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Introduction of chirality at C1 position of 1-substituted-3,4-dihydroisoquinoline by its enantioselective reduction: synthesis of chiral 1-substituted-1,2,3,4-tetrahydroisoquinoline – a review

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There is a wide range of biological activities associated with C1 chiral carbon containing 1-substituted-1,2,3,4-tetrahydroisoquinolines (1-substituted-THIQs) which constitute the isoquinoline alkaloids, a large group of natural products. This work summarizes several novel catalytic stereoselective approaches to enantioselectively reduce the 1-substituted-3,4-dihydroisoquinolines (1-substituted-DHIQs) to produce the desired 1-substituted-THIQs. The 1-substituted-DHIQs were prepared by using the Bischler–Napieralski reaction. The enantioselective reduction of 1-substituted-DHIQs was accomplished by using chiral hydride reducing agents, by hydrogenation with a chiral catalyst, by enantioselective reduction of DHIQs possessing a chiral auxiliary at the imine nitrogen by achiral metallic hydride reducing agents, or by enzymatic catalysis. Among these methods, much more work was carried out on the hydrogenation of 1-substituted-DHIQs in the presence of a chiral catalyst. This review summarizes articles and advancements on this topic from 1972 to 2023.

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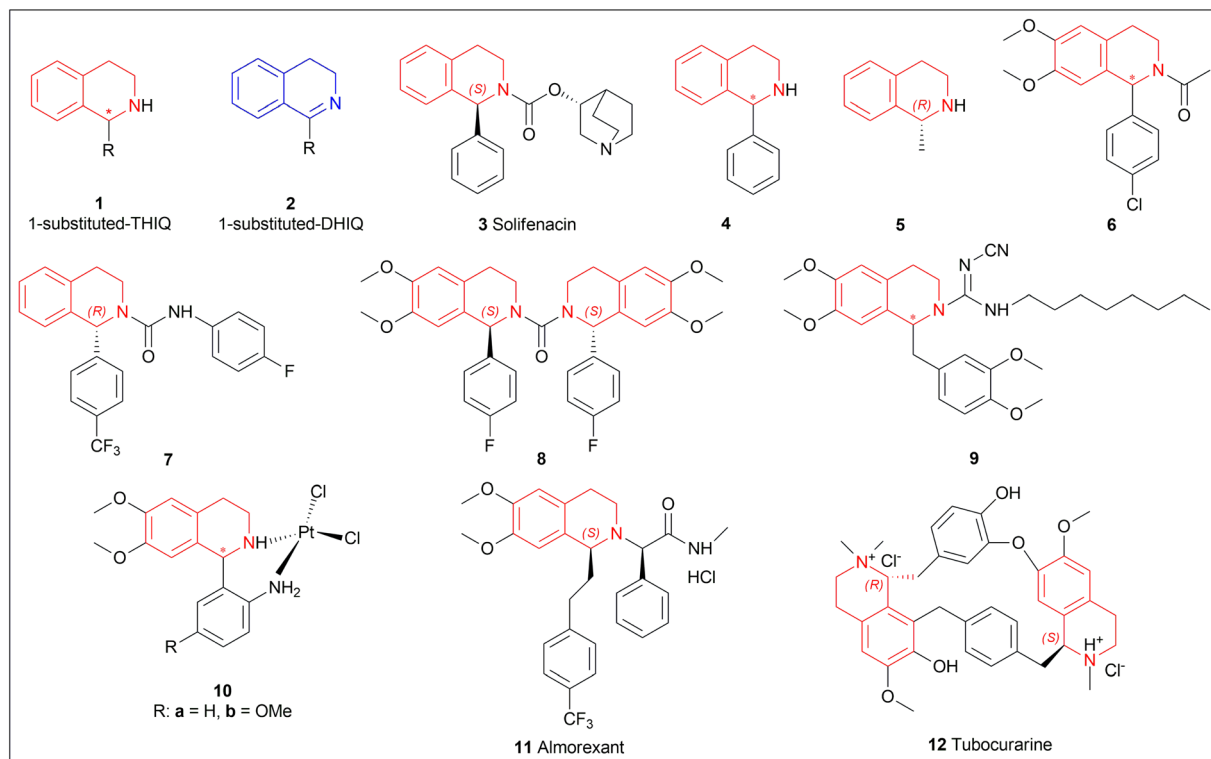


Fig. 1 Structures of compounds having 1-substituted-THIQs.

1 Introduction

The isoquinoline alkaloids occur primarily in nature and demonstrate a wide range of biological activity and structural



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diversity. Several effective synthetic techniques have been developed extensively over the last few decades to synthesize these alkaloids in their chiral form with a high enantiomeric excess (% ee). Most of them utilize the diastereoselective or enantioselective catalysis methods for production. These alkaloids have constantly been prominent candidates for organic synthesis because of their structure, bioactivities, and prospective as intriguing intellectual challenges as well as potential therapeutic compounds.^{1–5}

The following examples show that the 1-substituted-THIQs **1**, reduction result of 1-substituted-DHIQs **2**, possess various biological activities such as solifenacin **3** against overactive bladders,⁶ **4** shows ataxia,⁷ **5** against 1-benzyl-THIQ and THIQ-induced Parkinson's disease symptoms,^{8,9} **6** as a potential noncompetent antagonist of 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl) propionic acid (AMPA) receptor,^{10,11} **7** and **8** as transient receptor potential cation channel subfamily M (melastatin) member 8 (TRPM8) channel receptor antagonist,^{12,13} **9** shows multidrug resistance reversal in cancer,¹⁴ **10a** and **10b** as 2 times more cytotoxic than *cis*-diaminedichloroplatinum(II) complex against L1210 murine leukemia cells,¹⁵ almorexant **11** in sleep disorders,¹⁶ tubocurarine **12** in the South American arrow poisons¹⁷ (Fig. 1).

1-substituted-THIQs **1** are also important for the synthesis of much more complex isoquinoline alkaloids, for example, 1-benzyl-THIQs **13** are necessary precursors for biologically important alkaloids *e.g.*, morphinans **14**, protoberberines **15**, and apomorphines **16** (Fig. 2).¹⁸

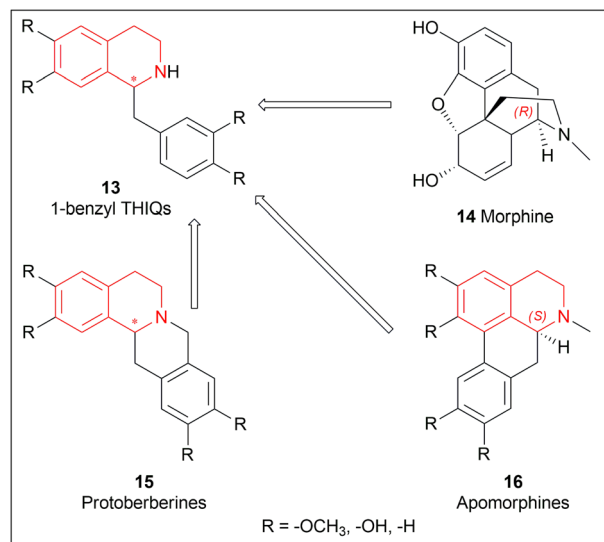
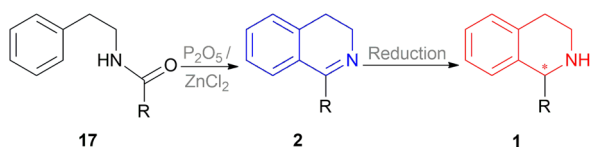


Fig. 2 Generation of complex isoquinoline alkaloids from 1-substituted-THIQs.

A vast majority of asymmetric natural and synthetic 1-substituted-THIQ alkaloids show their asymmetry due to the occurrence of an asymmetric center at the C1 carbon. Hence developing the methodologies to obtain these compounds stereo selectively and access their center for configurational integrity has already been the area of focus. In the past, the classical Bischler–Napieralski reaction has been the topmost recurrently used approach for the synthesis of prochiral 1-substituted-DHIQs **2** (Scheme 1) in which *N*-(2-phenylethyl)acyl amides **17** was cyclized with P_2O_5 or dehydrated $ZnCl_2$.¹⁹ The subsequent reduction of **2** can result in **1** in which a chiral carbon is generated at the C-1 position (Scheme 1). Therefore, the enantioselective reduction of **2** may provide optically active 1-substituted-THIQs **1**.

The United States Food and Drug Administration mandated in 1992 that information about the biological activity and toxicity of the two enantiomers of each listed racemic medicine must be supplied.²⁰ All the early registered racemic medicines also have to be substituted with the appropriate chiral enantiomer under the 1997 complementary regulation.²¹ For this reason, a chiral molecule's enantioselective production of both enantiomers is, therefore, crucial. So, developing an asymmetric synthesis method of 1-substituted-THIQs **1** is highly desirable. The enantioselective reduction of **2** (Scheme 1) can be one for such synthesis. Therefore, we have attempted to discuss here the recent strategies of enantioselective reduction of the 1-substituted-



Scheme 1 Bischler–Napieralski cyclization.

DHIQs **2** to produce the intended 1-substituted-THIQs **1**. Besides the conventional methodologies mentioned, this review also includes updates from 1972 to 2021 in this discipline. Various electronic databases such as SciFinderⁿ, Google Scholar, and Google Patents were searched widely to obtain information about the synthesis of 1-substituted-THIQs **1**.

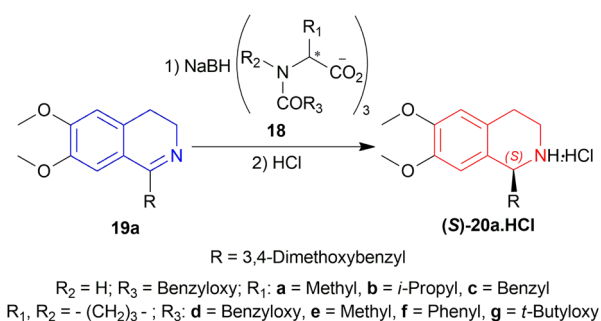
2 Enantioselective reductions of 1-substituted-dihydroisoquinolines (1-substituted-DHIQ)

The enantioselective reduction of the DHIQs **2** may be carried out by the following four methods:

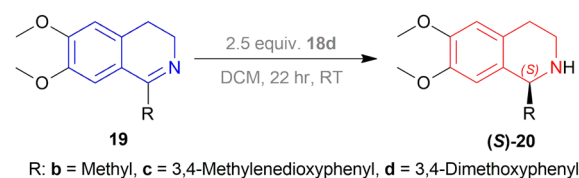
- (1) Enantioselective reduction of DHIQs by chiral hydride reducing agents.
- (2) Enantioselective reduction of DHIQs by hydrogenation with the help of a chiral catalyst.
- (3) Enantioselective reduction of DHIQs possessing chiral auxiliary at the imine nitrogen by achiral metallic hydride reducing agents.
- (4) Enantioselective reduction of DHIQs by enzymatic catalysis.

2.1 Examples of enantioselective reduction of 1-substituted-DHIQs by chiral hydride reducing agents

2.1.1 Asymmetric reduction with chiral sodium triacyloxyborohydrides. Yamada *et al.* screened chiral sodium triacyloxyborohydrides **18a–18g** in THF for the asymmetric reduction of 3,4-dihydropapaverine **19a**.²² **18d–18g** were highly successful in producing (*S*)-norlaudanosine·HCl (*S*)-**20a**·HCl in high ee of 55–60% with 57–72% chemical yield (Scheme 2).

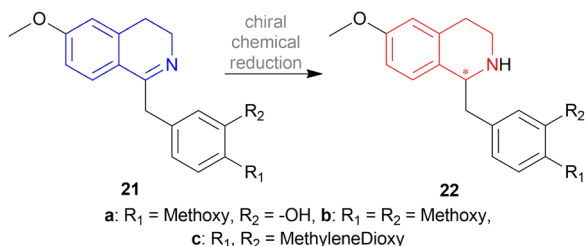


Scheme 2 Screening of chiral sodium triacyloxyborohydrides.



Scheme 3 Reduction into (*S*)-salsolidine, (*S*)-norcryptostyline I, and (*S*)-norcryptostyline II.





Scheme 4 Asymmetric chemical reduction of 1-benzyl-DHIQs.

Among the sodium triacyloxyborohydrides, **18d**, prepared from *N*-benzyloxycarbonyl-L-proline and NaBH_4 , was chosen to examine different solvent systems among which, dichloromethane (DCM) and 1,1-dichloroethane produced high chemical yields of 70%, 79% and ee of 71%, 70% respectively. For later experiments, DCM was chosen as the solvent.

Then 1-substituted-DHIQs **19b–19d** were reduced with 2.5 equiv. of **18d** in DCM for 22 h to produce 1-substituted-THIQs (*S*)-salsolidine (*S*)-**20b**, (*S*)-norcryptostyline I (*S*)-**20c**, (*S*)-norcryptostyline II (*S*)-**20d** in high chemical yield of 85%, 90%, 87% and ee of 70%, 86%, 73% respectively (Scheme 3).

So, **18d** gave (*S*)-configured products.

2.1.2 Asymmetric chemical reduction of 1-benzyl DHIQs.

To synthesize natural and synthetic morphinan compounds, 1-benzyl-1,2,3,4-THIQs are highly useful. For this purpose, rice reduced 1-benzyl-6-methoxy-1,2,3,4-DHIQs **21a–21c** to 1-benzyl-6-methoxy-1,2,3,4-THIQs **22a–22c** through asymmetric chemical reduction (Scheme 4).²³

The chiral synthesis of **22a–22c** from **21a–21c** by asymmetric chemical reduction can be done by many chiral reducing agents. The first one is **18d**. With this reducing agent, 85–90% ee was achieved which can be increased by several

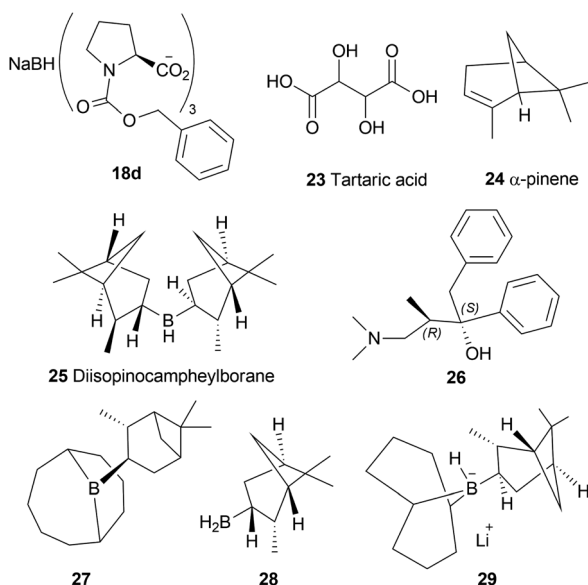


Fig. 3 Chiral hydride reducing agents for the reduction of 1-benzyl-DHIQs.

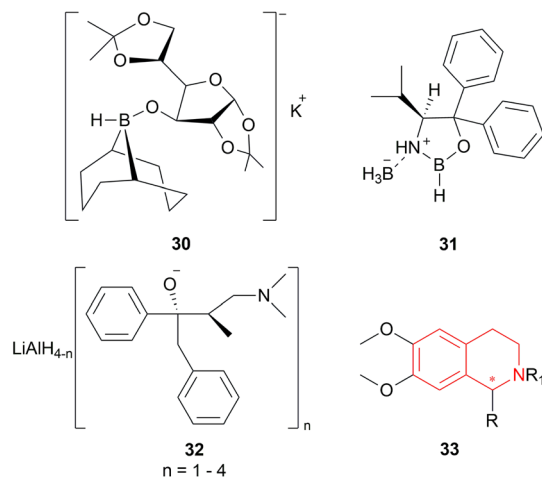


Fig. 4 K-glucoride, Itsuno's reagent, and Mosher's reagent to get 1-substituted-6,7-dimethoxy-THIQs.

crystallization. By reacting NaBH_4 with (+) or (–) tartaric acid **23**, other similar chiral reducing agents can be made (Fig. 3).

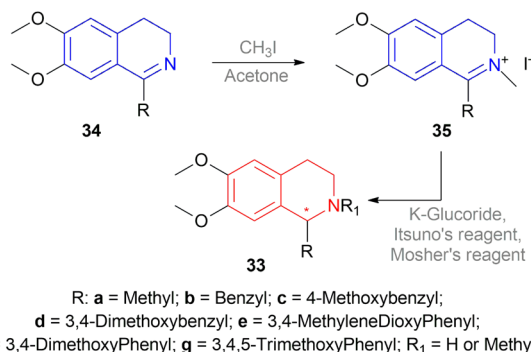
A 2 : 1 mixture of α -pinene **24** and BH_3 can produce another reducing agent, diisopinocampheylborane **25**. For this agent, 75% chemical yield and 85% ee was observed. (2*S*,3*R*)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol or darvon alcohol **26**, β -3-pinanyl-9-borabicyclo[3.3.1]nonane **27**, mono-isopinocampheylborane **28**, and lithium β -isopinocampheyl-9-borabicyclo[3.3.1]nonyl hydride **29** can also be used (Fig. 3).

The advantages of this process are:

- (1). The desired product or isomer has >85–100% ee.
- (2). The racemization of the undesirable product and re-resolution is not needed.

2.1.3 Reduction using K-glucoride, Itsuno's reagent, Mosher's reagent. K-glucoride **30**,²⁴ Itsuno's reagent **31**,^{25,26} and Mosher's reagent **32**²⁷ were previously utilized for asymmetric reduction of various ketones (Fig. 4). This led to Cho and Han to examine these reagents to stereoselectively synthesize 1-substituted-6,7-dimethoxy-THIQs **33** (Scheme 5).²⁸

But they failed to enantioselectively reduce 1-substituted-6,7-dimethoxy-DHIQs **34** to **33** by asymmetric reduction with the above-mentioned chiral hydride reagents. **34a** was reduced very



Scheme 5 Reduction using K-glucoride, Itsuno's reagent, Mosher's reagent.

poorly by **30** with 4 equiv. of excess hydride at room temperature. **31** increased yield with the addition of 1 equiv. AlCl_3 but of low ee of 4.7%.

The authors then converted **34** to their quaternary salt 1-substituted-6,7-dimethoxy-dihydroisoquinolium iodide **35** with excess methyl iodide. This **35** was then readily reduced to **33** (Scheme 5).

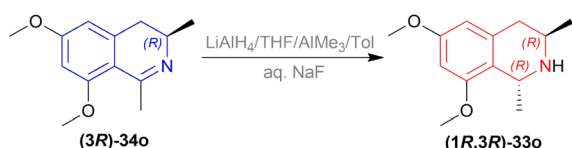
35a in dry CH_2Cl_2 was reduced by 1.1 equiv. **30** in THF at -78°C with 52.3% ee. This reaction condition was also helpful in reducing **35e–35g** with 25.2–43% ee; but not very good for 1-benzyl-6,7-dimethoxy-dihydroisoquinolium iodides **35b–35d**. **31** (in THF at 30°C) reduced **35a–35g** with 5.9–21.1% ee while **32** (in THF at 0°C) reduced **35a** with 66.4% ee, and **35e–35g** with 1.5–16% ee.

To conclude, **30** and **32** provide the best results for the reduction of **35a**; **30** gave better results than those given by **31** and **32** for 1-aryl-6,7-dimethoxy-dihydroisoquinolium iodides (**35e–35g**); no hydrides gave sufficient results for 1-benzyl-6,7-dimethoxy-dihydroisoquinolium iodides (**35b–35d**).

So, **30** mainly gave (*R*)-configured products, **32** mainly gave (*S*)-configured products, and **31** gave (*S*) & (*R*) mix-configured products.

2.1.4 Asymmetric reduction of 6,8-dimethoxy-1,3-dimethyl-DHIQ with $\text{LiAlH}_4/\text{AlMe}_3$. Michellamine A **36a** is active against HIV strains in lymphocytes *in vitro*. Upender *et al.* synthesized two analogs of **36a** which were **36b** and **36c** (Scheme 6) (Fig. 5).²⁹

To produce the THIQ structure, (*3R*)-6,8-dimethoxy-1,3-dimethyl-DHIQ (**3R**)-**34o** was reduced with $\text{LiAlH}_4/\text{AlMe}_3$ to get (*1R,3R*)-6,8-dimethoxy-1,3-dimethyl-THIQ (*1R,3R*)-**33o** of which the chemical yield was 89% (Scheme 6). Here the single (*1R,3R*) diastereomer was obtained due to the presence of the (*R*)-methyl group in position 3.



Scheme 6 Reduction into (*1R,3R*)-6,8-dimethoxy-1,3-dimethyl-THIQ.

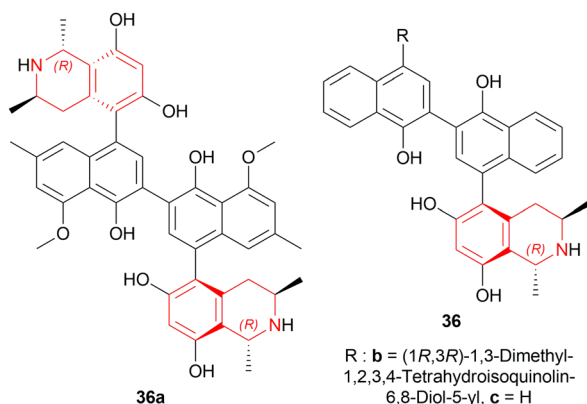
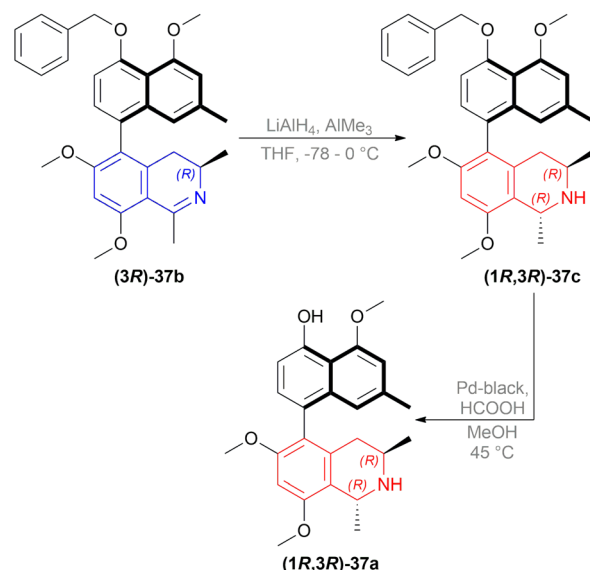


Fig. 5 Michellamine A and its two analogs.

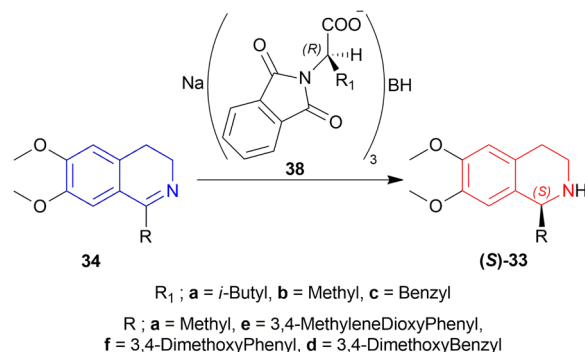


Scheme 7 Synthesis of *O,O*-dimethylkorupensamine A.

2.1.5 Synthesis of *O,O*-dimethylkorupensamine A. Watanabe and Uemura synthesized *O,O*-dimethylkorupensamine A (*1R,3R*)-**37a**.³⁰ In the last two steps of the synthesis, (*3R*)-5-(4-benzyloxy-5-methoxy-7-methylNaphthalen-1-yl)-6,8-dimethoxy-1,3-dimethyl-DHIQ (*3R*)-**37b** was reduced with LiAlH_4 , AlMe_3 in THF to (*1R,3R*)-5-(4-benzyloxy-5-methoxy-7-methylNaphthalen-1-yl)-6,8-dimethoxy-1,3-dimethyl-THIQ (*1R,3R*)-**37c** in 70% chemical yield with 86% ee (Scheme 7). Then, debenzoylation of (*1R,3R*)-**37c** was carried out with Pd-black and HCOOH in MeOH to produce *O,O*-dimethylkorupensamine A (*1R,3R*)-**37a** with 91% yield.

2.1.6 Asymmetric reduction with sodium *N,N*-phthaloylamino acyloxy borohydride. Hajipour and Hantehzadeh described the asymmetric reduction of 1-substituted-6,7-dimethoxy-DHIQs with sodium *N,N*-phthaloylamino acyloxy borohydrides **38** (Scheme 8).³¹

33a, **33d–33f** had ee of 65–75% (chemical yield 76–80%); **33a** having the most (75% ee) and **33e** having the least (65% ee) in the presence of **38a** only. With ZnCl_2 added with **38a**, their ee



Scheme 8 Asymmetric reduction of 1-substituted-6,7-dimethoxy-DHIQs with sodium *N,N*-phthaloylamino acyloxy borohydrides.



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increased to 72–80% (chemical yield 71–80%); **33a** having the most (80% ee) and **33e** having the least (72% ee) as before.

Among **38a–38c**, **38a** had yielded 78% of **33a** with 71% ee in 5 h whereas **38b** and **38c** yielded 82% and 80% of **33a** with 60% and 62% ee in 4 h. So, **38a** was chosen for later reduction.

THF, diethyl ether, DCM, 1,2-dimethoxyethane, and 1,1,2,2-tetrachloroethane were experimented with as solvents. THF had yielded 78% of **33a** with 71% ee in just 5 h reaction time without ZnCl_2 .

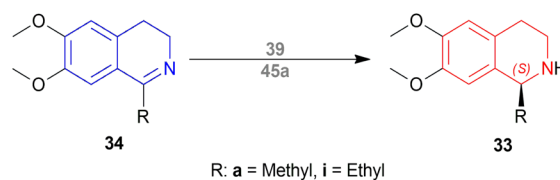
In solid state condition, **33a**, **33d–33f** had ee of 93–100% (chemical yield 80–90%); **33a** had the most (100% ee) in 60 min reaction time and **33e** had the least (93% ee) in 55 min reaction time.

So, **38a** gave (*S*)-configured products.

2.2 Examples of enantioselective reduction of 1-substituted-DHIQs by hydrogenation with the help of a chiral catalyst

2.2.1 Asymmetric hydrogenation (AH) with diphosphine-Ir(i) catalyst and phthalimide co-catalyst. Morimoto and Achiwa examined several co-catalysts for AH of 1-alkyl-6,7-dimethoxy-DHIQs **34** with diphosphine-Ir(i) as a catalyst.³² The ratio of substrate **34** : diphosphine : Ir(i) ligand $[\text{Ir}(\text{COD})\text{Cl}]_2$: co-catalyst was used as 200 : 2.4 : 1 : 4 with 100 atm H_2 . (2*S*,4*S*)-*tert*-butyl 4-(dicyclohexylphosphino)-2-((diphenyl-phosphino)methyl)pyrrolidine-1-carboxylate or (2*S*,4*S*)-BCPM (2*S*,4*S*)-**39**, [[(4*R*,5*R*)-5-bis[[4-methoxy-3,5-dimethylphenyl]-phosphanyl]methyl]-2,2-dimethyl-1,3-dioxolan-4-yl]-(4-methoxy-3,5-dimethylphenyl)-phosphanyl-methyl]-(4-methoxy-3,5-dimethylphenyl)phosphane or (4*R*,5*R*)-MOD-DIOP (4*R*,5*R*)-**40** were the catalysts chosen for the test. Bismuth(III) iodide **41**, tetrabutylammonium iodide **42**, succinimide **43**, hydantoin **44**, phthalimide **45a**, 4-chlorophthalimide **45b**, 4,5-dichloro-phthalimide **45c** and 2,3-naphthalenedicarboximide **46** (Fig. 6) were the co-catalysts used.

With (2*S*,4*S*)-**39**, there was 10–18% ee of **33a** from **34a** (Scheme 9) when no co-catalyst or **41**, **2** was used. But the ee



Scheme 9 Reduction into (*S*)-salsolidine and (*S*)-1-ethyl-6,7-dimethoxy-THIQ.

increased to 43–93% with the use of **43**, **44**, **45a–45c**, and **46**. Less polar solvent and lower reaction temperature were the critical factors to increase enantioselectivity. For this reason, a maximum of 85–93% ee was observed for **45a** co-catalyst in toluene as solvent at 2–5 °C reaction temperature.

With (4*R*,5*R*)-**40**, **45a** in benzene–methanol solvent at –10 °C had 68% ee. So, (2*S*,4*S*)-**39** was chosen as the intended one.

34a and **34i** were reduced with (2*S*,4*S*)-**39** and **45a** to (*S*)-salsolidine (*S*)-**33a** and (*S*)-**33i** with 93% and 79% ee respectively (Scheme 9).

So, (2*S*,4*S*)-**39** catalyst gave rise to (*S*)-configured products, and when the 1-substitution increases in length, % ee decreases.

2.2.2 Asymmetric transfer hydrogenation (ATH) of 1-substituted-DHIQs. Uematsu *et al.* first described the ATH of 1-substituted-DHIQs **34** with the 5 : 2 $\text{HCOOH-Et}_3\text{N}$ azeotrope and catalysts **47** (Fig. 7) (Scheme 10).³³

For screening, 1-methyl-6,7-dimethoxy-DHIQ **34a** (5 mmol) was reduced asymmetrically to (*R*)-salsolidine (*R*)-**33a** (>99% yield, 95% ee) with (1*S*,2*S*)-**47a**, 5 : 2 $\text{HCOOH-Et}_3\text{N}$ azeotrope mixture in ACN at 28 °C, *S/C* = 200 : 1, $\text{HCOOH}/\text{34a}$ = 6 : 1 for 3 h. The same result was found when the catalyst was prepared *in situ* without isolating. Without Et_3N , no (*R*)-**33a** was produced. The authors also showed that the asymmetric reduction was caused by the transfer hydrogen by formic acid,

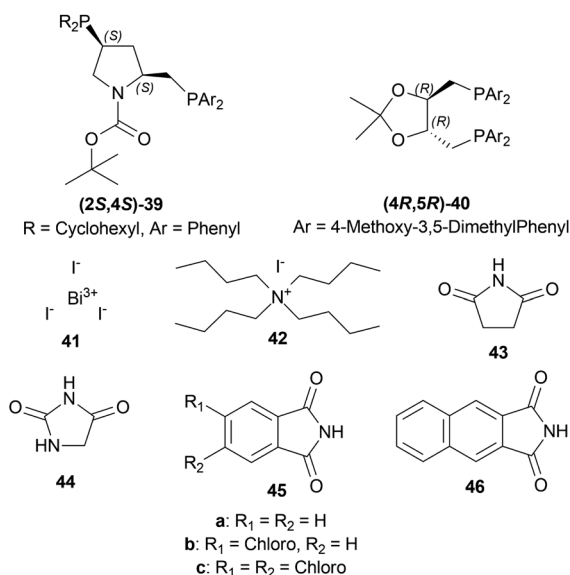


Fig. 6 (2*S*,4*S*)-BCPM, (4*R*,5*R*)-MOD-DIOP and the co-catalysts.

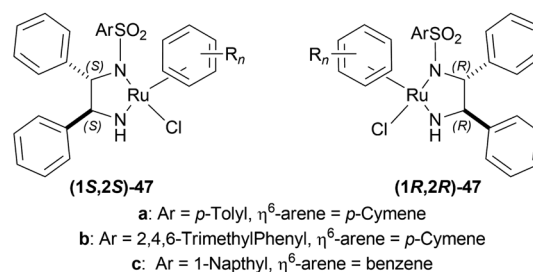
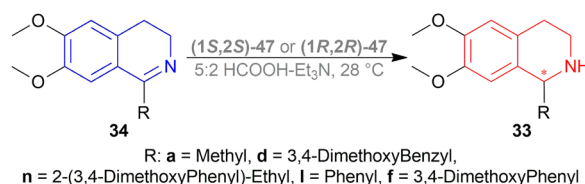
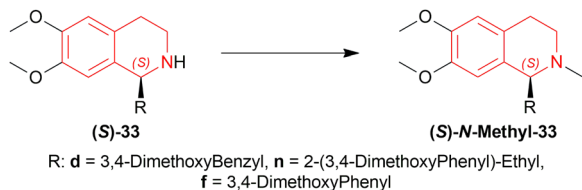


Fig. 7 Ru(II) catalysts for ATH of 1-substituted-DHIQs.



Scheme 10 ATH of 1-substituted-DHIQs.





Scheme 11 Synthesis of (S)-laudanosine, (S)-homolaudanosine, and (S)-cryptostyline II.

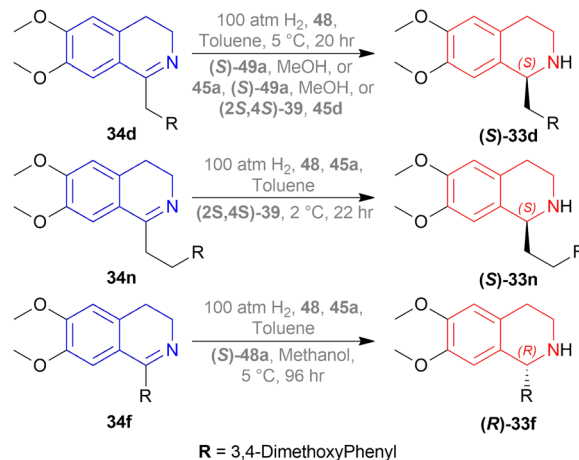
no molecular H_2 interferes here. The above reaction is done under a 600 atm D_2 atmosphere (where $D_2:HCOOH = 24:1$) gave (R)-33a (>99% yield, 93% ee) without D_2 incorporated into the C1 position. Again, 2-propanol-2-d with $HCOOH$ or CH_3COOH showed that 2-propanol (IPA) can not be used as a hydrogen source.

Then increasing S/C of **34a**/(1*S*,2*S*)-**47a** to 1000:1 in a 20 mmol scale reaction produced 97% yield and 94% ee of (R)-33a in 12 h in ACN. **34d** and **34n** with (1*R*,2*R*)-**47b** ($S/C = 200:1$) in *N,N*-dimethylformamide (DMF), and DCM afforded 90% and 99% yield; 95% and 92% ee of (S)-33b and (S)-33c in 7 and 12 h respectively. **34l** with (1*S*,2*S*)-**47c** ($S/C = 200:1$) in DCM had 99% yield and 84% ee of (R)-33d in 8 h **34f** with (1*R*,2*R*)-**47c** ($S/C = 100:1$) in DCM gained >99% yield and 84% ee of (S)-33e in 12 h (Scheme 10).

So, (S)-configured **47** catalysts afforded (R)-configured products and (R)-configured **47** catalysts afforded (S)-configured products in good % ee.

N-methylation of (S)-33d, (S)-33n, and (S)-33f can result in naturally occurring (S)-*N*-methyl-33d (S)-laudanosine, (S)-*N*-methyl-33n (S)-homolaudanosine, and (S)-*N*-methyl-33f (S)-cryptostyline II, respectively (Scheme 11).

2.2.3 Production of (S)-norlaudanosine, (S)-tetrahydrohomopapaverine, and (R)-norcryptostyline II by catalytic asymmetric hydrogenation. Morimoto *et al.* hydrogenated **34d**, **34n**, and **34f** catalytically with different chiral diphosphine-Ir(I)-phthalimide complex catalysts to produce (S)-norlaudanosine (S)-33d, (S)-tetrahydroHomoPapaverine (S)-33n and (R)-norcryptostyline II (R)-33f.³⁴ Chloro(1,5-cyclooctadiene)iridium(I) dimer or $[Ir(COD)Cl]_2$ **48**, (S)-2,2'-



Scheme 12 Reduction into (S)-norlaudanosine, (S)-tetrahydrohomopapaverine, and (R)-norcryptostyline II.

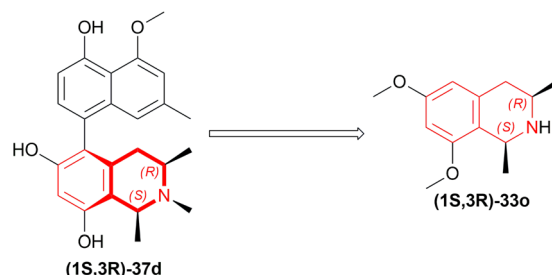


Fig. 9 Korupensamine D and its precursor.

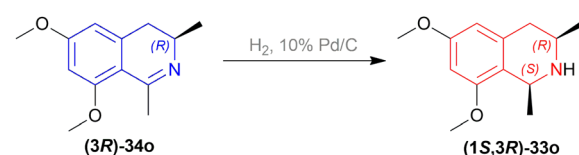
bis(diphenylphosphino)-1,1'-binaphthyl or (S)-BINAP (S)-**49a**, (2*S*,4*S*)-BCPM (2*S*,4*S*)-**39**, phthalimide **45a**, and 3,4,5,6-tetrafluorophthalimide **45d** (Fig. 8) were used in this experiment.

When reducing **34d** to (S)-33d, **48**, (S)-**49a** with methanol (MeOH) had a low conversion of 18% and 35% ee. But when **45a** was added to **48**, (S)-**49a**, and MeOH, conversion rose to 67% with 84% ee. Also **48**, **49** with **45d** had the highest conversion of 84% and 88% ee.

With **48**, **49**, and **45a**, reducing **34n** gave (S)-33n up to 75% conversion and 87% ee, though **48**, **45a**, and (S)-**49a** with MeOH reduced **34f** to (R)-33f with 50% conversion and 31% ee (Scheme 12).

So, (2*S*,4*S*)-**39** and (S)-**49** catalysts gave rise to (S)-configured products, but when the 1-substitution increases steric hindrance, (R)-configured product is found.

2.2.4 Asymmetric reduction of 6,8-dimethoxy-1,3-dimethyl-DHIQ with Pd/C. Hoyer and Chen carried out a total synthesis of Korupensamine D (1*S*,3*R*)-**37d** (Fig. 9) for the very first time.³⁵



Scheme 13 Reduction of (3*R*)-6,8-dimethoxy-1,3-dimethyl-DHIQ.

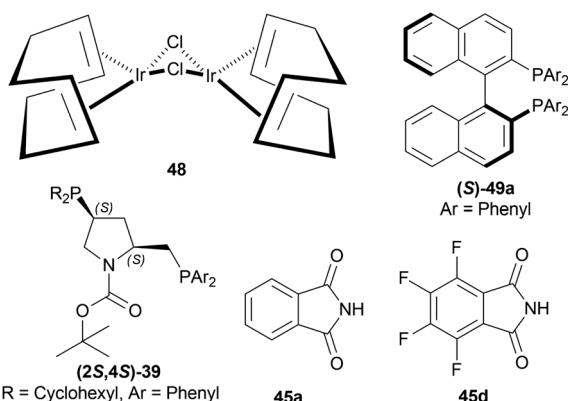
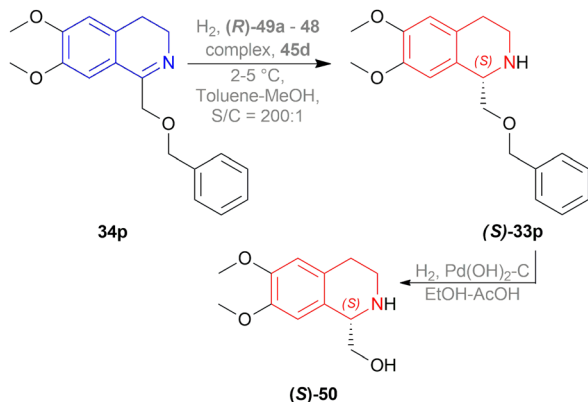
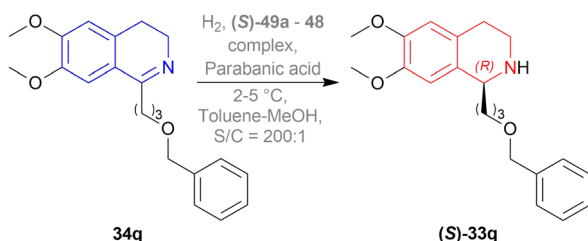


Fig. 8 $[Ir(COD)Cl]_2$, (S)-BINAP, (2*S*,4*S*)-BCPM, phthalimide, and 3,4,5,6-tetrafluorophthalimide.





Scheme 14 Synthesis of (S)-calycotomine.



Scheme 15 Reduction into 1-[3-(benzyloxy)propyl]-6,7-dimethoxy-THIQ.

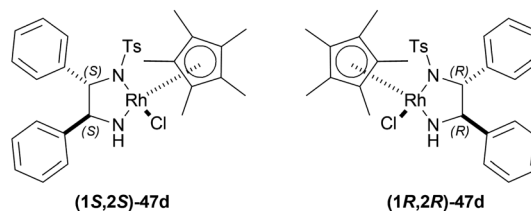
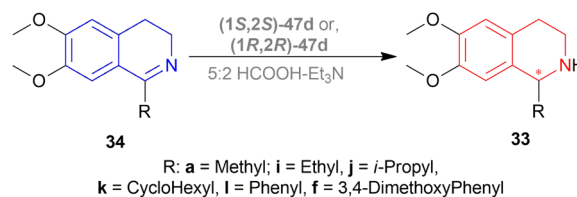
In the fifth step of this synthesis, they reduced (3*R*)-6,8-dimethoxy-1,3-dimethyl-DHIQ (3*R*)-33*o* to optically pure (1*S*,3*R*)-6,8-dimethoxy-1,3-dimethyl-THIQ (1*S*,3*R*)-32*o* with H₂, 10% Pd/C and had 93% conversion (Scheme 13).

2.2.5 Synthesis of (S)-calycotomine via AH. (S)-calycotomine (S)-50 is a naturally occurring alkaloid. To synthesize (S)-50, Morimoto *et al.* reduced 1-benzyloxymethyl-6,7-dimethoxy-DHIQ 34*p* by AH to (S)-1-benzyloxymethyl-6,7-dimethoxy-THIQ (S)-33*p* (85% yield and 86% ee) with 100 atm H₂, 0.5 mol% (R)-49*a*-48 complex, 1 mol% 45*d* (Fig. 8) in toluene-methanol (Scheme 14).³⁶ If 45*a* (Fig. 8) was used as an additive, lower enantioselectivity (75% ee) was observed. Then, hydrogenolysis of the benzyloxy group of (S)-33*p* was carried out by 1 atm H₂, Pd(OH)₂ catalyst in a 10 : 1 mixture of ethanol-acetic acid to yield 93% of (S)-50 with 86% ee.

They also hydrogenated 1-[3-(benzyloxy)propyl]-6,7-dimethoxy-DHIQ 33*q* under the above-mentioned asymmetric hydrogenation process to yield 99% of 1-[3-(benzyloxy)propyl]-6,7-dimethoxy-THIQ (S)-32*q* using (S)-49*a*-48 complex (Fig. 8) and parabanic acid (Scheme 15). The product (S)-33*q* was obtained in 89% ee.

So, (R)-49*a* catalyst gave rise to (S)-configured product when the benzyloxy part was closer to the 1-substitution, and (S)-49*a* catalyst gave rise to (S)-configured product when the benzyloxy part was far away from the 1-substitution.

2.2.6 Asymmetric transfer hydrogenation (ATH) by chiral rhodium complexes. Mao and Baker catalysed 1-substituted-6,7-dimethoxy-DHIQs 34 to 1-substituted-6,7-dimethoxy-THIQs 33

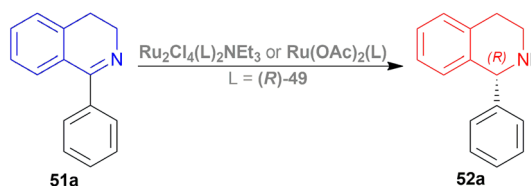
Fig. 10 (1*S*,2*S*)-Cp*RhClTsDPEN and (1*R*,2*R*)-Cp*RhClTsDPEN.Scheme 16 Reduction with (1*S*,2*S*)-Cp*RhClTsDPEN and (1*R*,2*R*)-Cp*RhClTsDPEN.

by ATH with the help of (1*S*,2*S*)-Cp*RhClTsDPEN (1*S*,2*S*)-47*d*, a chiral rhodium complex and its enantiomer (1*R*,2*R*)-Cp*RhClTsDPEN (1*R*,2*R*)-47*d* (Fig. 10).³⁷ As the hydrogen source, 5 : 2 HCOOH-Et₃N azeotrope was used. ATH is advantageous over other reduction processes because it does not require the use of H₂ (g).

At first, 34*j* was catalyzed with (1*S*,2*S*)-47*d* along with substrate/catalyst (*S/C*) molar ratio of 200 : 1, 5 : 2 HCOOH-NEt₃ azeotrope, 20 °C temperature, DCM as solvent (Scheme 16). After 10 minutes, (R)-33*j* was found with 99% ee. But with an *S/C* molar ratio of 1000 : 1, ee reached 93% after 60 minutes. The use of acetonitrile (ACN) as solvent produced a slightly higher ee of 95% at *S/C* of 1000 : 1 after 60 minutes.

34*a* was hydrogenated using (1*S*,2*S*)-47*d*, ACN as solvent to produce (R)-33*a* in 89% ee; (S)-33*a* was produced in 90% ee with (1*R*,2*R*)-47*d*, DCM as solvent in a *S/C* molar ratio of 200 : 1 after 10 minutes of reaction. 34*i* was catalyzed using (1*S*,2*S*)-47*d* with dropped 83% ee of the product (R)-33*i*, while 34*k* was catalyzed using the same catalyst with an increased 97% ee of the product (R)-33*k*. These showed that the ee stayed within a good range because the substituted alkyl group, R, increased in steric bulk on the imine carbon of 34.

But when aryl groups were introduced, such as in 34*l* and 34*f*, they blocked the catalyst (1*S*,2*S*)-47*d* to bind and as a result, ee dropped dramatically {4.4% and 3.2% respectively for (R)-33*l* and (R)-33*f*, even after 180 minutes}. Here, the second aromatic ring system intervenes with the selective catalyst binding.



Scheme 17 Synthesis of 1-phenyl-THIQ.



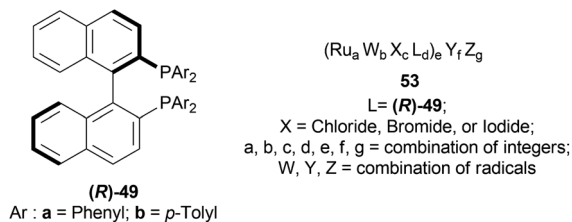


Fig. 11 (R) -BINAP, (R) -T-BINAP, and the ruthenium-optically active phosphine complex.

So, $(1S,2S)\text{-}47d$ catalyst gave rise to (R) -configured products, and $(1R,2R)\text{-}47d$ catalyst gave rise to (S) -configured products.

2.2.7 AH by ruthenium-optically active phosphine complex. Kuriyama *et al.* described the process of converting 1-phenyl-DHIQ **51a** to 1-phenyl-THIQ **52a** by AH (Scheme 17).³⁸ It is done in presence of a ruthenium-optically active phosphine complex derived from an optically active phosphine.

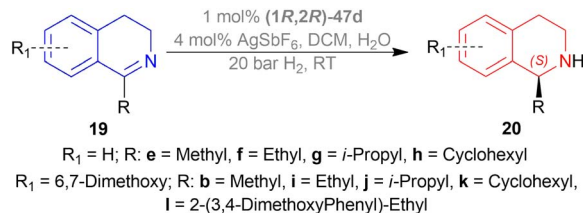
The optically active phosphines are (R) -BINAP $(R)\text{-}49a$, and (R) -T-BINAP $(R)\text{-}49b$ (Fig. 11). The ruthenium-optically active phosphine complex has the general formula of **53** *e.g.*, $Ru_2Cl_4(L)_2NEt_3$, $Ru(OAc)_2(L)$, *etc.* Here, L is the optically active phosphines $(R)\text{-}49$ (Fig. 11).

There are 4 examples of the invention described in this patent which had a conversion rate of 56.9–91.4% and ee of 59.7–88.9%. Example 1 had the highest ee of 88.9% with the lowest conversion of 56.9% for the product $(R)\text{-}52a$. $Ru_2Cl_4\{(R)\text{-}T\text{-}BINAP\}_2NEt_3$ and **51a** were used in approximately 1 : 400 molar ratio. Toluene was added after N_2 purge, stirred for 15 h at 90 °C, and 6 MPa H_2 pressure after H_2 purge. Example 2 showed 59.7% ee and 89.3% conversion of $(R)\text{-}52a$. $Ru_2Cl_4\{(R)\text{-}T\text{-}BINAP\}_2NEt_3$ and HCl salt of **51a** was used in approximately 1 : 400 molar ratio. MeOH was added after N_2 purge, stirred for 19 h at 90 °C, and 3 MPa H_2 pressure after H_2 purge, toluene and 1 M NaOH (aq) solution were added, and stirred.

Example 3 had 66.7% ee with 91.4% conversion of $(R)\text{-}52a$. $Ru_2Cl_4\{(R)\text{-}BINAP\}_2NEt_3$ and **51a** were used in approximately 1 : 1000 molar ratio. Toluene and formic acid were added after N_2 purge, stirred for 15 h at 90 °C, and 3 MPa H_2 pressure after H_2 purge, toluene and 1 M NaOH (aq) solution were added and stirred. And, example 4 showed 65.4% ee and 83.1% conversion of $(R)\text{-}52a$. $Ru(OAc)_2\{(R)\text{-}BINAP\}$ and HCl salt of **51a** were used in approximately 1 : 200 molar ratio. MeOH and methyl salicylate were added after N_2 purge, stirred for 19 h at 90 °C and 3 MPa H_2 pressure after H_2 purge, toluene and 1 M NaOH (aq) solution was added and stirred.

So $(R)\text{-}49a$ catalyst, used as phosphine in a ruthenium-optically active phosphine complex, gave rise to (R) -configured products. The addition of toluene and 1 M NaOH (aq) solution to the reaction mixture and stirring at the last step, increased the conversion rate of the product but decreased the % ee.

2.2.8 AH with ionic $Cp^*Rh(III)$ catalyst. Li *et al.* hydrogenated 1-alkyl-DHIQs **19b**, **19e–19l** with 50 bar H_2 in the presence of 1 mol% $(1R,2R)\text{-}47d$ (Fig. 10), 4 mol% $AgSbF_6$ in DCM with water (Scheme 18).³⁹



Scheme 18 AH with ionic $Cp^*Rh(III)$ catalyst.

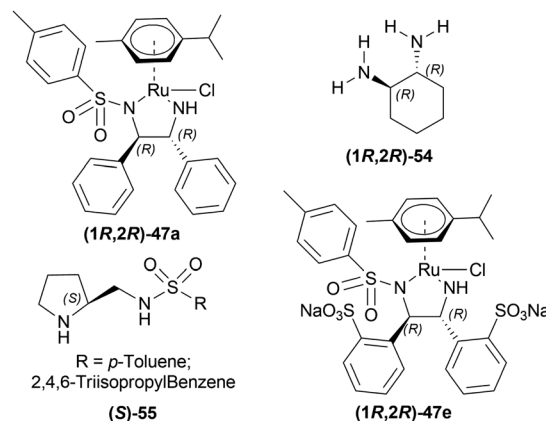


Fig. 12 Catalysts for AH in aqueous media.

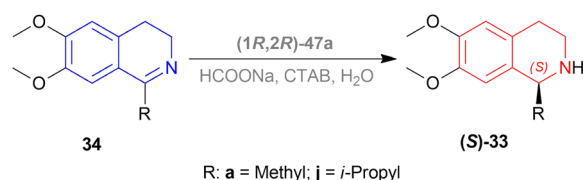
$(S)\text{-}20e\text{--}(S)\text{-}20h$ had 90–95% yield but, as the bulkier group were introduced in the 1-position, % ee decreased and reaction time increased. When IPA was used instead of DCM, % ee of $(S)\text{-}20g$ and $(S)\text{-}20h$ increased to 83–91%.

$(S)\text{-}20b$, $(S)\text{-}20i\text{--}(S)\text{-}20l$ had 90–95% yield and 93–99% ee. So, not only the steric hindrance but also the electron availability are the critical factors.

So, $(1R,2R)\text{-}47d$ produced (S) -configured products.

2.2.9 AH in aqueous media with Noyori type catalysts. Canivet *et al.*, Canivet and Süß-Fink previously reported the use of a catalyst based on $(1R,2R)\text{-}1,2\text{-diaminocyclohexane}$ $(1R,2R)\text{-}54$ ⁴⁰ and $(S)\text{-(sulfonylamino)methylpyrrolidines}$ $(S)\text{-}55$ ⁴¹ chiral ligands for reactions in aqueous solution. Ma *et al.*, and Wu *et al.* have also used $(1R,2R)\text{-}47e$, a sulfonated variant of $(1R,2R)\text{-}47a$ (Fig. 12).^{42,43}

Evanno *et al.* reported asymmetric hydrogen-transfer reductions of 1-substituted-6,7-dimethoxy-DHIQs **34** (Scheme 19) with sodium formate (aq) as hydride source and or cetyltrimethylammonium bromide ($CH_3\text{--}(CH_2)_{15}\text{--}N^+(CH_3)_3Br^-$, CTAB) as cationic surfactant.⁴⁴ Using $(1R,2R)\text{-}47a$, they obtained



Scheme 19 Reduction with sodium formate (aq) solution and CTAB.



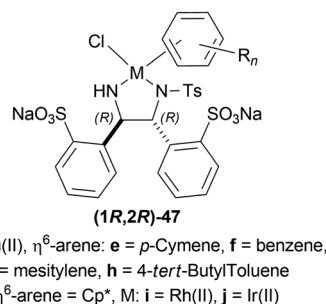
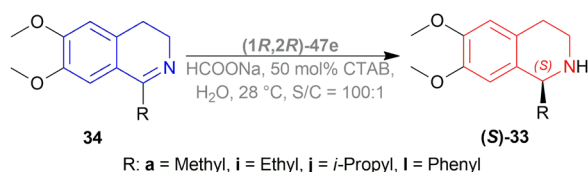


Fig. 13 Metal complexes of *O,O'*-disulfonated *N*-tosyl-1,2-diphenylethylene diamine.



Scheme 20 Reduction of 1-substituted-6,7-dimethoxy-DHIQs.

the products (*S*)-33a and (*S*)-33j in excellent ee (99% at 25 °C and 99.5% at 40 °C respectively) (Scheme 19).

So, (1R,2R)-47a catalyst gave rise to (*S*)-configured products.

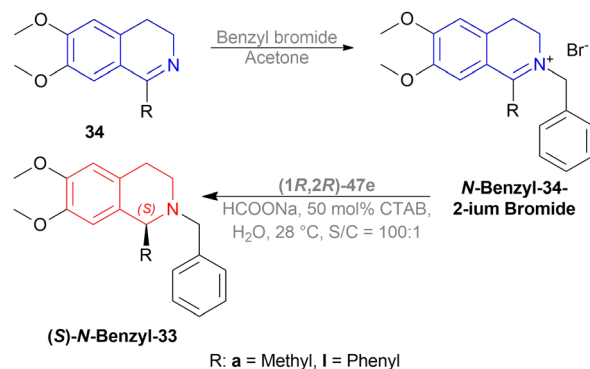
2.2.10 ATH in water. Wu *et al.* described ATH of 1-substituted-6,7-dimethoxy-DHIQs **34** in water with the help of metal complexes of *O,O'*-disulfonated *N*-tosyl-1,2-diphenylethylene diamine (1R,2R)-47 (Fig. 13).⁴³

When no surfactant was used with (1R,2R)-47e and S/C = 100 : 1 for 10 h of reaction time at 28 °C, 89% yield was found for (*S*)-33a from **34a** (90% ee). Adding 50 mol% of sodium dodecyl sulfate (SDS), poly(ethylene glycol) mono [4-(1,1,3,3-tetramethylbutylphenyl) ether] (triton X-100), cetylpyridium bromide (CPB), 3-(*N,N*-dimethyldodecylammonio)propane-sulfonate (DDAPS), or tetrabutylammonium bromide (TBAB) did not improve % ee. But with CTAB, the yield was 97% with 95% ee. Increasing or decreasing the mol% of CTAB, and increasing the reaction temperature also did not improve the % ee. Other complexes like (1R,2R)-47f-(1R,2R)-47j had similar results but the reaction time was 20–48 h. So, (1R,2R)-47e with 50 mol% CTAB was chosen. Then, **34i** and **34j** were reduced with the optimum conditions for 25 h and their yield was 68% (92% ee) and 90% (90% ee) respectively (Scheme 20). But **34l** did not react even after 72 h.

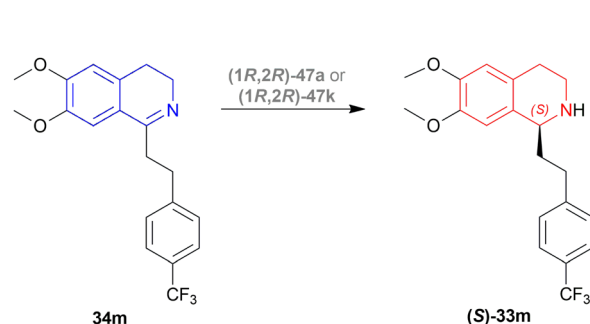
The authors then benzylated **34a** and **34l** with benzyl bromide in acetone to produce 1-substituted-2-benzyl-6,7-dimethoxy-3,4-dihydroisoquinolin-2-ium bromides. These were reduced readily with the optimum conditions to yield 86% (*S*)-*N*-benzyl-33a (90% ee) and 94% (*S*)-*N*-benzyl-33l (95% ee) (Scheme 21).

So, (1R,2R)-47e catalyst gave rise to (*S*)-configured products.

2.2.11 ATH with ruthenium catalyst. Rádl *et al.* described the process of ATH of 6,7-dimethoxy-1-[2-(4-trifluoromethylphenyl)ethyl]-DHIQ **34m** to produce (*S*)-6,7-



Scheme 21 Synthesis of 1-substituted-2-benzyl-6,7-dimethoxy-DHIQs.



Scheme 22 Production of (*S*)-6,7-dimethoxy-1-[2-(4-trifluoromethylphenyl)ethyl]-THIQ.

dimethoxy-1-[2-(4-trifluoromethylphenyl)ethyl]-THIQ (*S*)-33m (Scheme 22) along with (1R,2R)-47 as catalysts (Fig. 14).⁴⁵

There were 10 examples of this process of hydrogenation in which **34m** was reduced to (*S*)-33m with 59–100% ee and 52–88% conversion. Only example no. 2, 4, 6, and 9 had more than 80% conversion and 99.4–100% ee (Scheme 22).

Example 2 had a 4 : 3 mix of HCOOH and TEA with (1R,2R)-47a directly added, the mixture was stirred in N₂ at 30 °C for 3 hours. With 7.5 mmol of **33m** in 30 mL dimethylfumarate, the mixture was evaporated and evaporation residue dissolved in 30 mL of DCM, washed with NaHCO₃, water, and brine saturated solution, then dried with MgSO₄, and solvent was evaporated, the residue dissolved in IPA and ethanolic solution of HCl (5 M, 3 mL) dropwise under intensive stirring, the solvent was

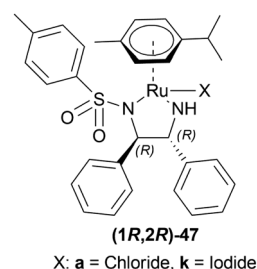


Fig. 14 Ruthenium catalysts for ATH of 6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)ethyl]-DHIQ.

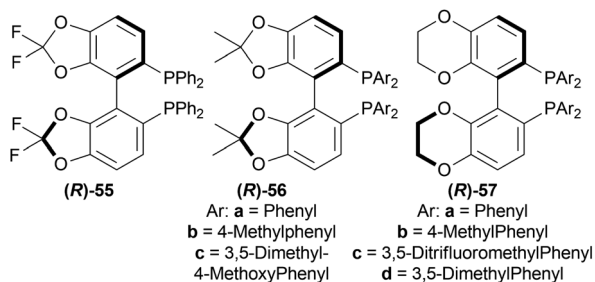


Fig. 15 Difluorophos ligand, sunphos ligands, and synphos ligands.

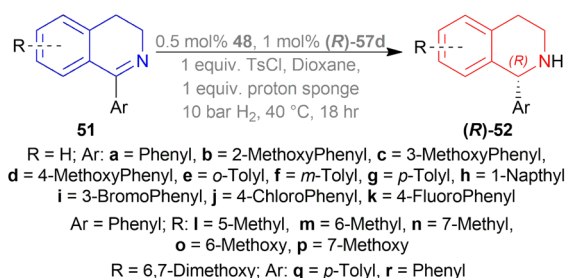
evaporated, then the residue was crystallized out of an IPA/MeOH mixture. 83% conversion with 99.6% ee was found for this example.

In the case of example no. 4 and 9, (1*R*,2*R*)-47a was prepared *in situ*, and TEA solution in ACN by stirring at 80 °C for 1 h 4 : 3 mix of HCOOH and TEA was added with 33m in dimethylfumarate, and dimethylfumarate with TEA respectively; stirred at 35 °C in N₂ for 3 hours. In example 4, the reaction mixture was evaporated, the residue dissolved in 250 mL ethyl acetate, and the rest of the process was the same as in example no. 2 with 88% conversion and 99.8% ee. While, example 9 reaction mixture was poured into water, extracted 3 times with ethyl acetate, washed 3 times with brine, dried with MgSO₄, dropwise addition of HCl (g) in ethanol, stirred for 30 min, then the solid is sucked off, washed with ethyl acetate, dried, recrystallized out of an IPA/MeOH mixture. 86% conversion with 100% ee was found for this example. We think that example 9 is the best process for ATH of 34m to (S)-33m.

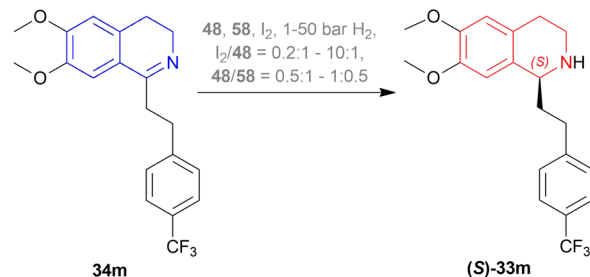
In example 6, (1*R*,2*R*)-47k (Fig. 14) was prepared *in situ*, THF was solvent of 34m, the mixture was stirred at 40 °C in N₂ for 6 h, and the rest of the process was the same as example 2 with 82% conversion and 99.4% ee.

So, (1*R*,2*R*)-47a and (1*R*,2*R*)-47k catalysts gave rise to (S)-configured products.

2.2.12 AH with synphos ligand and iridium catalyst. Berhal *et al.* experimented with 1 mol% difluorophos ligand (R)-55, sunphos ligands (R)-56a-(R)-56c, and synphos ligands (R)-57a-(R)-57d (Fig. 15) in THF along with 0.5 mol% 48 (Fig. 8), 30 bar H₂ for 18 h at 40 °C for AH of 1-phenyl-DHIQ 51a to (R)-1-phenyl-THIQ (R)-52a (Scheme 23).⁴⁶ Among the ligands, 55 and (R)-56a-(R)-56c gave moderate ee of 35–39%; (R)-57a-(R)-57d improved ee to 46, 42, 69, and 71% respectively. So, (R)-3,5-diMe-synphos (R)-57d was selected as the ligand.



Scheme 23 Generation of (R)-1-aryl-THIQs.



Scheme 24 AH of 6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)ethyl]-DHIQ.

Dioxane was chosen as solvent as it maximized chemical yield to 95% and optical yield ee to 73%. 1 equivalent tosyl chloride was successful in increasing ee to 92% as an additive but a side product was formed which was nullified by using 1 equivalent proton sponge as a base. Using 10 bar H₂ gave the highest yield of 95% and ee of 94%.

Lastly, 1-aryl-DHIQs 51a–51r were hydrogenated with the above conditions to produce (R)-1-aryl-THIQs (R)-52a-(R)-52r in good yields and the ee varied from 81–94% (Scheme 23). This variation was due to substitution in the aromatic rings. (R)-52b, (R)-52e, and (R)-52h (*ortho*-substituted in the 1-phenyl ring) had 83, 80 and 82% ee respectively compared to (R)-52a (94% ee) because of steric hindrance.

(R)-52i-(R)-52k (bearing electron-withdrawing group in the 1-phenyl ring) had 82, 81, and 84% ee respectively; while (R)-52d, (R)-52f, (R)-52g (bearing electron-donating group in the 1-phenyl ring) had 90% ee each. Methyl substitution in the 5, 6, or 7 position of the THIQs had lower ee (84, 84, and 88% for (R)-52l – (R)-52n respectively) than one or two methoxy substitution in the 6, or/and 7 position of the THIQs (88, 89, 88, and 92% ee for (R)-52o-(R)-52r respectively). Even after single crystallization, the ee can be enhanced to 90–99%.

So, (R)-55, (R)-56, and (R)-57 catalysts gave rise to (R)-configured products.

2.2.13 AH with taniaphos ligand and iridium catalyst. Bappert *et al.* stated 3 methods of hydrogenation of (S)-33m from 34m (Scheme 24) with taniaphos ligand 58 (Fig. 16),⁴⁷ 48 (Fig. 8), I₂, 1–50 bar H₂.⁴⁸ I₂/48 is needed in between 0.2 : 1 and 10 : 1, and the ratio of 48/58 is in between 0.5 : 1 and 1 : 0.5 (Scheme 24).

The first method involved 58 adding to a solution of 48 in DCM at 20 °C, and a solution of I₂ in DCM is added to it until

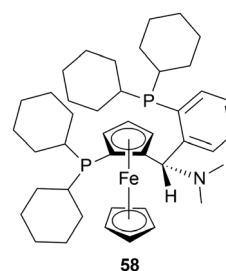


Fig. 16 Taniaphos ligand.



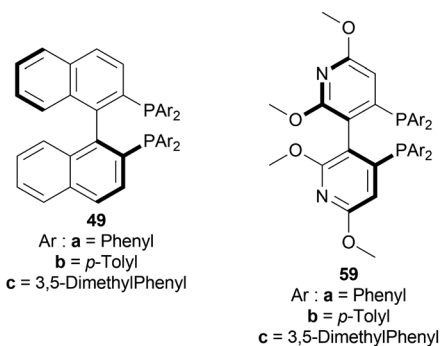


Fig. 17 BINAP and P-phos moieties.

dissolved. Then **34m** is added to this at 5 bar H_2 . $I_2/48$ ratio of 1 : 1 and S/C ratio of 20 : 1 had a full conversion and 89% ee. When the S/C ratio was increased to ten folds, both conversion and ee decreased. $I_2/48$ ratio of 2 produced 100% conversion with the highest 95% ee whether the S/C ratio is 20 : 1 or 200 : 1. But the $I_2/48$ ratio of 4 : 1 decreased ee to 92% when the S/C ratio is 20 : 1 and ee was further decreased when S/C ratio is 200 : 1.

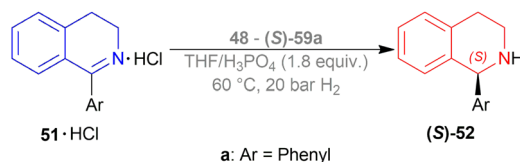
The second method had DCM and MeOH mixed instead of DCM only. 4 : 1 mix of toluene and heptane, only toluene as a solvent for **34m** was experimented with of which both had 98% conversion and 99% ee of (*S*)-**33m** after work-up.

The third method required mixing of **58** and **48** put under 4 cycles of high vacuum (1–2 mbar) and argon (1 bar). The mix is kept under argon, degassed MeOH is added, stirred at 25 °C (RT) for 3 h, solid I_2 is added, stirred again for 30 min. Under 1 mbar and RT, solvent is removed and dried for 30 min. DCE is added next under argon, solution of **34m** is added to the intended solvent, mixed with the above-prepared solution at 5 bar H_2 . When 24 mL of 9 : 2 : 1 toluene : THF : DCE solvent system was used to react 7.5 mmol of **34m** at RT, $I_2/48$ ratio of 3 : 1, S/C ratio of 1000 : 1, and the catalyst stirred with MeOH for 1 h; 100% conversion with the highest ee of 97% was found. But when the catalyst was stirred with MeOH for 3 h, no reaction had full conversion except when the catalyst was stored one day after its preparation before being used. In that case, 91 mL of the same ratio of the solvent system was used to react with 38 mmol of **34m** at 16 °C with the same $I_2/48$ ratio and increased S/C ratio of 2500. But the ee was reduced to 95.2%. Both the reaction took almost the same time (30 and 29 min). Also, when 119 mL of 13 : 4 : 1 toluene : THF : DCE solvent system was used to react 38 mmol of **34m** at 16 °C with the same $I_2/48$ ratio, stirred for 3 h, S/C ratio of 3000; 98.8% conversion with 95% ee was found after 60 min of reaction time.

There are some technical advantages of this process, compared to the previously known processes-

(1) For the AH of **34m**, various chiral catalysts have been tested. It has been found that only the taniaphos catalyst **58** shows a surprisingly high ee of 92–95%; not even the Noyori transfer hydrogenation catalyst.

(2) This novel process of AH does not need the separation of enantiomers through diastereomeric salt formation. And so, the

Scheme 25 AH with $[Ir(COD)Cl]_2$ and (*S*)-P-phos.

error of recycling the other enantiomer does not occur, which is disadvantageous of the racemic resolution.

(3) Large-scale production shows that the taniaphos catalyst **58** shows a more stable ee in the AH as compared to the Noyori transfer hydrogenation catalyst.

So, **58** catalyst gave rise to (*S*)-configured product.

2.2.14 AH with P-phos ligands and BINAP catalysts. Ružič *et al.* tested various BINAP **49** and P-phos **59** moieties (Fig. 17) in DCE (with S/C of 43 : 1, 50 °C, 30 bar H_2 , 3 h) for screening phosphine ligands with $[Ir(COD)Cl]_2$ **48** (Fig. 8) to reduce HCl salt of **51a** to (*S*)-**52a** (Scheme 25).⁴⁹ Among them (*S*)-BINAP (*S*)-**49a**, (*R*)-Tol-BINAP (*R*)-**49b**, (*R*)-Xyl-BINAP (*R*)-**49c**, (*R*)-P-phos (*R*)-**59a**, (*S*)-tol-P-phos (*S*)-**59b**, (*R*)-xyl-P-phos (*R*)-**59c** showed good yields (86–98%) but only (*R*)-**59a** and (*S*)-**59b** had excellent ee (84% and 78% respectively).

To choose additives, **48** and **49** catalysts in THF (with S/C of 43 : 1, 50 °C, 30 bar H_2 , 3 h) were experimented with. 0.2 equiv. NaI, 0.2 equiv. MgI_2 , 0.2 equiv. BuN_4Br had 82–92% yield but low ee (46–62%). Different amounts of H_3PO_4 such as 1.2 equiv. (anhydrous), 1.2 equiv. (aq, 85% w/w in water), 2.4 equiv. (anhydrous), 2.4 equiv. (anhydrous) with 0.1 equiv. Potassium iodide (KI) showed full conversion (>97% yield) and ee (82–94%). 12 equiv. CH_3COOH and 1.2 equiv. (*R*)-1,1-binaphthyl-2,2-diyl hydrogen phosphate also yielded high results (89% and >97% respectively) and ee (78% and 96% respectively).

More tests were done for fine tuning S/C , temperature, and H_2 pressure. The use of **48** – (*S*)-**59a** in THF/ H_3PO_4 was preferred over other combinations in terms of high % ee values (Scheme 25). Increasing S/C from 340 : 1 at 50 °C to 425 : 1 at 60 °C increased yield from 97% to full conversion (>97% yield) with the same 95% ee at 30 bar H_2 . And lower reaction pressure reduced yield values. So ultimately, S/C was increased to 850 : 1 and 1275 : 1 at increased reaction temperatures (60 °C), increased reaction pressure (20 bar H_2), and longer reaction times (72 h) for optimal results.

So, (*S*)-**59a** catalyst gave rise to (*S*)-configured product.

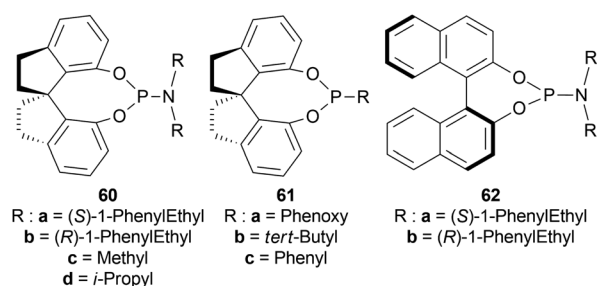
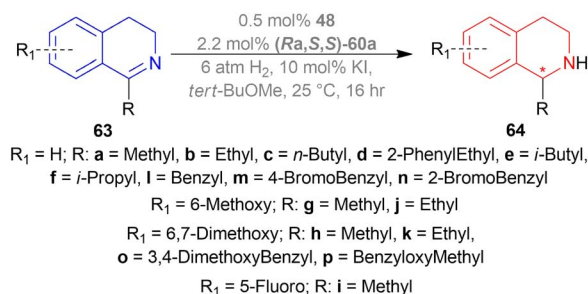


Fig. 18 Various chiral spiro iridium phosphoramidite complexes.





Scheme 26 AH with chiral spiro iridium phosphoramidite complex.

2.2.15 AH by chiral spiro iridium phosphoramidite complex. Xie *et al.* chose different chiral ligands *e.g.* (*Ra,S,S*)-**60a**, (*Ra,R,R*)-**60b**, (*R*)-**60c**, (*R*)-**60d**, (*R*)-**61a**, (*R*)-**61b**, (*R*)-**61c**, (*Sa,S,S*)-**62a**, (*Sa,R,R*)-**62b** (Fig. 18) for screening to optimally reduce **63a** to (*S*)-**64a** (Scheme 26).⁵⁰

Among the spiro phosphoramidites **60**, (*Ra,S,S*)-**60a** was the best ligand with 100% conversion and 91% ee of (*S*)-**64a** with THF as the solvent, I_2 as an additive, and 50 atm H_2 pressure. Et_2O and *tert*-BuOMe solvent provided 100% conversion with 99% ee. With *tert*-BuOMe, H_2 pressure can be reduced to 20 atm without losing conversion or ee. When I_2 was taken away, only 9% conversion occurred. Lithium iodide and KI as additives also showed 99% ee with 100% conversion. With KI, H_2 pressure can be reduced to 6 atm without losing conversion or ee.

The spiro phosphite (*R*)-**61a** and the spiro phosphonites (*R*)-**61b**, (*R*)-**61c** had shown good conversion (90–100%) but not very good ee (16–77%). (*Sa,S,S*)-**62a** and (*Sa,R,R*)-**62b** ligands also showed 95% conversion with 87% ee of (*S*)-**64a** and 22% conversion with 82% ee of (*R*)-**64a** respectively. (*Ra,S,S*)-**60a** was chosen for later tests.

Under the optimal conditions, (*S*)-**64a**–(*S*)-**64o**, (*R*)-**64p** were hydrogenated from various 1-substituted-DHIQs **63a**–**63p** (Scheme 26). When the substituted part increased in bulk, ee decreased for (*S*)-**64a**–(*S*)-**64f** even after H_2 pressure and/or reaction time increased. Substitution on the benzene ring (with electron-donating two methoxy groups in (*S*)-**64h** and (*S*)-**64k**, or an electron-withdrawing fluoride in (*S*)-**64i**) of THIQs decreased ee (91–94%) with 93–96% conversion. 1-Benzyl-DHIQs **63l**–**63o** were hydrogenated to (*S*)-**64l** – (*S*)-**64o** with high ee (96–97%) and 88–96% conversion. 1-Benzyloxymethyl-DHIQ **63p** was also hydrogenated with 95% ee and 94% conversion to produce (*R*)-**64p**.

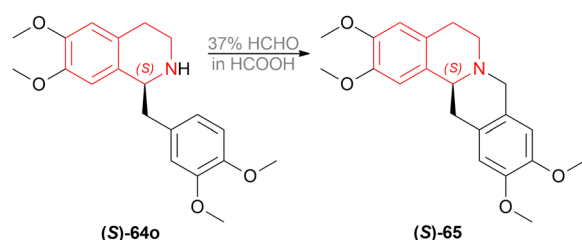
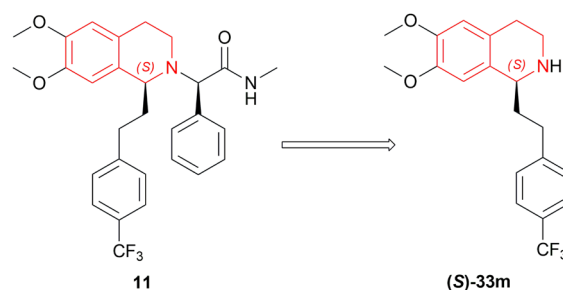
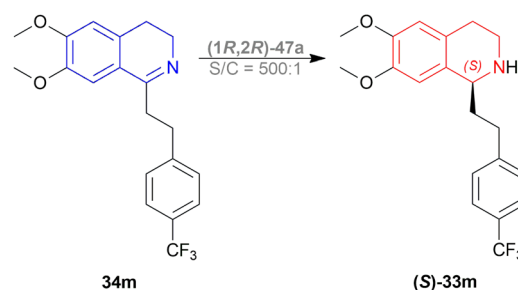
Scheme 27 Synthesis of (*S*)-xylopinine.

Fig. 19 Almorexant and its intermediate.



Scheme 28 Synthesis of the almorexant intermediate.

So, (*Ra,S,S*)-**60a** catalyst gave rise to (*S*)-configured products except for **63p**, (*R*)-configured product was found.

(*S*)-**64o** was prepared by the optimum reaction condition with 88% yield and 96% ee; which was reacted with 37% HCHO in HCOOH for 2 h at 90 °C to yield (*S*)-xylopinine (*S*)-**65** (85%) with the same 96% ee (Scheme 27).

2.2.16 Catalytic asymmetric reduction using Noyori catalyst. Almorexant **11** is an efficient antagonist for orexin receptors which was active on both orexin OX_1 and OX_2 receptors.⁵¹ Verzijl *et al.* prepared **11** by asymmetric reduction of **34m** to the key intermediate (*S*)-**33m** (Fig. 19).⁵²

On a 250–300 g scale using (*1R,2R*)-**47a** (Fig. 12), **11** was obtained in high yield (95%) with good ee (81–95%) at *S/C* of 500 : 1 (Scheme 28). In MeOH, HCl salt of the product was found up to 99% ee. And during a 30 kg production campaign, the

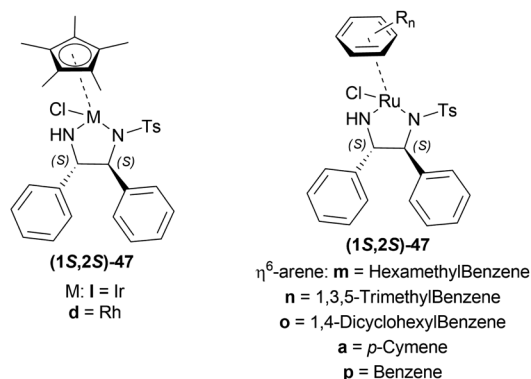
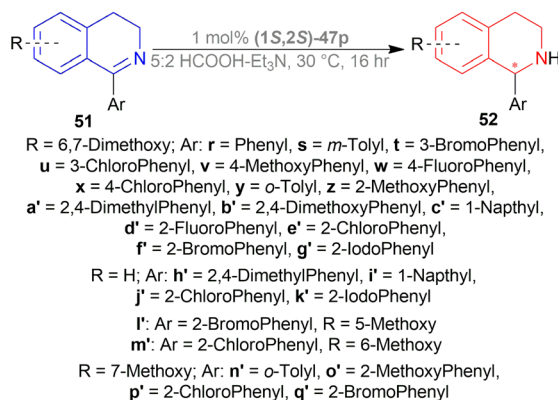


Fig. 20 TsDPEN complexes.





Scheme 29 ATH with TsDPEN complexes.

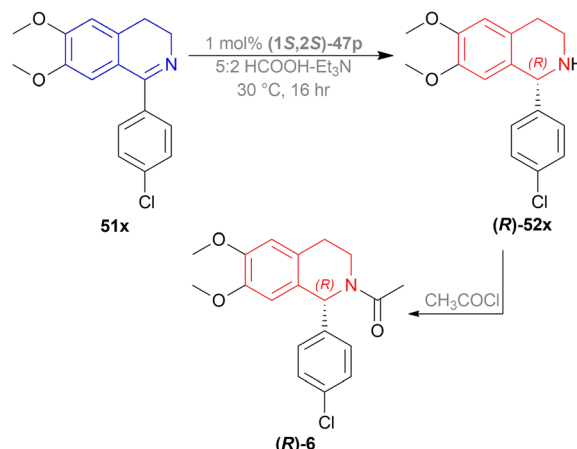
product yield dropped to 57–60% and ee also dropped to 76–80%; because of the *N*-formylated THIQ, a by-product.

So, (1*R*,2*R*)-47a catalyst gave rise to (*S*)-configured product.

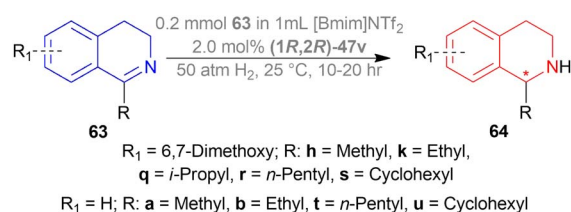
2.2.17 Ruthenium-catalyzed ATH of 1-aryl DHIQs. Wu *et al.* screened for ATH of 1-phenyl-DHIQ **51r** in DCM at 30 °C with a 5:2 azeotropic mixture of HCOOH-Et₃N and TsDPEN complexes **47** (Fig. 20) for 16 h.⁵³ Cp*Ir(III)-TsDPEN (1*S*,2*S*)-**47l** or Cp*Rh(III)-TsDPEN (1*S*,2*S*)-**47d** gave 100% conversion with racemic **52r**. Conversion declined significantly for (1*S*,2*S*)-**47m**–(1*S*,2*S*)-**47p** and (1*S*,2*S*)-**47a**, but (1*S*,2*S*)-**47p** had 100% conversion with enantiomeric ratio (er) of 87.5 : 12.5 (75% ee). Then different solvents were experimented with instead of DCM and 100% conversion was found for each of them only varying in er. ACN, DMF, dioxane, MeOH, THF, toluene, IPA gradually increased er from 72.5 : 27.5 (45% ee) to 91 : 9 (82% ee). For IPA, reaction at 50 °C only decreased er to 86 : 14 (72% ee) and reaction at 0 °C decreased conversion to 30% while er was 90.5 : 9.5 (81% ee).

Then, **51r**–**51q'** were tested under optimum conditions which showed 72–97% yields of **52r**–**52q'** with 90.5 : 9.5–99.5 : 0.5 er (81–99% ee). Methyl, bromide, and chloride substitution at the *meta* position of the 1-phenyl moiety of 6,7-dimethoxy-THIQs **52s**–**52u** had similar ee (82–84%) as **52r** (82%) but higher yields were found (90–93% vs. 82%). Methoxy, fluoride, and chloride substitution at the para position of the 1-phenyl moiety of 6,7-dimethoxy-THIQs **52v**–**52x** had not only higher ee (87–91%) but also higher yields (91–94%). Electron-withdrawing or electron-donating groups at the *ortho* position of the 1-phenyl moiety of 6,7-dimethoxy-THIQs **52y**–**52g'** had also excellent ee (96–99%) and higher yields (83–97%). These results represent that when the bulkiness of the *ortho*-position substituents increases, enantioselectivity also gradually increases.

On a different note, THIQs bearing no substituents, **52h'**–**52k'** had lower yields (72–75%) and lower ee (90–92%) than similar 6,7-dimethoxy-THIQs **52a'**, **52c'**, **52e'**, **52g'** even after 40 h reaction time. Again, in the case of **51l'**–**51q'** having one methoxy at 5, 6, or 7 position of DHIQ core, reaction results are less affected for electron-withdrawing groups bearing substrates (**51e'**, **51f'** vs. **51l'**, **51m'**, **51p'**, **51q'**) than for electron-donating groups bearing substrates (**51y**, **51z** vs. **51n'**, **51o'**),



Scheme 30 Synthesis of an AMPA receptor antagonist.



Scheme 31 AH of 1-alkyl-DHIQs.

producing **52l'**–**6q'** in high yields (86–90%) and 97.5 : 2.5–98 : 2 er (95–96% ee) (Scheme 29).

A gram synthesis of compound **6**, an AMPA receptor antagonist, was done *via* **51x** by optimum ATH conditions having 93% yield and 93.5 : 6.5 er (87% ee). When recrystallized in MeOH, the yield was 80% and had an ee of 98% (Scheme 30).

2.2.18 Ruthenium-catalyzed AH of 1-alkyl DHIQs in ionic liquid. Ding *et al.* investigated AH reactions of 1-alkyl-DHIQs **63** (Scheme 31) using different chiral cationic Ru complex as catalysts in imidazolium ionic liquids.⁵⁴

Hydrogenation of 6,7-dimethoxy-1-methyl-DHIQ **63h** in the presence of (1*R*,2*R*)-**47q** (Fig. 21) in *n*-butyl-3-methyl-imidazolium hexafluorophosphate or [Bmim]PF₆ afforded the (*S*)-6,7-dimethoxy-1-methyl-THIQ (*S*)-**64h** with 100% conversion

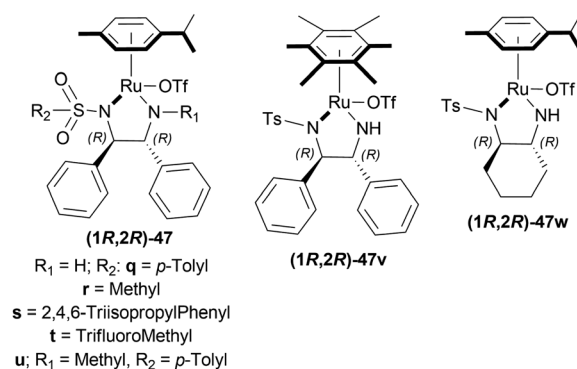


Fig. 21 Chiral cationic Ru complexes.



with an ee of 96%. Then, hydrogenation of **63h** in [Bmim]SbF₆ showed 95% ee. The highest ee of 98% was observed in [Bmim]NTf₂, which was better than that in MeOH (96% ee). So [Bmim]NTf₂ was selected as the solvent for the ATH of 1-alkyl-DHIQs **63**.

After that, (1*R*,2*R*)-**47q**-(1*R*,2*R*)-**47w** (Fig. 21) catalysts were screened at 2.0 mol%. The *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine or TsDPEN ligand (1*R*,2*R*)-**47u** gave the best result (100% conversion, 99% ee). The *N*-(*p*-toluenesulfonyl)-1,2-cyclohexanediamine or TsCYDN ligand (1*R*,2*R*)-**47w** showed a much lower conversion of 78% and a lower ee of 75%. So, (1*R*,2*R*)-**47u** was the best choice of catalyst. Also, low temperature (0 °C) or low hydrogen pressure (20 atm) resulted in lower conversions of 70 and 83%. 1.0 mol% catalyst also afforded a lower conversion of 75% with 97% ee.

At 25 °C and 50 atm H₂, various 1-alkyl-DHIQs **63** was hydrogenated in [Bmim]NTf₂ with 2.0 mol% (1*R*,2*R*)-**47v** (Scheme 31). All had excellent 93–99% ee. Compared to **63h**, substrates having more steric (*i*-propyl, cyclohexyl) or longer (ethyl, *n*-pentyl) side chains gave slightly lower ee of 97%, 93%, 98%, 97% for **63k**, **63q**, **63r**, **63s** respectively. Hydrogenation of DHIQs with no 6,7-dimethoxy substitutions bearing ethyl or cyclohexyl side chain had a slight decrease in % ee (96 and 94% for **63b** and **63u**; compared to **63k** and **63s**).

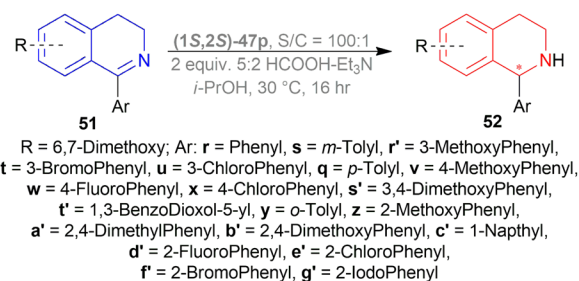
So, (1*S*,2*S*)-**47v** catalyst gave rise to (*S*)-configured products for **63h**, **63k**, **63s**, **63b**, **63t** and (*R*)-configured products for **63q**, **63r**, **63a**, **63u**.

2.2.19 ATH in water varying molar ratio of HCOOH and NEt₃. Shende *et al.* screened molar ratio of HCOOH and NEt₃ for ATH of 6,7-dimethoxy-1-methyl-DHIQ **34a** with (1*S*,2*S*)-**47d** (Fig. 10) at 40 °C.⁵⁵ The azeotropic mixture of 2.5 : 1 molar ratio of HCOOH and NEt₃ in DCM (pH 5) had 99% conversion and 89% ee in 10 min. While the same mixture in water (pH 3) took 24 h to reach 99% conversion with just 2% ee. But a molar ratio of 1.1 : 1 of HCOOH and NEt₃ in water (pH 5.1) needed 10 min for full conversion. So, 1.1 : 1 molar ratio was chosen for later tests.

Then **34a**, **34f**, **34i**–**34l**, **34r**–**34t** were reduced with (1*S*,2*S*)-**47d**, *S/C* = 200 : 1, HCOOH : NEt₃ = 1.1 : 1, 40 °C in water (Scheme 32). 6,7-dimethoxy-1-alkyl-THIQs (*R*)-**33a**, (*R*)-**33i**–(*R*)-**33k**, (*R*)-**33r**–(*R*)-**33t** had 95–98% yield with 83–99% ee in 6 min. But 1-aryl-DHIQs had lower yields and % ee. (*R*)-**33l** and (*R*)-**33f** had 87 and 29% yield with 5 and 2% ee respectively.

Here, (1*S*,2*S*)-**47d** gave rise to (*R*)-configured products.

2.2.20 Ru-Catalyzed ATH of 1-aryl-DHIQs. Perez *et al.* optimized the ATH of 1-phenyl-6,7-dimethoxy-DHIQ **51r** to form 1-phenyl-6,7-dimethoxy-THIQ **52r** (Scheme 33).⁵⁶ They experimented with 1 mol% of 14 metal-based diamine complexes at 30 °C in DCM for 16 h using a 5 : 2 HCOOH–Et₃N azeotropic



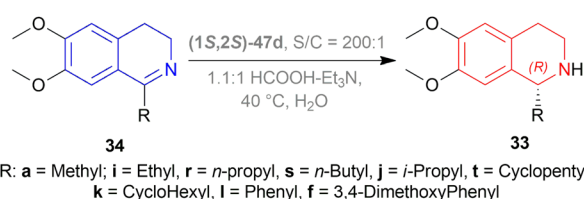
Scheme 33 ATH of 1-aryl-6,7-dimethoxy-DHIQs.

mixture as a hydrogen source. Among the complexes, (1*S*,2*S*)-**47p** (Fig. 20) (with 100% yield and 74% ee) was selected for later optimization.

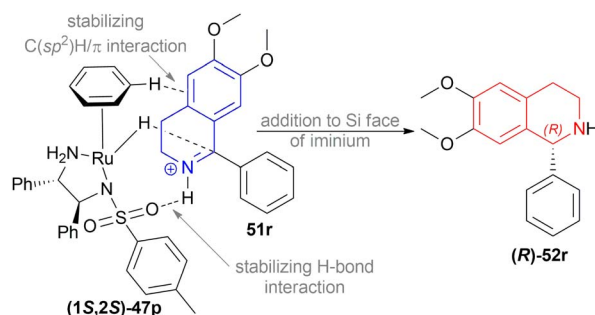
THF, toluene, and dioxane (less polar solvents) yielded products with a higher ee of 65–70% than ACN and DMF (polar aprotic solvents) of 45–48% ee. But when IPA was used, the best yield of 90% and ee of 82% was achieved. Decreasing the temperature from 30 °C to 20 or 10 °C, the yield or ee did not fluctuate that much. Decreasing the temperature to 0 or –10 °C reduced yield dramatically to 27–28% while maintaining ee to 80%. Again, increasing the temperature to 50 °C provided a yield of 87% but decreased ee to 72%. When catalyst loading was lowered to 0.5 mol% at 30 °C for 30 h, yield decreased slightly to 83% while ee was almost the same (81%). So, optimal conditions for ATH of 1-aryl-6,7-dimethoxy-DHIQs **51q**–**51g'**, **51r'**–**51t'** were as following: 1 mol% of catalyst (1*S*,2*S*)-**47p**, IPA as solvent, 5 : 2 HCOOH–Et₃N azeotropic mixture as H₂ source, 30 °C for 16 h (Scheme 33).

In **51s**–**51u**, where there are electron-withdrawing or electron-donating substituents on the *meta* position, yield and ee were 90–93% and 82–84%, almost the same as **51r**. Except in **51r'**, the methoxy group provides such steric and electronic effects that reduce yield to 83% and ee to 69%.

Para-substituted DHIQ **51q**, **51v**–**51x** were reduced with a similar range of good yields (90–92%) and ee (87–91%). *Meta*- and *para*-disubstituted DHIQs **51s'** and **51t'** had a drop in both yield (85 and 87%) and ee (75 and 82%). *Ortho*-substituted DHIQs **51y**–**51g'** had excellent yields (83–97%) and ee (96–99%) irrespective of having electron-donating or withdrawing groups. These results are proof that steric effects are more responsible than the electronic effects. **51d'**–**51g'** had a fluoride, a chloride,

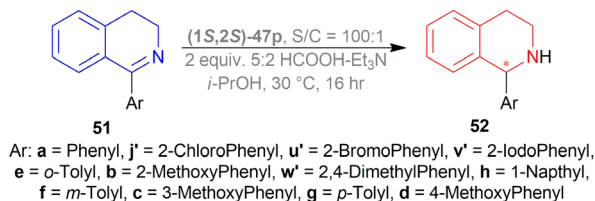


Scheme 32 ATH in water with 1.1 : 1 molar ratio of HCOOH and NEt₃.



Scheme 34 Reduction using Ru(II)-TsDPEN catalyst.





Scheme 35 ATH of 1-aryl-DHIQs.

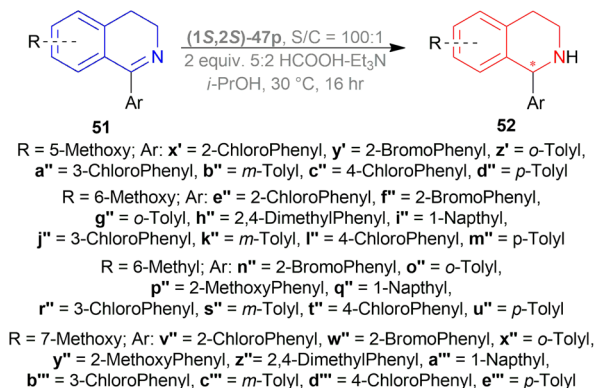
a bromide, and an iodide on the *ortho*-position and as the atom size of the halogen increases, ee also increased from 96% to 99%.

Then, 1-aryl-DHIQs **51a–51h**, **51u'–51x'** were reduced using Ru(II)-TsDPEN catalyst under the optimized conditions (Scheme 33). **51a** was reduced with a high yield of 90% but a low ee of 29% than **51r**. This may be due to the fact that the two methoxy groups in **51r** donate electron that increases the C=N bond electron density. Thus, stronger C(sp₂)H/π interactions between a hydrogen atom on the η⁶-benzene ligand and the aromatic ring of the isoquinoline skeleton are possible (Scheme 34).

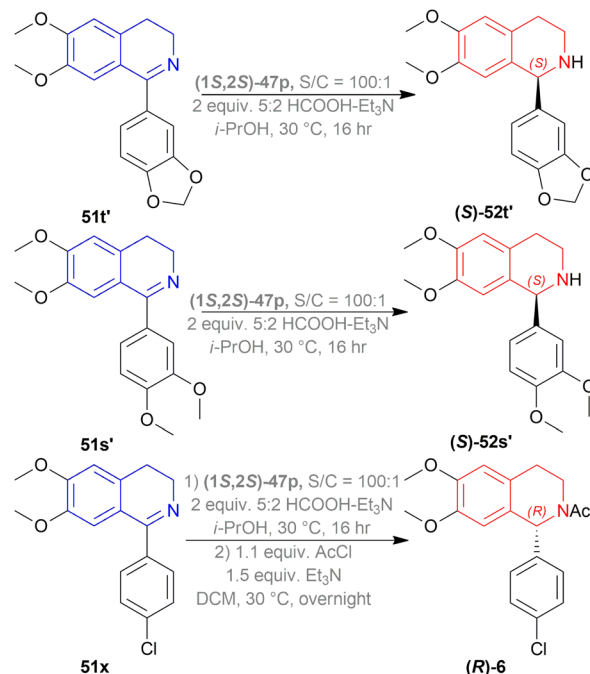
Ortho-substituted 1-aryl-DHIQs **51b**, **51e**, **51h**, **51j'**, **51u'–51w'** had lower yields (71–78%) and ee (79–94%) than *ortho*-substituted 1-aryl-6,7-dimethoxy-DHIQs **51y–51g'**. *Meta*- and *para*-disubstituted 1-aryl-DHIQs **51c**, **51d**, **51f**, **51g** had higher yield (87–93%) but lower ee (33–39%) than *meta*- and *para*-disubstituted 1-aryl-6,7-dimethoxy-DHIQs **51s'** and **51t'** (Scheme 35).

1-Aryl-5-methoxy-DHIQs **51x'–51d''**, 1-aryl-6-methoxy-DHIQs **51e''–51m''**, 1-aryl-6-methyl-DHIQs **51n''–51u''**, 1-aryl-7-methoxy-DHIQs **51v''–51e'''** (Scheme 36) were also reduced by ATH to outline the effects of electron-rich substituents present on the isoquinoline core.

Ortho-substituted DHIQs **51x'–51z'**, **51e''–51i''**, **51n''–51q''**, and **51v''–51a'''** had good ee (84–95%, 91–96%, 79–93%, and 92–96% respectively). This confirms that the *ortho*-substitution on the 1-phenyl ring is important for achieving high levels of selectivity, as also seen for 1-aryl-6,7-dimethoxy-DHIQs **51y–51g'** (Scheme 33) and 1-aryl-DHIQs **51b**, **51e**, **51h**, **51j'**, **51u'–51w'** (Scheme 35), irrespective of the substitution pattern on the benzene ring of the isoquinoline core.



Scheme 36 ATH of 1-aryl-5-methoxy-DHIQs, 1-aryl-6-methoxy-DHIQs, and 1-aryl-7-methoxy-DHIQs.



Scheme 37 Synthesis of (S)-norcryptostyline I, (S)-norcryptostyline II, and an AMPA receptor antagonist.

51a''–51d'' having a methoxy group at the 5-position, were reduced with ee of 3–34%. **51j'–51m''** and **51r''–51u''**, bearing a methyl or a methoxy group at the 6-position, were reduced with ee from 33–60% and 27–53% respectively. **51b''–51e'''** having a methoxy group at the 7-position, were reduced with a higher ee of 54–80% (Scheme 36).

Rather than electronic effects, the catalytic efficiency of the process for monosubstituted DHIQs **51x'–51e'''** (Scheme 36) was due to the increased steric hindrance near the reactive center during the approach of the Ru catalyst.

51t', **51s'**, **51x** were used to synthesize (S)-**52t'** or (S)-norcryptostyline I (87% yield, 82% ee), (S)-**52s'** or (S)-norcryptostyline II (85% yield, 75% ee) and AMPA receptor antagonist **6** (80% yield, 98% ee) respectively (Scheme 37).

2.2.21 Ir-catalysed hydrogenation of DHIQ hydrochlorides with P-trifluoromethyl ligands derived from Josiphos. Schwenk and Togni reduced 1-phenyl-DHIQ **63v** with [(S_P)-**66a**]Cl, [(R_P)-**66a**]Cl, **[66b]**Cl, and [(R,S)-**66c**]Cl (Fig. 22).⁵⁷ [(S_P)-**66a**]Cl and [(R_P)-**66a**]Cl (Fig. 22) both yielded poorly (25% and 18%

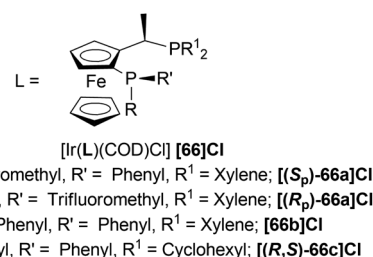
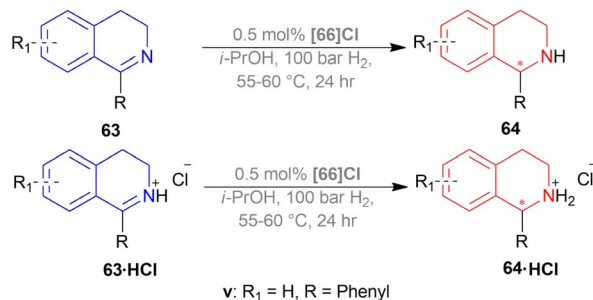
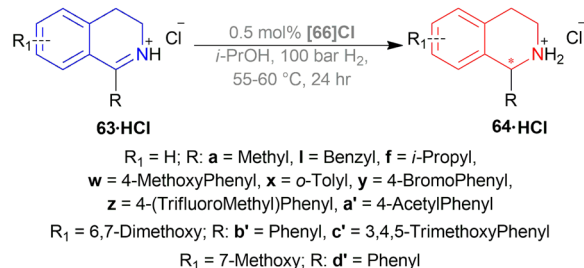


Fig. 22 P-Trifluoromethyl ligands.



Scheme 38 AH of DHIQ hydrochlorides with P-trifluoromethyl ligands and by Ir-catalyst.



Scheme 39 AH of DHIQ hydrochlorides with P-trifluoromethyl ligands and by Ir-catalyst.

respectively) and ee values were also low (30% and 16% respectively). [66b]Cl yielded more than them (75%) but ee value did not increase (21%). When **63v** was activated by protonation, **63v·HCl** gave more yield than free **63v**. (R)-1-[(S)-2-(Diphenylphosphino)-ferrocenyl]EthylDicyclohexylPhosphine or (R,S)-josiphos [(R,S)-66c]Cl catalyzed **63v·HCl** poorly (yield 60%, ee 30%) but (S)-P-phos (S)-59a (Fig. 17) gave high yield (>99%) and ee value (97%). While [(R_p)-66a]Cl had low enantioselectivity (23% ee), [(S_p)-66a]Cl gave a satisfactory ee of 96%. These two catalysts also had >99% yield without the use of any additives (Scheme 38).

Then, **63a·HCl**, **63l·HCl**, **63f·HCl**, **63v·HCl**-**63d'·HCl** were reduced with [(S_p)-66a]Cl and [66b]Cl catalysts. Having steric bulk moieties in position 1, **64v·HCl** and **64f·HCl** (ee of 96% and 84%; 93% and 85% respectively) had higher ee than **64a** and **64l** (ee of 28% and 50%; 35% and 38% respectively). Again, electron-rich moieties in position 1 lowered ee in **64w**, **64b'**, **64c'**, and **64d'** (ee of 89% and 90%; 34% and 46%, 57% and 33%; 75% and 77% respectively) (Scheme 39).

(S_p)-66a is the relatively electron-poor ligand, so [(S_p)-66a]Cl produced **64v·HCl** of 96% ee than [(S_p)-66a]I (**64v·HI** of 93% ee). On the other hand, **66b** is an electron-rich ligand. For this reason, [66b]I afforded **64v·HI** of 93% ee than [66b]Cl (**64v·HCl** of 84% ee).

2.2.22 AH of DHIQs by Noyori – Ikariya half – sandwich complexes and their analogs. Vilhanová *et al.* screened solvents for AH of 6,7-dimethoxy-1-methyl-DHIQ **63h** with (1S,2S)-47a (Fig. 23) (Scheme 40).⁵⁸ ACN did not even start the reaction and DMSO, MeOH had a very low conversion rate (2–4% and 6–10% respectively). To undergo reduction, the imine needed to be

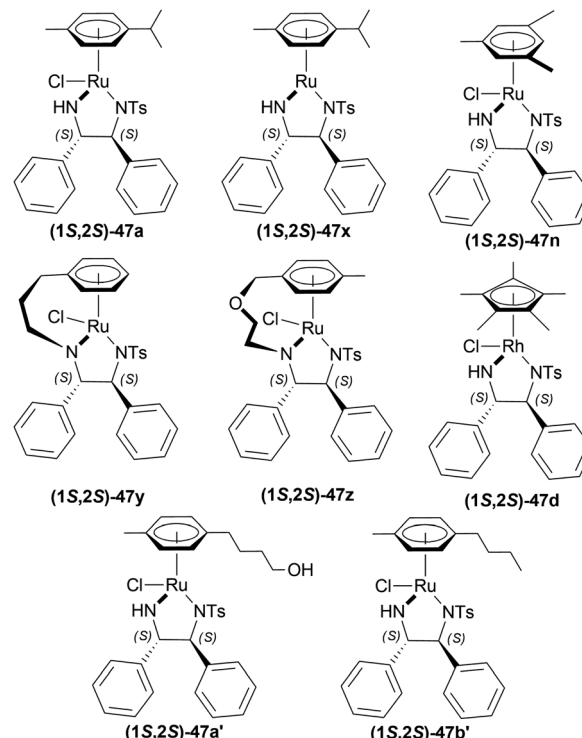
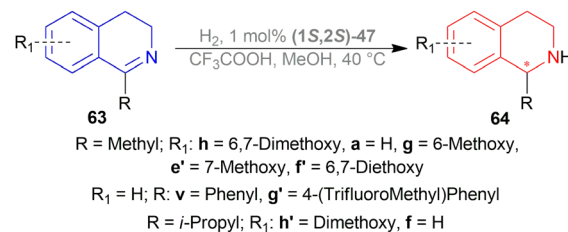


Fig. 23 Noyori – Ikariya half – sandwich complexes and their analogs.



Scheme 40 AH of 1-alkyl-DHIQs.

activated by the polarization of the C=N bond. For this, an acid was required in MeOH. 1 equiv. Trifluoromethanesulfonic acid had no effect of its own, showing a 9% conversion. While 1 equiv. of HBF₄ (48% in water), and trifluoroacetic acid increased conversion to 19% and 57% separately. When the temperature was increased to 40 °C, the conversion was satisfactory (96%). But then it was found that the order of addition of the mixture was critical as the substrate had to be protonated first as follows: substrate, MeOH, acid, and then catalyst. In these optimal conditions, substrates **63a**, **63f**–**63h**, **63v**, **63e'**–**63h'** (Scheme 40) were catalyzed with (1S,2S)-47a, (1S,2S)-47d, (1S,2S)-47n, (1S,2S)-47x–(1S,2S)-47b' respectively (Fig. 23).

63a, **63g**, **63h**, **63e'** showed full conversion (>99%) with (1S,2S)-47a (87–96% ee), (1S,2S)-47x (85–96% ee), (1S,2S)-47n (81–96% ee), and (1S,2S)-47d (75–90% ee). (1S,2S)-47a and (1S,2S)-47x had similar results which meant that the auto-dissociation of the Ru–Cl bond of (1S,2S)-47a is not a rate-limiting step. With (1S,2S)-47y, **63h**, **63a**, **63e'** had also full conversion (>99%) except **63g** (96%) with 59–78% ee. (1S,2S)-47z



had lower conversion for **63h** (44%; 94% ee) and **63g** (84%; 90% ee) than **63a** and **63e'** (>99% for both; 84% and 91% ee respectively) (Scheme 40).

63f' and **63v**, which are 1-aryl-DHIQs, had full conversion (>99%) only with (1*S*,2*S*)-**47d** having 7% and 9% ee respectively. So, it is clear that 1-aryl-DHIQs require more reactive and different catalysts.

63g' and **63h'**, the 6,7-dialkoxy-DHIQs had high conversion except for (1*S*,2*S*)-**47y** (70% and 90% conversion; 83–96% ee) and (1*S*,2*S*)-**47z** (31% and 27% conversion; 95–98% ee). **63h'** and **63f** both are 1-*i*-propyl-DHIQs but **63f** only showed full conversion (>99%) for (1*S*,2*S*)-**47y** (66% ee).

(1*S*,2*S*)-**47a'** and (1*S*,2*S*)-**47b'** also showed similar or larger conversion and ee values compared to (1*S*,2*S*)-**47a**, (1*S*,2*S*)-**47n**, (1*S*,2*S*)-**47x** – (1*S*,2*S*)-**47z**. Greater conversion was found for substrate **63f** (88% and >99% conversion respectively) which was noteworthy (Scheme 40).

For ATH, (1*S*,2*S*)-**47a**, (1*S*,2*S*)-**47a'** and (1*S*,2*S*)-**47b'** showed good ee values for **63a**, **63g**, **63h**, **63e'**, **63h'** (>85%). And again, (1*S*,2*S*)-**47a'** and (1*S*,2*S*)-**47b'** had large ee values (70% and 76% respectively) than (1*S*,2*S*)-**47a** (50%). It was suggested that (1*S*,2*S*)-**47a** followed first-order kinetics, and (1*S*,2*S*)-**47a'**, (1*S*,2*S*)-**47b'** showed zero-order kinetics for ATH.

2.2.23 ATH of 1-aryl-DHIQs using a Cp*Ir(TsDPEN) complex. Vilhanová *et al.* observed (1*S*,2*S*)-**47d** (Fig. 23), (1*S*,2*S*)-**47c'**, (1*S*,2*S*)-**47d'** (Fig. 24) complexes in ACN, IPA, DCM, DMSO, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), HCOOH/TEA hydrogen-donor solvents for 24 h but no combinations gave full conversion to **52a** from **51a** (Scheme 41).³⁹ ACN gave a very low conversion of 2–3% with (1*S*,2*S*)-**47d**, (1*S*,2*S*)-**47c'** but a good conversion of 87% with (1*S*,2*S*)-**47d'** (10% ee). IPA had an increasing conversion rate with the complexes (64%, 66%, and 83% respectively) but moderate ee (60%) with (1*S*,2*S*)-**47d'** only. Reaction without TEA had a lower conversion of 54% (34% ee)

and without HCOOH or both had almost no conversion at all. DCM had moderate conversion (57%, 7% ee) but DMSO and HFIP had no reaction done. HCOOH/TEA mixture at a molar ratio of 2.5 : 1 had 80% conversion with 71% ee while at 1 : 1 had 72% conversion with 77% ee. A 1 : 1 molar ratio was selected for further tests.

Several additives were also experimented on. Among them, 85% aq. solution of orthophosphoric acid increased the ee to 82%. Anhydrous Phosphoric Acid (APA) increased ee to 86% at >99% conversion with anhydrous IPA as a solvent and (1*S*,2*S*)-**47d'** as complex.

But without APA, conversion lowered to 65% with lower ee also (77%). Without HCOOH, TEA, or both, the reaction would not proceed. (1*S*,2*S*)-**47a**, (1*S*,2*S*)-**47x**, (1*S*,2*S*)-**47d** (Fig. 23), (1*S*,2*S*)-**47c'** (Fig. 24) also resulted in low conversion.

According to the optimum conditions, 1-phenyl-DHIQ **51a** had full conversion (>99%) with 86% ee in 3 h while 6,7-dimethoxy-1-phenyl-DHIQ **51r** had 88% conversion with 72% ee. The high conversion of **51d**, **51g'''**–**51k'''** was not altered to a significant extent even after changing the *para*-substitution of the 1-phenyl moiety. For **51l'''** and **51e**, trifluoromethyl substitution in the *meta*-position of the 1-phenyl moiety decreased catalytic activity (93% conversion in 18 h) and methyl substitution in *ortho*-position had poor reactivity (55% conversion). **51m'''** having the 3,4,5-trimethoxyphenyl group needed 6 h to gain 96% conversion. As **51r**, highly methoxylated **51f'''** showed a decrease in conversion (only 46%). Common features of these two substrates may be the reason for inhibiting ATH under these conditions (Scheme 41).

A decrease of ee is seen in ATH of 1-methyl-6,7-dimethoxy-DHIQ **34a** (Scheme 42) catalyzed by (1*S*,2*S*)-**47d'** as the reaction time increases, and sometimes producing the other enantiomeric product. In ACN with APA, ee changed from 14% to 45% of (*S*)-1-methyl-6,7-dimethoxy-THIQ (*S*)-**33a**; without APA, ee changed from 77% to 58% of (*R*)-1-methyl-6,7-dimethoxy-

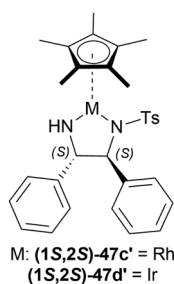
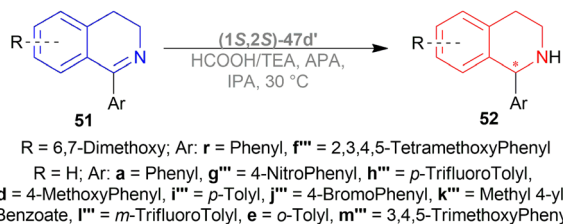


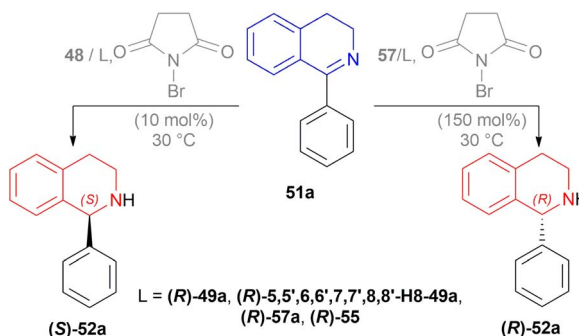
Fig. 24 Cp*Rh(TsDPEN) and Cp*Ir(TsDPEN) complex.



Scheme 41 ATH of 1-aryl-DHIQs.

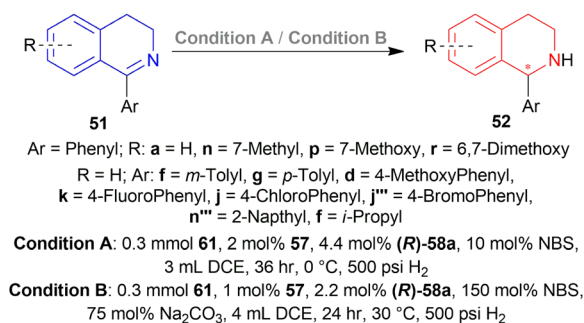


Scheme 42 ATH of 1-methyl-6,7-dimethoxy-DHIQ.



Scheme 43 AH of 1-phenyl-DHIQs with dual stereo-control.





Scheme 44 AH of 1-aryl-DHIQs with dual stereo-control.

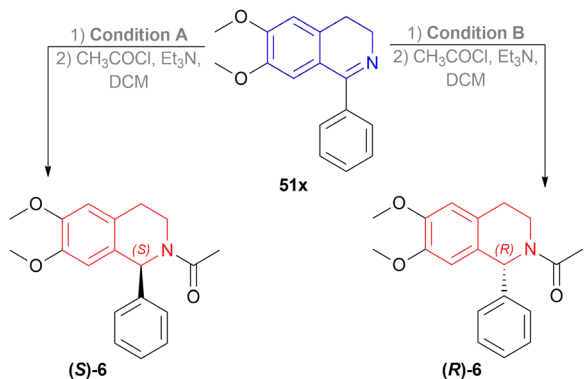
THIQ (**R**)-**33a**. Similarly, in IPA with APA, ee changed from 43% of (**R**)-**33a** to 56% of (**S**)-**33a**; without APA, ee changed from 80% to 74% of (**R**)-**33a**.

So, (1*S*,2*S*)-**47d'** catalyst gave rise to (*S*)-configured products with APA, and (*R*)-configured products without APA.

2.2.24 Dual stereocontrol for AH of DHIQs by changing the mol% of *N*-bromosuccinimide. Instead of using two chiral reagents or two ligands of opposite configuration to get both enantiomers of chiral THIQs, Ji *et al.* explored dual enantioselective hydrogenation of 1-aryl-DHIQs with a single chiral catalyst.⁶⁰ *N*-BromoSuccinimide (NBS) elevated the valence state of iridium (1 to 3) which improved the catalytic performance or reacted with the substrate as an oxidant. This enabled dual stereo-control (Scheme 43) in iridium-catalysed AH of 1-aryl-DHIQs **51** by changing the amount of NBS.

1-phenyl-DHIQ **51a** substrate with **48** – (*R*)-**49a** catalyst was evaluated. (*S*)-1-phenyl-THIQ (**S**)-**52a** was obtained in 82% ee (and full conversion) with 10 mol% NBS in 1,2-dichloroethane (DCE). Other ligands *e.g.*, (*R*)-5,5',6,6',7,7',8,8'-H₈-**49a**, (*R*)-**57a**, (*R*)-**55** and other solvents *e.g.*, toluene, THF, or MeOH produced ee in the range of 63–79%. The ee increased to 86% when the reaction temperature was lowered to 0 °C.

The ee decreased to 55 and 13% when NBS was increased to 50 and 75 mol%. Increasing NBS to 90, 100, 120, and 150 mol% even produced (*R*)-1-phenyl-THIQ (**R**)-**52a** with increasing ee of 16–91%.



Scheme 45 Synthesis of an AMPA receptor antagonist with dual stereo-control.

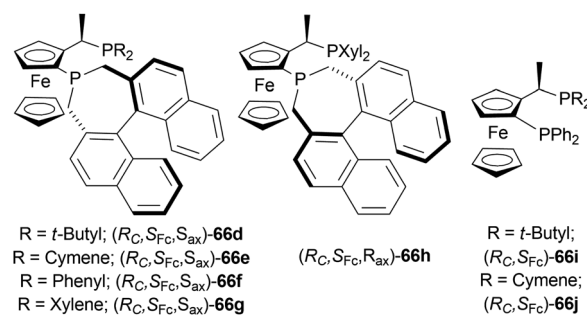
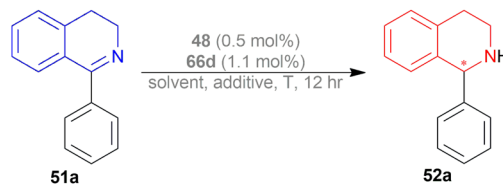


Fig. 25 Josiphos-type binaphane ligands.



Scheme 46 Screening AH of 1-phenyl-DHIQ with Josiphos-type binaphane ligands.

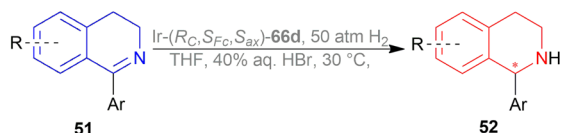
Then 2 conditions were set, condition A and condition B (Scheme 44). For condition A, high ee was not dependent on the electronic properties of the substrates. Quite the opposite happened for condition B. The electronic properties of the substituted group of the benzene ring in the isoquinoline core affected the ee. Electronically deficient groups on 1-aryl position containing **51k**, **51j**, **51j'''** had high ee of 95%, 94%, and 93% respectively. Electron-donating groups on 1-aryl position containing **51f**, **51g**, and **51d** had low ee of 89%, 83%, and 66%. The methoxy group on the 1-aryl position containing **51d** had a low ee of 66%. *i*-Propyl groups on 1-aryl position containing **51f** had low ee of 66%.

6, a biologically active compound, was prepared under the above standard conditions of the dual enantioselective hydrogenation of **51x** (Scheme 45). condition A followed by acylation with acyl chloride, TEA, and DCM yielded 97% (*S*)-**6** having 81% ee. While condition B with the same acylation process produced (*R*)-**6** (98% yield, 91% ee) which is a potent non-competitive AMPA receptor antagonist.

2.2.25 Josiphos-type binaphane ligands for iridium-catalyzed AH of 1-aryl-DHIQs. Nie *et al.* evaluated the ligands **66d–66j** (Fig. 25) for asymmetric reduction of 1-phenyl-DHIQ **51a** with **48** (Fig. 8), I₂, and TFA in toluene at 30 °C (Scheme 46).⁶¹ **66d–66h** produced >99% yield. Among them, **66d** had the highest 81% ee. **66i** and **66j** gave very poor results (65% and 60% yield; 35% and 21% ee respectively). So, **66d** was chosen for the following experiments.

With I₂ and TFA as additives, and THF as the solvent, **66d** had >99% yield and 84% ee. No additive, I₂, and TFA separately did not increase ee that much. Though 40% aq. solution of HBr was able to produce >99% ee. For this experiment, 40% aq. solution of HBr solution activated the substrate through HBr,





R = H; Ar: a = Phenyl, o''' = 2-FluoroPhenyl, b = 2-MethoxyPhenyl, p''' = 3-FluoroPhenyl, c = 3-MethoxyPhenyl, f = *m*-Tolyl, k = 4-FluoroPhenyl, g = *p*-Tolyl, h''' = *p*-Trifluorotolyl

R = 6,7-Dimethoxy; Ar: r = Phenyl, d' = 2-FluoroPhenyl, z = 2-MethoxyPhenyl, y = *o*-Tolyl, q''' = 3-FluoroPhenyl, r' = 3-MethoxyPhenyl, s = *m*-Tolyl, w = 4-FluoroPhenyl, x = 4-ChloroPhenyl, v = 4-MethoxyPhenyl, q = *p*-Tolyl, s' = 3,4-DimethoxyPhenyl, m''' = 3,4,5-TrimethoxyPhenyl

Scheme 47 AH of 1-aryl-DHIQ with Josiphos-type binaphane ligands.

and improved the catalytic activity by a six-membered cyclic transition state, forming salts between the substrate and HBr. Then increasing the temperature to 50 °C while reducing catalyst loading from 0.5 mol% to 0.1 mol% and 0.02 mol% decreased both yield and % ee.

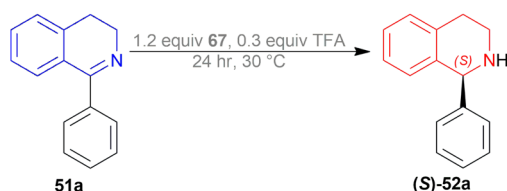
Then **51a–51c**, **51f**, **51g**, **51k**, **51q–51s**, **51v–51z**, **51d'**, **51r'**, **51s'**, **51h'''**, **51m'''**, **51o'''–51q'''** were reduced under the above-mentioned conditions by AH (Scheme 47). All of these produced excellent results (94–99% yield, 85–99% ee). Some products such as **52b**, **52c**, **52f**, **52g**, **52k**, **52h'''**, **52o'''**, and **52p'''** had similar ee despite the difference in substituent position and electronegativity on the 1-phenyl ring.

For some products, increased ee were observed because of the 6,7-dimethoxy substitution in the THIQ core *e.g.*, **52q**, **52v–52z**, **52d'**, **52r'**. **52s'** and **52m'''** having more than one methoxy substitution on the 1-phenyl ring caused decreased ee (Scheme 47).

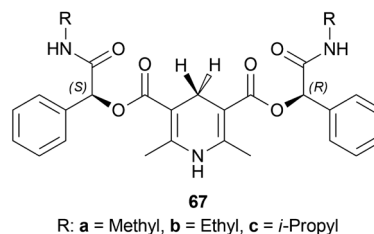
52a, **52w**, **52s'**, and **52m'''** were intermediates of biological active compounds, such as solifenacin, TRPM8 channel receptor antagonist IV, (*S*)-cryptostyline II, and (*S*)-cryptostyline III. And (*R*)-**52h'''** and (*R*)-**52x** can be obtained with the ligand **66d** enantiomer, which were the intermediates of the TRPM8 channel receptor antagonist V and AMPA receptor antagonist I.

2.2.26 Synthesis method of (*S*)-1-phenyl-THIQ. Li *et al.* patented a method for synthesizing (*S*)-1-phenyl-THIQ (**52a**) (Scheme 48).⁶² Among the 9 examples described in this patent, example no. 1, 7, and 8 had the optimum yield, purity, and ee for chiral catalysts **67a–67c** (Fig. 26) respectively.

The substrate **51a**, catalyst **67**, and TFA were dissolved in a ratio of 1:1.2:0.3 in 200 mL of toluene. The mixture was vigorously stirred for 24 h at 30 °C; adding water, quenched, extracted with ethyl acetate, concentrating the organic phase, purifying by recrystallization of the white crude product, and compound (*S*)-**52a** was obtained with the yield of 89, 85, and 75% and ee of 99.6, 99, and 98% for chiral catalysts **67a–67c** respectively (Scheme 48).



Scheme 48 Reduction of 1-phenyl-DHIQ.



R: a = Methyl, b = Ethyl, c = *i*-Propyl

Fig. 26 Chiral catalysts for the reduction of 1-phenyl-DHIQ.

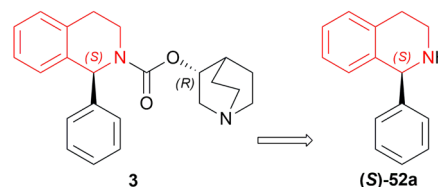
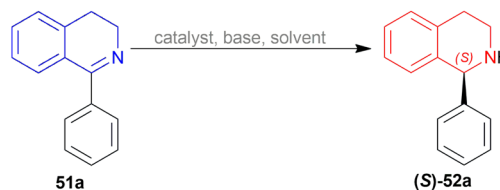


Fig. 27 Solifenacin and its intermediate.



Scheme 49 Reduction into solifenacin intermediate.

2.2.27 Refining method of solifenacin intermediate. Solifenacin **3** has two chiral intermediates. Between them, Li *et al.* developed methods to synthesize and purify (*S*)-**52a** (Fig. 27) (Scheme 49).⁶³

Among the 10 examples described in this patent, example 1 provided the most refined (*S*)-**52a** and the least impurity. In a high-pressure kettle, 1000 g of **51a** dissolved in 10 L of ethanol is degassed completely under continuous argon introduction for 1 h 5 g of (*S*)-DIOP RuCl₂ (*R*)-P-Me-BIMAH with 120 g potassium *tert*-butoxide was added to it and then hydrogen is replaced with the argon. The reaction was stirred at 25–35 °C and after completion, concentrated under reduced pressure to get 96% pure crude (*S*)-**52a**.

200 g of this crude was added to 1 L solution of a 5:1 mix of toluene and chlorobenzene, heated at 60 °C to dissolve, cooled to 5 °C, crystallized for 1 h, dried under reduced pressure to get 95% yield which was 99.8% pure with 0.02% maximum single purity.

Example 2–4 differed in the refinement of the crude, the second step, from example 1. When 1 L toluene was used in example 2, 90% yield with 99.3% purity and 0.07% maximum single impurity was found. 1 L chlorobenzene was used in example 3 where 94% yield with 99.6% purity and 0.06% maximum single impurity was found. In example 4, 1 L xylene caused a 90% yield with 99.2% purity and 0.06% maximum single impurity.

Example 5–6 differed in the refinement of the crude, the second step, from example 4. 40 °C temperature and 3 L xylene was used to dissolve the crude that yielded 82% with 99.6%



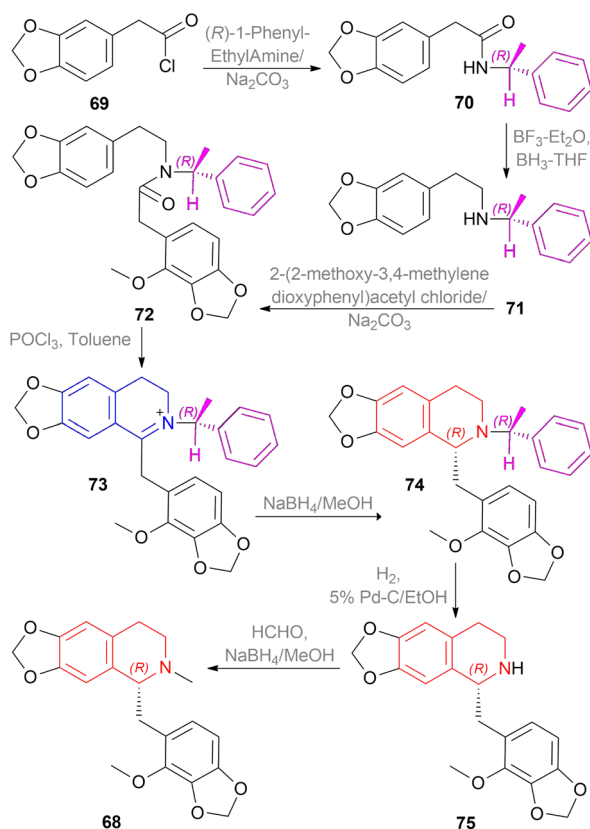
purity and 0.04% maximum single purity in example 5. In example 6, 0.6 L xylene and 75 °C temperature dissolved the crude which caused 95% yield with 99.2% purity and 0.06% maximum single impurity.

Example 7–10 differed in the refinement of the crude, the second step, from example 1. 1 L solution of a 9 : 1 mix of toluene and chlorobenzene was used in example 7 where 89% yield with 99.5% purity and 0.04% maximum single impurity was found. In example 8, 1 L solution of a 5 : 1 mix of toluene and xylene caused 91% yield with 98.6% purity and 0.03% maximum single impurity. When 1 L solution of a 5 : 1 mix of xylene and chlorobenzene was used in example 9, 91% yield with 98.6% purity and 0.03% maximum single impurity was found. 1 L solution of a 5 : 1 mix of toluene and chlorobenzene and a crystallization temperature of 0 °C was used in example 10 where 96% yield with 98.6% purity and 0.08% maximum single impurity was found.

The only comparative example differed in the refinement of the crude, the second step, from example 1. 1 L THF was used here where 72% yield with 98.3% purity and 0.4% maximum single impurity was found (Scheme 49).

2.3 Examples of enantioselective reduction of 1-substituted-DHIQs possessing chiral auxiliary at the imine nitrogen by achiral metallic hydride reducing agents

2.3.1 Asymmetric synthesis of fumarizine. Kunitomo *et al.* used Polniaszek and McKee's method⁶⁴ of chiral auxiliary to enantioselectively synthesize fumarizine **68** (Scheme 50).⁶⁵



Scheme 50 Asymmetric synthesis of fumarizine.

2-(3,4-methylenedioxyphenyl)acetyl chloride **69** was reacted with the chiral auxiliary (*R*)-1-phenylethylamine to produce *N*-[(*R*)-1-phenylethyl]-2-(3,4-methylenedioxyphenyl)acetamide **70**. In this step, the chiral auxiliary was introduced into the substrate. Then **70** is reduced to *N*-[(*R*)-1-phenylethyl]-2-(3,4-methylenedioxyphenyl)ethylamine **71** with $\text{BH}_3\text{-THF}$. After that, the Schotten–Baumann reaction of **71** and 2-(2-methoxy-3,4-methylenedioxyphenyl)acetyl chloride afforded *N*-[(*R*)-1-phenylethyl]-*N*-[2-(3,4-methylenedioxyphenylethyl)]-2-(2-methoxy-3,4-methylenedioxyphenyl)acetamide **72**.

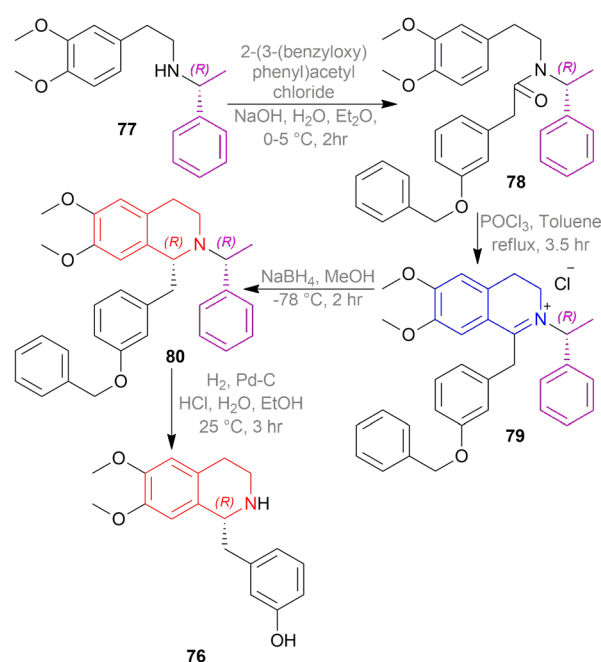
Then, the Bischler–Napieralski reaction of **72** with POCl_3 in toluene produced 1-[(*R*)-1-phenylethyl]-6,7-methylenedioxy-3,4-dihydroisoquinolin-2-ium **73** which was asymmetrically reduced with NaBH_4 in MeOH to afford (*R*)-1-[(*R*)-1-phenylethyl]-6,7-methylenedioxy-3,4-dihydroisoquinolin-2-ium **74**. The chiral auxiliary was then removed by catalytic hydrogenation of **74** over Pd–C in ethanol to give rise (*R*)-1-[(*R*)-1-phenylethyl]-6,7-methylenedioxy-3,4-dihydroisoquinolin-2-ium **75** having a total yield of 30% from **71**. Treating **75** with HCHO and NaBH_4 produced (*R*)-1-[(*R*)-1-phenylethyl]-6,7-methylenedioxy-3,4-dihydroisoquinolin-2-ium **76** or fumarizine **68**.

So, (*R*)-configured chiral auxiliary afforded (*R*)-configured product.

2.3.2 Asymmetric synthesis of (*R*)-noranicanine. Kunitomo *et al.* used chiral auxiliary to synthesize (*R*)-noranicanine **76** (Scheme 51).⁶⁶

At first, (*R*)-*N*-(2-(3,4-dimethoxyphenyl)ethyl)-1-phenylethylamine **77** was reacted with 2-(3-(benzyloxy)phenyl)acetyl chloride to produce (*R*)-2-(3-(benzyloxy)phenyl)-*N*-(2-(3,4-dimethoxyphenyl)ethyl)-*N*-(1-phenylethyl)acetamide **78**.

Then, the Bischler–Napieralski reaction of **78** with POCl_3 in toluene produced (*R*)-1-(3-(benzyloxy)benzyl)-2-(1-phenylethyl)-



Scheme 51 Asymmetric synthesis of (*R*)-noranicanine.



Review

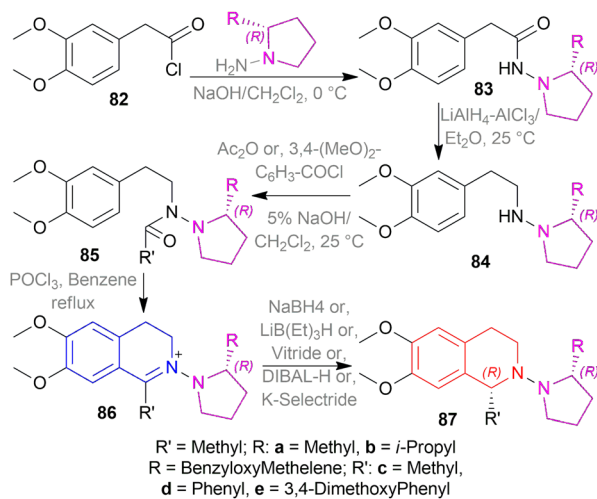
6,7-dimethoxy-3,4-dihydroisoquinolin-2-ium chloride **79**. In this example, (*R*)-1-phenylethyl is the chiral auxiliary. **79** was asymmetrically reduced with NaBH₄ in MeOH to afford (*R*)-1-(3-(benzyloxy)benzyl)-6,7-dimethoxy-2-((*R*)-1-phenyl-ethyl)-THIQ **80**. At last, the chiral auxiliary was removed with H₂/Pd-C to get (*R*)-1-(3-hydroxy)benzyl-6,7-dimethoxy-THIQ or (*R*)-nor-anicanine **76**.

So, (*R*)-configured chiral auxiliary afforded (*R*)-configured product.

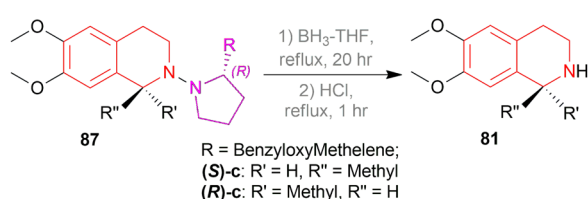
2.3.3 Asymmetric synthesis of (*S*)- and (*R*)-salsolidines and (*R*)-cryptostyline. Suzuki *et al.* synthesized (*S*)- and (*R*)-salsolidines **81c** and (*R*)-cryptostyline (*R*)-*N*-methyl-**81e** with a chiral auxiliary (Schemes 52–54).⁶⁷

2-(3,4-Dimethoxyphenyl)acetyl chloride **82** was reacted with (*R*)-2-substituted-pyrrolidin-1-amine to produce (*R*)-2-(3,4-dimethoxyphenyl)-*N*-(2-substituted-pyrrolidin-1-yl)acetamides **83**. Then, **83** was reduced to (*R*)-*N*-(2-(3,4-dimethoxy-phenyl)ethyl)-2-substituted-pyrrolidin-1-amine **84** which was reacted with Ac₂O or 3,4-dimethoxybenzoyl chloride to afford (*R*)-*N*-(3,4-dimethoxyphenethyl)-*N*-(2-substituted-pyrrolidin-1-yl) amides **85**.

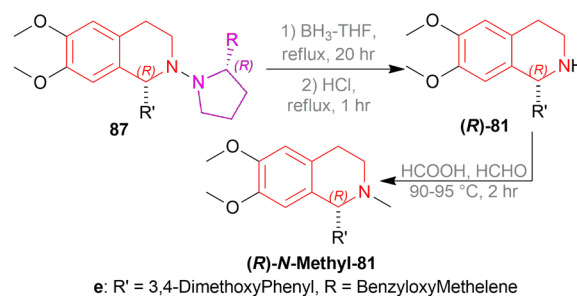
Then, the Bischler-Napieralski reaction of **85** with POCl₃ in benzene produced (*R*)-6,7-dimethoxy-1-substituted-2-(2-substituted-pyrrolidin-1-yl)-3,4-dihydroisoquinolin-2-iums **86**. Here, 2-substituted-pyrrolidin-1-yl is the chiral auxiliary. **86** was asymmetrically reduced with various metal hydride reagents to afford (*R*)-6,7-dimethoxy-1-substituted-2-((*R*)-2-substituted-pyrrolidin-1-yl)-THIQs **100**.



Scheme 52 Asymmetric synthesis of (*S*)- and (*R*)-salsolidines and (*R*)-cryptostyline.



Scheme 53 Asymmetric synthesis of (*S*)- and (*R*)-salsolidines.



Scheme 54 Asymmetric synthesis of (*R*)-cryptostyline.

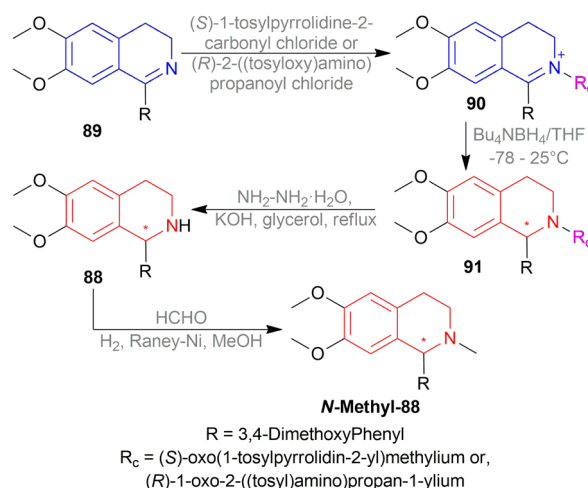
NaBH₄ in MeOH at –50 °C yielded 73% (*R*)-**87a** (84% ee), 71% (*R*)-**87b** (86% ee), 75% (*R*)-**87c** (94% ee), and 70% (*R*)-**87d** (90% ee) respectively. NaBH₄ in MeOH at –10, –50, and –90 °C yielded 88%, 84%, 81% (*R*)-**87c** (90%, 92%, 94% ee) respectively. Again, LiB(Et)₃H, vitride, DIBAL-H, and K-selectride in THF at –50 °C yielded 68%, 63%, 42%, and 44% (*R*)-**87c** (92%, 92%, 92%, and 96% ee) respectively.

So, (*R*)-configured chiral auxiliary afforded (*R*)-configured product.

Then, the chiral auxiliary was removed by refluxing (*S*)-**87c**, (*R*)-**87c**, and (*R*)-**87e** in BH₃-THF for 20 h and in HCl for 1 h producing 77% (*S*)-6,7-dimethoxy-1-methyl-THIQ or (*S*)-salsolidine (*S*)-**87c**, 77% (*R*)-6,7-dimethoxy-1-methyl-THIQ or (*R*)-salsolidine (*R*)-**81c** (Scheme 53), and 71% (*R*)-**94e**; which was *N*-methylated with HCOOH, HCHO to afford 73% (*R*)-6,7-dimethoxy-1-(3,4-dimethoxyphenyl)-2-methyl-THIQ or (*R*)-cryptostyline II (*R*)-*N*-Methyl-**94e** (Scheme 54).

2.3.4 Enantioselective synthesis of (*R*)- and (*S*)-cryptostyline II. Czarnocki and Mieczkowski synthesized (*R*)- and (*S*)-cryptostyline II *N*-Methyl-**88** using chiral auxiliary (Scheme 55).⁶⁸

1-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-DHIQ **89** were reacted with (*S*)-1-tosylpyrrolidine-2-carbonyl chloride or (*R*)-2-((tosyloxy)amino)propanoyl chloride to introduce the chiral auxiliary and produced 1-(3,4-dimethoxyphenyl)-2-substituted-6,7-dimethoxy-3,4-dihydroisoquinolin-2-ium **90**. Here, (*S*)-



Scheme 55 Enantioselective synthesis of (*R*)- and (*S*)-cryptostyline II.

oxo(1-tosylpyrrolidin-2-yl)methylum and (R)-1-oxo-2-((tosyloxy)amino)propan-1-ylum were the chiral auxiliary respectively. **90** were reduced to (S)- or (R)-1-(3,4-dimethoxy-phenyl)-2-substituted-6,7-dimethoxy-THIQ **91**. Then the chiral auxiliaries will be removed to get (S)- or, (R)-1-(3,4-dimethoxy-phenyl)-6,7-dimethoxy-THIQ **88** which were *N*-methylated to get (S)- or (R)-1-(3,4-dimethoxy-phenyl)-2-methyl-6,7-dimethoxy-THIQ or, (S)- or (R)-cryptostyline II *N*-methyl-**88**.

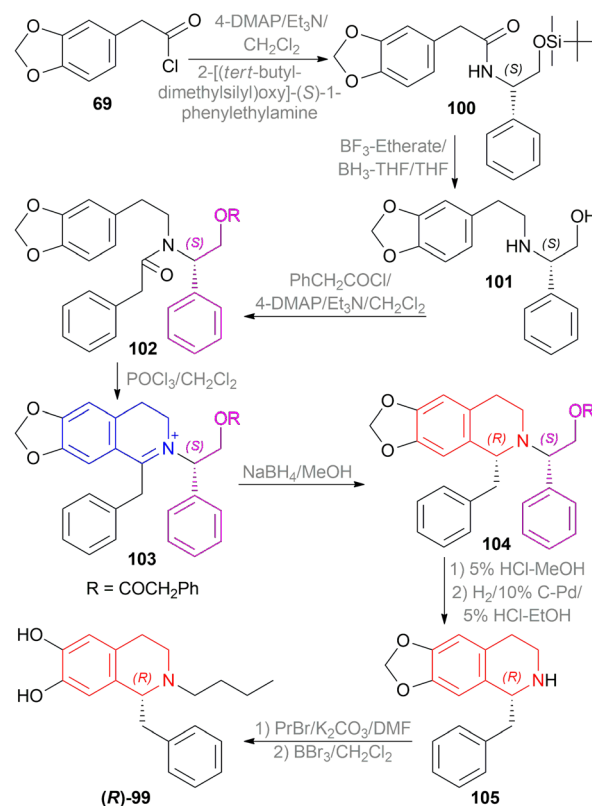
When (S)-1-tosylpyrrolidine-2-carbonyl chloride was used, 94% (S)-*N*-methyl-**88** (66% ee) was found. But when (R)-2-((tosyl)-amino)propanoyl chloride was used, 87% yield and 59% ee of (R)-*N*-methyl-**88** was seen.

So, (S)-configured chiral auxiliary afforded (S)-configured product and (R)-configured chiral auxiliary afforded (R)-configured product in moderate ee.

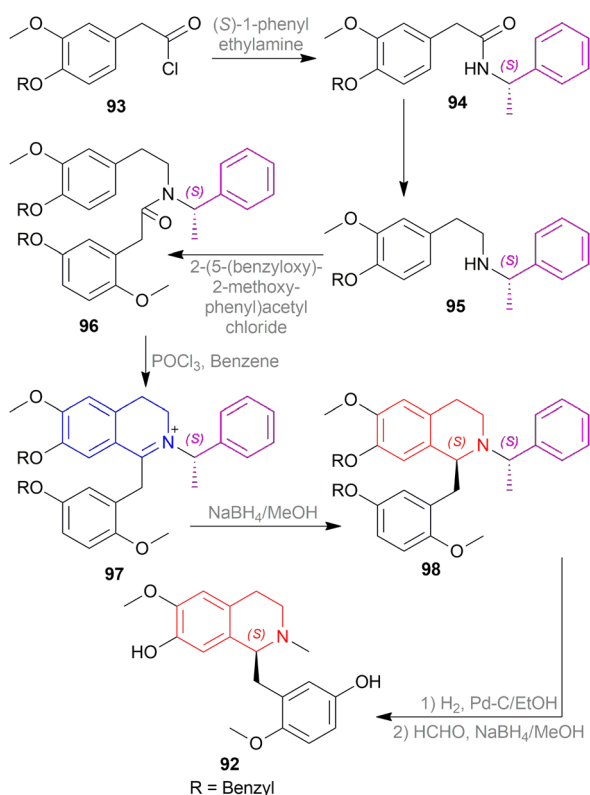
2.3.5 Asymmetric synthesis of dehasiline. Kunitomo *et al.* afforded dehasiline **92** after using a chiral auxiliary for asymmetric synthesis (Scheme 56).⁶⁹

2-(4-(Benzyloxy)-3-methoxyphenyl)acetyl chloride **93** was reacted with (S)-1-phenylethylamine to produce 2-(4-(benzyloxy)-3-methoxyphenyl)-*N*-((S)-1-phenylethyl)-acetamide **94**. Then, **94** was reduced to *N*-(2-(4-(benzyloxy)-3-methoxyphenyl)ethyl)-((S)-1-phenylethyl)amine **95** which was reacted with 2-(5-(benzyloxy)-2-methoxyphenyl)acetyl chloride to afford 2-(5-(benzyloxy)-2-methoxyphenyl)-*N*-(2-(4-(benzyloxy)-3-methoxyphenyl)ethyl)-((S)-1-phenylethyl)-acetamide **96**.

Then, the Bischler-Napieralski reaction of **96** with POCl₃ in benzene produced 6-methoxy-7-(benzyloxy)-1-(5-(benzyloxy)-2-



Scheme 57 Enantioselective synthesis of (S)-1-benzyl-2-propyl-6,7-dihydroxy-THIQ.

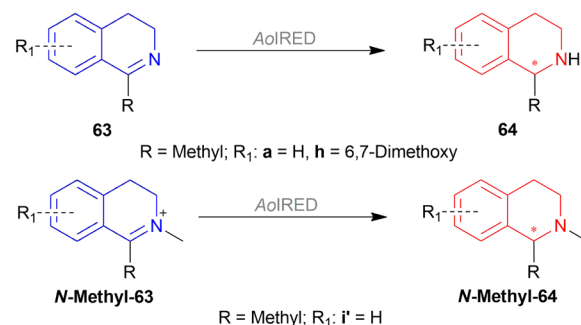


Scheme 56 Asymmetric synthesis of dehasiline.

methoxybenzyl)-2-((S)-1-phenylethyl)-3,4-dihydro-isoquinolin-2-ium **97**. Here, (S)-1-phenylethyl is the chiral auxiliary. **97** was asymmetrically reduced with NaBH₄ in MeOH at −78 °C to afford (S)-7-(benzyloxy)-1-(5-(benzyloxy)-2-methoxybenzyl)-6-methoxy-2-((S)-1-phenylethyl)-THIQ **98**. Then the chiral auxiliary was removed, *N*-methylated, and debenzylated to afford (S)-1-(5-hydroxy-2-methoxybenzyl)-7-hydroxy-6-methoxy-2-methyl-THIQ or dehasiline **92**.

So, (S)-configured chiral auxiliary afforded (S)-configured product.

2.3.6 Enantioselective syntheses of dopaminergic (R)- and (S)-benzyltetrahydroisoquinolines. Cabedo *et al.* synthesized (R)- and (S)-1-benzyl-2-propyl-6,7-dihydroxy-THIQ **99** with chiral auxiliary (Scheme 57).⁷⁰



Scheme 58 Enantioselective reduction by AolRED.



2-(3,4-Methylenedioxyphenyl)acetyl chloride **69** was reacted with 2-[(*tert*-butyldimethylsilyl)oxy]-(*S*)-1-phenylethylamine to produce *N*-[2-*tert*-butyldimethylsilyl-(*S*)-1-phenylethoxy]-2-(3,4-methylenedioxyphenyl)acetamide **100** which was reduced to *N*-[2-(3,4-methylenedioxyphenyl)ethyl]-(*S*)-1-phenyl-ethanolamine **101**. Then, **101** was added with phenylacetyl chloride to afford *N*-[(*S*)-1-phenyl-2-phenylacetylthoxy-*N*-2-(3,4-methylenedioxyphenyl)ethyl]-2-phenylacetamide **102**.

Then, the Bischler–Napieralski reaction of **102** with POCl₃ in DCM produced 1-benzyl-2-[(*S*)-1-phenyl-2-phenylacetylthoxy]-6,7-methylenedioxy-3,4-dihydroisoquinolin-2-ium **103** which was asymmetrically reduced with NaBH₄ in MeOH to afford (*R*)-1-benzyl-2-[(*S*)-1-phenyl-2-phenylacetylthoxy]-6,7-methylenedioxy-THIQ **104**. The chiral auxiliary was removed in two steps using 5% HCl in MeOH and H₂ over 10% C–Pd in 5% HCl–EtOH producing (*R*)-1-benzyl-6,7-methylenedioxy-THIQ **105**. Lastly, **105** was *N*-propylated with 1-bromopropane and K₂CO₃ in DMF and the 6,7-methylenedioxy part was cleaved with boron tribromide in DCM to obtain (*R*)-1-benzyl-2-propyl-6,7-dihydroxy-THIQ (*R*)-**99** in 69% yield.

In the above scheme, if 2-[(*tert*-butyldimethylsilyl)oxy]-(*R*)-1-phenylethylamine was used without changing any other reagents, the final product yielded 58% (*S*)-1-benzyl-2-propyl-6,7-dihydroxy-THIQ (*S*)-**99**.

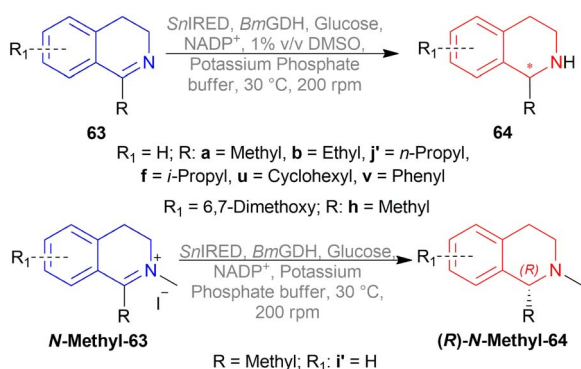
So, (*S*)-configured chiral auxiliary afforded (*R*)-configured product.

2.4 Enantioselective reduction of 1-substituted-DHIQs by enzymatic catalysis

2.4.1 Enantioselective reduction by imine reductase AoIRED from *Amycolatopsis orientalis*. Aleku *et al.* reduced **63a**, **63h**, and *N*-methyl-**63i'** by freshly purified imine reductase AoIRED (UniProt: R4SNK4) from *Amycolatopsis orientalis* (Scheme 58).⁷¹ (*S*)-**64a**, (*S*)-**64h** and (*S*)-*N*-methyl-**64i'** was found with 100%, 50%, and 40% conversion (81%, 79%, and 92% ee) respectively. Also, fresh lysate produced a similar 85% ee of (*S*)-**64a**.

But, 98% and >99% ee of (*R*)-**64a** was produced by AoIRED stored at 4 °C for 24 h and after 14 days respectively.

When bovine serum albumin (BSA) added to AoIRED was aged for 24 h, 76% ee of (*S*)-**64a** was found.



Scheme 59 Enantioselective reduction by SnIRED.

AoIRED derived from Y179A mutant of *Amycolatopsis orientalis* was the highest in catalytic efficiency for **63a**.

2.4.2 Enantioselective reduction by imine reductase SnIRED from *Stackebrandtia nassauensis*. Li *et al.* screened several imine reductases (IREDs) such as SnIRED from *Stackebrandtia nassauensis*, SeIRED from *S. espanaensis*, and AdIRED from *A. decaplanina* to reduce **63a** (Scheme 59).⁷² For highest specific activity and >99% ee of (*S*)-**64a**, SnIRED was chosen.

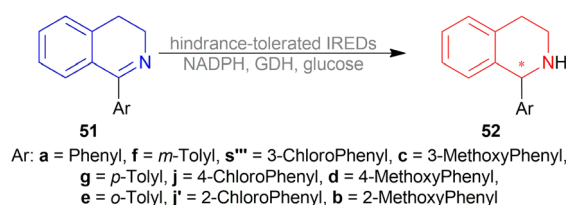
Substrate concentration and % (v/v) of DMSO as co-solvent was also screened. 100 mM substrate with 5% DMSO had only 18% conversion even after 24 h of reaction. Then decreasing concentration, or % DMSO, or both lowered reaction time (0.5–12 h) with >99% conversion.

Then **63a**, **63b**, **63f**, **63h**, **63u**, **63v**, and **63j'** were reduced with SnIRED, Glucose Dehydrogenase from *Bacillus megaterium* (*BmGDH*), glucose, NADP⁺, 1% DMSO, potassium phosphate buffer (pH 7.0) while no DMSO was used for reducing *N*-methyl-**63i'**. 100 mM of **63a**, **63b**, and **63h** were totally converted to (*S*)-**64a**, (*S*)-**64b**, and (*S*)-**64h** in 2–4 h in 72–81% yields and 93–99% ee. The other substrates were used in 5–50 mM concentration for 3–12 h to yield 73–81% of their respective products. (*S*)-**64f** and (*S*)-**64v** was produced in 98% and 51% ee, while (*R*)-**64j'**, (*R*)-**64u**, and (*R*)-*N*-methyl-**64i'** was produced in 8%, 80%, and 87% ee respectively. So, size of 1-substitution and substrate binding mode was a critical factor in the stereoselectivity of SnIRED.

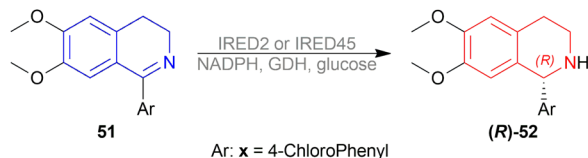
2.4.3 Enantioselective reduction by hindrance-tolerated IREDS. Zhu *et al.* screened 88 novel IREDS to reduce **51a** at 30 °C for 24 h with NADPH, glucose dehydrogenase (GDH) and glucose (Scheme 60).⁷³ Among those IRED2, IRED8, IRED17, IRED19, IRED20, IRED32, and IRED45 had 99–100% conversion with 96 – >99% ee. *Meta*-substituted **51f**, **51s'''**, **51c** also had similar conversion of 99–100% and ee of 91 – >99% with these IREDS. Except IRED45, *para*-substituted **51g**, **51j**, **51d** had good conversion of 99–100% and ee of >99% with these IREDS. But only IRED2 and IRED45 showed little conversion for *ortho*-substituted **51e**, **51j'**, **51b**. IRED8, IRED17, IRED19, IRED20, IRED32 produced (*R*)-1-aryl-THIQs. IRED2 also had (*R*)-configured products except for (*S*)-**52j'**. In contrast, IRED45 had (*S*)-configured products except for (*R*)-**52j'** and (*R*)-**52b**.

Then, IRED2 and IRED45 were selected for reducing **51x** (Scheme 61). IRED2 produced 62% conversion with 99% ee of (*R*)-**52x**, and IRED45 produced 53% conversion with 92% ee of (*R*)-**52x**.

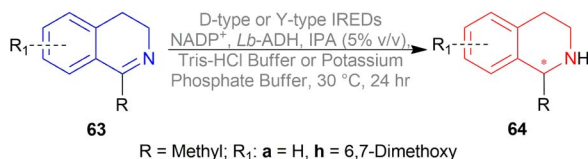
2.4.4 Enantioselective reduction by two types of IREDS. Velikogne *et al.* screened IRED-A-IRED-H (D-type) and IRED-I-IRED-N (Y-type) to reduce **63a** and **63h** with NADP⁺, alcohol dehydrogenase from *Lactobacillus brevis* (*Lb*-ADH), Tris-HCl



Scheme 60 Enantioselective reduction by hindrance-tolerated IREDS.



Scheme 61 Enantioselective reduction by IRED2 or IRED45.



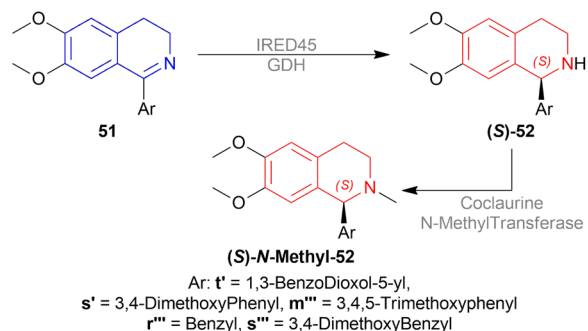
Scheme 62 Enantioselective reduction by D-type and Y-type IREDs.

buffer (pH 7.5, for IRED-A-IRED-E, IRED-I-IRED-M) or potassium phosphate buffer (pH 6.0, for IRED-F-IRED-H, IRED-N), IPA (5% v/v), 30 °C, 24 h (Scheme 62).⁷⁴

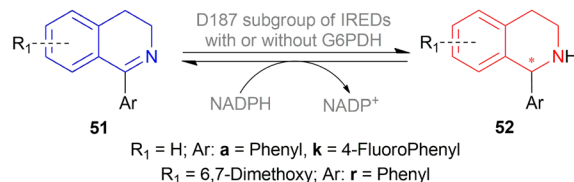
Except IRED-B, all the D-type IREDs had conversion of 83 – >99% and 71 – >99% ee for **64a**. But only IRED-D-IRED-G had low conversion of 15–49% for **64h**. These IREDs mainly produced (*R*)-configured products except IRED-G. Among these, IRED-C (from *Micromonospora* sp. M42, UniProt: W7VJL8), IRED-D (*Mesorhizobium* sp. L2C089B000, UniProt: V7GV82), IRED-E (*Nocardiopsis alba*, UniProt: J7LAY5), and IRED-G (from *Streptomyces rimosus* ATCC 10970, UniProt: L8EIW6) had the highest conversion >99% and >99% ee for **64a**.

All the Y-type IREDs had 59 – >99% conversion and 91 – >99% ee for (*S*)-**64a**. And except IRED-N, these had >99% conversion and >99% ee for (*S*)-**64h**. These IREDs produced mainly (*S*)-configured products. Among these, IRED-J (from *Kribbella flavida* DSM 17836, UniProt: D2PR38), IRED-L (from *Nocardia brasiliensis* ATCC 700358, K0F8R0), and IRED-M (from *saccharothrix espanaensis* ATCC 51144, UniProt: K0K4C6) had the highest conversion and % ee for both (*S*)-**64a** and (*S*)-**64h**.

2.4.5 Enantioselective reduction by IRED45 and its mutant. Yang *et al.* described reduction of **51t'**, **51s'**, **51m'''**, **51r'''**, **51s'''** by IRED45 (as of Section 2.4.3) and its mutant at 30 °C for 24 h (Scheme 63).⁷⁵ IRED45 was able to produce (*S*)-**52t'**, (*S*)-**52r'''**, (*S*)-**52s'''** with full conversion and >99% ee. But it did



Scheme 63 Enantioselective reduction by IRED45 and its mutant.



Scheme 64 Enantioselective reduction by D187 subgroup of IREDs.

not reduce **51s'**, **51m'''** which was bulkier than **51a**. While the mutant W191F was not useful at all, it's another mutant F190M-W191F was similar in activity as IRED45. Another mutant F190L-W191F had full conversion and >99% ee for (*S*)-**52t'**, (*S*)-**52m'''**, (*S*)-**52r'''**, (*S*)-**52s'''** and 75% conversion and >99% ee for (*S*)-**52s'**.

Then *N*-methylation of (*S*)-**52t'**, (*S*)-**52s'**, (*S*)-**52m'''**, (*S*)-**52r'''**, and (*S*)-**52s'''** with coclaurine *N*-methyltransferase produced (*S*)-cryptostyline I, (*S*)-cryptostyline II, (*S*)-cryptostyline III, (*S*)-1-benzyl-6,7-dimethoxy-2-methyl-THIQ, and (*S*)-laudanosine with 100% conversion.

2.4.6 Enantioselective reduction by D187 subgroup of IREDs. Cárdenas-Fernández *et al.* reduced **51a**, **51k**, and **51r** with pQR2595, pQR2600, pQR2601, and pQR2612 which are four D187 subgroup of IREDs (Scheme 64).⁷⁶

pQR2600 produced 93% ee of (*R*)-**52a**, 84% and 21% yield with and without glucose-6-phosphate dehydrogenase (G6PDH) respectively. Similarly, pQR2601 had shown >99% ee of (*R*)-**52a**, 98% and 23% yield with and without G6PDH respectively.

pQR2595 produced >99% ee of (*R*)-**52k**, 74% and 33% yield with and without G6PDH respectively. Similarly, pQR2612 had shown >99% ee of (*S*)-**52r**, 76% and 23% yield with and without G6PDH respectively.

3 Conclusion

Most of the isoquinoline alkaloids, a large family of natural products, are comprised of the 1-substituted-1,2,3,4-tetrahydroisoquinolines. Because of their (1-substituted-THIQs) diversified structure, innumerable biological activities, and a chiral center in their nucleus have made them fascinating targets for organic synthesis. Since these compounds contain a chiral carbon, a wide range of enantioselective synthetic methods have been reported in the last forty-one years.

The enantioselective reductions of 1-substituted-DHIQs, obtained by the Bischler–Napieralski reaction, to get the intended 1-substituted-1,2,3,4-tetrahydroisoquinoline in chiral form were accomplished by using chiral hydride reducing agents, by hydrogenation in the presence of a chiral catalyst, by enantioselective reduction of DHIQs possessing a chiral auxiliary at the imine nitrogen by achiral metallic hydride reducing agents, or by enzymatic catalysis. It has been found that using hydrogen gas and a very small quantity of chiral catalysts, asymmetric hydrogenation provides the most efficient way to synthesize enantio-enriched compounds. Therefore, there is more scope and potential for research concerning the remaining three methods.



No specific, general, or simple methods were found in this review article for the preparation of all types of isoquinoline alkaloids with high optical purity. Moreover, moderate to poor yields and stereoselectivity, inaccessibility, or high costs of starting materials and reagents are the limitations of these methods. Hence, the development of novel methods for finding 1-substituted-THIQs in optically active form can still be a subject of research.

Author contributions

M. M. A. Asif: writing – original draft, visualization, writing – review & editing. S. R. Lisa: writing – original draft, writing – review & editing. N. Qais: supervision, writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

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