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Second-Generation DBFOX Ligands for the Synthesis of β-Substituted α-Amino Acids via Enantioselective Radical Conjugate Additions

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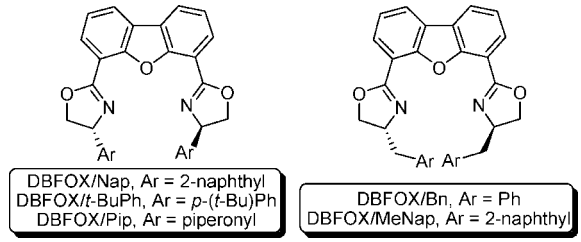

A set of second-generation DBFOX ligands possessing extended aryl or benzyl-type groups was synthesized. The requisite amino alcohols were either commercially available (DBFOX/Bn) or constructed via Sharpless asymmetric aminohydroxylation (DBFOX/Nap, DBFOX/*t*-BuPh, DBFOX/Pip) or phase-transfer-catalyzed asymmetric alkylation (DBFOX/MeNap). Complexes of the ligands with $Mg(NTf_2)_2$ were evaluated as promoters of enantioselective radical conjugate additions to α,β-unsaturated α-nitro amides and esters. Reactions employing the DBFOX/Nap ligand exhibited improved enantioselectivity relative to previously published additions mediated by DBFOX/Ph. However, the relatively modest increase in diastereomeric ratio suggests that our substrate−Lewis acid binding model, which was formulated based on results from DBFOX/Ph-promoted radical conjugate additions, is in need of revision.

Introduction

Recently, we discovered that the DBFOX/Ph ligand developed by Kanemasa and Curran (**1**, Figure 1)[1] is uniquely effective at facilitating the synthesis of β-substituted α-amino acids via enantioselective Lewis acid promoted radical conjugate additions (Scheme 1).[2] β-Substituted α-amino acids are constituents of several peptide natural products;[3] additionally, they are valued as conformationally constrained analogues of α-amino acids.[4] Therefore, numerous means have been devised for their construction.[5] The radical conjugate addition approach[6] to these compounds is attractive due to compatibility of the mild reaction conditions with acidic amide hydrogens and other functional groups present in peptides.[7] In theory, this feature would allow generation of a β-substituted α-amino acid from a complex peptidic substrate possessing the requisite radical acceptor. Consequently, this method should have great utility in the total synthesis of peptide natural products.

The primary drawback to the DBFOX/Ph-promoted radical conjugate additions is the lack of diastereoselectivity. Although the adducts could be obtained in reasonable ee values, the diastereomeric ratios were uniformly poor (<2:1 in almost every case).[2] After determining the absolute configurations of the adducts, we formulated an empirical substrate−Lewis acid binding model (Figure 2). This model is consistent with Curran and Kanemasa's proposal of octahedral geometry for $Mg(ClO_4)_2$−DBFOX/Ph complexes.[1b] Additionally, it accounts for the fact that the hydrogen atom abstraction step occurring at the substrate α-carbon is much more stereoselective than the addition step, which takes place at the β-carbon.[2] Apparently, the ligand is shielding the α-carbon more efficiently than the β-carbon. We reasoned that modifying the ligand by extending the size of the phenyl groups would lead to increased diaster-

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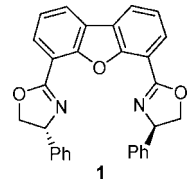

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FIGURE 1. DBFOX/Ph.

SCHEME 1. Mg/1-Promoted Enantioselective Radical Conjugate Additions

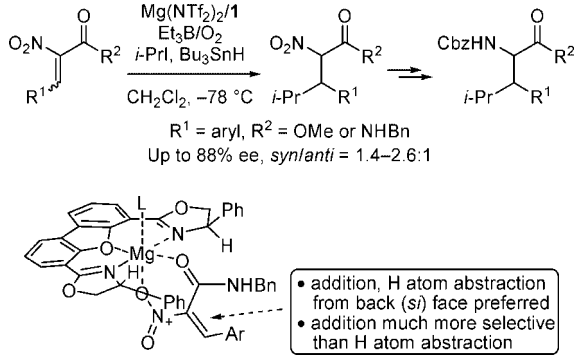


FIGURE 2. Substrate−Lewis acid binding model.

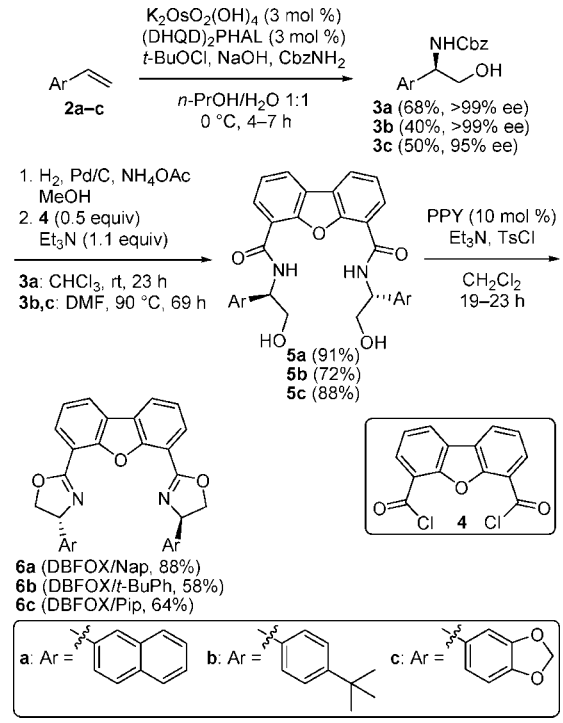
eomeric ratios due to enhanced shielding of the substrate β-carbon. Herein, we present the synthesis of second-generation DBFOX ligands bearing extended aryl or benzyl groups and an evaluation of their performance in the radical conjugate addition reaction.

Results and Discussion

The initial set of ligands that we targeted replaced the phenyl groups of **1** with larger aryl groups. The synthesis of **1** reported by Curran and Kanemasa is quite straightforward, involving bis-amidation of dibenzofuran-4,6-dicarbonyl chloride (**4**, Scheme 2) with (*R*)-phenylglycinol followed by bis-cyclodehydration to form the oxazoline rings.[1c] Thus, to replace the phenyl groups of **1**, we required enantiopure arylglycinols other than phenylglycinol. We elected to synthesize these intermediates via Sharpless asymmetric aminohydroxylation (SAA)[8] of the corresponding styrenes, as shown in Scheme 2. The SAA of 2-vinylnaphthalene (**2a**) has been performed previously,[8b] and afforded **3a** in good yield and excellent ee. Use of the 4-*tert*-butylphenyl (**2b**) and piperonyl (**2c**) congeners resulted in lower yields, but the ee values remained excellent. In each case, the desired *N*-Cbz amino alcohol **3a**−**c** could be isolated by crystallization from the reaction mixture. In some instances the regioisomeric amino alcohol could be detected as a minor product in the reaction mixture, but its isolation and quantification was not pursued.

The Cbz groups of **3a**−**c** were cleaved via hydrogenolysis, and the resulting crude amino alcohols were subjected to amidation with **4**. The amidation of **4** with (*R*)-naphthylglycinol derived from **3a** proceeded in analogous fashion to the reported reaction with (*R*)-phenylglycinol.[1c] However, amidations employing the amino alcohols derived from **3b** and **3c** were sluggish, requiring elevated temperatures and extra time for completion. Presumably, the increased steric bulk of these amino alcohols relative to phenylglycinol is responsible for the decreased reactivity, although it is unclear to us why naphthylglycinol behaves similarly to phenylglycinol.

SCHEME 2. Synthesis of Aryl-Type DBFOX Ligands



The final step in the Curran−Kanemasa synthesis of **1** is a high-yielding (94%) bis-cyclodehydration mediated by diethylaminosulfur trifluoride (DAST).[1c] However, DAST-mediated cyclodehydrations of diamides **5a**−**c** were capricious and low-yielding. It is reported that recrystallization of the diamide precursor to **1** is essential for obtaining good yields of the DBFOX/Ph ligand by this method.[1c] Recrystallizations of **5a**−**c** were impractical due to the small scale of this exploratory project; consequently, the diamides were purified by silica gel chromatography. Thus, it is likely that trace impurities present in our samples of **5a**−**c** are responsible for the poor results with DAST as the cyclodehydration agent. Fortunately, treatment of the diamides with Et_3N, TsCl, and a catalytic amount of 4-pyrrolidinopyridine (PPY)[9] allowed reliable production of

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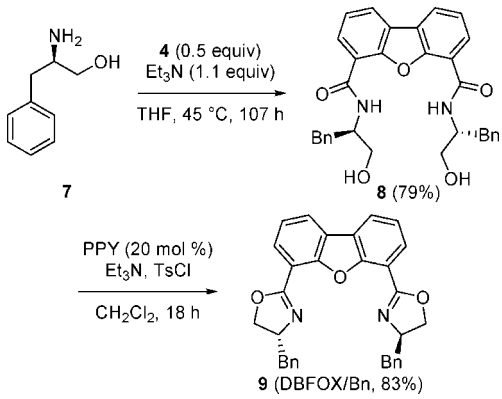
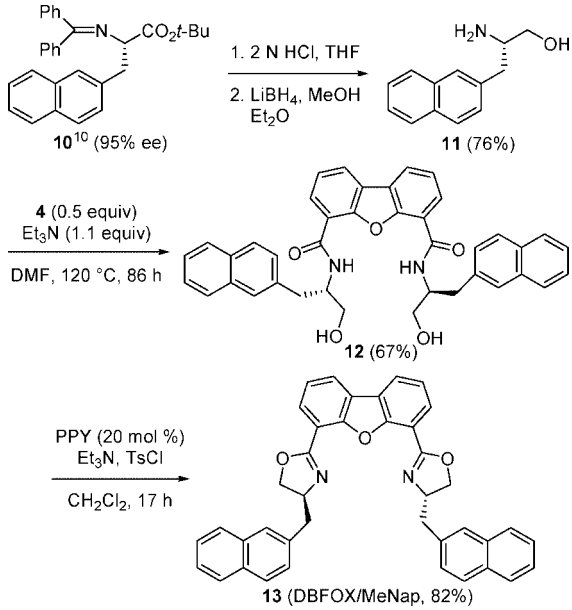
SCHEME 3. Synthesis of DBFOX/Bn



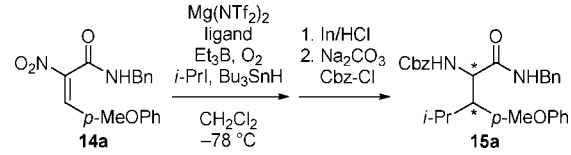
SCHEME 4. Synthesis of DBFOX/MeNap



DBFOX/Nap (**6a**), DBFOX/*t*-BuPh (**6b**), and DBFOX/Pip (**6c**). Notably, the inclusion of PPY was critical, as use of the weaker nucleophilic catalyst DMAP resulted in sluggish, low-yielding reactions.

Later, we decided to expand our study to include DBFOX ligands in which the aryl group is separated from the oxazoline ring by a methylene spacer. Accordingly, commercially available (*R*)-phenylalaninol (**7**, Scheme 3) was subjected to the two-step amidation−cyclodehydration protocol, yielding DBFOX/Bn (**9**). The synthesis of **9** proceeded in similar fashion to the preparation of **6b** and **6c** with the exception that additional quantities of PPY (20 mol %) were required for the cyclodehydration. DBFOX/MeNap (**13**), which incorporates a naphthyl group attached to the methylene spacer, was constructed as outlined in Scheme 4. The requisite naphthylalanine derivative **10** was available in high ee via a previously reported enantioselective alkylation mediated by a chiral phase-transfer catalyst.[10] Hydrolysis of the benzophenone imine followed by reduction of the *tert*-butyl ester provided amino alcohol **11**.[11] The bis-amidation of **4** with **11** was more sluggish than the analogous reactions used to synthesize **5a**−**c** and **8**, requiring higher temperatures and longer reaction times to yield a satisfactory amount of amide **12**. The cyclization of **12** to form **13** proceeded under the conditions employed for DBFOX/Bn (**9**). Ligand **13** was prepared as the opposite enantiomer relative to **6a**−**c** and **9** due to the ready availability of the cinchonidine-derived phase-transfer catalyst (as opposed to the cinchonine-derived catalyst) in our laboratory.

TABLE 1. Evaluation of Ligands in Radical Conjugate Addition[a]



ligand	yield (%)	*syn*/*anti*	% ee (*syn*, *anti*)[b]
1[c]	76	1.4:1	88, 76
6a	65	1.8:1	97, 92
6b	57	1.6:1	84, 79
6c	75	1.2:1	76, 79
9	80	1.5:1	82, 80
13	44	1.6:1	92, 90[d]

[a] 1.0 equiv of $Mg(NTf_2)_2$ and ligand were employed in each reaction. [b] Determined by chiral HPLC (see the Experimental Section for details). [c] Data from ref 2. [d] Major enantiomers were opposite those obtained from reactions employing **1**, **6a**−**c**, and **9**.

With ligands **6a**−**c**, **9**, and **13** in hand, we turned our attention to evaluating their performance in the enantioselective conjugate addition of isopropyl radical to α,β-unsaturated α-nitroamide **14a** (Table 1). To facilitate analysis, the crude adduct was reduced to the corresponding amine and protected, affording carbamate **15a** as a mixture of diastereomers. The data from this investigation are presented in Table 1 alongside our previously reported results with DBFOX/Ph (**1**).[2] The DBFOX/Nap ligand (**6a**) afforded both diastereomers of **15a** in excellent ee (97% for *syn*-**15a**, 92% for *anti*-**15a**) and acceptable yield. DBFOX/*t*-BuPh (**6b**), DBFOX/Pip (**6c**), and DBFOX/Bn (**9**) each provided the adducts in comparable or lower ee than did DBFOX/Ph. DBFOX/MeNap (**13**) delivered both diastereomers of **15a** in >90% ee; however, the combined yield was low (44%). This reduction in yield is likely a consequence of the increased bulk of ligand **13**. The reactions listed in Table 1 were conducted in identical fashion to previously reported radical conjugate additions employing ligand **1**[2] with the exception that longer times were required to ensure complete complexation of $Mg(NTf_2)_2$ to the new, bulkier ligands. Conversion of the $Mg(NTf_2)_2$/ligand/CH_2Cl_2 mixture from a cloudy suspension to a clear solution was used as evidence that complexation had been achieved. Reactions initiated prior to observation of complexation afforded products derived from reduction of the double bond rather than from radical conjugate addition. Presumably, $Mg(NTf_2)_2$ is a stronger Lewis acid than the Mg/DBFOX complex, which possesses a large, relatively electron-rich ligand. Accordingly, the stronger Lewis acid ($Mg(NTf_2)_2$)

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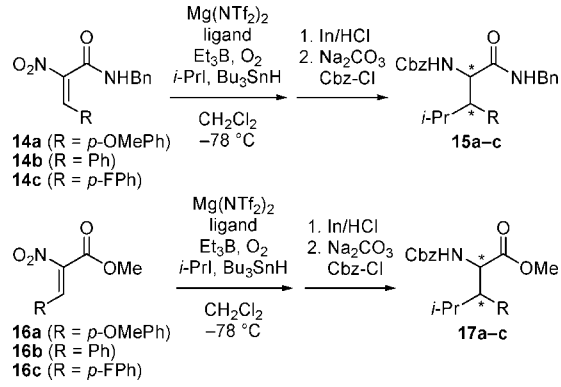
TABLE 2. Scope of Additions with DBFOX/Nap



substrate	ligand	yield (%)	*syn/anti*	% ee (*syn*, *anti*)[a]
14a	**6a**	65	1.8:1	97, 92
14a	**1**[b]	76	1.4:1	88, 76
14b	**6a**	60	1.7:1	74, 87
14b	**1**[b]	66	1.4:1	64, 62
14c	**6a**	63	2.0:1	70, 63
14c	**1**[b]	59	1.6:1	72, 50
16a	**6a**	38	2.2:1	10, 7
16a	**1**[b]	75	2.6:1	21, 28
16b	**6a**	28	1.3:1	7, 5
16b	**1**[b]	60	1.7:1	9, 17
16c	**6a**	17	1.4:1	3, 3
16c	**1**[b]	66	1.7:1	6, 12

[a] Determined by chiral HPLC (see the Experimental Section for details). [b] Data from ref 2.

promotes conjugate reduction of **14a** by Bu_3SnH, whereas the weaker Lewis acid (Mg/DBFOX) mediates the desired radical conjugate addition. In fact, conjugate reduction of **14a** and related acceptors was observed in our prior work when strong Lewis acids such as $MgBr_2 \cdot OEt_2$ and lanthanide triflates were employed.[2]

We were disappointed by the lack of significant improvement in reaction diastereoselectivity (1.8:1 dr with **6a** compared to 1.4:1 dr with **1**). Nevertheless, the increased ee values obtained with DBFOX/Nap warranted further investigations of enantioselective radical conjugate additions with this ligand. Consequently, we examined Mg-DBFOX/Nap-mediated additions of isopropyl radical to acceptors other than **14a**. The results of these reactions are summarized in Table 2 along with data from the analogous reactions employing ligand **1**.[2] Amide substrates **14b**,**c** underwent Mg/**6a**-promoted radical conjugate additions to provide adducts **15b**,**c** in equivalent or greater ee than was observed in Mg/**1**-mediated reactions. Additionally, the *syn/anti* ratios were slightly higher with the new ligand. Both ligands gave best results with substrate **14a** bearing an electron-rich *p*-methoxyphenyl group at the alkene β-position. Unfortunately, Mg/**6a**-promoted additions to ester substrates **16a**−**c** were characterized by significantly lower yields and ee values than resulted from the previous reactions employing Mg/**1** as the chiral Lewis acid.

Chiral HPLC elution profiles established that the same major enantiomers are produced from reactions utilizing either DBFOX/Ph or DBFOX/Nap. Thus, it appears the chiral Lewis acids formed by complexation of these ligands with $Mg(NTf_2)_2$ are binding to the substrates in the same fashion. However, our new results do indicate that the binding model shown in Figure 2 may need revision. We previously determined the absolute configuration of the adducts derived from substrate **14b**.[2] If we

TABLE 3. Selectivity of α and β Stereocenter Formation in Reactions with Ligand 6a[a]

substrate	α (*R*):(*S*)	β (*R*):(*S*)
14a	98:2 (92:8)	35:65 (40:60)
14b	89:11 (82:18)	43:57 (44:56)
14c	84:16 (82:18)	37:63 (37:63)

[a] Values in parentheses are data from reactions with ligand **1** (ref 2).

extend this assignment by analogy to the adducts derived from substrates **14a** and **14c** (a reasonable assumption given the similarities in chiral HPLC elution profiles), we can calculate the selectivity of the radical addition and hydrogen atom abstraction steps. These values are expressed in ratios as "β (*R*):(*S*)" and "α (*R*):(*S*)", respectively, in Table 3. The binding model predicted that extension of the ligand aryl groups would lead to higher *syn/anti* ratios due to a more selective addition process. However, the selectivity of this step increased very slightly; in fact, improvements in the hydrogen atom abstraction were more significant, albeit still modest. The fact that the high *syn/anti* ratios forecast by the binding model failed to materialize suggests that the substrates are interacting with the chiral Lewis acid in a manner different from that depicted in Figure 2.

Moreover, the dramatic contrast in additions to amides **14** versus esters **16** may indicate that the ester substrates bind only weakly to the chiral Lewis acid, thereby allowing the reaction to proceed at least partially through a nonselective pathway with uncomplexed substrates. Indeed, our prior work demonstrated that a relatively slow radical conjugate addition can occur in the absence of Lewis acid promoters.[2] α,β-Unsaturated amides have been shown to complex to Lewis acids more strongly than the corresponding esters.[12] This lower affinity of esters versus amides for Lewis acids could lead to slower, less-selective reactions with substrates **16**. Additionally, the lower yields and ee values of additions to **16a**−**c** with **6a** in place of **1** could be a consequence of the extra bulk of the DBFOX/Nap ligand further discouraging ester−Lewis acid complexation. These data suggest that the major determining factor in the stereoselective radical conjugate additions is the strength of Lewis acid binding to the carbonyl group. In contrast, the nitro group may be interacting weakly or not at all with the chiral Lewis acid. Although complexation of nitro groups to Lewis acids has been reported previously,[13] the minimal improvement in β (*R*):(*S*) with ligand **6a** casts doubt on the existence of bidentate chelation involving the nitro moiety as portrayed in Figure 2.

For substrates **14** and **16** to coordinate to the Mg-$(NTf_2)_2$−DBFOX complex in a bidentate fashion, one of the triflimide ligands must be displaced from the Lewis acid (Figure 3). In an attempt to probe the structure of the complex, we conducted ^{19}F NMR experiments in CD_2Cl_2.[14] The ^{19}F NMR spectrum of the $Mg(NTf_2)_2$−DBFOX/Nap complex consisted of a single peak at temperatures ranging from 20 to −90 °C.

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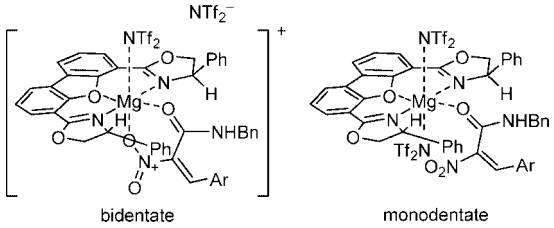
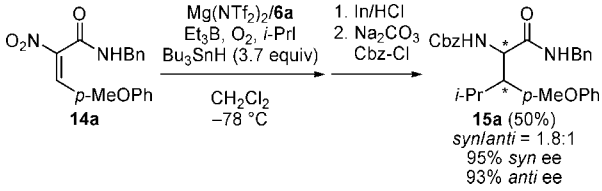


FIGURE 3. Potential substrate−Lewis acid binding modes.

SCHEME 5. Reduced Tin Loadings



Then, amide **14a** was added to the solution, which was stirred at −78 °C for 30 min to promote complexation. These are the identical conditions used to form the complex prior to initiation of the radical conjugate addition. Again, ^{19}F NMR spectra of the resulting complex exhibited only one signal across the aforementioned temperature range. These observations are consistent with a monodentate binding mode of substrate **14a**, which does not require displacement of a triflimide ligand. If the substrate were bound in a bidentate fashion, then two ^{19}F signals should have been observed due to the presence of both bound and free triflimide ions. We cannot rule out the possibility of rapid triflimide ligand exchange on the complex; however, our data require any such exchange to be rapid even at −90 °C. The precise structure of a monodentate substrate−Lewis acid complex would be hard to characterize, as numerous modes of binding can be envisioned. Nonetheless, it is plausible that the existence of either a relatively loose monodentate complex or multiple types of monodentate complexes would have a negative impact on the stereoselectivity of the radical conjugate addition.

It should be noted that α,β-unsaturated amides **14a**−**c** were employed as the *E*-isomers, whereas the *Z*-isomers of esters **16a**−**c** were utilized in the radical conjugate additions. The amides were obtained exclusively as *E*-isomers from Knoevenagel-type condensations, while the esters were produced as ca. 2:1 mixtures of olefinic isomers from which *Z*-**16a**−**c** could be isolated via recrystallization.[2] Previously conducted additions to both isomerically pure and impure samples of **16a**−**c** employing achiral Lewis acids provided the adducts in 1:1 dr.[2] Thus, it appears that the newly formed β-stereocenter does not impact the subsequent hydrogen atom abstraction. This phenomenon could be attributed to the fact that the aryl and isopropyl groups attached to the β-carbon are of roughly similar size. Although the olefin geometry does not impact the diastereomeric ratio, it is possible that the *E*-amides **14** may bind to the chiral Lewis acid in a different manner than do the *Z*-esters **16**.

The reactions summarized in Tables 1 and 2 were conducted with substantial quantities of Bu_3SnH (three portions of 2.5 equiv each) to ensure complete conversion. With the goal of enhancing the preparative value of this transformation, we performed the DBFOX/Nap-mediated addition of isopropyl radical to **14a** with reduced tin loadings (Scheme 5). The dr and ee values were comparable to those obtained from the earlier experiments, but the yield diminished somewhat. No attempt was made to optimize other parameters such as reaction time; thus, it is conceivable that the yield could be restored to its previous level or even increased by careful experimentation. Although further work is necessary, it appears that the radical conjugate addition can be rendered more practical by decreasing the reagent amounts.

Conclusions

Prompted by an empirical substrate−Lewis acid binding model developed to explain the results of our Mg-DBFOX/Ph-promoted enantioselective radical conjugate additions, we have designed and synthesized second-generation DBFOX ligands bearing extended aryl or benzyl groups. Although the DBFOX/Nap ligand (**6a**) did afford improved enantioselectivity in the radical conjugate addition, the increase in diastereomeric ratio was disappointingly small. Accordingly, it seems that the substrate−Lewis acid binding model is in need of revision. The available data from reactions and NMR experiments suggest that the nitro group of substrates **14** and **16** is not complexing strongly to the Lewis acid. Despite the fact that these ligands did not perform as anticipated in the radical conjugate addition, they may be useful in other asymmetric reactions. In particular, the concise syntheses of **6a**−**c**, **9**, and **13** reported herein (2−4 steps from commercially available or known materials) makes them easily accessible. Consequently, the utility of these second-generation DBFOX ligands in other transformations as well as the design of new promoters for the radical conjugate addition will be subjects of future investigations.

Experimental Section

(*R*)-Benzyl 2-Hydroxy-1-(naphthalen-2-yl)ethylcarbamate (3a). A stirred solution of benzyl carbamate (309.0 mg, 2.04 mmol) in *n*-propanol (2 mL) was treated with a freshly prepared NaOH solution (1.25 M in H_2O, 1.0 mL, 1.25 mmol). *tert*-Butyl hypochlorite[15] (240.7 mg, 2.22 mmol) was then added, followed by $(DHQD)_2PHAL$ (30.9 mg, 0.040 mmol). The resulting mixture was stirred until homogeneous, then cooled to 0 °C and stirred for 10 min. 2-vinylnaphthalene (206.0 mg, 1.34 mmol) was then added, followed by a solution of $K_2OsO_2(OH)_4$ (10.0 mg, 0.027 mmol) in 1.25 M NaOH (1.0 mL, 1.25 mmol). The resulting solution was stirred at 0 °C for 4.5 h, at which time stirring was ceased and the flask was cooled to −25 °C. The product was collected by filtration, washed with cold *n*-PrOH-H_2O (1:1), and dried overnight on the benchtop to afford **3a** (288.3 mg, 0.90 mmol, 68%) as a white solid. Spectral data for **3a** were identical with those previously reported.[8b,16]

***N*^{4},*N*^{6}-Bis((*R*)-2-hydroxy-1-(naphthalen-2-yl)ethyl)dibenzo-[*b*,*d*]furan-4,6-dicarboxamide (5a).** A solution of **3a** (161.0 mg, 0.50 mmol) in MeOH (4.0 mL) was treated with NH_4OAc (117.9 mg, 1.53 mmol) followed by 10% Pd/C (21.4 mg, 0.13 wt equiv). The resulting mixture was stirred at rt under H_2 (1 atm) for 21 h, then

(15) Mintz, M. J.; Walling, C. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 184. For best results, this reagent was used within two weeks of preparation.

(16) Occasionally, the product would fail to crystallize from the reaction mixture. In these cases, the following workup and isolation procedure was employed. The solution was treated with saturated aq Na_2SO_3 (10 mL), then stirred at 0 °C for 15 min. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 2 × 20 cm, 30−50% EtOAc in hexanes gradient elution) afforded **3a**. In some cases, repeated chromatography was required to separate **3a** from its undesired amino alcohol regioisomer and excess benzyl carbamate.

filtered through Celite (washed with MeOH) to afford the crude amino alcohol, which was used directly in the next step.

A solution of **4**[1c] (73.8 mg, 0.25 mmol) in anhydrous $CHCl_3$ (2.0 mL) was stirred at 0 °C under Ar for 5 min, then treated dropwise with a solution of the crude amino alcohol and Et_3N (80 μL, 58.2 mg, 0.58 mmol) in anhydrous $CHCl_3$ (1.0 mL). The resulting mixture was stirred at 35 °C under Ar for 24 h, then treated with solid NH_4Cl (50 mg), stirred at rt for 30 min, and filtered. The solid was stirred in THF (10 mL) for 30 min, and the mixture was filtered. The combined organic solutions were concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 20 cm, 50−100% EtOAc in hexanes gradient elution) afforded **5a** (133.9 mg, 0.23 mmol, 91%) as a yellow oil: $[\alpha]^{25}_D$ +131 (*c* 0.10, EtOH); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.10 (d, *J* = 7.5 Hz, 2H), 8.03 (d, *J* = 7.0 Hz, 4H), 7.86 (s, 2H), 7.80−7.72 (m, 8H), 7.50−7.47 (m, 4H), 7.42−7.39 (m, 2H), 5.45 (dd, *J* = 10.0, 6.5 Hz, 2H), 4.07 (dd, *J* = 12, 3.5 Hz, 2H), 3.99 (dd, *J* = 11.5, 6.5 Hz, 2H), 3.51 (br s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.5 (2C), 153.4 (2C), 136.5 (2C), 133.3 (2C), 132.9 (2C), 128.6 (2C), 127.9 (2C), 127.6 (2C), 127.5 (2C), 126.2 (2C), 125.9 (2C), 125.6 (2C), 124.8 (2C), 124.3 (2C), 124.2 (2C), 123.6 (2C), 118.9 (2C), 66.0 (2C), 56.6 (2C); IR (film) ν_{max} 3325, 2920, 2850, 1731, 1695, 1682, 1658, 1641, 1592, 1547, 1539, 1531, 1462, 1060 cm^{-1}; HRMS (ESI) *m*/*z* 595.2226 (MH^+, $C_{38}H_{30}N_2O_5H$ requires 595.2228).

4,6-Bis((*R*)-4-(naphthalen-2-yl)-4,5-dihydrooxazol-2-yl)dibenzo[*b*,*d*]furan (6a). A solution of **5a** (59.2 mg, 0.10 mmol) in anhydrous CH_2Cl_2 (1.5 mL) was treated with Et_3N (40 μL, 29.1 mg, 0.29 mmol) and 4-pyrrolidinopyridine (4.8 mg, 0.032 mmol). The mixture was stirred at 0 °C for 10 min, then treated dropwise with a solution of TsCl (45.9 mg, 0.23 mmol) in anhydrous CH_2Cl_2 (1.5 mL). The resulting mixture was vigorously stirred at rt for 19 h, then treated with saturated aq NH_4Cl (7 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 19 cm, 20−100% EtOAc in hexanes gradient elution) afforded **6a** (49.1 mg, 0.088 mmol, 88%) as an off-white solid: $[\alpha]^{25}_D$ −28 (*c* 0.13, EtOH); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.24 (d, *J* = 8.0 Hz, 2H), 8.17 (d, *J* = 7.5 Hz, 2H), 7.87 (s, 2H), 7.80 (d, *J* = 8.0 Hz, 4H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.53−7.48 (m, 4H), 7.44−7.36 (m, 4H), 5.68 (t, *J* = 9.0 Hz, 2H), 4.96 (t, *J* = 9.0 Hz, 2H), 4.40 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.5 (2C), 154.4 (2C), 145.3 (2C), 139.8 (2C), 133.4 (2C), 132.8 (2C), 128.8 (2C), 128.6 (2C), 127.9 (2C), 127.7 (2C), 126.2 (2C), 125.8 (2C), 125.5 (2C), 124.9 (2C), 124.8 (2C), 123.9 (2C), 123.1 (2C), 74.8 (2C), 70.1 (2C); IR (film) ν_{max} 2928, 1650, 1494, 1427, 1185, 1124, 984 cm^{-1}; HRMS (ESI) *m*/*z* 559.2026 (MH^+, $C_{38}H_{26}N_2O_3H$ requires 559.2016).

General Procedure for Enantioselective Radical Conjugate Additions Promoted by $Mg(NTf_2)_2$ and 6a. A solution of $Mg(NTf_2)_2$ (64.0 mg, 0.11 mmol) and ligand **6a** (50.0 mg, 0.11 mmol) in anhydrous CH_2Cl_2 (1.5 mL) was stirred at rt for 16 h, then treated with **14** or **16** (0.11 mmol). The walls of the reaction vessel were washed with CH_2Cl_2 (0.5 mL), and the mixture was stirred at −78 °C for 30 min. Isopropyl iodide (60 μL, 100 mg, 0.60 mmol), Bu_3SnH (72 μL, 78 mg, 0.27 mmol), Et_3B (3.45 M solution in CH_2Cl_2, 157 μL, 0.55 mmol), and O_2 (5 mL) were added sequentially, and identical quantities of these reagents were added twice more at 1.5 h intervals. The mixture was stirred at −78 °C for an additional 1 h (4 h total since initiation of radical reaction), treated with 2 N HCl (5 mL), and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were concentrated in vacuo.

The crude adducts were treated with concd HCl (0.30 mL, 3.6 mmol), H_2O (1 mL), THF (1 mL), and indium powder (101.0 mg, 0.88 mmol). The resulting mixture was stirred at rt for 15 h, the solids were removed, and the volatiles were removed in vacuo. The residue was diluted with 1 N HCl (5 mL), and tin byproducts were removed by extraction with hexanes (5 × 5 mL). The aqueous layer was treated with Na_2CO_3 (added until pH ∼8) and saturated aq sodium potassium tartrate solution (5 mL), then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Fifty percent of the crude amine mixture was subjected to flash chromatography (SiO_2, 1−4% MeOH in CH_2Cl_2 gradient elution) to afford samples of the pure *syn* and *anti* diastereomers suitable for chiral HPLC analysis after further derivatization (either *N*-Cbz or *N*-Ac protection; see below).

The remaining 50% of the crude amine mixture was treated with benzyl chloroformate (15 μL, 18.1 mg, 0.098 mmol), Na_2CO_3 (12.0 mg, 0.11 mmol), and THF (1 mL). The resulting mixture was stirred at rt for 18 h, concentrated in vacuo, and purified by flash chromatography (90:10 SiO_2−KF,[17] 0−30% EtOAc in hexanes gradient elution), affording carbamates **15** or **17** as white solids that were mixtures of diastereomers. Spectral data for **15a**−**c** and **17a**−**c** were consistent with previously reported data.[2]

***N*-Benzyl 2-Benzyloxycarbonylamino-3-(4-methoxyphenyl)-4-methylpentanamide (15a).** *syn*-**15a** was obtained in 97% ee, as analyzed by HPLC (Chiralcel OD-H, 98:2 hexane:*i*-PrOH, 0.7 mL/min; t_R = 20.6 min (major), 28.6 min). *anti*-**15a** was obtained in 92% ee, as analyzed by HPLC (Chiralcel OD-H, 98:2 hexane:*i*-PrOH, 1 mL/min; t_R = 25.0 min (major), 31.6 min).

***N*-Benzyl 2-Benzyloxycarbonylamino-4-methyl-3-phenylpentanamide (15b).** *syn*-**15b** was obtained in 74% ee, as analyzed by HPLC of the derivative in which the *N*-Cbz group is replaced by an acetate[2] (Chiralcel OD-H, 98:2 hexane:*i*-PrOH, 1 mL/min; t_R = 6.2 min (major), 8.8 min). *anti*-**15b** was obtained in 87% ee, as analyzed by HPLC under identical conditions (t_R = 18.1 min (major), 22.9 min).

***N*-Benzyl 2-Benzyloxycarbonylamino-3-(4-fluorophenyl)-4-methylpentamide (15c).** *syn*-**15c** was obtained in 70% ee, as analyzed by HPLC of the derivative in which the *N*-Cbz group is replaced by an acetate[2] (Chiralcel OD-H, 98:2 hexane:*i*-PrOH, 1 mL/min; t_R = 5.9 min (major), 9.2 min). *anti*-**15c** was obtained in 63% ee, as analyzed by HPLC under identical conditions (t_R = 16.2 min (major), 21.2 min).

Methyl 2-Benzyloxycarbonylamino-3-(4-methoxyphenyl)-4-methylpentanoate (17a). *syn*-**17a** was obtained in 10% ee, as analyzed by HPLC (Chiralcel OD-H, 98:2 hexane:*i*-PrOH, 1 mL/min; t_R = 17.4 min (major), 23.9 min). *anti*-**17a** was obtained in 7% ee, as analyzed by HPLC under identical conditions (t_R = 11.8 min (major), 23.0 min).

Methyl 2-Benzyloxycarbonylamino-4-methyl-3-phenylpentanoate (17b). *syn*-**17b** was obtained in 7% ee, as analyzed by HPLC (Chiralcel OD-H, 98:2 hexane:*i*-PrOH, 1 mL/min; t_R = 11.7 min (major), 18.3 min). *anti*-**17b** was obtained in 5% ee, as analyzed by HPLC under identical conditions (t_R = 7.3 min (major), 21.8 min).

Methyl 2-Benzyloxycarbonylamino-3-(4-fluorophenyl)-4-methylpentanoate (17c). *syn*-**17c** was obtained in 3% ee, as analyzed by HPLC (Chiralcel OD-H, 98:2 hexane:*i*-PrOH, 1 mL/min; t_R = 11.5 min (major), 16.7 min). *anti*-**17c** was obtained in 3% ee, as analyzed by HPLC under identical conditions (t_R = 7.6 min (major), 14.9 min).

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Supporting Information Available: General experimental details, synthetic procedures, spectral data, and ^1H and ^{13}C NMR spectra for all new compounds, as well as HPLC traces for enantioselective radical conjugate additions. This material is available free of charge via the Internet at http://pubs.acs.org.

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