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Synthesis of Chiral Tetrahydroisoquinoline and C_2-Symmetric Bistetrahydroisoquinoline Ligands and Their Application in the Enantioselective Henry Reaction

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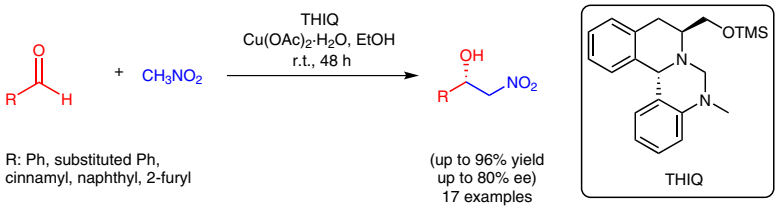

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Abstract Application of chiral tetrahydroisoquinoline and bistetrahydroisoquinoline scaffolds in asymmetric reactions is limited by the inefficient synthesis of their chiral structural variants. We have conveniently synthesized 24 such variants and applied them as ligands in the enantioselective Henry reaction. The conformational rigidity of these ligands and the size of the coordination sphere control the enantioselectivity of the products. The conformationally rigid chiral tetrahydroisoquinoline THIQ–Cu(OAc)$_2$·H$_2$O complex successfully catalyzed the enantioselective Henry reaction between various aldehydes and nitromethane and gives the β-nitro alcohol adducts in up to 96% yield and 80% ee.

Key words tetrahydroisoquinoline, C_2-symmetric ligand, bistetrahydroisoquinoline, Henry reaction, asymmetric catalysis

The Henry (or nitroaldol) reaction is a classical C–C bond-forming reaction between carbonyl compounds and nitroalkanes. It is used to construct β-nitro alcohol adducts.[1] The adducts can be converted into β-amino alcohols,[2] β-amino acids,[3] nitroalkenes,[3] and α-nitro ketones.[4] These compounds are key intermediates in the total syntheses of numerous biologically active molecules.[5] Shibasaki et al. reported the first asymmetric Henry reaction using chiral BINOL–La(O-*t*-Bu)$_3$ complexes.[6] Since then, complexes of various ligands with metals, such as rare earth metals, zinc, copper, cobalt, and magnesium, have been used with varying degrees of success.[7,8] Earlier work revealed that chiral aza-ligand–Cu complexes, such as bisoxazoline–,[7,9] diamine–,[10] aminopyridine–,[11] *N*,*N*′-dioxide–,[12] and tetrahydro-Salen–Cu complexes,[13] are particularly efficient for this reaction.

Our group and others have used tetrahydroisoquinolines[14] (THIQs) **1** as well as their dimers C_1-bisisoquinolines (C_1-BIQs) **2** and C_2-bistetrahydroisoquinolines (C_2-BIQs) **3** (Figure 1) as chiral aza-ligands for asymmetric hydrogenation,[15] alkynylations,[16] alkylation,[17] aluminum- and borane-mediated reductions,[18] and Henry[19] reactions. For example, chiral THIQs **1** (R^1 = oxazolinyl and R^3 = Ph) catalyzed the reaction between aromatic aldehydes and nitromethane and gave the β-nitro alcohol adducts with 40–77% ee.[19] However, chiral isoquinolines catalyzed the asymmetric Henry reaction between nitrobenzaldehyde and nitromethane and gave the β-nitro alcohol adducts with just 11% ee.[19b] The enantioselectivity obtained suggested the potential of these aza-ligands in the asymmetric Henry reaction. The reported THIQs have structural variations mostly at R^1 and R^2 while R^3 is limited to either hydrogen or phenyl, since the synthesis of chiral THIQs with varying R^3 is very challenging.[18b,20] Further development of THIQs and its dimers BIQs into efficient chiral ligands is hindered by the difficulty in synthesizing their structural variants for ligand optimization.

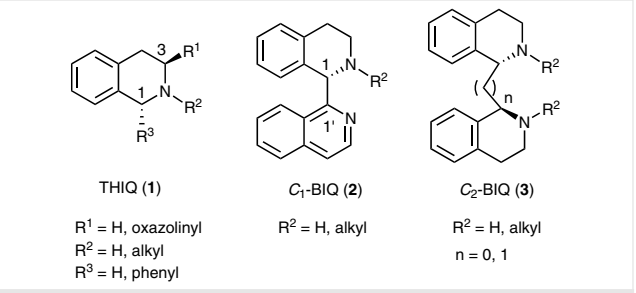


Figure 1 Chiral THIQ, and C_1- and C_2-BIQ ligands

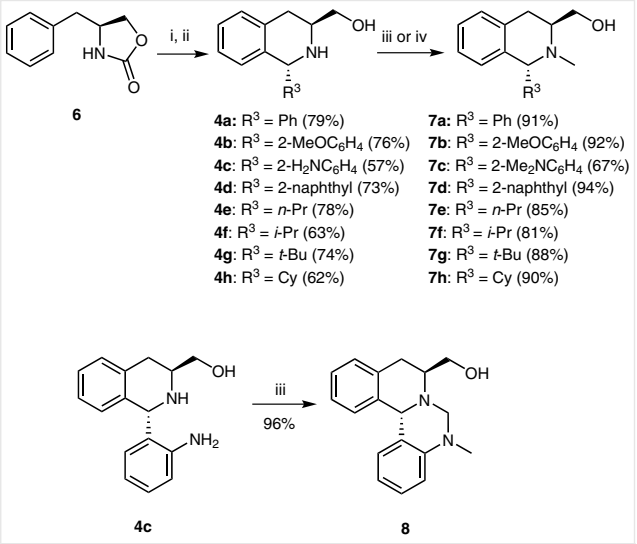
We have recently reported the simple, modular, and direct synthesis of chiral THIQs **4** with varying R^3 substituents at C1 (Scheme 1) and successfully extended the synthesis to chiral C_2-BIQs **5** (Scheme 2).[21] This, in combination with the successful application of C_1-BIQs **2**[17,22] and C_2-BIQs **3**[23] (Figure 1) as ligands for the asymmetric Henry reaction

as well as other asymmetric reactions,[22e,24] prompted us to query if our new THIQs **4** (Scheme 1) and C_2-BIQs **5** (Scheme 2) could be effective aza-ligands for the enantioselective Henry reaction.

Herein, we report the synthesis of chiral THIQ and C_2-BIQ ligands and their application in the enantioselective Henry reaction.

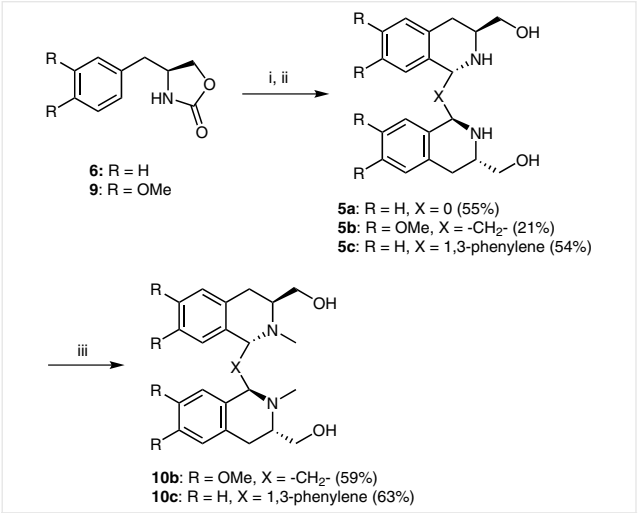
Synthesis of Chiral THIQ and C_2-BIQ Ligands

The synthesis of THIQs **4a**–**h** is depicted in Scheme 1.[21] The key step involved Pictet–Spengler condensation between (*S*)-4-benzyloxazolidin-2-one (**6**) and several aliphatic and aromatic aldehydes to give the respective cycloadducts as one diastereomer. Subsequent treatment of the cycloadducts with NaOH cleanly afforded THIQs **4a**–**h** in overall 57–79% yields. Based on our previous experience,[24b] *N*-methylated chiral BIQ ligands gave better enantioselectivity in the Henry reaction in comparison to the non-methylated counterparts.[24b] Therefore, we also prepared the *N*-methylated THIQs **7a**–**h** (Scheme 1). Reductive methylation of THIQs **4a**,**b**,**d**–**h** using HCHO/$NaCNBH_3$[25] provided the corresponding *N*-methylated THIQs **7a**,**b**,**d**–**h** in 81–94% yield. However, under such condition, *N*-methylation of THIQ **4c**, bearing a free *o*-amino group, afforded instead cyclic aminal THIQ **8** in 96% yield. Nevertheless, reaction of THIQ **4c** with MeI provided the desired *N*-methylated THIQ **7c** in 67% yield (Scheme 1).



Scheme 1 Synthesis of chiral THIQs **4a**–**h**, **7a**–**h**, and **8**. *Reagents and conditions*: (i) R^3CHO, H_2SO_4, $CHCl_3$, r.t., 12 h; (ii) NaOH, MeOH, H_2O, reflux, 24 h; (iii) 37% HCHO, $NaCNBH_3$, AcOH, THF, r.t., 4–5 h (for **4a**,**b**,**d**–**h** to **7a**,**b**,**d**–**h**); (iv) MeI, r.t. (for **4c** to **7c**).

Likewise, Pictet–Spengler condensation between oxazolidinones **6** or **9** and the dialdehydes glyoxal, malondialdehyde, and isophthalaldehyde followed by NaOH hydrolysis of the cycloadducts afforded C_2-BIQs **5a**–**c** (Scheme 2).[21] MeI was used to *N*-methylate C_2-BIQs **5a**–**c** to C_2-BIQs **10a**–**c** (Scheme 2).[23b] While we successfully isolated C_2-BIQs **10b** and **10c** in 59% and 63% yield, respectively, C_2-BIQ **10a** was unstable and decomposed during purification on column chromatography.

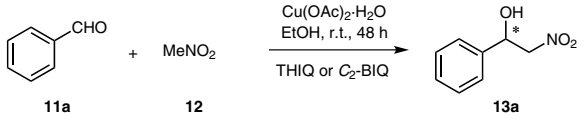


Scheme 2 Synthesis of chiral C_2-BIQs **5a**–**c**, and **10b**–**c**. *Reagents and conditions*: (i) glyoxal trimer dihydrate (**5a**), maldondialdehyde (**5b**), isophthalaldehyde (**5c**), H_2SO_4, $CHCl_3$, reflux, 12 h; (ii) NaOH, MeOH, H_2O, reflux, 48 h; (iii) MeI, r.t., 12 h.

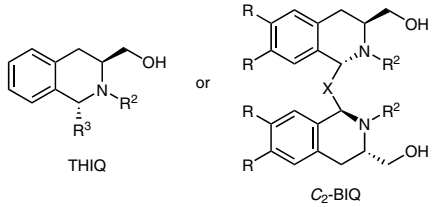
Screening of the THIQ and BIQ Ligands in the Cu-Catalyzed Enantioselective Henry Reaction

With the enantiopure THIQs **4a**–**h**, **7a**–**h**, **8** and C_2-BIQs **5a**–**c**, **10b**, and **10c** in hand, we examined their catalytic abilities in the enantioselective benchmark Henry reaction between benzaldehyde (**11a**) and nitromethane (**12**) in the presence of $Cu(OAc)_2{\cdot}H_2O$ (Table 1).[7a] The chiral ligand–copper complexes were prepared in situ by mixing the respective ligand with $Cu(OAc)_2{\cdot}H_2O$ in 1:1 molar ratio in EtOH at room temperature for 2 hours to ensure effective complex formation before addition of benzaldehyde (**11a**). In all cases, the Henry reaction proceeded smoothly to provide β-nitro alcohol **13a** in moderate to excellent 42–93% yields (Table 1). THIQs with aryl substituents at C1 afforded better enantioselectivities in comparison to the same with alkyl substituents (Table 1, entries 1–4 vs 5–8). However, differences in the stereoelectronic effects of the C1-aryl substituents has no significant impact on the enantioselectivity since β-nitro alcohol **13a** was obtained in ~ 34% ee in all cases (Table 1, entries 1–4). However, with C1-alkyl substituents, as the steric size of the alkyl substituents increased from *n*-Pr (THIQ **4e**) to *i*-Pr (THIQ **4f**) to *t*-Bu (THIQ **4g**), the enantioselectivity of the β-nitro alcohol **13a** changed from 22% ee to 2% ee to 34% ee, respectively (Table 1, entries 5–7). THIQ **4h**, where C1 is cyclohexyl provided similar results to THIQ **4f** (Table 1, entries 6 vs 8).

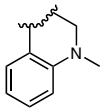
Table 1 Screening of Chiral THIQ and C_2-BIQ Ligands in the Enantioselective Henry Reaction[a]

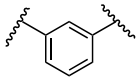
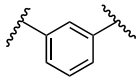


11a 12 13a



THIQ C_2-BIQ

Entry	THIQ	R^2	R^3	Yield[b] (%)	ee[c] (%)
1	**4a**	H	Ph	73	34 (*R*)
2	**4b**	H	2-$MeOC_6H_4$	78	36 (*S*)
3	**4c**	H	2-$H_2NC_6H_4$	42	27 (*S*)
4	**4d**	H	2-naphthyl	74	34 (*R*)
5	**4e**	H	*n*-Pr	78	22 (*R*)
6	**4f**	H	*i*-Pr	70	2 (*S*)
7	**4g**	H	*t*-Bu	71	34 (*S*)
8	**4h**	H	Cy	67	5 (*S*)
9	**7a**	Me	Ph	75	39 (*R*)
10	**7b**	Me	2-$MeOC_6H_4$	83	73 (*S*)
11	**7c**	Me	2-$H_2NC_6H_4$	80	28 (*S*)
12	**7d**	Me	2-naphthyl	78	44 (*R*)
13	**7e**	Me	*n*-Pr	86	43 (*R*)
14	**7f**	Me	*i*-Pr	67	59 (*R*)
15	**7g**	Me	*t*-Bu	71	70 (*R*)
16	**7h**	Me	Cy	70	60 (*R*)
17	**8**			74	76 (*S*)

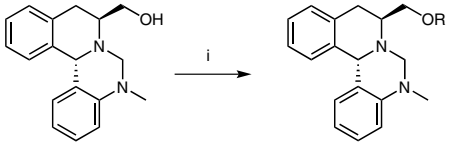
	C_2-BIQ	R	R^2	X		
18	**5a**	H	H	–	80	55 (*S*)
19	**5b**	OMe	H	-CH_2-	93	11 (*R*)
20	**5c**	H	H		85	6 (*S*)
21	**10b**	OMe	Me	-CH_2-	85	26 (*R*)
22	**10c**	H	H		85	14 (*R*)

[a] Reaction conditions: benzaldehyde (**11a**, 0.2 mmol), $MeNO_2$ (**12**, 10 equiv), ligand–$Cu(OAc)_2·H_2O$ (1:1, 10 mol%), EtOH (2 mL).
[b] Isolated yields.
[c] Measured by HPLC (Chiralcel OD-H column, hexane/*i*-PrOH 90:10, flow rate = 0.8 mL/min, λ = 215 nm): t_R = 18.1 (*R*), 22.2 min (*S*). Absolute configuration of **13a** was assigned by comparison with the literature values (see Supporting Information for details).

Though conformational analysis of THIQ–Cu(II) complexes is beyond the scope of this work, we speculate that the modest ees can be attributed to the low conformational rigidity of THIQ–Cu(II) complexes. With a low energy barrier for *N*-inversion,[26] Bowen et al.[27] demonstrated the significant presence of two conformers of THIQs in which the N–H was at the pseudoaxial or pseudoequatorial positions.[28] We believe that restricting the *N*-inversion would give more conformationally restricted THIQ ligands and this would lead to improvement in the enantioselectivity. Therefore, we prepared *N*-methylated ligands **7a**–**h**. To examine the axial/equatorial disposition at the nitrogen, the chemical shifts of the C1-protons of the THIQs were compared before and after *N*-methylation. After *N*-methylation, the chemical shift of the C1-protons moved upfield due to the shielding effect experienced from the axial nitrogen lone pair electrons (see Table 1 in the Supporting Information). This suggested that the *N*-methyl groups occupied the equatorial position in all THIQs (except THIQ **7e**) forcing the nitrogen lone pair electrons into the axial position.[27]

Indeed, the *N*-methylated counterparts THIQs **7a**–**h** gave the β-nitro alcohol **13a** in higher yields (up to 86%) and with significantly improved enantioselectivities (up to 73% ee) (Table 1, entries 1–8 vs 9–16). THIQs **7e**–**h** with C1-alkyl substituents demonstrated a positive relationship between the bulkiness of the alkyl groups and the enantioselectivity. The enantioselectivity increased as the steric size of the C1-alkyl substituents increased from Pr to *i*-Pr (or Cy) to *t*-Bu (Table 1, entries 13–16). THIQ **7g** with a C1 *t*-Bu substituent gave 70% ee. In comparison, C_2-BIQs **5a**–**c** and *N*-methylated counterparts C_2-BIQs **10b**–**c** gave lower enantioselectivities for the β-nitro alcohol **13a** most probably as a result of their larger and conformationally more flexible copper coordination sphere (six- to eight-membered-ring structure) (Table 1, entries 18–22).

We envisioned that further conformational restriction of THIQs would be beneficial. Indeed, the highly restricted THIQ **8** with a methylene bridging group between the two nitrogens gave the β-nitro alcohol **13a** in 74% yield with 76% ee (Table 1, entry 17). We anticipated that further steric hindrance at the hydroxyl group of THIQ **8** could influence the enantioselectivity. Therefore, we prepared the silylated THIQs **14a** and **14b** in high yields as shown in Scheme 3. Asymmetric Henry reaction with THIQs **14a** and **14b** proceeded smoothly to give the β-nitro alcohol **13a** in 82% and 75% yield (Table 2). THIQ **14a** with moderately bulky trimethylsilyl group improved the ee to 80% (Table 2, entry 1), THIQ **14b** with bulkier *tert*-butyldimethylsilyl group severely reduced the ee to 52% (Table 2, entry 2). The results showed that the steric hindrance at the hydroxyl group has little influence on the enantioselectivity of the Henry reaction.



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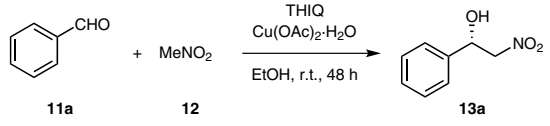
14a: R = TMS (71%)
14b: R = TBDMS (76%)

Scheme 3 Synthesis of THIQs **14a** and **14b** by *O*-silylation of THIQ **8**. *Reagents and conditions*: (i) RCl, 1*H*-imidazole, r.t., 3 h.

Table 2 Screening of THIQs **14a** and **14b** in the Enantioselective Henry Reaction[a]



11a **12** **13a**

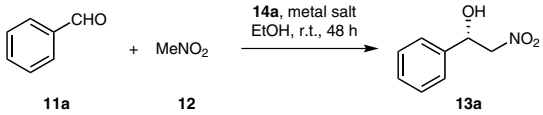
Entry	THIQ	Yield[b] (%)	ee[c] (%)
1	**14a**	82	80 (*S*)
2	**14b**	75	52 (*S*)

[a] Reaction conditions: benzaldehyde (**11a**, 0.2 mmol), $MeNO_2$ (**12**, 10 equiv), ligand–$Cu(OAc)_2·H_2O$ (1:1, 10 mol%), EtOH (2 mL).
[b] Isolated yields.
[c] Measured by HPLC (Chiralcel OD-H column, hexane/*i*-PrOH 90:10, flow rate = 0.8 mL/min, λ = 215 nm): t_R = 18.1 (*R*), 22.2 min (*S*).) Absolute configuration of **13a** was assigned as (*S*) by comparison with the literature values (see Supporting Information for details).

Optimization of the Enantioselective Henry Reaction Using THIQ 14a

With THIQ **14a** as the optimal ligand, we proceeded to optimize the reaction by exploring the effects of metal salts, catalyst loading, solvents, and external bases on the yield and enantioselectivity. First, the effect of metal salts was examined. All THIQ **14a**–metal acetate complexes successfully catalyzed the reaction and gave the β-nitro alcohol **13a** in 54–85% yield (Table 3, entries 1–7). However, only Cu(II) and Cu(I) complexes effectively induced enantioselectivity (Table 3, entries 5–7) while other metal acetate complexes gave racemic products (Table 3, entries 1–4).[8b] THIQ **14a** by itself did not yield the β-nitro alcohol **13a** suggesting its insufficient basicity to deprotonate nitromethane (**12**).[29] The effect of the counterion of the copper salts was also examined (Table 3, entries 8–13). Complexes of $Cu(acac)_2$, CuI, or $Cu(NO_3)_2·2.5H_2O$ with THIQ **14a** failed to give β-nitro alcohol **13a** as they were barely soluble in EtOH (not shown). Complexes of $CuCl_2$, CuCl, and $Cu(OTf)_2$ with THIQ **14a** were soluble, but gave inferior yields and enantioselectivities in comparison to those obtained from THIQ **14a**–$Cu(OAc)_2·H_2O$ complex (Table 3, entries 8–10 vs 5). Anhydrous $Cu(OAc)_2$ gave slightly inferior results in comparison to those obtained with $Cu(OAc)_2·H_2O$ (Table 3, entries 5 and 6). Addition of equimolar amount of H_2O to anhydrous $Cu(OAc)_2$ during the complex formation step provided a comparable ee to the reaction from $Cu(OAc)_2·H_2O$. The exact role of water in this mechanism is not clear.[29] We concluded that $Cu(OAc)_2·H_2O$ is the optimal metal salt and it was used for further optimization.

Table 3 Screening of Metal Salts in the Enantioselective Henry Reaction Catalyzed by THIQ **14a**[a]



11a **12** **13a**

Entry	Metal salts	Catalyst (mol%)	Yield[b] (%)	ee[c] (%)
1	$Co(OAc)_2$	10	65	1
2	$Mn(OAc)_2$	10	54	1
3	$Zn(OAc)_2·2H_2O$	10	85	0
4	$Ni(OAc)_2·4H_2O$	10	80	1
5	$Cu(OAc)_2·H_2O$	10	82	80
6	$Cu(OAc)_2$	10	78	76
7	CuOAc	10	76	72
8	$CuCl_2$	10	35	14
9	CuCl	10	56	68
10	$Cu(OTf)_2$	10	73	3

[a] Reaction conditions: benzaldehyde (**11a**, 0.2 mmol), $MeNO_2$ (**12**, 10 equiv), ligand–metal (1:1, 10 mol%), EtOH (2 mL).
[b] Isolated yields.
[c] Measured by HPLC (Chiralcel OD-H column, hexane/*i*-PrOH 90:10, flow rate = 0.8 mL/min, λ = 215 nm): t_R = 18.1 (*R*), 22.2 min (*S*).

Next, the effect of THIQ **14a**–$Cu(OAc)_2·H_2O$ catalyst loading using 2.5, 5, 10, 15, and 20 mol% was examined (Figure 2). As catalyst loading increased, a gradual increase in the yield of β-nitro alcohol **13a** from 53% to 91% was observed. As the catalyst loading increased from 2.5 to 5 to 10 mol%, the enantioselectivity gradually increased from 67% to 73% to 80% ee, respectively. However, further increase in the loading to 15 mol% and then to 20 mol%, caused no effect on the ee which remained constant at ~80% ee. Therefore, catalyst loading of 10 mol% was deemed optimal (Figure 2).

Next, solvent effects were examined (Table 4). Polar protic solvents such as MeOH, EtOH, and *i*-PrOH afforded the highest yields of 85%, 82%, and 86%, respectively, of β-nitro alcohol **13a** (Table 4, entries 1–3). Ether-type solvents such as THF, Et_2O, and *i*-Pr_2O caused the Henry reaction to become very sluggish, and even after seven days, only modest yields of up to 31% of the β-nitro alcohol **13a** were obtained with inferior ee (Table 4, entries 4–6). Other solvents including CH_2Cl_2, MeCN, and $MeNO_2$ (Table 4, entries 7–9) gave similar results to ether-type solvents. Therefore, EtOH remained as the optimal solvent of choice (Table 4, entry 2). These conditions were very similar to the Evan's conditions under which bisoxazoline ligands worked best.[7a]

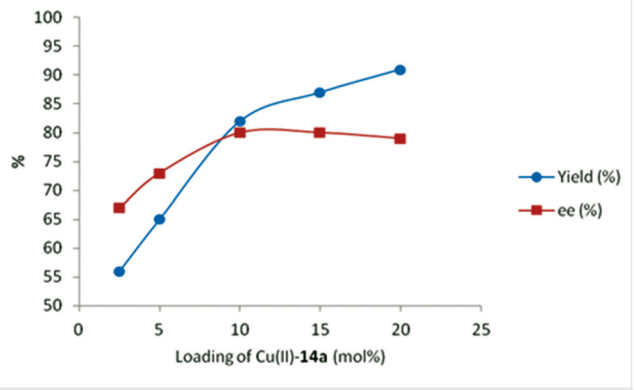
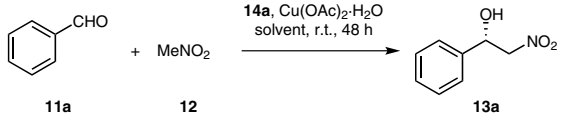


Figure 2 Screening of the loading of THIQ **14a**–$Cu(OAc)_2·H_2O$ complex in the enantioselective Henry reaction

Table 4 Screening of Solvents in the Enantioselective Henry Reaction Catalyzed by THIQ **14a**–$Cu(OAc)_2·H_2O$ Complex[a]



Entry	Solvent	Yield[b] (%)	ee[c] (%)
1	MeOH	85	63
2	EtOH	82	80
3	*i*-PrOH	86	70
4[d]	THF	25	58
5[d]	Et_2O	31	74
6[d]	*i*-Pr_2O	12	63
7[d]	CH_2Cl_2	21	68
8[d]	MeCN	15	28
9	$MeNO_2$	79	71

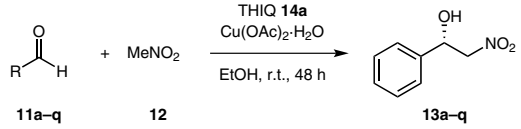
[a] Reaction conditions: benzaldehyde (**11a**, 0.2 mmol), $MeNO_2$ (**12**, 10 equiv), ligand–$Cu(OAc)_2·H_2O$ (1:1, 10 mol%), EtOH (2 mL).
[b] Isolated yields.
[c] Measured by HPLC (Chiralcel OD-H column, hexane/*i*-PrOH 90: 10, flow rate = 0.8 mL/min, λ = 215 nm): t_R = 18.1 (*R*), 22.2 min (*S*).
[d] Reactions run for 7 d.

ortho-Iodobenzoates as counterions in copper-catalyzed reactions increased the enantioselectivity of the Henry reaction.[7b] Likewise, the use of catalytic or stoichiometric amount of external tertiary amine bases (e.g., DIPEA, DABCO, etc.) has been reported in some cases to improve the ee and yield of the enantioselective Henry reactions.[10i,30] However, under our experimental conditions, addition of DIPEA slightly improved the yield to 93%, but significantly reduced the enantioselectivity to 70%. In this case, most likely DIPEA catalyzed the Henry reaction and produced racemic β-nitro alcohol **13a**.

Scope and Limitations of the Asymmetric Henry Reaction

The scope and limitations of the asymmetric Henry reaction under the optimized conditions (Table 4, entry 2) were examined using various aldehydes (Table 5). Aromatic aldehydes **11a**–**q** with electron-donating and -withdrawing substituents reacted smoothly with nitromethane (**12**) to give the corresponding β-nitro alcohols **13a**–**q** in high yields (67–96%) and with moderate to high enantioselectivities (54–80% ee). An exception to this is *p*-nitrobenzaldehyde (Table 5, entry 2), which due to its strong electron-withdrawing activating nitro group, its faster reaction rate led to higher 91% yield and lower 54% ee. Interestingly, the substitution pattern at the aromatic rings had no major effect on the enantioselectivity, but more pronounced effects on the yield of the β-nitro alcohols with *meta* substituents providing lower yields in comparison to *ortho* or *para* substituents (Table 5, entry 4 vs 3; entry 6 vs 5 and 7, and entry 11 vs 10). Other aromatic aldehydes such as 2-naphthalde-

Table 5 Scope of the Enantioselective Henry Reaction Catalyzed by THIQ **14a**–$Cu(OAc)_2·H_2O$[a]



Entry	R	Aldehyde	Product	Yield[b] (%)	ee[c](%)
1	Ph	**11a**	**13a**	82	80
2	4-$O_2NC_6H_4$	**11b**	**13b**	91	54
3	4-ClC_6H_4	**11c**	**13c**	88	77
4	3-ClC_6H_4	**11d**	**13d**	80	71
5	2-BrC_6H_4	**11e**	**13e**	96	76
6	3-BrC_6H_4	**11f**	**13f**	79	74
7	4-BrC_6H_4	**11g**	**13g**	95	80
8	2-FC_6H_4	**11h**	**13h**	94	78
9	4-FC_6H_4	**11i**	**13j**	67	78
10	4-MeC_6H_4	**11j**	**13k**	83	74
11	3-MeC_6H_4	**11k**	**13l**	61	71
12	2-MeC_6H_4	**11l**	**13m**	96	78
13	4-PhC_6H_4	**11m**	**13n**	93	68
14	3-$MeOC_6H_4$	**11n**	**13o**	80	64
15	2-naphthyl	**11o**	**13p**	93	78
16	*trans*-PhCH=CH	**11p**	**13q**	76	61
17	2-furyl	**11q**	**13r**	76	77

[a] Reaction conditions: benzaldehyde **11a**–**m** (0.2 mmol), $MeNO_2$ (**12**, 10 equiv), ligand–$Cu(OAc)_2·H_2O$ (1:1, 10 mol%), EtOH (2 mL).
[b] Isolated yields.
[c] Measured by HPLC. Absolute configuration of the β-nitro alcohol products **13a**–**q** was assigned by comparison with the literature values (see Supporting Information for details).

hyde (**11o**), *trans*-cinnamaldehyde (**11p**), and furfural (**11q**) also gave the corresponding β-nitro alcohols **13o**, **13p**, and **13q**, respectively, in good yields and ee (Table 5, entries 15–17).

Fortunately, with this catalytic system, no side products such as nitroalkenes and epimerization were observed and no special precautions were taken to exclude moisture or air from the reaction flask. The modular synthesis of these THIQ ligands provides opportunities for flexible ligand design and optimization to further improve the enantioselectivity of the enantioselective Henry reaction.

We synthesized chiral THIQ and C_2-BIQ ligands and applied them successfully in enantioselective Henry reactions. The results showed strong dependence of the enantioselectivity on the conformational rigidity of the ligands and size of the copper coordination sphere rather than the type of aldehyde used. The configurationally rigid complex THIQ **14a**–$Cu(OAc)_2{\cdot}H_2O$ catalyzed the enantioselective Henry reaction of a broad range of aldehydes and gave the β-nitro alcohol adducts in up to 93% yield and 80% ee. The prospects of the newly synthesized THIQs and C_2-BIQs in asymmetric catalysis are very promising. A great variety of structures can be synthesized in a modular and direct fashion that require no chiral resolution steps according to the protocol developed in this work. Application of these chiral ligands in other asymmetric reactions will be reported soon.

Chemical reagents were purchased from Sigma-Aldrich or Alfa Aesar and used as received without further purification. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker Avance DPX 300. Unless stated otherwise, data refer to solutions in $CDCl_3$ with TMS as an internal reference. ^{13}C NMR spectra were recorded at 75.47 MHz on a Bruker Advanced DPX 300. HRMS were recorded on Qstar XL MS/MS system. FTIR spectra were recorded on Perkin Elmer FTIR system Spectrum BX. Analytical TLC was performed using Merck 60 F_{254} precoated silica gel plates (0.2-mm thickness) and visualized using UV radiation (254 nm). Flash chromatography was performed using Merck silica gel 60 (230–400 mesh). Optical rotation values were measured on JASCO P-1020 polarimeter.

N-Methylation Using HCHO/$NaCNBH_3$; General Procedure

A 37 wt% aq solution of HCHO (0.75 mL, 10 equiv) was added to a solution of THIQ (1 mmol, 1 equiv) in THF (5 mL) and the mixture was stirred for 15 min at r.t. $NaCNBH_3$ (310 mg, 5 equiv) was then added and the mixture was stirred for an additional 15 min. Glacial AcOH (0.6 mL, 10 equiv) was then added dropwise and the mixture was stirred for a further 3–4 h. Sat. $NaHCO_3$ solution (10 mL) was then added and the mixture extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude mixture was purified by column chromatography. The procedure was used to synthesize the following compounds:

[(1*R*,3*S*)-2-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl]methanol (7a)

The crude product from *N*-methylation of THIQ **7a** was purified by column chromatography (hexane/EtOAc, 1:3) to give THIQ **7a** as a white solid; yield: 230 mg (91%); mp 137 °C; $[\alpha]_D^{21}$ –144 (*c* 1.0, MeOH).

FTIR (KBr): 709, 2917, 1459, 1050, 753, 709 cm^{-1}.

^{1}H NMR: δ = 2.41 (s, 3 H), 2.61–2.80 (m, 2 H), 3.20 (quint, *J* = 4.8 Hz, 1 H), 3.50 (dd, *J* = 5.4, 10.5 Hz, 1 H), 3.60 (dd, *J* = 5.4, 10.5 Hz, 1 H), 4.89 (s, 1 H), 6.99 (d, *J* = 7.5 Hz, 1 H), 7.12–7.29 (m, 8 H).

^{13}C NMR: δ = 25.9, 35.9, 53.6, 61.1, 67.9, 126.2, 127.0, 127.5, 128.2, 129.2, 129.4, 129.6, 133.4, 134.2, 142.3.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{19}NO$: 254.1545; found: 254.1536.

[(1*S*,3*S*)-1-(2-Methoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-3-yl]methanol (7b)

The crude product from *N*-methylation of THIQ **7b** was purified by column chromatography (hexane/EtOAc, 1:3) to give THIQ **7b** as a white solid; yield: 260 mg (92%); mp 95 °C; $[\alpha]_D^{22}$ –140 (*c* 1.0, MeOH).

FTIR (KBr): 1594, 1484, 1241, 1098, 1027, 746 cm^{-1}.

^{1}H NMR: δ = 2.39 (s, 3 H), 2.66–2.82 (m, 2 H), 3.32 (s, 1 H), 3.51–3.65 (m, 2 H), 3.91 (s, 3 H), 5.35 (s, 1 H), 6.61 (d, *J* = 7.2 Hz, 1 H), 6.74–6.79 (m, 1 H), 6.92 (d, *J* = 7.8 Hz, 2 H), 7.10–7.26 (m, 4 H).

^{13}C NMR: δ = 25.9, 35.3, 53.3, 55.8, 60.8, 61.2, 110.7, 119.9, 126.1, 126.4, 128.4, 129.0, 129.4, 130.7, 131.6, 134.3, 135.9, 157.9.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{21}NO_2$: 284.1651; found: 284.1713.

[(1*R*,3*S*)-2-Methyl-1-(naphthalen-2-yl)-1,2,3,4-tetrahydroisoquinolin-3-yl]methanol (7d)

The crude product from *N*-methylation of THIQ **7d** was purified by column chromatography (hexane/EtOAc, 1:3) to give THIQ **7d** as a white solid; yield: 285 mg (94%); mp 127–129 °C; $[\alpha]_D^{22}$ –197 (*c* 1.0, MeOH).

FTIR (KBr): 2926, 1454, 1042, 747 cm^{-1}.

^{1}H NMR: δ = 2.46 (s, 3 H), 2.66–2.84 (m, 2 H), 3.24 (quint, *J* = 2.4 Hz, 1 H), 3.49 (dd, *J* = 5.4, 10.5 Hz, 1 H), 3.65 (dd, *J* = 5.4, 10.5 Hz, 1 H), 5.02 (s, 1 H), 7.03 (d, *J* = 7.5 Hz, 1 H), 7.14–7.32 (m, 4 H), 7.39–7.51 (m, 3 H), 7.66–7.69 (m, 1 H), 7.76–7.81 (m, 2 H).

^{13}C NMR: δ = 26.1, 36.0, 53.3, 61.12, 67.9, 125.8, 125.9, 126.1, 126.8, 127.3, 127.6, 128.0, 128.0, 129.4, 129.8, 132.7, 132.9, 133.9, 134.8, 141.1.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{21}NO$: 304.1701; found: 304.1701.

[(1*R*,3*S*)-2-Methyl-1-propyl-1,2,3,4-tetrahydroisoquinolin-3-yl]methanol (7e)

The crude product from *N*-methylation of THIQ **7e** was purified by column chromatography (hexane/EtOAc, 1:3) to give THIQ **7e** as a yellow oil; yield: 186 mg (85%); $[\alpha]_D^{22}$ –27 (*c* 1.0, MeOH).

FTIR (KBr): 1962, 1456, 1035, 752 cm^{-1}.

^{1}H NMR: δ = 0.99 (t, *J* = 7.5 Hz, 3 H), 1.53–1.65 (m, 3 H), 1.74–1.83 (m, 1 H), 2.22 (s, 3 H), 2.46 (dd, *J* = 5.1, 16.8 Hz, 1 H), 2.60 (dd, *J* = 5.1, 16.8 Hz, 1 H), 3.34–3.43 (m, 1 H), 3.54–3.66 (m, 3 H), 7.06–7.26 (m, 4 H).

^{13}C NMR: δ = 14.0, 20.2, 24.5, 34.5, 37.9, 52.3, 61.8, 63.6, 126.1, 126.1, 128.1, 129.0, 133.1, 138.7.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{21}NO$: 220.1701; found: 220.1701.

[(1*R*,3*S*)-1-Isopropyl-2-methyl-1,2,3,4-tetrahydroisoquinolin-3-yl]methanol (7f)

The crude product from *N*-methylation of THIQ **7f** was purified by column chromatography (hexane/EtOAc, 1:3) to give THIQ **7f** as a yellow oil; yield: 177 mg (81%); $[\alpha]_D^{22}$ –14 (*c* 1.0, MeOH).

FTIR (KBr): 2967, 1457, 1241, 1033 cm^{-1}.

^{1}H NMR: δ = 1.03 (d, *J* = 6.6 Hz, 3 H), 1.11 (d, *J* = 6.6 Hz, 3 H), 1.92–2.04 (m, 1 H), 2.15 (s, 3 H), 2.52 (d, *J* = 8.4 Hz, 2 H), 3.13 (d, *J* = 9.3 Hz, 1 H), 3.48 (quint, *J* = 7.5 Hz, 1 H), 3.62 (dd, *J* = 2.1, 9.5 Hz, 2 H), 7.09–7.20 (m, 4 H).

^{13}C NMR: δ = 20.7, 21.3, 24.9, 32.0, 34.6, 52.7, 62.2, 70.7, 125.2, 126.2, 129.0, 129.8, 133.5, 136.5.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{21}NO$: 220.1701; found: 220.1698.

[(1*R*,3*S*)-1-*tert*-Butyl-2-methyl-1,2,3,4-tetrahydroisoquinolin-3-yl]methanol (7g)

The crude product from *N*-methylation of THIQ **7g** was purified by column chromatography (hexane/EtOAc, 1:3) to give THIQ **7g** as a yellow solid; yield: 205 mg (88%); mp 67 °C; $[\alpha]_D^{22}$ –3 (*c* 1.0, MeOH).

FTIR (KBr): 2978, 2887, 1091, 1041, 756 cm^{-1}.

^{1}H NMR: δ = 1.03 (s, 9 H), 2.18 (s, 3 H), 2.51 (d, *J* = 7.5 Hz, 2 H), 3.39 (s, 1 H), 3.56–3.68 (m, 3 H), 7.07–7.26 (m, 4 H).

^{13}C NMR: δ = 24.5, 29.8, 35.0, 36.6, 52.6, 62.5, 73.2, 125.3, 126.3, 129.1, 129.8, 133.8, 135.6.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{23}NO$: 234.1858; found: 234.1858.

[(1*R*,3*S*)-1-Cyclohexyl-2-methyl-1,2,3,4-tetrahydroisoquinolin-3-yl]methanol (7h)

The crude product from *N*-methylation of THIQ **7h** was purified by column chromatography (hexane/EtOAc, 1:3) to give THIQ **7h** as a yellow oil; yield: 233 mg (90%); $[\alpha]_D^{22}$ –49.5 (*c* 1.0, MeOH).

FTIR (KBr): 2936, 2857, 1759, 1453, 1037, 754 cm^{-1}.

^{1}H NMR: δ = 1.05–1.18 (m, 6 H), 1.46–1.67 (m, 5 H), 2.05 (s, 3 H), 2.44 (d, *J* = 8.1 Hz, 2 H), 2.82 (br s, 1 H), 3.13 (d, *J* = 9 Hz, 1 H), 3.38 (quint, *J* = 8.0 Hz, 1 H), 3.51 (d, *J* = 3.3 Hz, 1 H), 3.53 (d, *J* = 0.9 Hz, 1 H), 6.97–7.11 (m, 4 H).

^{13}C NMR: δ = 24.8, 26.44, 26.49, 26.51, 30.8, 31.5, 34.5, 41.4, 52.4, 62.3, 69.7, 125.0, 126.3, 129.1, 130.0, 133.5, 136.2.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{25}NO$: 260.2014; found: 260.2018.

[(8*S*,13b*S*)-5-Methyl-6,8,9,13b-tetrahydro-5*H*-isoquinolino[2,1-*c*]quinazolin-8-yl]methanol (8)

The crude product from *N*-methylation of THIQ **8** was purified by column chromatography (hexane/EtOAc, 1: 1) to give THIQ **8** as a white solid; yield: 270 mg (96%); mp 179 °C; $[\alpha]_D^{22}$ +260 (*c* 1.0, CH_2Cl_2).

FTIR (KBr): 1605, 1328, 1219, 1087, 1016, 742 cm^{-1}.

^{1}H NMR: δ = 1.65 (br s, 1 H), 2.67–2.84 (m, 2 H), 2.88 (s, 3 H), 3.23–3.28 (m, 1 H), 3.46 (dd, *J* = 6.3, 9 Hz, 1 H), 3.68 (dd, *J* = 6.3, 9 Hz, 1 H), 4.03 (d, *J* = 10.8 Hz, 1 H), 4.3 (d, *J* = 10.8 Hz, 1 H), 5.23 (s, 1 H), 6.61 (dt, *J* = 0.9, 7.5 Hz, 1 H), 6.68 (d, *J* = 8.4 Hz, 1 H), 6.76 (d, *J* = 7.5 Hz, 1 H), 7.10–7.25 (m, 5 H).

^{13}C NMR: δ = 30.6, 36.6, 56.0, 59.9, 65.1, 70.2, 111.5, 117.1, 122.4, 125.6, 127.4, 127.8, 128.0, 128.3, 128.4, 134.5, 137.6, 145.8.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}N_2O$: 281.1654; found: 281.1659.

***N*-Methylation of THIQ and C_2-BIQ Using MeI; General Procedure**

A solution of the respective THIQ or C_2-BIQ (1 mmol) in MeI (4 mL) was stirred for 12 h at r.t. The mixture was then evaporated under reduced pressure to give a dark gum. CH_2Cl_2 (5 mL) and 5 M aq NaOH solution (5 mL) were added to the gum. The resulting biphasic mixture was stirred for 1 h, and then the layers were separated. The aqueous phase extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product obtained was purified by column chromatography. The procedure was used to synthesize the following compounds:

[(1*S*,3*S*)-1-{2-(Dimethylamino)phenyl]-2-methyl-1,2,3,4-tetrahydroisoquinolin-3-yl}methanol (7c)

The crude product was purified by column chromatography (hexane/EtOAc, 1:1) to give compound **7c** as a white solid; yield: 200 mg (67%); mp 155–156 °C; $[\alpha]_D^{22}$ –88 (*c* 1.0, MeOH).

FTIR (KBr): 2939, 1488, 1454, 1102, 947, 744 cm^{-1}.

^{1}H NMR: δ = 2.41 (s, 3 H), 2.75 (d, *J* = 6.9 Hz, 2 H), 2.85 (s, 6 H), 3.48–3.70 (m, 3 H), 5.59 (s, 1 H), 6.70 (d, *J* = 7.2 Hz, 1 H), 6.83–6.94 (m, 2 H), 7.06–7.10 (m, 1 H), 7.11–7.23 (m, 4 H).

^{13}C NMR: δ = 25.5, 35.1, 45.9, 53.2, 61.3, 61.4, 120.6, 123.5, 126.3, 128.0, 128.9, 129.6, 131.2, 133.7.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{24}N_2O$: 297.1967; found: 297.1973.

Bis[(1*S*,3*S*)-3-(hydroxymethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]methane (10b)

The crude product was purified by column chromatography (CH_2Cl_2/MeOH, 95:5) to give **10b** as a white foam; yield: 286 mg (59%); mp 144 °C; $[\alpha]_D^{22}$ –19 (*c* 1.0, MeOH).

FTIR (KBr): 2940, 1514, 1467, 1350, 1242, 1119, 1029 cm^{-1}.

^{1}H NMR: δ = 2.12 (t, *J* = 7.5 Hz, 2 H), 2.32 (s, 6 H), 2.40–2.61 (m, 4 H), 3.36–3.42 (m, 2 H), 3.57–3.73 (m, 4 H), 3.89 (s, 6 H), 3.90 (s, 6 H), 3.98 (t, *J* = 7.8 Hz, 2 H), 6.54 (s, 2 H), 6.58 (s, 2 H).

^{13}C NMR: δ = .23.9, 34.1, 38.8, 50.06, 50.49, 55.9, 61.9, 109.9, 111.7, 124.9, 129.3, 147.63, 147.68.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{38}N_2O_6$: 487.2808; found: 487.2816.

(1*R*,3*R*)-3-(Hydroxymethyl)-1-{3-[(1*R*,3*R*)-3-(hydroxymethyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]phenyl}-2-methyl-1,2,3,4-tetrahydroisoquinoline (10c)

The crude product was purified by column chromatography (CH_2Cl_2/MeOH, 95: 5) to give **10c** as a white foam; yield: 270 mg (63%); $[\alpha]_D^{22}$ –140 (*c* 1.0, MeOH),

FTIR (KBr): 2943, 1738, 1654, 1454, 1243, 1042, 748 cm^{-1}.

^{1}H NMR: δ = 2.38 (s, 6 H), 2.41–2.73 (m, 4 H), 3.13 (quint, *J* = 3.8 Hz, 2 H), 3.46–3.62 (m, 4 H), 4.87 (s, 2 H), 6.87 (dd, *J* = 7.65, 1.5 Hz, 2 H), 7.16 (d, *J* = 7.2 Hz, 2 H), 7.09–7.25 (m, 8 H).

^{13}C NMR: δ = 25.8, 35.6, 52.9, 61.7, 67.9, 126.0, 126.8, 127.6, 128.2, 129.2, 129.6, 130.1, 133.8, 134.6, 142.8.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{32}N_2O_2$: 429.2542; found: 429.2549.

O-Silylation of THIQ 8; General Procedure

To a solution of THIQ **8** (280 mg, 1 mmol) in CH_2Cl_2 (5 mL) was added 1*H*-imidazole (136 mg, 2 mmol) followed by gradual addition of the silyl chloride (3 equiv). The mixture was stirred at r.t. for 3 h, and then the reaction was quenched with distilled H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude residue was purified by column chromatography (hexane/EtOAc, 5: 1). The procedure was used to synthesize *O*-silylated THIQs **14a** and **14b**.

(8*S*,13b*S*)-5-Methyl-8-[(trimethylsilyloxy)methyl]-6,8,9,13b-tetrahydro-5*H*-isoquinolino[2,1-*c*]quinazoline (14a)

THIQ **8** was reacted with TMSCl; purification using column chromatography gave **14a** as a white solid; yield: 250 mg (71%); mp 173 °C; $[\alpha]_D^{22}$ +131 (*c* 0.4, CH_2Cl_2).

FTIR (KBr): 1726, 1603, 1508, 1322, 1277, 756 cm^{-1}.

^{1}H NMR: δ = 0.1 (s, 9 H), 2.72–2.83 (m, 2 H), 2.88 (s, 3 H), 3.22–3.26 (m, 1 H), 3.43 (t, *J* = 8.9 Hz, 1 H), 3.56–3.61 (m, 1 H), 4.09 (d, *J* = 11.1 Hz, 1 H), 4.46 (d, *J* = 11.1 Hz, 1 H), 5.33 (s, 1 H), 6.52 (t, *J* = 7.4 Hz, 1 H), 6.56 (d, *J* = 8.1 Hz, 1 H), 6.66 (d, *J* = 7.5 Hz, 1 H), 7.09 (t, *J* = 7.6 Hz, 1 H), 7.15–7.25 (m, 4 H).

^{13}C NMR: δ = –0.5, 30.6, 36.3, 55.7, 60.7, 65.1, 70.1, 110.7, 116.4, 122.6, 125.4, 127.2, 127.3, 127.8, 128.4, 128.7, 137.8, 145.9.

HRMS (ESI–): *m*/*z* [M]$^-$ calcd for $C_{21}H_{28}N_2OSi$: 352.1971; found: 352.1754.

(8*S*,13b*S*)-8-[(*tert*-Butyldimethylsilyloxy)methyl]-5-methyl-6,8,9,13b-tetrahydro-5*H*-isoquinolino[2,1-*c*]quinazoline (14b)

THIQ **8** was reacted with TBDMSCl; purification using column chromatography gave **14b** as viscous oil; yield: 299 mg (76%); $[\alpha]_D^{22}$ +2 (*c* 1.0, CH_2Cl_2).

FTIR (KBr): 1605, 1505, 1258, 1099, 838, 747 cm^{-1}.

^{1}H NMR: δ = 0.1 (s, 6 H), 0.86 (s, 9 H), 2.72–2.83 (m, 2 H), 2.88 (s, 3 H), 3.22–3.26 (m, 1 H), 3.43 (t, *J* = 8.9 Hz, 1 H), 3.56–3.61 (m, 1 H), 4.09 (d, *J* = 11.1 Hz, 1 H), 4.46 (d, *J* = 11.1 Hz, 1 H), 5.33 (s, 1 H), 6.49 (t, *J* = 7.5 Hz, 1 H), 6.58 (d, *J* = 8.1 Hz, 1 H), 6.62 (d, *J* = 7.5 Hz, 1 H), 7.05 (t, *J* = 7.8 Hz, 1 H), 7.11–7.23 (m, 4 H).

^{13}C NMR: δ = –5.4, –5.3, 18.4, 26.0, 30.5, 36.3, 56.2, 60.5, 65.8, 70.3, 110.8, 116.6, 122.7, 125.5, 127.1, 127.3, 127.8, 128.3, 128.7, 134.6, 138.1, 146.1.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{34}N_2OSi$: 395.2519; found: 395.2514.

Enantioselective Henry Reaction Using THIQ 14a under Optimal Conditions; General Procedure

A solution of THIQ **14a** (7 mg, 0.02 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (4 mg, 0.02 mmol) in EtOH was stirred at r.t. for 2 h followed by addition of the aldehyde (0.2 mmol) and then nitromethane (**12**, 125 µL, 2 mmol). The resulting mixture was stirred at r.t. for 48 h. The mixture was then evaporated. The crude mixture was purified by column chromatography (EtOAc/hexane, 1:5) to give the corresponding β-nitro alcohol products. The configuration and ee were determined by HPLC and compared with literature data (see Supporting Information).

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Supporting Information

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