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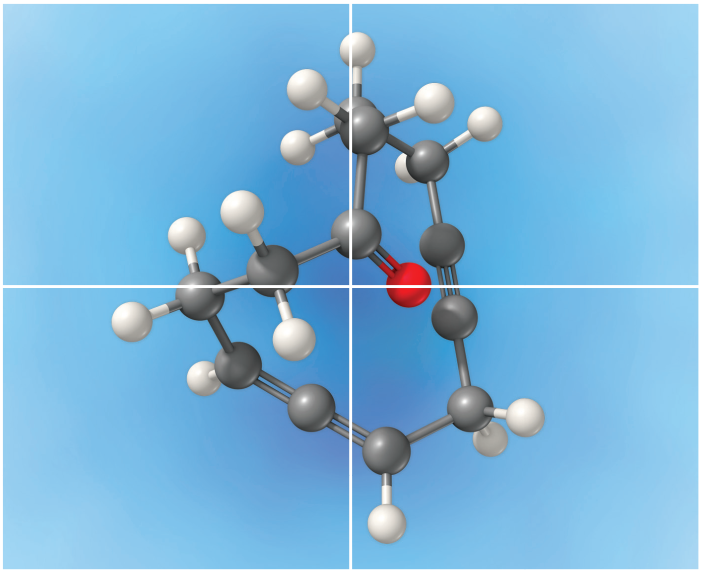

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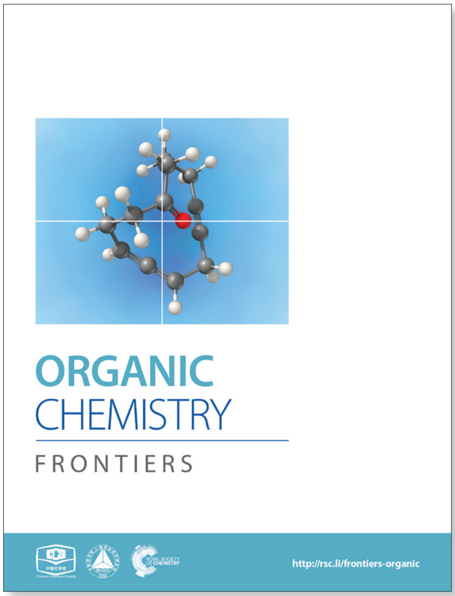

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A Challenging Heck Reaction of Maleimides

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Maleimides are extremely susceptible to basic hydrolysis and gave poor yields under Heck conditions. The longstanding problem is solved with the use of a weak base KOAc in a carbonate solvent.

Palladium-catalyzed Heck reaction enables arylation and vinylation of olefins and is commonly used to prepare drugs, fragrance, agrochemicals and advanced materials.[1] Electron-deficient olefins such as enones, acrylates and acrylonitrile are commonly used and they react efficiently with aryl halides and sulfonates.[2] However, maleimides typically give very poor yields due to fast hydrolysis of the cyclic imides under basic conditions. Pd-catalyzed couplings of halomaleimides were often used as alternative methods.[3] In synthesis of drug candidates, copper-catalyzed Meerwein reaction of maleimides and aryldiazonium salts is also used, although yields are often low-to-moderate.[4] Recently, other metal-catalyzed methods were invented to prepare substituted maleimides, for example, carbonylative couplings of alkynes and amines[5] or isocyanates[6].

Herein, we report an efficient general Heck reaction of problematic substrates, maleimides using aryl iodides. A weak acetate base KOAc was used to prevent hydrolysis of maleimides and arylated products. The motifs of 3-arylmaleimide and related arylsuccinimide are present in many bioactive compounds and some drugs (Fig 1).[7] For example, phensuximide is an anticonvulsant drug[8] and another succinimide exhibited both immunostimulatory and anti-inflammatory activities.[9]

In a model reaction of parent maleimide (MI), after many experiments we found that a combination of a weak base KOAc in ethylene carbonate was crucial to secure good yield at 60 °C after 12 hours (Table 1, entry 3). Notably, longer reaction time led to diminished yields due to increased hydrolysis of the products. This testified to the challenge associated with this particular olefin. We noticed that many bases including K_2CO_3, Cs_2CO_3, CsF, KF and K_3PO_4 caused hydrolysis of both maleimide and Heck products and led to poor yields (entry 6-11). In addition, trialkylamines also caused fast hydrolysis of the imide linkage (entry 12-13).

Fig 1 Bioactive arylated maleimides and succinimides.

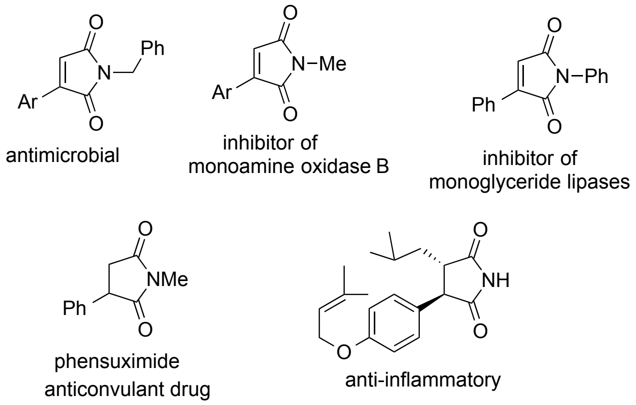
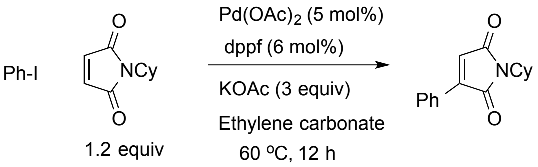


Table 1 Optimization of bases in a model Heck reaction of maleimide (GC yield and conversion based on 120% of maleimide)



Entry	Ligand	Conv (% PhI)	Conv (% MI)	Yield (%)
1	LiOAc	25	57	17
2	NaOAc	40	89	31
3	KOAc	100	112	**88**
4	$NaHCO_3$	91	116	71
5	$KHCO_3$	100	120	**80**
6	Li_2CO_3	9	98	5
7	Na_2CO_3	49	74	41
8	K_2CO_3	21	120	4
9	Cs_2CO_3	35	120	0
10	KF	80	120	52
11	K_3PO_4	88	119	49
12	Et_3N	72	119	30
13	*i*-Pr_2NEt	97	119	36

The choice of solvents was also important (Table 2). For example, in THF, dioxane, toluene and DCE, the yield was only poor-to-moderate (entry 1-5). Notably, in highly polar solvents of DMF and DMSO (entry 7-8), base hydrolysis of the cyclic imide became much faster and gave rise to the poor yields. Better solvation of metal ion in these solvents leaves acetate ion more exposed and more nucleophilic. However, in ethylene carbonate, a good yield was obtained (entry 9).[10] It is a highly polar aprotic solvent with an exceptionally high dielectric constant of 95 at 25°C.

Table 2 Effect of solvents in a model Heck reaction (GC yield and conversion based on 120% of maleimide)

Entry	Solvent	Conv (% PhI)	Conv (% MI)	Yield (%)
1	THF	85	92	62
2	1,4-Dioxane	82	85	69
3	Diglyme	97	102	64
4	Toluene	26	35	15
5	DCE	55	56	46
6	DMA	96	108	64
7	DMF	66	120	38
8	DMSO	8	120	0
9	Ethylene carbonate	100	112	88

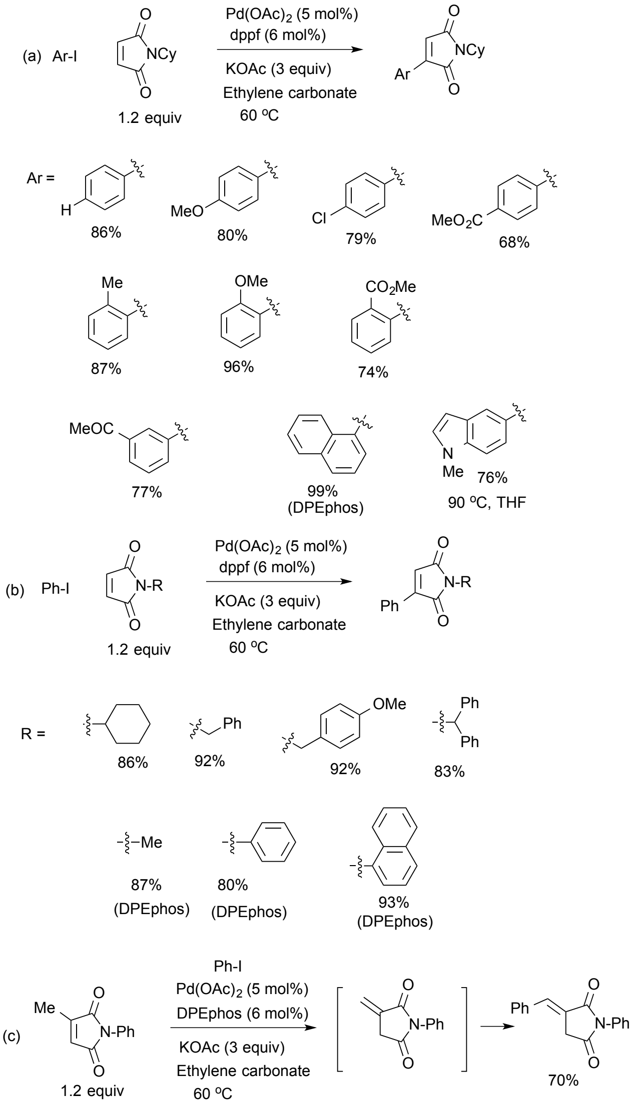
Many phosphines can support the Pd catalysis well (Table 3). Good examples of ligands including SPhos and MePhos, Q-Phos, PCy_3, dppe and DPEphos. A ferrocene bisphosphine dppf also afforded good yield and was used for isolations, due to its substrate generality and low cost (entry 10). In the absence of a phosphine, the ligand-free procedure also gave 64% yield, probably via an anionic pathway of $[(aryl)PdX_2]^-$ or $[(aryl)PdX_3]^{2-}$ (entry 17).[11]

Table 3 Effect of phosphine ligands in a model Heck reaction (GC yield and conversion based on 120% of maleimide)

Entry	Ligand	Conv (% PhI)	Conv (% MI)	Yield (%)
1	P*t*-Bu$_3$	69	114	45
2	PCy$_3$	100	120	**90**
3	PPh$_3$	100	117	60
4	P(2-furyl)$_3$	95	107	73
5	XPhos	99	116	61
6	SPhos	100	111	**92**
7	DavePhos	100	117	61
8	MePhos	100	112	**93**
9	Q-Phos	98	106	**97**
10	dppf	100	112	**88**
11	dppe	100	116	**89**
12	dppp	57	119	37
13	dppb	87	116	63
14	Xantphos	96	108	78
15	BINAP	5	80	<5
16	DPEphos	100	105	**96**
17	No added ligand	85	100	64

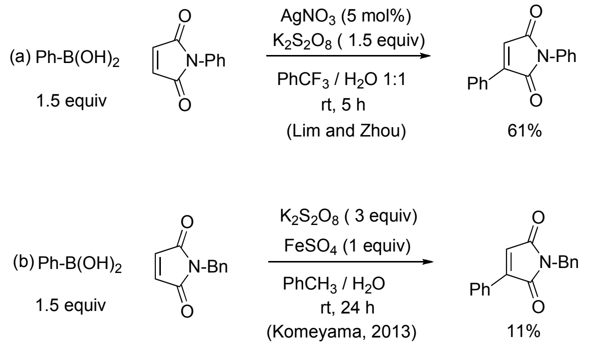
Next, we explored the scope of aryl iodides (Fig. 2a). In a typical procedure, $Pd(OAc)_2$, dppf, KOAc, ArI and maleimide were mixed in dry ethylene carbonate under argon (or nitrogen) and heated with stirring at 60 °C for 12 hours. Notably, higher temperatures or a longer reaction time led to decreased yields due to partial hydrolysis of both maleimide and arylated products. The aryl rings can have electron-withdrawing and donating groups. The *ortho*-substituted aryl iodides led to slightly higher yields than *para* ones, because of slower hydrolysis of products. One indolyl iodide also reacted smoothly and the yield was much higher in THF than ethylene carbonate. Common aryl bromides remained unreactive under similar conditions. The *N*-groups can be both alkyl and aryl groups (Fig 2b). When *N*-arylmaleimides were used, another bisphosphine DPEphos proved to be a better catalyst. The *N*-anisylmethyl group in Heck products can be cleaved by treatment of $AlCl_3$ or CF_3CO_2H.[3b] Additionally, the Heck reaction of 3-methylmaleimide afforded a product containing an *exo*-benzylidene unit. This is probably formed via base-induced isomerization of the endocyclic olefin in maleimide (Fig 2c).[12]

Fig 2 Examples of Heck reaction of maleimides (isolated yield on 0.5 mmol scale unless stated otherwise).



As a side note, we attempted radical arylation by modifying Baran's procedure using $PhB(OH)_2$ and oxone.[13] Unfortunately, the yield was only 61% even after extensive optimization (Fig 3a). Other arylboronic acids led to very poor yields. In another procedure for radical arylation using $FeSO_4$ and oxone, only 11% was reported previously by Komeyama et al. (Fig 3b).[14] These unsatisfactory results confirmed that maleimides are very sensitive to hydrolysis under very mild conditions.

Fig 3 Radical arylation methods



In summary, we report an efficient Heck method for arylation of challenging maleimides, which are prone to undergo facile hydrolysis. A specific combination of KOAc and a carbonate solvent allowed formation of Heck products in good yields with generality.

Notes and references

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Difficult heck reaction of base-sensitive maleimides is realized by using a weak base in a carbonate solvent.