Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 2417–2428

TETRAHEDRON: *ASYMMETRY*

Enantioselective conjugate radical addition reactions mediated by chiral Lewis acid complexes of (*R*,*R*)-4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline) (DBFOX/Ph)

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Received 27 May 1999; accepted 9 June 1999

Abstract

A high-yielding synthesis (50% overall yield) of tridentate bisoxazoline ligand (*R*,*R*)-4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline) (DBFOX/Ph) was developed. DBFOX/Ph was subsequently tested in enantioselective conjugate radical additions onto 3-(3-phenyl-2-propenoyl)-2-oxazolidinone. Two dozen Lewis acids were evaluated, and $Mg(ClO_4)_2$ emerged as the best Lewis acid in terms of yield and enantioselectivity (100% yield, 75.4% ee (*S*)).

1. Introduction

Free radical reactions have emerged as a powerful synthetic tool, and have recently attracted considerable attention in the context of stereoselective carbon–carbon bond formation.[1] The increased understanding of the principles governing stereoselectivity in radical chemistry[2] has translated into successful enantioselective bond formations,[3] and examples of chiral Lewis acid mediated radical reactions[4] have been reported in the past few years. Complexes of C_2-symmetric chiral bisoxazolines[5] and Lewis acids such as **4** (Scheme 1) have been employed to achieve excellent facial selectivity in conjugate radical additions onto planar prochiral oxazolidinone **1** and pyrazole templates **2**.[6]

Sibi and Porter[6a] have found that a matching of ligand Lewis basicity and metal salt Lewis acidity is crucial to achieve sufficient turnover at −78°C for radical reactions of α,β-unsaturated acyloxazolidinone **1a**. Under these low-temperature conditions, the uncatalyzed background rate of radical addition proved to be negligible. For unfavorable ligand/Lewis acid combinations, activation of the substrate was insufficient and poor conversion and low enantioselectivity were observed. Initially, stoichiometric ratios

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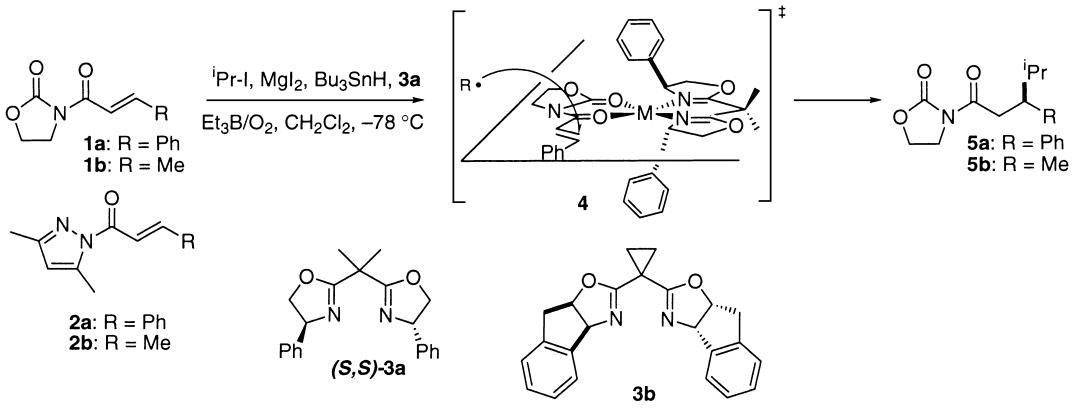
0957-4166/99/$ - see front matter
PII: S0957-4166(99)00238-4



Scheme 1. Enantioselective conjugate radical additions

of ligand/Lewis acid/substrate were employed, but subsequent studies showed that the best ees could be realized with 40 mol% of ligand **3b**[7] (97% ee, 94% yield). Faster reactions were generally observed with the crotonoyloxazolidinone **1b** compared to cinnamoyl oxazolidinone **1a**. However, ee analysis proved to be easier for the cinnamoyl-derived product **5a**, which is slightly UV-active.

Kanemasa and co-workers recently reported highly enantioselective Diels–Alder reactions and nitrone cycloadditions catalyzed by Lewis acid complexes of (*R*,*R*)-4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline) (DBFOX/Ph) **6**.[8] Temperature-dependent ^{1}H NMR studies[9] of DBFOX/Ph-derived complexes of $Zn(ClO_4)_2$ and 3-acetyl-2-oxazolidinone indicated that octahedral and trigonal–bipyramidal complex geometries are in rapid equilibrium at 25°C. To rationalize the observed stereochemical outcome in Diels–Alder reactions, Kanemasa advanced an octahedral transition state geometry for the complexes formed from DBFOX/Ph **6**, cinnamoyl oxazolidinone **1a** and a Lewis acidic metal cation (Fig. 1, R=Ph). Interestingly, the geometry of this complex resembles the proposed transition state complex for radical reactions onto crotonoyl oxazolidinone, bound to bidentate bisoxazoline ligand **3b** and MgI_2.[6b] Assuming a similar reactive conformation for the DBFOX/**1a**/Lewis acid complexes, we hoped to achieve enantioselectivities comparable to Sibi's results[6b] and set out to test this novel ligand in enantioselective radical reactions.

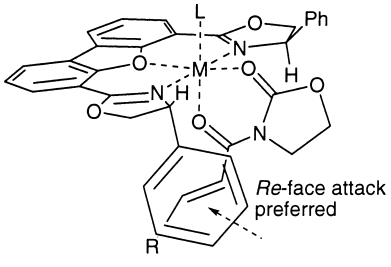


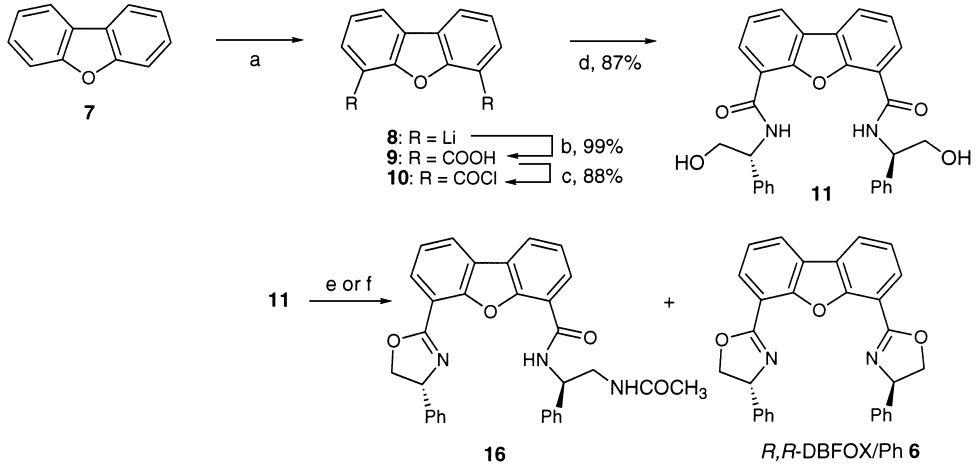
Figure 1. Octahedral DBFOX–substrate complex

In this paper, we report an improved synthesis of the DBFOX/Ph ligand and present our results for enantioselective conjugate radical additions to cinnamoyl oxazolidinone **1a**. About two dozen Lewis acids were evaluated, and $Mg(ClO_4)_2$ emerged as the best Lewis acid in terms of yield and enantioselectivity (100% yield, 75.4% ee (*S*)).

2. Results and discussion

2.1. Synthesis of DBFOX/Ph

The original DBFOX/Ph preparation[8b] provides the ligand **6** in an overall yield of 28%, starting from commercially available dibenzofuran **7**. However, this procedure proved difficult to execute consistently on a gram-scale. Thus, we developed an improved and more reliable procedure (Scheme 2). In the original procedure, dibenzofuran **7** was dilithiated with *n*-butyllithium in THF. The resulting reaction mixture was poured onto dry CO_2, acidified and the solid diacid was filtered off (44% yield from **7**). Diacid **9** was subsequently suspended in trifluoroacetic acid (TFA) and refluxed with an excess of thionyl chloride ($SOCl_2$). After isolation of the crude diacid chloride, **10** was treated with a mixture of (*R*)-phenylglycinol and NEt_3 in $CHCl_3$, followed after 24 h by addition of an excess of $SOCl_2$. The resulting dichloride was briefly worked up, resuspended in $CHCl_3$/MeOH/H_2O, and cyclized to DBFOX/Ph **6** with NaOH (63% from **9**).



Scheme 2. Improved synthesis of DBFOX/Ph **6**. Reagents and conditions: (a) ^{s}BuLi, TMEDA, Et_2O, 25°C, 24 h; (b) CO_2 (g), −78°C; then H^+, 99%; (c) $SOCl_2$, $CHCl_3$, rfx, 3 h; filtration, 88%; (d) (*R*)-phenylglycinol, Et_3N, $CHCl_3$, 25°C, 24 h: recryst. (EtOH), 87%; (e) 2.3 equiv. DAST, CH_2Cl_2, −78°C, 6 h, 61% **6**; (f) 2.4 equiv. Burgess rgt, THF, rfx, 18 h, 25% **16**, 64% **6**

Bisoxazolines are usually synthesized by the addition of readily available β-amino alcohols to diacid chlorides or related activated precursors at the oxidation state of an acid (dinitriles, diimidates, diesters or diacids).[10,11] The key problem in the synthesis of DBFOX/Ph proved to be the insolubility of both the dibenzofuran-4,6-dicarboxylic acid **9** and other bifunctionalized precursors such as the diiodide **12**, dinitrile **13** and diimidate **15** in common organic solvents. The diacid **9** is soluble in DMSO, but virtually insoluble in any other organic solvent tested (CH_2Cl_2, $CHCl_3$, THF, Et_2O, toluene, acetone, DMF), presumably due to hydrogen bonding. Eventually, we discovered high-yielding conditions leading to intermediates with enhanced solubility profiles.

The synthesis of diacid **9** (99% from **7**) was improved by dilithiating **7** with *sec*-butyllithium in diethyl ether/tetramethylethylenediamine (TMEDA),[18] followed by introduction of gaseous, dry CO_2 into the reaction mixture at −78°C. The suspension was warmed to 25°C under a CO_2 atmosphere, and the resulting dilithio carboxylate was filtered off and treated with HCl (aq.). Subsequently, diacid **9** was successfully converted to the diacid chloride **10** in 88% yield by refluxing a mixture of the diacid with 30 equiv. of thionyl chloride in $CHCl_3$ for several hours. The analytically pure diacid chloride **10** was obtained by simple filtration from the reaction mixture.[12]

The desired dihydroxy diamide adduct **11** was obtained in 87% yield from the reaction of dibenzofuran-4,6-dicarbonyl dichloride **10** and (*R*)-phenylglycinol despite gel formation during the reaction (in both THF and $CHCl_3$). The recrystallized dihydroxy diamide **11** was then converted into DBFOX/Ph **6** through cyclization with (diethylamino)sulfur trifluoride (61% yield).[13] Alternatively, cyclization effected by the Burgess reagent afforded the desired ligand in 64% yield, along with 25% of monocyclized oxazoline methyl urethane **16**. The formation of **16** is precedented,[14] and proved to be independent of the reaction stoichiometry (3 equiv. vs 2.1 equiv. Burgess reagent) or reaction solvent (THF vs dioxane). Several other common cyclization approaches[15,16] were screened, but did not lead to enhanced yields. In general, protocols involving insoluble intermediates led to poor yields (<10% **6**), whereas activated cyclization precursors underwent competing S_N2 reactions under the basic cyclization protocols.

*2.2. Enantioselective conjugate radical additions to cinnamoyl oxazolidinone **1a***

Acyclic enantioselection in radical reactions has only recently been developed into a reliable method for generating enantiomerically enriched compounds. Commonly, substrate complexation with a Lewis acid effects a rigid transition state geometry and simultaneously offers activation. The advantages of ligand-mediated reactions are that: (1) the chirality inducing element is only temporarily present during the reaction; and (2) it can, in principle, be recovered from the reaction mixture. To compare the DBFOX/Ph ligand **6** with previously studied bisoxazoline ligands, we conducted radical reactions under the conditions reported by Sibi (−78°C, CH_2Cl_2, Et_3B/O_2 initiation, stoichiometric ligand/metal salt/substrate).[6a,b]

A key difference between radical reactions employing bisoxazoline ligand systems **3a**/**3b** and DBFOX/Ph **6** (Scheme 1) is the ease with which the product **5** can be separated from the reactants and ligand. Sibi subjected the crude reaction mixture to an acidic wash, thereby hydrolyzing the chiral bisoxazoline to the highly polar diacid and the parent β-amino alcohol, both of which could be efficiently removed by column chromatography. In our case, hydrolysis of DBFOX/Ph left decomposition products of intermediate polarity behind. Even traces (<0.1 mg) of these decomposition products prevented accurate ee-determination due to the highly UV-active dibenzofuran core. To obtain the product cleanly, the reaction product was subjected to semi-preparative HPLC after aqueous workup and column chromatography, followed by chiral HPLC (Chiracel OD, 7% *i*PrOH/hexane). Thus, isolated yields were generally lower compared to Sibi's results.

Over two dozen Lewis acids were initially screened (Table 1). Most of these salts did not lead to considerable conversion, and both isolated yields and enantiomeric excesses were low. Reactions with $CuBr_2$, $Cu(ClO_4)_2 \cdot 6H_2O$, $NiBr_2$, $MnBr_2$ and $FeCl_3$ (entries 2–4, 7 and 21) led to poor conversions and the products were not further analyzed. The highest yield and enantiomeric excess was realized with $Mg(ClO_4)_2$ (entry 14, 100% yield, 75% ee (*S*)-**5a**). Inspection of entries 10–14 shows that the absolute configuration remained the same for various magnesium salts, regardless of the counterion. With three exceptions (entries 8, 18 and 19), this also holds for the other metal salts screened. While the ee was reproducible within limits of error for the screened radical reactions, isolated yields tended to be variable due to the small reaction scale. Another pertinent feature of conjugate radical additions onto α,β-unsaturated acyloxazolidinones was their low inherent reactivity towards radicals. The insufficient reactivity brought about two problems: (1) initiation at low temperature (−78°C) requires Et_3B/O_2, which generates an ethyl radical that competes with the desired isopropyl radical in the addition reaction. Thus, some of the substrate was always transformed into the ethyl adduct (in most cases, the ethyl adduct formed in <5%); and (2) several equivalents of ^{i}PrI had to be employed presumably to overcome direct

Table 1
Initial screening results with various Lewis acids[a]

Entry	Lewis acid[a]	Yield[b] (%)	ee[c] (%)	Config.[d]
1	CuCl	4	–	–
2	$CuBr_2$	<1	–	–
3	$Cu(ClO_4)_2 \cdot 6H_2O$	<1	–	–
4	$NiBr_2$	<1	–	–
5	$NiCl_2$	23	50	R
6	$Ni(ClO_4)_2 \cdot 6H_2O$	14	11	R
7	$MnBr_2$	<1	–	–
8	$MnCl_2$	17	8	R
9	$Mn(ClO_4)_2 \cdot 6H_2O$	19	3	S
10	MgI_2	23	61	S
11	$MgCl_2$	7	30	S
12	$MgCl_2$[e]	10	<1	S
13	$MgBr_2 \cdot OEt_2$	10	55	S
14	$Mg(ClO_4)_2$	100	75	S
15	ZnI_2	3	22	R
16	$ZnBr_2$	3	10	R
17	$ZnCl_2$	22	36	R
18	$Zn(ClO_4)_2 \cdot 6H_2O$	37	70	S
19	$Zn(OTf)_2$	22	55	S
20	$FeCl_2$	2	2	R
21	$FeCl_3$	<1	–	–
22	$Fe(ClO_4)_3 \cdot H_2O$	2	8	R
23	$Yb(OTf)_3$	5	6	S
24	$CeCl_3$	10	69	R
25	$GaCl_3$	3	2	R
26	$Ba(ClO_4)_2$	3	6	R

[a] 10.5 equiv. iodide, 4.4 equiv. $HSnBu_3$, 4 equiv. Et_3B, 1 equiv. LA and **6** used.
[b] Yields are for isolated and purified materials.
[c] Ees were determined by chiral HPLC analysis using a Chiracel OD column.
[d] The absolute stereochemistry was established by comparison of retention times to those reported by Sibi. See the literature.[6a]
[e] $MgCl_2$ and ligand were stirred 12 h prior to substrate addition.

reduction of ^{i}PrI to propane. To compare yields of radical adducts, 10.5 equiv. ^{i}PrI, 4.4 equiv. $HSnBu_3$ and 4 equiv. Et_3B were uniformly employed, regardless of individual conversion.

The sense of asymmetric induction in the optimum experiment with $Mg(ClO_4)_2$ (entry 14, 75% ee, (*S*)-**5a**) is consistent with the model in Fig. 1. For most of the other experiments, low ees and especially low yield suggest that in-depth analysis of the trends is not warranted. The reversal in enantioselectivity could be caused by metal–substrate binding in a bidentate mode from that shown in Fig. 1 or also by reaction through a mono-dentate complex.

This initial screening reveals that, in general, stronger Lewis acids effect higher yields and ees. For low-

Table 2
Magnesium counterion effects[a]

Entry	Lewis acid (1 equiv.)	Silver salt (2 equiv.)	Yield (%)	ee[b] (%)
1	$MgCl_2$	AgOTf	3	13
2	$MgCl_2$	$AgBF_4$	15	22
3	$MgCl_2$	$AgSbF_6$	43	48
4	$MgCl_2$	$AgSbF_6$[c]	80	58
5	$MgCl_2$	$Ag(ClO_4)$	62	46
6	$MgCl_2$	$Ag(ClO_4)\bullet H_2O$	63[d]	62
7	$Mg(ClO_4)_2$	–	79[d]	56
8	$MgBr_2$	$Ag(ClO_4)$	50	33

[a]See Table 1 footnotes a–d.
[b]The absolute configuration (*S*) was the same for each product.
[c]$MgCl_2$, 2 equiv. $AgSbF_6$ and ligand were stirred 12 h prior to substrate addition.
[d]100 mg 4A MS per 0.1 mmol Lewis acid.

temperature radical additions onto cinnamoyl oxazolidinone **1a** to occur efficiently, substantial activation of the substrate is required by the chiral Lewis acid complex. Keeping in mind that the Lewis acidity of the free metal salt is reduced through complexation to the tridentate DBFOX ligand, Lewis acidity can be partially restored by using less nucleophilic metal salt counterions.

The validity of this principle was shown in several experiments (Table 2). Magnesium salts of trifluoromethane sulfonate, tetrafluoroborate, hexafluoroantimonate and perchlorate were generated from one equiv. of magnesium chloride or bromide and two equiv. of the respective silver salts.[17] Radical reactions with the in situ generated magnesium salts revealed that both the yield and enantiomeric excess increase with less nucleophilic counterions: $Mg(OTf)_2 < Mg(BF_4)_2 < Mg(SbF_6)_2 < Mg(ClO_4)_2$ (entries 1–3 and 5). Adding molecular sieves to ensure strictly anhydrous conditions increased only modestly the yield and ee (entries 5–7); similarly, the nature of the initial magnesium salt ($MgCl_2$ vs $MgBr_2$, entry 5 vs 8) affected yield and ee. However, these additives proved less efficient as compared to anhydrous $Mg(ClO_4)_2$ alone, and thus we did not engage in further investigations.

To evaluate the reaction temperature–enantioselectivity profile, three experiments at 25, 0 and −78°C with stoichiometric $Mg(ClO_4)_2$ as the Lewis acid were conducted (Table 3). As expected, enantiomeric excess increased strongly with decreasing reaction temperature (reaching a maximum at −78°C (entry 3)) as the background rate becomes negligible. At the same time, yields dropped only marginally (from 67 to 54%; entries 1 and 3). Experiments at even lower reaction temperatures were impossible due to extremely low reaction rates. Substituting CH_2Cl_2 with THF as reaction solvent led to lower yields and a 22% net decrease of ee (entry 3 vs 4).

3. Conclusions

The reported synthesis of DBFOX/Ph **6** represents the most efficient and reliable approach towards this interesting tridentate bisoxazoline ligand. Although many protocols for the elaboration of dihydroxy diamides into the bisoxazolines are known from the literature, only the cyclodehydrations mediated by (diethylamino)sulfur trifluoride and the Burgess reagent led to an acceptable yield for **6**.

Table 3
Temperature–enantioselectivity/yield profile[a]

Entry	Lewis acid	T (° C)	Yield (%)	ee[b] (%)
1	$Mg(ClO_4)_2$	25	67	34
2	$Mg(ClO_4)_2$	0	65	53
3	$Mg(ClO_4)_2$	–78	54	65
4	$Mg(ClO_4)_2$	–78[c]	48	44

[a]See Table 2, footnotes a–d.
[b]The absolute configuration (*S*) was the same for each product.
[c]THF instead of CH_2Cl_2 as solvent.

In terms of conjugate radical additions onto **1a**, chiral Lewis acid complexes of DBFOX/Ph do not provide sufficient substrate activation, as required for fast and high-yielding reactions. While we showed that use of less nucleophilic counterions is beneficial to restore some Lewis acidity, stronger Lewis acids cannot be employed, because they will hydrolyze the ligand.[8b] A less electron-donating ligand such as the bidentate bisoxazoline ligand **3b** is therefore clearly preferable to achieve high levels of enantioselectivity in conjugate radical additions onto α,β-unsaturated acyloxazolidinones. However, several other problems remain unresolved: (1) at present, only a limited number of achiral templates are available. All these oxazolidinone- and pyrazole-based templates (**1** and **2**, Scheme 1) have a low inherent reactivity towards carbon radicals; which (2) requires multiple equivalents of radical precursors. This major shortcoming restricts application of the technology in complex natural product synthesis, where radical precursors are often precious molecules; and (3) initiation at low temperature (−78°C) requires Et_3B/O_2, which generates an ethyl radical competing with the desired radical in the addition reaction. Thus, some of the acceptor is always transformed into the undesired ethyl adduct.

4. Experimental

4.1. General methods

All glassware was dried in an oven at 140°C prior to use. All experiments were conducted under an atmosphere of dry argon unless indicated otherwise. Solvents were distilled over an appropriate desiccant. All NMR spectra were recorded on a Bruker model DPX-300 (^{1}H: 300 MHz, ^{13}C: 75 MHz) or a Bruker model DPX-500 (^{1}H: 500 MHz, ^{13}C: 125 MHz) NMR spectrometer. Infrared spectra were taken on an ATI Mattson Genesis Series FTIR spectrometer using thin film deposition on polished NaCl plates. Low and high resolution mass spectra were obtained from a VG 70-G or VG-Autospec double focusing instrument under EI mode, unless noted otherwise. Low-pressure column chromatography was performed with ICN silica gel 60 (230–400 mesh). Thin layer chromatography (TLC) was carried out on Merck silica gel 60 F-254 glass-backed plates.

The following materials were obtained from commercial suppliers, and were used as received: carbon dioxide (commercial grade) (Matheson Gas Products Inc.), thionyl chloride, zinc trifluoromethane sulfonate (Acros); cupric bromide (Baker); silver perchlorate hydrate (Alfa Products); silver perchlorate (Alfa Aesar); manganese(II) bromide (Fluka); ferric chloride (Fisher Scientific); all other materials were purchased from Aldrich Chemical Co.

4.2. Dibenzofuran-4,6-dicarboxylic acid **9**[18]

Commercial dibenzofuran (97%) was purified as reported.[19] An oven-dried, argon-flushed 1 L three-neck roundbottom flask was fitted with an internal thermometer and a large stirbar. The flask was charged with dry diethyl ether (350 mL), dibenzofuran (10.0 g, 59.4 mmol) and TMEDA (27 mL, 178 mmol) and the resulting mixture was cooled to −78°C. *sec*-Butyllithium (137 mL, 178 mmol) was added via cannula and the beige-colored reaction mixture was stirred for 24 h at 25°C. After replacing the magnetic stirbar with a mechanical stirrer, the mixture was cooled to −78°C. Gaseous carbon dioxide (from lecture bottle, dried with conc. H_2SO_4) was introduced through a wide pipette, keeping the internal temperature below −65°C. The beige-colored suspension turned white, and the reaction was warmed after 4 h to 25°C under a constant CO_2 stream. At −25°C, the white suspension turned red-brown. The yellow supernatant (TMEDA and Et_2O) was decanted and the mixture was filtered through a Büchner funnel. The brown residue was suspended in water (200 mL), acidified with 2 N HCl, aq. (to pH 3) and stirred for 1 h. After filtration, the off-white solid was dried in a vacuum desiccator over P_2O_5 to yield the title compound **9** (15.1 g, 59.0 mmol, 99.3%). Mp 324–325°C under decomposition; ^{1}H NMR (DMSO-d_6) δ 7.55 (dd, 2H, J=7.65 Hz and 5.79 Hz), 8.06 (d, 2H, J=7.65 Hz), 8.47 (d, 2H, J=7.62 Hz), 13.30 (bs, 2H); ^{13}C NMR (DMSO-d_6) δ 116.4, 123.3, 124.5, 125.9, 130.0, 154.2, 165.3; LRMS 256 (M^+, 95), 239 (40), 212 (75), 194 (35), 139 (100); HRMS calcd for $C_{14}H_8O_5$ (M^+) 256.0372, found 256.0363.

4.3. Dibenzofuran-4,6-dicarbonyl chloride **10**[18]

Diacid **9** (5.0 g, 19.6 mmol) was suspended in dry $CHCl_3$ (68 mL), and thionyl chloride (44 mL, 600 mmol) and DMF (1 drop) were added at 25°C. The mixture was refluxed for 3 h at 68°C and then stirred for 2 h at 25°C. The solid was removed via filtration through a Büchner funnel, washed with $CHCl_3$ and dried in a vacuum desiccator overnight to give a white powder (5.00 g, 17.12 mmol, 87.4%). ^{1}H NMR ($CDCl_3$) δ 7.60 (dd, 2H, J=Hz and Hz), 8.32 (dd, 2H, J=Hz and Hz); IR 1777, 1760 (s), 1622, 1598, 1585, 1472, 1425, 1238, 1184, 1139; LRMS 292 (M^+, 30), 257 (100), 194 (45), 173 (20), 138 (40), 111 (25); HRMS calcd for $C_{14}H_6Cl_2O_5$ (M^+) 291.9694, found 291.9697.

4.4. Dibenzofuran-4,6-dicarboxylic acid bis(2-hydroxy-1-phenylethyl) amide **11**

To a suspension of diacid chloride **10** in dry $CHCl_3$ (135 mL) at 0°C was slowly added via addition funnel a solution of (*R*)-phenylglycinol (5.18 g, 37.74 mmol), Et_3N (5.26 mL, 37.74 mmol) in $CHCl_3$ (25 mL). Slow addition is necessary to avoid formation of a thick slurry.[20] The thick mixture was stirred overnight at 25°C, during which it turned into a fine white suspension. The suspension was acidified with sat. NH_4Cl solution. The mixture was filtered and the residue taken up in THF, filtered (removal of insoluble $Et_3N{\cdot}HCl$) and concentrated in vacuo. The crude adduct was purified by recrystallization from EtOH:hexane (95:5) to yield 6.092 g of **11** (72%, combined two crops). The mother liquor was concentrated in vacuo and chromatographed (50–80–100% ethyl acetate (EtOAc)/hexanes) to yield an additional 1.261 g (14.9%) **11**. Overall yield: 7.4 g, 14.9 mmol, 86.9%. ^{1}H NMR (DMSO-d_6) δ 3.72 (m, 4H, CH_2OH), 5.02 (t, 2H, J=5.89 Hz, CH_2OH), 5.20 (dd, 2H, J=7.36 Hz and 13.67 Hz, CHPh), 7.12–7.27 (m, 6H), 7.47–7.60 (m, 6H), 8.01 (dd, 2H, J=0.92 Hz and 7.35 Hz), 8.39 (dd, 2H, J=0.97 Hz and 7.67 Hz), 8.84 (d, 2H, J=8.13 Hz, PhCHNH); ^{13}C NMR ($CDCl_3$) δ 56.02, 64.88, 119.72, 123.54, 123.95, 124.34, 126.95, 127.16, 127.76, 128.27, 140.85, 152.64, 163.37; LRMS 464 (M−CH_2O, 15), 446 (M−OH−CH_2OH, 100), 340 (60), 313 (45), 238 (50), 220, 194, 155, 138, 111, 91, 77; HRMS calcd for $C_{29}H_{24}N_2O_4$ (M^+−HCHO) 464.1736, found 464.1715.

4.5. (R,R)-4,6-Dibenzofurandiyl-2,2′-bis(4-phenyloxazoline), DBFOX/Ph **6**

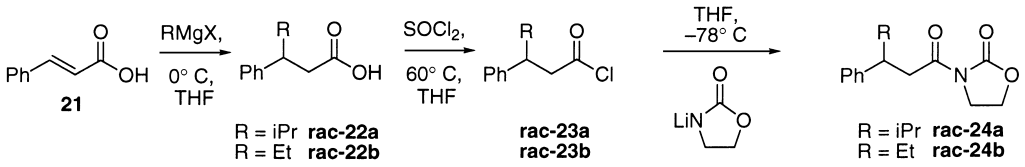
To a suspension of **11** (0.49 g, 0.99 mmol) in dry CH_2Cl_2 (10 mL) at −78°C was slowly added (diethylamino)sulfur trifluoride (DAST, 0.30 mL, 2.27 mmol) at 25°C. After stirring for 6 h at −78°C and overnight at 25°C, 4 N NH_4OH, aq. (1 mL) was added. Water (10 mL) was added to the orange solution, and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried over $MgSO_4$, concentrated under vacuum, and the resulting off-white solid was chromatographed on silica (40:160:1 EtOAc:hexanes:NEt_3, then 80:120:1 EtOAc:hexanes:NEt_3) to yield 276 mg **6** (0.60 mmol, 61%). Alternatively, **11** could be cyclized with Burgess reagent.[21] To a suspension of **11** (1.0 g, 2.0 mmol) in dry THF (60 mL) and dry CH_2Cl_2 (20 mL) was added Burgess reagent (1.46 g, 6.13 mmol) at 25°C. After 5 min, a colorless solution formed, and this was refluxed at an oil bath temperature of 75°C for 18 h. The solution was concentrated in vacuo and the resulting oil was chromatographed on silica (40% EtOAc/hexanes) to yield 591 mg **6** (1.29 mmol, 64%). The enantiomeric purity of **6** was established by chiral HPLC on a Chiracel OD column.[8b]

R_f (**6**)=0.19 (40% EtOAc/hexanes), R_f (**16**)=0.37 (40% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$) δ 4.36 (dd, 2H, J=8.52 and 8.51 Hz), 4.93 (dd, 2H, J=8.36 Hz and 10.11 Hz), 5.52 (dd, 2H, J=9.52 and 9.41 Hz), 7.23–7.45 (m, 12H), 8.05–8.19 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 70.0, 74.9, 113.3, 123.1, 123.9, 124.9, 126.9, 127.6, 128.8, 142.6, 154.4, 162.4; IR 3063, 3029, 2983, 2968, 2899, 2234, 1651, 1492, 1472, 1453, 1428, 1412, 1367, 1349, 1189.

4.6. Representative procedure for radical reactions

An oven-dried vial (Ø 2×8 cm) was fitted with a septum, flushed with argon and charged with the metal salt (0.1 mmol). DBFOX/Ph was added (45.8 mg, 0.1 mmol in 1 mL CH_2Cl_2) from a freshly prepared stock solution in dry CH_2Cl_2. The mixture was stirred at 25°C for 40 min, by which time most of the metal salt had usually gone into solution (some reactions were heterogeneous). 3-(3-Phenyl-2-propenoyl)-2-oxazolidinone[22] was added (21.7 mg, 0.1 mmol in 1 mL CH_2Cl_2) from a freshly prepared stock solution in dry CH_2Cl_2, and the mixture was stirred for 30 min at 25°C, then for 30 min at −78°C. The following set of operations was repeated five times every 60 min: isopropyl iodide (30 μL, 0.264 mmol), $HSnBu_3$ (30 μL, 0.11 mmol), Et_3B (1 M in hexane, 100 μL, 0.1 mmol) and O_2 (3 mL, into the headspace of the reaction vessel) were injected in this order, followed by another injection of O_2 (3 mL) after 30 min. Thin-layer chromatography revealed the presence of varying amounts of starting material **1a** (except for reactions mediated by $Mg(ClO_4)_2$). After 5 h, the cold reaction mixture was transferred to a separatory funnel and diluted with $CHCl_3$, then washed with H_2O. The aqueous layer was back-extracted with $CHCl_3$ and the combined organic layers were washed with brine. The brine layer was again back-extracted with $CHCl_3$, and the combined organic layers were drained into a 250 mL flask filled with 2.2 g of silica. The solvent was carefully removed under vacuum (water-bath <30°C), and the silica was poured onto a hexane-leached plug of silica (coarse fritted funnel, Ø 4×1.3 cm). After elution of tributyltin-derived products with 200 mL hexane, the solvent was switched to 20% ethyl acetate/hexane. The fractions containing products with an R_f >0.30 (40% ethyl acetate/hexane) were combined and separated by semi-preparative HPLC (Waters μ-Porasil 7.8×300 mm column, 20% ethyl acetate/hexane, 3 mL/min) using UV detection at 254 nm to monitor product elution (product elutes after 16–22 min). The isolated product was analyzed by ^{1}H NMR spectroscopy and the ee was determined on a chiral HPLC column (Chiracel OD 4.6×250 mm, 7% *i*PrOH/hexane, 1 mL/min). Retention times for both enantiomers were compared to a racemic authentic sample, and showed excellent agreement[6a] (R_t 19.7 min (*S*-isomer ^{i}Pr) R_t 26.3 min (*R*-isomer ^{i}Pr)). Regardless of employed metal salt, a minor amount

(<5%) of product derived from ethyl radical addition (Et_3B) was detected (R_t 23.5 min (*S*-isomer Et), R_t 32.6 min (*R*-isomer Et) as established by an authentic sample (Scheme 3).



Scheme 3.

4.7. Preparation of racemic, authentic samples: (a) 3-(4-methyl-3-phenylpentanoyl)oxazolidin-2-one rac-***24a*** *and (b) 3-(3-phenylpentanoyl)oxazolidin-2-one* rac-***24b***

4.7.1. 4-Methyl-3-phenylpentanoic acid rac-***22a***

A solution of cinnamic acid **21** (7.47 g, 50.42 mmol) in dry THF (38 mL) was cooled to 0°C, and ^{i}PrMgCl (2 M THF, 75 mL, 150 mmol) was added dropwise. After addition of 25 mL, gas evolution subsided and the solution turned dark brown. After stirring for 3 h at 25°C, the reaction mixture was poured into a mixture of 6 N HCl (aq.) (32 mL) and ice (60 mL). The aqueous layer was extracted with ether (3×30 mL Et_2O) and the combined organic layers were dried over Na_2SO_4, concentrated under vacuum, and distilled (115–125°C at 0.09 torr) to give *rac*-**22a** (6.2 g, 32.3 mmol, 64%). This material had spectral properties as described in the literature.[23]

4.7.2. 3-Phenylpentanoic acid rac-***22b***

The ethyl adduct was prepared in an analogous way with EtMgBr (3 M THF). The product was purified by distillation (110–120°C at about 1.0 torr) to yield *rac*-**22b** in 37.4% yield (3.3 g, 18.7 mmol). ^{1}H NMR spectrum as described.[24]

4.7.3. 4-Methyl-3-phenylpentanoyl chloride rac-***23a*** *and 3-phenylpentanoyl chloride* rac-***23b***

According to the literature,[24] acid *rac*-**22a** (5.5 g, 28.6 mmol) was dissolved in THF (2 mL), and treated with $SOCl_2$ (12 mL, 164 mmol) at 25°C. After heating to 70°C for 2 h, the excess $SOCl_2$ was distilled off, and the residue was distilled (80–85°C at 0.35 torr) to yield pure *rac*-**23a** (4.5 g, 21.4 mmol, 75%). *rac*-**23b** was obtained in a similar fashion (67%).

4.7.4. 3-(4-Methyl-3-phenylpentanoyl)oxazolidin-2-one rac-***24a*** *and 3-(3-phenylpentanoyl)oxazolidin-2-one* rac-***24b***

According to the literature procedure,[25] 2-oxazolidone (1.75 g, 20.12 mmol) was dissolved in dry THF (70 mL). The solution was stirred at −78°C for 15 min, and ^{n}BuLi (21 mmol, solution in hexane) followed by the acid chloride *rac*-**23a** (4.5 g, 21.4 mmol) was added. After stirring for 36 h at 25°C, the solution was acidified with sat. NH_4Cl (20 mL), concentrated in vacuo, and extracted with CH_2Cl_2 (320 mL). The combined organic layers were washed with 1 N NaOH (20 mL), brine (20 mL) and dried over $MgSO_4$. After removing the solvent, the residue was recrystallized from hexane/ethyl acetate to yield 3.7 g *rac*-**24a** (14.2 mmol, 71%); white solid, mp (recrystallized from EtOH) 97–98°C; ^{1}H NMR ($CDCl_3$) δ 0.75 (d, 3H, *J*=6.72 Hz), 0.98 (d, 3H, *J*=6.66 Hz), 1.91 (m, 1H), 2.98 (m, 1H), 3.21 (dd, 1H, *J*=4.56 Hz and 16.5 Hz), 3.52 (dd, 1H, *J*=10.41 Hz and 16.5 Hz), 3.81 (m, 2H), 4.25 (m, 2H), 7.15–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.8, 21.0, 33.4, 38.8, 42.7, 48.7, 62.1, 126.5, 128.3, 128.6, 143.2, 153.7, 172.8; IR 2961, 2926, 2843, 1778, 1701, 1494, 1478, 1453, 1387, 1272, 1224, 1100; LRMS 261 (M^+, 8), 218 (45),

174 (15), 131 (100), 104 (26), 103 (25), 91 (32), 77 (13); HRMS calcd for $C_{15}H_{19}NO_3$ (M^+) 261.1365, found 261.1355. *rac*-**24b** was synthesized similarly in 84% yield (after recrystallization); white solid, mp (recrystallized from EtOH) 65.5–67°C; ^{1}H NMR ($CDCl_3$) δ 0.80 (t, 3H, *J*=7.33 Hz), 1.73 (m, 2H), 3.18 (m, 2H), 3.39 (dd, 1H, *J*=8.30 Hz and 16.16 Hz), 3.90 (m, 2H), 4.32 (m, 2H), 7.17–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 12.0, 29.3, 41.5, 42.5, 43.2, 62.0, 126.4, 127.7, 128.3, 144.0, 153.5, 172.1; IR 2963, 2926, 2873, 1779, 1700, 1497, 1480, 1453, 1388, 1224, 1094; LRMS 247 (M^+, 25), 218 (25), 160 (40), 131 (100), 118 (14), 103 (25), 91 (60), 77 (17); HRMS calcd for $C_{14}H_{17}NO_3$ (M^+) 247.1208, found 247.1210.

Acknowledgements

We thank the National Science Foundation for funding this work. We also thank Dr. Yoji Oderaotoshi for helpful comments and suggestions.

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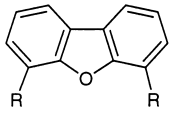
11. Preparation of the 4,6-diiodide **12**, dinitrile **13**, and diethyl ester **14** of dibenzofuran has been previously described: Tsang, K. Y.; Diaz, H.; Graciani, N.; Kelly, J. W. *J. Am. Chem. Soc*. **1994**, *116*, 3988–4005. Elaboration of diacid **9**, dinitrile **13**, diester **14**, and diimidate **15** to the desired dihydroxy diamide **11** or DBFOX **6** was prevented by marginal solubility of starting materials or reaction intermediates.



12: R = I **14**: R = CO_2Et
13: R = CN **15**: R = C(NH)OEt•HCl

12. Acidic hydrolysis of recrystallized dinitrile **13** led cleanly to diacid **9**. We attempted conversion of this diacid into diacid chloride **10**, but failed with various combinations (THF/oxalyl chloride, DMF/$SOCl_2$, dioxane/$SOCl_2$, acetonitrile/$SOCl_2$, TFA/$SOCl_2$, DCE/$SOCl_2$/NEt_3BnCl). The better solubility of the crude diacid **9**, prepared from carboxylation, may account for this difference.
13. (Diethylamino)sulfur trifluoride (DAST) is more stable and cheaper (US$2.76/mmol, Aldrich) than the Burgess reagent (US$10.38/mmol, Aldrich).

14. The Burgess reagent reacts with 1°-alcohols by formation of alkyl-*N*-methoxycarbonyl sulfamate salts, which decompose on thermolysis via an S_N2 mechanism to give methyl urethanes in good yield. See (a) Burgess, E. M.; Penton, H. R.; Taylor, E. A.; Williams, W. M. *Organic Syntheses, Coll. Vol. 6* **1988**, 788–791; (b) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem*. **1973**, *38*, 26–31.
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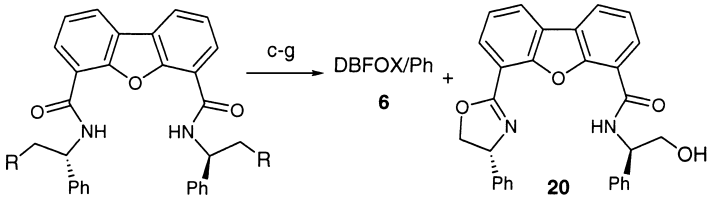
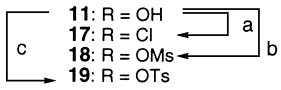
16. Transformation of the dihydroxy diamide **11** into activated cyclization precursors (dichloride **17**, dimesylate **18** or ditosylate **19**), followed by base-mediated cyclization only led to small amounts of DBFOX. Moreover, the resulting product mixtures were difficult to separate. Other routes, via one-pot protocols were also unsuccessful.



	SM	Base	11	20	6
c	(OTs)	TEA	39	–	36*
d	OH	TEA	++	+	0
e	Cl	MeOLi	50	–	38
f	OMs	NaOH	13	–	33*
g	OMs	MeOLi	–	19	49*

* 2 steps



Reagents and conditions. (a) $SOCl_2$ (xs), DMF (cat), $CHCl_3$, rfx, 88%; (b) MsCl, NEt_3, CH_2Cl_2, 25°C; (c) TsCl, NEt_3 (4.4 equiv.), DMAP (cat), CH_2Cl_2; (d) **11**, PPh_3, CCl_4, NEt_3, CH_3CN, 80°C; (e) MeOH, ^{n}BuLi; then **17**, rfx; (f) NaOH, MeOH/H_2O, then **18**, 25°C; (g) MeOH, ^{n}BuLi; then **18**, rfx; TEA=Et_3N.

17. $Mg(OTf)_2$, $Mg(BF_4)_2$, $Mg(SbF_6)_2$ are not commercially available. Upon mixing a suspension of $MgCl_2$ or $MgBr_2$ with the appropriate Ag(I) salt, AgCl or AgBr precipitated out immediately.
18. We are grateful to Professor X. Zhang, Penn State University, for suggesting this improved protocol. For double deprotonation see: (a) Haenel, M. W.; Jakubik, D.; Rothenburger, E.; Schroth, G. *Chem. Ber*. **1991**, *124*, 1705–1710; (b) Jean, F.; Melnyk, O.; Tartar, A. *Tetrahedron Lett*. **1995**, *36*, 7657–7660.
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