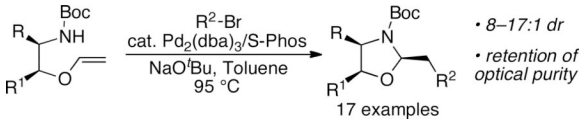
NIH Public Access
Author Manuscript
Org Lett. Author manuscript; available in PMC 2012 September 2.

Published in final edited form as:
Org Lett. 2011 September 2; 13(17): 4728–4731. doi:10.1021/ol2020048.

Stereoselective Synthesis of Substituted 1,3-Oxazolidines via Pd-Catalyzed Carboamination Reactions of *O*-Vinyl-1,2-Amino Alcohols

Amanda F. Ward and **John P. Wolfe***
Department of Chemistry, University of Michigan, 930 N. University Avenue, Ann Arbor, Michigan, 48109-1055

Abstract



The stereoselective synthesis of 2,4- and 2,5-disubstituted 1,3-oxazolidines is accomplished via Pd-catalyzed carboamination of *O*-vinyl-1,2-amino alcohol derivatives. The transformations generate *cis*-disubstituted products with good to excellent diastereoselectivity, and enantiomerically enriched substrates are converted without loss of optical purity. In addition to yielding synthetically useful products that are difficult to generate with existing methods, these transformations illustrate that electron-rich enol ethers are viable substrates for alkene carboamination processes.

Substituted 1,3-oxazolidines are displayed in many biologically active compounds,[1] and are also broadly employed in asymmetric synthesis as chiral auxiliaries, or as chiral ligands for transition metal catalysts.[2] The classical approach to 2,4- and 2,5-disubstituted 1,3-oxazolidines involves condensation of an aldehyde with an amino alcohol,[2] and alternative routes that involve carbon-heteroatom bond-forming cycloaddition,[3] conjugate addition,[4] or aza-Wacker type reactions[5] have also been explored. However, most methods for the preparation of 1,3-oxazolidines effect the construction of the C–N and the C–O bond during the ring-forming event. Transformations that generate both a carbon-heteroatom bond *and a carbon-carbon bond* during oxazolidine formation are relatively rare, and are typically not amenable to the stereocontrolled preparation of 2,4- or 2,5-disubstituted products.[6]

We sought to develop a new method for the preparation of 1,3-oxazolidines (e.g., **4**) via Pd-catalyzed carboamination reactions[7] between aryl or alkenyl bromides and enol ethers **1** derived from readily available 1,2-amino alcohols (Scheme 1). This approach has significant potential utility, as the reactions should proceed with kinetic control of stereochemistry and provide enantiomerically pure products with good levels of diastereoselectivity.[7,8] However, in order to accomplish this goal it was necessary to overcome two key obstacles. The transformations were expected to proceed via intramolecular *syn*-aminopalladation of intermediate **2**,[7,8,9] but enol ethers (or similarly electron-rich alkenes) have not previously been employed in Pd-catalyzed carboaminations between unsaturated amines and aryl/

jpwolfe@umich.edu.

Supporting Information Available. Experimental procedures, characterization data for all new compounds, descriptions of stereochemical assignments with supporting structural data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds reported in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

alkenyl halides.[10] No studies have demonstrated that such highly electron-rich alkenes can undergo *syn*-migratory insertion into Pd–N bonds of $L_nPd(R^1)(NR_2)$ complexes.[11] Moreover, mechanistic experiments by Stahl indicate that the transition state for *syn*-aminopalladation exhibits characteristics of a N-nucleophile/alkene electrophile combination,[12] which suggests that insertions of electron rich alkenes could have relatively high barriers.[13] In addition to the challenges associated with *syn*-aminopalladation of an electron-rich alkene, the reductive elimination of intermediate **3** was also expected to be difficult. The two inductively electron-withdrawing heteroatoms on the carbon beta to Pd will slow the rate of C–C bond-formation from **3**.[9a–b,14] Thus, competing beta-hydride elimination[15] to generate **6** or beta-alkoxide elimination[11,16] to form **5** could be problematic.

In preliminary feasibility studies we elected to examine the reactivity of bromobenzene with the simple, geometrically constrained enol ether **7**. Given the anticipated challenges described above, we focused our catalyst optimization studies on two classes of ligands: (a) bis-phosphine ligands with relatively wide bite angles; and (b) bulky monodentate phosphine ligands (Table 1). These classes of ligands have been shown to promote rapid C–C bond-forming reductive elimination,[17] and prior studies suggested they could also potentially facilitate the key aminopalladation step.[18] A preliminary survey of catalysts composed of $Pd_2(dba)_3$ and a wide bite angle ligand indicated that the yield of **8** increased with increasing bite angle, and promising results were obtained with Xantphos (58% yield).[19] However, our experiments with monodentate phosphines showed the monodentate S-Phos ligand was superior to Xantphos,[20] as the 1,3-oxazolidine product **8** was isolated in 70% yield when this phosphine was employed.

Having discovered a suitable catalyst system for enol ether carboamination, we sought to probe the scope of this new method. A variety of substrates were synthesized via *O*-vinylation of the corresponding amino alcohols.[21] As shown in Table 2, substrates bearing substituents adjacent to the oxygen or nitrogen atom were transformed to 2,5-*cis*- or 2,4-*cis*-disubstituted-1,3-oxazolidines in good yield (entries 4–14).[19] The products were typically generated with 8–17:1 dr (crude). Additionally, in many cases diastereomers could be partially separated by chromatography, and upon isolation the desired products were obtained with up to >20:1 dr. Disubstituted substrate **(−)-15** was converted to trisubstituted products **(−)-30** and **(−)-31** with good stereocontrol (entries 15–16).[22] The transformations were effective with a wide range of aryl bromides, and alkenyl halides were also successfully used as coupling partners (entries 3 and 13).

A model that accounts for the relative stereochemistry of the products is illustrated in Figure 1. Transformations of substrates **12–14** proceed via transition state **32**, in which the substituent adjacent to the nitrogen atom is oriented in an axial position to minimize $A^{1,3}$ strain in alternative transition state **33**. Reactions of **10–11** undergo cyclization via transition state **34**, in which the substituent adjacent to the oxygen atom is equatorial to avoid 1,3-diaxial interactions that would be present in transition state **35**. The nature of the aryl or alkenyl halide appears to have a small effect on diastereoselectivity, but no clear trend is apparent.

In summary, we have developed a concise approach to the synthesis of enantiomerically pure 2,4- and 2,5-disubstituted 1,3-oxazolidines. The heterocyclic products are generated in only three steps from commercially available amino alcohols in good yield and diastereoselectivity. This transformation provides access to compounds that are difficult to prepare in a stereocontrolled manner with existing methods. These transformations also illustrate the viability of enol ethers as participants in alkene carboamination processes, and highlights the efficacy of S-Phos in promoting challenging sp^3-sp^3 C–C bond forming reductive elimination from Pd(II).

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors acknowledge the NIH-NIGMS for financial support of this work. Additional funding was provided by GlaxoSmithKline, Amgen, and Eli Lilly. A.F.W. acknowledges Novartis for a graduate research fellowship.

References

1. (a) Yu L, Zhou W, Wang Z. Bioorg. Med. Chem. Lett. 2011; 21:1541. [PubMed: 21288715] (b) Gudaprthi V, Bharathi K, Omprakash G. Asian. J. Chem. 2011; 23:765.(c) Zhou, XX.; Dmitry, MA.; Sun, P. PCT Int. Appl. WO 2011056126. 2011. (d) Scott JD, Williams RM. J. Am. Chem. Soc. 2002; 124:2951. [PubMed: 11902886]
2. Review: Wolf C, Xu H. Chem. Commun. 2011; 47:3339.
3. For selected recent examples, see: (a) Michaelis DJ, Shaffer CJ, Yoon TP. J. Am. Chem. Soc. 2007; 129:1866. [PubMed: 17260993] (b) Gandhi S, Bisai A, Bhanu Prasad BA, Singh VK. J. Org. Chem. 2007; 72:2133. [PubMed: 17300205] (c) Chen D, Chen X, Du T, Kong L, Zhen R, Zhen S, Wen Y, Zhu G. Tetrahedron Lett. 2010; 51:5131. (d) Williamson KS, Yoon TP. J. Am. Chem. Soc. 2010; 132:4570. [PubMed: 20232850] (e) Kang B, Miller AW, Goyal S, Nguyen ST. Chem. Commun. 2009:3928.
4. (a) Sriramurthy V, Barcan GA, Kwon O. J. Am. Chem. Soc. 2007; 129:12928. [PubMed: 17924625] (b) Fan YC, Kwon O. Molecules. 2011; 16:3802. [PubMed: 21546881]
5. Elliott LD, Wrigglesworth JW, Cox B, Lloyd-Jones GC, Booker-Milburn KI. Org. Lett. 2011; 13:728. [PubMed: 21244048]
6. Transformations that lead to C–C bond-formation during oxazolidine generation typically involve 1,3-dipolar cycloaddition reactions between carbonyl ylides and imines or between azomethine ylides and aldehydes. For selected examples, see: (a) Bentabed-Ababsa G, Derdour A, Roisnel T, Saez JA, Perez P, Chamorro E, Domingo LR, Mongin F. J. Org. Chem. 2009; 74:2120. [PubMed: 19199802] (b) Kim NS, Kang SY, Lee SH. Bull. Korean Chem. Soc. 2010; 31:553. (c) Kielland N, Catti F, Bello D, Isambert N, Soteras I, Luque FJ, Lavilla R. Chem. Eur. J. 2010; 16:7904. (d) Seashore-Ludlow B, Torssell S, Somfai P. Eur. J. Org. Chem. 2010:3927. (e) Huo C, Wei R, Zhang W, Yang L, Liu Z-L. Synlett. 2005:161.
7. For reviews on Pd-catalyzed carboamination reactions between aryl/alkenyl halides and amines bearing pendant alkenes, see: (a) Wolfe JP. Eur. J. Org. Chem. 2007:571. (b) Wolfe JP. Synlett. 2008:2913.
8. Bertrand MB, Neukom JD, Wolfe JP. J. Org. Chem. 2008; 73:8851. [PubMed: 18942792]
9. For recent mechanistic studies on *syn*-aminopalladation reactions of palladium(aryl)(amido) complexes, see: (a) Neukom JD, Perch NS, Wolfe JP. Organometallics. 2011; 30:1269. (b) Neukom JD, Perch NS, Wolfe JP. J. Am. Chem. Soc. 2010; 132:6276. [PubMed: 20397666] (c) Hanley PS, Markovic D, Hartwig JF. J. Am. Chem. Soc. 2010; 132:6302. [PubMed: 20408534]
10. For examples of oxidative coupling reactions between allylic sulfonamides and butyl vinyl ether that afford 2-alkoxypyrrolidines, see: Scarborough CC, Stahl SS. Org. Lett. 2006; 8:3251. [PubMed: 16836378]
11. Stahl has reported the Pd(II)-catalyzed transfer of vinyl groups from enol ethers to nitrogen nucleophiles. These reactions proceed via aminopalladation of a cationic Pd(II) alkene complex followed by β-alkoxide elimination. See: (a) Brice JL, Meerdink JE, Stahl SS. Org. Lett. 2004; 6:1845. [PubMed: 15151429] The stereochemistry of the aminopalladation step in the vinyl exchange reactions is not entirely clear, but subsequent studies suggest these reactions may occur through an outer-sphere *anti*-aminopalladation pathway rather than an inner-sphere (migratory insertion) *syn*-aminopalladation mechanism. See: (b) Maleckis A, Jaunzeme I, Jirgensons A. Eur. J. Org. Chem. 2009; 36:6407.
12. Ye X, Liu G, Popp BV, Stahl SS. J. Org. Chem. 2011; 76:1031.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

13. The insertion of electron-poor alkenes, such as acrylonitrile, into Pt–N bonds of platinum amido complexes is much more facile than analogous reactions of electron-neutral alkenes. See: Cowan RL, Trogler WC. Organometallics. 1987; 6:2451.

14. Culkin DA, Hartwig JF. Organometallics. 2004; 23:3398.

15. Competing β-hydride elimination from intermediate **3** could be facilitated by the nonbonding electrons on the N- and O-atoms. For further discussion, see: (a) Mueller JA, Sigman MS. J. Am. Chem. Soc. 2003; 125:7005. [PubMed: 12783555] (b) Hay MB, Wolfe JP. J. Am. Chem. Soc. 2005; 127:16468. [PubMed: 16305233]

16. (a) Muzart J. Tetrahedron. 2005; 61:4179.(b) Zhao H, Ariafard A, Lin Z. Organometallics. 2006; 25:812.

17. (a) Surry DS, Buchwald SL. Angew. Chem. Int. Ed. 2008; 47:6338.(b) Birkholz M-N, Freixa Z, van Leeuwen PWNM. Chem. Soc. Rev. 2009; 38:1099. [PubMed: 19421583]

18. Mechanistic studies suggest that the insertion of alkenes into Pd–N bonds occurs via intermediate palladium complexes that contain a single bound phosphine. For further discussion, see reference 9a.

19. Enamide and ketene aminal side products with structures similar to **5** and **6** were not isolated and could not be unambiguously identified through ^{1}H NMR analysis of crude reaction mixtures. However, these side products may be prone to hydrolysis during workup.

20. Ligand definitions: Dpe-Phos = bis(diphenylphosphinophenyl)ether; dppb = 1,4-bis(diphenylphosphino)butane; Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene; Ru-Phos = 2-dicyclohexylphosphino-2',6'-di-*i*-propoxy-1,1'-biphenyl, S-Phos = 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl.

21. (a) McKinley NF, O'Shea DF. J. Org. Chem. 2004; 69:5087. [PubMed: 15255741] (b) Bosch M, Schlaf M. J. Org. Chem. 2003; 68:5225. [PubMed: 12816481] (c) Okimoto Y, Sakaguchi S, Ishii Y. J. Am. Chem. Soc. 2002; 124:1590. [PubMed: 11853429]

22. For a representative case, chiral HPLC analysis indicated complete retention of enantiomeric purity (99% ee) during the three-step conversion of (*R*)-phenylglycinol to **(+)-27**.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

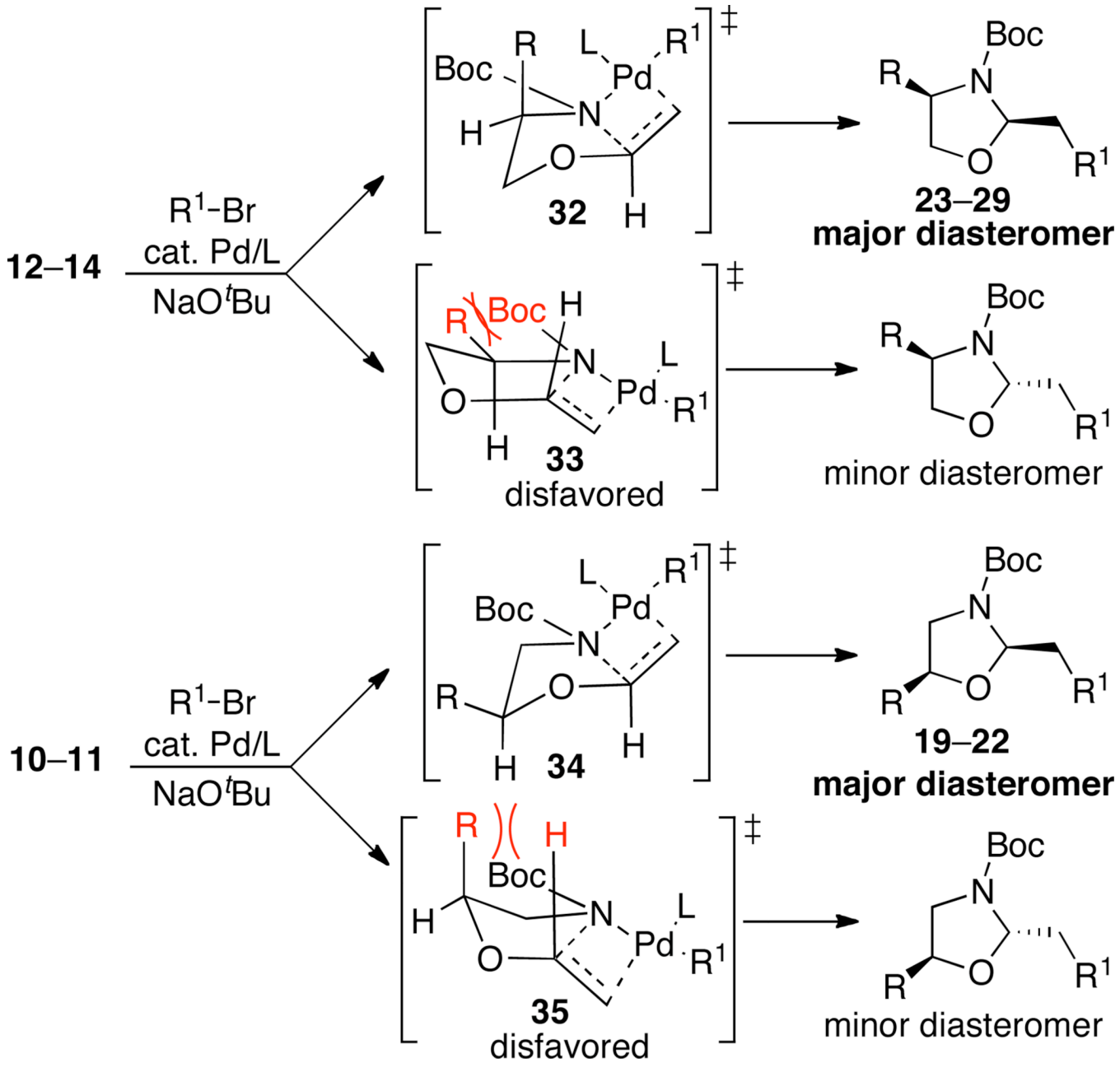
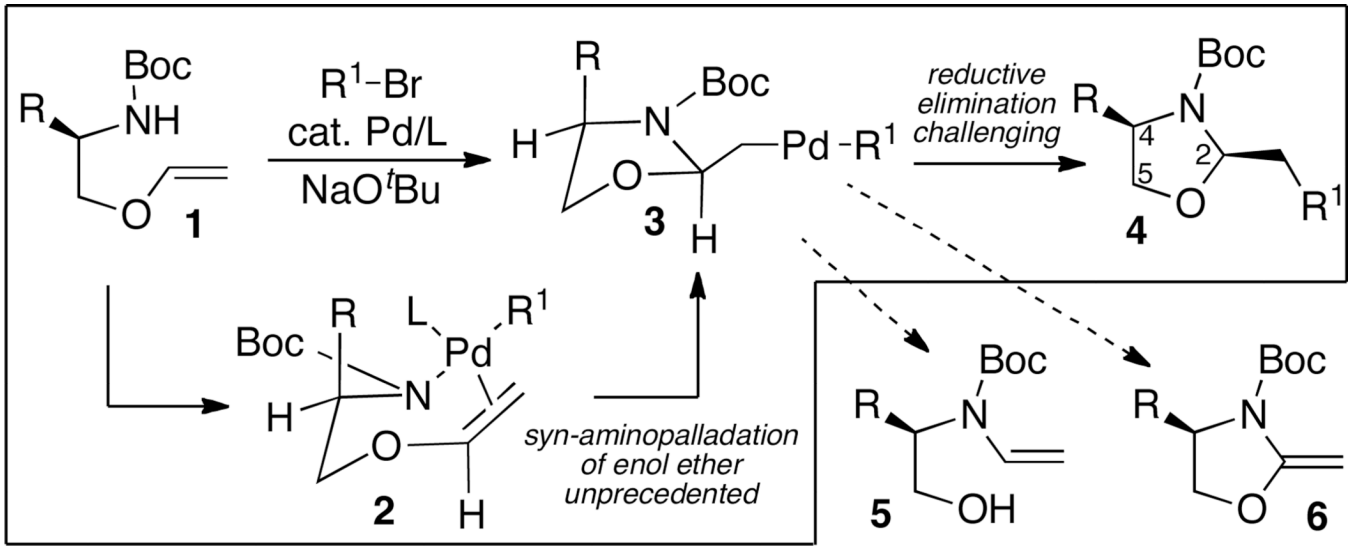


Figure 1.
Stereochemical model.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript



Scheme 1.
Carboamination Strategy for Stereoselective Oxazolidine Synthesis

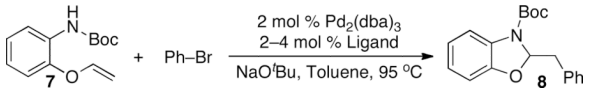
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 1

Catalyst Optimization Studies[a]



entry	ligand	yield[b]
1	dppb	0%
2	Dpe-Phos	13%
3	Xantphos	58%
4	P(*o*-tol)$_3$	0%
5	Ru-Phos	20%
6	S-Phos	70%[c]

[a]Conditions: 1.0 equiv **7**, 2.0 equiv PhBr, 2.0 equiv NaO^{t}Bu, 2 mol % $Pd_2(dba)_3$, 2–4 mol % ligand, Toluene, 95 °C.

[b]Yields were determined by ^{1}H NMR analysis of crude reaction mixtures using phenanthrene as an internal standard.

[c]Isolated yield (average of two experiments).

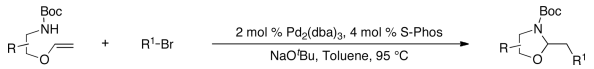
NIH-PA Author Manuscript

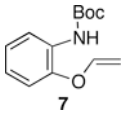
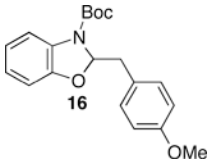
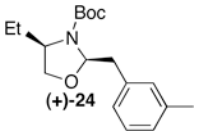
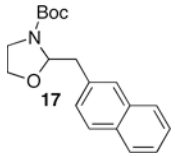
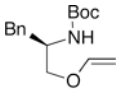
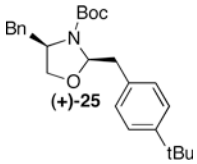
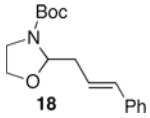
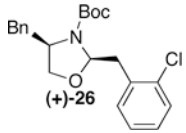
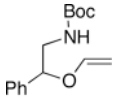
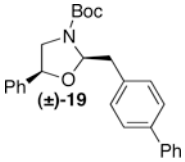
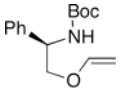
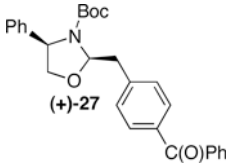
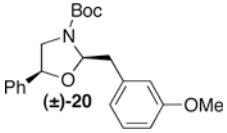
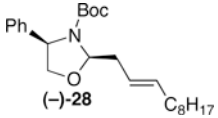
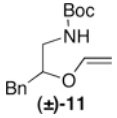
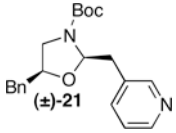
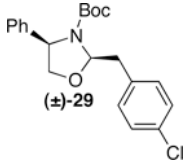
NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 2

Stereoselective Synthesis of Substituted Oxazolidines

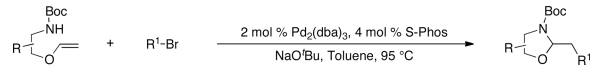


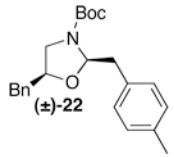
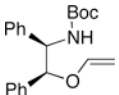
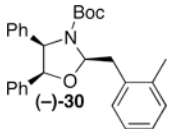
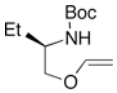
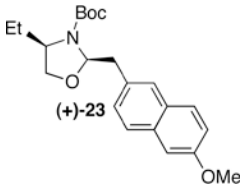
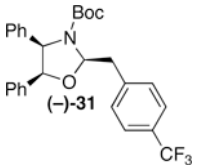
entry	substrate	product	dr[b]	yield[c]	entry	substrate	product	dr[b]	yield[c]
1	 **7**	 **16**	–	69%	9	**(+)-12**	 **(+)-24**	19:1 (9:1)	63%
2	**9**	 **17**	–	63%	10	 **(+)-13**	 **(+)-25**	>20:1 (8:1)	67%
3	**9**	 **18**	–	57%	11	**(+)-13**	 **(+)-26**	17:1 (17:1)	62%
4	 **(±)-10**	 **(±)-19**	12:1 (9:1)	83%	12	 **(−)-14**	 **(+)-27**	11:1 (8:1)	72%
5	**(±)-10**	 **(±)-20**	>20:1 (14:1)	89%	13	**(−)-14**	 **(−)-28**	9:1 (9:1)	58%
6	 **(±)-11**	 **(±)-21**	12:1 (12:1)	69%	14	**(±)-14**	 **(±)-29**	18:1 (9:1)	53%

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript



entry	substrate	product	dr[b]	yield[c]	entry	substrate	product	dr[b]	yield[c]
7	**(±)-11**	 **(±)-22**	>20:1 (9:1)	83%	15	 **(−)-15**	 **(−)-30**	16:1 (16:1)	76%
8	 **(+)-12**	 **(+)-23**	15:1 (15:1)	58%	16	**(−)-15**	 **(−)-31**	17:1 (15:1)	70%

[a]Conditions: 1.0 equiv amine, 2.0 equiv R^1Br, 2.0 equiv NaO^tBu, 2 mol % $Pd_2(dba)_3$, 4 mol % S-Phos, Toluene, 95 °C.

[b]Diastereomeric ratios were determined by ^1H NMR analysis of the pure, isolated material. Numbers in parentheses are diastereomeric ratios observed by NMR analysis of crude reaction mixtures.

[c]Isolated yields (average of two or more experiments).