JOC Article

Influence of Hydroxylamine Conformation on Stereocontrol in Pd-Catalyzed Isoxazolidine-Forming Reactions

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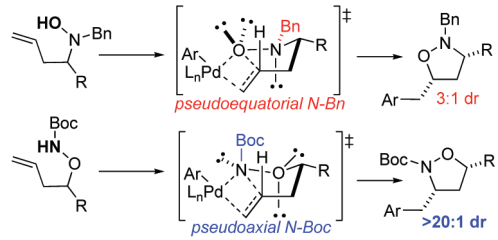
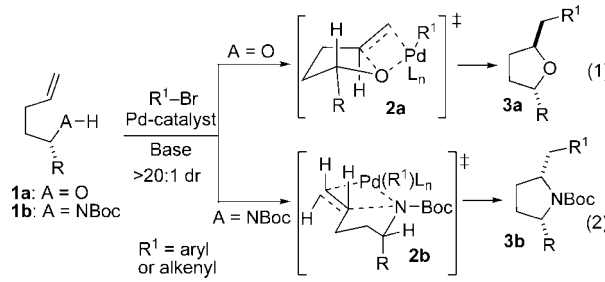


Palladium-catalyzed carboamination reactions between *N*-Boc-*O*-(but-3-enyl)hydroxylamine derivatives and aryl or alkenyl bromides afford *cis*-3,5- and *trans*-4,5-disubstituted isoxazolidines in good yield with up to >20:1 dr. The diastereoselectivity observed in the formation of *cis*-3,5-disubstituted isoxazolidines is superior to selectivities typically obtained in other transformations, such as 1,3-dipolar cycloaddition reactions, that provide these products. In addition, the stereocontrol in the C−N bond-forming Pd-catalyzed carboamination reactions of *N*-Boc-*O*-(but-3-enyl)hydroxylamines is significantly higher than that of related C−O bond-forming carboetherification reactions of *N*-benzyl-*N*-(but-3-enyl)hydroxylamine derivatives. This is likely due to a stereoelectronic preference for cyclization via transition states in which the Boc group is placed in a perpendicular orientation relative to the plane of the developing ring, which derives from the conformational equilibria of substituted hydroxylamines.

Introduction

Over the past several years, our group has been involved in the development of Pd-catalyzed alkene carboetherification and carboamination reactions for the stereoselective synthesis of 5-membered oxygen and nitrogen heterocycles,[1] including tetrahydrofurans,[2] pyrrolidines,[3] imidazolidin-2-ones,[4] and pyrazolidines.[5] For example, we have transformed substrates of general structure **1a** into *trans*-2,5-disubstituted tetrahydrofurans (**3a**) with >20:1 dr (eq 1). Similarly high diastereoselectivities are obtained in reactions of **1b** that generate *cis*-2,5-disubstituted pyrrolidines (**3b**, eq 2). Both of these reactions are believed to occur via intramolecular *syn*-oxypalladation or *syn*-aminopalladation of the alkene through organized cyclic transition states in which substituents are positioned to minimize nonbonding interactions.[6] As shown below, pseudoequatorial orientation of the R group in transition state **2a** leads to the formation of **3a**.[1,2a] The formation of *cis*-disubstituted product **3b** likely occurs via transition state **2b**, in which the Boc group is positioned in the same plane as the developing ring and the R group is placed in a pseudoaxial position to minimize $A^{(1,3)}$-strain.[1,3,7]



(1) For reviews, see: (a) Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571–582. (b) Wolfe, J. P. *Synlett* **2008**, 2913−2937.
(2) (a) Hay, M. B.; Hardin, A. R.; Wolfe, J. P. *J. Org. Chem.* **2005**, *70*, 3099–3107. (b) Hay, M. B.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 16468–16476, and references cited therein.
(3) (a) Bertrand, M. B.; Wolfe, J. P. *Tetrahedron* **2005**, *61*, 6447–6459. (b) Bertrand, M. B.; Leathen, M. L.; Wolfe, J. P. *Org. Lett.* **2007**, *9*, 457–460, and references cited therein. (c) Bertrand, M. B.; Neukom, J. D.; Wolfe, J. P. *J. Org. Chem.* **2008**, *73*, 8851–8860.
(4) Fritz, J. A.; Wolfe, J. P. *Tetrahedron* **2008**, *64*, 6838–6852, and references cited therein.
(5) Giampietro, N. C.; Wolfe, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 12907–12911.

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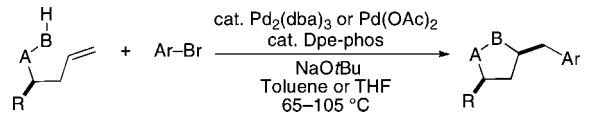
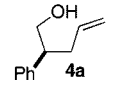
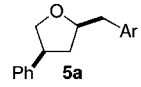
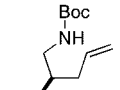
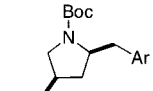
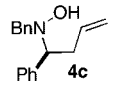
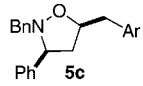
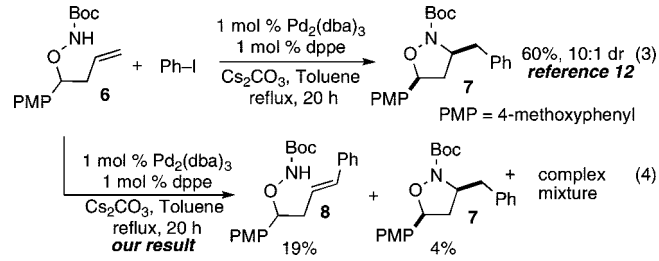
TABLE 1. Limitations of Stereocontrol[2a,3a,8]



entry	substrate	Ar	product	yield (%)	dr
1	 **4a**	*m*-OMePh	 **5a**	84	2:1
2	 **4b**	*p*-CO_2tBuPh	 **5b**	72	3:1
3	 **4c**	3-pyridyl	 **5c**	77	3:1

We recently reported a variant of this chemistry in which *N*-benzyl-*N*-(but-3-enyl)hydroxylamine derivatives were converted to isoxazolidine products via Pd-catalyzed alkene carboetherification.[8,9] The isoxazolidine products are of significance due to the fact that substituted isoxazolidines are displayed in biologically active compounds,[10] and also serve as precursors to 1,3-amino alcohols.[11] However, the synthetic utility of our carboetherification reactions that generate *cis*-3,5-disubstituted products is somewhat limited due to the modest diastereoselectivities that are obtained. For example, the coupling of **4c** with 3-bromopyridine generated **5c** in 77% yield, but with only 3:1 dr (Table 1, entry 3). A similar limitation is observed in related tetrahydrofuran- and pyrrolidine-forming reactions of **4a** and **4b**, which generated **5a** and **5b** with 2−3:1 dr (entries 1 and 2).

In light of our prior results, we were intrigued by a report from Dongol on the synthesis of isoxazolidines via Pd-catalyzed carboamination reactions of *N*-Boc-*O*-(but-3-enyl)hydroxylamine derivatives (e.g., **6**) with aryl iodides, which generated *cis*-3,5-disubstituted isoxazolidines (e.g., **7**) with up to 10:1 diastereoselectivity (eq 3).[12,13] Unfortunately, in our hands the conditions described by Dongol failed to provide more than trace amounts (ca. 4% by ^{1}H NMR) of the isoxazolidine product **7**, and instead afforded **8** (19% yield) as the major product, along with numerous side products.



In this paper we describe the development of conditions to effect the conversion of *N*-Boc-*O*-(but-3-enyl)hydroxylamines to isoxazolidines via Pd-catalyzed carboamination reactions.[14,15] The reactions proceed in good yield and provide *cis*-3,5- or *trans*-4,5-disubstituted isoxazolidines with excellent diastereoselectivity. Importantly, the selectivities obtained in the formation of *cis*-3,5-disubstituted products exceed those typically observed in other transformations, such as dipolar cycloaddition reactions, that generate these products.[16] We also describe experiments that suggest the high diastereoselectivities in these transformations result from a stereoelectronic preference for cyclization via transition states in which the Boc group is placed in a perpendicular orientation relative to the plane of the developing ring. *This preference is in sharp contrast to other carboamination and carboetherification processes, which appear to proceed via transition states similar to* ***2b*** *wherein carbamate groups are positioned in the same plane as the ring being formed*. In addition, this stereoelectronic effect, which likely derives from the relative energies of substituted hydroxylamine conformers, has not previously been noted in alkene difunctionalization processes.

Results

Optimization and Scope. In initial experiments we examined coupling reactions between **9** and 2-bromonaphthalene using catalysts generated in situ from mixtures of $Pd_2(dba)_3$ and phosphine ligands. We elected to employ NaO*t*Bu as the base for these studies, as NaO*t*Bu has provided good results in related transformations that generate other heterocycles.[1,17] As shown in Table 2, the nature of the phosphine ligand had a significant effect on both the chemical yields and the diastereoselectivities of these reactions. Use of the chelating phosphines dppe or (±)-BINAP, which have relatively small bite angles (≤93°),[18] failed to provide significant amounts of the desired product **10** at 65 °C and gave poor yields and diastereoselectivities at 110 °C (entries 1 and 2). Use of chelating ligands with wider bite angles led to better results, and good stereocontrol was obtained with Dpe-phos and Xantphos (entries 5 and 6). Both dppf and dppf-

(6) Alternative mechanisms involving alkene carbopalladation have been ruled out on the basis of deuterium labeling experiments and observed side products. For further discussion see: (a) Reference 2b. (b) Reference 3c. (c) Ney, J. E.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 8644−8651.

(7) Bertrand, M. B.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 2353–2356.

(8) Hay, M. B.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 6492–6494.

(9) For related studies, see: Jiang, D.; Peng, J.; Chen, Y. *Tetrahedron* **2008**, *64*, 1641–1647.

(10) (a) Minter, A. R.; Brennan, B. B.; Mapp, A. K. *J. Am. Chem. Soc.* **2004**, *126*, 10504–10505. (b) Ishiyama, H.; Tsuda, M.; Endo, T.; Kobabyashi, J. *Molecules* **2005**, *10*, 312–316.

(11) (a) Iida, H.; Kasahara, K.; Kibayashi, C. *J. Am. Chem. Soc.* **1986**, *108*, 4647–4648. (b) Fredrickson, M. *Tetrahedron* **1997**, *53*, 403–425.

(12) Dongol, K. G.; Tay, B. Y. *Tetrahedron Lett.* **2006**, *47*, 927–930.

(13) Six examples were described in ref 12 with GC yields ranging from 8% to 74% and dr from 2 to 10:1. An isolated yield was reported for only one example.

(14) For related Pd-catalyzed carboamination reactions of *N*-aryl-*O*-(but-3-enyl)hydroxylamines with aryl bromides that afford *N*-arylisoxazolidines, see: (a) Peng, J.; Jiang, D.; Lin, W.; Chen, Y. *Org. Biomol. Chem.* **2007**, *5*, 1391–1396. (b) Peng, J.; Lin, W.; Yuan, S.; Chen, Y. *J. Org. Chem.* **2007**, *72*, 3145–3148.

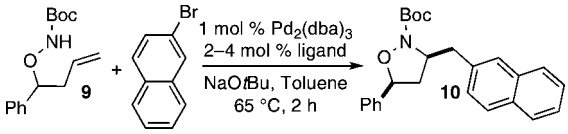
(15) For Pd-catalyzed Wacker-type carbonylative cyclofunctionalization reactions of *N*-Boc-*O*-(but-3-enyl)hydroxylamines, see: Bates, R. W.; Sa-Ei, K. *Org. Lett.* **2002**, *4*, 4225–4227.

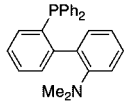
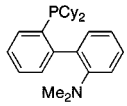
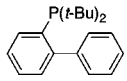
(16) Intermolecular 1,3-dipolar cycloaddition reactions between nitrones and terminal alkenes that afford 3,5-disubstituted isoxazolidine products typically proceed with ≤3:1 diastereoselectivity, and formation of mixtures of regioisomers can also be problematic. For reviews, see: (a) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1–173. (b) Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–909. (c) Kanemasa, S. *Synlett* **2002**, 1371−1387. For representative examples, see: (d) DeShong, P.; Leginus, J. M.; Lander, S. W. *J. Org. Chem.* **1986**, *51*, 574–576. (e) Ali, S. A.; Senaratne, P. A.; Illig, C. R.; Meckler, H.; Tufariello, J. J. *Tetrahedron Lett.* **1979**, *20*, 4167–4170.

(17) In ref 12 Dongol reported that use of this base led to *N*-arylation of the substrate. However, during the course of our studies we have not observed significant amounts of side products resulting from competing *N*-arylation.

(18) For a comprehensive list of bite angles for chelating bis-phosphine ligands, see: Fey, N.; Harvey, J. N.; Lloyd-Jones, G. C.; Murray, P.; Orpen, A. G.; Osborne, R.; Purdie, M. *Organometallics* **2008**, *27*, 1372–1383.

TABLE 2. Ligand Effects[a]



entry	ligand	**9** (%)[b]	**10** (%)[b]	dr
1	dppe	0	22[d]	2:1[c]
2	(±)-BINAP	0	36[d]	3:1[c]
3	dppf	34	57	9:1
4	Dppf-*i*Pr	8	77[d]	8:1
5	Dpe-phos	9	84	13:1
6	Xantphos	41	57	12:1
7	PPh_3	43	5[d]	2:1
8	P(*o*-tol)$_3$	65	22[d]	2:1
9	PCy_3•HBF_4	0	32[d]	2:1[e]
10	PCy_2(*t*Bu)	18	73	2:1
11	PCy(*t*Bu)$_2$	14	82	7:1
12	P*t*Bu$_3$•HBF_4	3	88[d] (87)[f]	28:1
13		7	87[d]	7:1
14		0	84	11:1
15		45	28[g]	13:1

[a] Conditions: 1.0 equiv of **9**, 1.2 equiv of 2-bromonaphthalene, 1.2 equiv of NaO*t*Bu, 1 mol % of $Pd_2(dba)_3$, 2 mol % of ligand (chelating bis-phosphines) or 4 mol % of ligand (monodentate phosphines), toluene (0.25 M), 65 °C, 2 h. [b] ^{1}H NMR yield against an internal standard (average of two experiments). Incomplete mass balance is attributed to small errors in NMR integration unless otherwise noted. [c] The reaction was conducted at 110 °C. [d] A product resulting from Heck arylation of the substrate was also formed. [e] The reaction was conducted for ca. 45 h, as very low conversion (<10%) was observed after 2 h. [f] Isolated yield (average of two experiments). [g] An unidentified side product was also formed in ca. 13% yield (NMR).

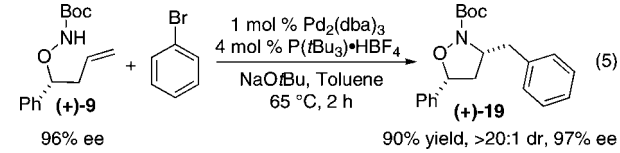
*i*Pr, which have identical backbones but different substituents on the phosphorus atoms, provided similar diastereoselectivities (entries 3 and 4).

The best yield and diastereoselectivity (87%, 28:1 dr) was obtained with the bulky, monondentate ligand P(*t*Bu)$_3$ (entry 12). Use of smaller trialkyl phosphines led to lower diastereoselectivity (entries 9−11), and monodentate triaryl phosphines also provided unsatisfactory results (entries 7 and 8). Biphenyl-derived phosphines did not perform as well as P(*t*Bu)$_3$, and provided diastereoselectivities ranging from 7 to 13:1 (entries 13−15). Diastereomeric ratios did not change during the course of reaction, and the ratio of ligand to metal did not have any effect on diastereoselectivity for cases examined (PCy_3, P(*t*Bu)$_3$, and P(*o*-tol)$_3$).

Interestingly, the influence of ligand structure on diastereoselectivity in the isoxazolidine-forming transformations contrasts with tetrahydrofuran- and pyrrolidine-forming reactions, wherein the ligand has not been observed to affect dr.[2,3] In addition, the effect of ligand structure on the diastereoselectivity of reactions involving **9** is much larger than that in related C−O bond-forming carboetherification reactions of **4c** that generate isoxazolidines (e.g., Table 1, entry 3). In the latter transformations, diastereoselectivities observed with different phosphines are typically in the range of 1 to 3:1.[8,9,19]

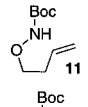
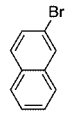
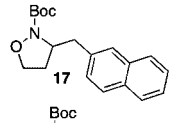
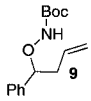
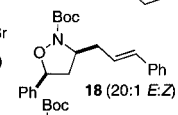
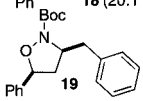
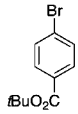
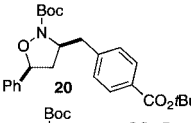
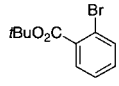
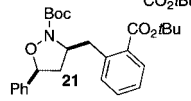
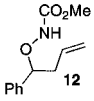
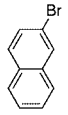
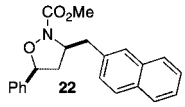
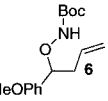
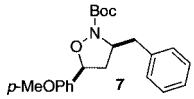
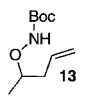
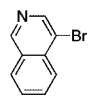
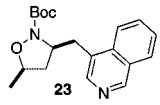
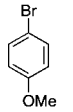
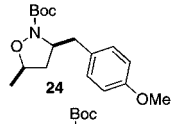
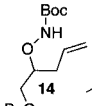
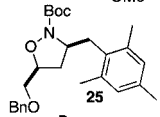
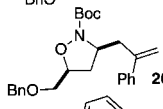
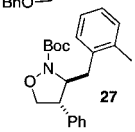
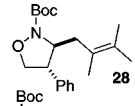
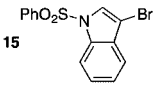
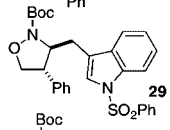
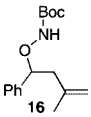
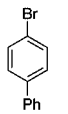
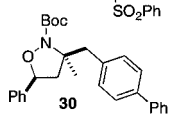
Following our optimization studies, we explored the scope of the isoxazolidine-forming reactions using several different combinations of 1-substituted *N*-Boc-*O*-(but-3-enyl)hydroxylamines[20] and electrophilic coupling partners. As shown in Table 3, a number of different *cis*-3,5-disubstituted isoxazolidines were prepared in good yields with diastereoselectivities ranging from 6:1 to >20:1 (entries 2−11). Significantly, the diastereoselectivities obtained in these reactions are superior to those typically observed when 3,5-disubstituted isoxazolidines are prepared via nitrone/alkene dipolar cycloaddition reactions.[16] A broad range of electron-rich, electron-poor, electron-neutral, sterically hindered, and heterocyclic aryl bromides proved to be suitable coupling partners, and reactions of alkenyl halides also provided good results. However, the reaction of **9** with *tert*-butyl 2-bromobenzoate proceeded in low yield (44%) due to competing Heck arylation of the substrate, and relatively low diastereoselectivity (6:1) was also observed in this reaction (entry 5). Use of iodobenzene in the conversion of **9** to **19** provided similar results as obtained with bromobenzene (entry 3), and a substrate protected as a methyl carbamate (**12**) was also efficiently transformed with high stereoselectivity (entry 6). In most cases efforts to employ substrates bearing disubstituted alkenes were not successful. However, the coupling of 4-bromobiphenyl with **16**, which contains both a disubstituted alkene and a substituent adjacent to the oxygen atom, proceeded with 4:1 diastereoselectivity. Upon isolation, **30** was obtained in 58% yield as a single stereoisomer (entry 15). The hydroxylamine carboamination reactions were also effective for the stereoselective preparation of *trans*-4,5-disubstituted products (entries 12−14) from a substrate substituted at C2.

To examine the feasibility of generating enantiopure disubstituted isoxazolidines via Pd-catalyzed carboamination, enantiomerically enriched substrate (+)-**9** was prepared from (*S*)-1-phenylbut-3-en-2-ol (96% ee).[21] As shown below (eq 5), the coupling of (+)-**9** with bromobenzene proceeded in 90% yield with no erosion of enantiomeric purity.[22]



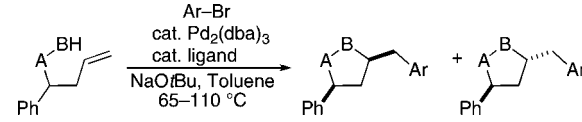
***N*-Substituent Effects.** The diastereoselectivities observed in Pd-catalyzed carboamination reactions of 1-substituted *N*-Boc-*O*-(but-3-enyl)hydroxylamines **6**, **9**, **13**, and **14** (Table 3, up to >20:1 dr) are significantly higher than those obtained in our previously reported carboetherification reactions of 1-substituted *N*-benzyl-*N*-(but-3-enyl)hydroxylamines (e.g., Table 1, **4c**, 3:1

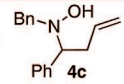
TABLE 3. Synthesis of Isoxazolidines[a]

entry	substrate	R–Br	product	yield (%)[b]	dr[c]
1	 **11**		 **17**	59	–
2[d,e]	 **9**	 (~7:1 *E*:*Z*)	 **18** (20:1 *E*:*Z*)	54	35:1 (>20:1)
3	**9**		 **19**	X = I: 61 X = Br: 68	>20:1 (>20:1) >20:1 (>20:1)
4	**9**		 **20**	78	>20:1 (>20:1)
5	**9**		 **21**	44	8:1 (6:1)
6	 **12**		 **22**	84	>20:1 (>20:1)
7	 **6** *p*-MeOPh		 **7** *p*-MeOPh	75	>20:1 (>20:1)
8	 **13**		 **23**	68	20:1 (17:1)
9	**13**		 **24**	68	>20:1 (>20:1)
10	 **14** BnO		 **25** BnO	74	20:1 (20:1)
11	**14**		 **26** BnO Ph	55	>20:1 (17:1)
12	 **15** Ph		 **27**	71	14:1 (13:1)
13	**15**		 **28** Ph	62	>20:1 (>20:1)
14[d]	**15**		 **29** SO_2Ph	67	5:1 (5:1)
15	 **16** Ph	 Ph	 **30** Ph Ph	58	>20:1 (4:1)

[a] Conditions: 1.0 equiv of substrate, 1.2 equiv of R-Br, 1.2 equiv of NaO*t*Bu, 1 mol % of $Pd_2(dba)_3$, 4 mol % of P(*t*Bu)$_3$·HBF$_4$, toluene (0.25 M), 65 °C. [b] Average isolated yields obtained from two or more experiments. [c] Diastereomeric ratio of the isolated material. Numbers in parentheses represent diastereomeric ratios observed in crude reaction mixtures. [d] The reaction was conducted with 1.5 mol % of $Pd_2(dba)_3$ and 9 mol % of P(*t*Bu)$_3$·HBF$_4$ at 90 °C. [e] The reaction was conducted with 2.0 equiv of *β*-bromostyrene and NaO*t*Bu.

TABLE 4. Diastereoselectivity in Carboetherification vs. Carboamination[a]



entry	ligand	substrate	major product	dr[b]	yield (%)[c]
1	Dpe-phos	 **4c**	**35**[d]	4:1	83
2	Xantphos	**4c**	**36**[d]	1:2	69[f]
3	Dpe-phos	**31**	**37**[e]	3:1	79
4	Xantphos	**31**	**37**[e]	1:1	75
5	Dpe-phos	**32**	—	—	0[g]
6	Xantphos	**32**	**38**[d]	1:7	33[g]
7	Dpe-phos	**33**	**39**[e]	1:1	22–46[h]
8	Xantphos	**33**	**39**[e]	2:1	38[h]
9	Dpe-phos	**34**	—	—	0[i]
10	Xantphos	**34**	—	—	0[i]
11	Dpe-phos	**9**	**10**[e]	12:1	66[j]
12	Xantphos	**9**	**10**[e]	12:1	71[k]

[a] Conditions: 1.0 equiv of hydroxylamine, 1.2−1.4 equiv of ArBr, 1.2−1.4 equiv of NaO*t*Bu, toluene (0.25 M), 65 or 110 °C. [b] Diastereomeric ratio observed in the crude reaction mixture. [c] Isolated yield of the major diastereomer (average of two experiments). [d] Ar = Ph. [e] Ar = 2-naphthyl. [f] From ref 9. We have obtained nearly identical results. [g] A mixture of products resulting from either Heck arylation or isomerization of the starting alkene was obtained. [h] Significant amounts of products derived from substrate N−O bond cleavage were also formed. [i] The major product was benzaldehyde *O*-1-phenylbut-3-enyl oxime. [j] Isolated as a 12:1 mixture of diastereomers. [k] Isolated as a 12:1 mixture of diastereomers.

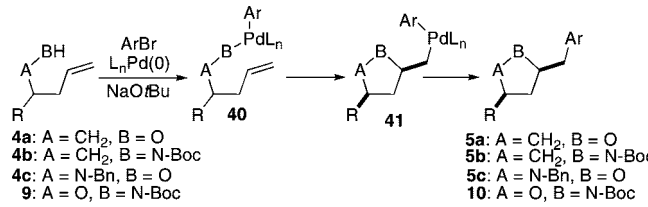
dr). To further probe the factors that influence diastereoselectivity in isoxazolidine-forming reactions that generate C−N vs. C−O bonds, we sought to determine whether the nature of the substrate *N*-substituent influenced stereocontrol. To this end, we examined the carboamination and carboetherification of **4c**, **9**, and **31**−**34** with simple aryl bromides (Table 4). We quickly discovered that P(*t*Bu)$_3$, which provided optimal results in reactions of **9**, was not effective for carboetherification reactions of **4c**. As such, we elected to employ Dpe-phos and Xantphos as ligands for the experiments shown in Table 4, as these ligands provided the desired products in most transformations of interest,

and had previously been used in the reactions of **4a**−**c** described in Table 1. Use of Dpe-phos as ligand for the reactions of substrates of **4c**, **9**, and **31**−**34** provided slightly different results than were obtained with Xantphos. However, in most cases similar diastereoselectivities were observed with both catalyst systems.

As shown in Table 4, the selectivities and yields of these transformations were significantly influenced by the type of substituent on nitrogen. For example, $Pd_2(dba)_3$/Xantphos-catalyzed carboetherification reactions of *N*-benzyl- or *N*-phenyl substituted *N*-(but-3-enyl)hydroxylamines **4c** and **31** proceeded with low diastereoselectivity (entries 2 and 4, 1−2:1 dr). The analogous carboamination reaction of *N*-phenyl-*O*-(but-3-enyl-)hydroxylamine **33** also proceeded with low selectivity (entry 8, 2:1 dr)[23] whereas the reaction of the *N*-benzyl-protected derivative **34** failed to generate an isoxazolidine product. In contrast, the Pd-catalyzed carboetherification of *N*-Boc-*N*-(but-3-enyl)hydroxylamine derivative **32** with 2-bromonaphthalene afforded *trans*-disubstituted product **38** with relatively high selectivity (entry 6, 7:1 dr),[24,25] and the $Pd_2(dba)_3$/Xantphos-catalyzed carboamination of *N*-Boc-*O*-(but-3-enyl)hydroxylamine **9** proceeded with good selectivity for formation of *cis*-disubstituted product **10** (entry 12, 12:1 dr).[26] Thus, the presence of the *N*-Boc protecting group appears to have a large influence on stereoselectivity in both the carboetherification and the carboamination reactions.

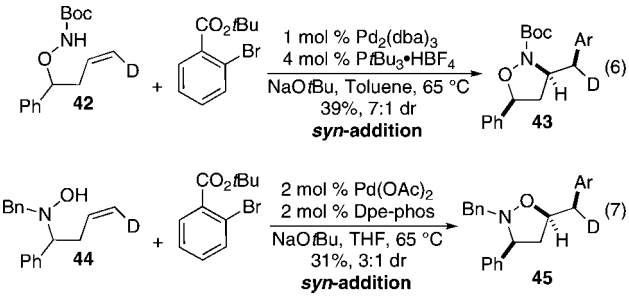
Mechanism of Heterocycle Formation and Origin of Stereocontrol. Palladium-catalyzed carboetherification and carboamination reactions of γ-hydroxyalkenes (e.g., **4a**) and γ-aminoalkenes (e.g., **4b**) that provide tetrahydrofuran or pyrrolidine products are believed to proceed through the mechanism outlined in Scheme 1.[1−3,6] In these transformations, formation of the carbon−heteroatom bond occurs via intramolecular alkene *syn*-heteropalladation from intermediate **40** (A = CH_2, B = O or NR^2) to generate **41**. This complex can then undergo C−C bond-forming reductive elimination to afford the observed products. We have previously suggested that the conversion of *N*-benzyl-*N*-(but-3-enyl)hydroxylamine substrates (e.g., **4c**) to isoxazolidine products (e.g., **5c**) occurs via a similar

SCHEME 1. Mechanism



mechanism.[8] This hypothesis is supported by the observation that transformations of a substrate bearing a cyclic internal alkene proceed with net *syn*-addition of the oxygen atom and the aryl group to the alkene.[8] Moreover, the fact that reactions involving **4a**, **4b**, or **4c** all provided *cis*-disubstituted products with similar diastereoselectivity (Table 1, ca. 2−3:1) is also suggestive of mechanistic similarities between the three processes.

As described above, Pd-catalyzed carboamination reactions of **9** also provide *cis*-disubstituted products. However, the diastereoselectivity of these transformations is quite high (up to >20:1) relative to the reactions of **4a**−**c** shown in Table 1. To rule out the possibility that the differences in diastereoselectivity observed in reactions of **9** were due to a change in mechanism, we conducted deuterium-labeling experiments to determine the stereochemistry of alkene addition. As shown in eq 6, treatment of **42** with *tert*-butyl 2-bromobenzoate under our optimized conditions afforded **43** in 39% yield as a 7:1 mixture of 3,5-cis:trans diastereomers (eq 6).[27,28] Similarly, the coupling of **44** with *tert*-butyl 2-bromobenzoate (eq 7) provided **45** in a modest 31% yield with 3:1 dr (3,5-cis:trans).[27] Importantly, *syn*-addition of the aryl group and the heteroatom across the alkene was observed in both the carboamination of **42** and the carboetherification of **44**, which suggests that both transformations proceed via the mechanism depicted in Scheme 1.



Discussion

Stereoselectivity Differences in Isoxazolidine-Forming Carboetherification vs. Carboamination Reactions. As noted above in Table 4, for a series of transformations involving identical catalysts (e.g., Pd/Dpe-phos), the nature of the *N*-substituent has a large effect on diastereoselectivity in Pd-catalyzed isoxazolidine-forming reactions of *N*- and *O*-butenyl

(19) Chen has reported that reactions of **4c** with bromobenzene in the presence of various ligands proceed with the following diastereoselectivities (trans:cis): (a) Dpe-phos, 2:1; (b) Xantphos, 1:2; (c) Ph_3P, 1:1; (d) dppf, 1:1; (e) BINAP, 1:1. See ref 9. We have observed that three reactions of **4c** with different aryl bromides all proceed with 3 to 4:1 dr when Dpe-phos is used as ligand. See ref 8 and Table 4, entry 1.

(20) Substrates were prepared in 45−85% overall yields from the corresponding alcohols via Mitsunobu reaction with *N*-hydroxyphthalimide followed by sequential treatment with hydrazine and $(Boc)_2O$.

(21) The enantiomerically enriched alcohol was prepared via lipase-catalyzed kinetic resolution of racemic 1-phenylbut-3-en-2-ol. See: Chalecki, Z.; Guibé-Jampel, E.; Plenkiewicz, J. *Synth. Commun.* **1997**, *27*, 1217–1222.

(22) The small difference between enantiomeric purity of the product (97% ee) and the substrate (96% ee) is likely due to small errors in the integration of HPLC traces.

(23) The Pd-catalyzed carboamination reactions of **33** also generated significant amounts of 1-phenylbut-3-en-1-ol and other side products resulting from substrate N−O bond cleavage. Control experiments indicated that the N−O bond cleavage occurred upon heating the substrate in the presence of NaO*t*Bu with no palladium catalyst.

(24) For related results in the synthesis of pyrazolidines via Pd-catalyzed carboamination reactions of *N*-(but-3-enyl)hydrazine derivatives see ref 5.

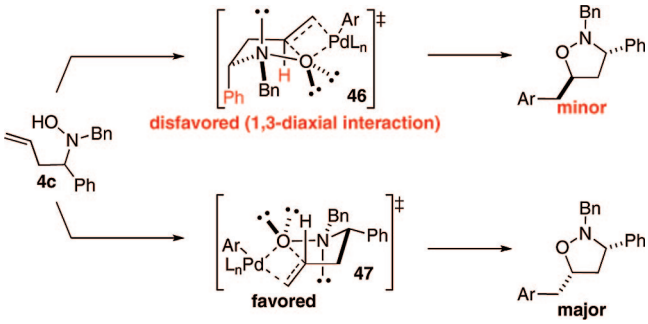
(25) The conditions originally developed for Pd-catalyzed carboetherification of *N*-benzyl-*N*-(but-3-enyl)hydroxylamines were not effective with *N*-Boc-*N*-(but-3-enyl)hydroxylamine substrates (ref 8). However, use of Xantphos as ligand with a reaction temperature of 110 °C led to the successful conversion of **32** to **38**.

(26) Similar results were obtained with methyl carbamate substrate **12**. The reaction of **12** with 2-bromonaphthalene provided 98% NMR yield (with phenanthrene as internal standard) of **22** with 12:1 dr with Xantphos as ligand, and 96% NMR yield and 13:1 dr with Dpe-Phos as ligand.

(27) *tert*-Butyl 2-bromobenzoate was employed as the aryl halide coupling partner to facilitate assignment of stereochemistry through subsequent derivatization. However, use of this aryl bromide led to the formation of relatively large amounts of side products resulting from competing Heck-arylation of the substrates.

(28) The diastereoselectivities observed in reactions of **9** (Table 3, entry 5) or **42** (eq 6) with *tert*-butyl 2-bromobenzoate were significantly lower than diastereoselectivities obtained in the reaction of **14** with 2-bromomesitylene (Table 3, entry 10). The origin of this difference is not completely clear, but may be due to coordination of the ester carbonyl group to the metal during key steps in the catalytic cycle.

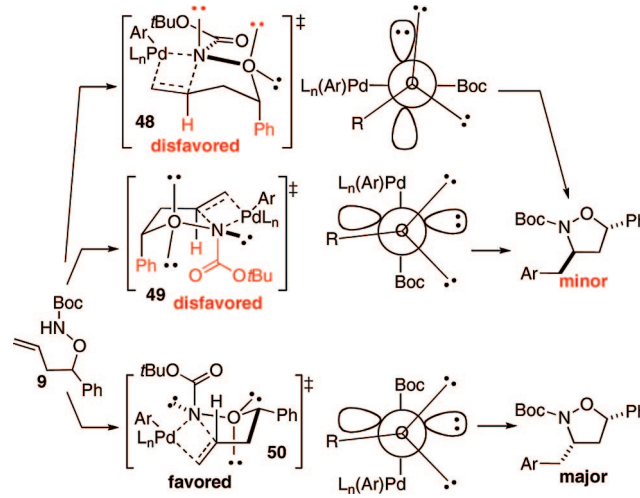
SCHEME 2. Transition States for Oxypalladation of 4c



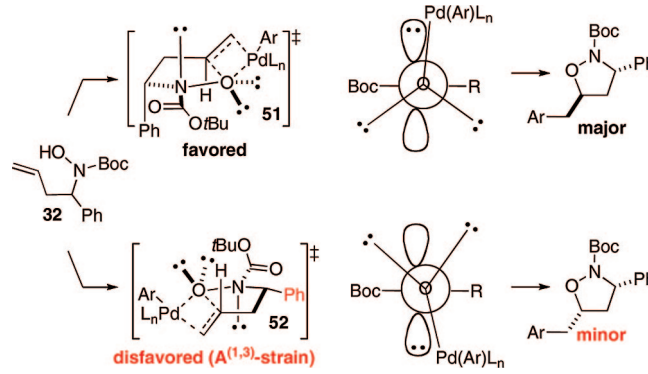
hydroxylamine derivatives. To account for these results, we suggest that the differences observed in diastereoselectivity of isoxazolidine-forming carboetherification vs. carboamination reactions may derive from conformational differences in the transition states for the heteropalladation step. In carboetherification reactions of **4c**, the most favorable transition state **47** (Scheme 2) would contain pseudoequatorial C1-phenyl and *N*-benzyl groups, and the nonbonded electrons on each heteroatom would be eclipsed with the substituents on the adjacent heteroatom.[29] An alternative transition state (**46**), which leads to the *trans*-disubstituted product, should be higher in energy due to axial orientation of the phenyl group. However, the difference in energy between transition states **46** and **47** should be relatively small, as **46** is destabilized by only a single 1,3-diaxial interaction (between the C1 phenyl group and the alkene C3 hydrogen atom).[30] This small energy difference is consistent with the modest diastereoselectivity (ca. 2−4:1 dr favoring *cis*-disubstitution) that is observed in Pd/Dpe-phos-catalyzed reactions of these substrates.[8,19]

The relatively high diastereoselectivity obtained in Pd/Dpe-phos-catalyzed carboamination reactions of **9** and related *N*-Boc protected substrates may be due to the fact that *O*-alkyl hydroxylamines bearing *N*-carbonyl groups prefer to assume conformations in which the *O*-alkyl substituent is oriented orthogonally to the Boc group.[31] Thus, cyclization of **9** via transition state **50** (Scheme 3) would minimize unfavorable eclipsing interactions between the nonbonded electrons on the oxygen and nitrogen atoms as well as 1,3-diaxial interactions, and would generate the observed major (*cis*-disubstituted) stereoisomer. Two transition states that would lead to the formation of the *trans*-disubstituted minor product are disfavored due to a combination of steric and stereoelectronic effects. Transition state **48** appears to be particularly unfavorable as it contains a 1,3-diaxial interaction between the phenyl group and the alkene C3 H-atom, *and* also suffers from electron-repulsion between the eclipsed nonbonding electrons on the adjacent N and O atoms. An alternative transition state **49**, which leads to the minor (trans) stereoisomer, minimizes this electron repulsion. However, **49** is destabilized by *two* 1,3-diaxial interactions, Ph-H and Ph-Boc, that are not present in the more favorable transition

SCHEME 3. Transition States for Aminopalladation of 9



SCHEME 4. Transition States for Oxypalladation of 32



state **50**.[52] Thus, the difference in energy between transition states **48**−**49** and **50** is expected to be greater than that between **46** and **47**, which leads to the observed higher diastereoselectivity in the reactions of **9** relative to **4c**.[33,34]

The stereochemical outcome of the Pd/Xantphos-catalyzed carboetherification of *N*-Boc-*N*-(but-3-enyl)hydroxylamine **32**,[25] which provides *trans*-disubstituted isoxazolidine **38**, may also be due to the preferred conformation of the *N*-Boc-hydroxylamine moiety. As shown in Scheme 4, cyclization through transition state **51** in which the C1-phenyl group is oriented in a pseudoaxial position would minimize allylic strain interactions with the *N*-Boc group, which would be oriented parallel to the forming ring.[24] In contrast, transition state **52** would suffer from significant $A^{(1,3)}$-strain.

Effect of Phosphine Ligand Structure on Diastereoselectivity in the Pd-Catalyzed Carboamination Reactions of 9. As illustrated above in Table 2, the structure of the

(29) Hydroxylamines prefer to adopt a conformation in which the substituents on the nitrogen atom are eclipsed with the nonbonding electrons on the oxygen group in order to minimize repulsion between nonbonding electron pairs on the adjacent heteroatoms. See: Riddell, F. G *Tetrahedron* **1981**, *37*, 849–858.

(30) The observation that most ligands examined provide ca. 1−2:1 dr in the reaction of **4c** with bromobenzene is also consistent with a very small difference in energy between these two transition states. See ref 9 and footnote 19.

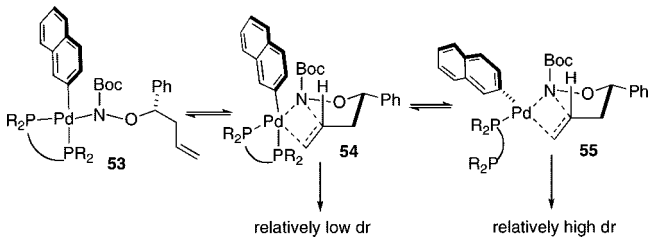
(31) Hartung, J.; Svoboda, I.; Fuess, H.; Duarte, M. T. *Acta Cryst. Sect. C* **1997**, *53*, 1629–1631.

(32) Examination of molecular models suggests there is no significant 1,3-diaxial steric interaction between the Boc group and the alkene C3 H-atom. Both the alkene and the N-atom are sp^2-hybridized, and the π-system of the Boc group is oriented parallel to the alkene π-system. As such, the steric bulk of the Boc group (the carbonyl oxygen atom and the O*t*Bu substituent) is not in close proximity to the C3 H-atom.

(33) The low diastereoselectivity observed in carboamination reactions of *N*-phenyl-substituted substrate **31** may result from twisting of the *N*-aryl group out of conjugation with the nonbonding electrons on nitrogen, which leads to pyramidalization of the nitrogen atom and cyclization via a transition state similar to **47**.

(34) The similar diastereoselectivities obtained with *N*-Boc and *N*-CO_2Me protected starting materials (Table 3, entry 6 and footnote 26) presumably result from orientation of the O-R group away from the center of reactivity. This would minimize the effect of the R group size on reactivity and selectivity.

SCHEME 5



phosphine ligand has a large influence on the diastereoselectivity of Pd-catalyzed carboamination reactions of *N*-Boc-*O*-(1-phenylbut-3-enyl)hydroxylamine **9**. This effect has not been previously observed in related Pd-catalyzed carboamination or carboetherification reactions that afford pyrrolidine, pyrazolidine, imidazolidin-2-one, or tetrahydrofuran products.[1−7] In addition, although ligands do affect diastereoselectivities in isoxazolidine-forming carboetherification reactions of *N*-benzyl-*N*-(but-3-enyl)hydroxylamine derivatives, the observed changes are modest.[19]

To summarize the ligand effects shown in Table 2, we have grouped the ligands examined into three categories: chelating ligands, monodentate ligands, and biaryl phosphine derivatives.[35] We have also defined the observed diastereoselectivities as either "relatively poor (2−3:1)" or "relatively good (≥7:1)".[36] Using these categories, the trends can be summarized as follows:

(a) Chelating ligands with small bite angles (≤93°) give relatively poor dr. Chelating ligands with large bite angles (≥97°) give relatively good dr.

(b) Monodentate triaryl phosphines give relatively poor dr regardless of size. However, with monodentate trialkyl phosphines dr increases as ligand size increases, and large ligands give relatively good dr.

(c) Biarylphosphine ligands give relatively good dr regardless of size or electronics.

The effect of bite angle on diastereoselectivity is consistent with two pathways for alkene insertion (Scheme 5): via a five-coordinate intermediate (**54**) or a four-coordinate intermediate (**55**), with higher selectivity occurring through the four-coordinate species.[37] Examination of molecular models suggests that the five-coordinate species **54** suffers from an unfavorable steric interaction between the Boc group and either the Pd−Ar moiety (as depicted) or the ligand, which could be expected to raise the energy of the most favorable transition state **50** (Scheme 3) and lead to lower selectivity.[38] When ligands with large bite angles are employed, the four-coordinate intermediate, which is generated via associative ligand substitution of alkene for one arm of the bis-phosphine ligand (**54** to **55**),[39] is more accessible than when tightly chelating ligands are used. The relatively high diastereoselectivities obtained with biaryl phosphines are also consistent with this model due to the hemilabile chelating nature of these ligands.[35]

The effect of monodentate triaryl and trialkyl phosphine ligand structure on diastereoselectivity in reactions of **9** appears to result from a combination of electronic and steric properties of the ligand. For example, both P(*t*Bu)$_3$ and P(*o*-tol)$_3$ are large ligands, but use of the electron-rich trialkylphosphine leads to excellent stereocontrol (28:1 dr), whereas use of the less electron-donating triarylphosphine provides low diastereoselectivity (2:1 dr). Smaller trialkyl phosphine ligands (e.g., PCy$_3$) also lead to poor diastereoselectivity, but the effect of ligand size on selectivity is subtle, as the difference in phosphine cone angle between PCy$_3$ (174°, 2:1 dr) and P(*t*Bu)$_3$ (182°, 28:1 dr) is relatively small. At the present time, the precise origin of these effects is unclear.

Summary and Conclusion

In conclusion, we have developed a highly stereoselective synthesis of disubstituted isoxazolidines via Pd-catalyzed carboamination reactions of *N*-Boc-*O*-(but-3-enyl)hydroxylamine derivatives. The majority of these products are formed with diastereoselectivities that are superior to those typically observed in other common methods for isoxazolidine synthesis, and a number of derivatives are easily accessible. In addition, a combination of deuterium labeling studies coupled with systematic variation of *N*-substituents has revealed two significant mechanistic details: (a) despite differences in stereoselectivity, carboamination and carboetherification reactions that generate tetrahydrofurans, pyrrolidines, and isoxazolidines appear to proceed via very similar mechanisms and (b) the effect of hydroxylamine *N*-substituent on conformation has a large effect on stereocontrol. This latter observation may be relevant to previously reported cyclization reactions of similar substrates,[15] and will likely be of use in the future design and planning of other stereocontrolled transformations.

Experimental Section

Representative Procedure for the Synthesis of Isoxazolidines. (±)-(3*S,5*S**)-3-Naphthalen-2-ylmethyl-5-phenylisoxazolidine-2-carboxylic Acid *tert*-Butyl Ester (10).** A flame- or oven-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with Pd$_2$(dba)$_3$ (2.3 mg, 0.0025 mmol), P(*t*Bu)$_3$·HBF$_4$ (2.9 mg, 0.01 mmol), sodium *tert*-butoxide (29 mg, 0.3 mmol), and 2-bromonaphthalene (62 mg, 0.3 mmol). The Schlenk tube was evacuated and refilled with nitrogen (3×). A solution of **9** (66 mg, 0.25 mmol) in toluene (4 mL) was added and the resulting mixture was heated to 65 °C until the starting material was consumed as judged by GC analysis (1.25 h). The reaction mixture was cooled to rt and treated with saturated aqueous ammonium chloride (2 mL) and ethyl acetate (5 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (2 × 5 mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford 90 mg (92%) of the title compound as a clear oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product

(35) The biaryl phosphine derivatives differ from the other two classes of phosphine ligands examined, as the nonphosphorylated aromatic ring can act as a hemilabile coordinating group with metal−ligand bonding that differs from that of a chelating (bis)phosphine. For further discussion, see: (a) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338−6361 and reference cited therein. (b) Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 12003–12010. (c) Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *Organometallics* **2007**, *26*, 2183–2192.

(36) In most instances ligands that gave poor dr also gave relatively low chemical yield.

(37) Analogous alkene insertions into Pd−C bonds are believed to occur from four-coordinate 16-electron species. Direct insertion from five-coordinate intermediates is thought to be significantly higher in energy. See: (a) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488–6499. (b) Samsel, E. G.; Norton, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 5505–5512. (c) Thorn, D. L.; Hoffmann, R. *J. Am. Chem. Soc.* **1978**, *100*, 2079–2090.

(38) This effect would also be expected to raise the energy of transition state **49** leading to the minor diastereomer. However, it does not appear that the energy of **48**, which also leads to the minor diastereomer, would be significantly perturbed.

(39) (a) Tober, M. L. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gilard, R. D., McCleverty, J. A., Eds.; Pergamon: Oxford, UK, 1987; Vol. 1, pp 281−329. (b) Cross, R. J. *Adv. Inorg. Chem.* **1989**, *34*, 219–292.

was formed as a 28:1 mixture of diastereomers; the isolated product was obtained with >20:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.75 (m, 3 H), 7.68 (s, 1 H), 7.48−7.38 (m, 3 H), 7.35−7.30 (m, 5 H), 4.89 (dd, J = 6.4, 10.0 Hz, 1 H), 4.67−4.58 (m, 1 H), 3.37 (dd, J = 6.4, 13.2 Hz, 1 H), 2.99 (dd, J = 8.0, 13.2 Hz, 1 H), 2.73−2.64 (m, 1 H), 2.12 (m, 1 H), 1.42 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 137.4, 135.5, 133.4, 132.2, 128.4, 128.3, 128.0, 127.8, 127.7, 127.52, 127.46, 126.5, 125.9, 125.4, 82.9, 81.8, 61.9, 42.8, 42.4, 28.1; IR (film) 2978, 1729 cm^{-1}; MS (ESI) 412.1880 (412.1889 calcd for $C_{25}H_{27}NO_3$, M + Na^+).

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Supporting Information Available: Experimental procedures, spectroscopic data, descriptions of stereochemical assignments, 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.

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