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Palladium-catalyzed hydrocarbonation of methyleneaziridines with carbon pronucleophiles

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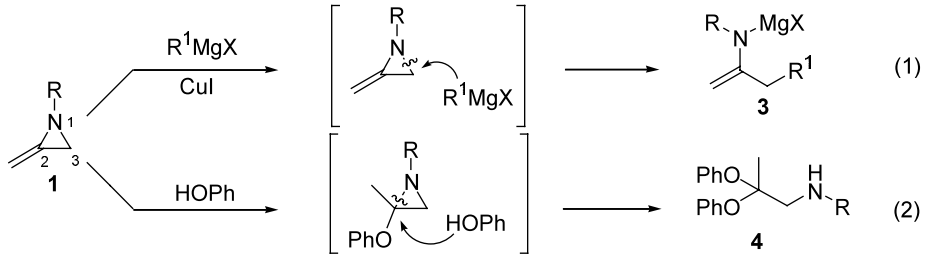
Abstract—The reaction of methyleneaziridine **1** with carbon pronucleophiles (**2**, H-CR_3) proceeds smoothly in the presence of a palladium catalyst affording the corresponding hydrocarbonation products **5** in good to high yield.

2-Methyleneaziridines are small ring compounds containing a nitrogen atom which have high ring strain. It is known that the ring opening of methyleneaziridines with Grignard reagents (or organolithium compounds),[1a–d] acid chlorides,[1e,f] and HCl[1g] occurs through N–C3 bond cleavage (Eq. (1)), while ring opening with HOPh proceeds through N–C2 bond cleavage[1h] (Eq. (2)). Accordingly, the reaction of 2-methyleneaziridines with nucleophiles produces ring-opened derivatives. We now report that the reaction of the methyleneaziridines **1** with carbon pronucleophiles **2** proceeds smoothly in the presence of a palladium catalyst to give the non-ring-opened products **5** in good to high yields (Eq. (3)). Formally, this is a hydrocarbonation reaction of the double bond of **1** with carbon pronucleophiles.

The results are summarized in Table 1. In the presence of catalytic amounts of $Pd(PPh_3)_4$ (5 mol%) and triphenylphosphine oxide (10 mol%), the reaction of 1-benzyl-2-methyleneaziridine **1a** (0.75 mmol) with methylmalononitrile **2a** (0.5 mmol) in THF at 120°C for 4 h gave **5a** in 87% yield (entry 1). The catalytic system $Pd(dba)_2/PPh_3$ was less effective, and $Pd_2(dba)_3{\cdot}CHCl_3$ or $Pd(PPh_3)_2Cl_2$ did not promote the reaction. The reaction using $Pd(OAc)_2/PPh_3$ as a catalyst gave **5a** in a moderate yield. The combination of $Pd(PPh_3)_4$ and monodentate phosphine ligands such as PPh_3, $P(O)Bu_3$, and P(*o*-tolyl)$_3$, gave **5a** in moderate to good yields. In the presence of just $Pd(PPh_3)_4$, **5a** was obtained in good yield (80%). However, even in the presence of $Pd(PPh_3)_4$, if bidentate ligands such as bis(diphenylphosphino)methane (dppm), 1,2-bis(diphenylphosphino)ethane (dppe), 1,3-bis(diphenylphosphino)propane (dppp) were used as a ligand, only small amounts of **5a** were obtained. The best results were obtained with the catalytic system, $Pd(PPh_3)_4$ and $P(O)Ph_3$. The reactions of 1-hexyl-2-methyleneaziridine **1b** with **2a**, and 1-butyl-2-methyleneaziridine **1c** with **2a** afforded **5b** and **5c** in yields of 71 and 63%, respectively (entries 2 and 3). The reactions of **1d** with **2a**, and **1e** with **2a** proceeded smoothly and the corresponding hydrocarbonation products **5d** and **5e** were produced in 65 and 79% yield, respectively (entries 4 and 5). The reaction of 1-*p*-chlorobenzyl-2-methyleneaziridine **1f**, which has an electron withdrawing group on the nitrogen atom, with **2a** required longer reaction times and



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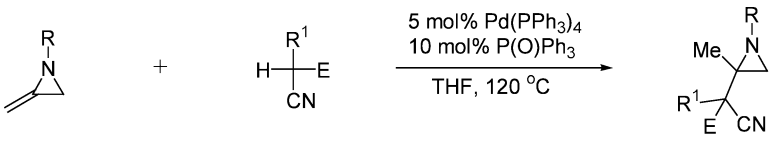


1a ; R = Bn
1b ; R = Hex
1c ; R = Bu
1d ; R = $CH_2CH_2CH_2OMe$
1e ; R = $CH_2CH(OMe)_2$
1f ; R = CH_2-*p*-C_6H_4Cl

2a ; R^1 = Me, E = CN
2b ; R^1 = Me, E = CO_2Et
2c ; R^1 = *i*-Pr, E = CN
2d ; R^1 = Bn, E = CN

5a ; R = Bn, R^1 = Me, E = CN
5b ; R = Hex, R^1 = Me, E = CN
5c ; R = Bu, R^1 = Me, E = CN
5d ; R = $CH_2CH_2CH_2OMe$, R^1 = Me, E = CN
5e ; R = $CH_2CH(OMe)_2$, R^1 = Me, E = CN
5f ; R = CH_2-*p*-C_6H_4Cl, R^1 = Me, E = CN
5g ; R = Bn, R^1 = Me, E = CO_2Et
5h ; R = Bn, R^1 = *i*-Pr, E = CN
5i ; R = Bn, R^1 = Bn, E = CN

(3)

Table 1. Palladium-catalyzed hydrocarbonation of **1** with **2**[a]

Entry	1	2	Time (h)	5	Yield (%)[b]
1	**1a**	**2a**	4	**5a**	87
2	**1b**	**2a**	5	**5b**	71
3	**1c**	**2a**	5	**5c**	63
4	**1d**	**2a**	4	**5d**	65
5	**1e**	**2a**	4	**5e**	79
6	**1f**	**2a**	10	**5f**	51
7	**1a**	**2b**	15	**5g**	63 (1:1)[c]
8	**1a**	**2c**	5	**5h**	71
9	**1a**	**2d**	5	**5i**	61

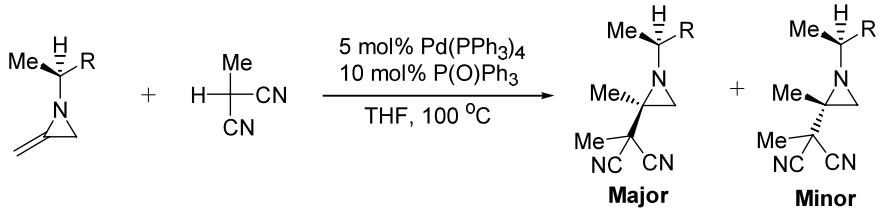
[a] The reaction of **1** (0.75 mmol) with **2** (0.5 mmol) was carried out in the presence of 5 mol% of $Pd(PPh_3)_4$ and 10 mol% of triphenylphosphine oxide in THF at 120°C.
[b] Isolated yield based on **2**.
[c] The diastereomeric ratio of **5g**.

gave **5f** in a lower yield (entry 6). The reaction of **1a** with 2-cyanopropionate **2b** afforded **5g** in 63% yield (entry 7). Other activated methynes such as *i*-propylmalononitrile **2c** and benzylmalononitrile **2d**, upon treatment with **1a**, gave products **5h** and **5i** in 71 and 61% yield, respectively (entries 8 and 9).

Significantly high de's (82%) were obtained in the reaction of (S)-*N*-(1-naphthylethyl)-2-methyleneaziridine **1h** with **2a**, although (S)-*N*-(1-phenylethyl)-2-methyleneaziridine **1g** produced only a moderate de (54%) (Eq. (4)). The absolute stereochemistry of **5k** was determined unambiguously by X-ray analysis and NOE experiments.

A plausible mechanism for the hydrocarbonation is illustrated in Scheme 1. The oxidative addition of palladium(0) into a C–H bond of the pronucleophile **2a** would give the hydridopalladium complex **6**.[2] The hydropalladation of the methyleneaziridines **1** with **6** would be facilitated by a chelation effect of the nitrogen atom **7**, giving the H–Pd addition product **8**. Reductive elimination of palladium(0) could then give the hydrocarbonation products **5**.[3]

The reaction with deuterated methylmalononitrile (**2a**-*d*, 90% D) substantiated the proposed mechanism. The reaction of **1a** with **2a**-*d* under the same reaction conditions as above gave **5a**-*d* in 82% yield in which the deuterium content was 76% (Eq. (5)). Interestingly, the reaction of **1a** with **2a** without any palladium catalyst in THF at 120°C for 4 days gave the vinylic amine **9** in 73% yield (Eq. (6)). This ring-opening reaction of the methyleneaziridine most probably occurred by the nucleophilic addition of the carbanion derived from **2a** to the C-3 position of the protonated methyleneaziridine, **10**.[1] It is now clear that the palladium catalyzed and thermal reactions of **2a** with **1a** take

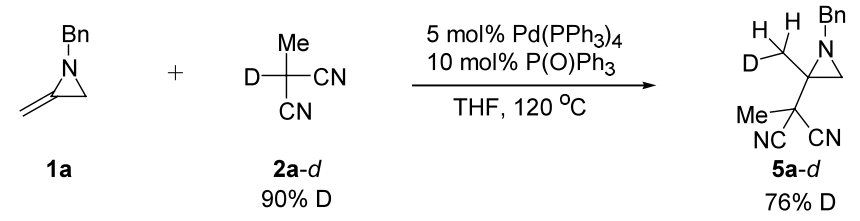


1g ; R = Ph
1h ; R = naphthyl

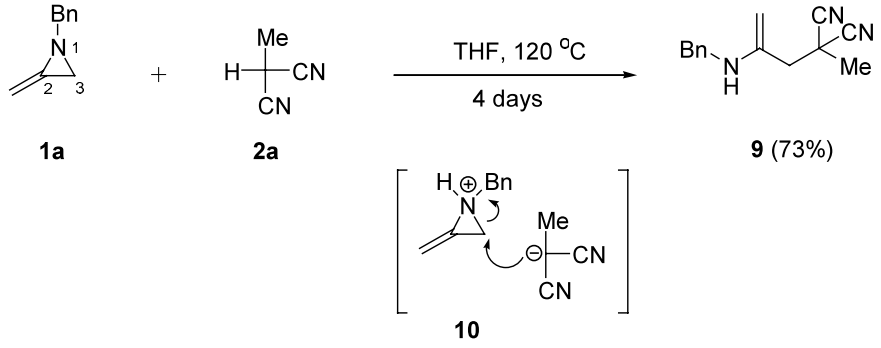
2a

5j ; R = Ph, 83% (54% de)
5k ; R = naphthyl, 68% (82% de)

(4)



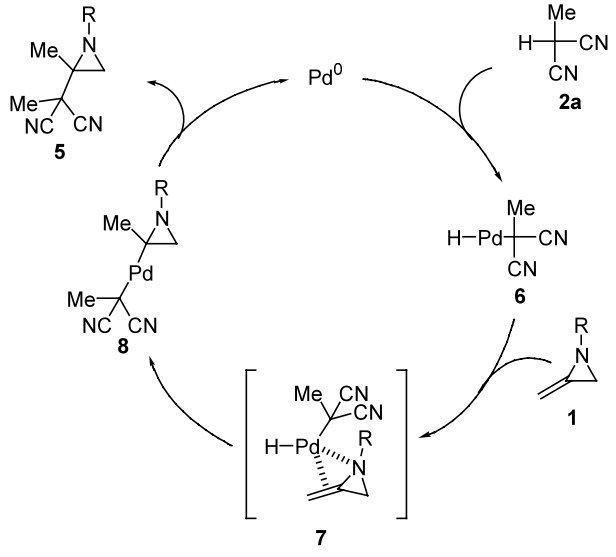
(5)



(6)

totally different reaction courses; the Lewis acidic Pd(II)–nitrogen interaction (**7**) leads to **5a** while the Brønsted acid H^+–nitrogen interaction (**10**) gives **9**. The addition of carbon pronucleophiles to *activated alkenes* catalyzed by transition metals, that is the Michael addition, is known.[4] Recently, we and other groups reported the palladium-catalyzed addition of carbon pronucleophiles **2** to *unactivated olefins* such as allenes,[5] enynes,[6] methylenecyclopropanes,[7] and 1,3-dienes.[8] The driving force for these reactions originates in the formation of stable π-allylpalladium complexes. The present hydrocarbonation reaction does not proceed through the formation of a π-allylpalladium intermediate, but most probably proceeds via a chelation effect of the nitrogen atom of the aziridine moiety.

In conclusion, we have developed the direct hydrocarbonation of methyleneaziridines[9] using carbon pronucleophiles in the presence of a palladium catalyst. The palladium-catalyzed reaction provides geminally disubstituted functionalized aziridines, while traditional reactions give ring-opening products upon treatment with nucleophiles.



Scheme 1. A plausible mechanism for hydrocarbonation.

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