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Hydrogen-bond directed palladium-catalyzed allylic substitution of cyclic substrates

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Abstract—The regioselectivity of the Pd-catalyzed allylic substitution of cyclic substrates possessing an adjacent amide functional group was investigated. With imide-like nucleophiles, six-membered ring substrates were found to proceed with a high level of regiodirection whereas hydrogen-bond directed addition was not a significant factor in the five-membered ring substrates.
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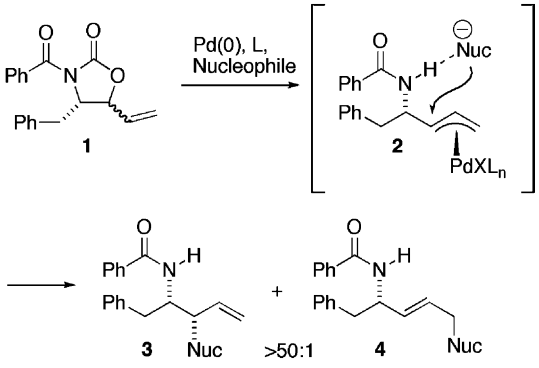
The palladium-catalyzed allylic substitution reaction has become a mainstay methodology in organic synthesis.[1] In the last decade, tremendous advances have been made in the development of new chiral catalysts for asymmetric allylic substitution.[2] Of great significance in these substitution reactions is the issue of regiocontrol. This is particularly relevant in asymmetric reactions as they often rely on a regiospecific addition to a pseudo-*meso* Pd–allyl complex for enantioselectivity. Unsymmetric substrates add even greater complexity to the problem of regiocontrol. It has been shown by both experiment and density functional calculations that polar substituents in the allylic position strongly favor a product with a 1,4-relationship between the polar group and the nucleophile.[3] In the last few years, there has been a lot of effort to reverse the preferred regioselectivity in the Pd-catalyzed allylic substitution to favor branched products. In the case of acyclic substrates, substituents on the allyl substrate that can coordinate to the Pd have been shown to alter the regioselectivity.[4] A few electronically[5] and sterically[6] biased ligands have also been effective to change the regioselectivity in favor of the branched product over the linear product. Other allyl metal complexes (Ir,[7] Rh,[8] Mo,[9] Ru,[10] and W[11]) generally afford the branched substitution products preferentially. With cyclic substrates possessing allylic polar functional groups, namely the desymmetrization reactions reported by the Trost group, regioselectivity is



Scheme 1.

complete for the formation of the 1,4-substituted product with an intermolecular nucleophile.[6] Recently, we reported that the allylic substitution of vinyloxazolidinones with imide-like nucleophiles proceeded to give the unusual branched product with very high regioselectivity (Scheme 1, >50:1 in some cases).[12] This unusual selectivity was found to be dependant on the presence of the allylic amide functionality, which was acting as a directing group by forming a hydrogen bond with the incoming imide nucleophile. Thus regioselectivity varied with changes in the nucleophile and solvent reflecting changes in the strength of the hydrogen bond. In order to determine the extent at which one may utilize such weak bonding for directing imide nucleophiles in the allylic substitution, we undertook an investigation of substrates that present the π-allyl complex within a six- or five-membered ring. In this letter, we disclose the results of these studies.

Keywords: Palladium catalysis; Allylic substitution; Regioselectivity; Hydrogen-bonding.
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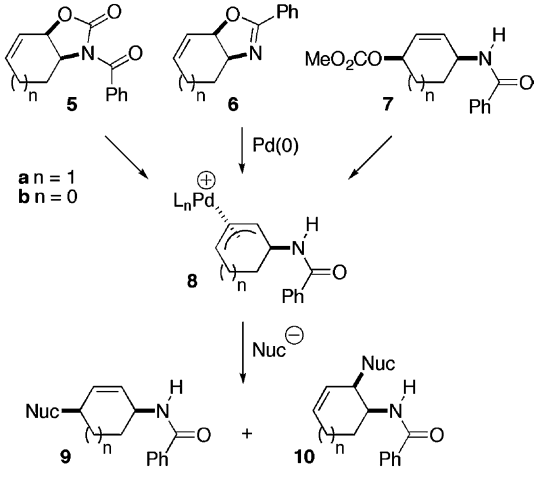
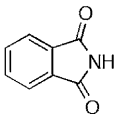
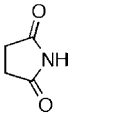
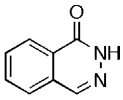
We began by preparing cyclic substrates for allylic substitution. The same π-allyl palladium intermediate **8** could be generated from oxazolidinone **5**, oxazoline **6**, or the allylic carbonate **7** upon treatment with a Pd(0) catalyst (Scheme 2). This intermediate could be intercepted by a nucleophile to afford the normal 1,4-regioisomer **9** or the H-bond directed isomer **10**. Substrates **5** and **6** were synthesized in several steps as described previously.[13] Recently, we have found it more convenient to utilize the carbonate **7** as it is readily obtained by an acylnitroso Diels–Alder reaction followed by N–O bond reduction[14] and acylation with methylchloroformate.

With the required substrates in hand, we investigated the effect of the solvent and the nucleophile on the regioselectivity of allylic substitution. Three imide-like nucleophiles were chosen; phthalimide, succinimide, and phthalazinone. These were selected as they offered the greatest H-bonded directing effects in prior studies with acyclic substrates.[12] Results of studies with the six-membered ring substrates are summarized in Table 1.[15] Interestingly, for all nucleophiles tested, lower regioselectivity was observed as compared with acyclic substrates. However, the same trend with regards to the solvent effects were found. That is, as the solvent becomes more polar, hydrogen bonds become weaker, and regioselectivity shifts toward the 1,4-disubstituted isomer **9a**. For phthalimide (entries 1–4), switching from toluene to acetonitrile changes the regioselectivity from 1:1 to 4:1 favoring the 1,4-isomer. A similar trend is seen with the succinimide nucleophile (entries 5–7). The best nucleophile for regioselective direction via H-bonding was phthalazinone (entries 10–12). This afforded high selectivity for the 1,2-isomer **10a** when the reaction was carried out in toluene. This was the major isomer for most other solvents investigated as well. When the reaction was run in methanol, the regioselectivity switched to favor the 1,4-isomer (2.8:1). This is in agreement with our hypothesis that hydrogen bonding between the amide and the nucleophile aids in regioselectivity. In non-polar solvents, this directing effect would be optimal whereas, in a protic solvent, H-bonds would be disrupted between the amide and the nucleophile affording the expected 1,4-isomer.



Scheme 2.

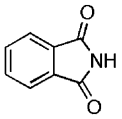
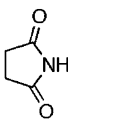
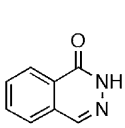
Table 1. Regioselectivity for the allylic substitution of six-membered ring substrates

Entry	Substrate	Nucleophile	Solvent	Conversion (%)[a]	**9a:10a**[b]
1	**6a**		Toluene	50	1:1
2	**6a**		THF	92	2.7:1
3	**6a**		CH_2Cl_2	59	1.9:1
4	**6a**		CH_3CN	83	4:1
5	**6a**		Toluene	99[c]	1.3:1
6	**7a**		THF	86	2:1
7	**7a**		CH_2Cl_2	86	3:1
8	**6a**		Toluene	99[d]	1:10
9	**6a**		THF	95	1:6.3
10	**6a**		CH_2Cl_2	97	1:2.9
11	**6a**		CH_3CN	95	1:1.5
12	**6a**		MeOH	34	2.8:1

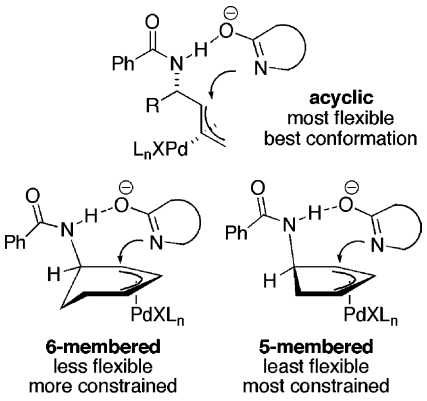
[a] Conversion based on remaining starting material, measured by ^{1}H NMR.
[b] Regioisomer ratio determined by ^{1}H NMR.
[c] Isolated yields 45% (**9a**) and 39% (**10a**).
[d] Isolated yields 4% (**9a**) and 84% (**10a**).

In contrast to the six-membered ring substrates, aminocyclopentenol derivatives **6b** and **7b** showed very little hydrogen-bond direction in the allylic substitution with imide nucleophiles. As shown in Table 2,[15] for both phthalimide and succinimide (entries 1–8), complete selectivity for the 1,4-isomer **9b** was obtained. This is the intrinsic regioselectivity usually observed for cyclopentene derivatives. Only phthalazinone demonstrated any measurable change in the regioselectivity giving **10b** as the major product in all cases (entries 9–12). As is typical for the solvent effects, optimal H-bonding regioselectivity was found for the more non-polar solvents and selectivity eroded in more polar acetonitrile. For both the five- and the six-membered ring substrates, phthalazinone was the nucleophile that was most influenced by hydrogen-bond directing effects.

Table 2. Regioselectivity for the allylic substitution of five-membered ring substrates

Entry	Substrate	Nucleophile	Solvent	Conversion (%)[a]	**9b:10b**[b]
1	**7b**		Toluene	99	99:1
2	**6b**		THF	99	99:1
3	**6b**		CH_2Cl_2	99	99:1
4	**7b**		CH_3CN	99	99:1
5	**7b**		Toluene	97	99:1
6	**6b**		THF	99	99:1
7	**6b**		CH_2Cl_2	99	99:1
8	**7b**		CH_3CN	99	99:1
9	**7b**		Toluene	95[c]	1:7.2
10	**7b**		THF	96	1:9
11	**7b**		CH_2Cl_2	97	1:5
12	**7b**		CH_3CN	97	1:1.7

[a] Conversion based on remaining starting material, measured by ^{1}H NMR.
[b] Regioisomer ratio determined by ^{1}H NMR.
[c] Isolated yields 11% (**9b**) and 79% (**10b**).



Scheme 3.

The large change in the magnitude of directing effects as one moves from acyclic to six-membered rings to five-membered rings could be due to an increasing restriction in the flexibility of the system. It is apparent that an optimal conformation in the seven-membered transition state must be achieved for the weak H-bond to exert a directing effect. This effect emerges as the structure of the nucleophile changes subtly from the imides to phthalazinone. The ability of the H-bonded complex to obtain a conformation for addition to the adjacent electrophilic carbon would be dependent on the degrees of freedom of the system. As illustrated in Scheme 3, acyclic substrates would be most flexible and allow for greatest H-bond directing by the amide. As the substrate becomes more rigid, optimal conformation may not be easily achieved, thus, the non-directed addition to the distal carbon competes favorably.

In conclusion, we have investigated the extent of hydrogen-bond directing effects from adjacent amide substituents in the palladium-catalyzed allylic substitution of cyclic substrates. As observed previously, the structure of the nucleophile plays a significant role in H-bond direction. Six-membered ring substrates demonstrated modest to good directing effects while five-membered ring substrates showed little H-bond direction. This suggests that flexibility in the substrate is important in order to capitalize on hydrogen-bonding for regiocontrol.

Acknowledgments

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15. General procedure: To a Schlenk flask were added the substrate **6** or **7** (1.00 equiv), the nucleophile (1.20 equiv), potassium phthalimide (0.05 equiv), $[(C_3H_5)PdCl]_2$ (0.025 equiv), and bis(diphenylphosphino)propane (0.10 equiv). The reaction vessel was evacuated and purged with N_2 three times and then degassed solvent (0.2 M) was added. The reaction was stirred for 24 h, filtered through a small plug of silica gel (EtOAc–CH_2Cl_2, 3/2) and concentrated. The mixture was analyzed by crude ^1H NMR. The products could be further purified by flash chromatography (silica gel) with 20–35% EtOAc–hexanes. All compounds displayed satisfactory spectroscopic characterization.