Communications

Heteroatom-Directed, Palladium-Catalyzed, Regioselective Allylation: Substitution with Inversion

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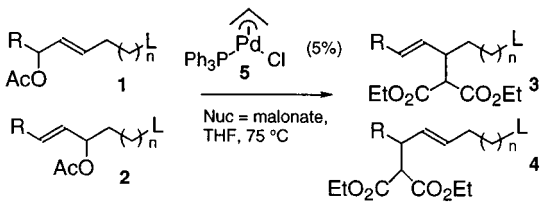
Reactions of allylic acetates and ethers with nucleophiles catalyzed by palladium and other metals is a well-established process.[1−3] Additions to monosubstituted allylic acetates are normally selective for the less substituted terminus. However, additions to 1,3-disubstituted π-allylmetal complexes normally yield a mixture of regioisomers. Partial solutions to this regiochemical issue include incorporation of large groups at one terminus of the allyl moiety[1,2,4] or the use of polarizing functional groups such as carbonyl or other oxygenated functionality[5−9] adjacent to the π-allyl to promote addition distal to that group. Modification of ligands on the metal can also be used to enhance the selectivity.[10,11]

We now report that a tertiary amine or thioether in the homoallylic position directs nucleophilic substitution to the terminus of the allylic moiety proximal to the heteroatom. For example, reaction of thioether **1a** with lithio diethyl malonate in THF in the presence of palladium catalyst **5** (5%) at 75 °C for 5 h gave rise to **3a** and **4a** (10:1) in 87% isolated yield.[12] The regiochemical outcome of the substitution is particularly striking, especially in cases such as this one where R = H. Despite the increased steric interactions, substitution occurs on the more substituted terminus of the intermediate π-allyl palladium species, whereas in the absence of the heteroatom directing group, substitution takes place almost exclusively at the unsubstituted terminus presumably due to steric bias. Additional examples, shown in Table 1, illustrate the generality of the directing effect. The selectivity is excellent in reactions of substrates bearing either the methylthio or the dimethylamino groups.[13] Reactions of allylic acetates **2e** and **1h**, bearing oxygenated functional groups two or three atoms away from the allylic residue, respectively, yield products from reaction at the allyl terminus distal to the heteroatom in accord with previous reports.[7−9] An increase in the length of the tether between the heteroatom and the allylic moiety led to a change in selectivity. Using the same reaction conditions, the major product resulted from substitution at the terminus of the allylic fragment distal to the heteroatom.[14]

The effect of the size and electronic nature of the alkyl groups on the heteroatom was also studied (Table 2). An increase in the size of the aliphatic group on the tertiary amine had a detrimental effect regardless of whether the allylic acetate was mono- or 1,3-disubstituted (Table 2, entries 1 and 3). The opposite selectivity with the aromatic amines **6b** and **6d**, which would not be expected to coordinate efficiently to palladium, strongly suggests a different role for the heteroatom compared to the substrates bearing the dimethylamino group. Of the tertiary amines, the dimethylamino group appears to provide the strongest directing effect. In the thioether cases, the change in selectivity as a function of the alkyl substituent was not so dramatic. Even with the phenylthio ether **6f**, influence from the heteroatom was apparently still observed.

Table 1



entry		R	*n*	L		**3a**−**h**:**4a**−**h**[a]	yield[b] (%)
1	**1a**	H	1	SMe	**3a**/**4a**	10:1	87
2	**1b**	Me	1	SMe	**3b**/**4b**	7:1	90
3	**1c**	H	1	NMe_2	**3c**/**4c**	19:1	76
4	**1d**	Me	1	NMe_2	**3d**/**4d**	9:1	73
5	**2e**	Me	1	OMe	**3e**/**4e**	1:10	85
6	**1f**	H	2	SMe	**3f**/**4f**	1:3	88[c]
7	**1g**	Me	2	NMe_2	**3g**/**4g**	1:3	78
8	**1h**	Me	2	OTBS	**3h**/**4h**	1:6	90

[a] Ratios determined by integration of ^{1}H NMR spectral signals (300 or 500 MHz). [b] Yields refer to isolated materials. [c] 10% of dialkylation at the unsubstituted terminus of the allyl moiety was observed.

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(2) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 4, p 585.

(3) For a review on asymmetric allylations, see: Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.

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(5) Moreno-Manas, M.; Ribas, J. *Tetrahedron Lett.* **1989**, *30*, 3109.

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(7) Genet, J. P.; Balabane, M.; Backvall, J. E.; Nystrom, J. E. *Tetrahedron Lett.* **1983**, *24*, 2745.

(8) For example, see: Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett.* **1981**, *22*, 2575.

(9) For an early explanation of the now generally accepted polarizing effect from an oxygenated functional group on the regiochemical outcome of the allylation, see: Genet, J. P.; Balabane, M.; Legras, Y. *Tetrahedron Lett.* **1982**, *23*, 331. Coordination of an allylic alcohol to palladium was proposed to be responsible for a regioselective alkylation at the terminus of the allyl moiety distal to the alcohol.

(10) Sjogren, M. P. T.; Hansson, S.; Akermark, B. *Organometallics* **1994**, *13*, 1963. Akermark, B.; Zetterberg, K.; Hansson, S.; Krakenberger, B. *J. Organomet. Chem.* **1987**, *335*, 133.

(11) Leutenneger, U.; Umbricht, G.; Fahrni, C.; V. Matt, P.; Pfaltz, A. *Tetrahedron* **1992**, *48*, 2143. Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339. von Matt, P.; Lloyd-Jones, G. C.; Minidis, A. B. E.; Pfaltz, A.; Macko, L.; Neuberger, M.; Zehnder, M.; Ruegger, H.; Pregosin, P. S. *Helv. Chim. Acta.* **1995**, *78*, 265.

(12) **Typical Experimental Procedures. Preparation of 3a/4a.** A solution of sulfide **1a** (75 mg, 0.43 mmol) in THF (2.7 mL), catalyst **5** (9.6 mg, 5 mol %) and lithio diethyl malonate (1.5 mL, 0.43 mmol of a 0.3 M solution in THF) was heated at 75 °C for 5 h. After cooling, the reaction mixture was filtered through a plug of silica gel and the solvent removed in vacuo. The residue was purified by flash column chromatography on silica gel eluting with 2% ethyl acetate/hexane to give a mixture of **3a** and **4a** as a colorless oil (103 mg, 0.38 mmol, 87%). **Preparation of a 0.3 M Solution of Lithio Diethyl Malonate in THF.** To a solution of diethyl malonate (320 mg, 2.0 mmol) in THF (6.7 mL) at −78 °C was added *n*-BuLi (1.25 mL, 2.0 mmol of a 1.6 M solution in hexanes) dropwise over 10 min. The reaction mixture was stirred for 30 min at −78 °C before being warmed to 0 °C over 1 h.

(13) Homoallylic secondary amines have been shown to react with allylic acetates under palladium catalysis to yield tertiary amines. Trost, B. M.; Godleski, S. A.; Genet, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 3930.

(14) Tin ethers have been shown to direct an oxygen nucleophile to an α-alkoxy π-allyl palladium intermediate proximal to the ether. Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 2931.

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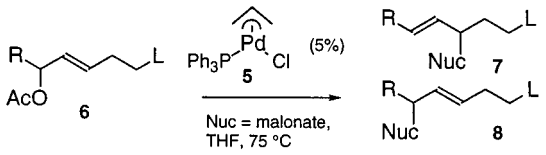
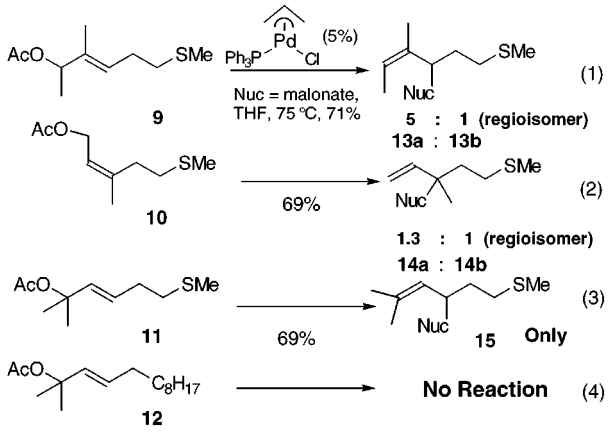
Table 2



entry	R		L		7a−f:8a−f[a]	yield[b] (%)
1	H	**6a**	N*n*Pr$_2$	**7a**/**8a**	1:1.7	69[c]
2	H	**6b**	NMe(Ph)	**7b**/**8b**	1:>15	77[c]
3	Me	**6c**	N*n*Pr$_2$	**7c**/**8c**	1:1.5	85[c,d]
4	Me	**6d**	NMe(Ph)	**7d**/**8d**	1:13	67
5	H	**6e**	S*i*Pr	**7e**/**8e**	7:1	63
6	H	**6f**	SPh	**7f**/**8f**	4:1	72

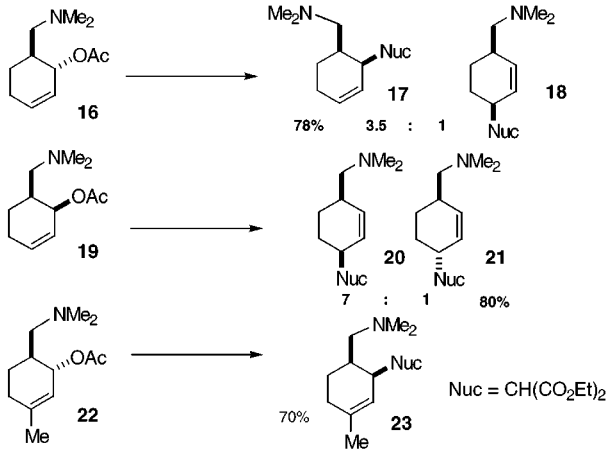
[a] Ratios determined by integration of ^{1}H NMR spectral signals (300 or 500 MHz). [b] Yields refer to isolated materials. [c] Mixtures of *E*/*Z* alkene isomers. [d] The reaction failed to proceed to completion under a variety of conditions.

Additional substitution on the three carbons of the allylic moiety led to variable results (eqs 1−3). Introduction of methyl groups at both the central and terminal carbons of the allyl moiety led to a decrease in selectivity, and, a 5:1 ratio of isomers was observed in which the major isomer still resulted from substitution proximal to the heteroatom (eq 1). The power of the directing effect can be seen upon disubstitution at the internal carbon of the allyl moiety (eq 2). While a 1.3:1 ratio of isomers was obtained, the major isomer resulted from direction by the thioether to form a



quaternary center. Interestingly, disubstitution at the terminus distal to the heteroatom (eq 3) yielded only the product of addition to the allyl moiety proximal to the thioether upon reaction with malonate anion in the presence of complex **5**. It is remarkable that, in the absence of the thioether, the analogous allylic acetate (eq 4) did not undergo nucleophilic substitution and the acetate was recovered unchanged. This result strongly suggests that the heteroatom provides an accelerating as well as a directing effect.

In addition, *the heteroatom controls the stereochemistry of allylation, leading to overall inversion of configuration*. This is illustrated by the conversion of **16**, under standard conditions,[12] to a 3.5:1 ratio of **17** and **18** in 78% yield, both of which are products on inversion of configuration. In contrast, acetate **19**, in which the amine should not participate through coordination to the metal, under the same reaction conditions, gave amines **20** and **21** in a 7:1 ratio in 80% yield. As expected, the major product resulted from overall retention of stereochemistry. For this case, there is no directing effect from the tertiary amine. Finally, when acetate **22** was treated with malonate in the presence of Pd(PPh$_3$)$_4$, only **23**, the isomer resulting from regioselective substitution with inversion at the allylic terminus proximal to the heteroatom, was obtained.[15]



In summary, we have shown that regioselective additions to allylic acetates, catalyzed by palladium, can be achieved by incorporation of a thioether or tertiary amine into the substrate. This demonstrates, for the first time, that heteroatoms capable of coordinating to palladium can change or even reverse the expected regiochemical and stereochemical outcome. Reactions with malonate anion proceed with high selectivity to provide the product substituted at the terminus of the allyl moiety proximal to the heteroatom, even if that position is more substituted. Work is in progress to evaluate the scope of the reaction, and our results will be reported in due course.

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Supporting Information Available: Proton NMR spectra and/or elemental analyses for all compounds (47 pages).

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(15) The stereochemistry of the cyclic allylated malonates was determined by ^{1}H NOE experiments at 500 MHz.