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PALLADIUM(0)-CATALYZED AMINO-HECK REACTION OF γ,δ-UNSATURATED KETONE *N*,*N*,*N*-TRIMETHYLHYDRAZONIUM SALTS

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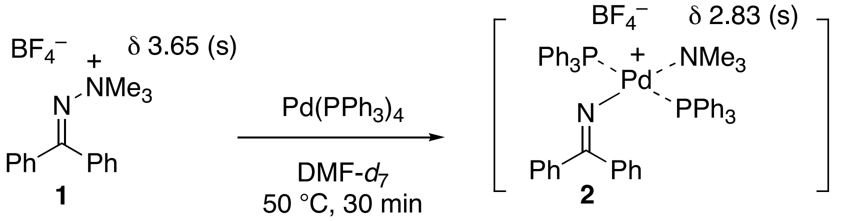
Abstract – Oxidative addition of *N*,*N*,*N*-trialkylhydrazonium salts takes place to a palladium(0) complex, resulting the formation of alkylideneaminopalladium(II) species. This N–N bond scission process is applied to the transformation of γ,δ-unsaturated ketone hydrazonium salts to pyrroles by amino-Heck reaction.

Recently, we reported that N–O bonds of oxime derivatives is cleaved by the oxidative addition to Pd(0) complexes to generate alkylideneaminopalladium(II) species.[1,2] When olefinic *O*-pentafluorobenzoyl-oximes are treated with a catalytic amount of $Pd(PPh_3)_4$ in the presence of Et_3N, Mizoroki-Heck-type cyclization (amino-Heck reaction) proceeds *via* the amino-palladium intermediates, affording various azaarenes such as pyrroles,[2a,b] pyridines,[2c] isoquinolines,[2c] spiroimines,[2d,e] and azaazulenes.[2f,g]

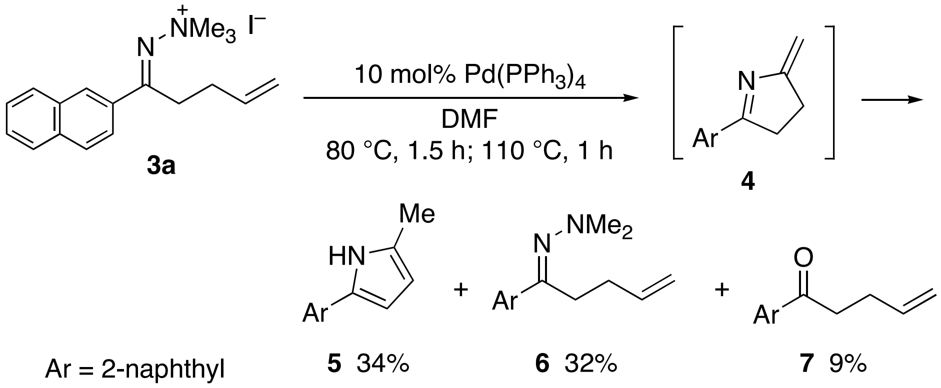
Concerning of N–N bond cleavage with transition metal complexes, the oxidative addition of azines to metal complexes has been reported, whereas there has been no example on the oxidative addition of hydrazone or hydrazonium salt to our knowledge.[3] We expected that *N*,*N*,*N*-trialkylhydrazonium salt would react with Pd(0) complexes like oxime derivative because trialkylammonio group is regarded as a leaving group.[4]

First, we monitored the reaction of 2-diphenylmethylene-1,1,1-trimethylhydrazonium tetrafluoroborate (**1**)[5] with an equimolar amount of $Pd(PPh_3)_4$ in DMF-d_7 by ^1H NMR spectrum (eq. 1). After 0.5 h at 50 °C, the singlet peak of methyl groups of **1** at 3.65 ppm disappeared and a new singlet peak was observed at 2.83 ppm. The methyl groups of $Me_3N•HCl$, $PdCl_2(NMe_3)_2$, and trimethylamine are observed at 2.83 ppm ($CDCl_3$, DMSO-d_6),[6] 2.58 ppm (CCl_4),[7] and 2.12 ppm (CCl_4),[8] respectively. Accordingly, it was suggested that the N–N bond of hydrazonium salt (**1**) was cleaved to form alkylideneaminopalladium species (**2**) coordinated with Me_3N.



(1)

Then, the catalytic amino-Heck cyclization[1] was tried by treating γ,δ-unsaturated ketone hydrazonium iodide (**3a**) with a catalytic amount of $Pd(PPh_3)_4$ in DMF (eq. 2). The reaction did not proceed at 80 °C, while hydrazonium salt (**3a**) was consumed after 1 h at 110 °C to give pyrrole (**5**) in 34% yield, which was the isomerization product of the initially formed methylidenedihydropyrrole (**4**), along with dimethylhydrazone (**6**) (32%) and ketone (**7**) (9%).

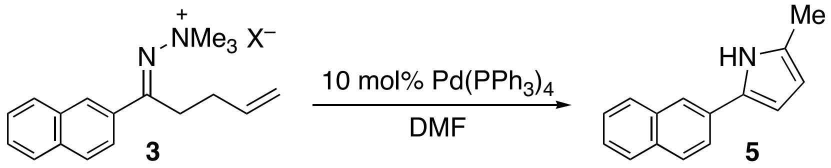


(2)

Hydrazone (**6**) was formed presumably by demethylation by the attack of iodide anion. To prevent this side reaction, hydrazonium salts (**3**) having other counter anions[5] were subjected to the amino-Heck reaction (Table 1). In the reaction of **3b** ($X^- = p\text{-}MeC_6H_4SO_3^-$) at 110 °C, the yield of pyrrole **5** increased to 48% (run 2). The reaction of **3c** ($X^- = BF_4^-$) was completed at 80 °C to afford **5** in 81% yield (run 3). In the case of hydrazonium hexafluorophosphate (**3d**), pyrrole (**5**) was obtained in 69% yield at 80 °C (run 4), and the yield was increased up to 85% by performing the reaction in *N,N*-dimethylacetamide (DMA) at 120 °C (run 5). Thus, hydrazonium salts having the counter anions with low nucleophilicity are favorable for the cyclization, probably due to 1) the suppression of the demethylation of hydrazonium salts and 2) the acceleration of the olefinic part insertion to the more cationic alkylideneaminopalladium(II) complexes.[9]

Furthermore, we investigated the effect of ligands, and PPh_3 was found to be suitable for the reaction among PPh_3, P(*c*-Hex)$_3$, P(*t*-Bu)$_3$, $P[3,5\text{-}(CF_3)_2C_6H_3]$, and $Ph_2P(CH_2)_4PPh_2$.

Table 1. Effect of Counter Anions

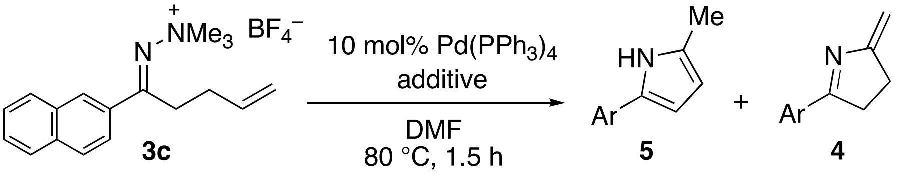


run	X^-	3	conditions	yield/%
1	I^-	**3a**	80 °C, 1.5 h; 110 °C, 1.0 h	34
2	p-$MeC_6H_4SO_3^-$	**3b**[a]	80 °C, 0.5 h; 110 °C, 1.5 h	48
3	BF_4^-	**3c**	80 °C, 1.5 h	81
4	PF_6^-	**3d**	80 °C, 1.5 h	69
5[b]	PF_6^-	**3d**	120 °C, 1.0 h	85

a) Prepared by the reaction of **3a** with p-$MeC_6H_4SO_3Ag$ and the succesive removal of AgI.
b) *N*,*N*-Dimethylacetamide (DMA) was used as solvent.

Although Heck reaction is performed in the presence of bases, no base was added to the present amino-Heck reaction because trimethylamine was formed during the course of the reaction. Then the influence of bases was examined (Table 2). Addition of Et_3N considerably disturbed the reaction (run 2), whereas bulkier i-Pr_2NEt did not interfere the reaction (run 3). Methyl transfer from hydrazonium salt (**3c**) to Et_3N may be the main reason of the low yield. Interestingly, addition of MS 4A prevented the preliminary cyclization product (**4**) from the isomerization to pyrrole (**5**), yielding methylidene-dihydropyrrole (**4**) as a major product (run 4). The abstraction of the generating acid with molecular sieve reduced the isomerization of **4**.

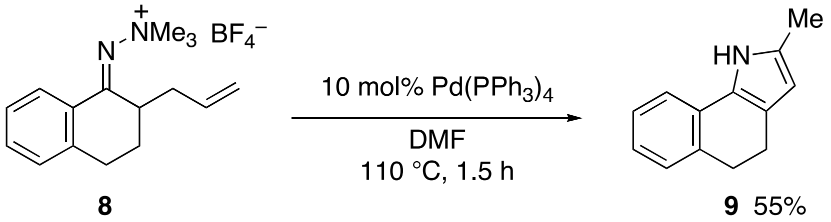
Table 2 Effect of Additives



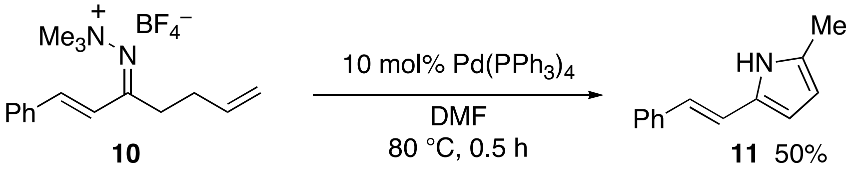
Ar = 2-naphthyl

run	additive (mol amt.)	**5**	**4**
1	none	81%	–
2	Et_3N (3.0)	18%	–
3	i-Pr_2NEt (3.0)	77%	–
4	MS 4A (4.0 wt/wt)	5%[a]	61%

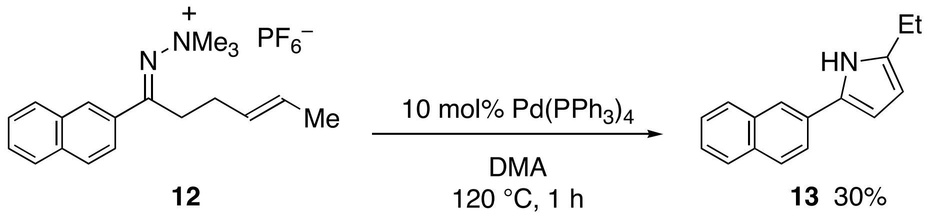
As shown in eqs. 3-5, some aryl ketones and α,β-unsaturated ketone hydrazonium salts were transformed to substituted pyrroles by the present amino-Heck reaction. Internal olefin was found to be less reactive than terminal olefin (eq. 5).



(3)



(4)



(5)

N,*N*-Dimethylhydrazones are widely employed as carbonyl equivalents in organic synthesis, particularly as aza-enolate. It has been hardly used hydrazones as nitrogen sources except hydrogenation to amino group due to the difficulty in the N-N bond cleavage.[10] The presented process would provide a possibility that hydrazone moiety can be used not only as a carbonyl equivalent but also as imino moiety. The reaction of alkyl ketone hydrazonium salts was not examined yet, since these salts are susceptible to be hydrolyzed. Efficient preparative method of alkyl ketone hydrazonium salts is now under investigation.

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