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C−N Bond Cleavage of Allylic Amines via Hydrogen Bond Activation with Alcohol Solvents in Pd-Catalyzed Allylic Alkylation of Carbonyl Compounds

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Supporting Information

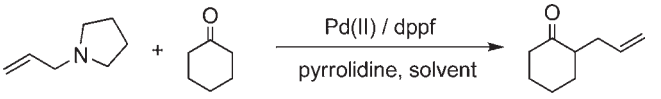
ABSTRACT: Hydrogen-bond-activated C−N bond cleavage of allylic amines was realized in Pd-catalyzed allylic alkylation to form the C−C bond product. The method could be expanded to a series of allylic amines and carbonyl compounds with excellent results. It provides a new and convenient access to C−C bond formation based on Pd-catalyzed allylic alkylation of allylic amines by using only inexpensive alcohol solvents.

Development of new methods for carbon−carbon (C−C) bond formation is a prime topic in organic chemistry. Transition-metal-catalyzed C−C bond-forming reactions have emerged as a powerful synthetic tool in this area.[1] Among these new methods, Pd-catalyzed allylic alkylation (the Tsuji−Trost reaction) has attracted much attention in recent decades, mainly due to its effectiveness in the synthesis of many kinds of valuable organic compounds.[2] Generally, this reaction realizes the formation of a C−C bond via the cleavage of a carbon−oxygen (C−O) bond such as C−OAc or C−OCO_2R.[2,3] In fact, allylic substrates with a good leaving group are indispensable for Pd-catalyzed allylic alkylations.

Carbon−nitrogen (C−N) bonds are common in numerous compounds including allylic molecules. It would therefore be useful if the amino group could be used as a leaving group in Pd-catalyzed allylic alkylation reactions. However, the C−N bond in allylic amines is highly stable, making its cleavage difficult.[4−9] Many efforts have been devoted to resolve this challenge. In the 1980s, Hirao and Yamamoto independently reported Pd-catalyzed allylic alkylation of allylic amines using the allylic ammonium cation as a key intermediate.[4] At the same time, Murahashi reported Pd-catalyzed 3-aza-Cope rearrangement of *N*-allylenamines to produce δ,ε-unsaturated imines with a strong acid as the cocatalyst.[5] An asymmetric version of that reaction was developed by List using a Pd/chiral phosphoric acid catalyst with excellent enantioselectivity.[6] The latter two procedures employed the allylic enammonium cation as a key intermediate to achieve cleavage of the C−N bond of an allylic amine. Recently, Yudin realized the isomerization of allylic amines via C−N bond cleavage with an allylic ammonium cation as an intermediate under the action of acid.[7] Very recently, Trost and Aggarwal adopted a vinyl aziridine to artfully achieve cleavage of the C−N bond of allylic amines by means of minicyclic tension.[8] Tambar just realized this goal in the catalytic enantioselective [2,3]-Meisenheimer rearrangement using nitrogen-oxidized allylic amines.[9] However, a simple and direct method in this area remains a challenge.

We envisioned that the hydrogen bond could simply promote cleavage of the C−N bond of allylic amines. Indeed, a very mild and convenient method was developed for formation of the C−C bond via hydrogen-bond-activated cleavage of the C−N bond of allylic amines in Pd-catalyzed allylic alkylation employing only an alcohol as solvent.

Table 1. Effects of Reaction Conditions on Pd-Catalyzed Allylic Alkylation[a]



entry	temp (°C)	solvent	pK_a[b]	time (h)	yield (%)[c]
1	20	MeOH	15.5	3	95
2	20	EtOH	15.9	4	94
3	20	*n*-PrOH	16.1	6	94
4	20	*i*-PrOH	17.1	24	trace
5	reflux	*i*-PrOH	17.1	2	92
6	20	CF_3CH_2OH	12.4	24	nd
7	20	CF_3CO_2H	0.23	24	nd
8	−20	MeOH	15.5	24	trace
9	0	MeOH	15.5	24	trace
10	40	MeOH	15.5	1	96
11	reflux	MeOH	15.5	1	95
12[d]	20	MeOH	15.5	7 d	36
13[d]	reflux	MeOH	15.5	4	75
14[e]	20	MeOH	15.5	8	94

[a] Reactions of *N*-allylpyrrolidine (0.50 mmol) with cyclohexanone (1.50 mmol) were performed in the presence of pyrrolidine (0.50 mmol) using 6.0 mol% dppf and 2.5 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ in solvent (2 mL). [b] See ref 11. [c] Isolated yields. [d] With a catalytic amount of pyrrolidine (0.15 mmol, 30 mol%). [e] In the presence of 20 mol% CH_3ONa.

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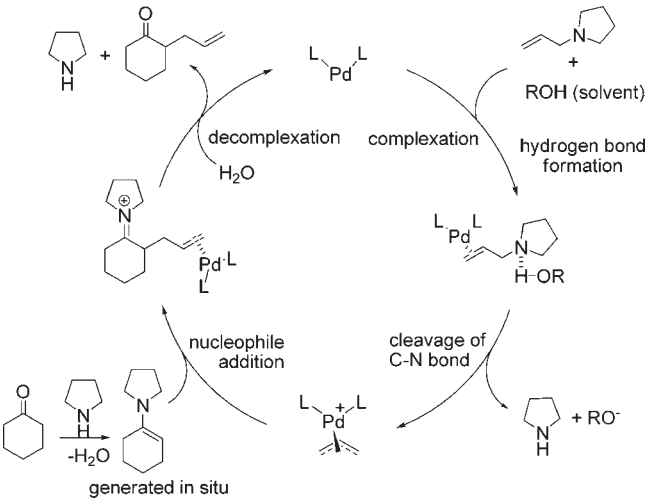
Scheme 1. Plausible Reaction Mechanism

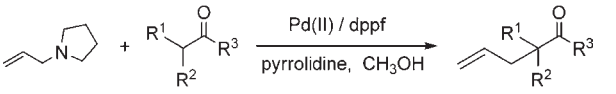


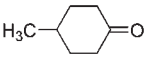
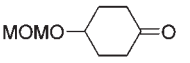
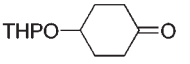
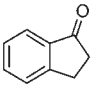
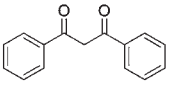
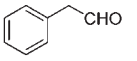
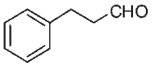
In our previous work, the Pd-catalyzed asymmetric allylic alkylation of ketones and aldehydes via enamines generated in situ as nucleophiles was developed with excellent results.[10] Therefore, we carried out the above reaction using allylic amines instead of allylic acetates. Thus, Pd-catalyzed allylic alkylation of cyclohexanone with *N*-allylpyrrolidine was first investigated using the $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/dppf system as a catalyst in the presence of pyrrolidine (Table 1).

When a protic solvent such as MeOH, EtOH, or *n*-PrOH was used, the reaction proceeded smoothly (entries 1−3).[12] However, only a trace amount of product was obtained with the secondary alcohol *i*-PrOH, probably due to its lower acidity (pK_a 17.1) and larger steric hindrance than the primary alcohol (entry 4). However, the reaction proceeded very well under reflux temperature for 2 h (entry 5). For comparison, CF_3CH_2OH and CF_3CO_2H, with stronger acidity than MeOH, EtOH, and *n*-PrOH, were used as solvents, and no reaction occurred (entries 6 and 7). The above results indicate that solvents had a pivotal effect on this reaction, with MeOH being the best solvent. Temperature also had a significant effect on the reaction. The reactivity was greatly reduced at lower temperatures, and only trace product was obtained below 0 °C, even after 24 h (entries 8 and 9). With the temperature increase from 20 °C to reflux, no further improvement in reaction yield was obtained, even though the reaction was completed within 1 h (entries 10 and 11). The reaction was then carried out with a catalytic amount of pyrrolidine (0.15 mmol, 30 mol%). Only 36% yield was obtained, even after 7 days at room temperature (entry 12). However, it afforded 75% yield under reflux for 4 h (entry 13). A stoichiometric amount of pyrrolidine was used in the following reaction at 20 °C. Finally, the reaction was carried out in the presence of 20 mol% CH_3ONa with the aim to neutralize HCl generated from the palladium precursor.[7a] Almost no different yield was found (entry 14), suggesting that the current reaction system was not affected by a catalytic amount of allylic ammonium cation that possibly formed under the action of HCl.

These results suggested that the presence of a protic solvent is responsible for cleavage of the C−N bond, which further results in formation of a new C−C bond. We therefore proposed a plausible reaction mechanism (Scheme 1) that begins with coordination of the Pd-catalyst to the allyl double bond to form a Pd−olefin complex.

Table 2. Pd-Catalyzed Allylic Alkylation with Different Ketones and Aldehydes[a]



Entry	Ketone/Aldehyde	T (h)	Yield (%)[b]
1		3	95
2		3	95
3		8	93
4		4	90
5		4	93
6		4	88
7		12	92
8		18	97
9[c]		18	79
10[c]		18	73

[a] Reactions of *N*-allylpyrrolidine (0.50 mmol) with ketones (1.50 mmol) were performed in the presence of pyrrolidine (0.50 mmol) using 6.0 mol% dppf and 2.5 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ in MeOH (2 mL) at 20 °C. [b] Isolated yields. [c] 5.0 mmol of aldehyde was used.

At the same time, a hydrogen bond forms between the N-atom of *N*-allylpyrrolidine and the H-atom of the alcohol solvent. The C−N bond of the *N*-allylpyrrolidine is thus activated by this hydrogen bond action, resulting in cleavage of the C−N bond and subsequent formation of a stable intermediate Pd−allylic complex. The complex is then attacked by the enamine generated in situ, followed by removal of the Pd-catalyst to give the C−C bond product.

To further clarify the role of methanol in hydrogen bond participation, the reactions of cyclohexanone with *N*-allylpyrrolidine were carried out in methanol and methanol-*d*, and 48% and 77% conversions were afforded after 0.5 h, respectively.[13] The deuterium bond of methanol-*d* is stronger than the hydrogen bond of methanol.[14] Therefore, the obviously different reaction rates might be due to the difference in bond strength between N···H and N···D. The existence of the hydrogen bond further explains why the acidity of the alcohol solvents has a key effect on the reaction. The weaker acidity of *i*-PrOH combined with larger steric hindrance results in weaker hydrogen bonding, and thus cleavage of the C−N bond becomes more difficult. CF_3CH_2OH

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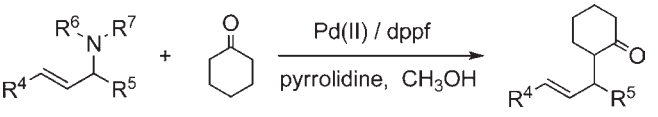
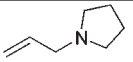
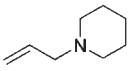
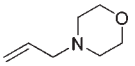
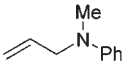
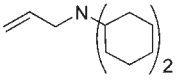
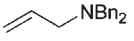
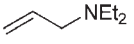
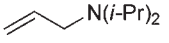
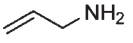
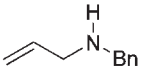
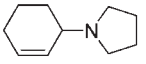
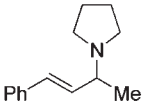
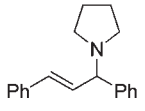
Table 3. Pd-Catalyzed Allylic Alkylation with Different Allylic Amines[a]



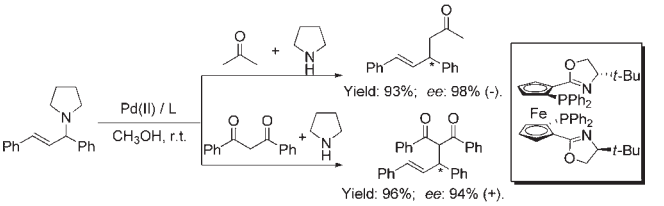
Entry	Allylamine	T (h)	Yield (%)[b]
1		3	95
2		8	92
3		8	91
4		12	88
5		12	78
6		12	90
7		12	93
8		12	83
9		4	94
10		4	92
11		12	96
12		12	95
13		12	95

[a] Reactions of allylic amines (0.50 mmol) with cyclohexanone (1.50 mmol) were performed in the presence of pyrrolidine (0.50 mmol) using 6.0 mol% dppf and 2.5 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ in MeOH (2 mL) at 20 °C. [b] Isolated yields.

and CF_3CO_2H with stronger acidity should show stronger hydrogen bond activity with the N-atom of the allylic amine, or perhaps could protonate the N-atom of the allylic amine. However, we have proved that the iminium ion rather than the enamine was formed from the ketone and pyrrolidine in these two solvents.[13] The iminium ion has no nucleophilicity; therefore, no reaction occurred with these solvents.

This Pd-catalyzed allylic alkylation could be expanded to a series of ketones. As shown in Table 2, the reactions with aliphatic ketones proceeded smoothly with high yields (entries 1−6). The size of cyclic ketone had an obvious effect on the reaction rate, as illustrated by cycloheptanone, which required more than twice as long to complete the reaction (entries 1−3).

Scheme 2. Preliminary Attempt at Pd-Catalyzed Asymmetric Allylic Alkylation[a]



[a] Reactions of *N*-(1,3-diphenyl-2-propenyl)pyrrolidine (0.50 mmol) with ketones (5.0 mmol) were performed in the presence of pyrrolidine (0.50 mmol) using 6.0 mol% chiral ferrocene-based phosphinooxazoline ligand and 2.5 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ in MeOH (2 mL) at 20 °C for 24 h.

It is worth noting that ketones with acid-labile groups could proceed well in our catalytic system (entries 5 and 6). As for aromatic ketones, both a monoketone and a diketone afforded high yields (entries 7 and 8). Furthermore, in order to expand the scope of nucleophiles, phenyl acetaldehyde and phenylpropyl aldehyde were also used in the reaction and afforded yields of 79% and 73%, respectively, after 18 h (entries 9 and 10). These results showed that both ketones and aldehydes could act as efficient nucleophiles directly, while aliphatic ketones showed higher reaction activity than aromatic ketones and aldehydes.

We also examined several kinds of allylic amines (Table 3). The reactions of *N*-allylic cyclic amines with cyclohexanone proceeded smoothly with high reaction activities and yields (entries 1−3). Aliphatic and aromatic *N*-allylic acyclic amines also afforded excellent results with somewhat lower reaction activities (entries 4−8). Furthermore, primary and secondary allylic amines were used here and afforded excellent results (entries 9 and 10). This showed that the present reaction system is suitable for primary, secondary, and tertiary allylic amines. In addition, excellent yields were also afforded for *N*-(cyclohex-2-enyl)pyrrolidine, (4-phenylbut-3-en-2-yl)pyrrolidine, and *N*-(1,3-diphenyl-2-propenyl)pyrrolidine with substituted allyl group (entries 11−13). It should be noted that the *N*-allylic cyclic amines with greater steric hindrance showed slower reaction rates than those with less steric hindrance (entries 1, 11−13).

Finally, we carried out a preliminary attempt at Pd-catalyzed asymmetric allylic alkylation of *N*-(1,3-diphenyl-2-propenyl) pyrrolidine with either acetone or 1,3-diphenylpropane-1,3-dione (Scheme 2). We obtained high yields and excellent enantioselectivities, with up to 98% ee, by using a chiral ferrocene-based phosphinooxazoline ligand.[15]

In summary, we have developed a new method for cleavage of the C−N bond of allylic amines via hydrogen-bond-activation with alcohol solvents in Pd-catalyzed allylic alkylation of carbonyl compounds to form C−C bond products. The method could be expanded to a series of allylic amines including primary, secondary, and tertiary species and carbonyl compounds, including those with acid-labile groups, with excellent results. A preliminary attempt at Pd-catalyzed asymmetric allylic alkylation of *N*-(1,3-diphenyl-2-propenyl)pyrrolidine with ketone was carried out and gave high yield and excellent enantioselectivity.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, compound characterization, HPLC spectra, and NMR spectra.

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