J|A|C|S
ARTICLES
Published on Web 04/05/2003

Hydrogen Bond Directed Highly Regioselective Palladium-Catalyzed Allylic Substitution

Gregory R. Cook,* Hui Yu, S. Sankaranarayanan, and P. Sathya Shanker

Contribution from the Department of Chemistry, North Dakota State University, Fargo, North Dakota 58105-5516

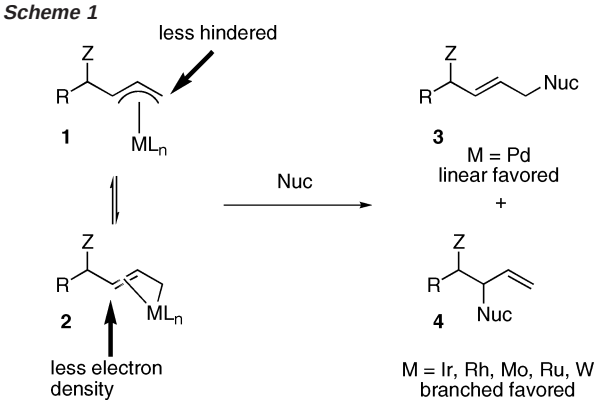
Received September 5, 2002; E-mail: Gregory.Cook@ndsu.nodak.edu

Abstract: The palladium-catalyzed allylic substitution of 5-vinyloxazolidinones and derivatives was investigated. Unusual and high regioselectivity for the branched product was observed. The regioselectivity was influenced by the type of substrate, the solvents, and the nucleophile. Imide-type nucleophiles were found to be directed to the internal carbon (branched:linear, 75:25 to >98:2), whereas sulfonamides, amines, and malonates added only to the terminal carbon of the allyl complex. Relatively nonpolar solvents such as toluene and THF favored the branched product (97:3 and 95:5, respectively). Acetonitrile and dichloromethane afforded lower regioselectivity (50:50 and 67:33, respectively), and the use of the protic solvent ethanol resulted in reversal of the regioselectivity (12:88). The directing group on the substrate was important. Amides afforded almost complete formation of the branched product, and carbamates gave a 50:50 mixture of regioisomers with phthalimide as the nucleophile. Evidence for direction of the nucleophile via hydrogen bonding was obtained by replacing the hydrogen of the amide with a methyl, resulting in the production of only the normal linear product.

Introduction

The palladium-catalyzed allylic substitution reaction has emerged as a powerful methodology in organic synthesis.[1] Stereoselective variants have focused primarily on enantioselective processes that utilize chiral ligands and achiral substrates.[2] Thus, in the past decade there has been a colossal development of new chiral catalysts for asymmetric allylic substitution. Of great significance in these substitution reactions is the problem of regiocontrol, particularly as many of the asymmetric reactions rely on a regiospecific addition to a pseudo-meso Pd-allyl complex for enantioselectivity. If the substrate is unsymmetrical, the issue of regiocontrol becomes even more complex. As shown in Scheme 1, a monosubstituted π-allylmetal complex can react with a nucleophile to afford either the linear (**3**) or the branched (**4**) product. Both sterics and electronics play a role in determining the outcome of the reaction, and the choice of metal exerts a significant influence. For palladium complexes, the sterics overwhelmingly favor addition of the nucleophile to the less hindered allyl terminus;[1,2] however, normally a mixture is obtained.[3] It has also been shown by both experiment and density functional calculations that polar substituents (Z) in the allylic position strongly favor the linear product to give a 1,4-relationship between the polar group and the nucleophile.[4]

Scheme 1



In the past few years, there has been intense interest in reversing the preferred regioselectivity in the Pd-catalyzed allylic substitution to favor branched products. Substituents on the allyl substrate that can coordinate to the Pd have been demonstrated to alter the regioselectivity.[5] A few electronically[6] and sterically[7] biased ligands have also been shown to change the regioselectivity to favor **4**. The Trost ligands, in particular, offer very high regioselectivity for sterically unencumbered substrates that can fit in the chiral pocket. Other metal-allyl complexes (Ir,[8]

(1) For recent reviews: (a) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 585. (b) Hegedus, L. In *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley: New York, 1994; pp 385−459. (c) *Palladium Reagents and Catalysis*; Tsuji, J., Ed.; Wiley: New York, 1995.

(2) For reviews on asymmetric palladium-catalyzed allylic substitutions, see: (a) Reiser, O. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 547. (b) Trost, B. M.; VanVranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (c) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089. (d) Consiglio, G.; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257.

(3) For additive and ligand effects to obtain greater selectivity for the linear product, see: (a) Kawatsura, M.; Uozumi, Y.; Hayashi, T. *Chem. Commun.* **1998**, 217. (b) van Haaren, R. J.; Oevering, H.; Coussens, B. B.; van Strijdonck, G. P. F.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Eur. J. Inorg. Chem.* **1999**, 1237. (c) Sjögren, M. P. T.; Hannson, S.; Åkermark, B. *Organometallics* **1994**, *13*, 1963. (d) Åkermark, B.; Zetterberg, K.; Hansson, S.; Krakenberger, B. *J. Organomet. Chem.* **1987**, *335*, 133.

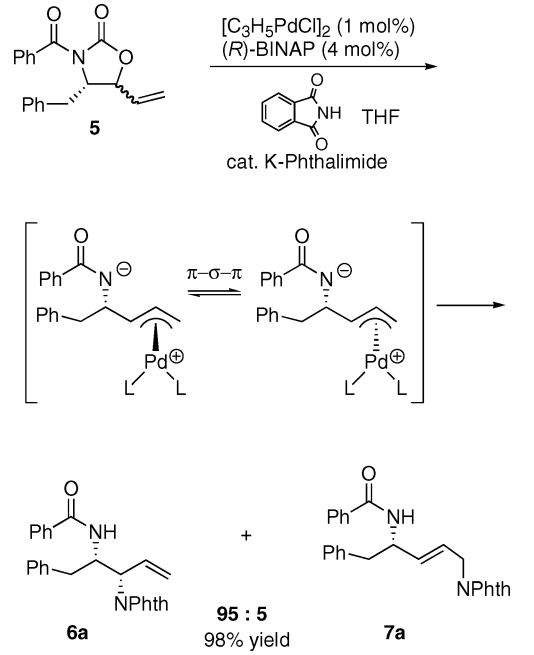
(4) (a) Szabó, K. J. *Chem. Soc. Rev.* **2001**, *30*, 136. (b) Johasson, C.; Kritikos, M.; Bäckvall, J.-E.; Szabó, K. *Chem.-Eur. J.* **2000**, *6*, 432. (c) Macsári, I.; Hupe, E.; Szabó, K. *J. Org. Chem.* **1999**, *64*, 9547. (d) Szabó, K. *Chem.-Eur. J.* **1997**, *3*, 592.

Rh,[9] Mo,[10] Ru,[11] W[12]) generally afford the branched substitution products **4** preferentially. This change in the regioselectivity with most metals other than palladium reflects the change in the metal-allyl structure toward the enyl complex **2** where electronic control of the selectivity predominates. The control of the Pd-catalyzed allylic substitution reaction to favor branched products remains an arduous challenge. Thus, new paradigms for directing regioselectivity are required.

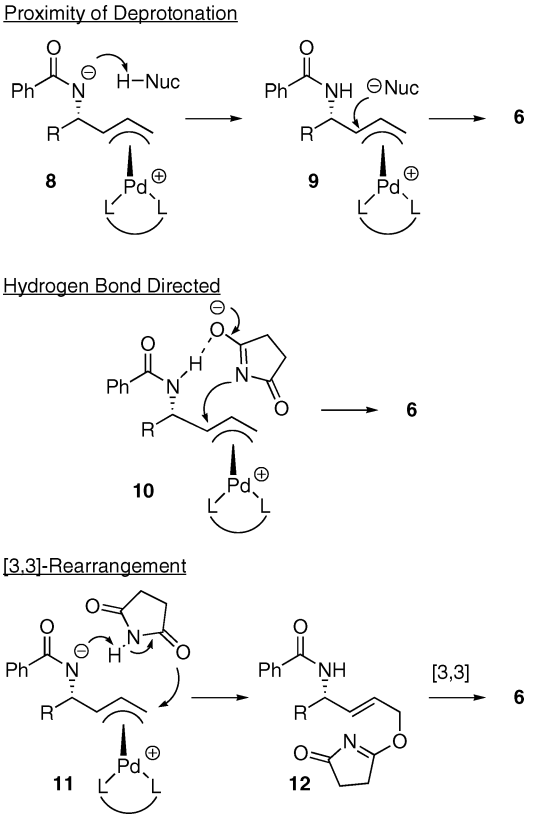
During the course of our investigation of the dynamic diastereoselective allylic substitution reaction of 5-vinyloxazolidinones with nitrogen nucleophiles (phthalimide), unusually high regioselectivity favoring addition to the internal allyl carbon was encountered.[13] The optimized reaction is described in Scheme 2. A mixture of oxazolidinone diastereomers **5**, readily obtained from L-phenylalanine, was treated with a Pd catalyst in the presence of phthalimide. A catalytic amount of potassium phthalimide was introduced to facilitate reduction of the Pd(II) precatalyst to the Pd(0) catalyst. Extremely high selectivity for the branched (1,2-diamine) product **6** was obtained (95:5). The application of chiral ligands (BINAP) with the chiral substrate provided the best diastereo- and regioselectivity. Interestingly, **6** was obtained as a single diastereomer (^{1}H NMR), and the chirality of the ligand had no influence on the stereoinduction. The same *syn*-diastereomer was produced whether the (*R*) or the (*S*) ligand was employed. However, a pronounced matched and mismatched effect was observed on the regioselectivity ((*R*)-BINAP, 95:5; (*S*)-BINAP, 75:25).

The high levels of regioselectivity for the branched product observed in the allylic substitution of 5-vinyloxazolidinones are extremely rare among palladium-catalyzed allylic substitution

Scheme 2



Scheme 3



reactions, and this result prompted us to investigate the origin of the unusual selectivity. Because the reaction presumably proceeds through a zwitterionic complex, we hypothesized that the amide moiety may be somehow directing the nucleophile (Scheme 3). As the amide is the only base in the reaction to deprotonate the nucleophile, we envisioned a "proximity effect" might be operative. That is, once the nucleophile is deprotonated, it reacts at the nearest electrophilic carbon (**8** → **9** → **6**) before it diffuses away from the complex to react at the less substituted allyl carbon (**8** → **9** → **7**). Another hypothesis is that after proton

(5) (a) Krafft, M. E.; Sugiura, M.; Abboud, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 9174. (b) Itami, K.; Koike, T.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2001**, *123*, 6957. (c) Ma, S.; Zhao, S. *J. Am. Chem. Soc.* **2001**, *123*, 5578. (d) Krafft, M. E.; Wilson, A. M.; Fu, Z.; Procter, M. J.; Dasse, O. A. *J. Org. Chem.* **1998**, *63*, 1748. (e) Farthing, C. N.; Kocovsky, P. *J. Am. Chem. Soc.* **1998**, *120*, 6661. (f) Krafft, M. E.; Fu, Z.; Procter, M. J.; Wilson, A. M.; Dasse, O. A.; Hirosawa, C. *Pure Appl. Chem.* **1998**, *70*, 1083.

(6) (a) Prétôt, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 323. (b) Steinhagen, H.; Reggelin, M.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2108. (c) Blacker, A. J.; Clarke, M. L.; Loft, M. S.; Williams, J. M. J. *Org. Lett.* **1999**, *1*, 1969.

(7) (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545. (b) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968. (c) Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727. (d) Hayashi, T.; Kawatsura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 1681. (e) Hayashi, T.; Kawatsura, M.; Uozumi, Y. *Chem. Commun.* **1997**, 561. (f) Trost, B. M.; Krische, M. J.; Radinov, R.; Zanoni, G. *J. Am. Chem. Soc.* **1996**, *118*, 6297. (g) Hayashi, T.; Kishi, K.; Yamamoro, A.; Ho, Y. *Tetrahedron Lett.* **1990**, *31*, 1743.

(8) (a) Takeuchi, R.; Tanabe, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 1975. (b) Takeuchi, R.; Shiga, N. *Org. Lett.* **1999**, *1*, 265. (c) Bartels, B.; Helmchen, G. *Chem. Commun.* **1999**, 741. (d) Fuji, K.; Kinoshita, N.; Tanaka, K.; Kawabata, T. *Chem. Commun.* **1999**, 2289. (e) Takeuchi, R.; Kashio, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 263.

(9) (a) Evans, P. A.; Kennedy, L. J. *J. Am. Chem. Soc.* **2001**, *123*, 1234. (b) Evans, P. A.; Robinson, J. E. *J. Am. Chem. Soc.* **2001**, *123*, 4609. (c) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2000**, *122*, 5012. (d) Fagnou, K.; Lautens, M. *Org. Lett.* **2000**, *2*, 2319. (e) Evans, P. A.; Kennedy, L. J. *Org. Lett.* **2000**, *2*, 2213. (f) Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6761. (g) Evans, P. A.; Robinson, J. E. *Org. Lett.* **1999**, *1*, 1929. (h) Evans, P. A.; Nelson, J. D. *Tetrahedron Lett.* **1998**, *39*, 1725. (i) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581.

(10) (a) Trost, B. M.; Dogra, K. *J. Am. Chem. Soc.* **2002**, *124*, 7256. (b) Belda, O.; Kaiser, N.-F.; Bremberg, U.; Larhed, M.; Hallberg, A.; Moberg, C. *J. Org. Chem.* **2000**, *65*, 5868. (c) Glorius, G.; Pfaltz, A. *Org. Lett.* **1999**, *1*, 141. (d) Trost, B. M.; Hildbrand, S.; Dogra, K. *J. Am. Chem. Soc.* **1999**, *121*, 10416. (e) Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104. (f) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1987**, *109*, 1469.

(11) Zhang, S.; Mitsudo, T.; Kondo, T.; Watanabe, Y. *J. Organomet. Chem.* **1993**, *450*, 197.

(12) (a) Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 462. (b) Trost, B. M.; Tometzki, G. B.; Hung, M. H. *J. Am. Chem. Soc.* **1987**, *109*, 9, 2176.

(13) Cook, G. R.; Shanker, P. S.; Pararajasingham, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 110.

transfer from the imide to the amide, the nucleophile forms a hydrogen bonded complex (**10**) and is delivered to the internal carbon in a diastereo- and regioselective fashion.[14,15] A third possibility is that the imide nucleophile reacts with the allyl substrate on the unsubstituted terminus at oxygen rather than nitrogen, perhaps through a concerted deprotonation/addition process (**11** → **12**). The resulting O-allylated intermediate **12** could subsequently undergo a [3,3]-sigmatropic rearrangement to afford **6**.[16] To delineate these possibilities, a rigorous examination of the influence of substrate, solvent, and nucleophile on the regioselectivity was carried out. To exclude effects of the catalyst, the catalyst/ligand system was not varied. In this article, we present the results of our study, which clearly demonstrates that hydrogen bonding to the substrate amide was responsible for the observed regioselectivity.

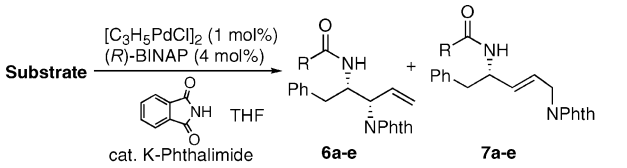
Results and Discussion

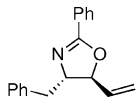
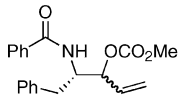
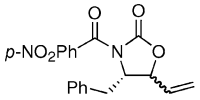
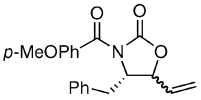
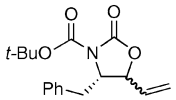
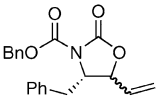
To test the theories described above, we have carried out extensive experiments. The basicity of the amide (substrate), the polarity of the solvent, and the pK_a of the nucleophile should all play a role in the regioselectivity if the amide moiety is intimately involved as a directing group. Thus, we have examined the reaction with a variety of substrates, nucleophiles, and solvents. We have also prepared O-allylated compounds such as **12** via an independent route to probe the possibility of concerted [3,3]-rearrangement.

We first examined the influence of the substrate amide moiety on the regioselectivity, and the results are summarized in Table 1. In the reaction of 5-vinyloxazolidinones with a palladium(0) catalyst, carbon dioxide is evolved after the oxidative insertion. It is not clear whether this carboxylate group departs before, during, or after the step in which the nucleophile adds. To see whether the carboxylate exerts any control on the regioselectivity, the oxazoline **13**, lacking the oxazolidinone carbonyl, was employed in the reaction. The same level of selectivity was found, suggesting that the oxazolidinone substrate underwent decarboxylation prior to the addition of the nucleophile and the CO_2 moiety was not involved in the regioselective addition step. Next, we investigated carbonate **14**, which would generate a base external to the π-allyl complex (methoxide or methyl carbonate). While the selectivity decreased slightly, it was still remarkably high (91:9), and this result disfavors a simple base proximity effect. Electron-withdrawing or -donating groups on the benzoyl (**15** and **16**) exhibited little change. Interestingly, when the benzoyl group was replaced with carbamoyl groups (BOC, **17** or Cbz, **18**), a 1:1 ratio of regioisomers was obtained. This implies that hydrogen bonding is important to control regioselectivity as the carbamates would be weaker hydrogen bond donors than the amide moieties.

The solvent played an important role in the regioselectivity of the allylic substitution of **5** with phthalimide nucleophile.

Table 1. Effect of Substrate on Regioselectivity



	Substrate	Regioselectivity (**6** : **7**)[a]	Yield (%)[b]
13		95 : 5	95
14		91 : 9	99
15		91 : 9	96
16		95 : 5	95
17		50 : 50	99
18		50 : 50	99

[a] Determined by ^{1}H NMR. [b] Combined yield of **6** and **7**.

Table 2. Effect of Solvent on Regioselectivity[a]

entry	solvent	ligand (*tol*-BINAP)	regioselectivity (**6a**:**7a**)[b]	yield (%)[c]
1	toluene	(*R*)	97:3	81
2	THF	(*R*)	95:5	98
3	CH_2Cl_2	(*R*)	67:33	95
4	CH_3CN	(*R*)	50:50	88
5	EtOH	(*R*)	**12:88**	85
6	toluene	(*S*)	83:17	95
7	THF	(*S*)	78:22	98
8	CH_2Cl_2	(*S*)	33:67	92
9	CH_3CN	(*S*)	22:78	90

[a] Reactions were carried out with substrate **5** with phthalimide employed as the nucleophile. [b] Determined by ^{1}H NMR. [c] Combined yield of **6** and **7**.

The results of the solvent effects are summarized in Table 2. The highest regioselectivity (97:3, **6a**:**7a**) was obtained when the reaction was carried out in toluene (entry 1). When methylene chloride was used, the selectivity dropped to 2:1 (entry 3), and acetonitrile afforded a 1:1 mixture (entry 4). These results strongly suggest that hydrogen bonding is important, as the strength of a hydrogen bond would vary in accordance with the solvent polarity.[17] That is, in the relatively nonpolar solvent toluene, hydrogen bonding would be strongest, thus affording more of the branched product. As the solvent polarity increases, less direction to the internal allyl carbon is observed, corre-

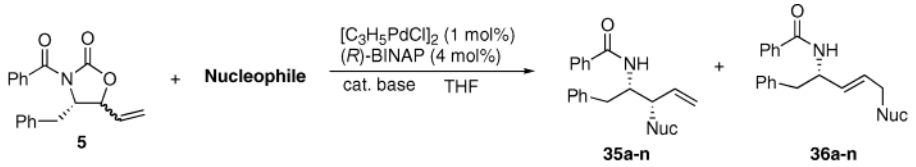
(14) Hydrogen bonding has been implicated in the asymmetric allylic substitution with ligands possessing pendant hydroxyl groups: (a) Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6301. (b) Yamazaki, A.; Morimoto, T.; Achiwa, K. *Tetrahedron: Asymmetry* **1993**, *4*, 2287.

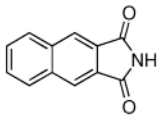
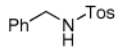
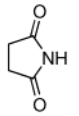
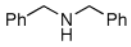
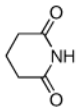
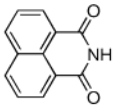
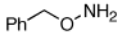
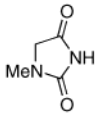
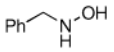
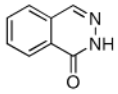
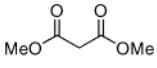
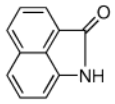
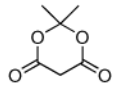
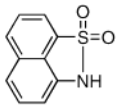
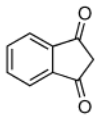
(15) Hydrogen bonding has been suggested in the allylic substitution of vinyl epoxides: Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968.

(16) For reviews of the Claisen rearrangement, see: (a) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 5, pp 827−873. (b) Blechert, S. *Synthesis* **1989**, 71. (c) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.

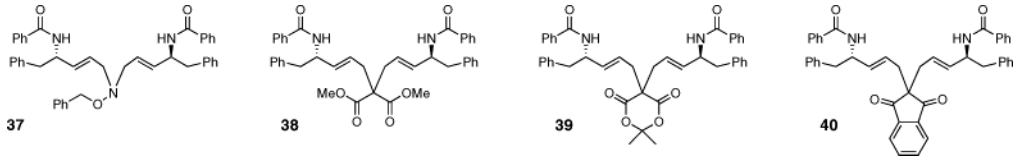
(17) The trend in the solvents observed can be correlated with their $E_t^N(30)$ values. Catalán, J. *J. Org. Chem.* **1997**, *62*, 8231.

Table 3. Effect of Nucleophile on Regioselectivity



	Nucleophile	Product	Regioselectivity (**35** : **36**)[a]	Yield (%)[b]		Nucleophile	Product	Regioselectivity (**35** : **36**)[a]	Yield (%)[b]
19		**a**	95 : 5	94	**27**		**i**	0 : 100	92
20		**b**	97 : 3	95	**28**		**j**	0 : 100	97
21		**c**	83 : 17	55	**29**		**k**	0 : 100	90
22		**d**	75 : 25	90	**30**		**37**	0 : 100[d]	78
23		**e**	95 : 5	82	**31**		**l**	0 : 100	77
24		**f**	>98 : 2[c]	94	**32**		**m, 38**	0 : 100[e]	83
25		**g**	88 : 12	85	**33**		**39**	0 : 100[d]	88
26		**h**	0 : 100	91	**34**		**40**	0 : 100[d]	91

[a] Determined by ^{1}H NMR. [b] Combined yield of **35** and **36**. [c] When carried out in ethanol, the regioselectivity was completely reversed (5:95). [d] Only the diallylated product (**38** or **39**) was obtained. The regioisomer ratio is for branched and linear isomers. [e] A mixture of mono- and diallylated products was obtained. Mono-:diallylated = 17:1. The regioisomer ratio is for branched and linear isomers. The yield reflects the total yield of both products.



sponding with a weaker hydrogen bond between the nucleophile and the substrate. When the protic solvent, ethanol, was employed in the reaction, the regioselectivity reversed to favor the linear isomer **7a** (entry 5). In protic media, hydrogen bonding to the substrate is disrupted due to hydrogen bonding with the solvent. As demonstrated in entries 6−9, the same trend was observed when the mismatched (*S*)-*tol*-BINAP ligand was employed. The solvent effects observed in this reaction are consistent with a mechanism where hydrogen bonding is intimately involved.

A diverse set of nucleophiles has been surveyed in the allylic substitution of **5** with very intriguing results (Table 3). All nucleophiles were examined with the same set of conditions using THF as the solvent. Imides performed well in the allylic substitution. Not surprisingly, naphthalimide **19** provided the same level of selectivity as phthalimide (95:5, **35**:**36**). Succinimide **20** gave a higher level of the branched product (97:3), while the six-membered ring imides **21** and **22** proved not as effective (83:17 and 75:25, respectively). Other imide-like nucleophiles also showed high regioselectivity for the branched

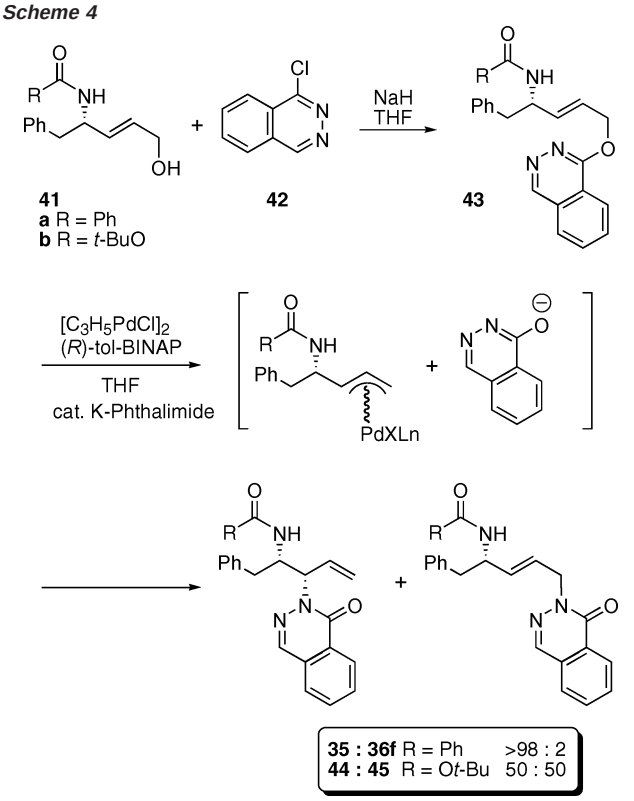
isomer. The hydantoin **23** was identical to phthalimide (95:5), and phthalazinone **24** was revealed to be superior to all other nucleophiles (>98:2). Interestingly, when the reaction with **24** was carried out in ethanol, complete reversal of regioselectivity was again observed (5:95). Comparison of structurally similar amide **25** with sulfonamide **26** revealed markedly different results. The amide afforded a greater amount of the branched isomer (88:12), while the sulfonamide provided the linear regioisomer as the sole product (0:100). Indeed, the simple benzyl sulfonamide **27** also yielded only the linear isomer. In addition, amines **28**−**31** and carbon nucleophiles **32**−**34** only delivered the linear regioisomers, demonstrating the same profound nucleophile effect in the allylic substitution of **5**. These data do not support the proximity effect as outlined in Scheme 3, as most of these nucleophiles (except amines) require deprotonation prior to addition and should show at least some formation of the branched product. Again, hydrogen bond direction is in concert with these results. The geometry of the nucleophile−substrate complex should be an important factor. This would explain the slight difference in regioselectivity between the five- and six-membered ring imides. Further, the sulfonamide bears a tetrahedral sulfur atom, which greatly distorts the geometry as compared to the planar carbonyl of the imides, and this is reflected in only addition through the non-hydrogen bonded complex. Although the dicarbonyl carbon nucleophiles could potentially hydrogen bond to the substrate amide, it is likely that the greater reactivity of the carbanion versus the nitrogen anion of the imide precludes the formation of the hydrogen bonded complex.

Although all of the data strongly suggest that hydrogen bonding direction is responsible for the high branched regioselectivity observed, an O-allylation-[3,3]-rearrangement pathway could not be ruled out. Thus, we have investigated the possibility of a concerted rearrangement of an intermediate like **12** (Scheme 3) prepared via an alternative route. As shown in Scheme 4, the allylic alcohols **41a**,**b** were coupled with chlorophthalazine **42** to afford the *O*-allyl phthalazine derivatives **43**. When **43a** (R = Ph) was subjected to the reaction conditions identical to those of the allylic substitution reaction of **5** with **24**, the same >98:2 mixture of the branched (**35f**) and linear (**36f**) regioisomers was obtained. This could result from either a concerted [3,3]-rearrangement or a stepwise ionization to form the π-allyl palladium intermediate and addition of the phthalazinone nucleophile. To establish whether the rearrangement was concerted or stepwise, the *N*-BOC-substituted **43b** was examined. A 50:50 mixture of regioisomers (**44** and **45**) was obtained. This was the same result as that obtained by the allylic substitution of the *N*-BOC derivative of **5** with phthalazinone. Consequently, the reaction of **43b** with the Pd(0) catalyst must proceed by a stepwise mechanism: ionization to generate a π-allyl complex followed by hydrogen bond directed nucleophilic addition. This is consistent with what is known about the Pd(0)-catalyzed Claisen and Cope rearrangements.[18] Therefore, it can be concluded that if **12** is formed in the reaction, it simply reionizes to the π-allyl palladium complex.

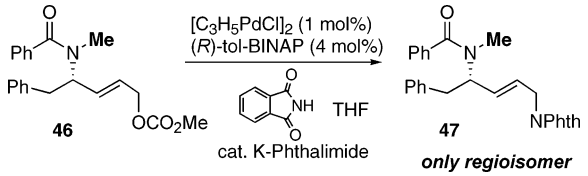
The lack of evidence for a concerted rearrangement and the large solvent, substrate, and nucleophile effects on the regioselectivity greatly favor a mechanism of hydrogen bond directed addition of the nucleophile. To garner further support for this

(18) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 206.

Scheme 4



Scheme 5



directed addition, we prepared the allylic carbonate substrate **46** where the H on the amide was replaced with a methyl group (Scheme 5). This would preclude any hydrogen bonding with the incoming nucleophiles. Treatment of **46** with phthalimide under the Pd(0)-catalyzed conditions afforded the linear allylic substitution product **47** as the sole regioisomer.

Conclusions

The results summarized herein shed light on one of the many factors that control selectivity in the palladium-catalyzed allylic substitution reaction. Although hydrogen bonding has been suggested previously to direct the introduction of nucleophiles onto an allyl palladium substrate, this article presents for the first time clear evidence for such a directing effect. The regioselectivity was influenced by the type of substrate, the solvents, and the nucleophile. Imide-type nucleophiles were found to be directed to the internal carbon, whereas sulfonamides, amines, and malonates added only to the terminal carbon of the allyl complex. Relatively nonpolar solvents such as toluene and THF favored the branched product. Acetonitrile and dichloromethane afforded lower regioselectivity, and the use of the protic solvent ethanol resulted in reversal of the regioselectivity. The directing group on the substrate was important. Amides afforded almost complete formation of the branched product, and carbamates gave a 50:50 mixture of regioisomers. Evidence for direction of the nucleophile via

hydrogen bonding was obtained by replacing the hydrogen of the amide with a methyl, resulting in the production of only the normal linear product.

Acknowledgment. We are grateful to the National Science Foundation (NSF CHE9875013) and the National Institutes of Health (GM58470-01, RR15566-01) for generous support of this work.

Supporting Information Available: Experimental details and characterization data, including NMR spectra, for compounds **6b**−**e**, **7b**−**e**, **35a**,**b**, **36a**−**m**, **37**−**40**, and **43a**,**b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA028426W