Amphiphilic Allylation

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Convenient Synthesis of Pyrrolidines by Amphiphilic Allylation of Imines with 2-Methylenepropane-1,3-diols**

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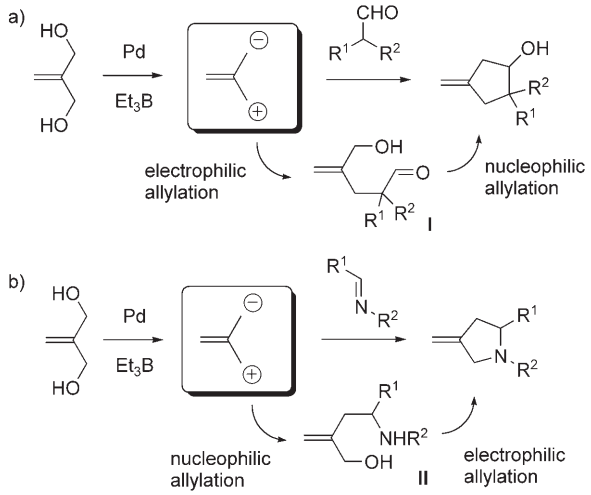
Cycloaddition reactions using trimethylenemethane (TMM) species are among the most interesting strategies for the construction of cyclic biologically active molecules and natural products.[1] Trost et al. reported that TMM–Pd complexes generated from 3-acetoxy-2-trimethylsilylmethyl-1-propene and Pd^0 metal served successfully as zwitterionic intermediates for 1,3-cycloaddition reactions with electron-deficient olefins, aldehydes, and imines to give cycloalkanes and heterocyclic compounds.[2]

In previous publications, we reported a method for the direct allylic activation of allyl alcohols, promoted by a combination of a Pd catalyst and triethylborane (Et_3B), to form a π-allylpalladium intermediate that serves as an allyl cation equivalent for a variety of soft nucleophiles and facilitates electrophilic allylation (Tsuji–Trost reaction).[3] In the absence of nucleophiles, π-allylpalladium undergoes an allyl–ethyl exchange reaction, thus providing allyldiethylborane as an allyl anion equivalent. This species reacts with aldehydes, acetals, and aldimines to provide homoallyl alcohols and homoallylamines.[4]

We recently established a straightforward and convenient method for amphiphilic allylation of *sec*-alkyl aldehydes with commercially available 2-methylenepropane-1,3-diol through a TMM equivalent by using a Pd catalyst/Et_3B system.[5] One of the allyl alcohol moieties of the symmetrical bis-allyl alcohol undergoes electrophilic allylation with the α position of the alkyl aldehyde to give a hemiacetal, while the remaining allyl alcohol moiety selectively reacts as an allyl anion equivalent with the carbonyl group of the aldehyde to furnish 4-methylenecyclopentanols (Scheme 1 a). The result of this reaction is in contrast to that of Trost's reaction, a [3+2] cycloaddition reaction with a TMM–Pd complex and aldehydes which provides 3-methylenetetrahydrofurans.[6]

Herein, we report that a catalytic system consisting of a Pd salt and Et_3B promotes amphiphilic (nucleophilic–electrophilic) allylation of aldimines, prepared from a wide variety of amines and aldehydes, with 2-methylenepropane-1,3-diol to give pyrrolidines (Scheme 1 b). This is the first example of the synthesis of pyrrolidines from nonactivated 2-methylenepropane-1,3-diol as zwitterionic carbon framework. Notably, the order of sequential amphiphilic allylation of aldimines is apparently opposite to that of aldehydes (Scheme 1 a and b).



Scheme 1. Amphiphilic allylation of aldehydes (a) and aldimines (b) with a bis-allyl alcohol promoted by Pd^0 and Et_3B.

Table 1 summarizes the Pd-catalyzed amphiphilic allylation reactions of aldimines prepared from a variety of aromatic and aliphatic aldehydes and amines. The reaction was conducted as follows: in situ aldimine formation (30 min at reflux in 1 mL dry THF), distillation of an azeotropic mixture of THF/H_2O (twice), and exposure of the imine residue to a mixture of 2-methylenepropane-1,3-diol, $Pd(OAc)_2$, nBu_3P, and Et_3B at 50 °C under a nitrogen atmosphere.[7] Aldimines generated from aromatic amines and aldehydes are suitable electrophiles for amphiphilic allylation. The reaction was successful for aromatic aldehydes and amines with either electron-donating or electron-withdrawing groups. When using aldimines substituted with halogens or acidic OH groups, there was no need for the addition of extra Et_3B to obtain the expected pyrrolidines (Table 1, entries 3, 5, and 6). Heteroaromatic and aliphatic aldehydes behaved similarly, providing the corresponding pyrrolidines in reasonable yields (Table 1, entries 7 and 8). Aldimines of aliphatic amines performed comparably to those of aromatic amines. *N*-benzylimines of aromatic and α,β-unsaturated aldehydes underwent amphiphilic allylation in high yields (Table 1, entries 9–12).

However, the combination of benzylamine and alkyl aldehyde did not react, and a complex mixture was produced (Table 1, entry 13). Therefore, we developed an alternative

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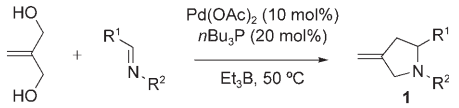
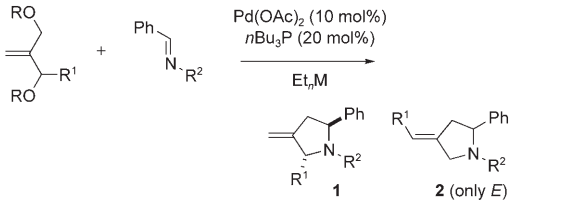
Table 1: Synthesis of pyrrolidines by amphiphilic allylation of imines with a bis-allyl alcohol.[a]



Entry	R^{1}[b]	R^{2}[b]	*t* [h]	Yield of **1** [%]
1	Ph	Ph	45	**1a**: 89
2	Ph	*p*-anis	18	**1b**: 91
3	Ph	*p*-ClC_6H_4	40	**1c**: 82
4	*p*-anis	*p*-anis	18	**1d**: 84
5	*p*-ClC_6H_4	*p*-anis	20	**1e**: 85
6	*p*-OHC_6H_4	*p*-anis	18	**1f**: 77
7	2-furyl	*p*-anis	18	**1g**: 74
8	*n*-C_5H_{11}	*p*-anis	18	**1h**: 81
9	Ph	Bn	18	**1i**: 71
10	*p*-ClC_6H_4	Bn	18	**1j**: 79
11	2-furyl	Bn	18	**1k**: 80
12	cinnamyl	Bn	18	**1l**: 67
13[c]	*n*-C_5H_{11}	Bn	18 (6)	**1m**: – (70)

[a] Reaction conditions: amine (1.05 mmol; R^2) and aldehyde (1 mmol; R^1) in dry THF (1 mL) at reflux for 0.5 h; distillation of THF (azeotropic removal of water) and then $Pd(OAc)_2$ (0.1 mmol), nBu_3P (0.2 mmol), 2-methylenepropane-1,3-diol (1.2 mmol), and Et_3B (4.8 mmol) in dry THF (1 mL) under nitrogen. [b] *p*-anis = *p*-anisidine, Bn = benzyl. [c] In parentheses: results when 2-methylenepropane-1,3-dibenzyl ether (1.2 mmol) and Et_2Zn (4.8 mmol) were used.

Table 2: Amphiphilic allylation of unsymmetrically substituted bis-allyl alcohols.[a]



Entry	R	R^{1}	R^{2}[b]	Et_nM	*t* [h]	Yield of **1** [%]	**2**
1	H	Ph	PMP	Et_3B	72	0	**2a**: 72
2	Bn	Ph	PMP	Et_2Zn	12	**1n**: 100	0
3	Bn	Ph	*p*-BrC_6H_4	Et_2Zn	12	**1o**: 83	0
4	H	Me	PMP	Et_3B	72	**1p**: 73[c]	0
5	Bn	Me	PMP	Et_2Zn	24	**1p**: 92	0

[a] Reaction conditions: amine (1.05 mmol) and aldehyde (1 mmol) in dry THF (1 mL) at reflux for 0.5 h; distillation of THF (azeotropic removal of water) and then $Pd(OAc)_2$ (0.1 mmol), nBu_3P (0.2 mmol), 2-methylenepropane-1,3-diol (1.2 mmol), Et_3B (4.8 mmol) at 50 °C (entries 1 and 4), bis-allyl dibenzyl ether (1.2 mmol), Et_2Zn (4.8 mmol) at room temperature (entries 2, 3, and 5). [b] PMP = *p*-methoxyphenyl. [c] As a diastereomeric mixture of *trans*-**1p** and *cis*-**1p** in a 10:1 ratio.

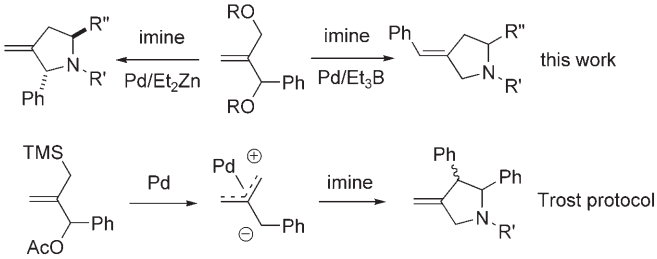
reaction route, by using a Pd catalyst and Et_2Zn, for the amphiphilic allylation of aldimines composed of an aliphatic aldehyde and an aliphatic amine with 2-methylenepropane-1,3-dibenzyl ether. In this case, the reaction proceeded smoothly at room temperature, reaching completion after 6 h, and the desired pyrrolidine was obtained in 70% yield (Table 1, entry 13, values in parentheses). The Pd/Et_2Zn system achieves amphiphilic allylation despite the fact that imines generated from aliphatic aldehydes and amines are generally far less reactive than their aromatic counterparts.[8] Thus, by employing either Et_3B or Et_2Zn, this one-pot synthesis of pyrrolidines may be carried out with a wide variety of aromatic and aliphatic aldehydes and amines.

Unsymmetrically substituted bis-allyl alcohols and bis-allyl dibenzyl ethers show intriguing regio- and stereoselectivities depending on whether Et_3B or Et_2Zn is used as promoter. In the presence of Pd catalyst and Et_3B, a 1-phenyl-substituted unsymmetrical bis-allylic alcohol underwent nucleophilic allylation at the less substituted allylic position, followed by intramolecular electrophilic allylation at the less sterically hindered end of the allyl moiety, to provide pyrrolidine *E*-**2a** as a single isomer (Table 2, entry 1). In contrast, the Pd/Et_2Zn catalytic system promoted nucleophilic allylation of the dibenzyl ether at the less substituted position, and subsequent electrophilic allylation proceeded at the Ph-substituted allylic position to afford *trans*-2,5-diphenylpyrrolidine **1n** quantitatively as a single stereoisomer (Table 2, entry 2). *p*-Bromoanaline imine displayed similar regio- and stereoselectivities, yielding pyrrolidine **1o** as a sole product (Table 2, entry 3). The structure of **1o** was unequivocally determined by means of X-ray single-crystal analysis.[9]

These regio- and stereoselectivities are in contrast to the results obtained by using the Trost protocol: cycloaddition with substituted TMM precursors generated from unsymmetrical 2-[(trimethylsilyl)methyl]allyl acetate by using a Pd catalyst (Scheme 2).[10] In that work, a 1-phenyl-TMM–Pd complex was found to react with the imine carbon atom at the more substituted allylic position to provide 2,3-diphenylpyrrolidines as a mixture of diastereomers. Thus, all conceivable isomers involving TMM precursors can be formed selectively by using either the reaction conditions described herein or those developed by Trost.

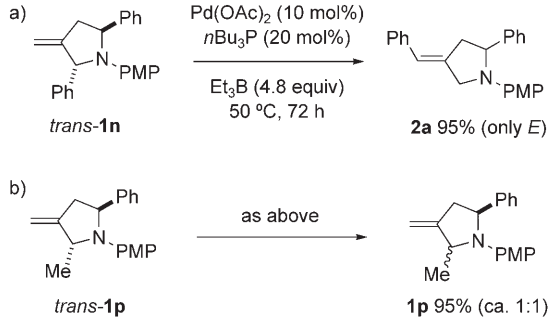
Unsymmetrical methyl-substituted bis-allyl alcohols show different regio- and stereoselectivities compared to those substituted with a phenyl group. In this case, intramolecular electrophilic allylation proceeds at the more substituted side of π-allylpalladium to give *trans*-**1p** predominantly along with a small amount of *cis*-**1p** (Table 2, entry 4), in contrast to the reaction using Ph-substituted bis-allyl alcohol. The use of Et_2Zn accelerated the amphiphilic allylation reaction smoothly at room temperature to afford *trans*-**1p** as a single isomer in excellent yield (Table 2, entry 5).

The single stereoisomer *trans*-**1n** obtained by using the Pd/Et_2Zn system was successfully converted into internal olefin *E*-**2a** with a Pd/Et_3B catalyst at 50 °C for 72 h



Scheme 2. Selective synthesis of conceivable substituted pyrrolidines. TMS = trimethylsilyl.

(Scheme 3a) Interestingly, under similar conditions, *trans*-**1p** isomerized to a diastereomeric mixture of *trans*- and *cis*-**1p** in an approximately 1:1 ratio (Scheme 3b). The results of these



Scheme 3. Different reactivity of alkyl- and aryl-substituted products **1** towards our Pd/Et_3B catalyst.

isomerization experiments indicated that intramolecular electrophilic allylation in the presence of Pd/Et_3B is a reversible process; hence, isomerization from the kinetically favorable pyrrolidines to the thermodynamically more stable species occurs readily under this system.[11]

In conclusion, we have developed a convenient and straightforward synthesis of pyrrolidines from commercially available 2-methylenepropane-1,3-diols and their benzyl ethers with a variety of aldimines prepared from aromatic and aliphatic amines and aldehydes. The application and extension of this method for the asymmetric synthesis of physiologically active molecules with pyrrolidine frameworks are currently being investigated.

Experimental Section

General procedure (see Table 1, entry 2): A solution of benzaldehyde (106 mg, 1.0 mmol) and *p*-anisidine (129 mg, 1.05 mmol) in dry THF (1 mL) was refluxed for 30 min under nitrogen and then the solvent was removed by distillation (azeotropic removal of water). THF (1 mL) was added and then removed by distillation under atmospheric pressure of nitrogen. $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), nBu_3P (50 μL, 0.2 mmol), 2-methylenepropane-1,3-diol (106 mg, 1.2 mmol), THF (1 mL), and Et_3B (3.6 mmol, 1M in hexane) were successively added to the imine residue. The homogeneous mixture was stirred and heated for 18 h at 50 °C under nitrogen. The mixture was diluted with EtOAc and washed with saturated $NaHCO_3$ and brine, and then the organic phase was dried ($MgSO_4$) and concentrated in vacuo to give a brown oil, which was purified by column chromatography over silica gel (eluent: hexane) to give **1b** (242 mg, 91%). $R_f = (0.70$, EtOAc/hexane = 1:4); IR (neat): $\tilde{\nu} = 2947$ (m), 1620 (w), 1234 (s), 1042 (m), 810 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 2.51$ (dd, $J = 3.4$, 15.1 Hz, 1H), 3.20 (dd, $J = 8.8$, 15.1 Hz, 1H), 3.70 (s, 3H), 4.09 (d, $J = 13.2$ Hz, 1H), 4.29 (d, $J = 13.2$ Hz, 1H), 4.78 (dd, $J = 3.4$, 8.8 Hz, 1H), 4.95 (s, 1H), 5.08 (s, 1H), 6.45 (d, $J = 9.0$ Hz, 2H), 6.75 (d, $J = 9.0$ Hz, 2H), 7.17–7.29 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 42.8$, 54.7, 55.8, 63.1, 106.7, 113.3, 114.7, 125.7, 126.6, 128.4, 141.3, 144.5, 144.8, 151.1 ppm; HRMS: *m/z* (%): calcd for $C_{18}H_{19}ON$: 265.1467 [M^+]; found: 265.1444 (100).

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Keywords: aldimines · allylation · amphiphiles · palladium · pyrrolidines

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[7] 4.8 equivalents of Et_3B were required to complete the amphiphilic allylation successfully. Although the reaction proceeded in the presence of 2.0 equivalents of Et_3B, the conversion decreased to 50%.

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[9] See the Supporting Information for the X-ray single-crystal structure of **1o**. Crystal data for **1o**: $C_{23}H_{20}BrN$, $M_r = 390.32$, orthorhombic, space group *Pbca* (no. 61), $a = 8.2414(4)$, $b = 18.2298(8)$, $c = 25.0459(13)$ Å, $V = 3762.9(3)$ Å^3, $T = 296$ K, $Z = 8$, $\rho_{calcd} = 1.378$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 0.7107$ mm^{-1}, 25546 reflections measured, 4287 unique ($R_{int} = 0.027$), $R(R_w) = 0.1071$-(0.1254). CCDC 671566 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[11] Contrary to the isomerization experiment with the Pd/Et_3B system, the single isomer **1n** was not converted to *E*-**2a** by treatment with a Pd catalyst and Et_2Zn at 50 °C for 72 h.

