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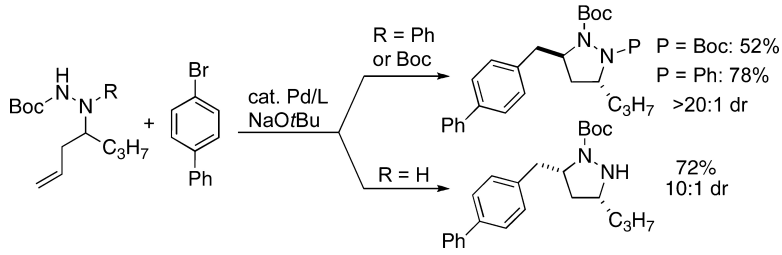

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Stereoselective Synthesis of *cis*- or *trans*-3,5-Disubstituted Pyrazolidines via Pd-Catalyzed Carboamination Reactions: Use of Allylic Strain to Control Product Stereochemistry Through *N*-Substituent Manipulation

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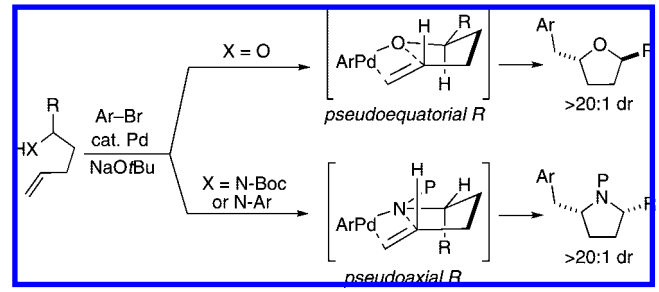
Abstract: The stereoselective synthesis of either *trans*- or *cis*-3,5-disubstituted pyrazolidines is accomplished via Pd-catalyzed carboamination reactions of unsaturated hydrazine derivatives. The products are obtained in good yield with up to >20:1 diastereoselectivity. Stereocontrol is achieved by modulating the degree of allylic strain in the transition state for *syn*-aminopalladation through a simple modification of the substrate N^2-substituent. The pyrazolidine products can be further transformed to 3,5-disubstituted pyrazolines via deprotection/oxidation, or to substituted 1,3-diamines via N−N bond cleavage.

Introduction

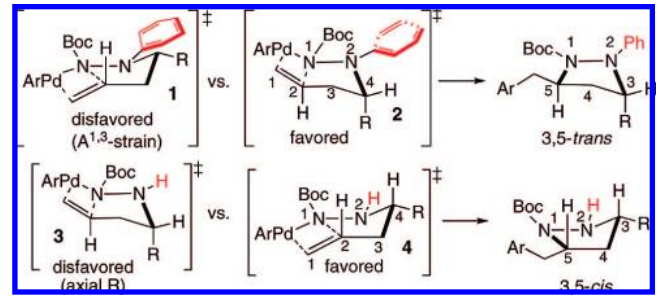
Pd-catalyzed reactions of γ-hydroxy- and γ-aminoalkenes with aryl bromides are efficient and convergent methods for the stereoselective construction of substituted oxygen- and nitrogen heterocycles.[1,2] However, despite the utility of these transformations, their stereochemical outcome is substrate-controlled, and it has not been possible to overcome inherent bias for formation of either *cis*- or *trans*-disubstituted products in a series. For example, secondary alcohol substrates always afford *trans*-2,5-disubstituted tetrahydrofurans via *syn*-oxypalladation through cyclic transition states with pseudoequatorial orientation of the R-group (Scheme 1).[2a,b] In contrast, reactions of analogous *N*-Boc or *N*-aryl amine substrates provide *cis*-2,5-disubstituted pyrrolidines via *syn*-heteropalladation with the R-group in a pseudoaxial position to minimize developing $A^{(1,3)}$-strain.[2c,d]

The model shown in Scheme 1 suggests that product stereochemistry in Pd-catalyzed carboamination reactions could be controlled through variation of N-substituents to maximize or minimize $A^{(1,3)}$-strain, which would allow the synthesis of either stereoisomer of a heterocyclic target with only minor substrate modification. Although the impact of $A^{(1,3)}$-strain on stereoselective reactions is well-documented,[3] manipulation of $A^{(1,3)}$-strain to allow for selective generation of two different product stereoisomers from closely related substrates is rare[4] and has not been demonstrated in Pd-catalysis.

Scheme 1. 2,5-Disubstituted Heterocycle Stereochemistry



Scheme 2. Transition States for Pyrazolidine Synthesis



N-Butenyl hydrazines were initially selected as substrates for our studies on the effect of $A^{(1,3)}$-strain on product stereochemistry in Pd-catalyzed carboamination reactions, as the N^2 substituent of these compounds can be varied with minimal electronic perturbation to the cyclizing N^1-atom. As shown in Scheme 2, it seemed that *trans*-3,5-disubstituted pyrazolidines could be prepared from hydrazine substrates bearing formally sp^2-hybridized N^2-atoms with π-accepting substituents, such as aryl groups or carbamates. These compounds should react via transition state **2** in which the C4 R-group is oriented in a pseudoaxial position to avoid unfavorable $A^{(1,3)}$-strain between the sp^2N−Ar group and the R-substituent that is present in

(1) For a recent review, see: (a) Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571.
(2) (a) Wolfe, J. P.; Rossi, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 1620. (b) Hay, M. B.; Hardin, A. R.; Wolfe, J. P. *J. Org. Chem.* **2005**, *70*, 3099. (c) Ney, J. E.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3605. (d) Bertrand, M. B.; Wolfe, J. P. *Tetrahedron* **2005**, *61*, 6447.
(3) (a) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841. (b) Maloney, D. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7789.
(4) (a) Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858. (b) Giese, B.; Bulliard, M.; Zeitz, H.-G. *Synlett* **1991**, 425. (c) Garcia, E.; Arrasate, S.; Lete, E.; Sotomayor, N. *J. Org. Chem.* **2005**, *70*, 10368.

transition state **1**. In contrast, we believed that selective synthesis of *cis*-3,5-disubstituted pyrazolidines could be accomplished through cyclizations of substrates lacking an N^2-substituent, which should occur via transition state **4** with the R-group in a pseudoequatorial position.

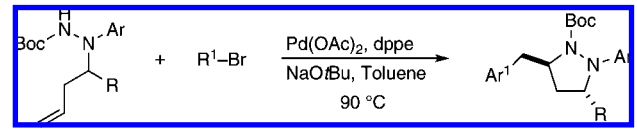
In addition to the fundamental significance of investigations on the effects of allylic strain in the reactions described above, the pyrazolidine products of these transformations are potentially useful precursors to biologically active molecules.[5a,6] The N−N bond of pyrazolidines can also be cleaved under reducing conditions to afford synthetically useful 1,3-diamines,[5c,d] and pyrazolidines can be oxidized to afford pyrazolines[7,8] or pyrazoles,[9,10] which are also of utility in medicinal chemistry applications.

In this Article we demonstrate the validity and application of this concept in Pd-catalyzed carboamination reactions, which provide a new stereoselective route to both 3,5-*cis*- and 3,5-*trans*-disubstituted pyrazolidines from simple precursors.[5] These are the first examples of the synthesis of pyrazolidine derivatives via Pd-catalyzed carboamination reactions between aryl/alkenyl halides and alkenes bearing pendant heteroatoms. Moreover, the transformations described herein are the first to illustrate that allylic strain interactions can be manipulated through a simple substrate modification (N^2-protection vs no N^2-protection) to allow for control of relative stereochemistry in Pd-catalyzed reactions.

Results and Discussion

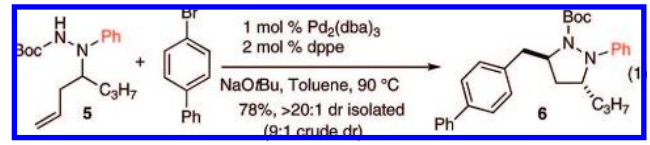
Stereoselective Synthesis of Disubstituted Pyrazolidines: Proof of Concept. To test the hypothesis outline above, we elected to initially examine Pd-catalyzed carboamination reactions of 4-bromobiphenyl with N^2-butenylhydrazine derivatives **5** and **7**. These substrates were prepared from butyraldehyde in two steps via condensation with the appropriate hydrazine, followed by addition of allylmagnesium bromide. After some optimization, we found that treatment of **5** with 4-bromobiphenyl and NaO*t*Bu in the presence of catalytic amounts of $Pd_2(dba)_3$ and dppe[11] afforded *trans*-3,5-disubstituted pyrazolidine **6** with 9:1 dr. Upon purification **6** was obtained in 78% yield with >20:1 dr (eq 1). Although the $Pd_2(dba)_3$/dppe catalyst was not effective in the analogous reaction of **7**,[12] use of a $Pd(OAc)_2$/dpe-phos catalyst provided satisfactory results and led to the generation of *cis*-3,5-disubstituted pyrazolidine **8** with 6:1 dr. After column chromatography, **8** was obtained in 72% yield with 10:1 dr (eq 2). *These results clearly demonstrate that product stereochemistry can be reversed by varying the degree of allylic strain in the transition state through a very simple modification of the substrate N^2-substituent.*

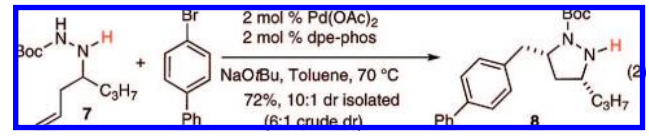
Table 1. Synthesis of *trans*-3,5-Disubstituted-N^2-Aryl Pyrazolidines[a]



entry	substrate	R	Ar	R^1	product	yield (%)[b]	dr[c]
1	**9**	Ph	Ph	*p*-PhC(O)Ph	**12**	74	20:1 (11:1)
2[d]	**10**	C_3H_7	PMP	*o*-MePh	**13**	61	>20:1 (10:1)
3	**10**	C_3H_7	PMP	*p*-*t*BuPh	**14**	55	>20:1 (8:1)
4	**10**	C_3H_7	PMP	*p*-CNPh	**15**	63	>20:1 (>20:1)
5[e]	**11**	$(CH_2)_4CH(OMe)_2$	Ph	*p*-CF_3Ph	**16**	64	>20:1 (>20:1)
6[f]	**5**	C_3H_7	Ph	α-styryl	**17**	70	10:1 (2:1)

[a] Conditions: 1.0 equiv hydrazine, 1.7 equiv ArBr, 1.7 equiv NaO*t*Bu, 2 mol % $Pd(OAc)_2$, 2 mol % dppe, toluene (0.25 M), 90 °C, 3−12 h. [b] Isolated yield, average of two or more experiments. [c] Diastereomeric ratios are reported for the isolated products. Diastereomeric ratios in parentheses were observed in crude reaction mixtures. [d] Reaction was conducted using $Pd_2(dba)_3$ as precatalyst. [e] Reaction was conducted with 4 mol % P(2-furyl)$_3$ in place of dppe. [f] Reaction was conducted with 4 mol % Dpe-phos in place of dppe.





Stereoselective Synthesis of *trans*-3,5-Disubsititued Pyrazolidines. Having demonstrated that the stereoselective synthesis of *trans*-3,5-disubstituted pyrazolidines can be achieved using N^2-arylated substrates such as **5**, we proceeded to examine the scope of these transformations. As shown in Table 1, the coupling reactions can be conducted with a variety of electron-rich, -neutral, and -poor aryl bromides, and a number of functional groups are tolerated. Several substrates bearing aryl or unbranched alkyl substituents at C4 (**9**−**11**) were successfully transformed to *trans*-3,5-disubstituted pyrazolidines **12**−**16** in

(5) For selected syntheses of 3,5-disubstituted or -trisubstituted pyrazolidines, see: (a) Yang, Q.; Jiang, X.; Ma, S. *Chem.−Eur. J.* **2007**, *13*, 9310. (b) de los Santos, J. M.; Lopez, Y.; Aparico, D.; Palacios, F. *J. Org. Chem.* **2008**, *73*, 550. (c) Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 11279. (d) Shirakawa, S.; Lombardi, P. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 9974. (e) Chauveau, A.; Martens, T.; Bonin, M.; Micouin, L.; Husson, H.-P. *Synthesis* **2002**, 1885. (f) Guerra, F. M.; Mish, M. R.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 4265.

(6) For examples of biologically active pyrazolidines, see: (a) Witherington, J.; Bordas, V.; Gaiba, A.; Green, P. M.; Naylor, A.; Parr, N.; Smith, D. G.; Takle, A. K.; Ward, R. W. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2256. (b) Ahn, J. H.; Kim, J. A.; Kim, H.-M.; Kwon, H.-M.; Huh, S.-C.; Rhee, S. D.; Kim, K. R.; Yang, S.-D.; Park, S.-D.; Lee, J. M.; Kim, S. S.; Cheon, H. G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1337. (c) Wilkinson, D. E. *Bioorg. Med. Chem.* **2003**, *11*, 4815.

(7) For examples of biologically active pyrazolines, see: (a) Johnson, M.; Younglove, B.; Lee, L.; LeBlanc, R.; Holt, H., Jr.; Hills, P.; Mackay, H.; Brown, T.; Mooberry, S. L.; Lee, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5897. (b) Ali, M. A.; Shaharyar, M. *Bioorg. Med. Chem.* **2007**, *15*, 1896. (c) Lange, J. H. M.; Kruse, C. G. *Curr. Opin. Drug. Discovery Dev.* **2004**, *7*, 498.

(8) For recent synthetic approaches to pyrazolines, see: (a) Alex, K.; Tillack, A.; Schwarz, N.; Beller, M. *Org. Lett.* **2008**, *10*, 2377. (b) Nair, V.; Biju, A. T.; Mohanan, K.; Suresh, E. *Org. Lett.* **2006**, *8*, 2213. (c) Reference 5b, 5e, and references cited therein.

(9) For a recent review on biologically active pyrazoles, see: (a) Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. In *Targets in Heterocyclic Systems Volume 6*; Attanasi, O. A., Spinelli, D. Eds.; Springer: Berlin, 2003; p 52.

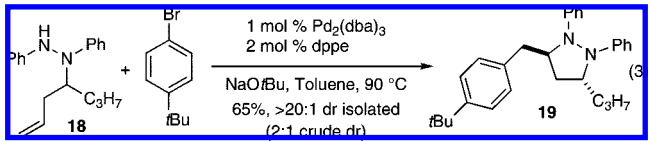
(10) For recent synthetic approaches to pyrazoles, see: 5. (a) Martin, R.; Rivero, M. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 7079. (b) Ahmed, M. S.; Kobayashi, K.; Mori, A. *Org. Lett.* **2005**, *7*, 4487. (c) Yet, L. *Prog. Heterocycl. Chem.* **2005**, *17*, 172–196. (d) Reference 7a and references cited therein.

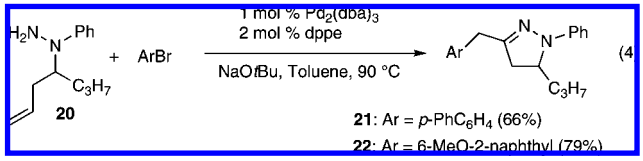
(11) Dppe = 1,2-bis(diphenylphosphino)ethane. Dpe-phos = bis(2-diphenylphosphino)phenyl ether.

(12) Use of dppe as ligand provided only trace amounts of pyrazolidine products, and afforded significant amounts of products resulting from Heck-arylation of the starting material.

moderate to good yield. Good to excellent levels of diastereoselectivity are obtained,[13] and pyrazolidines bearing differentially substituted nitrogen atoms (N^1-Boc, N^2-PMP) can be prepared in a straightforward manner. Curiously, although the coupling of 4-bromobiphenyl with hydrazine **5** proceeded with good diastereoselectivity (9:1 dr, eq 1), use of α-bromostyrene as an electrophilic coupling partner with this substrate (entry 6) led to the formation of **17** with only 2:1 dr. However, partial separation of diastereomers was achieved during purification, and **17** was isolated in 70% yield as a 10:1 mixture of stereoisomers. The origin of the diminished diastereoselectivity in this reaction is not clear, although this effect has been previously observed in related Pd-catalyzed carboamination reactions of *N*-allylureas.[14]

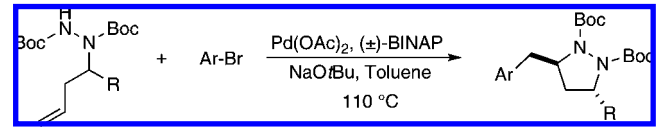
The presence of a Boc-group on N^1 was essential for the stereoselective preparation of *trans*-3,5-disubstituted N^2-aryl pyrazolidines. As shown in eq 3, the carboamination of 1,2-diphenylhydrazine-derived substrate **18** with 4-bromo-*tert*-butylbenzene proceeded with only 2:1 diastereoselectivity.[15] Efforts to carry out the Pd-catalyzed carboamination reactions of **20**, which lacks an N^1 substituent, did not generate pyrazolidines, but instead afforded pyrazolines **21**−**22** in synthetically useful yields (eq 4).[16]





The hypothesis outlined above in Scheme 2 suggests that replacement of the N^2-aryl substituent on the substrate with other π-accepting groups should also allow for the construction of *trans*-3,5-disubstituted pyrazolidines. Therefore, to examine the effect of the N^2-substituent on both reactivity and stereoselectivity, we prepared several butenylhydrazine derivatives bearing N^2-carbonyl functionality. Our initial attempts to employ substrates analogous to **5** but with N^2-Ac or Bz groups were unsuccessful, and led to the formation of complex mixtures of products. However, we were gratified to discover that the Pd/BINAP-catalyzed carboamination of 4-bromobiphenyl with **23**, which contains Boc-groups on both N^1 and N^2, provided the desired pyrazolidine **25** in moderate yield (52%), but with >20:1 diastereoselectivity (Table 2, entry 1).[17] The modest yield in this reaction was due to competing Heck arylation of **23**. Interestingly, coupling reactions of **23** with electron-poor aryl bromides were much cleaner, and afforded pyrazolidines **26**−**27** in good yield with excellent dr (entries 2−3). However, efforts to employ alkenyl bromides as coupling partners in carboamination reactions of **23** failed to generate the desired pyrazolidine products; competing Heck alkenylation of the substrates was observed. Coupling reactions of aryl bromides with the C4-phenyl substituted substrate **24** provided similar results as were obtained in transformations of **23** (entries 4−5).

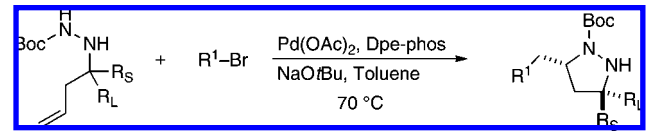
Table 2. Synthesis of *trans*-3,5-Disubstituted-N^2-Boc Pyrazolidines[a]



entry	substrate	R	Ar	product	yield (%)[b]	dr[c]
1	**23**	C_3H_7	*p*-PhPh	**25**	52	>20:1 (>20:1)
2	**23**	C_3H_7	*p*-PhC(O)Ph	**26**	78	>20:1 (>20:1)
3	**23**	C_3H_7	*m*-CF_3Ph	**27**	81	>20:1 (>20:1)
4	**24**	Ph	2-naphthyl	**28**	55	>20:1 (>20:1)
5	**24**	Ph	*m*-MeOPh	**29**	47	>20:1 (>20:1)

[a] Conditions: 1.0 equiv substrate, 1.7 equiv ArBr, 1.7 equiv NaO*t*Bu, 2 mol % $Pd(OAc)_2$, 2 mol % BINAP, toluene (0.25 M), 110 °C. Reactions were complete in 12−14 h; reaction times have not been minimized. [b] Isolated yield (average of two or more experiments). [c] Diastereomeric ratios are reported for the isolated products. Diastereomeric ratios in parentheses were observed in crude reaction mixtures.

Table 3. Synthesis of *trans*-Disubstituted and -Trisubstituted Pyrazolidines[a]



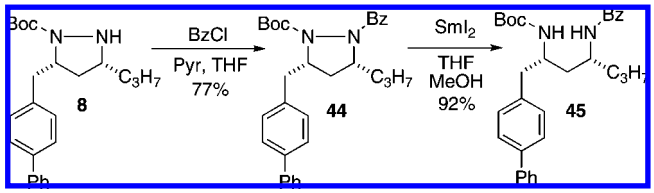
entry	substrate	R_S	R_L	R^1	product	yield (%)[b]	dr[c]
1	**7**	H	C_3H_7	*p*-ClPh	**35**	70	>20:1 (7:1)
2[d]	**7**	H	C_3H_7	β-styryl	**36**	54	5:1 (5:1)
3	**30**	H	Ph	*m*-MePh	**37**	66	13:1 (10:1)
4	**30**	H	Ph	*p*-^{t}BuO$_2$CPh	**38**	55	>20:1 (>20:1)
5[d]	**30**	H	Ph	α-styryl	**39**	63	11:1 (8:1)
6[d]	**31**	Me	Me	*p*-^{t}BuO$_2$CPh	**40**	80	–
7[d]	**32**	$(CH_2)_5$		*N*-(Bn)-5-indolyl	**41**	56	–
8	**33**	Me	Ph	*p*-PhPh	**42**	83	6:1 (6:1)
9	**34**	Me	*t*Bu	6-MeO-2-naphthyl	**43**	73	>20:1 (12:1)

[a] Conditions: 1.0 equiv hydrazine, 1.2 equiv ArBr, 1.2 equiv NaO*t*Bu, 2 mol % $Pd(OAc)_2$, 2 mol % Dpe-phos, toluene (0.25 M), 70 °C, 4−12 h. [b] Isolated yield, average of two or more experiments. [c] Diastereomeric ratios are reported for the isolated products. Diastereomeric ratios in parentheses were observed in crude reaction mixtures. [d] Reaction was conducted using 1.2 equiv ArBr and 1.2 equiv of NaO*t*Bu at 70 °C.

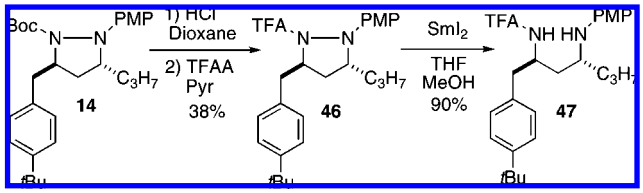
Stereoselective Synthesis of *cis*-3,5-Disubsititued Pyrazolidines and 3,3,5-Trisubstituted Pyrazolidines. To explore the scope of carboamination reactions of *N*-butenylhydrazine derivatives lacking N^2-substituents, several substrates were prepared and treated with various aryl or alkenyl bromides. These transformations proceeded with moderate to good yields and diastereoselectivities for several different substrate combinations (Table 3). Both aryl and alkenyl halides can be employed as coupling partners, although reactions involving alkenyl halides proceeded with somewhat lower yields and diastereoselectivities. The reactions were effective with both aldehyde-derived substrates (**7** and **30**, entries 1−5) and ketone-derived substrates (**31**−**34**, entries 6−9). Substrates **33**−**34** bearing two different

(13) Both $Pd_2(dba)_3$ and $Pd(OAc)_2$ precatalysts provided similar results in these reactions.
(14) Fritz, J. A.; Wolfe, J. P. *Tetrahedron* **2008**, *64*, 6838.
(15) The diminished stereoselectivity observed in this transformation may be due to an unfavorable steric interaction between the N^1-Ph group and the N^2-Ph group that leads to rotation of the N^2-Ph group and pyramidalization of the N^2-atom. This would decrease the allylic strain interaction present in transition state **1** (Scheme 2) and result in the formation of increased amounts of the minor stereoisomer.
(16) It is not clear if the oxidation to the pyrazoline product is Pd-catalyzed or if oxidation occurs upon workup. Air-oxidation of NH-pyrazolidines that lack electron-withdrawing substituents on the second nitrogen atom appears to be very facile.

Scheme 3. *syn*-1,3-Diamine Synthesis



Scheme 4. *anti*-1,3-Diamine Synthesis



substituents at C4 were converted to trisubstituted pyrazolidines **42**−**43** with moderate to good stereocontrol (entries 8−9).

Transformations of Pyrazolidine Products. To further illustrate the synthetic utility of the pyrazolidine-forming reactions described above, we have briefly examined transformations of the pyrazolidine products into other useful compounds such as 1,3-diamines and pyrazolines. Our initial attempts to cleave the N−N bond of the pyrazolidine products, using a number of different conditions, were unsuccessful. However, we were gratified to find that N−N bond cleavage of *cis*-3,5-disubstituted pyrazolidine **8** could be achieved after benzoylation of the unprotected nitrogen atom. As shown in Scheme 3, treatment of **8** with benzoyl chloride and pyridine provided **44** in 77% yield. The doubly protected pyrazolidine was then converted to *syn*-1,3-diamine **45** in 92% yield by treatment with SmI_2.[18]

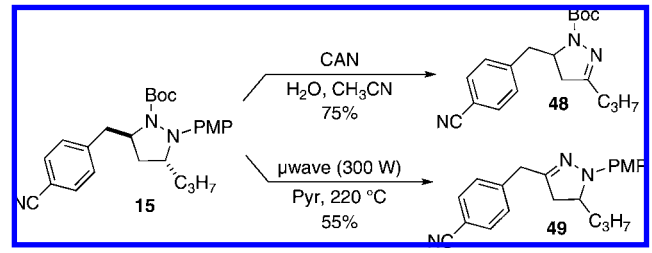
Conversion of *trans*-1,3-disubstituted pyrazolidine **14** to a 1,3-diamine required exchange of the *N*-Boc substituent for a trifluoroacyl group. However, standard conditions for cleavage of *N*-Boc groups led to complex mixtures of products, and competing oxidation of the deprotected pyrazolidine was also observed. After considerable experimentation we found that treatment of **14** with HCl/dioxane followed by addition of pyridine and trifluoroacetic anhydride generated **46** in a modest 38% yield. Fortunately, the N−N bond cleavage of **46** proceeded smoothly using conditions identical to those employed for the conversion of **44** to **45**, and the *anti*-1,3-diamine **47** was obtained in 90% yield (Scheme 4).

The selective conversion of *trans*-3,5-disubstituted pyrazolidine **15** to 3,5-disubstituted pyrazolines **48** and **49** was easily accomplished as shown in Scheme 5. Treatment of **15** with CAN led to cleavage of the *N*-PMP group with concomitant oxidation to pyrazoline **48** in 75% yield. Alternatively, use of microwave irradiation to remove the *N*-Boc group from **15** also led to facile oxidation, and provided **49** in 55% yield.

Summary and Conclusion

In summary, we have developed a new stereoselective synthesis of *cis*- and *trans*-disubstituted pyrazolidines from *N*-butenyl hydrazine derivatives. The products are generated

Scheme 5. Synthesis of 3,5-Disubstituted Pyrazolines



with good to excellent diastereoselectivity and chemical yield, and can be transformed to synthetically useful pyrazolines or 1,3-diamines via oxidation or reduction. These are the first examples of the use of hydrazine-derived substrates in Pd-catalyzed alkene carboamination reactions with aryl/alkenyl halides, and represent a significant extension of carboamination methodology. Importantly, these experiments also demonstrate that allylic strain interactions can be manipulated through a simple substrate modification (N^2-protection vs no N^2-protection) to allow for control of relative stereochemistry in Pd-catalyzed reactions. Further studies to extend this concept to other heterocyclic systems are currently underway.

Experimental Section

Pd-Catalyzed Synthesis of *trans*-3,5-Disubstituted Pyrazolidines: General Procedure. A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with either $Pd_2(dba)_3$ (1 mol % complex, 2 mol % Pd) or $Pd(OAc)_2$ (2 mol % complex, 2 mol % Pd), dppe (2 mol %), sodium *tert*-butoxide (1.7 equiv), and the aryl bromide (1.7 equiv). The Schlenk tube was purged with nitrogen and the hydrazine substrate (1.0 equiv) was added as a solution in toluene (4 mL solvent/ mmol substrate). The resulting mixture was heated to 90 °C until the starting material was consumed as judged by ^{1}H NMR analysis. 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 extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

(±)-(3*R*,5*R*)-*tert*-Butyl-5-(biphenyl-4-yl-methyl)-2-phenyl-3-propylpyrazolidine-1-carboxylate (6). The reaction of 50 mg (0.16 mmol) of **5** with 4-bromobiphenyl (65 mg, 0.28 mmol) was conducted for 18 h at 90 °C according to the general procedure using a catalyst composed of $Pd_2(dba)_3$ (1.5 mg, 0.002 mmol, 1 mol %) and dppe (1.3 mg, 0.003 mmol, 2 mol %). This procedure afforded 59 mg (79%) of the title compound as a yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 9:1 mixture of diastereomers; the isolated product was obtained with >20:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57−7.56 (d, J = 8.0 Hz, 2 H), 7.51−7.49 (d, J = 8.0 Hz, 2 H), 7.44−7.41 (t, J = 8.0 Hz, 2 H), 7.34−7.31 (t, J = 7.5 Hz, 1 H), 7.27−7.24 (m, 4 H), 6.97−6.96 (d, J = 8.0 Hz, 2 H), 6.91−6.88 (t, J = 7.0 Hz, 1 H), 4.41−4.36 (m, 1 H), 3.93−3.90 (m, 1 H), 3.44 (dd, J = 4.5, 12.5 Hz, 1 H), 2.56−2.51 (m, 1 H), 1.92−1.88 (m, 1 H), 1.84−1.81 (m, 1 H), 1.60−1.58 (m, 1 H), 1.47−1.42 (s, 9 H), 1.33−1.27 (m, 1 H), 1.27−1.25 (s, 2 H), 0.97−0.94 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 141.2, 139.5, 138.2, 129.7, 129.0, 128.8, 127.4, 127.2, 127.0, 120.5, 114.7, 80.7, 64.9, 60.5, 42.4, 37.3, 36.2, 28.6, 20.2, 14.3 (one carbon signal is absent due to incidental equivalence); IR (film) 2963, 1696 cm^{-1}. MS (ESI) 457.2855 (457.2855 calcd for $C_{30}H_{36}N_2O_2$, M + H$^+$).

Pd-Catalyzed Synthesis of *cis*-3,5-Disubstituted Pyrazolidines: General Procedure. A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and

(17) The high diastereoselectivity observed in these reactions relative to transformations involving N^2-arylated substrates (Table 1) may be due to the relatively high barrier to pyramidalization of the Boc-substituted N^2-atoms, which leads to greater differences in energy between transition states **1** and **2** (Scheme 2).

(18) Ding, H.; Friestad, G. K. *Org. Lett.* **2004**, *6*, 637.

charged with $Pd(OAc)_2$ (2 mol % complex, 2 mol % Pd), dpephos (2 mol %), sodium *tert*-butoxide (1.2 equiv), and the aryl bromide (1.2 equiv). The Schlenk tube was purged with nitrogen and the hydrazine substrate (1.0 equiv) was added as a solution in toluene (4 mL solvent/mmol substrate). The resulting mixture was heated to 70 °C until the starting material was consumed as judged by ^{1}H NMR analysis. 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 extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

(±)-(3*R*,5*S*)-*tert*-Butyl-5-(biphenyl-4-ylmethyl)-3-propylpyrazolidine-1-carboxylate (8). The reaction of 57 mg (0.25 mmol) of **7** with 4-bromobiphenyl (70 mg, 0.30 mmol) was conduced for 12 h at 70 °C according to the general procedure using a catalyst composed of $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 2 mol %) and dpephos (2.7 mg, 0.005 mmol, 2 mol %). This procedure afforded 70 mg (74%) of the title compound as a yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 6:1 mixture of diastereomers; the isolated product was obtained with 10:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59−7.57 (m, 2 H), 7.53−7.52 (m, 2 H), 7.45 (m, 2 H), 7.35−7.32 (m, 1 H), 7.27−7.24 (m, 2H), 4.26−4.24 (m, 1 H), 3.42 (s, br, 1 H), 3.14 (dd, J = 4.0, 8.0 Hz, 1 H), 3.02−2.99 (m, 1 H), 2.79 (dd, J = 5.5, 8.0 Hz, 1 H), 2.32−2.27 (m, 1 H), 1.59−1.54 (m, 1 H), 1.51 (s, 9 H), 1.36−1.29 (m, 3 H), 1.23−1.17 (m, 1 H), 0.89 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 140.8, 139.2, 137.2, 130.0, 128.8, 127.1, 127.0, 126.9, 80.2, 60.4, 59.6, 40.6, 34.4, 32.2, 28.5, 20.0, 14.2; IR (film) 3234, 2963, 2360, 1714 cm^{-1}. MS (ESI) 403.2346 (403.2361 calcd for $C_{24}H_{32}N_2O_2$, M + Na^+).

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Supporting Information Available: Characterization data for all new compounds in eqs 1−4, Tables 1−3, and Schemes 3−5 and descriptions of stereochemical assignments. This material is available free of charge via the Internet at http://pubs.acs.org.

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