Organic LETTERS

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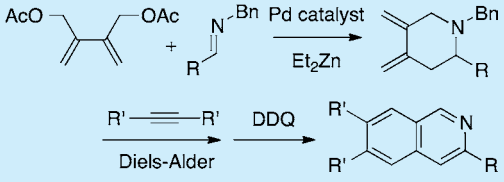
Palladium-Catalyzed [4 + 2] Cycloaddition of Aldimines and 1,4-Dipolar Equivalents via Amphiphilic Allylation

Goki Hirata, Naoshi Yamada, Shohei Sanada, Gen Onodera, and Masanari Kimura*

Graduate School of Engineering, Nagasaki University, Bunkyo-machi 1-14, Nagasaki 852-8521, Japan

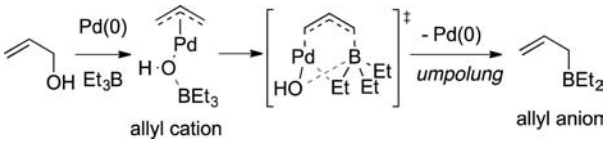
Supporting Information

ABSTRACT: The combination of Pd catalyst and diethylzinc with triethylborane promotes the amphiphilic allylation of aldimines with 2,3-bismethylenebutane-1,4-diol derivatives to serve as bis-allylic zwitterion species to form 3,4-bismethylenepiperidines via a formal [4 + 2] cycloaddition reaction. 3,4-Bismethylenepiperidine rings are applicable for the synthesis of isoquinoline derivatives via the Diels−Alder reaction followed by an oxidation reaction with DDQ.



π-Allylpalladium can serve as an important intermediate for efficient C−C bond transformations.[1] We have developed the direct formation of π-allylpalladium derived from allylic alcohols promoted by a Pd catalyst and triethylborane; e.g., the activation of allylic alcohols promoted by triethylborane as Lewis acid facilitated oxidative addition toward Pd(0) species to form a π-allylpalladium intermediate serving as an allylic cation equivalent (Scheme 1).[2]

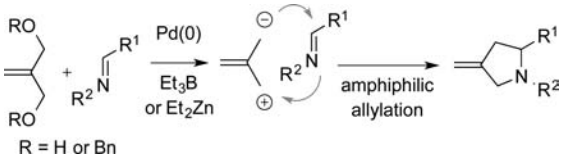
Scheme 1. Umpolung of π−Allylpalladium with Et_3B



Under the combination of Pd catalyst and triethylborane, soft nucleophiles such as active methylene compounds, amines, and indoles underwent electrophilic allylations with allylic alcohols, giving rise to allylated products.[3] On the other hand, in the presence of electrophiles, the similar catalytic system of Pd catalyst and triethylborane also promoted the nucleophilic allylation of carbonyl compounds, such as aldehydes and aldimines, to afford homoallyl alcohols and homoallylamines, respectively.[4] In these cases, umpolung of π-allylpalladium via triethylborane readily proceeded to afford the allyldiethylborane as an allyl anion equivalent for nucleophilic allylation involving an allyl−ethyl exchange reaction (Scheme 1).

Recently, we demonstrated a similar catalytic system consisting of Pd catalyst and triethylborane or diethylzinc promoted via the amphiphilic allylation of aldimines with allyl anion and allyl cation zwitterion species derived from 2-methylenepropane-1,3-diol to form 3-methylenepyrrolidines in a single manipulation (Scheme 2).[5] Aldimines were exposed to a mixture of 2-methylenepropane-1,3-diols, Pd catalyst, and triethylborane or diethylzinc and underwent [3 + 2] cycloaddition reactions of 1,3-zwitterion species to form the pyrrolidine rings. Triethylborane promoted the amphiphilic

Scheme 2. Amphiphilic Allylation of Aldimines with 2-Methylenepropane-1,3-diols



allylation of bis-allyl alcohols with aldimines to construct the pyrrolidine rings at 50 °C, while diethylzinc promoted a similar cycloaddition reaction with bis-allyl alcohol benzyl ethers to form the same cyclized products at room temperature. The regio- and stereoselectivities using substituted 2-methylenepropane-1,3-diols are in contrast to the results of TMM (trimethylenemethane) chemistry developed by Trost et al.[6] Thus, the amphiphilic allylation is among the most efficient and innovative methods for the synthesis of pyrrolidines in a [3 + 2] cycloaddition manner with 1,3-dipolar equivalent and aldimines.

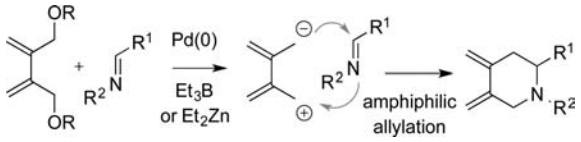
Efficient construction of 6-membered nitrogen-containing heterocyclic compounds is an important and crucial method for modern organic synthesis.[7] In particular, piperidine rings are widely distributed in nature and are useful physiologically active molecules as important building blocks. Piperidine alkaloids are a representative class of the potent biological activity and the broad range of the synthetic strategies, such as intramolecular mannich reaction, olefin metathesis, and biosynthesis, which have been reported.[8]

Herein, we disclose the novel and efficient synthetic methods for the formation of piperidine ring promoted by π-allylpalladium intermadiate (Scheme 3). This is the first example of the amphiphilic allylation of aldimines with bis-allylic moieties via [4 + 2] cycloaddition reaction followed by oxidative treatment with DDQ to construct isoquinoline analogues from 2,3-bismethylenebutane-1,4-diol.

Received: December 15, 2014
Published: January 28, 2015

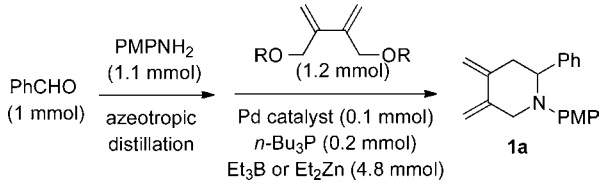
DOI: 10.1021/ol503614d
Org. Lett. 2015, 17, 600−603

Scheme 3. Amphiphilic Allylation of Aldimines with 2,3-Dimethylenebutane-1,4-diols



Initially, we investigated the amphiphilic allylation of aromatic aldimines, which are prepared from benzaldehyde and *p*-anisidine. The results of the amphiphilic allylation with bis-allylating agents, such as bis-allyl alcohol, acetate, and benzyl ether, utilizing triethylborane and diethylzinc as promoters are summarized in Table 1.[9]

Table 1. Pd-Catalyzed Cycloaddition of Aldimine and 1,4-Dipole[a]



entry	R	promoter	catalyst	temp (°C)/ time (h)	yield of **1a** (%)
1	H	Et_3B	$Pd(OAc)_2$	50/72	20
2	Bn	Et_2Zn	$Pd(OAc)_2$	rt/48	25
3	Ac	Et_2Zn	$Pd(OAc)_2$	rt/48	49
4	Ac	Et_2Zn	$PdCl_2(CH_3CN)_2$	rt/48	33
5	Ac	Et_2Zn	$PdCl_2(PPh_3)_2$	rt/48	75

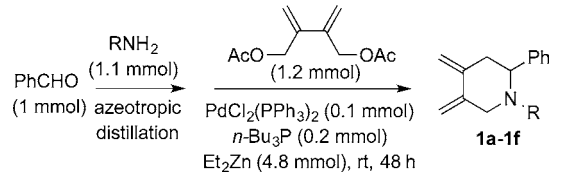
[a]Reaction conditions: *p*-anisidine (1.1 mmol) and PhCHO (1 mmol) in dry THF (1 mL) at reflux for 0.5 h; distillation of THF (azeotropic removal of water) and then Pd (0.1 mmol), *n*-Bu_3P (0.2 mmol), 2,3-bismethylenediol derivatives (1.2 mmol), Et_3B or Et_2Zn (4.8 mmol) in THF (1 mL) under nitrogen atmosphere.

Among these investigations using various kinds of Pd catalysts, promoters, and bis-allylating agents, it turned out that bis-allyl acetate serves as the most reactive 1,4-dipolar precursor in the presence of the $PdCl_2(PPh_3)_2$ catalyst with diethylzinc, although the amphiphilic allylation with 2-methylenebutane-1,3-diol is smoothly undertaken under the conditions of triethylborane.[5] Based on these results of Table 1, we have examined the reactions of wide variety of aldimines prepared from aromatic and aliphatic amines with benzaldehyde (Table 2).

Irrespective of the kinds of substituents of various aromatic amines which possess electron-donating and electron-deficient groups, the desired coupling products **1** were obtained in good to reasonable yields (entries 1−3, Table 2). Aliphatic amines such as benzylamine, *n*-hexylamine, and *c*-hexylamine also served as effective amines to provide the piperidines **1d**-**1f** in high yields (entries 4−6, Table 2). Increasing the nucleophilicity of the amines produced higher yields of cyclized products **1**. These results suggest that amines with a higher electron density enhance the nucleophilicity of π-allylpalladium intermediate for the intramolecular electrophilic allylation process.

Next, we have developed the amphiphilic allylation of aldimines prepared from various aldehydes and aliphatic amines (Table 3). Substituted benzaldehydes could participate in the cycloaddition reaction to form piperidine derivatives (entries 1−3, Table 3). α,β-Unsaturated aldehyde and heteroaromatic

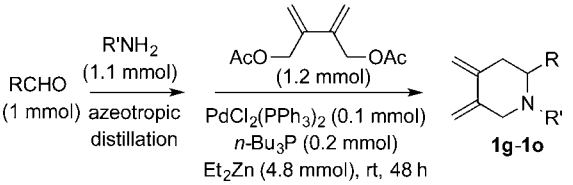
Table 2. Cycloaddition of PhCHO−Aldimine and 1,4-Dipole[a]



entry	amine R	yield of **1** (%)
1	(*p*-MeO)Ph	**1a**: 75
2	(*p*-HO)Ph	**1b**: 64
3	(*p*-Cl)Ph	**1c**: 50
4	CH_2Ph	**1d**: 85
5	*n*-Hex	**1e**: 73
6	*c*-Hex	**1f**: 68

[a]Reaction conditions: amine (1.1 mmol) and PhCHO (1 mmol) in dry THF (1 mL) at reflux for 0.5 h; distillation of THF (azeotropic removal of water) and then Pd (0.1 mmol), *n*-Bu_3P (0.2 mmol), 2,3-bismethylenediol derivatives (1.2 mmol), Et_2Zn (1.2 mmol) in THF (1 mL) at rt for 48 h under nitrogen atmosphere.

Table 3. Cycloaddition of Various Aldimines and 1,4-Dipole[a]



entry	aldehyde R	amine R′	yield of **1** (%)
1	(*p*-Cl)Ph	CH_2Ph	**1g**: 70
2	(*p*-MeO)Ph	CH_2Ph	**1h**: 68
3	(*p*-Me)Ph	CH_2Ph	**1i**: 71
4	$PhCH{=}CH_2$	CH_2Ph	**1j**: 50
5	3-pyridyl	CH_2Ph	**1k**: 51
6	2-furyl	*n*-Hex	**1l**: 80
7	*c*-Hex	CH_2Ph	**1m**: 77
8	*n*-Pent	*n*-Hex	**1n**: 53
9	*n*-Pent	*c*-Hex	**1o**: 51
10	*c*-Hex	*n*-Hex	**1p**: 60
11	*c*-Hex	*c*-Hex	**1q**: 65

[a]Reaction conditions: amine (1.1 mmol), aldehyde (1 mmol) in dry THF (1 mL) at reflux for 0.5 h; distillation of THF (azeotropic removal of water) and then Pd (0.1 mmol), *n*-Bu_3P (0.2 mmol), 2,3-bismethylenediol derivatives (1.2 mmol), Et_2Zn (1.2 mmol) in THF (1 mL) at rt under nitrogen atmosphere.

aldehyde aldimines provided the similar coupling products **1j**−**l** in modest to good yields (entries 4−6, Table 3). Aliphatic aldehyde aldimines were tolerated to the coupling reactions and constructed the 6-membered nitrogen heterocycles (entries 7−11, Table 3). In the presence of triethylborane, in place of diethylzinc, alkylaldehyde aldimine, prepared from *n*-hexanal with *p*-anisidine did not undergo the amphiphilic allylation at all; instead, an intractable mixture was obtained. On the other hand, diethylzinc promoted the expected reaction smoothly giving rise to the desired products **1n**,**o** in reasonable yields (entries 8 and 9, Table 3). In general, although the aldimines prepared from aliphatic amines and aliphatic aldehydes are so unreactive toward nucleohphiles,[4d,10] it is noteworthy that all of the combinations of amines and aldehydes could take part in the coupling reactions (entries 10 and 11, Table 3). Although both the triethylborane

DOI: 10.1021/ol503614d
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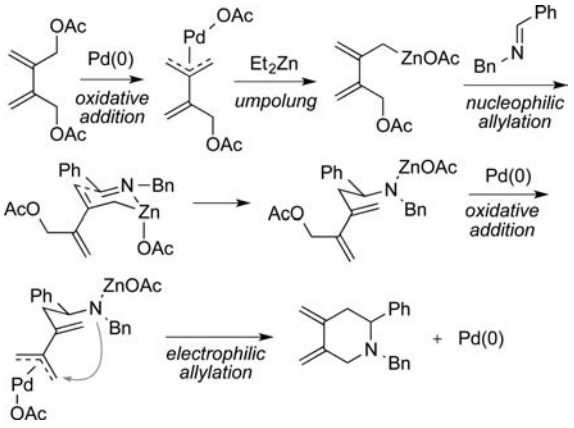
and diethylzinc systems were utilized for the formation of pyrrolidines from the aliphatic aldehyde and aliphatic amine imines, in this case, diethylzinc was superior to triethylborane for the formation of piperidine rings.[5]

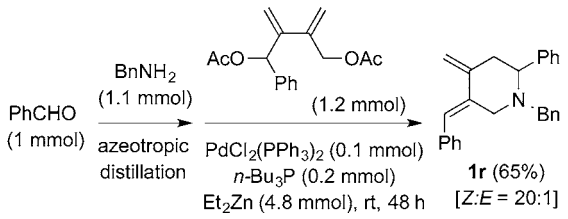
A plausible reaction mechanism is shown in Scheme 4. Oxidative addition of 2,3-bismethylenebutane-1,4-diacetate

Scheme 4. Plausible Reaction Mechanism for Pd/Et_2Zn-Promoted Amphiphilic Allylation of Aldimine



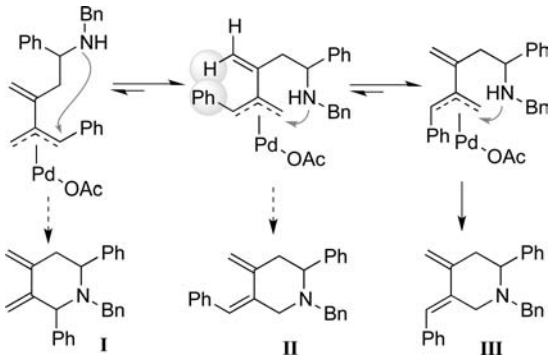
occurred using the Pd(0) catalyst to form the π-allylpalladium intermediate followed by transmetalation with diethylzinc to form the allylic anion species possessing the allylic acetate. This allyl anion species reacted with aldimine and then would construct the homoallylamine skeletons with the allyl acetate group. Furthermore, this intermediate underwent oxidative addition toward Pd catalyst, and the subsequent intramolecular electrophilic allylation formed piperidine rings with the liberation of Pd(0) catalyst. It might be possible that the steric repulsion of β-substituents on π-allylpalladium and the effect of entropy on 6-membered ring formations make the amphiphilic allylation more difficult than that of 5-membered ring formation so that a more reactive leaving group, such as acetate, would be required for the present amphiphilic allylation. In contrast to the results of 5-membered ring formation using triethylborane, the system using diethylzinc might be more expedient for an intramolecular electrophilic allylation process owing to the higher nucleophilicity of zinc amide intermediate.[11] Thus, it can be considered that 2,3-bismethylenebutane-1,4-diacetate serves as a 1,4-ziwitterion equivalent for the formal [4 + 2] cycloaddition reaction with aldimines.

This transformation is applicable to the selective formation of the substituted 3,4-dimethylenepiperidines. α-Phenyl-substituted 2,3-bismethylenebutane-1,4-diacetate in the presence of a Pd catalyst and diethylzinc provided the benzylidene pyrrolidine **1r** as a sole product (eq 1). In this case, the second step of the



electrophilic allylation was particularly suffered from the steric repulsion between Ph group and the vinylic proton, and the less-substituted allylic carbon tends to react with amines to give the Ph-substituted diene moiety with *Z*-stereoselectivity (Scheme 5). This selectivity may originate from the equilibrium among these

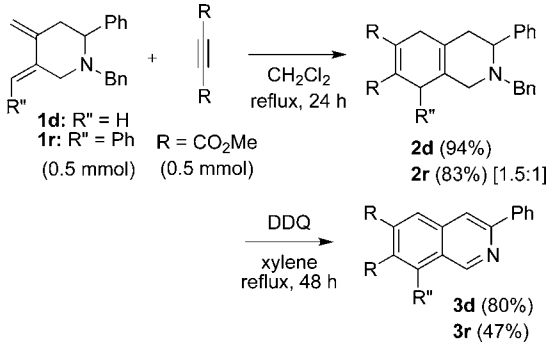
Scheme 5. Mechanism for Pd/Et_2Zn-Promoted Amphiphilic Allylation of Aldimine with Ph-Substituted Dipole



π-allylpalladium complexes, and thermodynamically stable three-substituted alkenes would be formed predominantly through the *anti*-π-allylpalladium intermediate.

Thus, the formed 3,4-bismethylenepiperidines were used for the synthesis of nitrogen-containing heterocyclic compounds. For example, electron-deficient acetylenes, such as acetylenedicarboxylates, underwent the Diels–Alder reaction to produce bicyclic compounds, i.e., hexahydroisoquinolines in high yields (Scheme 6). These heterocyclic compounds were converted into

Scheme 6. Synthesis of Isoquinoline via Diels–Alder reaction with 3,4-Bismethylenepiperidine and Alkyne



the isoquinoline compounds by treatment with DDQ under oxidized conditions via oxidative debenzylation. The structure of isoquinoline **3r** was determined by X-ray analysis.[12] Although some examples of the oxidative debenzylation by DDQ have been reported so far,[13] these application processes are utilized for the efficient synthesis of isoquinoline alkaloid from aldimines and 1,4-bisallyl acetate.

In summary, we have developed the Pd-catalyzed amphiphilic allylation of aldimines with 2,3-bismethylenebutane-1,4-diacetates to form piperidines via formal [4 + 2] cycloaddition. These heterocyclic compounds were converted into isoquinoline derivatives via a Diels–Alder reaction followed by an oxidative reaction with DDQ via the debenzylation process. These procedures could be used for the efficient synthesis of alkaloids and physiologically active molecules.

DOI: 10.1021/ol503614d
Org. Lett. 2015, 17, 600–603

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data of all new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: masanari@nagasaki-u.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Grants-in Aid for Scientific Research (B) (26288052) from the Ministry of Education, Culture, Sports and Technology (MEXT), Japan.

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(12) CCDC-914512 contains the supplementary crystallographic data for **3r**. This 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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DOI: 10.1021/ol503614d
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