

Enantioselective Synthesis of α -Oxy Amides via Umpolung Amide Synthesis

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Supporting Information

ABSTRACT: α -Oxy amides are prepared through enantioselective synthesis using a sequence beginning with a Henry addition of bromonitromethane to aldehydes and finishing with Umpolung Amide Synthesis (UmAS). Key to high enantioselection is the finding that *ortho*-iodo benzoic acid salts of the chiral copper(II) bis(oxazoline) catalyst deliver both diastereomers of the Henry adduct with high enantiomeric excess, homochiral at the oxygen-bearing carbon. Overall, this approach to α -oxy amides provides an innovative complement to alternatives that focus almost entirely on the enantioselective synthesis of α -oxy carboxylic acids.

The α -oxy amide functional motif is common to numerous biologically active natural products, with vitamin B₅ (pantothenic acid)¹ and mandelamide among the most prominent. α -Oxy amides are also effective chelating ligands, and in this role have been used for metal-centered catalysis.² These examples are chiral at the oxygen-substituted carbon, and preparative methods have focused almost entirely on enantioselective α -oxy acid synthesis, followed by standard condensative amide synthesis.³ For example, cyanohydrin synthesis is leveraged in this manner (Figure 1, path A), with the earliest examples relying on a

low selectivity.¹² Furthermore, the use of active ester intermediates to prepare α -oxy amides also provides a potential epimerization pathway. In this context, we wondered whether Umpolung Amide Synthesis (UmAS)^{13,14} might be leveraged to eliminate the functional group manipulation step common to carboxylic acid intermediates, while providing new opportunities for enantioselective catalysis in the first transformation. The latter could also stimulate innovative approaches to the enantioselective preparation of the β -oxy- α -bromonitroalkane donors. The recent demonstration that UmAS can be used to prepare isotopically labeled amides provides additional versatility to this strategic shift.¹⁴ We report herein the use of bromonitromethane as a carbonyl dianion synthon to achieve a fully convergent, enantioselective synthesis of α -oxy amides.

Examination of established methods^{15,16} for the Henry addition with commercial bromonitromethane produced the desired adduct in only moderate enantiomeric excess.¹⁷ For example, use of indenyl bis(oxazoline) ligand **L1** with copper(II) acetate in ethanol furnished the adduct as a mixture of diastereomers in 53/44% ee, respectively (Table 1, entry 1). The favored enantiomers of each diastereomer are homochiral at the benzylic carbon and, therefore, converge to the same α -oxy amide during the UmAS step (*vide infra*). Alternative ligands provided some increase in enantioselection, ultimately to the 87/89% ee level when using *tert*-butyl bis(oxazoline) **L6** (Table 1, entry 6). A slight but reproducible solvent effect was also detected, leading to the use of isopropyl alcohol to achieve 91/90% ee (Table 1, cf. entries 6–8). Although this catalyst system worked well for *ortho*-substituted aldehyde substrates, a decrease in enantioselection was observed for *meta*- and *para*-substituted aldehydes. Therefore, additional refinement to the catalyst was undertaken. In addition, it was determined that MOM-protection of the alcohol¹⁸ prior to a chromatographic step provided configurationally stable donors by restricting the possibility of a *retro*-Henry reaction.

Further refinement was achieved by following the hypothesis that the counterion may affect the structure of the substrate-bound catalyst.¹⁹ Although our attempts to crystallize the chiral complex have been uniformly unsuccessful, the copper(II) carboxylate complexes are bimetallic in nature, with bridging carboxylates and solvent bound at the terminal position.²⁰ Use of a pivalate counterion provided some improvement (86/89% ee) over the use of acetate (82/84% ee) (Table 2, entries 1, 3). Benzoate also resulted in increased selectivity (88/91% ee) (Table 2, entry 2). *ortho*-Methyl benzoate did not improve selectivity, a finding similar

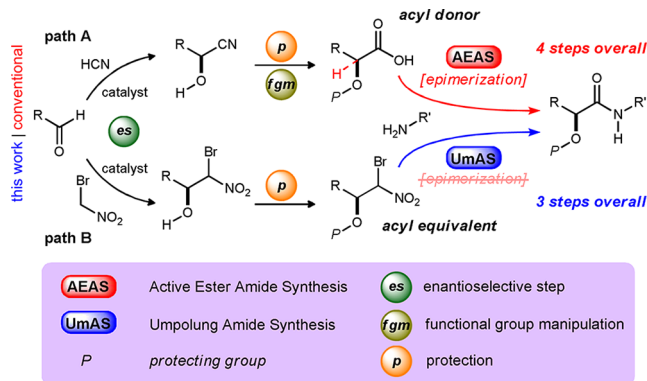
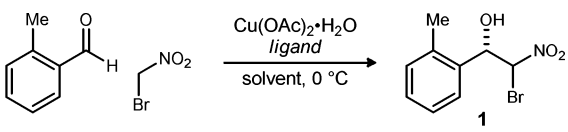


Figure 1. Comparison of conventional α -oxy amide synthesis approaches to the Henry/UmAS method used in this work.

resolution of racemic α -hydroxy acids prior to amide formation. Notable direct approaches to α -oxy amide synthesis include the Passerini reaction^{4–7} and its variants,⁸ as well as α -keto amide reduction^{9,10} and biocatalysis of cyanohydrin hydrolysis,¹¹ but these often exhibit a narrow substrate scope and/or suffer from

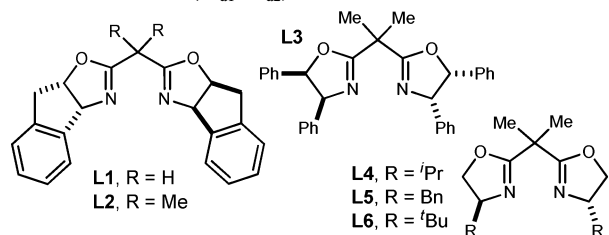
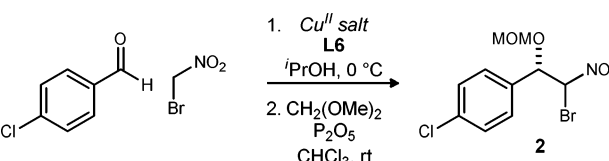
Received: June 29, 2012

Published: September 11, 2012

Table 1. Enantioselective Henry Addition of Bromonitromethane: Explorative Studies Using Chiral Copper(II) Complexes^a


entry	ligand	solvent	conv. (%) ^b	ee (%) ^c
1	L1	EtOH	90	53/44
2	L2	EtOH	97	70/50
3	L3	EtOH	94	74/60
4	L4	EtOH	95	66/14
5	L5	EtOH	94	76/81
6	L6	EtOH	95	87/89
7	L6	MeOH	94	76/81
8	L6	^t PrOH	95	91/90

^aAll reactions were conducted using aldehyde (1 equiv), 5 mol % Cu(OAc)₂·H₂O, 5.5 mol % ligand, and bromonitromethane (10 equiv) in solvent (0.5 M). ^bConversion based on ¹H NMR analysis of crude reaction mixtures. ^cEnantiomeric excesses determined by chiral HPLC using an IA column (Chiral Technologies). Values shown correspond to each diastereomer (ee_{d1}/ee_{d2}).

**Table 2. Enantioselective Henry Reaction: Effect of Cu(II) Counteranion on Enantioselection^a**


entry	Cu ^{II} source	yield (%) ^b	ee (%) ^c
1	Cu(OAc) ₂ ·H ₂ O	84	82/84
2	Cu(Bz) ₂ ·H ₂ O	80	88/91
3	Cu(Piv) ₂ ·H ₂ O	84	86/89
4	Cu(^o Me-Bz) ₂ ·H ₂ O	85	84/88
5	Cu(^p F-Bz) ₂ ·H ₂ O	78	87/90
6	Cu(^p Cl-Bz) ₂ ·H ₂ O	46	86/89
7	Cu(^o F-Bz) ₂ ·H ₂ O	70	79/83
8	Cu(^o Cl-Bz) ₂ ·H ₂ O	59	90/92
9	Cu(^o Br-Bz) ₂ ·H ₂ O	85	90/94
10	Cu(^o I-Bz) ₂ ·H ₂ O	70	93/94
11	Cu(^o OMe-Bz) ₂ ·H ₂ O	73	91/91

^aAll reactions were conducted using aldehyde (1 equiv, 0.3 M in ^tPrOH), 10 mol % Cu(II) complex, 10 mol % (S,S)-^tBuBOX (L6), and bromonitromethane (10 equiv). ^bIsolated yield (two steps). ^cEnantiomeric excess determined by chiral HPLC using an AD-H column (Chiral Technologies). Values shown correspond to each diastereomer (ee_{d1}/ee_{d2}). See Supporting Information for complete details.

to the use of *para*-fluoro, *para*-chloro, and *ortho*-fluoro benzoic acid derivatives (Table 2, entries 4–7). However, *ortho*-halo and *ortho*-methoxy benzoates did provide significant improvements

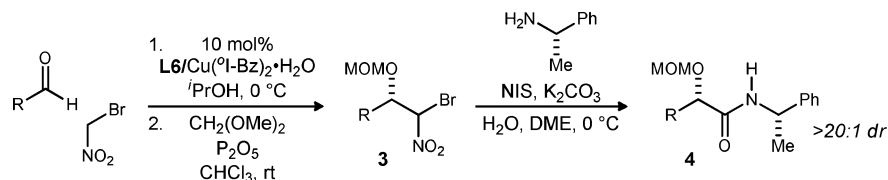
to selectivity (Table 2, entries 8–11). The effect was maximal for both diastereomeric adducts when preparing the chiral catalyst from copper(II) *ortho*-iodo benzoate.

The *tert*-butyl bis(oxazoline)/Cu(^oI-Bz)₂ combination in isopropanol was evaluated against a selection of aldehydes (Table 3). Since aldehydes are both plentiful and relatively inexpensive, it was gratifying that most cases examined provided high levels of enantioselection. The Henry protocol exhibited a broad tolerance for aromatic aldehydes bearing a variety of substituents. Benzaldehyde and similar substrates delivered the MOM-protected addition products (3a–c) with high ee and yield (Table 3, entries 1–3). Electron-donating substituents provided products with similar ee but with slightly depressed yields (56–64%) (Table 3, entries 4–5). Electron-withdrawing substituents at the *para*-position improved this to as high as 96% ee and 75% yield (Table 3, entries 6 and 7). *Meta*-substituted aryl aldehydes were converted to the corresponding α -bromo nitroalkanes with moderate yield and good enantioselection (Table 3, entries 8–9), although 2-naphthaldehyde suffered slightly (85% ee, Table 3, entry 10). *Ortho*-substituted aldehydes led to adducts with high ee and did not exhibit decreased reactivity (Table 3, entries 11–14), even when the substituent was a competent chelating Lewis base. Aliphatic aldehydes (Table 3, entries 15–16) delivered adducts in only moderate yield, but it was difficult to attribute a cause since their volatility hindered accurate measurements of conversion. However, selectivity for these additions was high. Finally, our investigation included several heteroaromatic aldehydes. Thiophene bearing an aldehyde at the 3-position led to the adduct in good ee and moderate yield (Table 3, entry 17), reflecting poor conversion. Nitrogen heterocycles also appeared to suffer from incomplete conversion, but a high ee was observed for a protected 2-pyrrole (97/95% ee for 3r, Table 3, entry 18). The analogous indole delivered adduct 3s with moderate selectivity (82/86% ee, Table 3, entry 19).

Table 3 provides details related to the subsequent UmAS step. Enantioenriched (99% ee) α -methyl benzyl amine was used to provide confirmation that the diastereomers 3 are homochiral at the benzylic carbon and remained enriched throughout the three-step sequence (Henry/MOM protection/UmAS). In each case, the coupling proceeded in moderate to good yield, providing the α -oxy amide (4) as a single diastereomer. This outcome is consistent with the mechanism of UmAS, which does not provide a pathway for epimerization at the carbon α to the carbonyl.^{13,14}

This approach was applied to the preparation of LY411575,^{21,22} a potent γ -secretase inhibitor developed for the treatment of Alzheimer's disease (Scheme 1). Although several preparations of this peptidic small molecule have been reported,²³ the difluoro mandelic acid is prepared as the racemate and coupled. The diastereomers that result are separated chromatographically. Using the chemistry described above, the mandelamide precursor was prepared in 52% yield and 91/92% ee. Subsequent coupling to alanine isopropyl ester was followed by hydrolysis of the ester. Coupling of the resulting acid and amine 9 followed by MOM deprotection delivered LY411575 as a single stereoisomer, for which all analytical data (NMR, optical rotation) matched those reported in the literature.

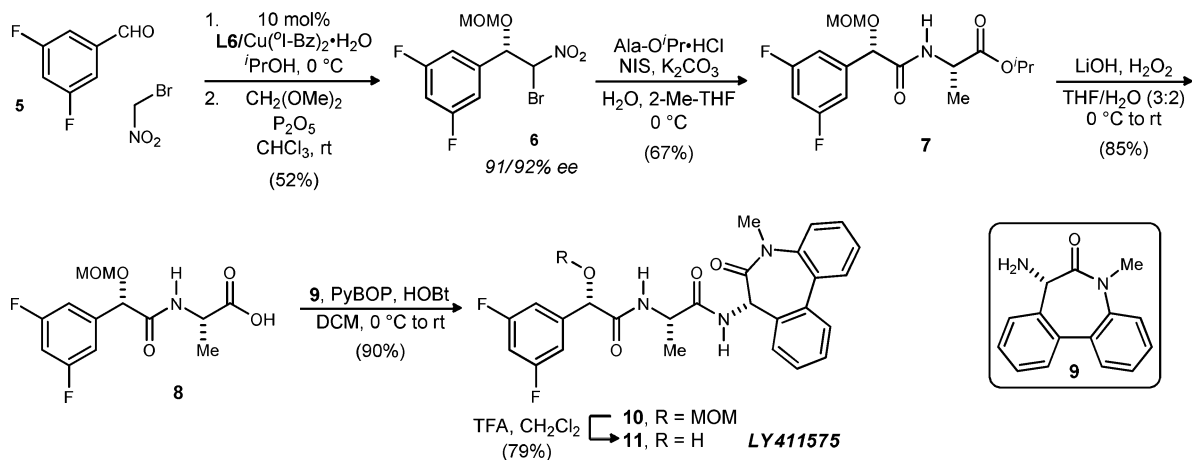
In summary, a new approach to α -oxy amides has been developed using a three-step sequence: enantioselective Henry addition, protection, and umpolung amide synthesis. An interesting counterion effect was used to improve the enantioselectivity of bromonitromethane addition using the Evans bis(oxazoline)–copper(II) system, for which an *ortho*-iodo benzoate salt provided substantial improvement. The selectivity achieved in the Henry

Table 3. Enantioselective Synthesis of MOM-Protected α -Bromonitroalkanes and Their Use in UmAS

entry	R	3 ^a	ee (%) ^b	yield (%) ^c	4 ^d	yield (%) ^c
1	C ₆ H ₅	a	92/92	62	a	61
2	^p MeC ₆ H ₄	b	91/91	81	b	60
3	^p PhC ₆ H ₄	c	93/85	85	c	56
4	^p MeOC ₆ H ₄	d	96/91	64	d	56
5	^p MeSC ₆ H ₄	e	91/86	56	e	54
6	^p FC ₆ H ₄	f	93/96	66	f	55
7	^p F ₃ CC ₆ H ₄	g	92/93	75	g	62
8	^m BrC ₆ H ₄	h	92/93	73	h	55
9	^m MeOC ₆ H ₄	i	95/95	62	i	57
10 ^e	² C ₁₀ H ₇	j	85/84	66	j	65
11	^o MeC ₆ H ₄	k	99/99	77	k	56
12	^o BrC ₆ H ₄	l	95/96	78	l	56
13	^o MeOC ₆ H ₄	m	96/99	74	m	57
14	^o MOMOC ₆ H ₄	n	99/99	72	n	69
15	C ₆ H ₁₁	o	99/99	45 ^f	o	53
16	PhCH ₂ CH ₂	p	89/92	47	p	46
17	³ thiophene	q	90/92	50	q	48
18	N-Ts- ² pyrrole	r	97/95	51	r	57
19	N-Ts- ³ indole	s	82/86	43	s	53

^aAll reactions were conducted using aldehyde (1 equiv, 0.3 M in ⁱPrOH), 10 mol % Cu(^oI-Bz)₂·H₂O, 10.5 mol % (S,S)-^tBuBOX (**L6**), and bromonitromethane (10 equiv) at 0 °C. ^bDetermined by chiral HPLC using chiral stationary phase. Values shown correspond to each diastereomer (ee_{d1}/ee_{d2}). ^cIsolated yield. ^dAll reactions were conducted using bromonitroalkane (1 equiv), H₂O (5 equiv), (S)- α -Me-benzylamine (1.2 equiv), K₂CO₃ (2 equiv), and NIS (1 equiv) in DME (0.2 M). ^eAmide isolated in 11:1 dr. ^fConducted at room temperature.

Scheme 1. Preparation of LY411575 Using the Enantioselective Mandelamide Synthesis



step is then translated through the UmAS step to prepare stereoisomerically pure α -oxy amides. Conceptually, this is one of the few approaches to chiral nonracemic α -oxy amides that avoids the ubiquitous α -oxy carboxylic acid intermediate, one that can suffer epimerization en route to amide derivatives.

■ ASSOCIATED CONTENT

⑤ Supporting Information

Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Research reported in this publication was supported by the National Institute of General Medical Sciences of the National Institutes of Health under Award Number R01 GM 063557.

■ REFERENCES

- (1) Spry, C.; Kirk, K.; Saliba, K. J. *FEMS Microbiol. Rev.* **2008**, *32*, 56.
- (2) Selected recent examples: Blay, G.; Fernández, I.; Marco-Aleixandre, A.; Pedro, J. R. *J. Org. Chem.* **2006**, *71*, 6674. Geoghegan, P.; O'Leary, P. *ACS Catalysis* **2012**, *2*, 573. Blay, G.; Fernández, I.; Marco-Aleixandre, A.; Pedro, J. R. *Org. Lett.* **2006**, *8*, 1287. Blay, G.; Fernández, I.; Hernández-Olmos, V.; Marco-Aleixandre, A.; Pedro, J. R. *Tetrahedron: Asymmetry* **2005**, *16*, 1953. Blay, G.; Fernández, I.; Hernández-Olmos, V.; Marco-Aleixandre, A.; Pedro, J. R. *J. Mol. Catal. A: Chem.* **2007**, *276*, 235. Blay, G.; Cardona, L.; Fernandez, I.; Marco-Aleixandre, A.; Munoz, M. C.; Pedro, J. R. *Org. Biomol. Chem.* **2009**, *7*, 4301.
- (3) Reduction of α -keto amides is an exception: Hatat, C.; Kokel, N.; Mortreux, A.; Petit, F. *Tetrahedron Lett.* **1990**, *31*, 4139. Pasquier, C.; Pelinski, L.; Brocard, J.; Mortreux, A.; Agbossou-Niedercorn, F. *Tetrahedron Lett.* **2001**, *42*, 2809. Turcry, V.; Pasquier, C.; Agbossou-Niedercorn, F. *C. R. Chim.* **2003**, *6*, 179. Cederbaum, F.; Lamberth, C.; Malan, C.; Naud, F.; Spindler, F.; Studer, M.; Blaser, H.-U. *Adv. Synth. Catal.* **2004**, *346*, 842. Xu, Z.; Zhu, S.; Liu, Y.; He, L.; Geng, Z.; Zhang, Y. *Synthesis* **2010**, 811.
- (4) Banfi, L.; Riva, R. *Org. React. (N.Y.)* **2005**, *65*, 1.
- (5) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7825.
- (6) Andreana, P. R.; Liu, C. C.; Schreiber, S. L. *Org. Lett.* **2004**, *6*, 4231.
- (7) Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 388.
- (8) Zeng, X.; Ye, K.; Lu, M.; Chua, P. J.; Tan, B.; Zhong, G. *Org. Lett.* **2010**, *12*, 2414.
- (9) De Vries, J. G.; Kellogg, R. M. *J. Am. Chem. Soc.* **1979**, *101*, 2759.
- (10) Carpentier, J.-F.; Mortreux, A. *Tetrahedron: Asymmetry* **1997**, *8*, 1083. Yamada, S.-i.; Mori, Y.; Morimatsu, K.; Ishizu, Y.; Ozaki, Y.; Yoshioka, R.; Nakatani, T.; Seko, H. *J. Org. Chem.* **1996**, *61*, 8586. Chiba, T.; Miyashita, A.; Nohira, H. *Tetrahedron Lett.* **1993**, *34*, 2351. Chiba, T.; Miyashita, A.; Nohira, H.; Takaya, H. *Tetrahedron Lett.* **1991**, *32*, 4745. Oxidative kinetic resolution: Salunke, S. B.; Babu, N. S.; Chen, C.-T. *Adv. Synth. Catal.* **2011**, *353*, 1234. Bette, V.; Mortreux, A.; Savoia, D.; Carpentier, J.-F. *Adv. Synth. Catal.* **2005**, *347*, 289.
- (11) Sosedov, O.; Matzer, K.; Buerger, S.; Kiziak, C.; Baum, S.; Altenbuchner, J.; Chmura, A.; van Rantwijk, F.; Stolz, A. *Adv. Synth. Catal.* **2009**, *351*, 1531. van Pelt, S.; Zhang, M.; Otten, L. G.; Holt, J.; Sorokin, D. Y.; van Rantwijk, F.; Black, G. W.; Perry, J. J.; Sheldon, R. A. *Org. Biomol. Chem.* **2011**, *9*, 3011. Baum, S.; van Rantwijk, F.; Stolz, A. *Adv. Synth. Catal.* **2012**, *354*, 113.
- (12) Additional selected examples: Yamamoto, Y.; Shirai, T.; Miyaura, N. *Chem. Commun.* **2012**, *48*, 2803. Kakei, H.; Nemoto, T.; Ohshima, T.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 317.
- (13) Shen, B.; Makley, D. M.; Johnston, J. N. *Nature* **2010**, *465*, 1027.
- (14) Shackelford, J. P.; Shen, B.; Johnston, J. N. *Proc. Natl. Acad. Sci. U.S.A.* **2012**, *109*, 44.
- (15) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692.
- (16) Blay, G.; Domingo, L. R.; Hernandez-Olmos, V.; Pedro, J. R. *Chem.—Eur. J.* **2008**, *14*, 4725. Blay, G.; Hernandez-Olmos, V.; Pedro, J. R. *Chem. Commun.* **2008**, 4840. Our use of this ligand in exploratory work led to varying results for reasons not understood. We can only speculate that some ligand systems may be more susceptible to impurities in the bromonitromethane, commercially available as 90% technical grade and used in excess. Our findings with the system described here were highly consistent.
- (17) Enantioselective Henry additions, selected examples: Jin, W.; Li, X.; Wan, B. *J. Org. Chem.* **2010**, *76*, 484. Christensen, C.; Juhl, K.; Jorgensen, K. A. *Chem. Commun.* **2001**, 2222. Kogami, Y.; Nakajima, T.; Ikeno, T.; Yamada, T. *Synthesis* **2004**, 1947. Du, D.-M.; Lu, S.-F.; Fang, T.; Xu, J. *J. Org. Chem.* **2005**, *70*, 3712. Palomo, C.; Oiarbide, M.; Laso, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3881. Bandini, M.; Piccinelli, F.; Tommasi, S.; Umani-Ronchi, A.; Ventrici, C. *Chem. Commun.* **2007**, 616. Liu, X.-G.; Jiang, J.-J.; Shi, M. *Tetrahedron: Asymmetry* **2007**, *18*, 2773. Qin, B.; Xiao, X.; Liu, X.; Huang, J.; Wen, Y.; Feng, X. *J. Org. Chem.* **2007**, *72*, 9323. Arai, T.; Takashita, R.; Endo, Y.; Watanabe, M.; Yanagisawa, A. *J. Org. Chem.* **2008**, *73*, 4903. Sanjeevakumar, N.; Periasamy, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1842. Ube, H.; Terada, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3895. Uraguchi, D.; Nakamura, S.; Ooi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 7562.
- (18) Fuji, K.; Nakano, S.; Fujita, E. *Synthesis* **1975**, 276.
- (19) Achiral counterion control of enantioselection, recent examples: Dobish, M. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2012**, *134*, 6068. Ding, Z.-Y.; Chen, F.; Qin, J.; He, Y.-M.; Fan, Q.-H. *Angew. Chem., Int. Ed.* **2012**, *51*, 5706.
- (20) Cotton, F. A.; Wilkinson, G.; Murillo, C. A.; Bochmann, M. *Advanced Inorganic Chemistry*; Wiley-Interscience: 1999, p 870. Wein, A. N.; Cordeiro, R.; Owens, N.; Olivier, H.; Hardcastle, K. I.; Eichler, J. F. *J. Fluorine Chem.* **2009**, *130*, 197. Chemler, S. R. *J. Organomet. Chem.* **2011**, *696*, 150.
- (21) Wu, J.; Tung, J. S.; Thorsett, E. D.; Pleiss, M. A.; Nissen, J. S.; Neitz, J.; Latimer, L. H.; John, V.; Freedman, S.; Britton, T. C.; Audia, J. E.; Reel, J. K.; Mabry, T. E.; Dressman, B. A.; Cwi, C. L.; Droste, J. J.; Henry, S. S.; McDaniel, S. L.; Scott, W. L.; Stucky, R. D.; Porter, W. J. *WO 98/28268*, 1998.
- (22) Audia, J. E.; Hyslop, P. A.; Nissen, J. S.; Thompson, R. C.; Tung, J. S.; Tanner, L. I. *WO 00/19210*, 2000.
- (23) Fauq, A. H.; Simpson, K.; Maharvi, G. M.; Golde, T.; Das, P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6392.