

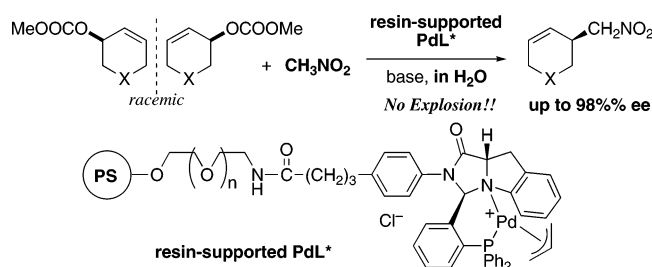
π -Allylic C1-Substitution in Water with Nitromethane Using Amphiphilic Resin-Supported Palladium Complexes

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Nitromethane was safely applied as a C1 nucleophile for palladium-catalyzed π -allylic substitution in water with amphiphilic PS-PEG resin-supported phosphine-palladium complexes. Catalytic asymmetric nitromethylation of cycloalkenyl esters was achieved in water as a single reaction medium under heterogeneous conditions using 5 mol % palladium of a PS-PEG resin-supported palladium-imidazoindolephosphine complex to give optically active (cycloalkenyl)nitromethanes with up to 98% ee.

The palladium-catalyzed allylic substitution reaction, the so-called Tsuji-Trost reaction, has been recognized as one of the most powerful carbon-carbon bond-forming catalytic transformations. However, in contrast to the vast amount of research on palladium-catalyzed π -allylic substitution with active methylene and methine compounds (e.g., malonates), only scattered attention has been paid to reactions with C1 nucleophiles. If the palladium-catalyzed π -allylic substitution of allylic esters took place with nitromethane as the C1 nucleophile, it would allow introduction of various C1 functionalities at the allylic position due to the versatile reactivity of the nitromethyl group. One of the major problems associated with nucleophilic utility of nitromethane lies in the explosive nature of nitromethane under basic conditions.¹ We have developed amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin-supported palladium complexes, which catalyze various synthetic organic reactions, π -allylic substitution, Heck reaction, carbonylation, cross-coupling, etc., in water under heterogeneous conditions.² These results prompted us to examine the π -allylic C1 substitution with nitromethane in water using amphiphilic polymeric palladium catalysts in which nitromethane should not explode

even under basic conditions. Here, we report a heterogeneous aquacatalytic π -allylic substitution with nitromethane as a safe C1 nucleophile^{3,4} where asymmetric catalysis (up to 98% ee) is also described.

Preliminary studies on the aquacatalytic π -allylic nitromethylation were carried out with the PS-PEG resin-supported triarylphosphine-palladium complex **3**. Thus, methyl cinnamyl carbonate (**1**) reacted with 3 equiv of nitromethane in aqueous Li₂CO₃ solution in the presence of 5 mol % palladium of the polymeric complex **3** at 60 °C for 12 h to give 92% isolated yield of the nitromethylated products **2** and **2'** (**2/2'** = 89/11) (Scheme 1). Nitromethylation of **1** with [PdCl(η^3 -C₃H₅)]₂/PPh₃ in THF or CH₂Cl₂ showed little or low reactivity at 25 °C to result in a poor chemical yield and exploded at 40 °C.

Acyclic and cyclic secondary allylic esters also underwent the aquacatalytic nitromethylation under similar conditions (Schemes 2 and 3). Thus, nitromethylation of benzylic esters **1'** proceeded smoothly under similar conditions to give a mixture of linear and branch products **2** and **2'** in 84% yield in a ratio of 86:14 where the plausible π -allylpalladium intermediate should be the same as the intermediate for the reaction of cinnamyl ester **1**. Benzylic esters **4** and **6** bearing 4-methyl and 4-methoxy aromatic substituents also gave the corresponding nitromethylation products **5/5'** (93:7) and **7/7'** (77:23) in 80% and 86% yield, respectively. 1,3-Diphenylpropenyl carbonate **8** gave 95% yield of **9** under similar conditions. The cyclic substrates **10**, **12**, and **14** also underwent π -allylic nitromethylation to afford the corresponding products **7**, **9**, and **11** in 78%, 90%, and 89% isolated yield, respectively (Scheme 3). 5-*cis*-Carbomethoxycyclohexenyl carbonate **16** reacted with nitromethane under similar conditions to give the *cis*-1-nitromethyl-5-carbomethoxy product **17** as a single diastereoisomer in 93% yield. The exclusive stereochemical outcome indicates that this nitromethylation proceeded via a double inversion pathway: π -allylpalladium complexation and nucleophilic attack of the nitromethyl group.

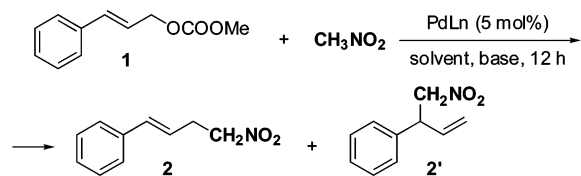
Using this safe π -allylic nitromethylation protocol, we examined catalytic asymmetric nitromethylation in water with an amphiphilic PS-PEG resin-supported chiral palladium complex (Scheme 4). We previously reported the heterogeneous aquacatalytic chiral process by catalytic asymmetric π -allylic alkylation and amination of cycloalkenyl esters using a palladium catalyst coordinated with a novel optically active ligand, (3*R*,9*S*)-(2-aryl-3-(2-diphenylphosphino)phenyl)tetrahydro-1*H*-imidazo[1,5-*a*]indol-1-one, anchored onto an amphiphilic polystyrene-poly(ethylene glycol) copolymer (PS-PEG) resin.^{5,6}

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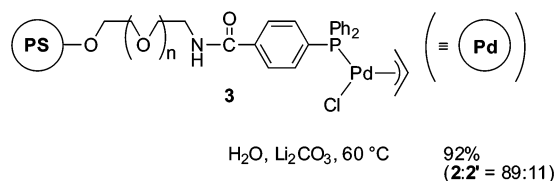
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SCHEME 1. π -Allylic Nitromethylation of Cinnamyl Carbonate

[PdCl(η^3 -C ₃ H ₅) ₂]/PPh ₃	THF, Li ₂ CO ₃ , 25 °C	no reaction
(Pd/P = 1/2)	THF, Li ₂ CO ₃ , 40 °C	explosion
	CH ₂ Cl ₂ , Li ₂ CO ₃ , 25 °C	24%
	CH ₂ Cl ₂ , Li ₂ CO ₃ , 40 °C	explosion



To the best of our knowledge, well-developed research on catalytic asymmetric substitution of cyclic substrates⁷ with C1 nucleophiles has been limited to Trost's report⁸ citing the asymmetric π -allylic nitromethylation of cycloalkenyl esters in dichloromethane. Though high enantioselectivity of up to 98% ee was achieved with Trost's chiral bisphosphine ligand, the risk of explosion still remains a serious problem.⁹ Clearly, while pioneering strides have been made, additional studies on water-based safe protocols are warranted.

π -Allylic nitromethylation of cycloalkenyl esters was found to proceed safely with high enantioselectivity in water. Thus, when a suspension of cycloheptenyl carbonate **14** and 3 equiv of nitromethane in water was shaken at 60 °C for 12 h in the presence of 5 molar equiv of lithium carbonate and the PS-PEG resin-supported chiral palladium-imidazoindole phosphine **18** (5 mol % palladium), 1-nitromethylcyclohept-2-ene (**15**) was obtained in 91% yield. The enantiomeric purity of **15** was determined by HPLC analysis (Chiralcel double AD-H, *n*-hexane) to be 98% ee, and the absolute configuration was determined to be *S* by measurement of the specific rotation ($[\alpha]^{25}_D + 3.4$ (*c* 0.5, chloroform)). The cyclic carbonates **10** and **12** took place asymmetric π -allylic nitromethylation to give the corresponding adducts **11** and **13** in 87% and 81% isolated yield with 80% and 70% ee, respectively (not optimized).

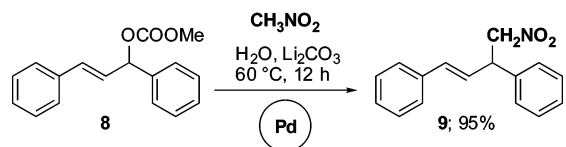
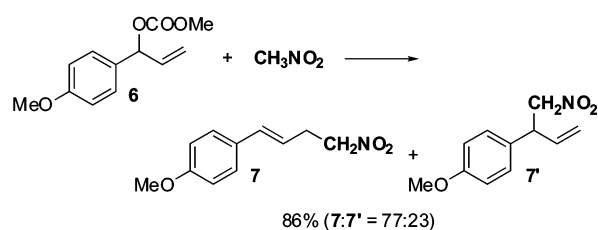
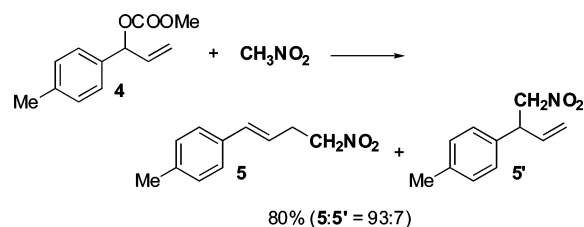
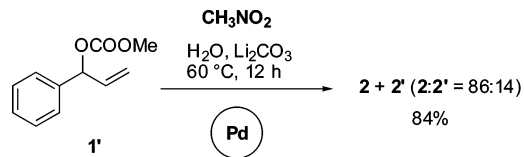
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(6) For other examples of heterogeneous aquacatalytic chiral processes with PS-PEG resin-supported transition-metal complexes, see: (a) Uozumi, Y.; Danjo, H.; Hayashi, T. *Tetrahedron Lett.* **1998**, *39*, 8303. (b) Hocke, H.; Uozumi, Y. *Synlett* **2002**, *12*, 2049. (c) Hocke, H.; Uozumi, Y. *Tetrahedron* **2003**, *59*, 619. (d) Hocke, H.; Uozumi, Y. *Tetrahedron* **2004**, *60*, 9297. (e) Otomaru, Y.; Senda, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 3357.

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(9) Trost's asymmetric nitromethylation was reproduced in our laboratories with the cycloheptenyl ester **8** (25 °C, 96 h, 71% yield, 96% ee), whereas the reaction mixture exploded at 40 °C.

SCHEME 2. π -Allylic Nitromethylation of Acyclic Secondary Esters

These results prompted us to examine the asymmetric nitromethylation of the tetrahydropyridyl ester *rac*-**19** to prepare the promising synthetic intermediate of Isfagomine¹⁰ and Siastatin B.¹¹ The tetrahydropyridyl ester *rac*-**19** underwent nitromethylation in water with the polymeric chiral catalyst **18** under similar conditions to give 81% isolated yield of (*R*)-nitromethyl(tetrahydro)pyridine **20** with 97% ee (Mosher's method for *tert*-butyl 5-aminomethyl-1,2,3,4,5,6-hexahydropyridinecarboxylate derived from 5-nitromethyl-1,2,5,6-tetrahydropyridinecarboxylate), which was readily converted to the tetrahydropyridyl carboxylic acid **21** also in water by the modified Carreira conditions¹² in the presence of *n*-BuI and TentaGel at 100 °C ($[\alpha]^{25}_D - 110$ (*c* 1.0, chloroform) [lit.¹³ for (*R*)-**21** of 99% ee: $[\alpha]^{25}_D - 112$ (*c* 3.0, chloroform)]).

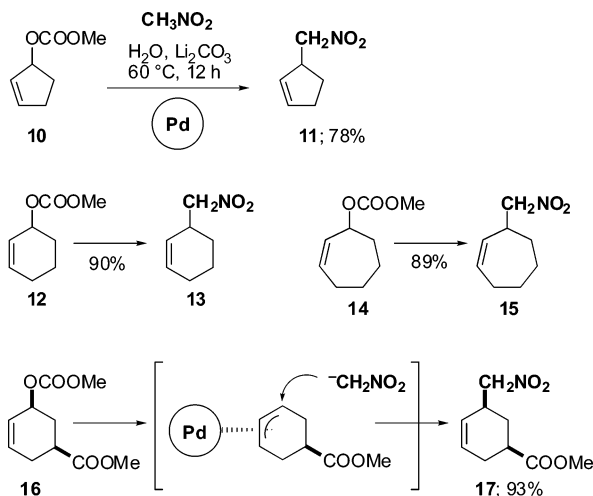
In summary, the palladium-catalyzed π -allylic C1 introduction was achieved with nitromethane, which was carried out in water to provide a safe nitromethylation protocol. Asymmetric nitromethylation of cycloalkenyl esters was achieved with up to 98% ee in water under heterogeneous conditions by use of the recyclable amphiphilic PS-PEG resin-supported palladium-imidazoindolephosphine complex.

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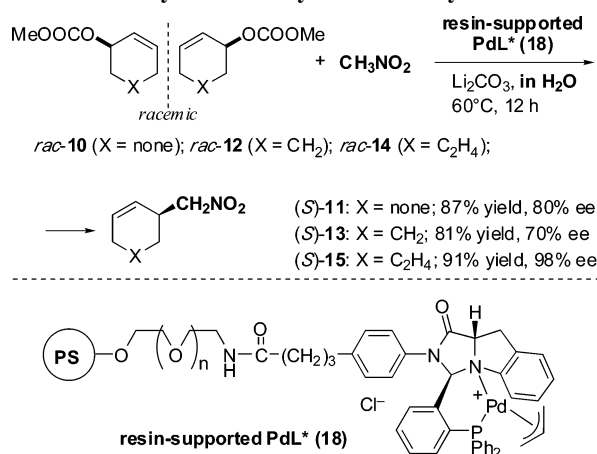
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SCHEME 3. π -Allylic Nitromethylation of Cycloalkenyl Esters

SCHEME 4. Asymmetric Allylic Nitromethylation

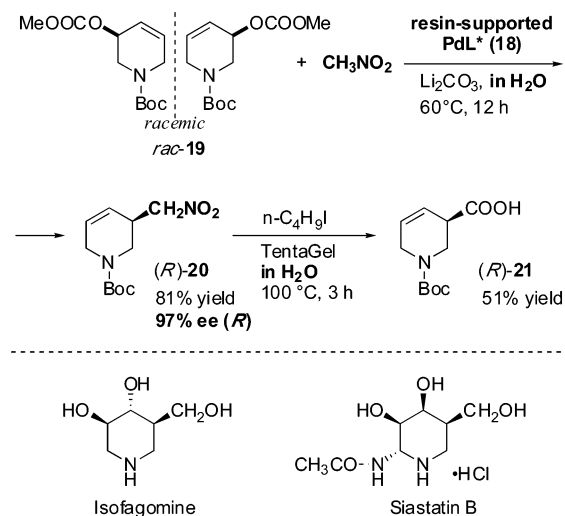


Experimental Section

Palladium-Catalyzed Allylic Substitution of Cinnamyl Carbonate (1) with Nitromethane (Schemes 1–3). A typical procedure is given for the reaction with nitromethane and methyl cinnamyl carbonate (2) (Scheme 1). To a solution of **3** (64.0 mg, 0.02 mmol), lithium carbonate (116 mg, 1.60 mmol), and methyl cinnamyl carbonate (2) (76.8 mg, 0.40 mmol) in H₂O (0.40 mL) was added nitromethane (73.2 mg, 1.2 mmol), and the mixture was stirred at 60 °C for 12 h. The reaction mixture was filtered, and the resin beads were rinsed three times with THF and MeOH. To the combined filtrate and washings were added aqueous NH₄Cl, and the mixture was extracted with MTBE. The combined extract was washed with aqueous sodium chloride and dried over anhydrous magnesium sulfate. After removal of the solvent, the residual oil was chromatographed on silica gel (hexane/ethyl acetate/Et₃N = 9/1/0.5) to give 65.1 mg (92% yield) of a mixture of 4-nitro-1-phenylbutene (2) and 4-nitro-3-phenylbutene (2') in a ratio of 89:11.

Palladium-Catalyzed Asymmetric Allylic Substitution of Cyclic Allylic Carbonates with Nitromethane (Schemes 4 and

SCHEME 5. Synthetic Application



5). A typical procedure is given for the reaction of methyl cycloheptenyl carbonate (14) with nitromethane. To a mixture of **18** (68.0 mg, 0.02 mmol of Pd), lithium carbonate (116 mg, 1.60 mmol), and methyl cycloheptenyl carbonate (14) (76.8 mg, 0.40 mmol) in H₂O (0.40 mL) was added nitromethane (73.2 mg, 1.2 mmol), and the mixture was stirred at 60 °C for 12 h. The reaction mixture was filtered, and the resin beads were rinsed three times with THF and MeOH. To the combined filtrate and washings was added aqueous NH₄Cl, and the mixture was extracted with MTBE. The combined extracts were washed with aqueous sodium chloride and dried over anhydrous magnesium sulfate. The solvent was evaporated, and the residue was chromatographed on silica gel ((hexane/ethyl acetate/Et₃N = 9/1/0.5) to give 56.4 mg (91% yield) of a cycloheptenyl nitromethane (15).

Reaction of the *tert*-Butyl (5*R*)-5-Nitromethyl-1,2,5,6-tetrahydropyridinecarboxylate (20) (97% ee) with Iodobutane Giving (3*S*)-*N*-*tert*-Butoxycarbonyl-1,2,3,6-tetrahydropyridin-3-carboxylic Acid (21). To a solution of *tert*-butyl (5*R*)-5-nitromethyl-1,2,5,6-tetrahydropyridinecarboxylate (20) (97% ee) (76 mg, 0.3 mmol), KOH (67 mg, 1.2 mmol), and Tenta Gel (48 mg, 0.015 mmol) in H₂O (1.0 mL) was added iodobutane (110 mg, 0.8 mmol), and the mixture was stirred at 100 °C for 3 h. The reaction mixture was filtered, and the resin beads were rinsed three times with H₂O. To the washings (H₂O) were added aqueous citric acid, and the mixture was extracted with MTBE. The combined extracts were washed with aqueous sodium chloride and dried over anhydrous magnesium sulfate. The solvent was evaporated, and the residue was chromatographed on silica gel (AcOEt) to give 34.1 mg (51% yield) of a corresponding carboxylic acid (21).

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Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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