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Enantioselective Oxidative Homo- and Cross-Coupling of 2-Naphthols Catalyzed by Chiral Iron Phosphate Complexes

Sachin Narute,[†] Regev Parnes,[†] F. Dean Toste,[‡] Doron Pappo*[,†]

[†]Department of Chemistry, Ben-Gurion University of the Negev, Beer-Sheva 84105, Israel

[‡]Department of Chemistry, University of California, Berkeley, California 94720, United States

Supporting Information Placeholder

ABSTRACT: Novel chiral iron phosphate complexes were prepared as catalysts for asymmetric oxidative coupling reactions. These catalysts were applied for the synthesis of enantio-enriched C_1- and C_2-symmetric BINOLs, in which the 3 and 3' positions are available for chemical modifications. It was proposed that the reaction takes place via an oxidative radical-anion coupling mechanism. A destructive BINOL racemization that competes with the enantioselective oxidative coupling of 2-naphthols was revealed, thereby offering new insights into this highly important reaction.

INTRODUCTION

Optically pure C_1- and C_2-symmetric 1,1'-bi-2-naphthols (BINOLs)[1] serve as auxiliaries and ligands for asymmetric transformations and as the infrastructure of key catalysts applied in numerous applications.[1f] The preparation of enantiomerically pure (*R*)- or (*S*)-BINOLs relies mainly on enzymatic or chemical resolution of racemic BINOLs.[1e,1f] In principle, the direct catalytic asymmetric oxidative coupling of 2-naphthol derivatives should be the preferred method of preparation in terms of simplicity and atom economy. However, this approach has proved challenging, in part due to the existence of an undesired secondary racemization process that competes with the enantioselective carbon-carbon bond-forming step.[2]

In recent years, considerable progress has been made in developing efficient catalytic systems for the enantioselective oxidative homocoupling of 2-naphthol derivatives. 3,3'-Disubstituted and 7,7'-disubstituted BINOLs have been prepared in high optical purity by chiral copper,[3] iron[4] and dinuclear vanadium[5] catalysts (Figure 1). Nonetheless, the direct preparation of optically pure unsubstituted BINOL **2a**, which is the building block for axially chiral ligands and catalysts,[1f,1g] and 6,6'-disubstituted BINOLs remains an unmet challenge. Moreover, the enantioselective oxidative cross-coupling of two different 2-naphthol coupling partners presents the additional challenge of chemoselectivity during the coupling step. The group of Katsuki[6] introduced iron(salan) complexes for enantioselective aerobic oxidative cross-coupling of 3-substituted-2-naphthols with 6-substituted-2-naphthols (Figure 1). This exceptional transformation enabled the preparation of C_1-symmetric BINOLs[1f,7] having a fixed 3-substituent with excellent enantioselectivity.[6]

The 3- and 3'-positions in BINOLs are generally used to control the steric and electronic properties of the catalytic center and to project axial chirality in asymmetric transformations. However, despite the tremendous amount of work in the field, a general method to optically pure 3- and 3'-unsubstituted C_1-symmetric BINOLs by direct coupling remains elusive. Therefore, the development of a complementary catalytic system for the enantioselective synthesis of BINOLs that have synthetic flexibility at the 3- and 3'-positions remains an important challenge.

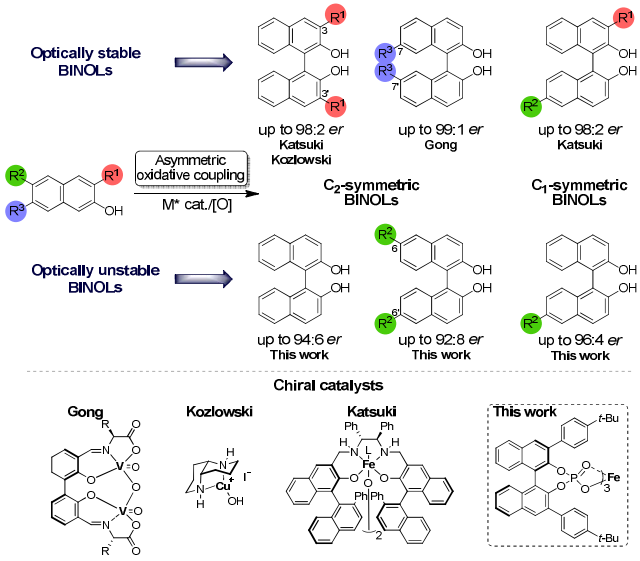


Figure 1. Enantioselective oxidative coupling of 2-naphthols by various catalytic systems

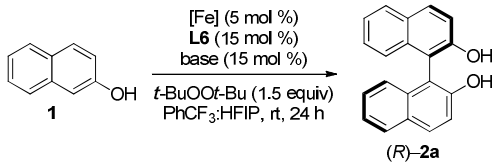
To address this emerging problem, we envisioned a chiral anion strategy[8] based on phosphoric acids[3e,9] derived from BINOLs.[10,11] Novel chiral iron[12] phosphate complexes were synthesized and examined as catalysts for the enantioselective oxidative coupling of two 3-unsubstituted-2-naphtholic components (Figure 1). Under our coupling conditions, the enantioselective carbon-carbon bond forming reaction was kinetically favored over the competitive racemization process, thereby enabling the preparation of C_1- and C_2-symmetric BINOLs in good yields and high enantioselectivity. On the basis of in-depth mechanistic studies, an oxidative radical-anion coupling mechanism is proposed. Finally, the optical instability of substituted BINOLs in the presence of Fe(III)

and Cu(II) complexes was revealed, thereby offering new insights into the chemistry of BINOLs.

RESULTS AND DISCUSSION

Method development. Recently, the Pappo group developed conditions for the oxidative cross-coupling of two phenolic components with a $FeCl_3$ catalyst in 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP).[13] On the basis of these results, the enantioselective homocoupling of 2-naphthol (**1**) was chosen as a model reaction for an asymmetric version based on chiral iron phosphate complexes. First, the conditions for the *in situ* preparation of an active iron phosphate complex were developed. Initially, $FeCl_3$ (5 mol %) and phosphoric acid **L6** (Table 2; 15 mol %) were preheated in $PhCF_3$-HFIP (1:1 mixture) prior to the addition of 2-naphthol (1 equiv) and *t*-BuOO*t*-Bu (1.5 equiv) at room temperature. However, these conditions were not successful, and the formation of racemic BINOL **2a** suggested that the iron phosphate complex was not formed (Table 1, entry 1). Therefore, the use of $Fe(ClO_4)_3$, which has a more labile perchlorate ligand, and inorganic bases were tested. Salts such as K_2CO_3, Cs_2CO_3 and Ag_2CO_3 were not effective, and **2a** was obtained in poor yields and low enantioselectivity (Table 1, entries 2-4). In contrast, group 2 metal salts such as $Mg(OMe)_2$, $CaCO_3$ and $SrCO_3$ (entries 5, 7 and 8) gave an enhancement in efficiency and selectivity.[14,15] Other peroxides, such as *t*-BuOOH, H_2O_2, dicumyl peroxide and 2,5-bis(tert-butylperoxy)-2,5-dimethylhexane, were found to be less effective than t-BuOOt-Bu as the terminal oxidant.

Table 1. Screening of Inorganic Bases for Oxidative Coupling of 2-Napthol (1)

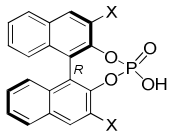


entry	[Fe]	Additive	Yield [%][a]	er[b]
1	$FeCl_3$	---	84	50:50
2	$Fe(ClO_4)_3$	K_2CO_3	~5	55:45
3	$Fe(ClO_4)_3$	Cs_2CO_3	12	54:46
4	$Fe(ClO_4)_3$	Ag_2CO_3	44	58:42
5	$Fe(ClO_4)_3$	$Mg(OMe)_2$	66	58:42
6	$FeCl_3$	$CaCO_3$	51	57:43
7	$Fe(ClO_4)_3$	$CaCO_3$	66	67:33
8	$Fe(ClO_4)_3$	$SrCO_3$	54	61:39

General conditions: 1) Fe(III) (5 mol %), **L6** (15 mol %), base (15 mol %), TFT:HFIP (1:1, 0.1 M), 50 °C, 2 h; then 2) 2-naphthol (**1**, 0.05 mmol), *t*-BuOO*t*-Bu, rt, 24 h; [a]HPLC yields using 4-bromoanisole as an internal standard; [b]enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase column.

A series of chiral phosphoric acids with different groups at the 3,3' positions were prepared and tested (Table 2). Phosphate ligands with 3,3'-(4-substituted aryl)groups, such as **L5**–**L12**, provided the highest enantioselectivity, with a correlation being found between the size of the aryl's 4-position and product enantioselectivity (H = Me < Et < ^{i}Pr = ^{i}pentyl < *t*-Bu > *t*-amyl > ^{c}Hex > 1-adamantyl). Accordingly, chiral phosphoric acid **L9** with the X = (4-*t*-butyl)C_6H_4 group[9f] was the most efficient ligand in terms of both enantioselectivity (87:13 *er*) and yield (89%).

Table 2. Ligand Screening for Oxidative Coupling of 2-Naphthol (1).



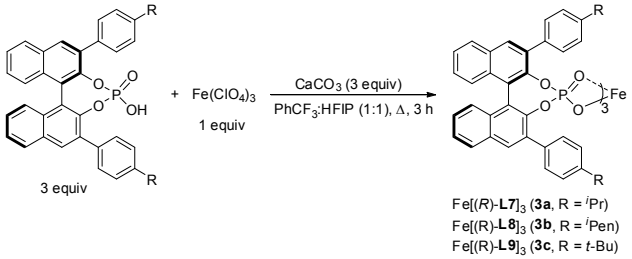
Phosphoric acids	X	Yield [%][a]	er[b]
L1	H	15	58:42
L2	Me	83	59:41
L3	TMS	61	57:43
L4	C_6H_5	86	58:42
L5	(4-Me)C_6H_4	91	58:42
L6	(4-Et)C_6H_4	65	67:33
L7	(4-^{i}Pr)C_6H_4	79	86:14
L8	(4-^{i}Pen)C_6H_4	81	86:14
L9	(4-*t*-Bu)C_6H_4	89	87:13
L10	(4-*t*-amyl)C_6H_4	84	75:25
L11	(4-^{c}Hex)C_6H_4	84	50:50
L12	(4-(1-adamantyl))C_6H_4	92	50:50
L13	(4-OMe)C_6H_4	51	73:27
L14	(4-CF_3)C_6H_4	73	56:44
L15	(4-Ph)C_6H_4	76	63:37
L16	(4-(2-naphthyl))C_6H_4	58	55:45
L17	(4-(9-anthracyl))C_6H_4	54	50:50
L18	(4-((2,4,6-tri-^{i}Pr)Ph))C_6H_4	68	50:50
L19	(2,4,6-tri-^{i}Pr)C_6H_2 [TRIP]	71	50:50
L20	(3,5-di-CF_3)C_6H_3	42	52:48
L21	2-naphthyl	74	54:46

Conditions: $Fe(ClO_4)_3$ hydrate (5 mol %), **L** (15 mol %), $CaCO_3$ (15 mol %), TFT:HFIP (1:1, 0.1 M), 50 °C, 2 h; then 2) 2-naphthol (**1**, 0.05 mmol), *t*-BuOO*t*-Bu (0.05 mmol), rt, 24 h. [a]HPLC yields using 4-bromoanisole as an internal standard; [b]enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase column.

Next, complex Fe[**L9**]$_3$ (**3c**) was prepared by heating $Fe(ClO_4)_3$ (1 equiv), **L9** (3 equiv) and $CaCO_3$ (3 equiv) in $PhCF_3$–HFIP (1:1 ratio, Scheme 1) at 50 °C to afford a non-crystalline solid with a MALDI-TOF mass spectrum consistent with complex **3c** (Figure S3 in SI). The oxidative coupling of **1** by complex **3c** (2.5 mol %) was highly selective in DCE-HFIP (1:1 mixture), furnishing (*R*)-**2a** in 94:6 *er* and 86% isolated yield (Table 3, entry 1). For comparison, the Katsuki iron(salan) complex[4] catalyzed the identical transformation in about 82:18 *er*,[4] while a comparable degree of selectivity to that obtained by complex **3c** was reported for dinuclear vanadium complexes developed independently by

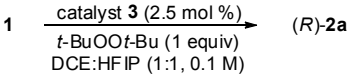
Gong[5e,5f] and Takizawa[5b,5c] (95:5 *er*) and for Gao's dinuclear copper complexes (94:6 *er*).[16]

Scheme 1. Preparation of Iron[phosphate]$_3$ Complexes 3a-3c.



Further studies revealed that the identity of the counterions is also important for the preparation of the iron phosphate catalysts.[15] Preparation of complex **3c** using other inorganic bases, such as $SrCO_3$, $Mg(OMe)_2$ or Ag_2CO_3, instead of $CaCO_3$, afforded iron complexes with reduced catalytic activity (Table 3, entries 2-4). Iron phosphate complexes Fe[**L7**]$_3$ (**3a**) and Fe[**L8**]$_3$ (**3b**) were also prepared. As expected, they were less efficient catalysts than complex **3c** in mediating the oxidative coupling of 2-naphthol **1**, affording BINOL **2a** in only moderate yields and selectivity (entries 5 and 6). Iron phosphate complex **3c** catalyzed this transformation in the presence of the dioxygen molecule (entry 7) and even under aerobic conditions (entry 8). Unfortunately, in both cases, low conversions were observed, and the enantiomeric ratios were lower than those obtained with *t*-BuOO*t*-Bu as the terminal oxidant.

Table 3. Oxidative Coupling of 2-Naphthol 1 by Iron Phosphate Catalysts 3

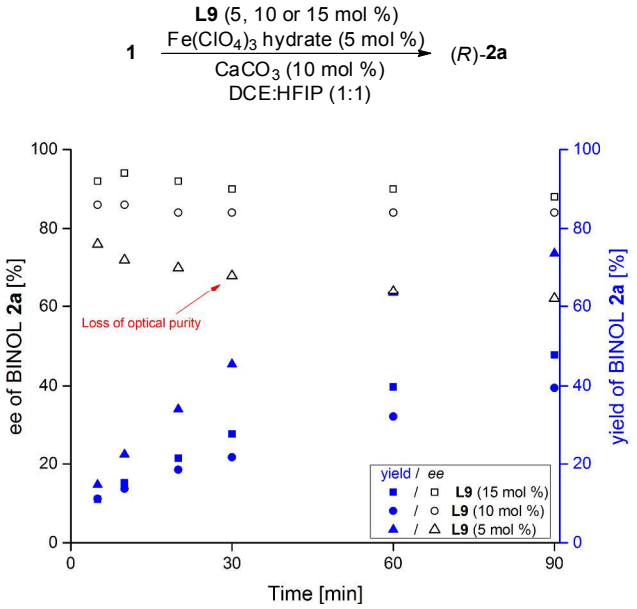


Entry	Catalyst	Time [h]	Yield [%][a]	er[b]
1	**3c**	7	86	94:6
2[c]	**3c**	7	38	84:16
3[d]	**3c**	24	14	56:44
4[e]	**3c**	48	NR	--
5	**3a**	24	48	87:13
6	**3b**	24	41	75:25
7[f]	**3c**	24	37	91:9
8[g]	**3c**	7	12	84:16

Conditions: 2-naphthol (**1**, 0.05 mmol), **3** (2.5 mol %), *t*-BuOO*t*-Bu (0.05 mmol), rt. [a]HPLC yields using 4-bromoanisole as an internal standard; [b]enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase column. [c]$SrCO_3$ (3 equiv) was used instead of $CaCO_3$ to prepare complex **3c**. [d]$Mg(OMe)_2$ (3 equiv) was used instead of $CaCO_3$ to prepare complex **3c**. [e]Ag_2CO_3(3 equiv) was used instead of $CaCO_3$ to prepare complex **3c**. [f]O_2 was used as the terminal oxidant instead of *t*-BuOO*t*-Bu. [g]Aerobic conditions (without *t*-BuOO*t*-Bu) at 50 °C. NR = no reaction.

The requirement for two vacant coordination sites in a *cis*-configuration, first for binding 2-naphthol(s) and thereafter for binding the BINOL ligand was stressed by Katsuki.[17] To obtain structural evidence for this premise, we performed the coupling of 2-naphthol **1** with different Fe/**L9** ratios (1:1, 1:2 and 1:3, Figure 2). While Fe/**L9** ratios of 1:2 and 1:3 catalyzed the coupling of **1** with approximately the same initial reactivity and enantioselectivity, a faster coupling rate and poor selectivity were observed for 1:1 Fe/**L9** ratio (Figure 2). This experiment implied that Fe[**L9**]$_3$ serves as a pre-catalyst and the active catalysts are probably iron bisphosphate complexes, which are generated by exchange of a single anionic ligand. Furthermore, the loss of optical purity during the coupling of **1** (Figure 2, red arrow) can be rationalized by the existence of either a competitive oxidation coupling by achiral iron salts, which were found in high concentration for 1:1 Fe/**L9** ratio,[18] or an undesired secondary racemization process that is enhanced when the number of vacant coordination sites around the iron catalysts increases. The loss in optical purity of **2a**, even after the concentration of 2-naphthol had fallen, led us to examine the kinetics of the secondary racemization process.

Figure 2. Enantioselective oxidative coupling of 2-naphthol (**1**) using different iron/**L9** ratios



Conditions: 1) $Fe(ClO_4)_3$ hydrate (5 mol %), **L9** and $CaCO_3$ (10 mol %), DCE:HFIP (1:1, 0.1 M), 50 °C, 2 h; then 2) 2-naphthol (1), *t*-BuOO*t*-Bu, rt.

Racemization of BINOL derivatives. This secondary racemization process was previously observed by Kočovski[2a] and Brussee[19] during their early works on oxidative coupling of **1** by stoichiometric amounts of Cu(II)–chiral amine complexes. Nevertheless, this undesired process has generally been overlooked during recent development of the catalytic versions of the reaction.[3f,3i,18] A set of kinetic experiments was performed with the aims of studying the rate of the racemization and of delineating the elements that control this undesired process. The optical purity of substituted BINOLs in the presence of iron complexes [10 mol %, DCE:HFIP (1:1 mixture), rt, Ar atmosphere] or copper complexes [10 mol %, dichloromethane (DCM), rt, Ar atmosphere] as a function of time were measured by chiral HPLC (Figures 3 and 4).

Our kinetic studies revealed that catalytic amounts of $FeCl_3$ (Figure 3, ▲) mediated the racemization of BINOL **2a**, while in the presence of *t*-BuOO*t*-Bu (X) a complete loss of optical activity was observed within 20 min. Importantly, in the presence of complex Fe[**L9**]$_3$ (**3**), BINOL **2a** showed optical stability (Figure

3, ■); however, in the presence of peroxide a ligand exchange process was initiated and the racemization was observed (Figure 3, •). As expected, BINOL **2a** also underwent racemization in the presence of Cu(II) salts, such as $Cu(NO_3)_2•(H_2O)_3$ (Figure 3, ○). The process was even faster in the presence of (*S*)-(−)-1-phenylethylamine (□).[20] These experiments and the fact that $FeCl_2$ does not promote this process suggest that the loss in optical activity involves a reversible single electron transfer (SET) process in the binaphthyl metal complex (eq. 1) that generates a delocalized binaphthoxyl radical (such as intermediate **E**, Scheme 2).

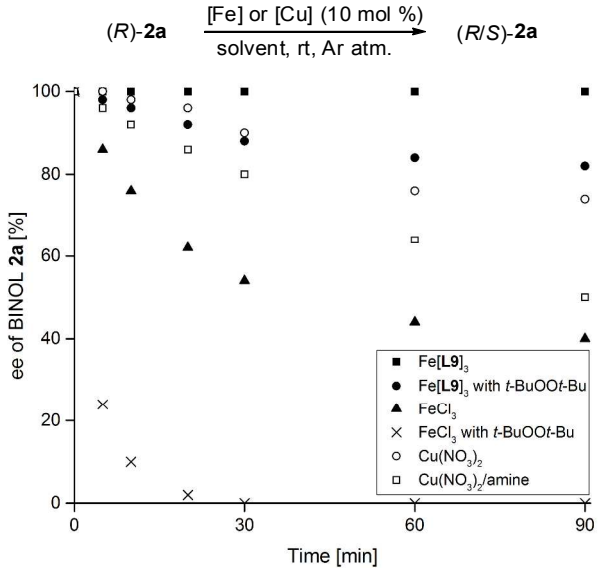
eq.1

$$[(R)\text{–BINOL}][M^{n+}] \leftrightarrow [\text{BINOL}]^{\bullet+}[M^{n-1}] \leftrightarrow [(S)\text{–BINOL}][M^{n+}]$$

$$M^{n+} = Fe^{3+}, Cu^{2+}$$

The existence of a racemization process[21] that competes with the enantioselective oxidative coupling of 2-naphthols provides a possible explanation for the fact that optically pure BINOL **2a** is still not accessible in pure form by direct oxidative coupling of naphthol **1**.[1d]

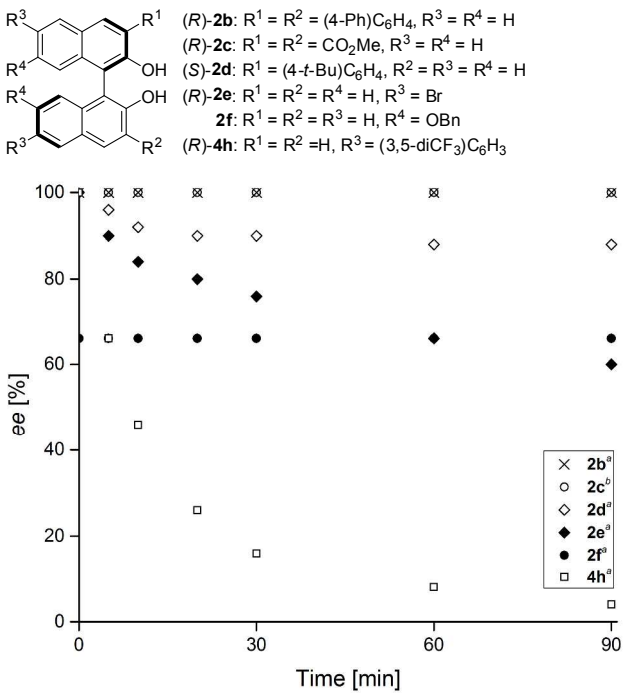
Figure 3. Racemization of BINOL **2a** by different complexes.



Conditions: a) racemization of (*R*)-**2a** by iron salts (10 mol %) in DCE:HFIP (1:1 mixture) at room temperature and under Ar atm.: complex **3** (■); complex **3c** with *t*-BuOO*t*-Bu (1.5 equiv, •); $FeCl_3$ (▲), $FeCl_3$ with *t*-BuOO*t*-Bu (1.5 equiv, X); b) racemization of (*R*)-**2a** by copper salts (10 mol %) in DCM at room temperature and under Ar atmosphere: $Cu(NO_3)_2•(H_2O)_3$ (○); $Cu(NO_3)_2•(H_2O)_3$ with (*S*)-(−)-1-phenylethylamine (80 mol %, □).

The racemization rates of substituted BINOLs by Fe(III) and Cu(II) salts were also studied. (*R*)-BINOL **2b** and (*R*)-BINOL **2c** (Figure 4, X and ○) with moieties at both C-3 and C-3' sites and 7,7'-dibenzyloxy-BINOL **2f** (Figure 4, •) were found to be optically stable for more than 48 h. This experimental evidence is highly important considering the fact that 3,3'-disubstituted BINOLs and 7,7'-disubstituted BINOLs have been prepared from their corresponding naphthols with a high degree of optical purity. BINOL **2b** has been prepared by Katsuki's Fe[salan] (Figure 1) complex in high purity (92:8 *er*),[4] while the group of Kozlowski obtained **2c** by using a Cu[diaza-*cis*-decaline] catalyst (Figure 1) in 96:4 *er*.[3l,22] Both catalysts were less successful in preparing BINOL **2a**, probably as a result of competitive racemization. Other less sterically demanding BINOLs, such as 3-(4-*t*-Bu)C_6H_4-BINOL **2d** (Figure 4, ◊), underwent racemization at a significantly diminished rate compared with BINOL **2a** (Figure 3), whereas 6,6'-disubstituted BINOL **4h** (Figure 4, □) underwent rapid racemization. Thus, it may be expected that the two asymmetric processes would compete (*vide infra*). Importantly, the optical instability of biphenols in the presence of redox metals should be taken into consideration in any future design of catalysts and products with axial chirality.

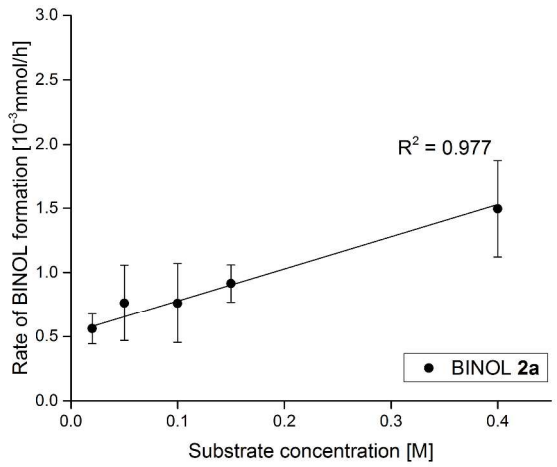
Figure 4. Racemization of optically pure BINOLs **2b**–**2f** and **4h**.

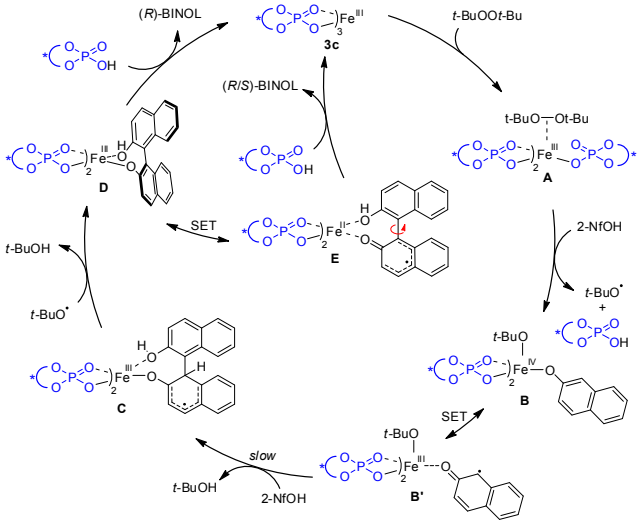


Conditions for the racemization of substituted BINOLs **2b**–**2e**. [a]Method A: $FeCl_3$ in DCE:HFIP (1:1 mixture) at room temperature under Ar atm.; [b]Method B: $Cu(NO3)_2•(H_2O)_3$ with (*S*)-(−)-1-phenylethylamine (80 mol %) in DCM at room temperature under Ar atm.

Postulated mechanism. A kinetic study of the oxidative coupling of 2-naphthol **1** by iron phosphate catalyst **3c** showed first-order dependence of the reaction rate on the concentration of 2-naphthol (Figure 5) and zero-order dependence on that of *t*-BuOO*t*-Bu (Figures S3 in SI). These results are consistent with the radical-anion coupling mechanism proposed by the group of Katsuki for the Fe[salan] catalyst,[6] with the exception that in the iron phosphate system the coordination of the oxidant to the iron is not a slow step. Thus, the proposed mechanism commences with coordination of the peroxide to the iron (complex **A**, Scheme 2), followed by peroxide bond cleavage to generate a high-valent iron complex.[23] The ability of the naphtholate ligand to transfer electron density to the metal is probably the driving force for the ligand-exchange process between one of the phosphate ligands and the 2-naphtholate that affords complex **B**. A radical-anion coupling step between electrophilic naphthoxyl radical **B'** with a second nucleophilic 2-naphthol(ate) coupling partner affords complex **D**. While the ligand exchange releases (*R*)-BINOL, an undesired SET process (**D** ↔ **E**) results in a reduction of the optical purity of the product.

Figure 5. Rate dependence on the concentration of 2-naphthol **1**





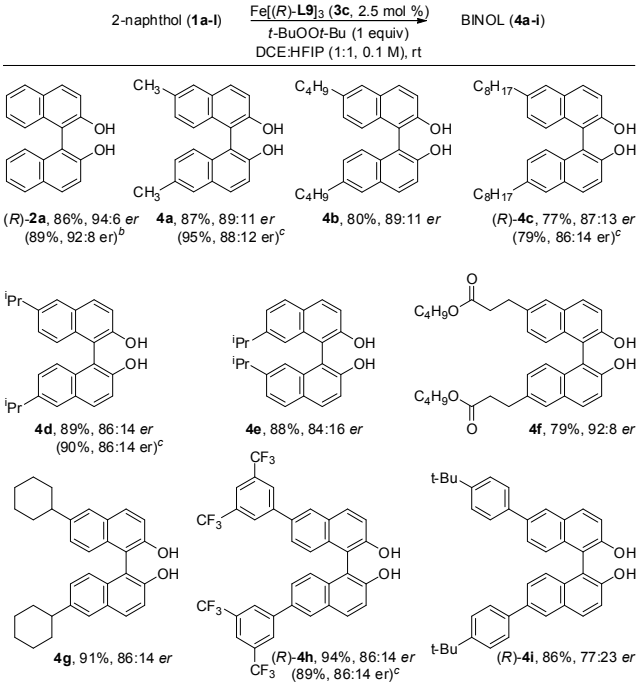
Scheme 2. Proposed Mechanism for the Oxidative Coupling of 2-Naphthols by Fe(L9)$_3$.

Reaction scope. The reaction scope was studied by coupling 6- and 7-substituted 2-naphthols catalyzed by iron phosphate complex **3c** (Figure 6). C_2-symmetric BINOLs substituted with either primary or secondary alkyl groups (**4a**–**4g**) were obtained in high yields and high enantiomeric ratios. BINOL **4c**, for example, is a key intermediate in the synthesis of phosphoric acid employed in enantioselective chiral anion phase transfer catalysis.[24] 6-Aryl-2-naphthols were also suitable coupling partners. The enantiomeric ratio of the products, such as BINOLs **4h** and **4i**, was highly dependent on their racemization rates, which depended on the electronic nature of the aryl substituents. Notably, despite the optical instability of **4h** (see Figure 4), it was obtained in excellent yield (94%) and high optical purity (86:14 *er*).

The mechanistic studies are consistent with the hypothesis that iron phosphate complex **3c** catalyzes the coupling of 2-naphthol via a radical-anion coupling mechanism. Therefore, oxidative cross-coupling reactions between pairs of naphthols with a complementary relationship should be possible.[13b] To examine this premise, 2-naphthol **1** (1 equiv) and 6- or 7-substituted 2-naphthols (1 equiv, Figure 7) were coupled under our general conditions, affording C_1-symmetrical BINOLs **5a-5j** in high enantioselectivity (up to 96:4 *er*). The oxidation potentials (E_{ox}) and the theoretical *N* values[13b] for the 2-naphthol series are close, and therefore it was expected that the homocoupling and the cross-coupling pathways would compete. Indeed, 2-naphthol **1** (E_{ox} = 0.48 V in HFIP) and 6-butyl-2-naphthol (**1b**, E_{ox} = 0.40 V), which do not have complementary relationship (E_{ox} of **1b** < E_{ox} of **1** and $\Delta N = N_{\mathbf{1}}$-$N_{\mathbf{1b}}$ = -0.13),[13b] afforded a mixture of symmetrical BINOLs **2a**, **4b** and unsymmetrical **5b** in a ratio of about 1:6:5; BINOL **5b** was isolated in 41% yield (92:8 *er*). The reaction of 6-anisyl-2-naphthol **1j** with **1** furnished unsymmetrical BINOL **5j** in 81:19 *er* and 53% yield. The yield was improved to 68% when the reaction was performed with three equivalents of naphthol **1**. However, this modification had a negative effect on the optical purity of the coupling product (72:28 *er*). A single recrystallization alone was needed to improve the enantiomeric ratio of BINOL **5j** to 97:3. The absolute configuration of BINOLs **2c**, **4c**, **4h**, **4i**, **5a**, **5h** and **5j** were determined as *R* by a multistep synthesis starting from enantiopure BINOL (see SI). The absolute stereochemistry of the remaining products could be assigned by analogy.

Finally, the scalability of the method was examined by preparing C_1- and C_2-symmetric BINOLs **4a**, **4c**, **4d**, **4h**, **5a**, **5h** and **5i** on a 0.5-mmol scale and BINOL **2a** and **5a** on a gram scale with comparable yields and enantiomeric ratios (Figures 6 and 7). Importantly, ligand **L9** was successfully recovered from the large-scale reactions in 74% yield (based on Fe[**L9**]$_3$) and recycled for the preparation of complex **3c**. The latter catalyst mediated the formation of **2a** in 84% yield and enantiomeric ratio of 91:9.

Figure 6. Enantioselective homocoupling of 6- and 7-substituted 2-naphthols.[a]



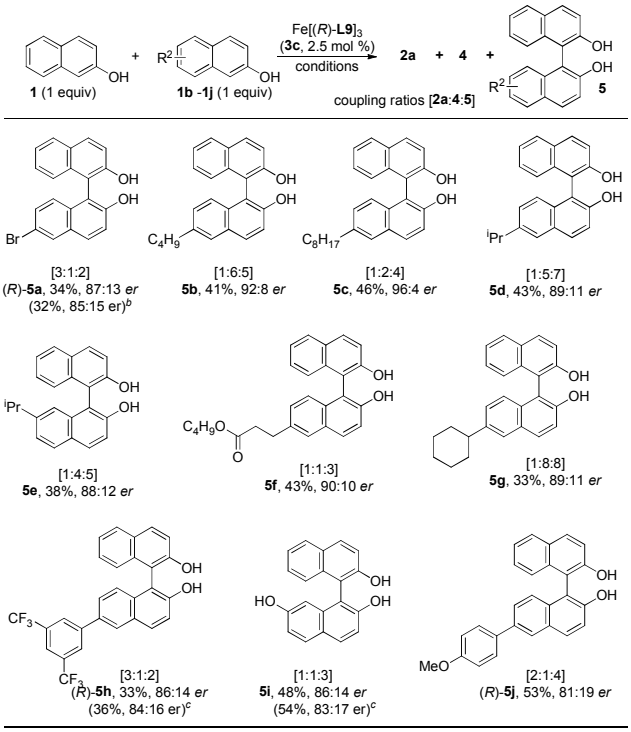
[a]Unless otherwise noted, reactions were performed on a 0.05-mmol scale; [b] the reaction was performed on a gram scale; [c]the reaction was performed on a 0.5 mmol scale.

SUMMARY

In summary, a novel class of chiral iron phosphate complexes for asymmetric oxidative coupling reactions was developed. Complex Fe[**L9**]$_3$ (**3c**) catalyzed the coupling of 2-naphthol derivatives with a high degree of optical purity and moderate chemoselectivity. For the first time, C_1-symmetric 1,1'-bi-2-naphthols with 3- and 3'- positions, available for further chemical modification,

were prepared by direct oxidative coupling methods. On the basis of kinetic studies an oxidative radical-anion coupling mechanism was proposed. The optically instability of substituted BINOLs in the presence of metals was studied, offering new insights into the chemistry of BINOLs. Overall, the work suggests that the use of chiral phosphate anions as ligands may provide a general platform for the application of chiral iron catalysts in asymmetric synthesis.

Figure 7. Enantioselective oxidative cross-coupling of 2-naphtols.[a]



[a]Unless otherwise noted, reactions were performed on a 0.05-mmol scale; [b] the reaction was performed on a gram scale; [c]the reaction was performed on a 0.5 mmol scale.

ASSOCIATED CONTENT

Supporting Information

Full experimental procedures, characterization data, and NMR spectra is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

pappod@bgu.ac.il

Notes

The authors declare no competing financial interests.

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REFERENCES

(1) (a) Moliterno, M.; Cari, R.; Puglisi, A.; Antenucci, A.; Sperandio, C.; Moretti, E.; Di Sabato, A.; Salvio, R.; Bella, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 6525-6529. (b) Wang, J.-Z.; Zhou, J.; Xu, C.; Sun, H.; Kürti, L.; Xu, Q.-L. *J. Am. Chem. Soc.* **2016**, *138*, 5202-5205. (c) Chen, Y.-H.; Cheng, D.-J.; Zhang, J.; Wang, Y.; Liu, X.-Y.; Tan, B. *J. Am. Chem. Soc.* **2015**, *137*, 15062-15065. (d) Wang, H. *Chirality* **2010**, *22*, 827-837. (e) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857-898. (f) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155-3212. (g) Berthod, M.; Mignani, G.; Woodward, G.; Lemaire, M. *Chem. Rev.* **2005**, *105*, 1801-1836. (h) Pu, L. *Chem. Rev.* **1998**, *98*, 2405-2494.

(2) (a) Smrcina, M.; Polakova, J.; Vyskocil, S.; Kocovsky, P. *J. Org. Chem.* **1993**, *58*, 4534-4538. (b) Brussee, J.; Groenendijk, J. L. G.; te Koppele, J. M.; Jansen, A. C. A. *Tetrahedron* **1985**, *41*, 3313-3319.

(3) (a) Zhang, Q.; Cui, X.; Chen, L.; Liu, H.; Wu, Y. *Eur. J. Org. Chem.* **2014**, *2014*, 7823-7829. (b) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. *Chemical Society reviews* **2009**, *38*, 3193-3207. (c) Hewgley, J. B.; Stahl, S. S.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 12232-12233. (d) Nakajima, M.; Miyoshi, I.; Kanayama, K.; Hashimoto, S.-i.; Noji, M.; Koga, K. *J. Org. Chem.* **1999**, *64*, 2264-2271. (e) Komanduri, V.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 16448-16449. (f) Temma, T.; Hatano, B.; Habaue, S. *Tetrahedron* **2006**, *62*, 8559-8563. (g) Podlesny, E. E.; Kozlowski, M. C. *Org. Lett.* **2012**, *14*, 1408-1411. (h) O'Brien, E. M.; Morgan, B. J.; Mulrooney, C. A.; Carroll, P. J.; Kozlowski, M. C. *J. Org. Chem.* **2010**, *75*, 57-68. (i) Temma, T.; Habaue, S. *Tetrahedron Lett.* **2005**, *46*, 5655-5657. (j) Li, X.; Hewgley, J. B.; Mulrooney, C. A.; Yang, J.; Kozlowski, M. C. *J. Org. Chem.* **2003**, *68*, 5500-5511. (k) Mulrooney, C. A.; Li, X.; DiVirgilio, E. S.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2003**, *125*, 6856-6857. (l) Li, X.; Yang, J.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 1137-1140.

(4) Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2009**, *131*, 6082-6083.

(5) (a) Sako, M.; Takizawa, S.; Yoshida, Y.; Sasai, H. *Tetrahedron: Asymmetry* **2015**, *26*, 613-616. (b) Takizawa, S. *Chem. Pharm. Bull.* **2009**, *57*, 1179-1188. (c) Takizawa, S.; Katayama, T.; Sasai, H. *Chem. Commun.* **2008**, 4113-4122. (d) Takizawa, S.; Katayama, T.; Somei, H.; Asano, Y.; Yoshida, T.; Kameyama, C.; Rajesh, D.; Onitsuka, K.; Suzuki, T.; Mikami, M.; Yamataka, H.; Jayaprakash, D.; Sasai, H. *Tetrahedron* **2008**, *64*, 3361-3371. (e) Guo, Q.-X.; Wu, Z.-J.; Luo, Z.-B.; Liu, Q.-Z.; Ye, J.-L.; Luo, S.-W.; Cun, L.-F.; Gong, L.-Z. *J. Am. Chem. Soc.* **2007**, *129*, 13927-13938. (f) Luo, Z.; Liu, Q.; Gong, L.; Cui, X.; Mi, A.; Jiang, Y. *Angew. Chem. Int. Ed.* **2002**, *41*, 4532-4535.

(6) Egami, H.; Matsumoto, K.; Oguma, T.; Kunisu, T.; Katsuki, T. *J. Am. Chem. Soc.* **2010**, *132*, 13633-13635.

(7) (a) Akiyama, T.; Mori, K. *Chem. Rev.* **2015**, *115*, 9277-9306. (b) Yadav, J.; Stanton, G. R.; Fan, X.; Robinson, J. R.; Schelter, E. J.; Walsh, P. J.; Pericas, M. A. *Chem. – Eur. J.* **2014**, *20*, 7122-7127. (c) Zbieg, J. R.; Yamaguchi, E.; McInturff, E. L.; Krische, M. J. *Science* **2012**.

(8) (a) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nat. Chem.* **2012**, *4*, 603-614. (b) Hamilton, G. L.; Kanai, T.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 14984-14986. (c) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496-499.

(9) (a) Zbieg, J. R.; Yamaguchi, E.; McInturff, E. L.; Krische, M. J. *Science* **2012**, *336*, 324-327. (b) Rauniyar, V.; Wang, Z. J.; Burks, H. E.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 8486-8489. (c) Campbell, M. J.; Toste, F. D. *Chem. Sci.* **2011**, *2*, 1369-1378. (d) Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 10275-10277. (e) Yang, L.; Zhu, Q.; Guo, S.; Qian, B.; Xia, C.; Huang, H. *Chem. -Eur. J.* **2010**, *16*, 1638-1645. (f) Liao, S.; List, B. *Angew. Chem. Int. Ed.* **2010**, *49*, 628-631. (g) Zhao, B.; Du, H.; Shi, Y. *J. Org. Chem.* **2009**, *74*, 8392-8395. (h) Rueping, M.; Antonchick, A. P.; Brinkmann, C. *Angew. Chem. Int. Ed.* **2007**, *46*, 6903-6906. (i) Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336-11337.

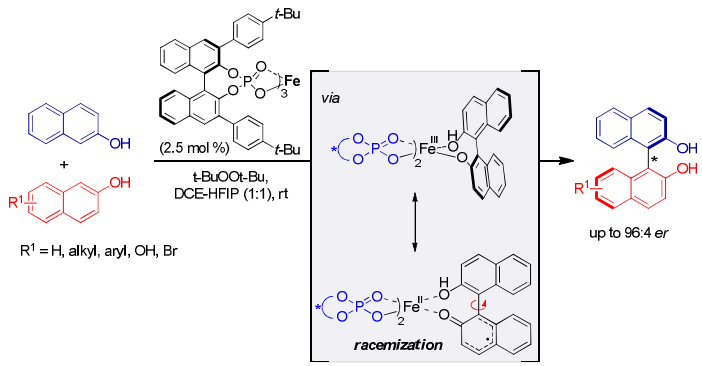
(10) (a) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047-9153. (b) Terada, M. *Bull. Chem. Soc. Japan* **2010**, *83*, 101-119. (c) Connon, S. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 3909-3912.

(11) (a) Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681-1684. (b) Cai, Q.; Zheng, C.; You, S.-L. *Angew. Chem. Int. Ed.* **2010**, *122*, 8848-8851. (c) Guo, Q.-S.; Du, D.-M.; Xu, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 759-762. (d) Kang, Q.; Zhao, Z.-A.; You, S.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1484-1485.

(12) Gopalaiah, K. *Chem. Rev.* **2013**, *113*, 3248-3296.

(13) (a) Dyadyuk, A.; Sudheendran, K.; Vainer, Y.; Vershinin, V.; Shames, A. I.; Pappo, D. *Org. Lett.* **2016**, *18*, 4324-4327. (b) Libman, A.; Shalit, H.; Vainer, Y.; Narute, S.; Kozuch, S.; Pappo, D. *J. Am. Chem. Soc.* **2015**, *137*, 11453-11460. (c) Gaster, E.; Vainer, Y.; Regev, A.;

Narute, S.; Sudheendran, K.; Werbeloff, A.; Shalit, H.; Pappo, D. *Angew. Chem. Int. Ed.* **2015**, *54*, 4198-4202.
(14) (a) Li, G.; Liang, T.; Wojtas, L.; Antilla, J. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 4628-4632. (b) Hatano, M.; Moriyama, K.; Maki, T.; Ishihara, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 3823-3826. (c) Drouet, F.; Lalli, C.; Liu, H.; Masson, G. r.; Zhu, J. *Org. Lett.* **2010**, *13*, 94-97.
(15) The role of calcium ions in this coupling is unclear. It is possible, as demonstrated by Borovik that calcium and iron ions form heterobimetallic complexes with improved reactivity, but we could not find evidence to support this premise. See: (a) Cook, S. A.; Borovik, A. S. Acc. Chem. Res. 2015, 48, 2407-2414. (b) Sano, Y.; Weitz, A. C.; Ziller, J. W.; Hendrich, M. P.; Borovik, A. S. Inorg. Chem. 2013, 52, 10229-10231. (c) Park, Y. J.; Cook, S. A.; Sickerman, N. S.; Sano, Y.; Ziller, J. W.; Borovik, A. S. Chem. Sci. 2013, 4, 717-726. (d) Lacy, D. C.; Park, Y. J.; Ziller, J. W.; Yano, J.; Borovik, A. S. J. Am. Chem. Soc. 2012, 134, 17526-17535. (e) Borovik, A. S. Chem. Soc. Rev. 2011, 40, 1870-1874. (f) Park, Y. J.; Ziller, J. W.; Borovik, A. S. J. Am. CHem. Soc. 2011, 133, 9258-9261.
(16) Gao, J.; Reibenspies, J. H.; Martell, A. E. *Angew. Chem. Int. Ed.* **2003**, *42*, 6008-6012.
(17) Matsumoto, K.; Egami, H.; Oguma, T.; Katsuki, T. *Chem. Commun.* **2012**, *48*, 5823-5825.
(18) Adao, P.; Barroso, S.; Carvalho, M. F. N. N.; Teixeira, C. M.; Kuznetsov, M. L.; Costa Pessoa, J. *Dalton Trans.* **2015**, *44*, 1612-1626.
(19) Brussee, J.; Jansen, A. C. A. *Tetrahedron Lett.* **1983**, *24*, 3261-3262.
(20) Feringa, B.; Wynberg, H. *Bioorg. Chem.* **1978**, *7*, 397-408.
(21) Zhang, Z.; Wang, Y.; Nakano, T. *Molecules* **2016**, *21*, 1541.
(22) Li, X.; Hewgley, J. B.; Mulrooney, C. A.; Yang, J.; Kozlowski, M. C. *J. Org. Chem.* **2003**, *68*, 5500-5511.
(23) (a) Sahu, S.; Goldberg, D. P. *J. Am. Chem. Soc.* **2016**, *138*, 11410-11428. (b) Ray, K.; Pfaff, F. F.; Wang, B.; Nam, W. *J. Am. Chem. Soc.* **2014**, *136*, 13942-13958.
(24) (a) Yang, X.; Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5225-5228. (b) Phipps, R. J.; Hiramatsu, K.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 8376-8379. (c) Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681-1684.


t-Bu
Fe
3
(2.5 mol %)
t-Bu
t-BuOOt-Bu,
DCE-HFIP (1:1), rt
OH
+
OH
R1
R1 = H, alkyl, aryl, OH, Br
via
racemization
OH
OH
R1
up to 96:4 er