Diastereo- and Enantioselective Allylation of Substituted Nitroalkanes

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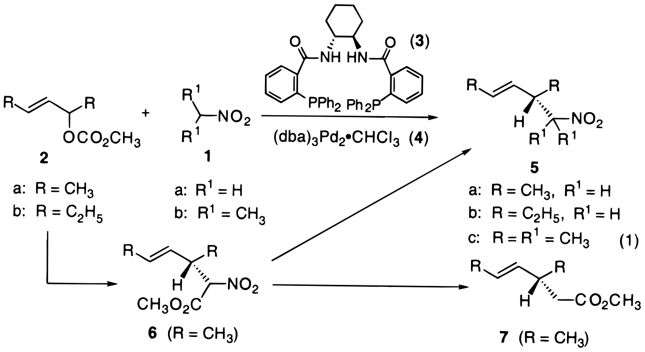
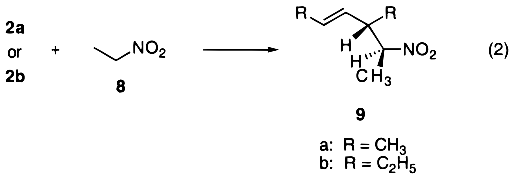
Nitroalkanes are valuable building blocks due to the diversity of their chemistry.[1] While their anions undergo carbonyl and conjugate additions, they normally do not participate in simple alkylations. Their employment in asymmetric reactions has largely revolved around the Henry reaction.[2,3] Only the reactions of nitromethane have been reported for the Pd-catalyzed asymmetric allylic alkylation (AAA) reaction with 2-diarylphosphino-4,5-dihydrooxazoles as ligands.[4,5] It is reported that nearly equal amounts of both *E*- and *Z*-alkenes for the 1,3-dimethyl and 1,3-diethyl substrates are formed, and the enantiomeric excesses (ee's) for the two isomers range from 28 to 84%.[4a] No reactions of higher nitroalkanes have been reported, probably because of the issue of diastereoselectivity. We report AAA reactions with such nitroalkanes for the first time and show that such reactions can proceed with good diastereoselectivity and excellent ee.

Our initial efforts focused on nitromethane (**1a**) as nucleophile. Treatment of a methylene chloride solution of **2a** and 4 equiv of **1** at room temperature, using the catalyst system derived from chiral ligand **3**, Pd(0) complex **4,** and tetra-*n*-butylammonium chloride,[6] led to a slow reaction to produce, after 48 h, the monoalkylated product **5a** as only the *E*-alkene (83% yield, 98% brsm) but only in 22% ee (eq 1). Switching to a much more polar medium to enhance reactivity led to similar results using substrate **2b**, in which an 81% yield (93% brsm) of **5b** of 20% ee was obtained after 72 h using cesium carbonate in DMSO. The absolute configuration was established as **5** as depicted by correlation. Alkylation of **2a** with a more traditional type of nucleophile for allylic alkylation, methyl nitroacetate, in methylene chloride using 2 mol % **4** and 6 mol % **3** with no base gave **6** as a 1:1 diastereomeric mixture in 97% yield. Hydrolysis and decarboxylation (NaOH, C_2H_5OH, H_2O, reflux, 70% yield) gave **5a** of 83% ee. Lowering the catalyst loading to 0.5 mol % **4** and 0.75 mol % **6** led to **5a** of 88% ee and constitutes the best source of **5a** of good ee. Radical denitronation[7] of **6** produced **7**, whose absolute configuration was previously established.[8]

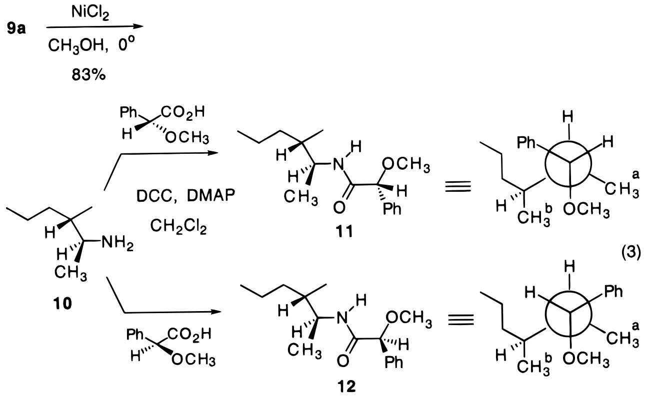


In contrast to nitromethane, nitropropane gave **5c**[9] in 62% ee (90% yield) under the same conditions that gave **5a** in only 3% ee [$(C_4H_9)_4NCl$, Cs_2CO_3, DMSO, room temperature]. Interestingly, catalyst loading had a dramatic effect on ee. Whereas the above result was obtained using 2 mol % **4** (6 mol % **3**), lowering the catalyst loading to 0.5 mol % **4** (1.5 mol % **3**) increased the ee of **5c** to 86%. Decreasing the catalyst loading to 0.25 mol % **4** (0.75 mol % **3**) led to **5c** of 91% ee.

Most interesting results were obtained with nitroethane (**8**) as nucleophile, as summarized in eq 2 and Table 1. Using cesium carbonate as base in DMSO gave **9a**[9] as a 1:1 ratio of diastereomers of modest ee (entry 1). Switching to *O*,*N*-bis(trimethylsilyl)acetamide (BSA) as base in methylene chloride in the absence or in the presence of a tetra-*n*-butylammonium chloride gave ee's in a similar range but with good diastereoselectivity (entries 2 and 3). As noted previously, dropping the catalyst loading increased both the diastereo- and the enantioselectivity (entries 4 and 7). Decreasing the amount of nitroethane to just 1.5 equiv had no significant effect on the ee but showed a slight decrease in diastereomer ratio (dr) (entry 5). Switching to allyl carbonate **2b** gave **9b** in 55% yield (99% brsm) as a 5:1 diastereomeric ratio wherein the major diastereomer has 96% ee using 1 mol % **4** and 3 mol % **3** in 12 h.



The stereochemistry of the carbon bearing the nitro group of **9a** was established by reduction to the amine **10** and conversion of the latter to the corresponding (*R*)- and (*S*)-*O*-methylmandelamides **11** and **12** (eq 3).[10] The lower field shift for H_a in **11** (δ 1.10) compared to that in **12** (δ 1.02) and the reverse for H_b (**11**, δ 0.81 vs **12**, δ 0.89) allows the configuration for the carbon bearing nitrogen to be assigned as *S*. Analogy to **5a** as well as the mnemonic allows assignment for C-3 also as *S*.



The unexpected control of stereochemistry at both the nucleophile and the electrophile led to exploration of a range of nitroalkanes, as summarized in eq 4. In all cases, good diaste-

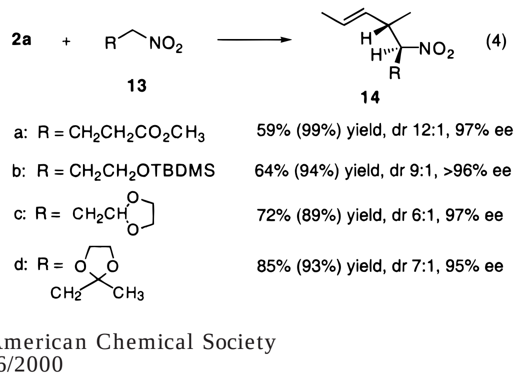


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Table 1. Asymmetric Allylic Alkylation of Methyl Carbonate of (*E*)-3-Penten-2-ol (**2a**) with Nitroethane[a]

entry	mol % **4**	mol % **3**	time (h)	base	additive	solvent	isolated yield **9a** (%)	dr[d]	ee[d,e] (%)
1	2.0	6	16	Cs_2CO_3	$(C_4H_9)_4NCl$	DMSO	84	1:1	45
2	2.0	6	6	BSA	none	CH_2Cl_2	99	5:1	36
3	2.0	6	6	BSA	$(C_4H_9)_4NCl$	CH_2Cl_2	96	6:1	53
4	0.5	1.5	24	BSA	$(C_4H_9)_4NCl$	CH_2Cl_2	95	10:1	92
5[b]	0.5	1.5	36	BSA	$(C_4H_9)_4NCl$	CH_2Cl_2	85 (98)[c]	8:1	97
6	0.5	1.5	72	BSA	$(C_6H_{13})_4NCl$	CH_2Cl_2	65 (99)[c]	11:1	96
7	0.25	0.75	48	BSA	$(C_4H_9)_4NCl$	CH_2Cl_2	71 (99)[c]	11:1	97

[a] All reactions were performed at 0.5 M in allyl substrate using 5−8 equiv of nitroethane unless stated otherwise. [b] Reaction performed with 1.2 equiv of nitroethane. [c] Yields in parentheses are based upon recovered starting material. [d] Determined by chiral GC analysis using a cyclosil B column. [e] Enantiomeric excess determined for the major diastereomer except for entry 1, where it represents the ee for both diastereomers.

reoselectivity and excellent enantioselectivity were observed when 2 equiv of the nitroalkanes **13a**−**d** was utilized. For the reactions of **13a**−**c**, 0.25 mol % of **4** and 0.75 mol % of ligand **3** were employed to generate the chiral complex in situ. In the case of **13d**, a higher catalyst loading of 1 mol % of **4** and 3 mol % of **3** was used since the reaction became too sluggish when it was lowered. The yields in parentheses are based upon recovered starting materials.

Thus, nitroalkanes are excellent substrates for the palladium-catalyzed AAA reaction reported herein using our ligands except for nitromethane. The diastereoselectivity observed is a kinetic phenomenon since base treatment equilibrates the diastereomers to nearly 1:1 mixtures. Given the high acidity of the nitroalkanes, the absence of significant epimerization of the product under the reaction conditions must arise from the lower kinetic acidity, despite the higher thermodynamic acidity, upon alkyl substitution.[11] Thus, BSA functions satisfactorily, whereas cesium carbonate did not. The strong dependence of selectivity on the catalyst loading is intriguing. A possible explanation relates to the "memory effect" we noted previously.[12] In this circumstance, the intermediate π-allylpalladium ion pair does not possess the symmetry expected. In proposing such an explanation, deviation of the symmetry with respect to the 1,3-disubstituted π-allyl system derives from both the unsymmetrical solvation of the ion pair which includes the counterion as part of the solvation shell and the conformation of the ligand which makes it deviate from its formal C_2 symmetry. To achieve high ee, the intermediate π-allyl complex must fully equilibrate faster than it is attacked by nucleophile. By lowering the catalyst loading which, in effect, reduces the concentration of the π-allylpalladium intermediate, the unimolecular equilibration event now out-competes the bimolecular nucleophilic addition. The effects of tetra-*n*-butylammonium chloride on rates of equilibration and enantioselectivity[6] provide additional support for this interpretation. Figure 1 depicts a rationale for the observed diastereoselectivity wherein steric interactions between the ligand and both the π-allyl unit and the nucleophile are minimized. Because of the ease of reduction of nitro groups to amines, this reaction provides facile entry to amines with high diastereo- and enantioselectivity.

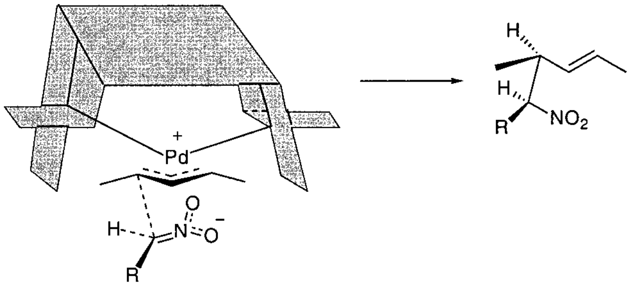

Figure 1. Cartoon depicting diastereoselectivity

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Supporting Information Available: Characterization data for **5c**, **9a**,**b**, and **14a**−**d** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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