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Stereoconvergent, Redox-Neutral Access to Tetrahydroquinoxalines by Relay Catalytic Epoxide Opening/Amination of Alcohol

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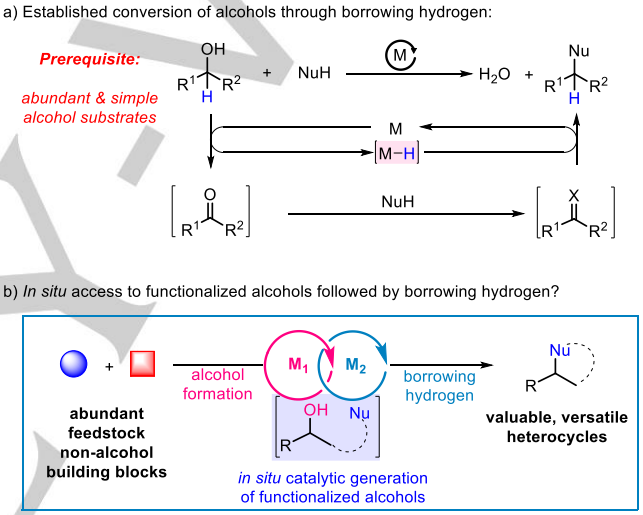
Abstract: We present herein an economical catalytic procedure to convert readily available 1,2-diaminobenzenes and terminal epoxides to valuable 1,2,3,4-tetrahydroquinoxalines in a highly enantioselective fashion. This procedure operates via relay zinc and iridium catalysis, and achieves redox-neutral and stereoconvergent production of valuable chiral heterocycles from racemic starting materials with water as the only side product. The use of commercially available reagents and catalysts and a convenient procedure also make this catalytic method attractive for practical application.

Borrowing hydrogen methodology has gained prominence as an example of green chemistry, due to its overall redox-neutral nature and minimized reagent use or waste generation.[1,2] Application to industrial scale synthesis has also been documented.[3] In these transformations, the alcohol substrates are converted to valuable amines, β-functionalized alcohols, etc., through the carbonyl intermediates followed by C-N or C-C bond formation (Scheme 1a). By the introduction of chiral catalysts, our group and others have achieved enantioselective alcohol aminations based on borrowing hydrogen methods.[4-5] Additionally, enantioselective dehydrogenative carbonyl additions of alcohol reactants have been developed.[6] However, all of these methods relied on the use of readily available alcohol substrates.[1] In some cases where functionalized alcohols are used,[7] the necessity to prepare them in a separate operation certainly reduces the overall efficiency of the synthetic procedure.

We reasoned that if catalytic construction of functionalized alcohols and the following borrowing hydrogen reaction can be merged into a one-pot catalytic relay, it may allow the construction of valuable heterocycles from abundant building blocks with high efficiency and economy (Scheme 1b). In addition, certain functionalized alcohols may be sensitive or difficult to handle; this catalytic generation *in situ* may help circumvent such purification problem. The use of relay catalysis will also open up the possibility for achieving enantioselective heterocycle synthesis.[8-9] On the other hand, such unprecedented methods certainly present significant challenges. The compatibility of multiple catalytic species needs to be addressed together with achieving high catalytic efficiency and enantioselectivity for such a complex relay catalysis system.



Scheme 1. Relay catalysis for more efficient and economical heterocycle synthesis via borrowing hydrogen methodology.

Chiral 1,2,3,4-tetrahydroquinoxalines represent an important class of *N*-heterocycles, which are present in a great number of biologically active substances including a novel bromodomain inhibitor GSK340 **I**, a cholesteryl ester transfer protein inhibitor **II** and a prostaglandin D2 receptor antagonist **III** (Scheme 2a).[10] Accordingly, extensive efforts have been devoted to the enantioselective synthesis of this class of heterocycles.[11] Among the different strategies, asymmetric hydrogenation or transfer hydrogenation of quinoxalines represents one of the most straightforward choices (Scheme 2b). Many elegant catalytic systems have been reported using transition metal or organocatalysis.[12] Despite the impressive progress, these methods were generally performed under high pressure of hydrogen gas or required stoichiometric amount of reductants such as Hantzsch ester, Et_3SiH, etc. The development of economical and sustainable catalytic methods to produce enantioenriched 1,2,3,4-tetrahydroquinoxalines from readily available starting materials is still highly desired.

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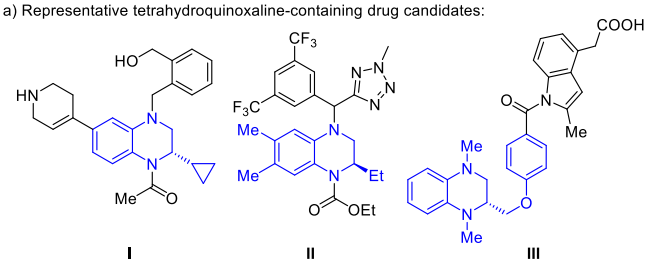
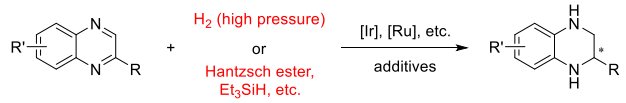
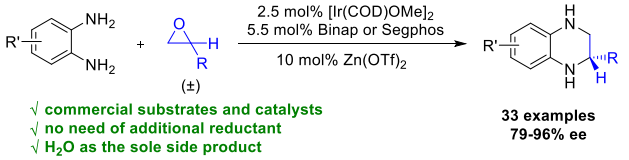
a) Representative tetrahydroquinoxaline-containing drug candidates:



b) Asymmetric hydrogenation and transfer hydrogenation of quinoxalines:



c) This work: Zn/Ir-catalyzed redox-neutral synthesis of tetrahydroquinoxalines

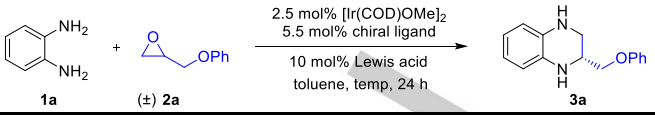


Scheme 2. Access to tetrahydroquinoxalines.

Herein, we report an unprecedented redox-neutral, stereoconvergent access to 1,2,3,4-tetrahydroquinoxalines from readily available and inexpensive diamines and racemic epoxides (Scheme 2c).[13] This transformation proceeds by merging Lewis acid-catalyzed epoxide ring opening with iridium-catalyzed intramolecular amination of alcohols with good to excellent level of enantiocontrol.[14] The use of commercially available catalysts and a simple procedure also bodes well for the wide application of this method.

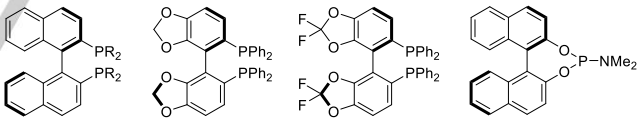
We initiated our investigation by reacting racemic epoxide **2a** with 1,2-diaminobenzene **1a** (Table 1), the product of which (**3a**) possesses the key structure in valuable compound **III** (Scheme 2a). Different iridium precursors were evaluated with (*R*)-Binap (**L1**) as the ligand of choice. While the reactions using $[IrCp^*Cl_2]_2$, $[Ir(COD)Cl]_2$, $[Ir(COE)_2Cl]_2$ only gave trace amount of the desired product, a noticeable yield of 7% was observed for the reaction employing $[Ir(COD)OMe]_2$ (entry 1). In all cases, a low consumption of the epoxide was observed. We then added various Lewis acids such as $Sc(OTf)_3$, $Mg(OTf)_2$ and $Zn(OTf)_2$ in an effort to improve the efficiency of ring-opening of epoxide **2a**. To our delight, the combination of Lewis acid and $[Ir(COD)OMe]_2$/(*R*)-Binap indeed led to the formation of **3a** in up to 86% yield with 94% ee (entries 2-4). **3a** could also be obtained in good enantioselectivity (93% ee) in the presence of the Brønsted acid diphenyl phosphate, albeit in a low yield of 28% (entry 5). At this point, a systematic ligand screening was carried out, from which Binap remained the optimal choice (entries 6-13 vs. entry 4). In general, axially chiral bisphosphine ligands performed better than other chiral bisphosphines or monophosphines. Lowering the reaction temperature to 90 °C led to an enhanced 95% ee, albeit with a lower yield of 71% (entry 14). With extended reaction time of 36 h, **3a** could be produced in 84% yield and 95% ee (entry 15). Clearly this reaction proceeded in a stereoconvergent fashion. The absolute configuration of **3a** was established by single crystal x-ray analysis.

Table 1. Reaction Condition Optimization.[a]

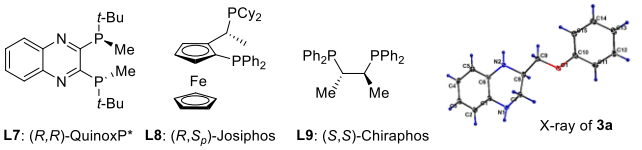


Entry	Ligand	Lewis Acid	Temp (°C)	Yield[b]	ee[c]
1	**L1**	--	110	7%	\
2	**L1**	$Sc(OTf)_3$	110	10%	80%
3	**L1**	$Mg(OTf)_2$	110	68%	84%
4	**L1**	$Zn(OTf)_2$	110	86%	94%
5	**L1**	$(PhO)PO_2H$	110	28%	93%
6	**L2**	$Zn(OTf)_2$	110	77%	90%
7	**L3**	$Zn(OTf)_2$	110	80%	81%
8	**L4**	$Zn(OTf)_2$	110	75%	94%
9	**L5**	$Zn(OTf)_2$	110	76%	90%
10	**L6**	$Zn(OTf)_2$	110	10%	60%
11	**L7**	$Zn(OTf)_2$	110	60%	68%
12	**L8**	$Zn(OTf)_2$	110	50%	73%
13	**L9**	$Zn(OTf)_2$	110	77%	6%
14	**L1**	$Zn(OTf)_2$	90	71%	95%
15[d]	**L1**	$Zn(OTf)_2$	90	84%	95%

[a] Reaction conditions: A mixture of **1a** (1.5 equiv.), **2a** (1 equiv.), Lewis acid (10 mmol %), $[Ir(COD)OMe]_2$ (2.5 mmol %), phosphine ligand (5.5 mmol %) were reacted in a solvent (0.5 mL) at 110 ºC for 24 h under N_2. [b] Determined by ^1H NMR analysis using CH_2Br_2 as an internal standard. [c] Determined by HPLC. [d] 36 h. COD = 1,5-cyclooctadiene.



L1: (*R*)-Binap
L2: (*R*)-Tol-Binap
L3: (*R*)-Xyl-Binap
L4: (*R*)-Segphos
L5: (*R*)-Difluorophos
L6: (*R*)-Monophos



L7: (*R*,*R*)-QuinoxP* **L8**: (*R*,S_p)-Josiphos **L9**: (*S*,*S*)-Chiraphos

X-ray of **3a**

With the optimized conditions in hand, we next investigated the scope and generality of this catalytic system. As shown in Scheme 3, a series of epoxides **2** were successfully converted to the corresponding 2-aryloxy-methyl-tetrahydroquinoxalines (**3a** to **3g**) in good yields with uniformly excellent enantioselectivity (93-96% ee) under the standard reaction conditions. Only in the case of *ortho* substituted product **3h**, a slightly decreased ee of 89% was observed. Substituted 1,2-diaminobenzene derivatives could also be converted to the corresponding products **3i**-**3k** with similarly high enantioselectivity (92-95% ee).

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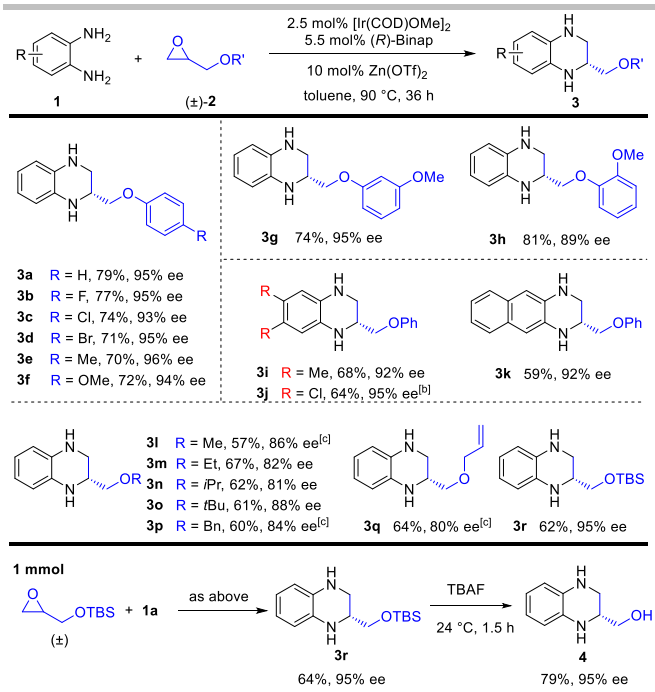
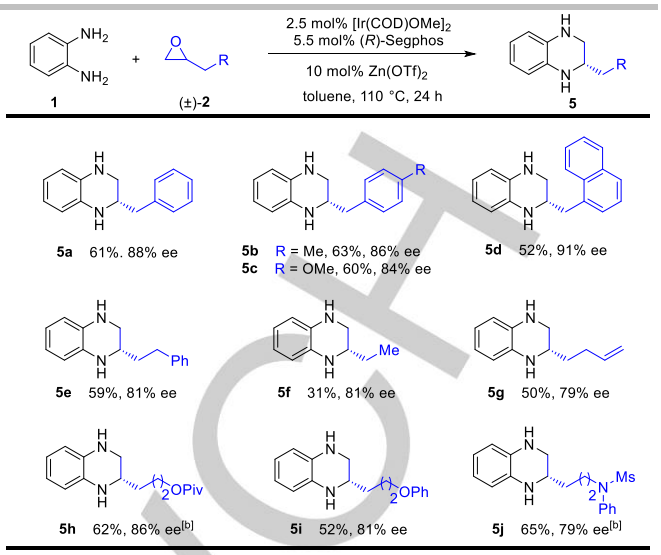


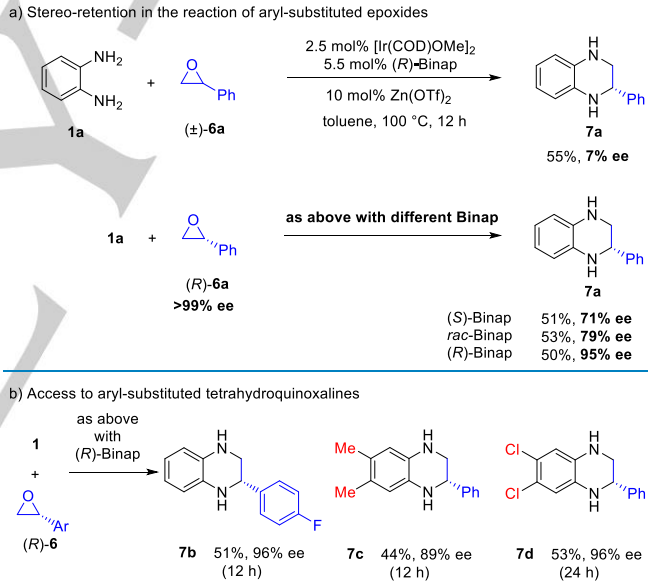
Scheme 3. Scope of ether-substituted products. [a] Unless stated otherwise, reactions were carried out in toluene at 90 ºC for 36 h. Isolated yields were shown and ees were determined by HPLC. [b] toluene/*t*-amyl alcohol (5/1) was used as the solvent. [c] The reaction was carried out with (*R*)-Segphos.

This catalytic system was not limited to 2-alkoxymethyl-substituted-tetrahydroquinoxalines. A range of heterocycles **5a**-**5j** bearing a simple alkyl substituent could also be accessed in good enantiopurity, when the reactions were carried out in the presence of (*R*)-Segphos in toluene at 110 ºC for 24 h (Scheme 4). In general products **5** with a bulkier substituent were obtained in higher ee. The relatively low yield of product **5f** was likely due to the low boiling point of the corresponding epoxide. It is noteworthy that several useful functional groups such as alkene, ester and sulphonamide were shown to be compatible with this catalytic system.

To further expand the scope of this catalytic system, we investigated the synthesis of chiral tetrahydroquinoxalines with an aryl substituent from **1a** and racemic styrene oxide (Scheme 5a). However, the target product **7** was generated in nearly racemic form (7% ee). This disappointing result could be rationalized by the well-established regio-selectivity of Lewis acid-catalyzed epoxide ring opening. The ring opening of aryl-substituted epoxide is under electronic control and should take place primarily at α carbon of the styrene oxide. This was confirmed by carrying out the reaction in the presence of only Lewis acid catalyst (see SI for details). Based on this step, the following amination of alcohol would then be irrelevant for enantio-control, leading to formation of nearly racemic product.



Scheme 4. Scope of alkyl-substituted products. [a] Unless stated otherwise, reactions were carried out in toluene at 110 ºC for 24 h. Isolated yields were shown and ees were determined by HPLC. [b] The reaction was carried out with (*R*)-Binap at 90 ºC for 36 h. Piv = Pivaloyl. Ms = Methanesulfonyl



Scheme 5. Reaction of aryl-substituted epoxides.

Alternatively, the use of an enantiopure substrate could result in a stereospecific transformation of aryl-epoxides to tetrahydroquinoxalines. When enantiopure **6a** was used instead, **7a** was indeed obtained in an enantioenriched form, however, with significant racemization (79% ee). With the matched case using (*R*)-Binap, **7a** could be obtained in 50% yield with an excellent 95% ee. This set of conditions could be successfully extended to the synthesis of various aryl-substituted tetrahydroquinoxalines **7b**-**7d** in good to high enantiopurity (89-96% ee, Scheme 5b).

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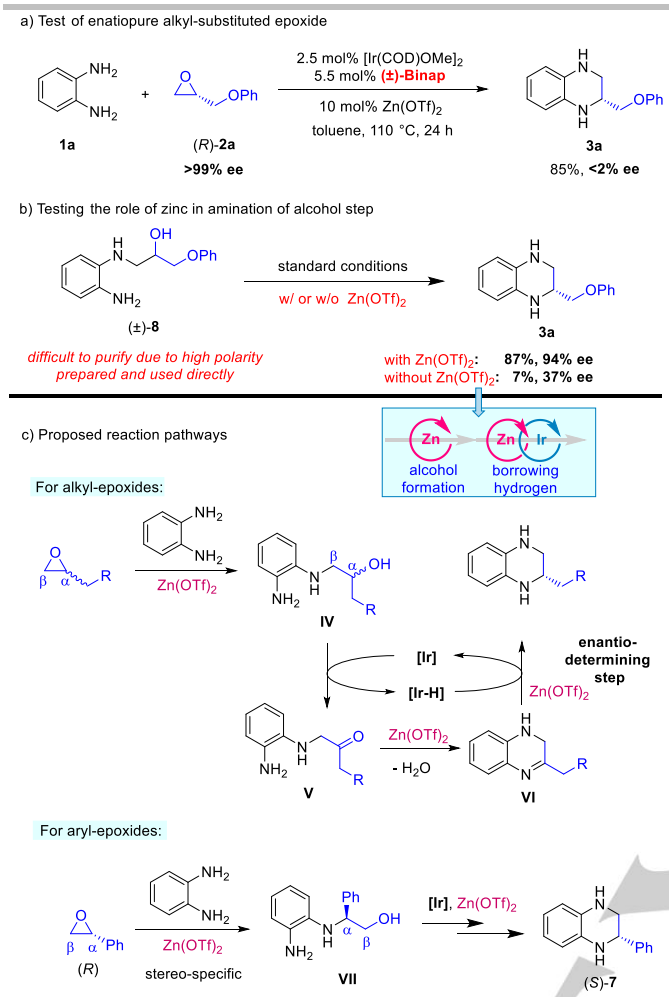
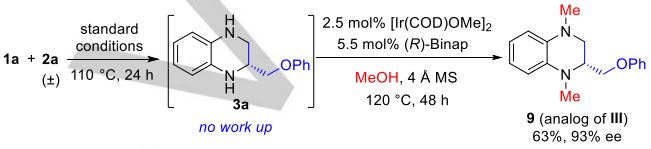


Scheme 6. Control reactions and proposed mechanism.

Several control reactions were also carried out for alkyl-substituted epoxide **2a** to shed light on the reaction pathway of this catalytic system. As shown in Scheme 6a, the reaction of enantiopure **2a** by the use of racemic Binap as the ligand produced **3a** in a racemic form, which is in sharp contrast to the reaction of enantiopure **6a** (Scheme 5a). This is consistent with the hypothesis that a regio-selective epoxide ring opening at the β-position produces a chiral amino alcohol intermediate. The following amination of alcohol then proceeds in a stereoconvergent fashion. The chirality from epoxide is thus completely erased in such a transformation.

Our previous studies showed that it is essential to have an acid co-catalyst to promote the amination of alcohols.[4] To test the role of $Zn(OTf)_2$ in the intramolecular amination step, the postulated intermediate **8** was synthesized and subjected to the standard reaction conditions (Scheme 6b). Similar level of efficiency and enantioselectivity was obtained for **3a** in the presence of $Zn(OTf)_2$. In contrast, very low yield and ee were observed in the absence of $Zn(OTf)_2$. These data suggested that not only is $Zn(OTf)_2$ involved for the epoxide ring opening step, but it is also essential as a Lewis acid to co-catalyze the amination step (cooperative catalysis with iridium). In addition, it is noteworthy that amino alcohol **8** is difficult to purify due to its high polarity. Our relay catalysis thus avoids handling such intermediate and results in a convenient procedure to access the valuable heterocycles directly from commercially available compounds.

Based on the above information, a plausible mechanism was proposed (Scheme 6c). For alkyl-substituted epoxide, the less hindered carbon (β-carbon) is attacked by **1a** to produce a β-amino secondary alcohol **IV**, catalyzed by $Zn(OTf)_2$. **IV** then undergoes a stereoconvergent amination through the achiral intermediate **V**. $Zn(OTf)_2$ is believed to catalyze both the imine condensation and the enantio-determining reduction of **VI**. In contrast, ring opening of aryl-containing epoxides mainly produces the β-hydroxy α-chiral amine **VII**. The following amination step then generates **7**, the chirality of which should come from that of **VII**. As aldehyde and imine intermediates are involved, partial racemization of the α-stereocenter in **VII** is expected. With a matched pair of chiral substrate and ligand, the extent of racemization could be minimized to produce **7a**-**7d** with high ee in moderate yield (Scheme 5).



Scheme 7. A triple relay to prepare analog of III.

As many medicinally relevant agents (such as **III** in Scheme 2a) bear alkyl substituents and especially methyl on the nitrogen atoms, we wondered whether we could achieve a convenient triple relay catalysis procedure that includes a final methylation step by borrowing hydrogen. To our delight, the addition of methanol and more catalyst following the generation of **3a** (without the need for workup) produced bis-methylated heterocycle **9** in one-pot from commercial compounds in good yield and excellent enantioselectivity (Scheme 7).[15]

In conclusion, we have developed a highly efficient catalytic method to convert readily available diamines and racemic epoxides to valuable 1,2,3,4-tetrahydroquinoxalines in a redox-neutral, stereoconvergent fashion. Commercially available zinc and iridium catalysts work in a relay/cooperative manner to achieve efficient heterocycle synthesis with a convenient procedure. The development of other relay catalysis systems featuring borrowing hydrogen for economical synthesis of valuable building blocks is currently underway in our laboratories.

Acknowledgements

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Keywords: borrowing hydrogen • tetrahydroquinoxaline • relay catalysis • redox-neutral catalysis • enantioselectivity

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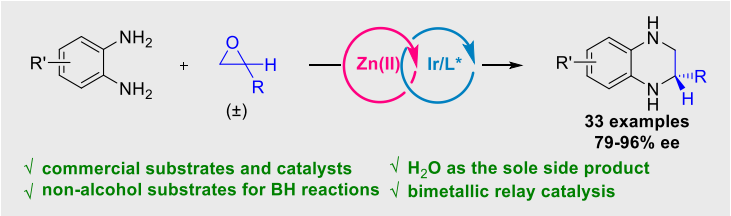

Bimetallic relay catalysis: We present herein an economical catalytic procedure to convert readily available diamines and terminal epoxides to valuable 1,2,3,4-tetrahydroquinoxalines in a highly enantioselective fashion. This procedure operates via relay zinc and iridium catalysis, and achieves redox-neutral and stereoconvergent production of valuable chiral heterocycles from racemic starting materials with water as the only side product.

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Stereoconvergent, Redox-Neutral Access to Tetrahydroquinoxalines by Relay Catalytic Epoxide Opening/Amination of Alcohol