Palladium Catalyzed Alkylation with Allylic Acetates under Neutral Conditions

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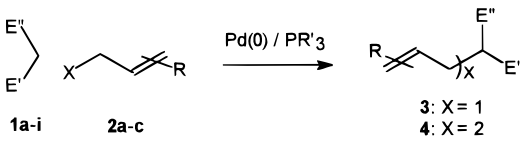
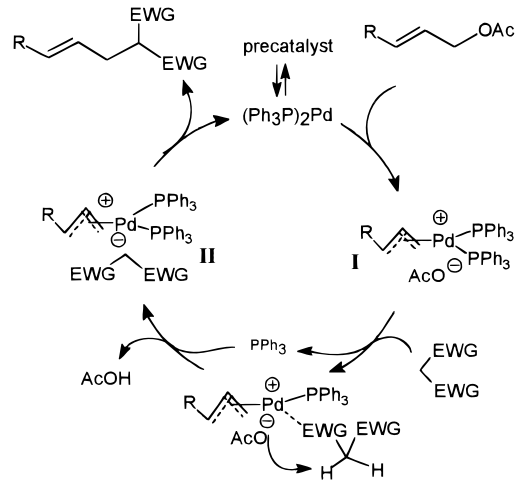
The palladium catalyzed allylic alkylation of soft nucleophiles represents one of the most useful organic transformations.[1] During our recent studies in palladium-catalyzed intramolecular allylic alkylations of activated carboxamides,[2] we noticed that small amounts of cyclization product could be intriguingly attained even in the absence of the enolizating system BSA/AcOK (cat.).[3] In order to shed light on this intriguing result, we decided to examine simple intermolecular reactions either in the presence of BSA/AcOK cat. (method A) or under base-free conditions (method B) (Scheme 1).[4]

When methyl nitroacetate was added to cinnamyl acetate the allylic alkylation proceeded only under base-free conditions (Table 1,[5] entries 1−3). A similar trend was observed in the addition of sulfonyl nitromethane to cinnamyl acetate (entries 6 and 7). When bis(phenylsulfonyl)methane was reacted with cinnamyl acetate or geranyl acetate, adducts **3ca** or **3cb** were respectively obtained with either method (entries 8−11). Methyl (phenylsulfonyl)acetate and ethyl acetoacetate behaved analogously (entries 14−17). Malononitrile afforded exclusively the diallylated adduct **4fa** with method A, whereas base-free conditions gave the monoallylated product **3fa** as the only new product (entries 18 and 19). High proportions, or even exclusive formation, of the diallylated adduct were also obtained with Meldrum's acid and barbituric acid under base-free conditions (entries 20−23). The condensation between the less acidic diethyl malonate and cinnamyl acetate took place only in the presence of the BSA/AcOK catalytic system (entries 24 and 25). The results of Table 1 suggest that the success of this new method can be reasonably accounted for by assuming that the leaving group displaced from the allylic system is capable of acting as the deprotonating species. Such an event

Scheme 1



Scheme 2



has ample precedents with allylic carbonates,[6] phenoxides,[7] and oxiranes,[8] since the pK_a values of the alcoholic species generated therefrom, i.e., of the conjugated acid of the displaced group, are unequivocally much higher than those of the active methylenes. On the other hand, a similar reasoning cannot be applied to allylic acetates.

The addition of 1 mol equiv of n-$Bu_4N^+AcO^-$ to a $CDCl_3$ solution of the disulfone **1c** or ethyl acetoacetate caused the immediate and total disappearance of their respective methylene singlets in the ^1H NMR spectra. When the same experiment was repeated with the less acidic diethyl malonate, such an effect was totally absent. This result suggests that the acetate anion can readily engage in deprotonation substrates of suitable pK_a value to give rapidly equilibrating species. The reaction appears also to be dramatically dependent on the nature of the phosphine used. Thus, when a bis-coordinating phosphine such as BINAP[9] or DPPE was used instead of PPh_3 as the ancillary ligand, the reaction between methyl nitroacetate and the acetate **2a** resulted seriously or totally inhibited, respectively (entries 4 and 5). The results so far obtained may be well rationalized according to the mechanistic path shown in Scheme 2.

Oxidative addition of $(Ph_3P)_2Pd(0)$ onto the allylic acetate generates first a cationic π-allyl palladium complex. Counterion exchange between the acetate and the nucleophile anion at the π-allyl palladium complex (**I** → **II**, Scheme 2) can then take place.[10] The above-mentioned inhibition by BINAP or DPPE suggests that such a process may pass through competitive coordination at the metal center between the nucleophiles and the phosphines, at least for those

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Table 1. BSA/AcOK Cat. Promoted and Base-Free Palladium-Catalyzed Allylic Alkylation of Active Methylenes[a]

Entry	pKa[b]	Nu		E		Solv.	Time (h)	Method	Prod.	3 : 4 ratio[c]	3 (%)[d]	4 (%)[d, e]
1	5.6 (H2O)	O_2N⟋CO_2Me	1a	cinnamyl acetate	2a	THF	6	A	-	-	-	-
2	8.0 (DMSO)	"		"	2a	THF	0.40	B	3aa	100 : 0	80	-
3		"		"	2a	CH_2Cl_2	0.25	B	3aa	100 : 0	82	-
4[f]		"		"	2a	CH_2Cl_2	20	B	3aa	100 : 0	8	-
5[g]		"		"	2a	CH_2Cl_2	19	B	-	-	-	-
6	7.1 (DMSO)	O_2N⟋SO_2Ph	1b	"	2a	THF	3	A	3ba	-	-	-
7		"		"	2a	THF	0.75	B	3ba 4ba	80 : 20	64	13
8	12.2 (DMSO)	PhO_2S⟋SO_2Ph	1c	"	2a	THF	12	A	3ca	100 : 0	73	-
9		"		"	2a	$Cl(CH_2)_2Cl$	12	B	3ca	100 : 0	95[h]	-
10				geranyl acetate	2b	THF	12	A	3cb	100 : 0	80	-
11				"	2b	$Cl(CH_2)_2Cl$	12	B	3cb	100 : 0	80	-
12				cinnamyl chloride	2c	THF	6.5	A	3ca	100 : 0	30	-
13				"	2c	$Cl(CH_2)_2Cl$	12	B	-	-[i]	-	-
14	14.0 (DMSO)	PhO_2S⟋CO_2Me	1d	cinnamyl acetate	2a	THF	9	A	3da	100 : 0	66	-
15		"		"	2a	CH_2Cl_2	30	B	3da	100 : 0	58	-
16	14.2 (DMSO)	$MeOC$⟋CO_2Et	1e	"	2a	THF	6	A	3ea	100 : 0	78	-
17		"		"	2a	CH_2Cl_2	11	B	3ea	100 : 0	69	-
18	11.0 (DMSO)	NC⟋CN	1f	"	2a	THF	12	A	4fa	0 : 100	-	38
19		"		"	2a	$Cl(CH_2)_2Cl$	12	B	3fa	100 : 0	65	-
20	7.3 (DMSO)	meldrum's acid	1g	"	2a	THF	0.5	A	-[j]	-	-	-
21		"		"	2a	CH_2Cl_2	0.5	B	4ga	0 : 100	-	43
22	8.4 (DMSO)	barbituric acid	1h	"	2a	THF	0.25	A	4ha	≤5 : ≥ 95	-	37
23		"		"	2a	CH_2Cl_2	0.25	B	4ha	≤ 5 : ≥ 95	-	37
24	16.4 (DMSO)	EtO_2C⟋CO_2Et	1i	"	2a	THF	4.5	A	3ia	100 : 0	83	-
25		"		"	2a	CH_2Cl_2	5	B	-	-	-	-

[a] Unless otherwise specified, the reactions were run at reflux of the solvent using a 1.2 nucleophile:acetate ratio. The following catalytic systems have been used: $Pd_2(dba)_3$ (0.05 equiv), PPh_3 (0.5 equiv) (experiments 1−5, 8−13, 18, 19, 24, 25), or $Pd(PPh_3)_4$ (0.07 equiv), PPh_3 (0.07 equiv) (experiments 6, 7, 14−17, 20−23). [b] For the source of tabulated pK_a values see ref 5. [c] The product ratios are based on the ^{1}H NMR spectra of the crude reaction mixtures. [d] Yields of isolated products. [e] Since the calculation is based on the reacted acetate, a theoretical yield of 50% has to be considered. [f] Racemic BINAP (0.25 equiv) was used as the phosphine. [g] 1,2-Bis(diphenylphosphino)ethane (0.25 equiv) was used as the phosphine. [h] Spectroscopic yield. [i] Allylic scrambling of the chloride was observed. [j] In this case, the initially generated adducts suffered BSA addition at the carboxyl function and subsequent monodecarboxylation to give a 90:10 mixture of $MeCONHCOCH(CH_2CH{=}CHPh)_2$ (41%) and $MeCONHCOCH(CH{=}CH_2)Ph$ (4.5%).

active methylenes having suitably coordinating Lewis bases.[11] Finally, ligand−ligand coupling[12] drives to the right side the preceding equilibria.

Two corollary experiments lent further support to this mechanistic rationale. Thus, when bis(phenylsulfonyl)-methane was reacted with cinnamyl chloride in the presence or in the absence of BSA/AcOK cat., only the former conditions gave successful allylic alkylation (entries 12 and 13). This indicates that the more coordinating and less basic chloride anion, in contrast to acetate anion,[13] is not capable of deprotonating the nucleophile.

In conclusion, this paper has disclosed that Pd(0)-catalyzed allylic alkylations under neutral conditions are not limited to allylic carbonates, phenates, or epoxides but also can be extended in many cases to the more popular allylic acetates. These results show that many experiments, previously conducted in the presence of bases, can be more simply performed in high yields via *direct palladation*, saving the use of an added base.[14] Such a variant does not consist in the bare omission of a reagent in the reaction protocol but implies the operation of a new mechanism where the templating palladium center holds the allyl and the anionic ligand at the same time.[15] Studies are underway to extend the reaction to other nucleophilic and electrophilic partners, as well as to study in more detail the mechanistic features of such a new method.

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Supporting Information Available: Experimental procedures and spectral data of all new compounds. ^{1}H NMR spectra relative to the interaction between n-$Bu_4N^+AcO^-$ and the carbon acids (20 pages).

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