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Intramolecular asymmetric reductive amination: synthesis of enantioenriched dibenz[*c*,*e*]azepines†

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An Ir-catalyzed intramolecular asymmetric reductive amination (ARA) of bridged biaryl derivatives has been described. Using this unprecedented approach, synthetically useful dibenz[*c*,*e*]azepines containing both central and axial chiralities are obtained with excellent enantiocontrol (up to 97% ee). This methodology represents a rare example of enantioselective chemocatalytic synthesis of chiral dibenz[*c*,*e*]azepines featuring a broad substrate scope, and their synthetic utilities are exhibited by derivatizing the products into a chiral amino acid derivative and chiral phosphoramidite ligands, which display excellent enantiocontrol in Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives. Remarkably, our method is also applicable to enantioselectively synthesize an allocolchicine analogue.

Introduction

Dibenz[*c*,*e*]azepines are a class of unique 7-membered cyclic amines featuring a biaryl bridge and have attracted increasing attention due to their importance in biological and synthetic chemistry.[1] For instance, compound **A** is the active ingredient in an anti-obesity drug,[2] and **B** is considered to be an allocolchicine analogue.[3] In addition, dibenz[*c*,*e*]azepine-based compounds **C**, **D**, and **E** and compound **F** have found promising applications in either organocatalysis or asymmetric transition metal catalysis (eqn (a), Fig. 1). Of particular interest is the phenomenon that a central to axial chirality relay occurs when a stereogenic substituent is placed at the α-position of the nitrogen atom of **2a**. Moreover, enantiomerically pure dibenz[*c*,*e*]azepines can function as a molecular switch with the axial chirality inverting upon N-Boc derivatisation caused by the center-axis relay effect (eqn (b), Fig. 1).[4a]

Despite their biological properties and promising applications in organic synthesis, asymmetric synthesis of this kind of framework lags behind and only a few examples were reported. In 2000, Kündig and coworkers developed a pioneering synthetic strategy towards chiral base **C**, featuring a Pd-catalyzed atropo-diastereoselective coupling to construct the Ar–Ar bond in a later stage with chiral-pool starting materials.[5a] Later, by making use of an auxiliary strategy,[4] Wallace *et al.* prepared a conformationally labile secondary amine **2a** involving

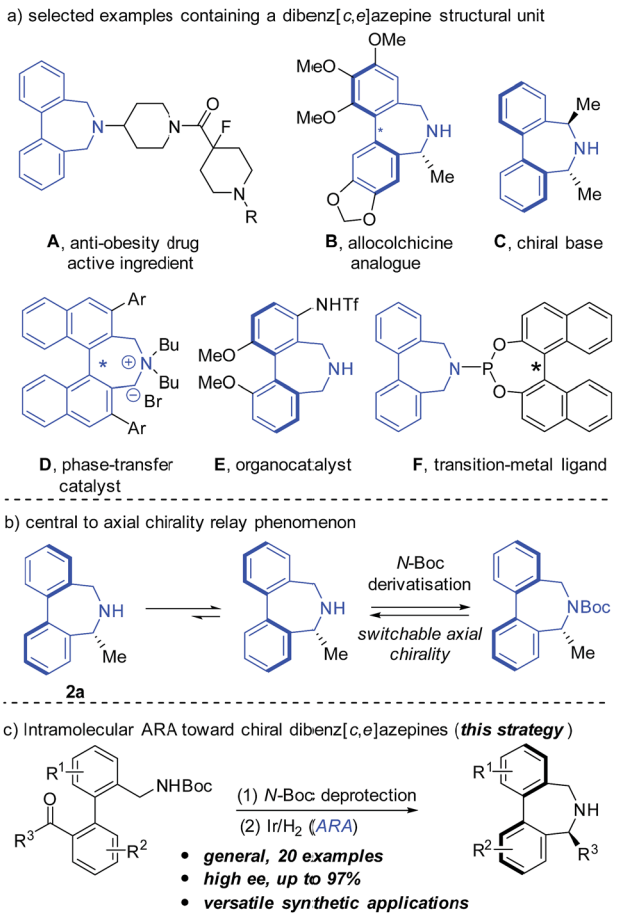

Fig. 1 (a) Selected examples containing a dibenz[*c*,*e*]azepine structural unit; (b) central to axial chirality relay phenomenon; (c) our proposed one pot N-Boc deprotection/intramolecular ARA sequence for the synthesis of enantioenriched dibenz[*c*,*e*]azepines.

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a center-axis stereochemical relay.[4a] Very recently, Turner and coworkers described an elegant biocatalytic route to access enantiomerically pure dibenz[*c*,*e*]azepines by utilizing imine reductase (IRED) biocatalysts.[6] To our knowledge, highly efficient chemical catalytic systems capable of directly providing structurally diverse chiral dibenz[*c*,*e*]azepines have never been reported.[7] The lack of efficient methods toward enantioenriched dibenz[*c*,*e*]azepines has greatly impeded deeper studies on the structure–function relationship and synthetic applications of these unique chiral cyclic amines.

Transition metal-catalyzed asymmetric reductive amination represents a straightforward and step-economical method for the synthesis of chiral amines from readily available ketones.[8] However, this field remains underdeveloped compared to the well-studied imine asymmetric hydrogenation.[9]

Recently, intramolecular ARA has exhibited great potential in the construction of chiral 5- and 6-membered N-heterocycles.[10] In contrast, related applications for the synthesis of 7-membered N-heterocycles remain underdeveloped. To continue our interest in ARA with molecular H_2,[8k] we wondered if this strategy was also applicable to synthesize chiral 7-membered dibenz[*c*,*e*]azepines efficiently. Herein, we report the first enantioselective synthesis of dibenz[*c*,*e*]azepines through a one pot N-Boc deprotection/intramolecular ARA sequence (eqn (c), Fig. 1). The synthetic utilities of the enantioenriched products are also presented.

Results and discussion

Inspired by Turner's elegant work[6] and our recent discovery on ARA,[11] aryl-bridged aminoketone **1a** was prepared and selected as the model substrate for our research. We envisaged that **1a** could undergo N-Boc deprotection promoted by HCl/Et_2O and subsequent ARA enabled by the Ir/ZhaoPhos complex to provide enantioenriched product **2a**. After the removal of all volatile components from the first step, the resulting mixture was treated with 30 atm of H_2 for the ARA step in the presence of a catalyst combination of $[Ir(COD)Cl]_2$ and ZhaoPhos using DCM as a solvent and $Ti(O^iPr)_4$ as an additive. Delightfully, the reaction gave the desired product **2a** in moderate conversion (65%) albeit with promising enantioselectivity (36% ee), together with the formation of imine intermediate **2a′** (Table 1, entry 1). Unexpectedly, without $Ti(O^iPr)_4$, the reduction process did not work, suggesting the key role of $Ti(O^iPr)_4$ in accelerating the reduction process.[12] Screening of other solvents, such as EtOAc, THF, ^{i}PrOH, MeOH, toluene and MeCN, disclosed that ^{i}PrOH was the best choice, providing the desired **2a** in 77% ee.[13] Despite moderate enantiocontrol in the Ir/ZhaoPhos catalytic system, these positive results confirmed our hypothesis and encouraged us to further modify the catalyst combination with the expectation of improving the ee to an excellent level.

We subsequently evaluated a diverse array of commercially available chiral diphosphine ligands (Table 2). The most popular diphosphine ligand BINAP was first tried, giving the

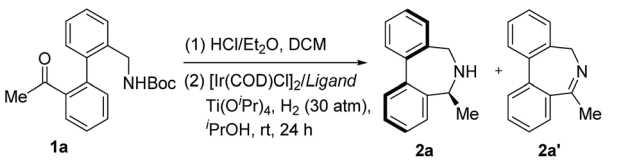
Table 1 Evaluation of additives and solvents for Ir/ZhaoPhos-catalyzed ARA of **1a**[a]

1a **2a** **2a'**

Entry	Additive	Solvent	Conv.[b] (%)	**2a**/**2a′**[b]	**2a**: ee[c] (%)
1	$Ti(O^iPr)_4$	DCM	>99	65/35	36 (*R*, a*S*)
2	—	DCM	>99	0/100	—
3	$Ti(O^iPr)_4$	EtOAc	>99	60/40	55 (*R*, a*S*)
4	$Ti(O^iPr)_4$	^{i}PrOH	>99	86/14	77 (*R*, a*S*)
5	$Ti(O^iPr)_4$	THF	>99	79/21	66 (*R*, a*S*)
6	$Ti(O^iPr)_4$	MeOH	>99	75/25	72 (*R*, a*S*)
7	$Ti(O^iPr)_4$	Toluene	>99	72/28	12 (*R*, a*S*)
8	$Ti(O^iPr)_4$	MeCN	>99	42/58	50 (*R*, a*S*)

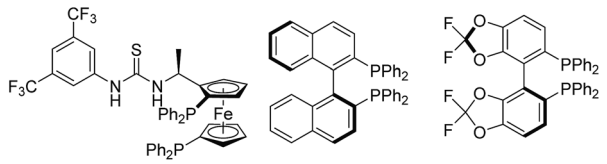
[a] Reaction conditions: **1a** (0.1 mmol), $[Ir(COD)Cl]_2$ (0.5 mol%), ZhaoPhos (1.1 mol%), HCl/Et_2O (4.0 equiv.), $Ti(O^iPr)_4$ (1 equiv.), and solvent (0.6 mL). [b] Determined by ^{1}H NMR. [c] Determined by HPLC for the corresponding benzamides.

Table 2 Further condition optimization of the ARA of **1a**[a]



1a **2a** **2a'**

Entry	Ligand	Conv.[b] (%)	**2a**/**2a′**[b]	**2a**: ee[c] (%)
1	ZhaoPhos	>99	86/14	77 (*R*, a*S*)
2	(*S*)-BINAP	>99	90/10	40 (*S*, a*R*)
3	(*S*)-SegPhos	>99	>99/1	92 (*S*, a*R*)
4	(*S*)-DM-SegPhos	>99	>99/1	80 (*S*, a*R*)
5	(*S*)-DTBM-SegPhos	>99	>99/1	40 (*S*, a*R*)
6	(*S*)-MeO-BiPhep	>99	>99/1	86 (*S*, a*R*)
7	(*S*)-MeO-DM-BiPhep	>99	>99/1	53 (*S*, a*R*)
8	(*S*)-DifluorPhos	>99	>99/1	94 (*S*, a*R*)
9[d]	**(*S*)-DifluorPhos**	**>99**	**>99/1 (89)**	**96 (*S*, a*R*)**
10[e]	(*S*)-DifluorPhos	>99	>90/10	96 (*S*, a*R*)



ZhaoPhos (*S*)-BINAP (*S*)-DifluorPhos

(*S*)-SegPhos (Ar= Ph)
(*S*)-DM-SegPhos (Ar= 3,5-diMeC$_6$H$_3$)
(*S*)-MeO-BiPhep (Ar= Ph)
(*S*)-MeO-DM-BiPhep (Ar= 3,5-diMeC$_6$H$_3$)

[a] Reaction conditions: **1a** (0.1 mmol), $[Ir(COD)Cl]_2$ (0.5 mol%), ligand (1.1 mol%), HCl/Et_2O (4.0 equiv.), $Ti(O^iPr)_4$ (1 equiv.) and solvent (0.6 mL). [b] Determined by ^{1}H NMR; isolated yield of **2a** in parentheses. [c] Determined by HPLC for the corresponding benzamides. [d] The reaction was conducted at 20 °C. [e] 20 atm of H_2 was used.

product **2a** in high conversion (90%) but low enantioselectivity (40% ee) (Table 2, entry 2). Satisfactorily, double oxygenated diphosphine ligands including SegPhos, MeO–BiPhep and DifluorPhos displayed higher enantiocontrol (Table 2, entries 3–8). Particularly, DifluorPhos delivered the highest enantioselectivity (94% ee; Table 2, entry 8). Lowering the reaction temperature to 20 °C led to a slight improvement of the enantiocontrol (96% ee, 89% yield; Table 2, entry 9). The pressure of H_2 was also evaluated, and the conversion slightly dropped to 90% with 20 atm of H_2, without affecting the enantioselectivity (Table 2, entry 10).

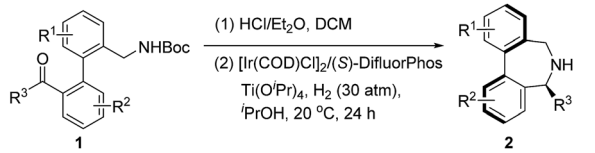
Under the optimal reaction conditions, the substrate scope was then studied, as depicted in Table 3. We first examined methyl ketones with various substituents (Me, MeO, F, Cl, CF_3, *etc.*) on both of the bridged benzene rings. In general, all tested substrates provided the corresponding enantioenriched dibenz[*c*,*e*]azepines in high yields and excellent ees (**2b–2k**, 87–94% yields, 89–97% ee), regardless of the nature and position of the substituents. Remarkably, pyridine-bridged substrate **1l** is also applicable, yielding the corresponding product **2l** in 89% yield and 84% ee. It is noteworthy that 2 equivalents of $Ti(O^iPr)_4$ are required to enable good conversion, which is possibly due to the competitive coordination of the N atom on the pyridine *versus* the N atom of imine. Disappointingly, the enantiocontrol is very susceptible to the steric bulk of the substituent R^3. Ethyl-substituted substrates (**1m**) afforded the product with dramatically decreased enantioselectivity (60% ee for **2m**).

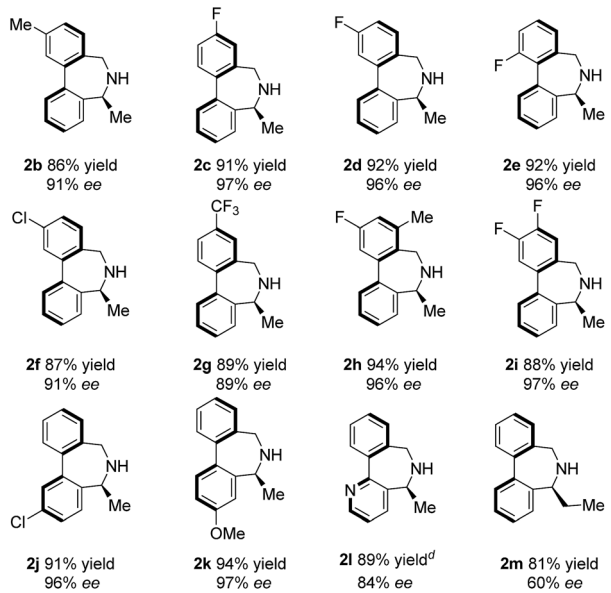
When we applied the above-mentioned standard reaction conditions to diarylketone-derived substrates, inferior performance was unfortunately observed in terms of both reactivity and enantiocontrol. After re-optimizing the reaction conditions with **1n**, including the evaluation of the ligands, H_2 pressure and the reaction time (see the ESI† for details), we were glad to discover that the desired reductive amination product **2n** could be obtained in 72% yield and 89% ee in the presence of the $[Ir(COD)Cl]_2$/(*S*)-SegPhos complex and 60 atm of H_2 for 48 h. The moderate yield of **2n** was caused by the low reactivity of the imine intermediate towards reduction.

With the slightly revised reaction conditions, we found that several substrates (**1o** to **1s**) contain either a Me, F, MeO or Cl substituent on each benzene ring, as summarized in Table 4. Gratifyingly, all examined substrates underwent the reaction smoothly to yield the corresponding products in decent to good yields with generally good ee (**2o–2s**, up to 81% yield and 91% ee).

To demonstrate the practical utility of this method, scale-up synthesis of **2a** was performed on the 1.5 mmol scale, producing **2a** in 88% yield and 96% ee. Dibenz[*c*,*e*]azepine **B** is an analogue of the alkaloid allocolchicine with bioactivity against anti-microtubules and was originally synthesized by Baudoin and co-workers[14] from chiral-pool starting materials. We were curious if our catalytic asymmetric method could be applied to achieve the biologically active molecule **B**. To test our idea, imine hydrochloride salt **3** was prepared because direct ARA was

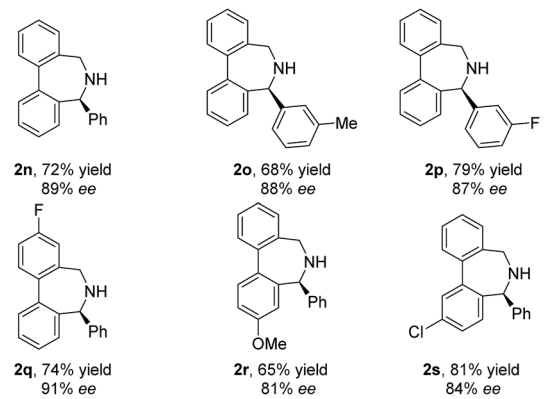
Table 3 Substrate scope for alkylketones[a,b,c]



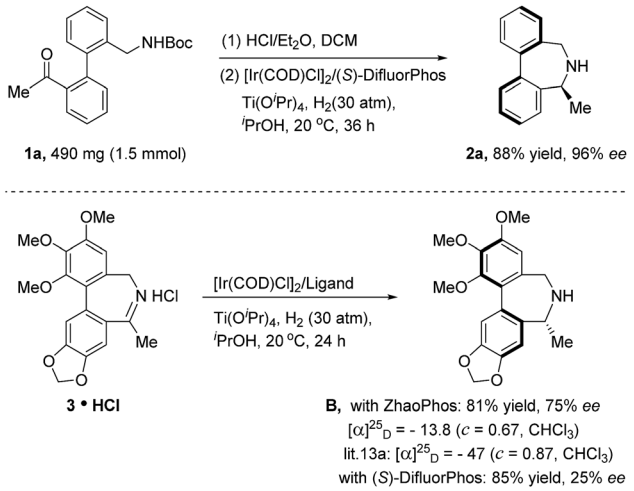


[a] Reaction conditions: **1** (0.1 mmol), $[Ir(COD)Cl]_2$ (0.5 mol%), (*S*)-DifluorPhos (1.1 mol%), HCl/Et_2O (4.0 equiv.), $Ti(O^iPr)_4$ (1.0 equiv.), and ^{i}PrOH (0.6 mL). [b] Isolated yields. [c] Determined by HPLC on a chiral stationary phase for the corresponding benzamides. [d] 2.0 equiv. of $Ti(O^iPr)_4$ was used.

Table 4 Substrate scope for diarylketones[a,b,c]



[a] Reaction conditions: **1** (0.1 mmol), $[Ir(COD)Cl]_2$ (2 mol%), (*S*)-SegPhos (4.4 mol%), HCl/Et_2O (4.0 equiv.), $Ti(O^iPr)_4$ (1.0 equiv.), and ^{i}PrOH (0.6 mL). [b] Isolated yields. [c] Determined by UPLC on a chiral stationary phase.

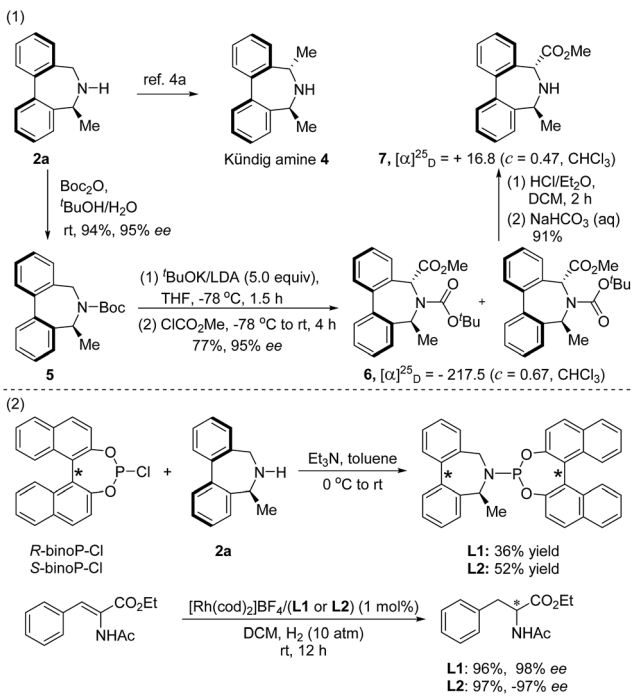


Scheme 1 Scale-up synthesis of **2a** and asymmetric hydrogenation towards bioactive compound **B**.

unsuccessful. When **3** HCl was subjected to the standard hydrogenation conditions (DifluorPhos as the ligand), the desired product **B** was unfortunately obtained with poor enantiocontrol (25% ee). Nevertheless, 81% yield and 75% ee of **B** were achieved when ZhaoPhos was used as the ligand (Scheme 1).

The obtained enantioenriched axially chiral biaryl amines could be easily derivatized into the Kündig amine **4** with a procedure reported by Wallace.[4a] Likely, treatment of the N-Boc derivative **5**, prepared from **2a**, with **5** equivalents of Schlosser's "LIDAKOR" base[15] at −78 °C, followed by a quenching operation with methyl chloroformate, provided **6** as a mixture of two rotamers.[16] Subsequent removal of the Boc group using HCl/Et_2O afforded enantioenriched seven-membered cyclic amino acid derivative **7** in a high yield (top, Scheme 2).

In addition, two chiral monodentate phosphorus ligands **L1** and **L2** were efficiently synthesized by condensation of the chiral amine **2a** with (*R*) or (*S*)-(1,1′-binaphthyl-2,2′-diyl) chlorophosphite. The application of both ligands in rhodium-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives[17] afforded the hydrogenated product with excellent enantioselectivity (bottom, Scheme 2).



Scheme 2 Synthetic applications of **2a**.

Conclusions

In summary, we have developed a highly enantioselective method towards chiral dibenz[*c*,*e*]azepines through a one pot N-Boc deprotection/intramolecular ARA sequence of bridged biaryl derivatives. Under optimal reaction conditions, dibenz[*c*,*e*]azepines containing both central and axial chiralities are conveniently obtained with generally excellent enantiocontrol (up to 97% ee). Our method represents an intriguing catalytic enantioselective synthesis of Ar-bridged axially cyclic amines. The synthetic utility of the developed method was exhibited by an unprecedented enantioselective synthesis of an analogue of allocolchicine. Derivatisation of the obtained product into more complicated and synthetically interesting amino acid derivatives and chiral ligands for transition metal catalysis was also performed.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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12 The real role of $Ti(O^iPr)_4$ is unclear at this stage. We also tested some other Lewis acids including $AlCl_3$, $InCl_3$, $FeCl_3$, $Zn(OTf)_2$, $BF_3\cdot Et_2O$ and $Ti(OEt)_4$, and the results disclosed that only titanium Lewis acid could efficiently accelerate the transformation (see the ESI† for details).

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