found that addition of alkyne was crucial for allylic substitution of alkyl alkoxide, probably due to the coordination of the triple bond with the iridium catalyst, which eliminated the isomerization of ether product.[11] Interestingly, Helmchen and coworkers realized an elegant synthesis of enantioenriched carbon-tethered 1,6-enyne by allylic alkylation of dimethyl malonate and then alkylation of the product thereof with propargyl bromide.[12]

Intrigued by the enantioselective synthesis of 3-azabicyclo[4.1.0]heptenes and 3-azabicyclo[3.2.0]heptenes, we recently found that *N*-tosyl propynylamine could be used directly in Ir-catalyzed allylic amination reaction. The enantioenriched *N*-tosyl allylpropynylamines were converted smoothly into 3-azabicyclo[4.1.0]hept-4-enes by catalytic amount of $PtCl_2$. Moreover, starting from products derived from *N*-tosyl 3-trimethylsilylpropynylamine (R^2 = TMS, Scheme 1), highly enantioenriched 3-azabicyclo-[3.2.0]heptenes were obtained under the same reaction conditions. Herein, we report our studies on this subject.

We began our studies to test the suitability of propynylamine as a nucleophile in Ir-catalyzed allylic amination reaction. Methyl cinnamyl carbonate (**1a**) and $CH_3C{\equiv}CCH_2NHTs$ (**2a**) were chosen as the model substrates. With [{Ir(cod)Cl}$_2$] (cod = 1,5-cyclooctadiene) and phosphoramidite **L1** in THF at 50 °C, no reaction occurred without base (Table 1, entry 1). Fortunately, the reaction proceeded in the presence of base (K_2CO_3, Cs_2CO_3, K_3PO_4, KOAc, LiHMDS,

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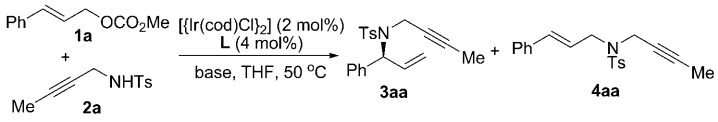
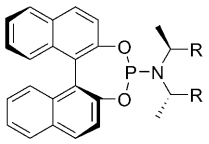
Table 1. Optimizing reaction conditions.[a]



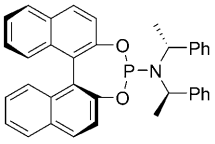
Entry	Ligand	Base	t [h]	Conv. [%][b]	**3aa**/**4aa**[c]	*ee* [%][d]
1	**L1**	–	15	<5	–	–
2	**L1**	K_2CO_3	28	93 (53)	90:10	93
3	**L1**	Cs_2CO_3	3	>99 (77)	87:13	94
4	**L1**	K_3PO_4	3	>99 (94)	88:12	95
5	**L1**	KOAc	28	95 (89)	88:12	95
6	**L1**	LiHMDS	24	52 (52)	89:11	93
7	**L1**	BSA	48	37 (33)	86:14	95
8	**L1**	TBD	24	52 (45)	88:12	95
9	**L1**	DBU	3	>99 (72)	90:10	92
10	**L1**	DABCO	3	>99 (97)	89:11	95
11[e]	**L1**	DABCO	3	>99 (92)	89:11	95
12[f]	**L1**	DABCO	80	73 (65)	84:16	92
13[e]	**L2**	DABCO	3	>99 (90)	90:10	97
14[e]	**L3**	DABCO	24	78 (75)	89:11	94
15[e]	**L4**	DABCO	24	63 (61)	69:31	74
16[e,g]	**L2**	DABCO	12	>99 (97)	95:5	99

[a] [{Ir(cod)Cl}$_2$] (2 mol%), **L** (4 mol%), **1a**, **2a** (1.1 equiv), and base (1.0 equiv) in THF at 50 °C. LiHMDS = lithium hexamethyldisilazide, BSA = N,O-bis(trimethylsilyl)acetamide, TBD = 1,5,7-triazabicyclo-[4.4.0]dec-1-ene, DBU = 1,5-diazabicyclo[5.4.0]undec-5-ene, DABCO = 1,4-diazabicyclo[2.2.2]octane. [b] Determined by ^{1}H NMR spectroscopy and isolated yields of **3aa** and **4aa** in the parenthesis. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by chiral HPLC analysis. [e] 0.5 equiv of DABCO was used. [f] 0.1 equiv of DABCO was used. [g] At RT.

BSA, TBD, DBU, DABCO), affording amination product with excellent regio- and enantioselectivity (Table 1, entries 2–10). DABCO was found to be the optimal base, yielding quantitative amination product with 89:11 regioselectivity in favor of branch product **3aa** (95% *ee*). The reaction was found to be compatible with various solvents, such as toluene, dioxane, DMF, CH_3CN, Et_2O, CH_2Cl_2, DME, and EtOH (see the Supporting Information); THF was found to be the best solvent. Excellent yield and selectivities were maintained with DABCO (0.5 equiv) in THF, but further lowering the loading resulted in a sluggish reaction with reduced yield (Table 1, entries 11 and 12).



(S,S,S_a)
L1: R = Ph
L2: R = 2-MeO-C_6H_4
L3: R = 2-naphthyl

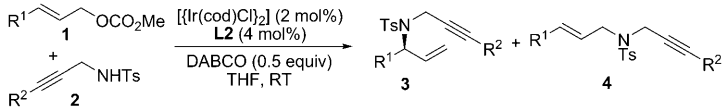


(R,R,S_a)
L4

Different, readily available chiral phosphoramidite ligands were tested. The catalysts derived from ligands **L2** and **L3** afforded the amination product with excellent regioselectivities in favor of branch product **3a** with 97 and 94% enantiomeric excess (*ee*), respectively (Table 1, entries 13 and 14). The catalyst derived from **L4**, the diastereoisomer of **L1**, could catalyze the reaction, but in a lower yield with decreased selectivities (Table 1, entry 15). To our delight, when the reaction was performed at room temperature with ligand **L2**, significant improvement of yield and selectivities was resulted (Table 1, entry 16, **3aa**/**4aa**: 95:5, **3aa**: 99% *ee*).

Under the above optimized reaction conditions, various allyl carbonates **1** and propargyl amines **2** were investigated. The data are summarized in Table 2. Several propargyl amines **2a–d** bearing methyl, TMS, phenyl, and *n*-butyl group were tolerated. In all cases, branch products **3** were isolated in 83–93% yields with 97–99% *ee* (Table 2, entries 1–4). No reaction occurred with unsubstituted propargyl amine **2e**, probably due to interference between the acidic terminal alkyne proton and the Ir-catalyst (Table 2, entry 5). With propargyl amines **2a** and **2b**, a wide range of allyl carbonates **1** with different substituents, including electron-donating or -withdrawing groups containing aryl, heteroaryl, and aliphatic groups, has been tested (Table 3, entries 6–20). Delightfully, good to excellent yields and branch-to-linear selectivities were generally obtained. In most cases, branch allylic amination products **3** were obtained with excellent level of enantioselectivities (>98% *ee*).

Table 2. The substrate scope of allylic amination.



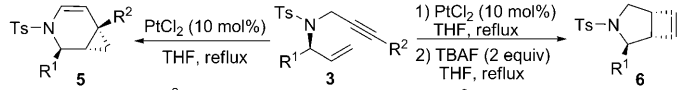
2a, R^2 = Me; **2b**, R^2 = TMS; **2c**, R^2 = *n*Bu; **2d**, R^2 = Ph; **2e**, R^2 = H

Entry	**1**, R^1	**2**	t [h]	**3**, Yield [%][a]	**3**/**4**[b]	*ee* [%][c]
1	**1a**, C_6H_5	**2a**	12	**3aa**, 93	95:5	99
2	**1a**, C_6H_5	**2b**	3	**3ab**, 83	90:10	99
3	**1a**, C_6H_5	**2c**	12	**3ac**, 84	94:6	97
4	**1a**, C_6H_5	**2d**	4	**3ad**, 89	95:5	99
5	**1a**, C_6H_5	**2e**	24	NR[d]	–	–
6	**1b**, 4-Me-C_6H_4	**2a**	4	**3ba**, 76	96:4	99
7	**1c**, 4-MeO-C_6H_4	**2a**	12	**3ca**, 93	98:2	99
8	**1d**, 4-Br-C_6H_4	**2a**	12	**3da**, 95	97:3	>99
9	**1e**, 4-CF_3-C_6H_4	**2a**	4	**3ea**, 82	96:4	>99
10	**1f**, 3-MeO-C_6H_4	**2a**	3	**3fa**, 85	97:3	99
11	**1g**, 3-Cl-C_6H_4	**2a**	10	**3ga**, 86	96:4	99
12	**1h**, 2-thienyl	**2a**	10	**3ha**, 83	95:5	>99
13	**1i**, Me	**2a**	3	**3ia**, 70	90:10	92
14	**1b**, 4-Me-C_6H_4	**2b**	12	**3bb**, 76	91:9	99
15	**1c**, 4-MeO-C_6H_4	**2b**	10	**3cb**, 92	99:1	99
16	**1d**, 4-Br-C_6H_4	**2b**	12	**3db**, 84	90:10	98
17	**1f**, 3-MeO-C_6H_4	**2b**	12	**3fb**, 77	91:9	98
18	**1g**, 3-Cl-C_6H_4	**2b**	12	**3gb**, 81	88:12	98
19	**1h**, 2-thienyl	**2b**	12	**3hb**, 81	94:6	99
20	**1i**, Me	**2b**	10	**3ib**, 82	90:10	92

[a] Isolated yields of **3**. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC analysis. [d] No reaction.

With highly enantioenriched *N*-tosyl allylpropynylamines in hand, their cycloisomerization reactions were examined. With $PtCl_2$ as the catalyst, 3-azabicyclo[4.1.0]hept-4-ene de-

Table 3. The scope of platinum-catalyzed cycloisomerization reaction.



Entry	R^1	R^2	**3** (*ee* [%])	*t* [h]	**5** or **6**, Yield [%] (*ee* [%])[a]
1	C_6H_5	Me	**3aa** (99)	24	**5aa**, 52 (99)
2	4-Me-C_6H_4	Me	**3ba** (99)	27	**5ba**, 61 (98)
3	4-MeO-C_6H_4	Me	**3ca** (99)	28	**5ca**, 51 (99)
4	4-Br-C_6H_4	Me	**3da** (99)	28	**5da**, 71 (99)
5	4-CF_3-C_6H_4	Me	**3ea** (99)	27	**5ea**, 60 (99)
6	3-MeO-C_6H_4	Me	**3fa** (99)	27	**5fa**, 58 (99)
7	3-Cl-C_6H_4	Me	**3ga** (99)	34	**5ga**, 61 (99)
8	2-thienyl	Me	**3ha** (99)	34	**5ha**, 24 (99)
9	Me	Me	**3ia** (92)	23	**5ia**, 68 (93)
10	C_6H_5	TMS	**3ab** (99)	48	**6ab**, 53 (99)
11	4-Me-C_6H_4	TMS	**3bb** (99)	46	**6bb**, 60 (99)
12	4-MeO-C_6H_4	TMS	**3cb** (99)	48	**6cb**, 31 (99)
13	4-Br-C_6H_4	TMS	**3db** (98)	48	**6db**, 57 (98)
14	3-MeO-C_6H_4	TMS	**3fb** (99)	45	**6fb**, 54 (98)
15	3-Cl-C_6H_4	TMS	**3gb** (98)	47	**6gb**, 55 (98)
16	2-thienyl	TMS	**3hb** (97)	58	**6hb**, 21 (97)
17	Me	TMS	**3ib** (92)	54	**6ib**, 51 (90)
18	C_6H_5	C_6H_5	**3ad** (97)	24	**5ad**, 70 (97)

[a] Isolated yields, and *ee* values were determined by chiral HPLC analysis.

rivatives **5** were obtained when *N*-tosyl allyl but-2-ynyl amines **3** (R^2=Me) and *N*-tosyl allyl phenylprop-2-ynyl amine **3ad** (R^2=Ph) were used. As summarized in Table 3, with 10 mol% $PtCl_2$ in THF at reflux, 3-azabicyclo-[4.1.0]hept-4-ene derivatives **5** were obtained in moderate yields with *ee* values greater than 98% in most cases (Table 3, entries 1–9, 18). The reactions proceeded to give the cycloisomerization product as a single diastereomer and there was no notable loss of the optical purity relative to the starting materials. To determine the absolute configuration of the product, X-ray crystallographic analysis of enantiopure bromine-containing compound **5da** disclosed the configuration as (1*S*,2*S*,6*S*) (Figure 1).[13] To our surprise, when **3ab**, containing a TMS group on the alkyne moiety, was subjected to the same reaction conditions, 3-azabicyclo-[3.2.0]hept-6-ene derivative **6ab** was obtained as the main product (Scheme 2a). The relative stereochemistry of **6ab** was further confirmed by X-ray analysis (Figure 1).[14] After tuning the reaction conditions, heating a solution of the crude products in tetrabutylammonium fluoride (TBAF)/THF at reflux led to the conversion of **3** (R^2=TMS) into 3-azabicyclo[3.2.0]hept-6-ene derivatives **6**. In general, 3-azabicyclo[3.2.0]hept-6-ene derivatives **6** were obtained in moderate yields without loss of the optical purity (Table 3, entries 10–17). Notably, the corresponding saturated side products **8** (normally less than 10%) were not isolated during the examination of the substrate scope. To understand the unusual chemoselectivities controlled by different substituents, enantioenriched *N*-tosyl allylpropynylamine **9** was syn-

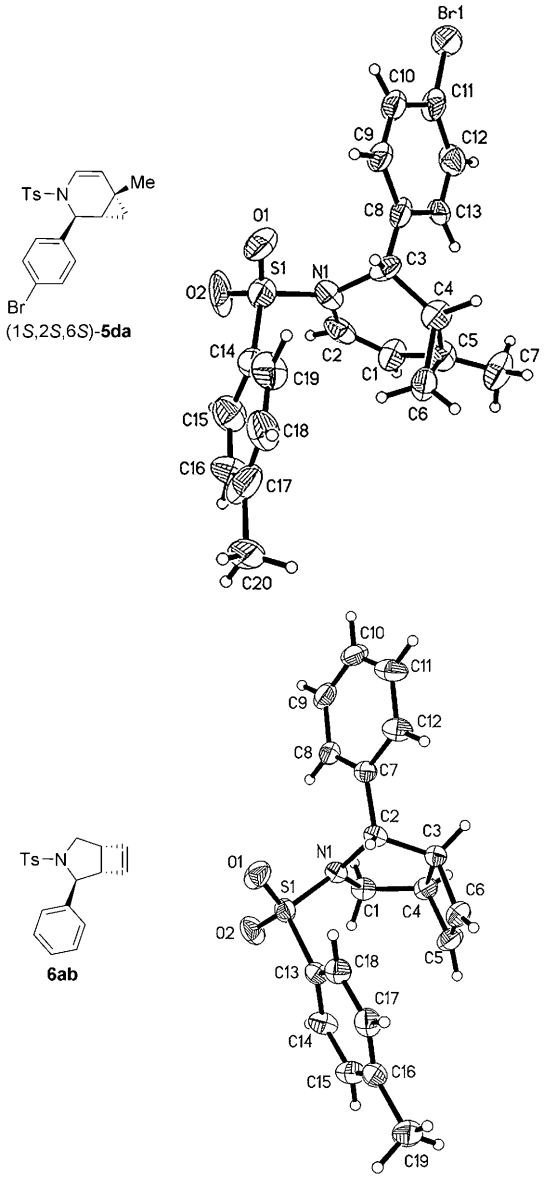
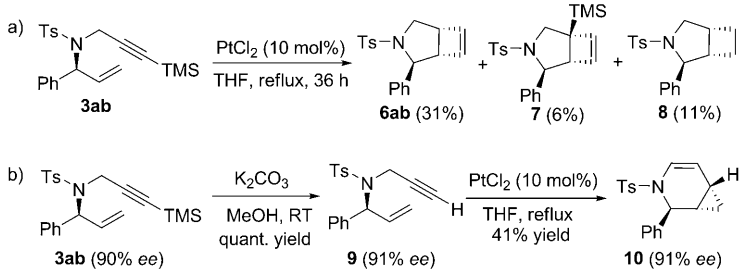


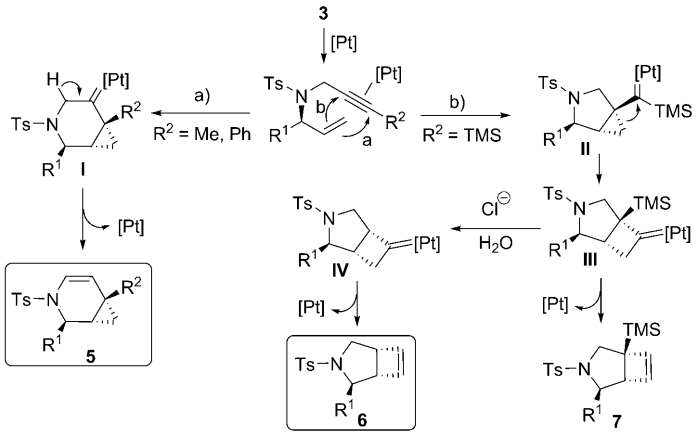
Figure 1. ORTEP representation of **5da** (top) and **6ab** (bottom).



Scheme 2. Role of the TMS group.

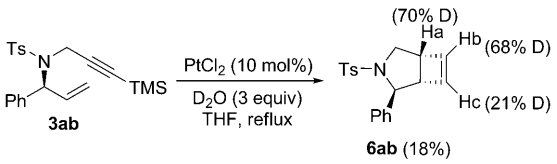
thesized by treating **3ab** with K_2CO_3 in methanol (Scheme 2b). When **9** was subjected to the standard cycloisomerization conditions, 3-azabicyclo[4.1.0]hept-4-ene derivative **10** was obtained in 41% yield without observation of the corresponding 3-azabicyclo[3.2.0]hept-6-ene product. These results indicate that the TMS group plays a key role for the formation of 3-azabicyclo[3.2.0]hept-6-ene skeleton.

A plausible mechanism for the Pt-catalyzed cycloisomerization was proposed, as depicted in Scheme 3.[15] When R^2 is a methyl or phenyl group (Scheme 3a), the reaction of **3** in



Scheme 3. Plausible mechanism of Pt-catalyzed cycloisomerization reaction.

the presence of $PtCl_2$ would undergo 6-*endo* cyclization, followed by elimination of the platinum catalyst in intermediate **I** to afford cyclized product **5**. When R^2 is a TMS group (Scheme 3b), 5-*exo* cyclization might occur first to afford carbenoid intermediate **II**. Then a 1,2-shift of the TMS group results in a ring expansion, leading to intermediate **III**. Loss of the TMS group in **III** leads to the formation of carbenoid **IV**, which eliminates the platinum catalyst to afford cyclized product **6**. The formation of **7** is likely to be due to the fact that the elimination of platinum occurs prior to the loss of the TMS group. As evidence for the loss of TMS group followed by protonation with trace amount of water in the reaction mixture, when **3ab** and catalytic $PtCl_2$ were heated at reflux in THF in the presence of D_2O (3 equiv), product **6ab** was obtained with Ha being deuterated at 70% (Scheme 4).



Scheme 4. Results of deuteration experiments.

In conclusion, the Ir-catalyzed allylic amination reaction of *N*-tosyl propynylamines has been realized in good to excellent yields with excellent regio- and enantioselectivities. $PtCl_2$-catalyzed cycloisomerization reactions of *N*-tosyl allylpropynylamines led to enantioenriched 3-azabicyclo[4.1.0]heptenes and 3-azabicyclo[3.2.0]heptenes, respectively, simply by tuning substituents on the alkyne. The current reactions provide an efficient way to prepare 3-azabicyclo[4.1.0]heptenes and 3-azabicyclo[3.2.0]heptenes with multiple chiral centers with an excellent level of optical purity.

Experimental Section

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

General procedure A for the Ir-catalyzed allylic amination: Propylamine (0.3 mL) was added to a dry schlenk tube containing [{Ir(cod)Cl}$_2$] (2.7 mg, 0.004 mmol) and phosphoramidite ligand **L2** (4.8 mg, 0.008 mmol) in THF (0.5 mL). The reaction mixture was heated at 50 °C for 30 min and then the volatile solvents were removed under vacuum to give a yellow solid. After that, allylic carbonate **1** (0.20 mmol), propargyl amine **2** (0.22 mmol), DABCO (0.10 mmol), and THF (2.0 mL) were added. The reaction was stirred at room temperature until the carbonate was fully consumed (monitored by TLC or ^{1}H NMR spectroscopy). Then the crude reaction mixture was filtered through a pad of Celite and washed with CH_2Cl_2. The solvents were removed under reduced pressure. The ratio of regioisomers was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. The crude residue was purified by flash column chromatography (petroleum ether/ethyl acetate) to give the desired products **3**.

General procedure B: Synthesis of 5aa by Pt-catalyzed cycloisomerization: Compound **3aa** (65.0 mg, 0.191 mmol) and $PtCl_2$ (5.1 mg, 0.019 mmol) were dissolved in THF (1.9 mL). The reaction mixture was heated at reflux until **3aa** was fully consumed (monitored by TLC). The reaction mixture was cooled to room temperature, filtered through a pad of Celite, and the Celite was washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure, and the residue was subjected to flash column chromatography with ethyl acetate/petroleum ether (1:45) as eluent to afford the desired product **5aa** as a white solid (34.0 mg, 52%).

General procedure C: Synthesis of 6ab by Pt-catalyzed cycloisomerization: Compound **3ab** (59.6 mg, 0.15 mmol) and $PtCl_2$ (4.0 mg, 0.015 mmol) were dissolved in THF (1.5 mL). The reaction mixture was heated at reflux until **3ab** was fully consumed (monitored by TLC). Then Bu_4NF (0.3 mL, 0.1 M in THF) was added. The reaction mixture was heated at reflux for another 24 h. The reaction mixture was cooled to room temperature, filtered through a pad of Celite, and the Celite was washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure, and the residue was subjected to flash column chromatography with ethyl acetate/petroleum ether (1:25) as eluent to afford the desired product **6ab** as a white solid (25.8 mg, 53%).

Acknowledgements

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Keywords: amination · asymmetric catalysis · cycloisomerization · enantioselectivity · iridium

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