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Aminations of allylic phenyl ethers *via* micellar catalysis at room temperature in water†

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Abstract

Especially mild, organic solvent-free conditions have been found that allow for allylic ethers to undergo Pd-catalyzed aminations.

Allylic ethers are not commonly regarded as reactive electrophiles in allylic substitution reactions. Indeed, unlike activated systems such as sulfonate, phosphate, halide, acetate, and carbonate groups, ethers (other than allylic epoxides) tend to be viewed more as hydroxyl protecting groups than as cross-coupling partners.[1] Characteristics of allylic ethers, such as limited susceptibility to direct (usually high temperature) displacement by nucleophiles, reduced tendencies to undergo transition metal-catalyzed insertion into an electron-rich C–O σ-bond, and no option for hydrolysis, offer significant synthetic advantages. Examples of allylic ethers as electrophiles matched with highly reactive nucleophiles (*e.g.*, Grignard reagents)[2] certainly exist; however, there appears to be no general methodology for allylic amination by this functional group under mild conditions. Literature examples of net substitution by nitrogen involve relatively special circumstances (*e.g.*, diphosphinidenecyclo-butene complexes, and use of phenolic resins).[3] We have recently described an approach to allylic aminations[4] of free allylic alcohols, which could be effected in water as the only medium in the presence of the non-ionic amphiphile PTS.[5] To avoid, in general, the hydroxyl protecting group issue, we now present our studies on allylic amination reactions that rely on allylic alcohol-derived phenyl ether derivatives as leaving group (Fig. 1).[6]

Palladium-catalyzed allylic aminations occurred readily in water as the only medium containing only 2 wt% of nanomicelle-forming PTS (global concentration = 0.5 M).[8] Optimization using cinnamyl phenyl ether (**1a**, 0.5 mmol) as a model educt, along with the sterically demanding nucleophile dibenzylamine (**2a**, 0.75 mmol), led to a very efficient coupling at room temperature (Table 1). Catalytic $[Pd(allyl)Cl]_2$ (0.0025 mmol, 0.5 mol%) exposed to DPEphos as ligand (0.005 mmol, 1 mol%) appears to be the most effective combination (Run 11). Addition of methyl formate was also crucial, as its presence had been found previously as well to increase reaction rates of allylic *alcohols* toward allylic aminations.[5] In the absence of this ester the amination was sluggish (Run 7) affording only 3% product after 30 minutes, and 24% after six hours (Run 11). Although dppf was quite effective as ligand among the mono- and bidentate ligands screened (Runs 1–9), rigid P–P ligand DPEphos gave the highest (quantitative) yield within the allotted 30 minute time frame (Run 11). By contrast, a biaryl bidentate P–N ligand was totally ineffective (Run 10).

†Electronic supplementary information (ESI) available: Experimental procedures and characterization data for all new compounds.

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Increasing rigidity in going from DPEphos to Xantphos resulted in only trace amounts of allylic amination (Run 12). The catalytic nanomicelle reactors formed spontaneously by PTS in water[8,9] appear to play an important role, as a corresponding reaction run in its absence, or essentially "on water", dropped the yield significantly (to 53%; Run 11). Surprisingly, there was no difference between reactions run under an inert argon atmosphere and those conducted fully exposed to air, notwithstanding the known instability of $[Pd(allyl)Cl]_2$ under such conditions.

Under optimized conditions, the antifungal drug naftifine[10] could be successfully synthesized from simple precursors in 98% yield in minutes at room temperature in water (Table 2, Run 1). Several analogs of naftifine derived from allylic phenyl ether derivatives were also prepared, as illustrated in Table 2. Methallyl phenyl ether (**1b**) reacted with *N*-methyl-*N*-naphthylmethylamine (**2b**) to afford **3c** in 81% yield in one hour (Run 2). Unhindered allyl phenyl ether was by far the most reactive of the allylic ethers tested, leading to allyl amine **3d** (91% yield) in five minutes (Run 3). Allylic phenyl ether **1d** possessing a highly lipophilic alkyl chain gave derivative **3e** in 90% yield with excellent linear- and *E*-selectivity (Run 4). Secondary phenyl ether **1e** also reacted with amine **2b** to produce **3f** in 80% yield after five hours at room temperature (Run 5).

Functional group tolerance with respect to the amine component was also examined using cinnamyl phenyl ether **1a** as the allylating agent (Table 3). Cross-coupling with the bulky secondary amine **2c** derived from phenylalanine gave the desired *trans*-cinnamylated product **3g** in 83% isolated yield. It is noteworthy that the aryl bromide present, normally a good coupling partner in Pd-catalyzed reactions, remained fully intact (Run A). Brominated product **3g** could then be used in a subsequent cross-coupling also in PTS–water at room temperature with 4-anisylboronic acid to produce the biphenyl-containing amino acid ester **4** in 80% yield (Scheme 1).[11] In the presence of both $[Pd(allyl)Cl]_2$ and amines, an aromatic bromide is known to be reactive in water.[12] Nonetheless, under our conditions allylation of the amine with an allylic phenyl ether occurred chemoselectively. The non-halogenated analog, phenylalanine derivative **2d**, reacted much faster than did **2c** with **1a** (Run B). Reaction of **1a** with *N*-4-bromobenzyl substituted benzylamine unexpectedly took longer, but allylic amine **3i** was obtained again chemoselectively in over 80% yield (Run C). Mono-substituted amines were too reactive to selectively give mono-substituted allylated products. However, increasing the steric demand of the aryl ring, as in the case of *o*-toluidine (**2f**), led to only traces of the doubly allylated by-product (Run D). To suppress double substitution of the allylic fragment, 2.5 equivalents of amines were used thereby affording an 80% yield of mono-cinnamylated amine **3k** (Run E). Ethyl phenyalanate (**2h**) gave mainly mono-allylated amine **3l** (Run F).

While functionalized amino acid **2i** was unreactive toward **1a**, allyl phenyl ether itself (**1c**) reacted smoothly to produce **3l** in 85% yield (Scheme 2). In the case of the allylic substrate **1f** having both acetate and ether moieties (Scheme 3), coupling first occurred chemoselectively (in the absence of methyl formate) at the acetate in the presence of Xantphos to give **3n**. That is, no product (**3p**) resulting from phenyl ether displacement was detected, nor was potential product **3o** observed from double substitution. While the resulting amine **3n** formed could be isolated (83%), its *in situ* generation allows for a second, single-flask coupling at the allylic phenyl ether site, once methyl formate and DPEphos has been added to the mixture. Thus, an unsymmetrical diamine such as **3q** could be realized in excellent overall yield (Scheme 4).

In summary, the first general method for Pd-catalyzed aminations of allylic *ethers* has been developed. These reactions occur in excellent yields, without inert atmosphere conditions, in

water as the only medium,[13] and at room temperature. Further applications from our laboratory will be described in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Notes and references

1. Lu Z, Ma S. Angew Chem Int Ed. 2008; 47:258., and references cited therein; Weissman SA, Zewge D. Tetrahedron. 2005; 61:7833.; Protective Groups in Organic Synthesis (3). Greene TW, Wuts PGM. John Wiley and SonsNew York1999:17.; Takahashi K, Miyake A, Hata G. Bull Chem Soc Jpn. 1972; 45:230.
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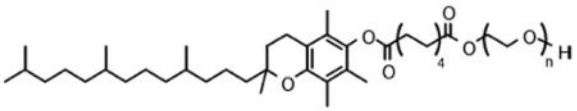

PTS (n = *ca.* 13; MW = *ca.* 1200)

6. Other leaving groups were not examined, although from related studies, it is expected to react far more slowly under similar conditions; see Nishikata T, Lipshutz BH. J Am Chem Soc. 2009; 131:12103. [PubMed: 19663513]
7. Arylboron reagents: Tobisu M, Shimasaki T, Chatani N. Angew Chem Int Ed. 2008; 47:4866.; Grignard reagents with aryl ether: Dankwardt JW. Angew Chem Int Ed. 2004; 43:2428.; Grignard reagents with vinyl ether: Wenkert E, Michelotti EL, Swindell CS. J Am Chem Soc. 1979; 101:2246.
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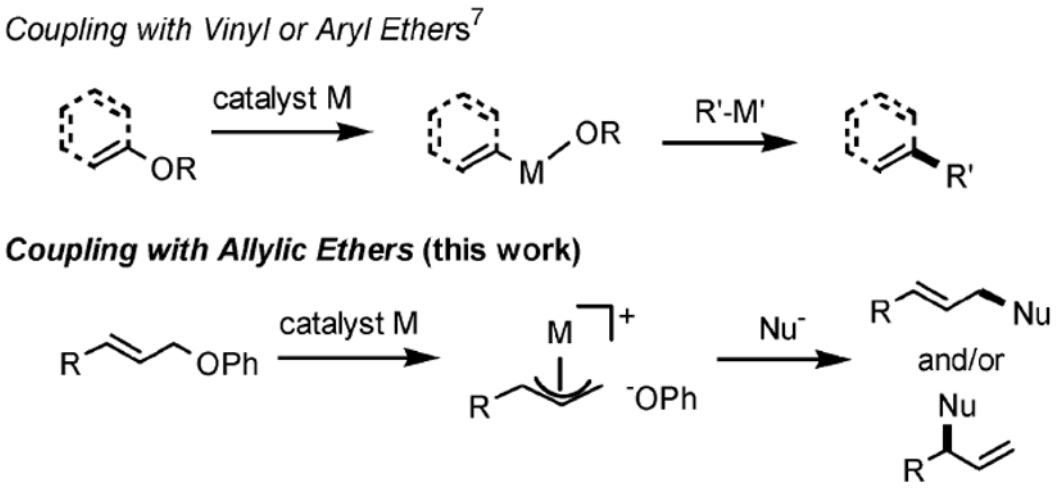
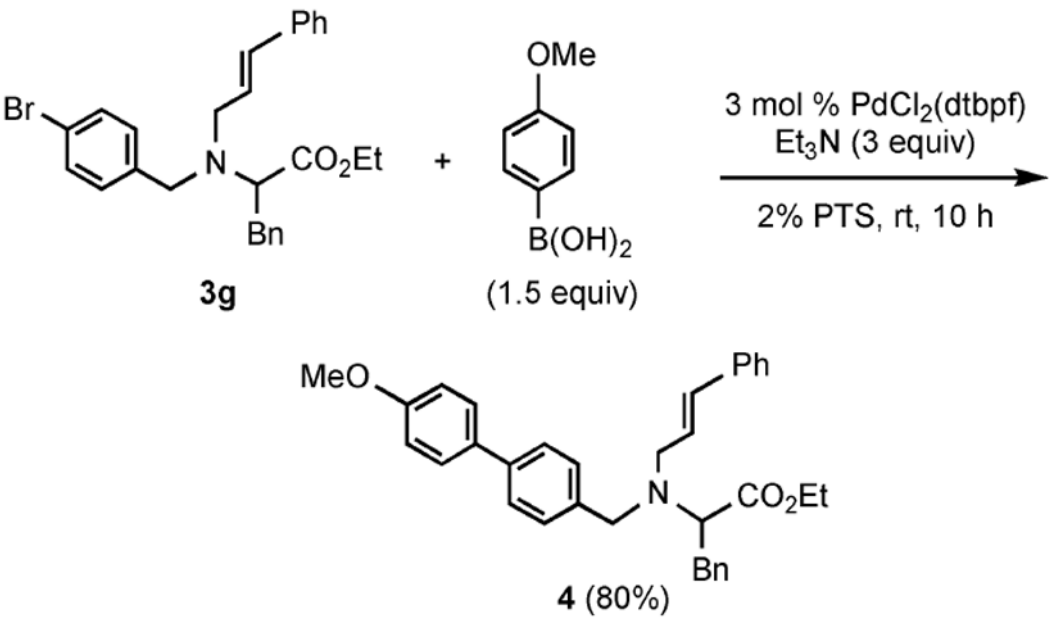
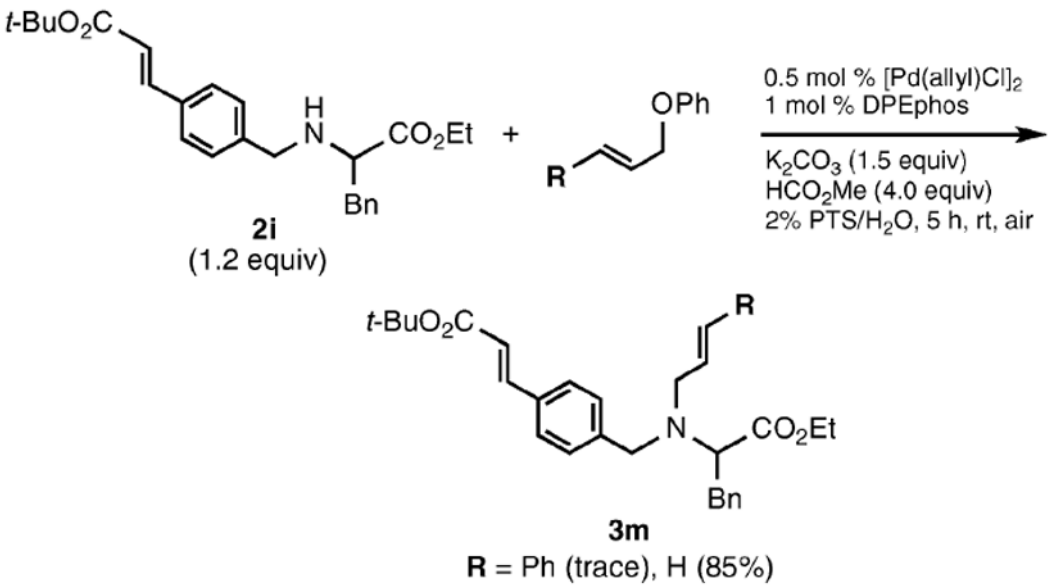


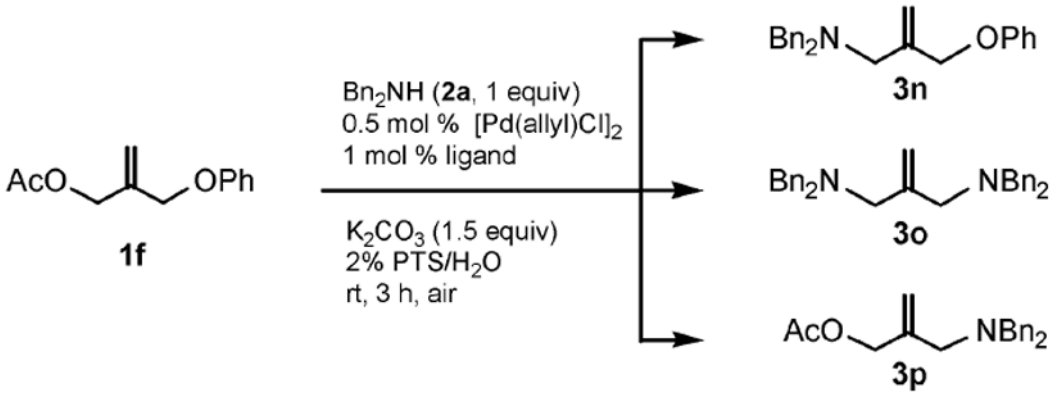
Fig. 1.
Use of phenyl ethers of allylic alcohols in coupling reactions.



Scheme 1.
Suzuki–Miyaura coupling of allylated product **3g** to **4**.



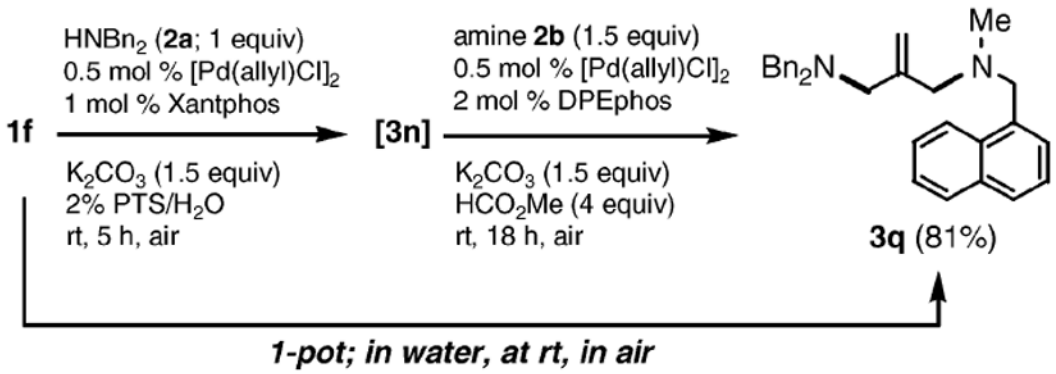
Scheme 2.
Limits of allylation.



	yield(%)		
ligand	**3n**	**3o**	**3p**
DPEphos	37	30	0
Xantphos[a]	83	0	0

[a] 1.5 equiv amine was used.

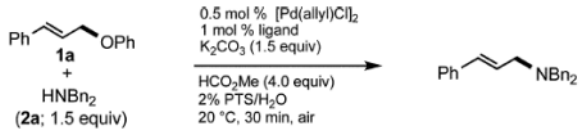
Scheme 3.
Chemoselective reaction of **1f**.

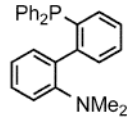
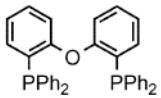
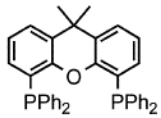


Scheme 4.
One-pot synthesis of diamine **3q** from **1f**.

Table 1

Ligand effects



Run	Ligand	Yield (%)	Run	Ligand	Yield (%)
1	PPh_3[a]	10	**10**		trace
2	P(*o*-tol)$_3$[a]	trace			
3	dppm	7			
4	dppe	8	**11**		99 (3,[b] 24,[b,c] 53[d])
5	dppp	8			
6	dppb	76			
7	dppf	90 (5)[b]	**12**		trace
8	biphep	57			
9	*rac*-binap	14			

[a] 2 mol% of ligand was used.

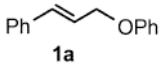
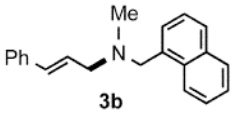
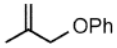
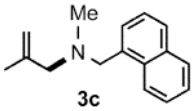
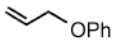
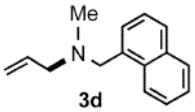
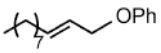
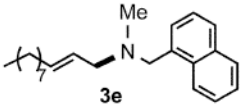
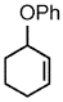
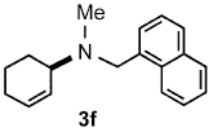
[b] In the absence of HCO_2Me.

[c] After 6 h.

[d] Reaction was carried out “on water”.

Table 2

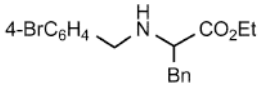
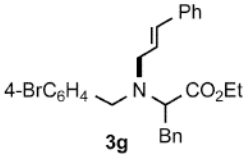
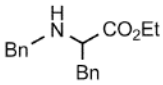
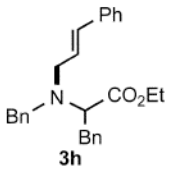
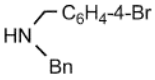
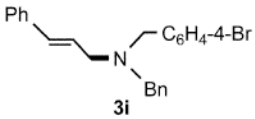
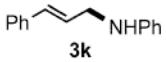
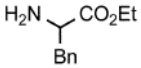
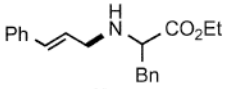
Reactions of allylic ethers (**1a–e**) with amine **2b**[a]

Run	Ether	Time (h)	Product	Yield (%)
1	 **1a**	[20 min]	 **3b**	98
2	 **1b**	1.0	 **3c**	81
3	 **1c**	[5 min]	 **3d**	91
4	 **1d**	1.5	 **3e** (E:Z = >25:1)	90
5	 **1e**	5.0	 **3f**	80

[a]Reactions were carried out under air at rt in 2 wt% PTS–water in the presence of $[Pd(allyl)Cl]_2$ (0.5 mol%), DPEphos (1 mol%), ether **1** (1 equiv.), amine **2b** (1.5 equiv.), K_2CO_3 (1.5 equiv.) and HCO_2Me (4 equiv.). Isolated yields.

Table 3

Reaction of *trans*-cinnamyl phenyl ether (**1a**) with amines[a]

Run	Amine	Time (h)	Product	Yield(%)[b]
A	 **2c**	7.0	 **3g**	83
B	 **2d**	2.5	 **3h**	91
C	 **2e**	14	 **3i**	82
D	H_2N(o-tol) **2f**	2.5	 **3j**	86
E	H_2NPh **2g** (2.5 equiv)	2.5	 **3k**	86 (9[c])
F	 **2h** (2.5 equiv)	2.5	 **3l**	80 (6[c])

[a]Reactions were carried out in air at rt in 2 wt% PTS–water in the presence of $[Pd(allyl)Cl]_2$ (0.5 mol%), DPEphos (1 mol%), ether **1a** (1 equiv.), amine **2** (1.5 equiv. or 2.5 equiv.), K_2CO_3 (1.5 equiv.) and HCO_2Me (4 equiv.).

[b]Isolated yields.

[c]Doubly allylated product.