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Pd-Catalyzed Regioselective Allylation of Mono- and Disubstituted Hydrazines

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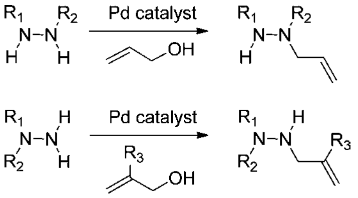
ABSTRACT



Palladium-catalyzed allylation of hydrazines using allyl alcohols is reported. This highly efficient protocol furnishes monoallylated hydrazines selectively, in 27−99% yields. Following an optimization of the reaction conditions and of the Pd-ligands, the allylations of both mono- and disubstituted hydrazines were investigated, as well as the effects of C2-substitution on the allylating agent. Of particular interest, a novel method for the selective monoallylation of monosubstituted hydrazines is demonstrated.

Hydrazine compounds are of particular interest due to their applicability: many of them show remarkable biological activity.[1] In addition, hydrazine derivatives are used as dyes and building blocks in organic synthesis.[2] However, the alkylation of hydrazines, and allylation in particular are not easy tasks, as selectivity and overallylation are endemic problems. Several methods of direct selective alkylation of mono- and disubstituted hydrazines exist;[3] however, selective monoalkylation of monosubstituted hydrazines is still challenging because of competitive dialkylation.

The synthesis of 1,2-disubstituted hydrazines bearing one or more alkyl groups is generally achieved by the condensation of monosubstituted hydrazines with aldehydes or ketones and the subsequent reduction of the obtained hydrazones.[4] There are few literature reports on the addition of Grignard reagents to monosubstituted azocompounds[5] or of electrophilic amination.[6] An orthogonal protective group strategy could be applied as well, but would involve numerous additional protection/deprotection steps.[7] To the best of our knowledge, only two reports of catalytic allylation of monosubstituted hydrazines exist. Sterically encumbered allyl carbonates or dienes are used in Ir or Pd catalysis to obtain 1,2-disubstituted or trisubstituted hydrazines.[8]

Inspired by amine allylation by alcohols,[9] it was decided to develop a new method to perform similar allylation on hydrazines. Transition metal catalyzed reactions with hydrazines remain widely unexplored, hence the novelty of this approach. Additionally, this allylation method does not require derivatization of the allyl alcohols prior to allylation, which makes it highly atom efficient. In this study, the use of different ligands on palladium, allyl

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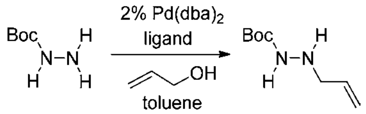
alcohols, and hydrazines was studied along with an optimization of the reaction conditions.

A test reaction was initially set up with a 1,2-disubstituted hydrazine (BocNHNHPh), allyl alcohol (10 equiv), and Pd[P(OPh)$_3$]$_4$ (5 mol %) in toluene at 80 °C, which resulted in the monoallylation of the phenyl-bearing nitrogen. This indicates that the presence of a carbamate-type protecting group prevents the allylation of the protected nitrogen due to the steric hindrance and the electron-withdrawing character of that group. Therefore, the number of possible products of the allylation reaction of BocNHNH$_2$ is theoretically limited to two: BocNHNHAll and BocNHN(All)$_2$. As such, the study was focused on allylation of monosubstituted hydrazines. *Tert*-butyl carbazate and unsubstituted allyl alcohol were chosen as model substrates, as they are cheap, nontoxic, and easily accessible.

Table 1. Optimization of Reaction Conditions and Catalytic System



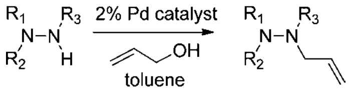
entry	ligand, equiv to Pd	hydrazine (equiv)	temp (°C)	time (days)	yield (%)[a]
1	P(OPh)$_3$, 4	1	80	1	34
2	P(OPh)$_3$, 4	1.2	80	1	45
3	P(OPh)$_3$, 4	1.5	80	1	49
4	P(OPh)$_3$, 4	2	80	1	57
5	P(OPh)$_3$, 4	1.2	55	1	44
6	P(OPh)$_3$, 4	1.5	55	1	50
7	P(OPh)$_3$, 4	2	23	1	-
8	PPh$_3$, 4[b]	2	55	1	-
9	P(Ph(OMe)$_3$)$_3$, 4	2	55	1	trace
10	XPhos, 2[c]	1.5	55	2	40
11	XPhos, 2[c]	2	55	1	47
12	XPhos, 2[c]	2	23	1	-
13	BrettPhos, 2[c]	2	55	2	52
14	dppf, 2	2	55	2	trace
15	dppf, 1	2	55	1	29
16	P(OPh)$_3$, 2; dppf, 1	2	55	1	71

[a] Isolated yields. [b] Pd(PPh$_3$)$_4$ was used as catalyst. [c] Pd(OAc)$_2$ was used.

As can be seen in Table 1, the reaction showed some degree of sensitivity to the equivalents of hydrazine employed, with the yield increasing from 34 to 57% (entries 1–4) by doubling its amount in relation to the allylating partner. In comparison to the reaction at 80 °C, a decrease of the temperature to 55 °C had no effect on the yields (entries 2,3 and 5,6); however, room temperature proved insufficient for the reaction to proceed (entry 7).

Having found optimal reaction conditions, a library of phosphine ligands were screened against the test compounds. The highly electron-donating triphenylphosphine failed to offer any conversion (entry 8), as well as the electron-poor tris(2,4,6-trimethoxyphenyl) phosphane (entry 9). It can be expected that an increase of the bulkiness of the ligands may lead to an improvement in selectivity toward the monoallylated product; therefore, more sterically hindered ligands were screened. Though no starting material was observed after employing XPhos in the reaction, a significant amount of the diallylated product was detected. When using XPhos, the overall yield was slightly lower than with Pd[P(OPh)$_3$]$_4$ (entries 10–12). A parent ligand, BrettPhos, gave a better mono-/diallylated ratio, but at the expense of a slower rate of the reaction (entry 13). Finally dppf was screened both alone and in combination with triphenyl phosphite. Two dppf ligands resulted in only trace amounts of product, presumably due to strong coordination of the ligand and saturation of the Pd coordination sphere (entry 14). For a single equivalent of dppf, the catalyst was unstable and black palladium quickly precipitated from the reaction mixture, hence the poor yield (entry 15). However, a combination of 1 equiv of the selective dppf with 2 equiv of P(OPh)$_3$ (which gave the fastest turnover) resulted in a 71% yield.

Table 2. Allylation of Mono- and Disubstituted Hydrazines

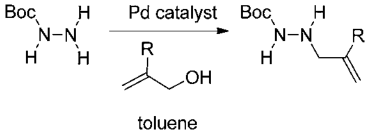


entry[a]	compd	hydrazine	yield (%)[b]
1	**1a**	BocNHNH$_2$	71
2	**2**	CbzNHNH$_2$	64
3	**3**	PhNHNH$_2$	53[c]
4	–	FmocNHNH$_2$	–[d]
5	–	TsNHNH$_2$	–[d]
6	–	PhthNNH$_2$	–[d]
7	**4**	Boc$_2$NNH$_2$	71
8	**5**	PhNHNHBoc	99[e]
9	**6**	EtNHNHBoc	77[e]
10	**7**	FmocNHNH*i*-Pr	27[e]

[a] Reaction conditions: 2% of Pd(dba)$_2$, 2% of dppf, 4% of P(OPh)$_3$, 2 equiv of hydrazine. [b] Isolated yields. [c] Yield of the corresponding hydrazone. [d] Hydrazine was insoluble in toluene under reaction conditions. [e] Pd(dba)$_2$ and 4 equiv P(OPh)$_3$ were used as catalysts.

With the optimized reaction conditions and the catalytic system in hand, a library of substituted hydrazines were used to test the scope of this method (Table 2). Boc proved to be the optimal protecting group and Cbz, with its similar size, provided a similar yield (entry 2). Phenyl monosubstitution made for a poorer substrate, likely due to the rapid and unselective oxidation of the generated product in air, to form 1-allylidene-2-phenylhydrazine. Decomposition of the hydrazone in an NMR tube was suppressed by employing d_8-THF under argon which allowed the confirmation of its structure. Entries 4–6 gave no conversion as the starting hydrazines were insoluble in the reaction media. An attempt to conduct the reaction in refluxing CH$_2$Cl$_2$ was made, but it afforded an unstable catalytic system and no product was formed.

Table 3. Allylation with Substituted Alcohols



entry	compd	Pd (%)[a]	$BocNHNH_2$ (equiv)	R	yield (%)[b]
1	**1a**	2	2	H	71
2	**1b**	2	2	Bn	71
3	**1c**	2	2	*n*-Pe	72
4	**1d**	2	2	*i*-Pr	70
5	**1e**	5	1.5	4-anisyl	78
6	**1f**	5	1.5	Ph	52
7	**1f**	5	2	Ph	74
8	**1g**	5	1.5	4-tolyl	60

[a] $Pd(dba)_2/dppf/P(OPh)_3$ 1:1:2. [b] Isolated yield.

The best result (99% yield) was obtained for entry 8, since diallylation was unlikely to proceed (in accordance with the initial test results). This shows the versatility of this methodology which allows the allylation of both mono- and disubstituted hydrazines. It is known from previous experience[10] that EtNHNHBoc is more reactive and more likely to give rise to byproducts. Indeed, some side products were observed by TLC, which explains the decrease of the yield to 77% (entry 9). Finally, much as in the case of its parent compound (entry 4), poor solubility prevented the azo-Valine precursor from reaching a high yield (entry 10). The aforementioned cases show that the general course of the reaction is strongly influenced by the solubility of the starting hydrazine.

The scope of the reaction was further studied by probing the effect of substitution on the allyl alcohol.

As can be seen in Table 3, the reaction proceeded efficiently and resulted in very similar yields to that of the unsubstituted allyl alcohol (entry 1) and for all the alkyl substituted alcohols regardless of sterics (entries 2–4). Greater differences in yields were obtained between the aromatic compounds. Generally the reactions with aromatic alcohols proceeded more slowly than with aliphatic alcohols; therefore, a higher catalytic loading was necessary. On the other hand, the same level of selectivity was achieved with fewer equivalents of hydrazine. The electron-donating *para*-methoxyphenyl substituent on allyl alcohol afforded the product in the highest yield (78%) owing to its high selectivity (entry 5). The other aromatic allyl alcohols gave slightly lower yields (entries 6, 8). However using 2 equiv of hydrazine instead of 1.5 equiv resulted in a significant yield increase (entry 7).

In conclusion, a new method for the selective monoallylation of monosubstituted hydrazines has been developed. Its scope was tested for different hydrazines and allyl alcohols. Up to a 99% yield was obtained when allylating the substituted hydrazines. The limitations of the method were tested, and the solubility of the starting material seems to be its current main impediment.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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