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A New Strategy for Designing Non-C_2-Symmetric Monometallic Bifunctional Catalysts and Their Application in Enantioselective Cyanation of Aldehydes

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Dedicated to Professor Rugang Xie on the occasion of his 70th birthday

Abstract: A monometallic bifunctional catalyst, in which only one imidazolyl moiety is directly attached at the 3-position of a binaphthol moiety, has been developed. The ligand (*R*)-**1**, which lacks C_2-symmetry and flexible linkers, in combination with Ti(O*i*Pr)$_4$, has been demonstrated to promote the enantioselective cyanation of aldehydes with trimethylsilylcyanide (TMSCN), giving excellent enantioselectivities of up to 98% *ee* and high yields of up to 99%. The use of this bifunctional catalytic system obviates the need for additives and is extremely simple as the reagents are added in one portion at the beginning of the reaction. The protocol has been found to tolerate a relatively wide range of aldehydes when 10 mol% of the (*R*)-**1**/Ti(O*i*Pr)$_4$ complex is deployed in CH_2Cl_2 at −40 °C, the conditions which proved most practical and effective. The asymmetric cyanations also proceeded with lower catalyst loadings (5 mol%, or even 2 mol%), still giving satisfactory enantiomeric excesses and yields. Interestingly, the use of freshly distilled TMSCN dried over CaH_2 gave a low enantioselectivity and only a moderate yield of the adduct as compared with direct use of the commercial reagent. The results of ^{13}C NMR spectroscopic studies implicate HCN as the actual reactive nucleophile.

Keywords: asymmetric catalysis · bifunctional catalysis · BINOL · imidazole · N ligands · nucleophilic addition

Introduction

In recent years, the concept of bifunctional catalysis has been successfully applied to asymmetric catalytic reactions, in which catalysts consist of LALB (Lewis acid/Lewis base) or LABB (Lewis acid/Brønsted base) moieties capable of simultaneously activating both an electrophile and a nucleophile.[1] Such bifunctional catalysis can facilitate the reaction in a synergistic manner similar to enzymatic processes, thus controlling the kinetics of the chemical reaction as well as the orientation of the substrates. Among the most impressive examples, 1,1′-bi-2-naphthol (BINOL)-based monometallic bifunctional chiral catalysts have received particular attention following the pioneering work of Shibasaki and co-workers.[2] These bifunctional catalysts generally incorporate one LA center connected to two naphthoxide moieties and two LB or BB side arms attached at the 3- and 3′-positions thereof by flexible linkers (Figure 1).[2–4]

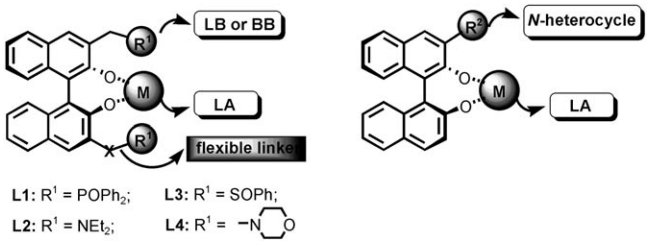

Figure 1. Strategy for designing non-C_2-symmetric monometallic bifunctional catalysts.

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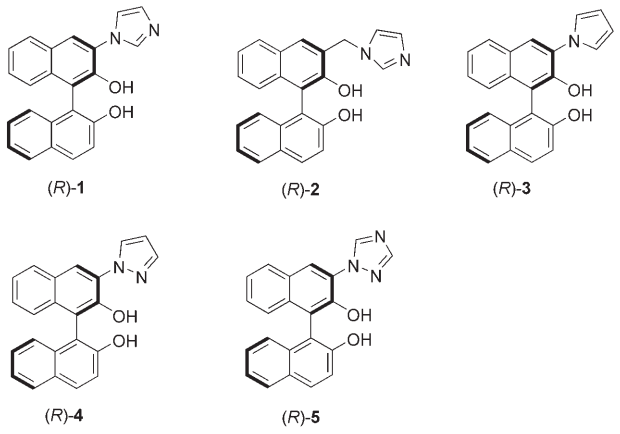
One of the key issues in the design of bifunctional catalysts is how to avoid internal coordination of the LB or BB to the LA.[1a,2a,g] This problem might be overcome by either shortening or reducing the flexibility of the linker, and/or by using a donor additive such as phosphine oxide or hexamethylphosphoramide (HMPA) and/or 4 Å molecular sieves (MS). For example, the aluminum complexes of C_2-symmetric **L1**, **L2**, and **L4**, incorporating methylene linkers at C3 and C3′, are capable of catalyzing the enantioselective cyanation of aldehydes with trimethylsilyl cyanide (TMSCN), whereas their analogues bearing more flexible ethylene linkers are not effective in promoting this reaction. Notably, **L1**, **L2**, and **L4** work very well in the presence of Bu_3PO, $CH_3P(O)Ph_2$, Ph_3PO, or HMPA as additives.[2a,g,3a,4] This effect might be the result of coordination of the external additive to the Lewis acid center, thereby suppressing internal complexation of the LB or BB to the LA. Clearly, however, it is highly desirable to develop a class of bifunctional catalysts capable of catalyzing a number of reactions without the assistance of extra additives.

The above-mentioned BINOL-based bifunctional catalysts bear two identical basic units. However, in the generally accepted catalytic mechanism only one side arm is presumed to function as a Lewis or Brønsted base.[2–4] It is reasonable to assume that the other might only serve as a steric hindrance.[2a,g,3c] Recently, optically pure, non-C_2-symmetric 3-monosubstituted BINOL has been demonstrated to catalyze the cyanation of aldehydes with TMSCN to afford products with low enantioselectivities.[4] Thus, the question arose as to whether the C_2-symmetric structure is indispensable for the design of BINOL-based monometallic bifunctional catalysts.

Imidazole (Im) and its derivatives play key roles in the synergistic catalytic mechanisms of many enzymes.[5] Some recent examples have demonstrated that imidazoles can serve as the base moiety in dual activation or as co-catalysts in some catalytic reactions.[6,7] Quite recently, we also presented facile, mild, and highly enantioselective additions of alkynylzinc reagents to aromatic aldehydes under BINOL/*N*-methylimidazole dual catalysis.[8] In continuation of our ongoing interest in the development of imidazole chemistry,[9] we present herein a new strategy for the design of monometallic bifunctional catalysts that lack C_2-symmetry and flexible linkers, in which only one imidazolyl moiety is directly attached at the 3-position of the binaphthol moiety (Figure 1). Molecular modeling studies suggested that intramolecular complexation of the 3-*N* of the imidazolyl unit of (*R*)-**1** to the internal Lewis acid center would be unfavorable on torsional grounds. On the other hand, this geometry would allow close approach of the two reaction partners. In our quest for highly efficient asymmetric syntheses of biologically active compounds, we expected that this novel class of bifunctional catalysts would serve as miniaturized artificial metalloenzymes.

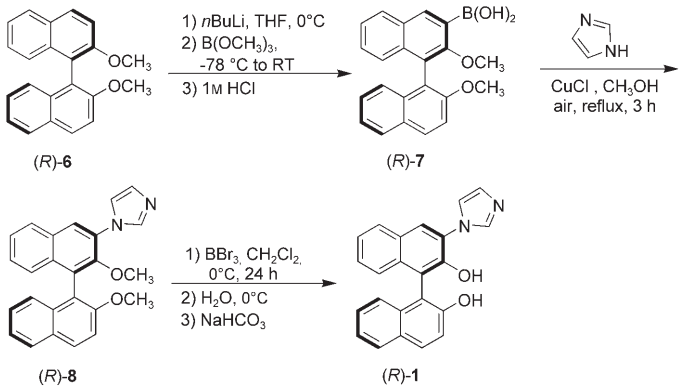


Results and Discussion

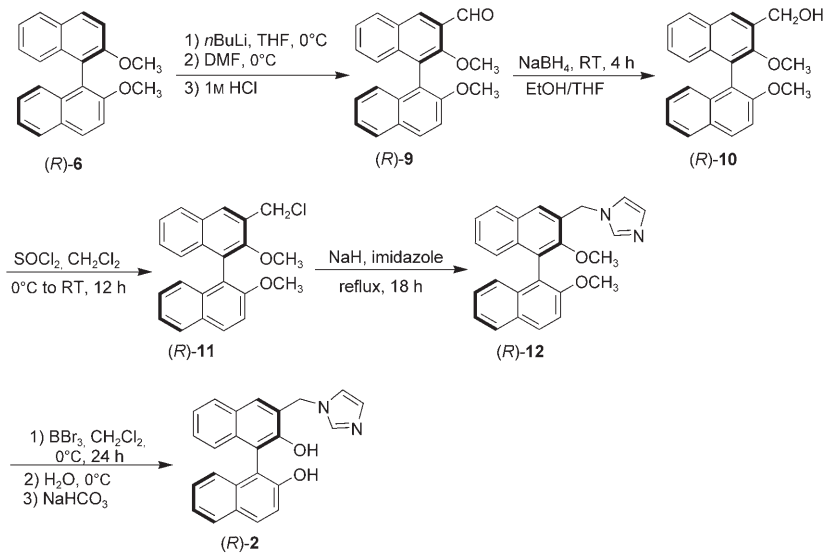
The syntheses of the target ligands involved *N*-arylation reactions of nitrogen-containing heterocycles with binaphthol derivatives bearing the notoriously recalcitrant, sterically hindered, and deactivated *ortho*-substituted alkyloxy group. It is worth noting that such *N*-arylation reactions involving hindered and deactivated substrates have hitherto proved difficult to achieve. Therefore, one of the key issues was to devise highly efficient protocols to carry out coupling reactions of a number of *N*-heterocycles so as to incorporate them at the 3-position of the binaphthol.

The synthesis of 3-imidazolyl-substituted BINOL [(*R*)-**1**] was accomplished by a straightforward process starting from 2,2′-dimethoxy-1,1′-dinaphthyl [(*R*)-**6**]. Treatment of (*R*)-**6** with *n*BuLi and $B(OMe)_3$ afforded (*R*)-3-hydroxyborane-2,2′-dimethoxy-1,1′-dinaphthyl [(*R*)-**7**], which could then be subjected to the *N*-arylation reaction with imidazole according to our previously described simple copper salt catalyzed procedure.[9b] The desired ligand was finally obtained by deprotection of (*R*)-**8** with BBr_3 (Scheme 1).

To investigate the influence of the linker that connects the BINOL unit and the *N*-heterocycle on the catalytic activity and stereoselectivity, we designed the ligand (*R*)-**2** containing a flexible methylene linker at the C3 position of



Scheme 1. Synthesis of the 3-imidazolyl-substituted BINOL (*R*)-**1**.

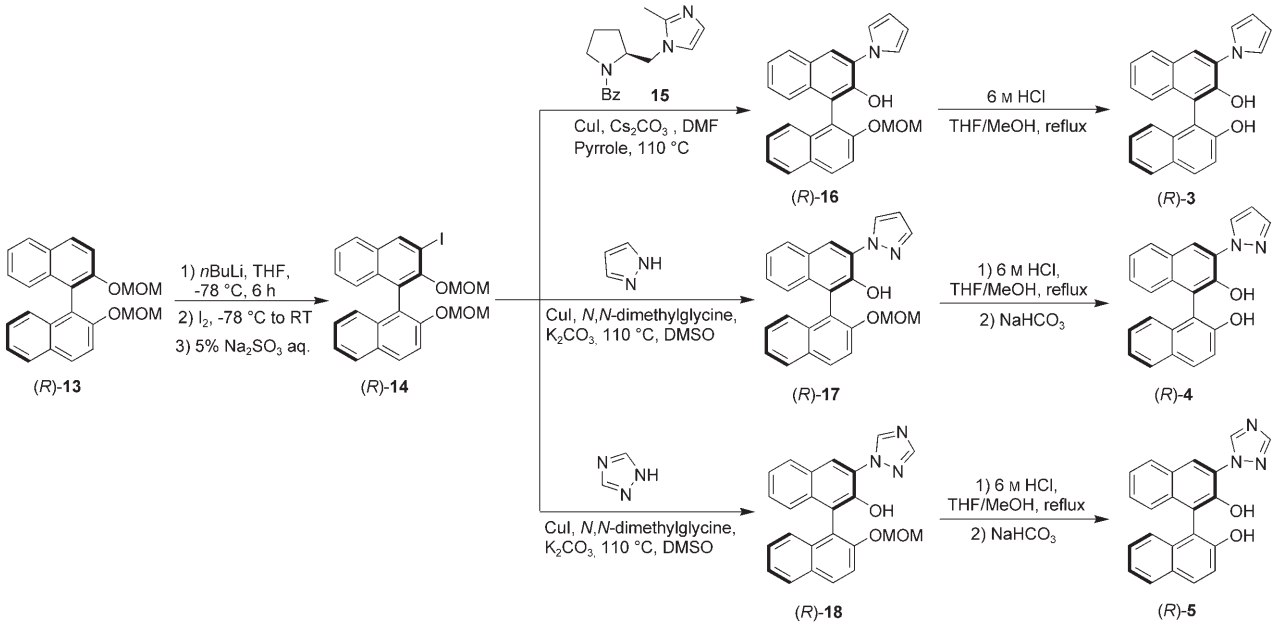


Scheme 2. Synthesis of the 3-imidazolylmethyl-substituted BINOL (*R*)-**2**.

BINOL. As shown in Scheme 2, the synthesis of (*R*)-**2** made use of the same starting material as described above. Formylation of (*R*)-**6** in the presence of *n*BuLi and DMF afforded (*R*)-2,2′-dimethoxy-1,1′-binaphthyl-3-carbaldehyde [(*R*)-**9**], which was then subjected to reduction with $NaBH_4$, chlorination with $SOCl_2$, and coupling with imidazole. The resulting (*R*)-3-(1*H*-imidazol-1-ylmethyl)-2,2′-dimethoxy-1,1′-binaphthyl [(*R*)-**12**] was deprotected with BBr_3 to afford the expected product (*R*)-**2**.

To further illustrate our concept, several analogues of (*R*)-**1** have been synthesized for comparison (Scheme 3). We first designed the pyrrole-derived ligand (*R*)-**3** that lacks the 3-nitrogen atom of the imidazolyl moiety. Additionally, we also synthesized (*R*)-**4** and (*R*)-**5**, which bear basic pyrazole and triazole rings, respectively. All three of these ligands were synthesized by *N*-arylation of the corresponding *N*-heterocycle with 3-iodo-2,2′-bis(methoxymethyl)-1,1′-bi-2-naphthol [(*R*)-**14**], which was easily prepared from readily available (*R*)-**13** through a lithiation–iodination sequence. It is noteworthy that initial attempts to synthesize (*R*)-**3** using either a catalytic system prepared in situ from *N*,*N*-dimethylglycine/CuI as reported by Ma and coworkers[10] or our simple copper salt catalyzed procedure[9b] were unsuccessful. Fortunately, the arylation could be achieved in the presence of pyrrolidinylmethylimidazole/CuI, as described quite recently by our group.[9c] Thus, various bifunctional BINOL ligands were prepared by structural variation of the linker and the *N*-heterocycle.

The catalytic enantioselective cyanation of aldehydes represents a very useful route to the corresponding enantiomerically pure cyanohydrins, which have been identified as highly versatile synthetic building blocks. It is therefore not surprising that great efforts have recently been directed towards the development of this important asymmetric reaction.[11] The majority of the catalytic systems reported to

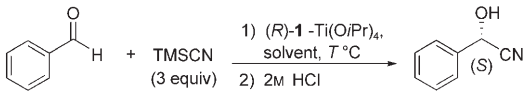


Scheme 3. Synthesis of the 3-(*N*-heterocycle)-substituted BINOL derivatives (*R*)-**3**, (*R*)-**4**, and (*R*)-**5**.

date have consisted of chiral metal complexes, and titanium(IV) catalysts have undoubtedly received the most attention among these Lewis acid systems.[11c,12,13] However, titanium(IV) complexes of BINOL and its derivatives suffer from issues of inadequate general applicability to aldehydes and non-ideal enantioselectivity in the asymmetric cyanohydrin synthesis, despite being excellent chiral catalysts.[11c,13a–c] For example, BINOL, 6,6′-dibromo-, 3,3′-dibromo-, 3,3′-diphenyl-, and 3,3′-dimethyl-BINOL in combination with Ti(O*i*Pr)$_4$ have all been found to provide much lower % *ee* values.[13d] The Ti-BINOL-based bifunctional catalysts proved not to be completely satisfactory even for the cyanation of aldehydes with TMSCN in terms of chemical yield and enantioselection, despite the excellent catalytic performances of their Al complex analogues.[2g,3a] In continuation of our interest in the development of new Ti-BINOL catalytic systems,[8,14] we chose to focus initial studies on evaluation of the behavior of (*R*)-**1** in combination with Ti(O*i*Pr)$_4$ in the asymmetric cyanation of aldehydes.

This work commenced with a preliminary survey of the reaction conditions using benzaldehyde and trimethylsilyl cyanide as model reagents in the presence of (*R*)-**1** in combination with Ti(O*i*Pr)$_4$ (Table 1). The catalytic system was

Table 1. Some representative results from the screening of reaction conditions for the addition of TMSCN to benzaldehyde.[a]



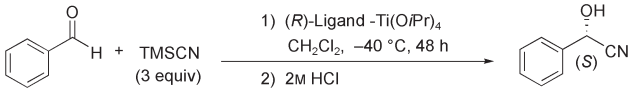
Entry	Ti(O*i*Pr)$_4$ [mol %]	Solvent (2 mL)	*T* [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1	20	Et_2O	−40	10	70	23
2	20	THF	−40	10	95	36
3	20	toluene	−40	10	99	9
4	20	CH_2Cl_2	−40	10	99	58
5	15	CH_2Cl_2	−40	36	99	75
6	12	CH_2Cl_2	−40	36	90	89
7	10	CH_2Cl_2	−40	36	88	97
8	10	CH_2Cl_2	−40	48	97	98
9[d]	10	CH_2Cl_2	−40	48	98	95
10	5	CH_2Cl_2	−40	48	51	54
11	10	CH_2Cl_2	−20	48	98	87

[a] Reactions were carried out on a 0.5 mmol scale with 3.0 equivalents of TMSCN and 0.1 equivalents of (*R*)-**1** in CH_2Cl_2 (2 mL). [b] Yield of isolated product based on the cyanohydrin after acidic hydrolysis. [c] Enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OD-H). [d] The reaction was carried out in CH_2Cl_2 (1.0 mL).

first prepared in situ by stirring (*R*)-**1** and Ti(O*i*Pr)$_4$ at room temperature for 1 h in the appropriate solvent, and then benzaldehyde and TMSCN were added at the selected temperature. To our great delight, in the presence of Ti(O*i*Pr)$_4$ at −40 °C the non-C_2-symmetric (*R*)-**1** smoothly promoted the asymmetric cyanation with excellent enantioselectivities of up to 98 % *ee* and in high yields of up to 97 %. However, the catalytic performance proved to be significantly influenced by the solvent, the reaction temperature, and the ratio of (*R*)-**1** and Ti(O*i*Pr)$_4$. A series of anhydrous solvents (e.g., diethyl ether, THF, toluene, and dichloromethane) was first investigated (Table 1, entries 1–4), of which dichloromethane turned out to be most favorable for the catalytic reaction. A screening of the Ti(O*i*Pr)$_4$/(*R*)-**1** ratio indicated that a 1:1 ratio was the best choice in terms of enantioselectivity (Table 1, entries 4–7). In addition, the reaction temperature was found to have a significant effect on the enantioselectivity of the adduct, although the yield of the product was not very sensitive to temperature (Table 1, entries 8 and 11). Thus, lowering the reaction temperature could dramatically improve the *ee* values. As indicated in Table 1, the best result was achieved with three equivalents of trimethylsilyl cyanide in the presence of 10 mol % of (*R*)-**1** and 10 mol % of Ti(O*i*Pr)$_4$ in CH_2Cl_2 (2 mL) at −40 °C after a reaction time of 48 h (Table 1, entry 8).

To shed light on the possible origin of the remarkable performance of (*R*)-**1**, (*R*)-**3** lacking the base moiety was first chosen for comparison. It was found that the reaction catalyzed by 0.1 equivalents of (*R*)-**3** in combination with 0.1 equivalents of Ti(O*i*Pr)$_4$ gave only a 7 % yield of the product with 20 % *ee*, similar to the results obtained with (*R*)-BINOL, indicating the key role of the 3-nitrogen atom of the imidazole ring (compare entries 6 and 9 in Table 2). This finding suggests that the highly enantioselective catalysis by (*R*)-**1** stems from the dual activation mechanism, a view which is further supported by the results of the following control experiments. First, in the presence of 10 mol % of *N*-methylimidazole (NMI) and 10 mol % of Ti(O*i*Pr)$_4$, the reaction of benzaldehyde with TMSCN gave the racemic cyanohydrin in 80 % yield at −40 °C, whereas the reaction proceeded to an almost negligible extent in the absence of NMI (Table 2, entries 2 and 4). Second, 10 mol % of NMI alone also promoted the cyanation to afford the racemic adduct in 68 % yield in the absence of Ti(O*i*Pr)$_4$ (Table 2, entry 3). Third, 10 mol % of (*R*)-**1** afforded the nearly racemic product without the assistance of Ti(O*i*Pr)$_4$ (Table 2, entry 5). It

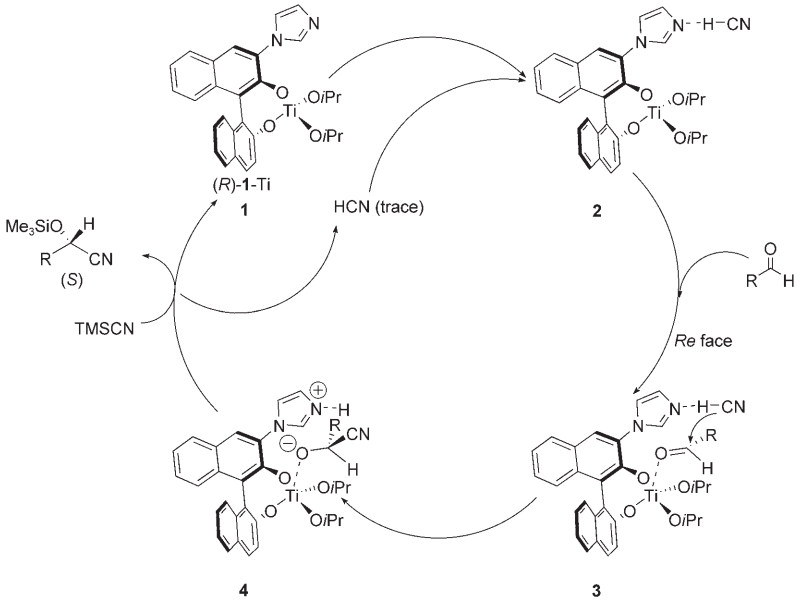
Table 2. Catalytic enantioselective addition of TMSCN to benzaldehyde in the presence of different ligands in combination with Ti(O*i*Pr)$_4$.[a]



Entry	Ligand (10 mol %)	Ti(O*i*Pr)$_4$ [mol %]	Yield [%][b]	*ee* [%][c]
1[d]	(*R*)-BINOL	10	5	7
2	NMI	10	80	–
3	NMI	none	68	–
4	none	10	trace	–
5	(*R*)-**1**	none	52	7
6	(*R*)-**1**	10	97	98
7	(*R*)-**2**	10	21	50
8[d]	(*R*)-**2**	10	44	51
9[e]	(*R*)-**3**	10	7	20
10	(*R*)-**4**	10	trace	–
11[f]	(*R*)-**5**	10	19	−32

[a] Reaction conditions: aldehyde/ligand/Ti(O*i*Pr)$_4$/TMSCN = 1.0:0.1:0.1:3.0 (molar ratio) on a 0.5 mmol scale in CH_2Cl_2 (2.0 mL) at −40 °C for 48 h. [b] Yield of isolated product based on the cyanohydrins. [c] Enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OD-H). [d] 40 mol % of triphenylphosphane oxide as additive. [e] Isolated yield of the corresponding cyanohydrin trimethylsilyl ether. [f] The absolute configuration of this adduct is *R*.

is therefore reasonable to suggest that our catalyst, generated in situ from (*R*)-**1** and Ti(O*i*Pr)$_4$, would serve as an LABB or LALB bifunctional catalyst, in which the Ti metal center is coordinated by the aldehyde while at the same time the 3-nitrogen atom of the imidazole ring is coordinated by cyanide. Then, cooperative interaction between the respective components of the catalyst could lead to excellent chemical yields and high enantioselectivities of the cyanohydrin products, largely circumventing the trouble potentially arising from the NMI-initiated background reaction (compare entries 3 and 6 in Table 2).



Scheme 4. Proposed catalytic cycle.

Interestingly, (*R*)-**2**, bearing an imidazolyl ring attached to a flexible methylene linker, displayed much lower catalytic activity (21% yield) and gave only moderate enantioselectivity (50% *ee*), whereas its analogue (*R*)-**1** that lacks an additional linker was a particularly effective ligand (compare entries 6 and 7 in Table 2). We speculated that the poor catalytic activity is most likely a consequence of internal coordination of the titanium by the 3-nitrogen atom of the imidazolyl moiety. As a consequence of this, the catalyst is unable to bring the two reaction partners into favorably close proximity, and therefore the enantioselectivity is reduced. Additionally, we also investigated the catalytic performances of (*R*)-**4** and (*R*)-**5** containing basic pyrazole and triazole rings, respectively. As expected, replacement of the imidazole with both the pyrazole and triazole rings led to dramatic decreases in both yield and enantioselectivity (compare entries 6, 10, and 11 in Table 2). We assume that the 2-nitrogen atom of the pyrazole or triazole ring lies close to metal center, thus favoring internal complexation, which is in good accordance with the proposal based on molecular modeling.

Although more detailed investigations of the reaction mechanism are currently underway, the proposed transition state model is consistent with experimental observations and accounts for the absolute configurations of some selected products (Scheme 4). A complex that simultaneously binds the two reaction partners should position the activated aldehyde at a perpendicular site close to the internal base unit, while the nucleophile, which interacts with the 3-*N* position of the imidazolyl moiety, could transfer cyanide to the aldehyde. A further question then arises as to whether the reactive nucleophile is HCN or TMSCN. Evidence in favor of the former was that the use of freshly distilled TMSCN dried over CaH_2, from which the release of HCN is far less likely, gave a low enantioselectivity and a moderate yield of the adduct (52% *ee* and 68%, respectively) in comparison with direct use of the commercial reagent. These results thus appear to implicate HCN as the actual reactive nucleophile. A small amount of HCN present in commercial TMSCN should be sufficient to give the corresponding intermediate. At this point, the ^{13}C NMR spectrum of a commercial sample of TMSCN (97% purity according to the supplier) was recorded, which revealed that it indeed contained a trace amount of HCN ($\delta = 108.9$ ppm, $CDCl_3$) (Figure 2), whereas no such signal was observed for the freshly distilled TMSCN.[3c,e] In this context, it is notable that successful simulation of the stereospecificity of an enzyme (oxynitrilase) has also been realized in the enantioselective reaction of HCN with aldehydes via the dual activation pathway by employing cyclic dipeptides composed of (*S*)-histidine, in which the imidazolyl moiety activates HCN to accelerate proton transfer while the carbonyl group is simultaneously activated by a hydrogen bond from the peptide hydrogen.[6]

The present bifunctional catalytic system proved to be capable of tolerating a relatively wide range of aldehydes when the reactions were conducted in the presence of 10 mol% of the (*R*)-**1**/Ti(O*i*Pr)$_4$ complex in CH_2Cl_2 at −40°C for 48 h (Table 3). A number of aromatic aldehydes with sterically hindered, electron-poor, electron-neutral or electron-rich substituents afforded the corresponding cyanohydrins in excel-

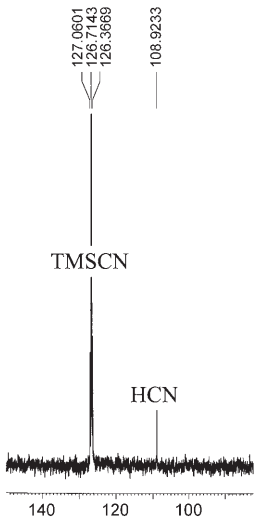
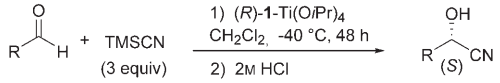


Figure 2. The ^{13}C NMR spectrum of a commercial sample of TMSCN.

Table 3. Enantioselective synthesis of cyanohydrins catalyzed by (*R*)-**1**-Ti.[a]



Entry	Catalyst loading [mol%]	Aldehyde (R)	Yield [%][b]	*ee* [%][c]
1	10	Ph	97	98
2	10	4-ClC_6H_4	92	92
3	10	2-$MeOC_6H_4$	94	91
4	10	4-MeC_6H_4	87	92
5	10	3-MeC_6H_4	93	93
6[d]	5	3-MeC_6H_4	86	93
7	10	2-naphthyl	94	94
8	10	2-furyl	88	91
9	10	$PhCH_2CH_2$	98	97
10	10	cyclohexyl	99	95
11	10	*i*Pr	93	98
12	10	*n*Bu	97	97
13	10	*i*Bu	91	97
14[d]	5	*i*Bu	90	97
15[e]	2	*i*Bu	64	91
16	10	*n*Oct	95	96
17[d]	5	*n*Oct	93	91
18	10	(*E*)-$CH_3CH{=}CCH_3$	85	90

[a] General reaction conditions: see Table 2. [b] Yield of isolated product based on the cyanohydrins. [c] Enantiomeric ratio was determined by chiral HPLC analysis (Chiralcel OD-H) or GC. The absolute configuration of the adduct was assigned by comparison with literature data. [d] The reaction was carried out on a 1.0 mmol scale in CH_2Cl_2 (4.0 mL) at −40 °C for 48 h. [e] The reaction was carried out on a 2.5 mmol scale in CH_2Cl_2 (10.0 mL) at −40 °C for 48 h.

lent yields with enantiomeric excesses in the range 91–98% (Table 3, entries 1–5, 7). The heteroaromatic aldehyde furfural also underwent highly efficient enantioselective cyanation with 91% *ee* in 88% yield (Table 3, entry 8). In general, the asymmetric cyanation of aliphatic aldehydes with TMSCN remains elusive despite a number of highly enantioselective catalysts for aromatic aldehydes. It is therefore highly desirable to develop a more general asymmetric catalyst that is applicable to a wider variety of aldehydes. Notably, our catalytic system efficiently promoted the reactions of TMSCN with a variety of aliphatic aldehydes, including linear and branched ones, in excellent yields (91–99%) and with high enantiomeric excesses (95–98% *ee*) (Table 3, entries 9–13, 16). It should be pointed out that the α,β-unsaturated aliphatic aldehyde (*E*)-2-methyl-2-butenal exclusively yielded the 1,2-addition product in excellent yield and with a high *ee* value (Table 3, entry 18).

Although not yet investigated in detail, the asymmetric cyanations also proceeded with lower catalyst loadings than under our standard conditions of 10 mol% of (*R*)-**1**. With 5 mol% of (*R*)-**1**/Ti(O*i*Pr)$_4$, cyanations of aldehydes with TMSCN were accomplished with satisfactory enantiomeric excesses and yields (Table 3, entries 6, 14, and 17). In particular, even in the presence of 2 mol% of catalyst, the reaction of *i*BuCHO with TMSCN gave an excellent enantioselectivity of 91% *ee*, albeit with a somewhat lower yield of 64% (Table 3, entry 15).

From a practical viewpoint, three notable advantages of our catalytic system may be highlighted. First, our procedure efficiently obviates the need for additives to afford cyanohydrins in good chemical yields and with excellent *ee* values.[2a,g,3a,4,15] Second, our protocol is extremely simple as the reagents are added in one portion at the beginning of the reaction (no slow pump addition is necessary[2a]). Third, our methodology presented here has proved applicable to a wide range of aldehydes, making it among the most practical and effective of strategies.

Conclusion

In summary, we have developed a new addition to the rational design of non-C_2-symmetric BINOL-based bifunctional ligands. The use of (*R*)-**1** in combination with Ti(O*i*Pr)$_4$ has been demonstrated to promote the general and highly enantioselective cyanation of aldehydes with TMSCN. ^{13}C NMR spectroscopic studies have suggested that HCN is likely to be the actual reactive nucleophile. Detailed mechanistic studies aimed at elucidating the origin of the excellent catalytic performance and further investigations into other versions of the asymmetric catalysis are currently underway and the results will be reported in due course.

Experimental Section

General remarks: ^1H and ^{13}C NMR spectra were recorded on a Bruker AV-300 (^1H: 300 MHz; ^{13}C: 75 MHz), a Varian Inova-400 (^1H: 400 MHz; ^{13}C: 100 MHz), or a Varian Inova-600 (^1H: 600 MHz; ^{13}C: 150 MHz) spectrometer. Elemental analyses were performed using a Heraeus CHN-O-Rapid instrument. Mass spectra were recorded with BioTOF Q or Finnigan-LCQ^{DECA} spectrometers. GC-MS analyses were performed using an Agilent 6890–5973 set-up. High-resolution FAB mass spectra and EI mass spectra were obtained using a JEOL JMS-SX/SX 102A instrument. Optical rotations were determined with a WZZ-2B polarimeter. Melting points were determined with XRC-1 and are uncorrected.

Materials: (*R*)-1,1′-Bi-2-naphthol [(*R*)-BINOL] (>99% *ee*) was purchased from Lian YunGang Chiral Chemicals (China) Co., Ltd. TMSCN (97% purity) was purchased from Lancaster and was used as received without further purification except where stated otherwise. Ti(O*i*Pr)$_4$ was purchased from Aldrich Chemical Co. and was freshly distilled under reduced pressure prior to use. Aldehydes were purchased from Aldrich, Lancaster, Acros, and AstatTech in China; all liquid reagents were distilled before use, while the others were used without further purification. Solvents were dried by heating at reflux for at least 24 h over CaH_2 (dichloromethane, DMF) or sodium/benzophenone (tetrahydrofuran, toluene, and diethyl ether) and were freshly distilled prior to use. Except where noted, commercial reagents were used as received without further purification. Unless otherwise indicated, all syntheses and manipulations were carried out under a dry nitrogen atmosphere. *n*BuLi in Et_2O was prepared according to the literature.[16]

Procedures for the preparation of chiral ligands (*R*)-1–(*R*)-5

(*R*)-3-Hydroxyborane-2,2′-dimethoxy-1,1′-dinaphthyl [(*R*)-7]: A flame-dried three-necked flask was charged with (*R*)-**6** (4.72 g, 15 mmol) and dry THF (250 mL) under N_2. *n*BuLi (1.5 M in diethyl ether, 12 mL, 18 mmol) was then slowly added over a period of 1 h at 0 °C and the mixture was stirred for 5 h at the same temperature. $B(OMe)_3$ (5.1 mL, 45 mmol) was then added to the resulting light-brown suspension by means of a syringe over a period of 30 min at −78 °C. The solution was

allowed to warm to room temperature and was then stirred overnight. After being cooled to 0 °C, 1 M HCl (100 mL) was added. The reaction mixture was stirred for 2 h, and then concentrated under reduced pressure. Et_2O (300 mL) was added to the residue and the phases were allowed to separate. The organic phase was washed with 1 M HCl (2× 40 mL) and with saturated aqueous NaCl (100 mL) and then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting white solid was purified by flash column chromatography on silica gel eluting with ethyl acetate/petroleum ether (1:2) to give (*R*)-**7** (4.41 g, 82 %) as white crystals. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.41 (s, 3H), 3.81 (s, 3H), 6.34 (br s, 2H), 7.14 (t, J = 8.4 Hz, 2H), 7.25–7.30 (m, 2H), 7.33–7.36 (m, 1H), 7.39–7.42 (m, 1H), 7.47 (d, J = 9.6 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 9.0 Hz, 1H), 8.57 ppm (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 56.5, 61.5, 113.4, 118.7, 123.6, 123.8, 124.9, 125.1, 125.3, 126.8, 127.5, 128.0, 128.9, 129.0, 130.1, 130.6, 133.8, 135.9, 138.6, 154.9, 160.3 ppm; MS (ESI): *m*/*z*: 314 [M^+−B(OH)$_2$+H].

(*R*)-3-(1*H*-Imidazol-1-yl)-2,2′-dimethoxy-1,1′-dinaphthyl [(*R*)-8]:[9b] Compound (*R*)-**7** (7.17 g, 20 mmol) was added in one portion to a vigorously stirred mixture of imidazole (2.72 g, 40 mmol) and a catalytic amount of CuCl (198.0 mg, 2 mmol) in absolute methanol (250 mL). The mixture was then refluxed for 3 h under dry air. It was then passed through a pad of Celite, the filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel eluting with CH_2Cl_2/C_2H_5OH (40:1 to 25:1) to give (*R*)-**8** (7.00 g, 92 %) as a yellow semi-solid. m.p. 83.0–84.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.13 (s, 3H), 3.82 (s, 3H), 7.12–7.18 (m, 2H), 7.25–7.31 (m, 3H), 7.33–7.37 (m, 1H), 7.44–7.49 (m, 3H), 7.88–7.91 (m, 3H), 8.01–8.05 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.5, 60.4, 113.5, 118.1, 120.5, 123.8, 123.9, 124.8, 125.8, 126.0, 126.9, 127.0, 127.7, 127.9, 128.1, 129.1, 129.5, 130.3, 130.4, 133.2, 133.8, 137.8, 149.6, 154.9 ppm; MS (ESI): *m*/*z*: 381 [M^++H].

(*R*)-3-(1*H*-Imidazol-1-yl)-1,1′-bi-2-naphthol [(*R*)-1]: A flame-dried Schlenk flask was charged with (*R*)-**8** (5.71 g, 15 mmol) and anhydrous CH_2Cl_2 (200 mL) under N_2. The solution was cooled to 0 °C, and then BBr_3 (1.0 M in CH_2Cl_2, 75 mL, 75 mmol) was added over a period of 1 h. The mixture was allowed to warm to room temperature and stirred for 24 h. Thereafter, water (20 mL) was carefully added at 0 °C to quench the reaction, followed by MeOH (10 mL) and solid $NaHCO_3$ to neutralize the mixture. The resulting mixture was stirred for a further 12 h at room temperature and then filtered through a pad of Celite. The filtrate was washed with saturated aqueous NaCl solution (100 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (2×50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with CH_2Cl_2/MeOH (20:1 to 16:1) to give (*R*)-**1** (4.76 g, 90 %) as a pale-yellow solid. m.p. 205.5–207.5 °C; $[\alpha]_D^{20}$ = +132.4 (c = 0.5 in DMSO); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.88 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 7.11 (s, 1H), 7.21–7.29 (m, 3H), 7.32–7.38 (m, 2H), 7.61 (s, 1H), 7.89–7.95 (m, 3H), 8.07 (s, 2H), 8.97 (br s, 1H), 9.50 ppm (br s, 1H); ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 113.0, 118.5, 118.8, 121.1, 122.5, 123.6, 123.8, 123.9, 124.5, 126.3, 126.6, 127.2, 127.8, 128.0, 128.1, 128.3, 129.8, 132.9, 134.2, 137.7, 146.6, 154.0 ppm; HRMS (FAB): calcd for $C_{23}H_{17}N_2O_2$ [M^++H]: 353.1290, found: 353.1283; elemental analysis calcd (%) for $C_{23}H_{16}N_2O_2$: C 78.39, H 4.58, N 7.95; found: C 78.21, H 4.69, N 7.75.

(*R*)-2,2′-Dimethoxy-1,1′-binaphthyl-3-carbaldehyde [(*R*)-9]: A flame-dried three-necked flask was charged with (*R*)-**6** (4.72 g, 15 mmol) and dry THF (250 mL) under N_2. *n*BuLi (1.5 M in diethyl ether, 12 mL, 18 mmol) was then slowly added over a period of 1 h at 0 °C and the mixture was stirred for 4 h at the same temperature. DMF (2.4 mL, 31 mmol) in anhydrous THF (20 mL) was then added dropwise over a period of 30 min and the resulting mixture was stirred for 90 min. Thereafter, 1 M HCl (100 mL, 100 mmol) was slowly added with vigorous stirring. The resulting mixture was stirred for 30 min and then concentrated under reduced pressure. Et_2O (300 mL) was added to the residue and the phases were allowed to separate. The organic layer was washed sequentially with 0.5 M HCl (100 mL), saturated $NaHCO_3$ solution (100 mL), and brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give a yellow solid. The crude product was filtered through a short column (silica gel, Et_2O) and then recrystallized from 95 % EtOH to give (*R*)-**9** (3.60 g, 70 %) as pale-yellow crystals. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.49 (s, 3H), 3.81 (s, 3H), 7.10–7.18 (m, 2H), 7.24–7.37 (m, 3H), 7.41–7.49 (m, 2H), 7.88 (d, J = 8.1 Hz, 1H), 8.03 (t, J = 6.5 Hz, 2H), 8.56 (s, 1H), 10.57 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.5, 62.5, 113.4, 117.9, 123.8, 124.9, 125.7, 126.2, 127.0, 128.1, 128.5, 129.0, 129.1, 130.0, 130.2, 130.3, 131.2, 133.9, 137.3, 155.0, 156.6, 190.9 ppm.

(*R*)-3-Hydroxymethyl-2,2′-dimethoxy-1,1′-binaphthyl [(*R*)-10]: $NaBH_4$ (0.83 g, 22.0 mmol) was added to a solution of (*R*)-**9** (6.85 g, 20.0 mmol) in absolute ethanol (150 mL) and THF (20 mL) at room temperature. After being stirred for 4 h, the reaction mixture was concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 (200 mL) and 3 M HCl (150 mL), stirring vigorously until the solid had dissolved. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give (*R*)-**10** (6.61 g, 96 %) as a white foam. The compound thus obtained was sufficiently pure for use in the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (br s, 1H), 3.37 (s, 3H), 3.77 (s, 3H), 4.87, 4.95 (AB system, J = 13.2 Hz, 2H), 7.11–7.39 (m, 6H), 7.43 (d, J = 9.1 Hz, 1H), 7.84 (s, 1H), 7.87 (s, 1H), 7.93 (s, 1H), 7.99 ppm (d, J = 9.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.6, 60.7, 62.5, 113.6, 119.0, 123.8, 124.5, 124.9, 125.2, 125.4, 126.1, 126.8, 127.8, 127.9, 128.0, 129.1, 130.0, 130.7, 133.7, 133.8, 134.0, 154.7, 155.0 ppm.

(*R*)-3-Chloromethyl-2,2′-dimethoxy-1,1′-binaphthyl [(*R*)-11]: $SOCl_2$ (23.2 mL, 320 mmol) was added dropwise to a stirred solution of (*R*)-**10** (5.51 g, 16 mmol) in anhydrous CH_2Cl_2 (80 mL) at 0 °C. The reaction mixture was then allowed to warm to room temperature and stirring was continued for 12 h. Thereafter, the volatiles were removed under reduced pressure to afford the crude product. Purification by column chromatography on silica gel, eluting with petroleum ether/CH_2Cl_2 (1:1), gave (*R*)-**11** (5.52 g, 95 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.41 (s, 3H), 3.80 (s, 3H), 4.91 (s, 2H), 7.11 (s, 1H), 7.14 (s, 1H), 7.20–7.28 (m, 2H), 7.30–7.41 (m, 2H), 7.45 (d, J = 9.1 Hz, 1H), 7.86 (s, 1H), 7.89 (s, 1H), 8.00 (s, 1H), 8.03 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.5, 56.6, 61.2, 113.6, 118.9, 123.7, 125.0, 125.1, 125.2, 125.4, 126.7, 126.8, 128.0, 128.1, 129.1, 130.0, 130.3, 130.5, 130.8, 134.0, 134.4, 154.6, 155.0 ppm.

(*R*)-3-(1*H*-Imidazol-1-ylmethyl)-2,2′-dimethoxy-1,1′-binaphthyl [(*R*)-12]: A flame-dried three-necked flask was charged with imidazole (1.43 g, 21 mmol) and NaH (60 % in mineral oil, 1.04 g, 26 mmol) under nitrogen, and then dry THF (200 mL) was added at 0 °C. After the mixture had been stirred for 3 h at room temperature, (*R*)-**11** (5.81 g, 16 mmol) was added in one portion, and the resulting mixture was refluxed for a further 18 h. Thereafter, water (60 mL) was slowly added at 0 °C, and the mixture was stirred for 20 min and then concentrated under reduced pressure. CH_2Cl_2 (200 mL) was added to the residue and the biphasic mixture was stirred until the solid had dissolved. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel eluting with CH_2Cl_2/MeOH (30:1) to give (*R*)-**12** (5.81 g, 92 %) as a white powder. m.p. 180.5–182.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.16 (s, 3H), 3.79 (s, 3H), 5.36 (s, 2H), 7.06–7.14 (m, 4H), 7.20–7.28 (m, 2H), 7.30–7.40 (m, 2H), 7.44 (d, J = 9.1 Hz, 1H), 7.58 (s, 1H), 7.67 (s, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 7.8 Hz, 1H), 8.00 ppm (d, J = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 47.2, 56.5, 60.3, 113.5, 118.6, 119.6, 123.8, 124.7, 125.0, 125.2, 125.4, 126.6, 126.9, 127.9, 128.0, 128.4, 129.1, 129.5, 130.2, 130.4, 133.7, 134.2, 137.7, 154.2, 155.0 ppm; MS (ESI): *m*/*z*: 395 [M^++H].

(*R*)-3-(1*H*-Imidazol-1-ylmethyl)-1,1′-bi-2-naphthol [(*R*)-2]: This compound was prepared following the same procedure as described above for [(*R*)-**1**] but using (*R*)-**12** as the starting material. (*R*)-**2** was obtained in 88 % yield as a pale-yellow solid after purification by column chromatography on silica gel eluting with CH_2Cl_2/MeOH (18:1 to 16:1). m.p. 167.0–168.5 °C; $[\alpha]_D^{20}$ = +104.9 (c = 0.5 in DMSO); ^{1}H NMR (600 MHz,

[D$_6$]DMSO): δ = 5.41 (s, 2H), 6.87 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.97 (s, 1H), 7.15–7.20 (m, 2H), 7.23–7.27 (m, 2H), 7.30 (s, 1H), 7.36 (d, J = 9.0 Hz, 1H), 7.55 (s, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.80 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.91 (d, J = 9.0 Hz, 1H), 9.11 ppm (br s, 2H); ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 46.1, 113.3, 116.2, 118.8, 119.9, 122.4, 123.0, 124.0, 124.3, 126.0, 126.1, 127.3, 127.7, 127.9, 128.0, 128.2, 128.3, 129.6, 133.6, 134.3, 137.7, 150.7, 154.0 ppm; HRMS (FAB): calcd for $C_{24}H_{19}N_2O_2$ [M^++H]: 367.1447, found: 367.1445; elemental analysis calcd (%) for $C_{24}H_{18}N_2O_2$: C 78.67, H 4.95, N 7.65; found: C 78.48, H 5.04, N 7.51.

(*R*)-3-Iodo-2,2′-bis(methoxymethyl)-1,1′-bi-2-naphthol [(*R*)-14]: A flame-dried three-necked flask was charged with (*R*)-**13** (7.50 g, 20 mmol) and dry THF (300 mL) under N_2. *n*BuLi (1.5 M in diethyl ether, 16 mL, 24 mmol) was slowly added over a period of 1 h at −78 °C and the mixture was stirred for 5 h at the same temperature. A solution of iodine (6.09 g, 24 mmol) in dry THF (30 mL) was then added dropwise to the chilled solution over a period of 1 h. After being stirred for 1 h at −78 °C, the solution was allowed to warm to room temperature and stirring was continued for 12 h. Aqueous Na_2SO_3 solution (5%, 100 mL) was then slowly added at 0 °C and the resulting mixture was stirred for 2 h. The mixture was subsequently concentrated under reduced pressure, and the residue was partitioned between ethyl acetate (250 mL) and H_2O (100 mL), stirring vigorously until the solid had dissolved. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2×100 mL). The combined organic layers were washed with brine (150 mL) and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization from hexane/ethyl acetate (8:1) to give (*R*)-**14** (8.21 g, 82%) as white crystals. m.p. 124.0–125.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.71 (s, 3H), 3.19 (s, 3H), 4.68, 4.72 (AB system, J = 5.2 Hz, 2H), 5.03, 5.12 (AB system, J = 6.8 Hz, 2H), 7.14–7.19 (m, 2H), 7.24–7.31 (m, 2H), 7.34–7.42 (m, 2H), 7.57 (d, J = 9.2 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 8.8 Hz, 1H), 8.51 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.9, 56.7, 92.9, 94.8, 99.1, 116.2, 120.1, 124.1, 125.4, 125.6, 126.1, 126.3, 126.7, 126.8, 126.9, 127.8, 129.5, 130.1, 132.4, 133.8, 139.8, 151.6, 152.9 ppm; MS (ESI): m/z: 523 [M^++Na].

(*R*)-3-(1*H*-Pyrrol-1-yl)-2′-methoxymethyl-1,1′-bi-2-naphthol [(*R*)-16]:[9c] A flame-dried Schlenk test tube fitted with a magnetic stirring bar was charged with CuI (76.0 mg, 0.4 mmol), pyrrolidinylmethylimidazole **15** (204.0 mg, 0.8 mmol), Cs_2CO_3 (2.6 g, 8 mmol), pyrrole (0.55 mL, 8 mmol), (*R*)-**14** (2.0 g, 4 mmol), and DMF (10 mL) under N_2. A rubber septum was replaced with a glass stopper, and the system was evacuated twice and back-filled with N_2. The reaction mixture was stirred for 30 min at room temperature, and then heated to 110 °C for 48 h. It was then cooled to ambient temperature, diluted with CH_2Cl_2 (15 mL), and filtered through a plug of silica gel. The silica was washed with CH_2Cl_2 (50 mL) and the combined filtrate and washing was concentrated. The resulting residue was purified by column chromatography on silica gel, eluting with petroleum ether/acetone (8:1) to afford the desired product (*R*)-**16** (506 mg, 32%) as a pale-yellow solid. m.p. 49.0–50.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.21 (s, 3H), 5.09, 5.12 (AB system, J = 6.8 Hz, 2H), 5.23 (br s, 1H), 6.39 (t, J = 2.2 Hz, 2H), 7.07–7.09 (m, 1H), 7.20–7.26 (m, 4H), 7.29–7.43 (m, 3H), 7.61 (d, J = 9.2 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.90 (s, 1H), 7.91 (d, J = 8.0 Hz, 1H), 8.04 ppm (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.1, 95.0, 109.6, 116.9, 117.3, 117.7, 122.3, 123.7, 124.3, 124.8, 124.9, 125.0, 126.5, 127.4, 127.8, 128.2, 128.7, 129.7, 130.2, 131.1, 132.3, 133.8, 145.5, 153.6 ppm; MS (ESI): m/z: 396 [M^++H].

(*R*)-3-(1*H*-Pyrrol-1-yl)-1,1′-bi-2-naphthol [(*R*)-3]: Aqueous HCl (6 M, 1.1 mL) was added to a solution of (*R*)-**16** (435 mg, 1.1 mmol) in THF (15 mL) and methanol (3 mL). The resulting solution was refluxed for 12 h until the conversion of (*R*)-**16** was complete. The solution was then cooled to room temperature and neutralized by the addition of saturated aqueous $NaHCO_3$ solution. The resulting mixture was concentrated under reduced pressure, and the residue was extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude product, which was purified by flash chromatography on silica gel eluting with petroleum ether/acetone (1:6) to afford (*R*)-**3** (367 mg, 95%) as a white solid. m.p. 55.5–57.0 °C; $[\alpha]_D^{20}$ = +106.4 (c = 0.5 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.11 (br s, 1H), 5.43 (br s, 1H), 6.39 (t, J = 2.2 Hz, 2H), 7.14–7.19 (m, 4H), 7.28–7.33 (m, 2H), 7.35–7.43 (m, 3H), 7.87–7.89 (m, 2H), 7.95 (s, 1H), 7.98 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 110.1, 110.9, 113.6, 117.8, 122.2, 124.1, 124.3, 125.1, 127.5, 127.6, 128.2, 128.5, 129.1, 129.5, 129.9, 131.6, 131.8, 133.2, 146.9, 152.6 ppm; HRMS (ESI): calcd for $C_{24}H_{18}NO_2$ [M^++H]: 352.1338, found: 352.1337; elemental analysis calcd (%) for $C_{24}H_{17}NO_2$: C 82.03, H 4.88, N 3.99; found: C 81.68, H 4.81, N 3.60.

(*R*)-3-(1*H*-Pyrazol-1-yl)-2′-methoxymethyl-1,1′-bi-2-naphthol [(*R*)-17]:[10] A flame-dried three-necked flask was charged with CuI (570.0 mg, 3.0 mmol), *N*,*N*-dimethylglycine (619.0 mg, 6.0 mmol), K_2CO_3 (16.5 g, 120 mmol), (*R*)-**14** (10.0 g, 20 mmol), pyrazole (2.8 g, 41 mmol), and DMSO (150 mL) at room temperature under nitrogen. After being heated at 110 °C for 60 h, the mixture was concentrated under reduced pressure. The resulting residue was then partitioned between water (100 mL) and CH_2Cl_2 (200 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by chromatography on a silica gel column eluting with petroleum ether/acetone (6:1 to 3:1). (*R*)-**17** was obtained in 44% yield (3.51 g) as a white solid. m.p. 188.0–189.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.19 (s, 3H), 5.01, 5.14 (AB system, J = 6.8 Hz, 2H), 6.56, 6.57 (AB system, J = 2.0 Hz, 1H), 7.13–7.37 (m, 6H), 7.59 (d, J = 9.2 Hz, 1H), 7.73 (d, J = 1.6 Hz, 1H), 7.83–7.99 (m, 4H), 8.24 (d, J = 2.0 Hz, 1H), 11.36 ppm (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.9, 95.3, 107.4, 116.4, 117.4, 119.9, 120.6, 124.1, 124.2, 125.1, 125.3, 126.4, 126.5, 127.6, 127.7, 128.0, 128.1, 129.7, 130.1, 132.9, 133.8, 139.6, 145.9, 152.8 ppm; MS (ESI): m/z: 397 [M^++H].

(*R*)-3-(1*H*-Pyrazol-1-yl)-1,1′-bi-2-naphthol [(*R*)-4]: Aqueous HCl (6 M, 22.0 mL) was added to a solution of (*R*)-**17** (3.50 g, 8.8 mmol) in THF (150 mL) and methanol (50 mL). The resulting solution was refluxed for 12 h until the conversion of (*R*)-**17** was complete. The solution was then cooled to room temperature and neutralized by the addition of saturated aqueous $NaHCO_3$ solution. The resulting mixture was stirred for a further 12 h, then concentrated under reduced pressure, and the residue was extracted with ethyl acetate (3×60 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude product, which was further purified by flash chromatography on silica gel eluting with petroleum ether/ethyl acetate (1:5 to 1:2) to afford (*R*)-**4** (3.05 g, 98%) as white crystals. m.p. 188.0–189.0 °C; $[\alpha]_D^{28}$ = +82.8 (c = 0.5 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.08 (br s, 1H), 6.60 (t, J = 2.0 Hz, 1H), 7.15–7.40 (m, 7H), 7.76 (d, J = 1.6 Hz, 1H), 7.86 (d, J = 8.0 Hz, 2H), 7.92 (d, J = 8.8 Hz, 1H), 8.04 (s, 1H), 8.27 (d, J = 2.8 Hz, 1H), 11.63 ppm (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 107.6, 114.4, 116.1, 117.3, 117.7, 123.3, 124.6, 124.7, 124.8, 126.6, 127.3, 127.8, 127.9, 128.0, 128.2, 129.2, 130.1, 132.6, 133.5, 139.7, 147.0, 151.4 ppm; HRMS (ESI): calcd for $C_{23}H_{17}N_2O_2$ [M^++H]: 353.1290, found: 353.1291; elemental analysis calcd (%) for $C_{23}H_{16}N_2O_2$: C 78.39, H 4.58, N 7.95; found: C 78.44, H 4.49, N 7.77.

(*R*)-3-(1*H*-1,2,4-Triazol-1-yl)-2′-methoxymethyl-1,1′-bi-2-naphthol [(*R*)-18]:[10] A flame-dried three-necked flask was charged with CuI (454.0 mg, 2.4 mmol), *N*,*N*-dimethylglycine (495.0 mg, 4.8 mmol), K_2CO_3 (13.2 g, 96 mmol), (*R*)-**14** (8.0 g, 16 mmol), triazole (2.3 g, 33 mmol), and DMSO (150 mL) at room temperature under nitrogen. After being heated at 110 °C for 60 h, the mixture was concentrated under reduced pressure. The resulting residue was then partitioned between water (100 mL) and ethyl acetate/THF (1:3, 200 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate/THF (1:3, 3×30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was loaded onto a silica gel column and eluted with petroleum ether/acetone (3:1 to 1:1) to afford the corresponding coupling product (*R*)-**18** (3.88 g, 61%) as a white solid. m.p. 193.5–195.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.19 (s, 3H), 5.07, 5.12 (AB system, J = 6.8 Hz, 2H), 7.13 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 7.27–7.31 (m, 2H), 7.36–7.41 (m, 2H), 7.60 (d, J = 9.2 Hz, 1H), 7.91 (t, J = 6.8 Hz, 2H), 8.00 (d, J = 9.2 Hz, 1H), 8.13 (s, 1H), 8.22 (br s, 1H), 8.25

(s, 1H), 8.89 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.1, 95.1, 117.0, 118.3, 119.5, 120.2, 124.6, 124.7, 124.9, 125.1, 127.1, 127.3, 128.0, 128.2, 130.1, 130.7, 133.2, 133.8, 143.3, 144.2, 151.4, 153.3 ppm; MS (ESI): m/z: 397 [M^+].

(*R*)-3-(1*H*-1,2,4-Triazol-1-yl)-1,1′-bi-2-naphthol [(*R*)-5]: This compound was prepared following the same procedure as described above for (*R*)-**4**, but with (*R*)-**18** as the starting material. (*R*)-**5** was obtained in 96% yield as white crystals after purification by column chromatography on silica gel eluting with CH_2Cl_2/MeOH (20:1 to 16:1). m.p. > 224.0 °C (dec.); $[\alpha]_D^{28}$ = +98.0 (c = 0.5 in THF); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.91 (d, J = 8.4 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 7.20–7.29 (m, 3H), 7.34–7.38 (m, 2H), 7.89 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 9.2 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 8.32 (d, J = 9.2 Hz, 2H), 9.11 (s, 1H), 9.26 (brs, 1H), 9.58 ppm (brs, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 113.2, 118.9, 119.0, 122.8, 123.0, 124.2, 124.3, 124.8, 126.6, 127.0, 127.2, 127.9, 128.4, 128.6, 130.1, 133.3, 134.4, 145.4, 145.8, 151.8, 154.1 ppm; HRMS (ESI): calcd for $C_{22}H_{14}N_3O_2$ [M^+−H]: 352.1086, found: 352.1086; elemental analysis calcd (%) for $C_{22}H_{15}N_3O_2$: C 74.78, H 4.28, N 11.89; found: C 74.86, H 3.64, N 11.89.

General procedure for the asymmetric cyanosilylation of aldehydes: A flame-dried reaction vessel was charged with (*R*)-**1** (0.05 mmol, 17.6 mg) under nitrogen, and then dry CH_2Cl_2 (2 mL) and Ti(O*i*Pr)$_4$ (0.05 mmol, 15 μL) were added. After stirring the mixture at room temperature for 1 h, TMSCN (200 μL, 1.5 mmol) was added at −40 °C, followed, after 10 min, by the requisite aldehyde (0.5 mmol). After stirring the reaction mixture at −40 °C for 48 h, aqueous hydrochloric acid (2 M, 3 mL) and ethyl acetate (3 mL) were added at the same temperature. The resulting mixture was stirred vigorously for 3 h at room temperature and then extracted with ethyl acetate (3 × 12 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by flash chromatography eluting with petroleum ether/ethyl acetate (6:1) afforded the pure cyanohydrins.

Each pure cyanohydrin was treated with acetyl chloride (0.5 mL) and TEA (0.5 mL) in CH_2Cl_2 (4 mL). After stirring the mixture for 1 h, the reaction was quenched by the addition of water and the resulting mixture was extracted with ethyl acetate (3 × 8 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated in a rotary evaporator. The residue was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate (15:1) to give the cyanoacetate. Enantiomeric excess was determined by chiral HPLC (Chiralcel OD-H) or chiral GC.

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