Tetrahedron Letters 52 (2011) 2288–2291

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A peptide bromoiodinane approach for asymmetric bromolactonization

Daniel C. Whitehead, Matthew Fhaner, Babak Borhan *

Department of Chemistry, Michigan State Univerisity, East Lansing, MI 48824, USA

ARTICLE INFO

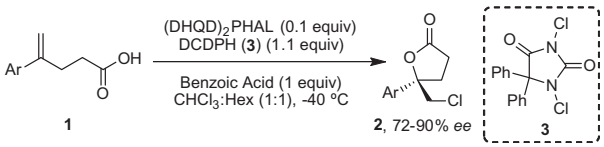
Article history:
Received 9 December 2010
Revised 12 February 2011
Accepted 14 February 2011
Available online 26 February 2011

Keywords:
Bromolactonization
Organocatalysis
Asymmetric
Peptides
Bromoiodinane

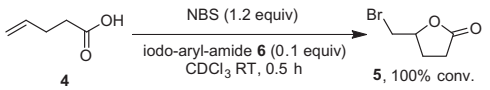
ABSTRACT

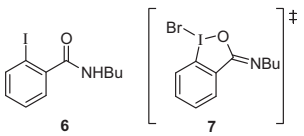
A series of 37 peptides containing an iodo-aryl amide active site were generated by means of both solid phase and conventional synthesis. These peptides were screened for asymmetric induction in the bromolactonization of 4-phenyl-4-pentenoic acid based on the generation of chiral bromoiodinane bromenium sources. The study culminated in the discovery of a tri-peptide iodo-aryl amide that effected the desired bromolactonization in quantitative conversion with 24% ee. The experiments disclosed herein provided valuable insight that ultimately facilitated the development of more synthetically useful enantioselective halocyclization methodology.

The development of asymmetric halocyclizations hinging on the selective delivery of a halenium source (X+) onto an olefin substrate is currently a burgeoning area of research in asymmetric catalysis.[1] Although transformations of this type have traditionally yielded only marginal selectivities,[2] select examples of asymmetric olefin halogenation reactions that proceed in high enantioselectivity have only recently begun to emerge. Ishihara and co-workers recently disclosed an elegant methodology for effecting highly enantioselective polyene cyclizations based on the formation of a chiral iodonium intermediate employing a chiral phosphoramidite promotor.[3] The Kang laboratory has developed an asymmetric iodoetherification protocol mediated by a catalytic loading of a chiral Co-salen complex.[4] Recently, the Snyder group featured a unique, highly enantioselective olefin chlorination as the key step in the total synthesis of Napyradiomycin A1.[5]



(1)





(2)

We disclosed a related enantioselective chlorolactonization protocol in early 2010 (Eq. 1).[6] This methodology allows for the enantioselective chlorolactonization of 4-arylpentenoic acids by the action of 1–10 mol % of $(DHQD)_2PHAL$ and 1,3-dichloro-5,5-diphenylhydantoin (DCDPH, **3**) as the terminal chlorenium source. The desired chiral chlorolactones are returned in good yield with enantioselectivities ranging from 72% ee to 90% ee. Contemporary with our report several elegant, highly selective asymmetric bromo[7] and iodolactonization[8] protocols have appeared in the literature. Very recently, we have extended our protocol to include the highly enantioselective chlorocyclization of allylic amides to generate chiral oxazolines and dihydrooxazines.[9]

A different approach to the problem has been our efforts in developing peptide-based chiral catalysts to promote halolactonizations. We drew inspiration from a work disclosed by Braddock and co-workers in 2009, whereby *ortho*-substituted aryl-iodo amides and amidines (e.g., **6**, Eq. 2) were able to significantly accelerate the NBS-mediated bromolactonization of various alkenoic acids by the formation of I(III) bromoiodinane intermediates such as **7**.[10] We envisioned rendering the process enantioselective by incorporating an aryl iodo amide active site motif into a chiral peptide framework. Disclosed herein is a full account of our efforts in this regard, which culminated in the development of a peptide-based catalyst library that returned the desired bromolactone product with selectivities up to 24% ee.

Initially, we targeted three peptide-based scaffolds that incorporated the *ortho*-iodo aryl amide precatalyst motif (Scheme 1). Linear scaffold **8** was loosely based on the linear peptidic scaffolds popularized by Hoveyda and Snapper.[11] The β-turn scaffold **10** made use of the well known Pro-D-Aaa turn motif.[12] Peptides containing the β-turn motif have been successfully employed as ligands[13] and organocatalysts.[14] Both of these scaffolds were

* Corresponding author.
E-mail address: babak@chemistry.msu.edu (B. Borhan).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.02.056

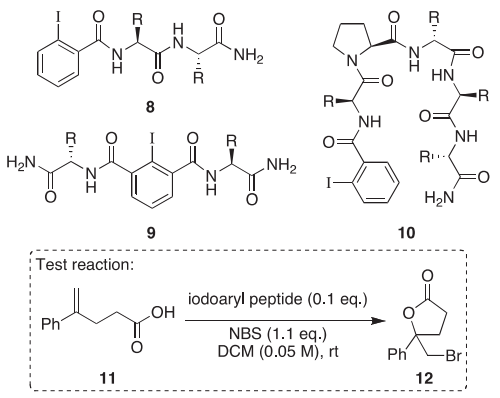
readily available by means of a well-established Fmoc Solid Phase Peptide Synthesis (SPPS).[15] While scaffold **8** and **10** only allowed for the incorporation of the *o*-iodo-amide active site at the N-terminus of the peptide chain, scaffold **9** allowed for the incorporation of the crucial active site within the heart of the peptide chain. Although not readily available by SPPS, scaffold **9** was easily accessible by conventional synthesis. Scaffold **9** vaguely resembles bis-amino acid pyridine scaffolds that have been applied previously for chiral recognition[16] and catalysis[17] applications.

We arrived at 4-phenyl-4-pentenoic acid **11** as a test substrate owing to the fact that it was readily prepared in quantity from commercially available methyl 3-benzoylpropionate by sequential Wittig olefination and saponification (see Supplementary data). Compound **11** is readily converted to the desired γ-bromolactone **12** under racemic organocatalytic conditions with 10 mol % *ortho*-iodobenzoic acid and NBS as reported by Braddock and coworkers.[10] The enantiomers of **12** are conveniently separated by chiral HPLC (Chiralcel OD-H). In addition to these operational conveniences, the choice of compound **11** was also driven by the fact that, at the time, some of the most recent attempts at the development of an asymmetric reagent-controlled halolactonization reaction focused on the 4-aryl-4-pentenoic acid substrate class.[2d,g] It seemed that initially targeting this substrate class would provide a convenient standard to which we might benchmark our progress. Furthermore, the lactonization of this class of alkenoic acids proceeds cleanly to provide the γ-lactone as the sole product without undergoing competing δ-lactone formation.

With regards to the scale of the screening protocol, we elected to perform reactions in microscale, screening the peptides for the asymmetric bromolactonization on a 0.05 mmol scale with respect to substrate **11** (9 mg loading). This approach was taken in order to facilitate a high-throughput screening approach. On this scale, product purification could be carried out by performing silica gel chromatography using packed Pastuer pipettes.

Additionally, this scale allowed for the judicious application of only a few milligrams of the relatively more precious and expensive peptide catalysts. The trade-off for such a small scale approach, however, was that tracking isolated yields on the scale of a few milligrams was untenable. As a result, we chose to optimize the catalyst scaffold and reaction conditions based upon the perturbations observed for the enantioselectivity of the transformation as the sole variable. Nonetheless, it warrants emphasis that all of the transformations described in this manuscript proceeded to completion as judged by TLC analysis prior to work-up.

Our initial efforts focused on the evaluation of scaffold **8**. Figure 1 depicts the structures of the catalysts prepared in this study. Peptides **13**–**21** represent our initial pilot library based upon scaffold **8**. All of the peptides in Figure 1 were prepared by conventional Fmoc SPPS (except **47**–**50**) and characterized by MALDI-TOF mass spectrometry (see Supplementary data for details). Catalysts **13**–**21** were screened at a 10 mol % loading in the test transformation of **11** to bromolactone **12** in dichloromethane at room temperature (Scheme 1, dashed box). In all cases, the desired bromolactone was generated in complete conversion as indicated by TLC.



Scheme 1. Aryl-iodo peptide scaffolds and test reaction for asymmetric induction.

Peptide **13** incorporated an aromatic side chain, while peptides **14**, **15**, and **16** incorporated various aliphatic side chains of increasing steric bulk. Peptides **17–21** incorporated a basic residue on the C-terminus separated from the aryliodo active site by a phenylalanine residue. The basic residues in these catalysts were incorporated in the hopes that they might serve to either deprotonate and thus activate the carboxylic acid nucleophile or to coordinate and thus orient the substrate in proximity with the active aryliodo site. While most of the series were completely unselective, peptide **16** returned **12** in 7% ee. Given that this result was reproducible, **16** was taken to be an initial 'hit' scaffold, and subsequent efforts centered around the iterative optimization of that scaffold.

Based on scaffold **16**, a second library of 10 peptides were prepared by modulating the C-terminal amino acid distal to the aryl iodoamide moiety. This residue was targeted for optimization based on the assumption that the proximal *tert*-leucine residue in **16** would be a crucial structural element for the selectivity that was initially observed. Catalysts **23**–**32** (see substructure **22**, Fig. 1) were screened in the test reaction. While none of the peptides from our second generation directed library out-performed the parent scaffold **16**, it is interesting to note some of the structural changes that result in reduced selectivity. Simply put, it appears that both *tert*-leucine residues housed in **16** are necessary to maintain the observed 7% ee. Modulating the C-terminal residue to benzyl (**23**), phenyl (**24**), basic (**25**), acidic (**26**), or carbinol (**27**) side chains proved to be detrimental. More interesting still are the changes observed by modulating the C-terminal *tert*-leucine to other aliphatic side chains. Incorporating unbranched aliphatic chains (**28**) or removing the site of branching farther away from the peptide backbone (**29**) resulted in inferior catalysts. Even those catalysts that maintained branching at the 1-position on the side chain (**30** and **31**) were less selective. Finally, incorporating a methyl group at the 3-position on the aryl iodoamide residue (**32**) resulted in a poorly selective catalyst.

Having established that both *tert*-leucine residues in **16** were necessary for the observed 7% ee, a longer analogue was prepared, thus incorporating a third *tert*-leucine moiety. When screened in the test reaction, tri-peptide **33** (see substructure **22**) proved to be twice as selective as its shorter cousin **16**, retuning **12** in 14% ee (peptide **33**). After this result, a battery of experiments were undertaken in an effort to enhance the selectivity of the transformation mediated by **33**, by systematically optimizing the reaction conditions. These efforts are disclosed in detail in the Supplementary data and include a solvent and temperature screen (Table S1), a moisture inclusion/preclusion study (Table S2), catalyst equivalency study (Table S3), concentration study (Table S4), and a scan of 15 alternate bromine sources (Table S5). Unfortunately these extensive efforts failed to improve upon the initially observed selectivity of 14% ee.

Having sufficiently exhausted reasonable means for optimizing the reaction conditions with catalyst **33**, we again returned to the generation of a third focused library in an attempt to improve the selectivity of the transformation. A series of eleven new peptides were prepared (Fig. 1, **34**–**44** Ar = *ortho*-iodophenyl). Peptides **34**–**36** were developed in order to determine if all three amino acids in the peptide chain of **33** necessarily needed to be *tert*-leucine residues to maintain selectivity. Peptides were, therefore, constructed whereby the amino acids in the peptide were sequentially replaced with valine residues starting at the C-terminus (**34**) and

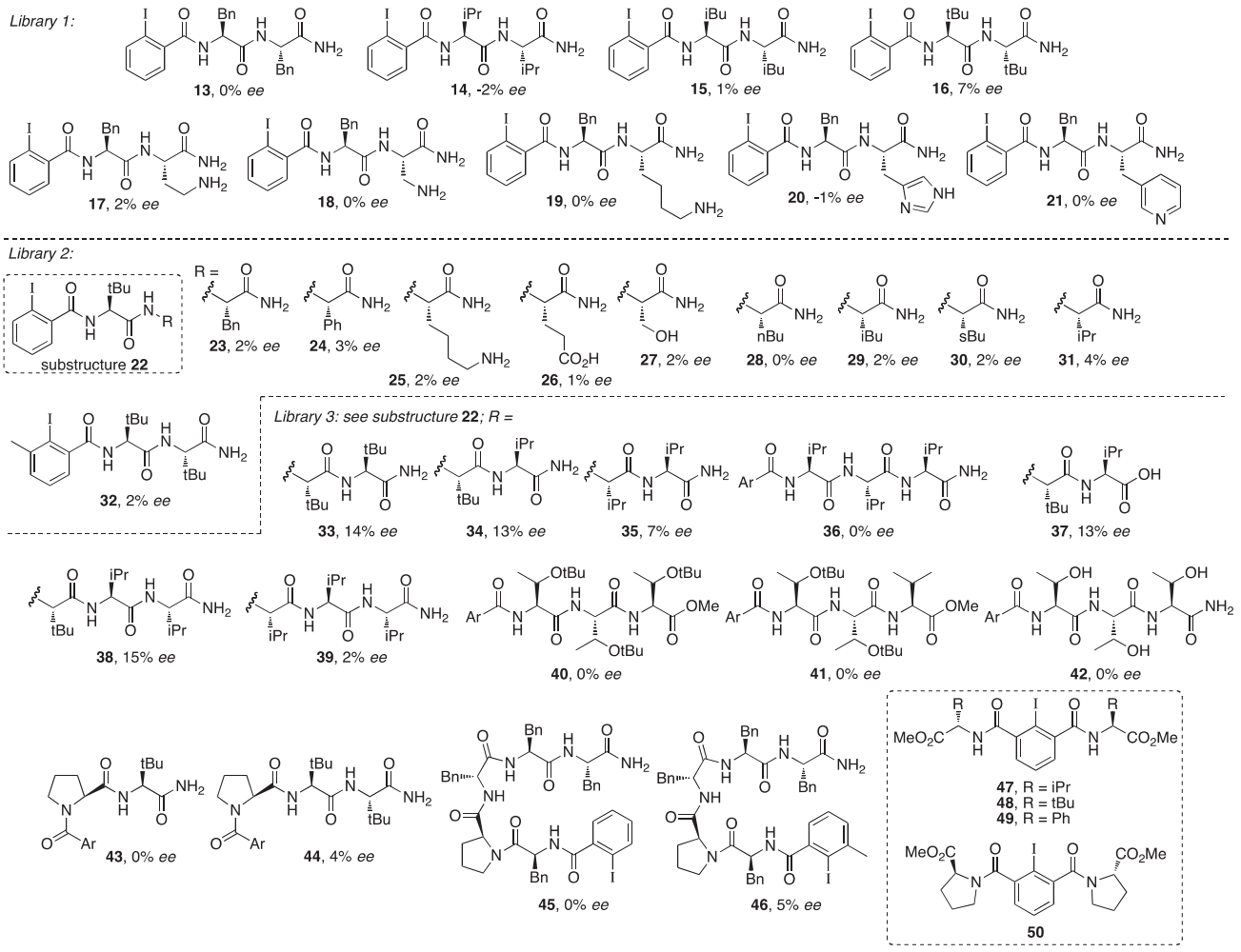
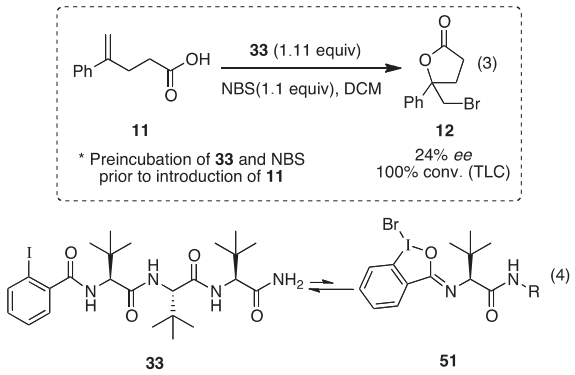


Figure 1. Aryl-iodo peptide catalysts for the asymmetric bromolactonization of **11**.

moving toward the N-terminus (**35** and **36**). Peptide **37** was constructed to probe the necessity of the C-terminal amide. Peptides **38** and **39** were assembled to evaluate the consequences of increasing the length of the peptide by the installation of a fourth amino acid residue on the C-terminus. Catalysts **40** and **41** were designed to evaluate the course of the reaction using a catalyst with even bulkier residues than those found in **33**. In this case *tert*-butyl threonine units were installed in lieu of the *tert*-butyl group resident in **33**. Simultaneously, **42** was prepared to provide the fully deprotected amide variant of **40**. Finally, **43** and **44** were assembled to probe the effects of installing an intervening proline residue between the *o*-iodoarylamide active site and the *tert*-leucine residues.

Peptides **34**–**44** were screened in the test transformation (**11** and **12**); the results are collected in Figure 1. As the C-terminal residues were sequentially modulated from *tert*-leucine to valine, a definite decline in selectivity was realized. While changing the C-terminal *tert*-leucine farthest removed from the iodoarylamido active site was tolerated (cf. 13% ee for **34** vs. 14% ee for **33**), further changes closer to the N-terminus of the scaffold resulted in poorly selective catalysts (peptides **35** and **36**). Switching all of the *tert*-leucine moieties with valine resulted in a completely unselective catalyst (**36**) while retaining only one *tert*-leucine (**35**) returned the lactone in 7% ee. These data are in excellent agreement with the initial experiments that lead to the discovery of **16** as a lead scaffold, and serve to confirm the assertion that two flanking *tert*-leucine residues represent a minimal structural element for stereoinduction. Modulating the C-terminal amide in **34** to a C-terminal carboxylic acid (**37**) had no effect on the selectivity of the bromolactonization (peptides **34** and **37**). On incorporating a fourth amino acid residue (valine) on the C-terminus, a negligible increase to 15% ee was realized with peptide **38**. The failure of peptide **38** to significantly improve upon the selectivity of **33** indicated that extending the peptide length by incorporating further residues would likely be fruitless. Peptide **39** again confirms the necessity of the two *tert*-leucine residues proximal to the iodoarylamido site (2% ee). Further increasing the steric bulk of the catalyst by incorporating *tert*-butyl threonine residues in lieu of *tert*-leucine resulted in inferior catalysts (peptides **40** and **41**). Similarly the unprotected threonine analogue **42** was completely unselective. The incorporation of a proline residue in between the iodoarylamido active site and the crucial neighboring *tert*-leucine produced peptides **43** and **44**, which were inferior to the second generation catalyst **33**. These experiments further underscore the necessity for the two *tert*-leucine residues neighboring the active site aryl-iodoamido moiety as a minimal scaffold for a selective peptide.

In addition to the series of peptides generated about the generalized scaffold **8**, we also briefly investigated alternate scaffolds including β-turn scaffold **10** and bis-amino acid scaffold **9**. In that vein, β-turn peptides **45** and **46** were prepared by standard SPPS and screened in the test reaction for the enantioselective preparation of **12**. While peptide **45** was completely unselective, peptide **46** returned lactone **12** in 5% ee. Perhaps a positional scanning regime originating from **46** would eventually yield a useful catalyst,



Scheme 2. Stoichiometric asymmetric bromolactonization mediated **33**.

but the size of these molecules might somewhat detract from their potential usefulness. For instance a 0.1 equiv loading of **46** requires the use of 10 mg of catalyst to convert only 17 mg of substrate **11**.

We targeted scaffold **9** by a three step conventional synthesis starting from a commercially available amino-*iso*-phthalic acid (see Supplementary data for details). Four potential catalysts were generated by employing the methyl esters of valine, *tert*-leucine, phenylglycine, and proline (**47**–**50**). On screening these catalysts in the test reaction, no detectable degree of enantioinduction was observed in the generation of **12**.

At the culmination of the experiments summarized in Figure 1, catalyst **33** had emerged as our most selective tripeptide. We set out to probe the 'ceiling' selectivity of this particular peptide by carrying out the analogous stoichiometric experiment (Scheme 2), whereby 1.11 equiv of peptide **33** was incubated with NBS for 30 min prior to the introduction of substrate **11**. The incubation period was instituted in the hopes of allowing for full conversion to the active chiral bromoiodinane reagent (see **51**) prior to the introduction of the substrate.

In the event, the desired bromolactone **12** was isolated with a higher, but disappointing 24% ee. This 'ceiling' enantioselectivity for catalyst **33** seemed to indicate a weak equilibrium concentration of active reagent **51** on treatment of **33** with NBS. This situation, taken with the rapid uncatalyzed background reaction of **11** with NBS alone (complete conversion to **12** in minutes at room temperature), ultimately lead us to abandon this approach toward effecting a catalytic asymmetric halolactonization. Although the enantioselectivity of our approach is significantly lower than that disclosed recently by Zhao and co-workers (90% ee in the conversion of **11** to **12**),[7b] the use of peptide-based ligands does constitute a new approach toward the asymmetric delivery of chiral bromenium via the generation of a chiral bromoiodinane intermediate. Further work on reaction conditions that limit uncatalyzed halolactonization, as well as the design of new, rigidified, chiral catalysts with a more defined asymmetric pocket is ongoing.

Acknowledgments

The authors thank Dr. Chrysoula Vasileiou and Dr. Kin-Sing Lee for performing MALDI-TOF analysis. We thank the ACS PRF (No. 47272-AC, and the NSF (CHE-0957462) for generous funding.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.02.056.

References and notes

1. For a recent review see: Chen, G.; Ma, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 8306.
2. (a) Kitagawa, O.; Hanano, T.; Tanabe, K.; Shiro, M.; Taguchi, T. *J. Chem. Soc., Chem. Commun* **1992**, 1005; (b) Grossman, R. B.; Trupp, R. J. *Can. J. Chem.* **1998**, *76*, 1233; (c) Cui, X. L.; Brown, R. S. *J. Org. Chem.* **2000**, *65*, 5653; (d) Haas, J.; Piguel, S.; Wirth, T. *Org. Lett.* **2002**, *4*, 297; (e) Wang, M.; Gao, L. X.; Yue, W.; Mai, W. P. *Synth. Commun.* **2004**, *34*, 1023; (f) Wang, M.; Gao, L. X.; Mai, W. P.; Xia, A. X.; Wang, F.; Zhang, S. B. *J. Org. Chem.* **2004**, *69*, 2874; (g) Haas, J.; Bissmire, S.; Wirth, T. *Chem. Eur. J.* **2005**, *11*, 5777; (h) Garnier, J. M.; Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2007**, 3281; (i) Ahmad, S. M.; Braddock, D. C.; Cansell, G.; Hermitage, S. A.; Redmond, J. M.; White, A. J. P. *Tetrahedron Lett.* **2007**, *48*, 5948; (j) Ning, Z.; Jin, R.; Ding, J.; Gao, L. *Synlett* **2009**, 2291.
3. Sakukara, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900.
4. (a) Kang, S. H.; Lee, S. B.; Park, C. M. *J. Am. Chem. Soc.* **2003**, *125*, 15748; (b) Kwon, H. Y.; Park, C. M.; Lee, S. B.; Youn, J.-H.; Kang, S. H. *Chem. Eur. J.* **2008**, *14*, 1023.
5. Snyder, S. A.; Tang, Z.-Y.; Gupta, R. *J. Am. Chem. Soc.* **2009**, *131*, 5744.
6. (a) Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* **2010**, *132*, 3298; (b) Yousefi, R.; Whitehead, D. C.; Mueller, J. M.; Staples, R. J.; Borhan, B. *Org Lett.* **2011**, *13*, 608.
7. (a) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. *J. Am. Chem. Soc.* **2010**, *132*, 3664; (b) Zhou, L.; Tan, C. K.; Jiang, X.; Chen, F.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 15474; (c) Murai, K.; Matsushita, T.; Nakamura, A.; Fukushima, S.; Shimura, M.; Fujioka, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 9174.
8. Veitch, G. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 7332.
9. Jaganathan, A.; Garzan, A.; Whitehead, D. C.; Staples, R. J.; Borhan, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 2593.
10. (a) Braddock, D. C.; Cansell, G.; Hermitage, S. A.; White, A. J. P. *Chem. Commun.* **2006**, 1442–1444; (b) Braddock, D. C.; Cansell, G.; Hermitage, S. A. *Synlett* **2004**, 461; (c) Braddock, D. C.; Cansell, G.; Hermitage, S. A. *Chem. Commun.* **2006**, 2483.
11. (a) Shimizu, K. D.; Snapper, M. L.; Hoveyda, A. H. *Chem., Eur. J.* **1998**, *4*, 1885; (b) Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. A. *Chem. Commun.* **2004**, 1779; (c) Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nature* **2006**, *443*, 67.
12. Imperiali, B.; Fisher, S. L.; Moats, R. A.; Prins, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 3182.
13. Agarkov, A.; Greenfield, S. J.; Ohishi, T.; Collibee, S. E.; Gilbertson, S. R. *J. Org. Chem.* **2004**, *69*, 8077.
14. Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601.
15. Fields, G. B.; Noble, R. L. *Int. J. Pept. Protein Res.* **1990**, *35*, 161.
16. (a) Moriuchi, T.; Shen, X. L.; Hirao, T. *Tetrahedron* **2006**, *62*, 12237; (b) Moriuchi, T.; Nishiyama, M.; Yoshida, K.; Hirao, T. *Heterocycles* **2006**, *67*, 375.
17. Derdau, V.; Laschat, S.; Hupe, E.; Konig, W. A.; Dix, I.; Jones, P. G. *Eur. J. Inorg. Chem.* **1999**, 1001.