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Synthesis and Application of Quinazoline–Oxazoline-Containing (Quinazox) Ligands

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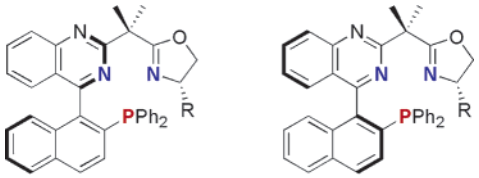
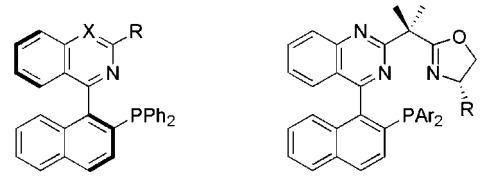
ABSTRACT



A practical synthesis of potentially tridentate P,N,N-ligands containing two stereogenic elements incorporated into the axially chiral Quinazolinap and centrally chiral 2-oxazoline subunits is reported. The application of these novel hybrid ligands in Pd(0)-catalyzed asymmetric allylic alkylation revealed the matched and mismatched diastereomer, dominant stereogenic element, as well as the effect of the oxazoline R substituent on the level of enantioselectivity (ee's up to 81%).

From the modest beginnings in the late 1960s,[1] transition-metal-mediated asymmetric catalysis has blossomed into an elegant and strategically powerful synthetic tool.[2] Despite that, its relentless progress still heavily relies on the well-balanced synergy between the development of asymmetric variants of valuable transformations and the design and synthesis of novel ligand candidates. Such topologically unprecedented molecular architectures, capable of creating a suitably tailored asymmetric environment around the central metal atom, are pivotal to the success in any exploratory studies of enantioselective processes.[3]

Inspired by the current surge of interest in the development of heterobidentate ligands[4] and, in particular, by the work of Brown et al. on the axially chiral Quinap ligand **1** (Figure 1),[5] we have recently reported on the synthesis of structurally related Quinazolinaps **2**.[6] These two classes of biaryls have been shown to be successful P,N-bidentate ancillary ligands



1: X = CH; R = H
2: X = N; R = H, alkyl, (hetero)aryl

3 (R_a or S_a)

Figure 1. Quinap and Quinazolinap-based ligands.

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(1) (a) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1999−2007. (b) Knowles, W. S.; Sabacky, M. J. *Chem. Commun.* **1968**, *22*, 1445−1446. (c) Horner, L.; Siegel, H.; Büthe, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 942.

(2) (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: New York, 1999. (b) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; VCH: Weinheim, Germany, 2000.

(3) Ligbank (www.ligbank.com), the European Ligand Bank, provides a venue for the exchange of ligands between interested research groups. This initiative is expected to facilitate matching optimal ligand structures with a particular asymmetric transformation.

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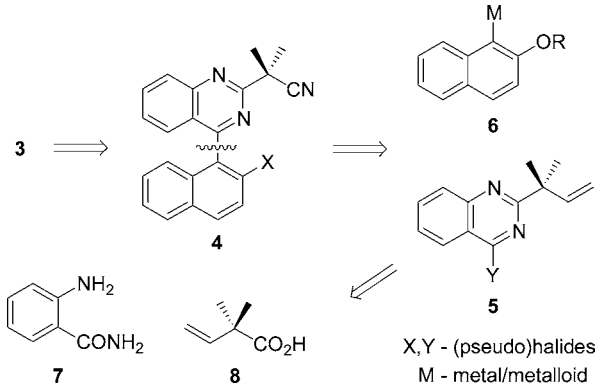
in a wide variety of important catalytic asymmetric transformations,[7] including hydroboration,[6b,7a] allylic alkylation,[7b] azomethine cycloaddition,[7c] ketone hydrogenation,[7d] diboration,[7e] and alkyne addition.[7f]

The present letter details our studies on the synthesis of potentially tridentate P,N,N-ligands **3**[8] incorporating the parent biaryl core of Quinazolinap as a well-defined scaffold and 2-oxazoline, one of the most ubiquitous privileged[9] motifs in ligand design.[10,11] The two subunits of **3** are linked via a one-carbon bridge in such a fashion as to secure a fused 6,6-chelation mode for metal binding, thus ensuring resting-state thermodynamic stability of the resulting complexes. Moreover, thanks to the combination of electronically dissimilar soft (P) and hard (N) ligating sites, which enable **3** to act as a hemilabile tridentate ligand, the propagation of a requisite catalytic cycle should also be ensured.

As we planned to develop a synthetic protocol that would provide an easy, modular access to a wide array of ligands **3**, our synthetic plan (Scheme 1) called for a late-stage

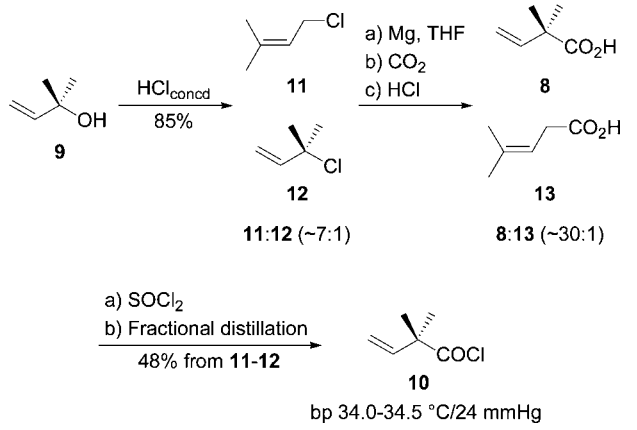
Scheme 1. Retrosynthesis of Quinazox Ligands **3**



common intermediate **4**. This biaryl could be assembled from the electrophilic partner **5** and metalated naphthalene **6**. Disconnecting further, quinazoline **5** could be accessed by cyclocondensation between anthranilamide (**7**) and acid **8**.

In the forward sense, the synthesis commenced with a three-step conversion of the commercially available and inexpensive alcohol **9** into acyl chloride **10** via double allylic rearrangement as outlined in Scheme 2. When treated with

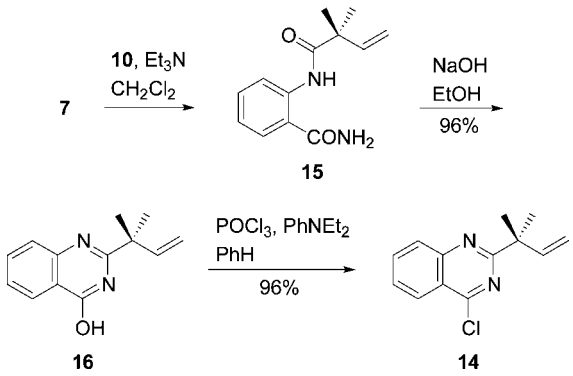
Scheme 2. Synthesis of Acyl Chloride **10**



concentrated HCl, alcohol **9** gave a mixture of prenyl chloride (**11**) and its isomer **12** in a ~7:1 ratio, respectively.[12,13] Attempted fractional distillation proved counterproductive, as **11** was found to thermally rearrange into the undesired isomer **12** with the ratio of the two products dropping to 2.7:1, respectively. To circumvent this obstacle, the crude mixture of the allylic chlorides **11** and **12** (**11**:**12**, ~7:1) was converted, via carbonation of the corresponding Grignard derivatives,[14] to a >30:1 mixture of acids **8** and **13**, respectively.[15] Apparently, the allylic rearrangement pathway leading from chloride **12** to acid **13** does not operate to a significant degree under the reaction conditions. Subsequent treatment with thionyl chloride, followed by fractional distillation (the only purification step in the entire sequence from alcohol **9**) gave acyl chloride **10** in 41% overall yield and high (>99%) isomeric purity.

With the acyl chloride **10** in hand, preparation of the requisite coupling partner **14** was accomplished in expedient fashion as depicted in Scheme 3. Thus, treatment of anthranilamide (**7**) with **10** in the presence of Et_3N gave

Scheme 3. Preparation of Aryl Chloride **14**



(4) (a) Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497−537. (b) McCarthy, M.; Guiry, P. J. *Tetrahedron* **2001**, *57*, 3809−3844.

(5) Alcock, N. W.; Brown, J. M.; Hulmes, D. I. *Tetrahedron: Asymmetry* **1993**, *4*, 743−756.

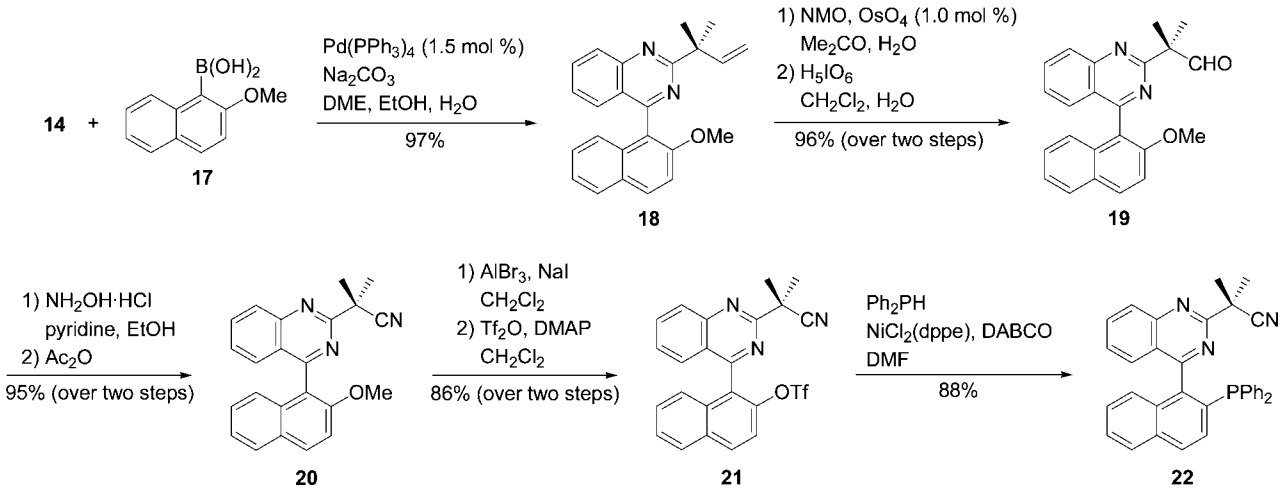
(6) (a) Flanagan, S. P.; Goddard, R.; Guiry, P. J. *Tetrahedron* **2005**, *61*, 9808−9821. (b) Connolly, D. J.; Lacey, P. M.; McCarthy, M.; Saunders, C. P.; Carroll, A.-M.; Goddard, R.; Guiry, P. J. *J. Org. Chem.* **2004**, *69*, 6572−6589. (c) McCarthy, M.; Hooper, M. W.; Guiry, P. J. *Chem. Commun.* **2000**, *14*, 1333−1334. (d) McCarthy, M.; Guiry, P. J. *Polyhedron* **2000**, *19*, 541−543. (e) Lacey, P. M.; McDonnell, C. M.; Guiry, P. J. *Tetrahedron Lett.* **2000**, *41*, 2475−2478. (f) McCarthy, M.; Goddard, R.; Guiry, P. J. *Tetrahedron: Asymmetry* **1999**, *10*, 2797−2807.

(7) (a) Doucet, H.; Fernandez, E.; Layzell, T. P.; Brown, J. M. *Chem.−Eur. J.* **1999**, *5*, 1320−1330. (b) Brown, J. M.; Hulmes, D. I.; Guiry, P. J. *Tetrahedron* **1994**, *50*, 4493−4506. (c) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174−10175. (d) Rautenstrauch, V.; Challand, R.; Churlaud, R.; Morris, R. H.; Abdur-Rashid, K.; Brazi, E.; Mimoun, H. PCT Int. Appl. WO 0222526, 2002. (e) Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8702−8703. (f) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763−5766.

(8) Following a well-established tradition, we assigned the name Quinazox to a class of ligands with the general structure **3**.

(9) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691−1693.

Scheme 4. Synthesis of Biaryl **22**

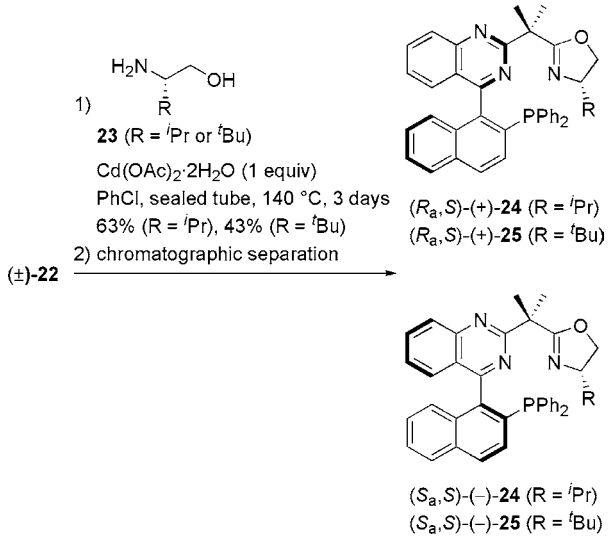


amide **15** that, when exposed to NaOH in boiling EtOH,[16] furnished quinazolinol **16**. Subsequent reaction with $POCl_3$ provided the desired aryl chloride **14** in excellent overall yield (92%) from **7**. It is noteworthy that the entire sequence requires only one chromatographic purification (i.e., of **14**) and can be conveniently carried out on a >100 gram scale.

Suzuki−Miyaura cross-coupling between arylboronic acid **17**[17] and aryl chloride **14** in the presence of $Pd(PPh_3)_4$ (1.5 mol %) gave biaryl **18** in excellent yield (Scheme 4). We observed that, at lower catalyst loadings, S_NAr ethanolysis of **14** manifested itself as a significant side reaction (see Supporting Information). Subjecting the terminal alkene **18** to OsO_4-mediated dihydroxylation furnished the corresponding diol that was then transformed via oxidative cleavage with H_5IO_6 to aldehyde **19** in excellent overall yield (96% from **18**). Subsequent reaction with hydroxylamine gave the corresponding, isomerically pure about the double carbon−nitrogen bond, oxime that was dehydrated by boiling in Ac_2O[18] to furnish nitrile **20** in 95% yield from **19**. The southern region of biaryl **20** was elaborated by demethylation with $AlBr_3$/NaI, followed by treatment with Tf_2O in the presence of DMAP to give triflate **21** (86% yield over two steps). This compound constitutes the late-stage, electronically and sterically modifiable common intermediate (corresponding to **4**) serving as a progenitor to an entire family of ligands **3**. All in all, this key compound was prepared from **9** in approximately 14 steps and 27% overall yield. Gratifyingly, nickel-catalyzed cross-coupling between triflate **21** and Ph_2PH according to the method of Cai et al.[19] led smoothly to triarylphosphine **22** in good yield.

As detailed in Scheme 5, the oxazoline subunit was installed by heating the racemic nitrile **22** with an appropriate homochiral amino alcohol **23** in PhCl in the presence of $Cd(OAc)_2$ (**CAUTION**: Carcinogenic).[20,21] Oxazolines **24** and **25** were formed in moderate yield as ∼1:1 mixtures of

Scheme 5. Preparation of Quinazox Ligands **24** and **25**



(10) (a) Meyers, A. I. *J. Org. Chem.* **2005**, *70*, 6137−6151. (b) McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151−4202. (c) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103*, 3119−3154. (d) Jönsson, C.; Hallman, K.; Andersson, H.; Stemme, G.; Malkoch, M.; Malström, E.; Hult, A.; Moberg, C. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1857−1867. (e) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1−45.

(11) For examples of oxazoline-containing axially chiral *bidentate* ligands, see: Zhang, W.; Xie, F.; Yoshinaga, H.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Synlett* **2006**, *8*, 1185−1188 and references therein.

(12) (a) Vani, P. V. S. N.; Chida, A. S.; Srinivasan, R.; Chandrasekharam, M.; Singh, A. K. *Synth. Commun.* **2001**, *31*, 219−224. Contrary to our results, the authors found that conversion of **9** to **11** was accompanied by no significant amounts of **12** as the byproduct. See also: (b) Mori, I.; Ishihara, K.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 1114−1117.

(13) Although **11** is commercially available, its high cost makes its synthesis from inexpensive **9** an attractive alternative, especially for large-scale preparations of acyl chloride **10**.

(14) Goering, H. L.; Blanchard, J. P. *J. Am. Chem. Soc.* **1954**, *76*, 5405−5408.

(15) For an alternative, four-step synthesis of **8** from ethyl isobutyrate that we used in our exploratory studies, see: Hayashi, Y.; Orikasa, S.; Tanaka, K.; Kanoh, K.; Kiso, Y. *J. Org. Chem.* **2000**, *65*, 8402−8405.

(16) (a) Mhaske, S. B.; Argade, N. P. *J. Org. Chem.* **2004**, *69*, 4563−4566. (b) Bergman, J.; Witt, A. *Tetrahedron* **2000**, *56*, 7245−7253. (c) Lemus, R. H.; Skibo, E. B. *J. Org. Chem.* **1988**, *53*, 6099−6105.

(17) Lim, C. W.; Tissot, O.; Mattison, A.; Hooper, M. W.; Brown, J. M.; Cowley, A. R.; Hulmes, D. I.; Blacker, A. J. *Org. Proc. Res. Dev.* **2003**, *7*, 379−384.

atropdiastereomers. To our delight, each pair of the isomers proved separable by column chromatography, and the structures of ligands (S_a,*S*)-(−)-**24** and (S_a,*S*)-(−)-**25** were unequivocally established by single-crystal X-ray diffraction analyses (Figure 2).[22]

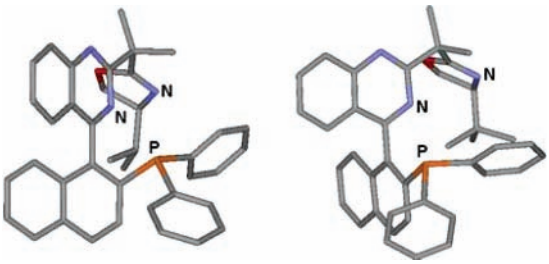
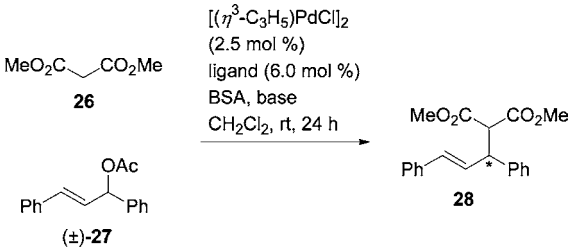


Figure 2. Single-crystal X-ray structures of ligands (S_a,*S*)-(−)-**24** (left) and (S_a,*S*)-(−)-**25** (right). Hydrogen atoms are omitted for clarity.

Our initial studies on application of ligands **24** and **25** in catalysis focused on the asymmetric allylic alkylation (AAA) of the racemic acetate **27** with dimethyl malonate (**26**). Due to its synthetic utility, the detailed understanding of the catalytic cycle, and broad literature coverage, this process is widely regarded as the most reliable testing ground for new ligand candidates.[23] The results (Table 1) clearly indicate that the axial chirality of the Quinazolinap subunit, and not the central chirality of the 2-oxazoline appendage, is the dominant stereogenic element that governs the stereochemical outcome of the reaction (e.g., entries 2 and 4).[24] It is also apparent that the sterically less-demanding R substituent on the oxazoline ring (^{i}Pr vs ^{t}Bu) is beneficial for the level of enantioselection (entries 1 and 3 vs entries 5 and 7). Moreover, for the valinol-based ligand **24**, the match/mismatch of the two stereogenic elements is well-pronounced with (R_a,*S*)-(+)-**24** giving **28** of consistently higher enantiopurity than its (S_a,*S*)-(−)-**24** counterpart (e.g., entries 1 and 3).[25]

Table 1. Enantioselective Asymmetric Allylic Alkylation (AAA) with Quinazox Ligands **24** and **25**



entry	ligand	base	yield (%)[a]	ee (%)[b]
1	(R_a,*S*)-(+)-**24**	LiOAc	>95	81 (*R*)
2	(R_a,*S*)-(+)-**24**	KOAc	>95	55 (*R*)
3	(S_a,*S*)-(−)-**24**	LiOAc	>95	58 (*S*)
4	(S_a,*S*)-(−)-**24**	KOAc	>95	15 (*S*)
5	(R_a,*S*)-(+)-**25**	LiOAc	>95	60 (*R*)
6	(R_a,*S*)-(+)-**25**	KOAc	>95	7 (*S*)
7	(S_a,*S*)-(−)-**25**	LiOAc	88	39 (*S*)
8	(S_a,*S*)-(−)-**25**	KOAc	>95	55 (*R*)

[a] Isolated yield of **28**. [b] Determined by CSP HPLC (see Supporting Information). BSA: *N*,*O*-bis(trimethylsilyl)acetamide.

In conclusion, we have developed a flexible synthesis of potentially tridentate quinazoline−oxazoline-containing hybrid ligands that provide good levels of enantioselectivity in the prototypical AAA reaction. Work is currently underway to fine-tune the structure of Quinazox **3** by modifying the electronic and steric environment in the vicinity of its binding sites. The results of our studies in this arena will be reported shortly.

Acknowledgment. This work was supported by European Community's Sixth Framework Programme (FP6-505267-1). A generous donation of equipment by Radleys Discovery Technologies, Ltd., is also gratefully acknowledged.

Supporting Information Available: Full experimental procedures, ^{1}H/^{13}C/^{31}P NMR spectra for all new compounds, and crystallographic data for (S_a,*S*)-(−)-**24** and (S_a,*S*)-(−)-**25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Ireland, R. E.; Kierstead, R. C. *J. Org. Chem.* **1966**, *31*, 2543−2559.
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(20) Witte, H.; Seeliger, W. *Liebigs Ann. Chem.* **1974**, 966−1009.
(21) $ZnCl_2$, the most commonly used activator for the formation of 2-oxazolines from nitriles, proved ineffective. Only complexation of Zn(II) with **22** (in itself a potentially tridentate ligand) was noted.
(22) Crystal data for (S_a,*S*)-(−)-**24**: $C_{39}H_{36}N_3OP$; MW = 593.68; 0.40 × 0.30 × 0.20 mm; orthorhombic; space group $P2_12_12_1$; T = 100(2) K; λ = 0.71073 Å; a = 10.6365(12), b = 16.1655(19), c = 18.138(2) Å; V = 3118.7(6) Å^3; Z = 4; D_{calc} = 1.264 Mg m^{-3}; F(000) = 1256; μ(Mo Kα) = 0.125 mm^{-1}; 24106 reflections collected with 1.69 < Θ < 26.00°, 6061 of which were independent (R_{int} = 0.0300); 541 parameters; R_1 = 0.0378, wR_2 = 0.0908 [for reflections with $I > 2\sigma(I)$]; R_1 = 0.0403, wR_2 = 0.0924 (all data). Crystal data for (S_a,*S*)-(−)-**25**: $C_{40}H_{38}N_3OP$; MW = 607.70; 0.80 × 0.60 × 0.20 mm; orthorhombic; space group $P2_12_12_1$; T = 100(2) K; λ = 0.71073 Å; a = 10.9951(15), b = 16.296(2), c = 18.095(3) Å; V = 3242.1(8) Å^3; Z = 4; D_{calc} = 1.245 Mg m^{-3}; F(000) = 1288; μ(Mo Kα) = 0.122 mm^{-1}; 25065 reflections collected with 2.17 < Θ < 26.00°, 6375 of which were independent (R_{int} = 0.0264); 558 parameters; R_1 = 0.0310, wR_2 = 0.0752 [for reflections with $I > 2\sigma(I)$]; R_1 = 0.0331, wR_2 = 0.0767 (all data).
(23) (a) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813−5837. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921−2943. (c) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336−345. (d) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689−1708. (e) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422.
(24) An initial screening with (S_a,*S*)-(−)-**25** (see Supporting Information) revealed that CH_2Cl_2 and LiOAc are the optimal solvent and base, respectively, leading to an improved enantiopurity of **28**.
(25) When a ~1:1 mixture of (R_a,*S*)-(+)-**24** and (S_a,*S*)-(−)-**24** was used as the ligand (CH_2Cl_2, KOAc), the reaction furnished **28** in 21% ee (*R*). This, combined with other results (Table 1, entries 2 and 4), indicates that the rates of the AAA reaction for the two diastereomers are very similar.