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Palladium-Catalyzed Selective α-Alkenylation of Pyridylmethyl Ethers with Vinyl Bromides

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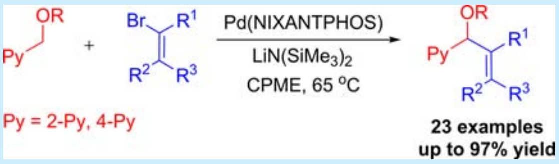
S *Supporting Information*

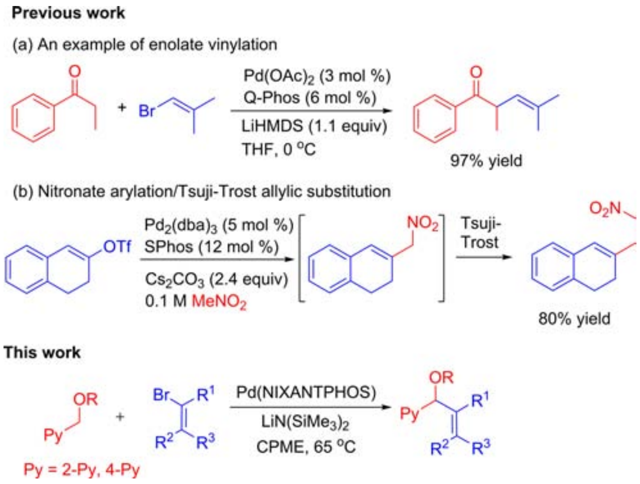
ABSTRACT: An efficient palladium-catalyzed α-alkenylation of pyridylmethyl ethers with vinyl bromides is presented. A Pd/NIXANTPHOS-based catalyst system enables a mild and chemoselective coupling between a variety of pyridylmethyl ethers and vinyl bromides in good to excellent yields. Under the mild conditions, β,γ-unsaturated products are obtained without isomerization or Heck byproducts observed.



Transition metal catalyzed vinylations of organic compounds with alkenyl halides is an attractive transformation as well as a long-standing challenge to synthetic chemists.[1] Direct alkenylation of carbanion nucleophiles with vinyl halides is one of the most efficient and economic approaches for installing β,γ-unsaturated units. Despite the large number of transition metal catalyzed methods to mediate C(sp^3)−H functionalization reactions with aryl halides electrophiles, use of vinyl halides has been limited to enolate[2] and nitronate[3] nucleophiles (Scheme 1a−b). Methods employing less acidic nucleophiles have met with very limited success.

We have reported a series of catalytic functionalizations of weakly acidic sp^3-hybridized C−H bonds via a deprotonative−cross-coupling process (DCCP).[4] These reactions involve reversible in situ deprotonation of substrates (pronucleophiles) to generate nucleophiles for transmetalation with the catalyst. Recently, we disclosed a versatile and chemoselective arylation of 2-pyridylmethyl ethers and tandem arylation/[1,2]-Wittig rearrangement.[5] Despite these efforts, the direct intermolecular C−H alkenylation of pyridylmethyl ethers with vinyl bromides remains unknown. Herein, we report a novel monoalkenylation of pyridylmethyl ethers with vinyl bromides. The pK_a values of the benzylic C−H's of 2- and 4-pyridylmethyl ethers are unknown, but likely similar to those of 2- and 4-methylpyridine (pK_a's 32−34 in THF).[6] These high pK_a values make the identification of base/solvent and catalyst combinations that will promote deprotonation of the pyridylmethyl ether, but not the more acidic product, challenging. Furthermore, because the product contains an olefin, byproduct formation derived from the Heck reaction must be suppressed.

Scheme 1. Transition-Metal-Catalyzed Alkenylation Chemistry



We initiated studies of the coupling between 4-pyridylmethyl ethyl ether **1a** and 2-bromoprop-1-ene **2a** with ligand screening on a microscale (0.01 mmol). A total of 41 electronically diverse mono- and bidentate phosphines were examined using $Pd(OAc)_2$ as the metal source, $LiN(SiMe_3)_2$ as the base, CPME as the solvent, 12 h of reaction time, and 65 °C (see the Supporting Information for details). The four most promising ligands from this screen were NIXANTPHOS (**L1**), DCE-Phos (**L2**), *rac*-BINAP (**L3**), and PXy_3 (**L4**) (Figure 1). Laboratory scale-up (0.1 mmol) led to the alkenylation product in 78% (NIXANTPHOS), 60% (DCE-Phos), 59% (*rac*-BINAP), and 49% (PXy_3) assay yields (AY) after 1 h (AY determined by ^{1}H NMR analysis, Table 1, entries 1−4). Interestingly, reducing the catalyst loading from 10 to 2.5 mol % led to a similar assay yield (75%, entry 5). The moderate yield inspired us to conducted a second microscale screen (0.01 mmol) focusing on palladium sources {$Pd(OAc)_2$, $Pd(dba)_2$, $[PdCl(allyl)]_2$,

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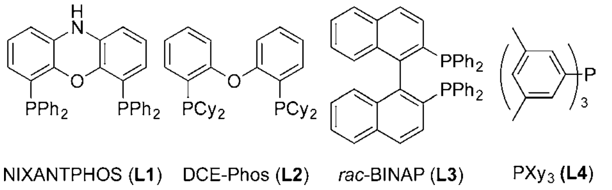
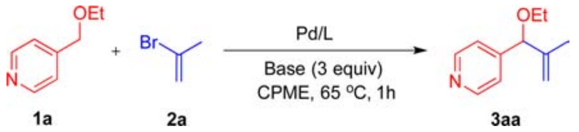


Figure 1. Structures of leading ligands in preliminary catalyst identification with $Pd(OAc)_2$ (Table 1).

Table 1. Optimization of Alkenylation of 4-Pyridylmethyl Ethyl Ether with 2-Bromoprop-1-ene 2a[a,b]



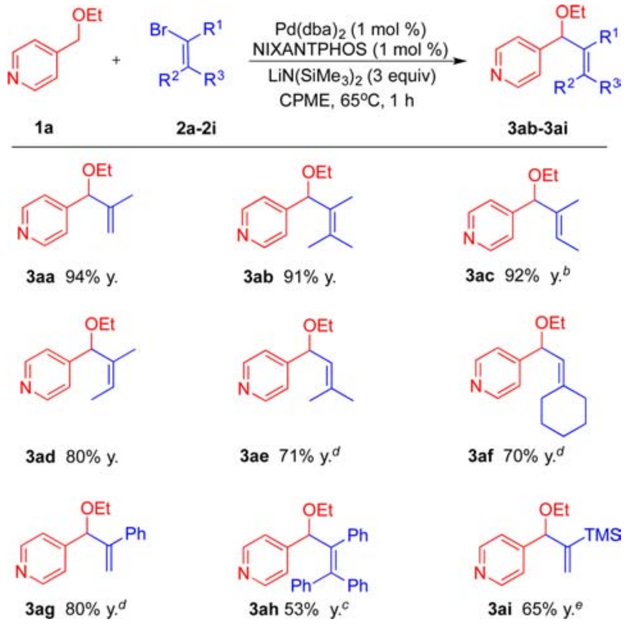
	Pd source	L	Pd/L (mol %)	base	assay yield (%)
1	$Pd(OAc)_2$	**L1**	10/15	$LiN(SiMe_3)_2$	78
2	$Pd(OAc)_2$	**L2**	10/15	$LiN(SiMe_3)_2$	60
3	$Pd(OAc)_2$	**L3**	10/15	$LiN(SiMe_3)_2$	59
4	$Pd(OAc)_2$	**L4**	10/15	$LiN(SiMe_3)_2$	49
5	$Pd(OAc)_2$	**L1**	2.5/3.75	$LiN(SiMe_3)_2$	75
6	$[PdCl(allyl)]_2$	**L1**	2.5/3.75	$LiN(SiMe_3)_2$	74
7	$Pd(dba)_2$	**L1**	2.5/3.75	$LiN(SiMe_3)_2$	88
8	$Pd(dba)_2$	**L1**	2.5/5.0	$LiN(SiMe_3)_2$	88
9	$Pd(dba)_2$	**L1**	2.5/2.5	$LiN(SiMe_3)_2$	96
10	$Pd(dba)_2$	**L1**	2.5/2.5	$NaN(SiMe_3)_2$	60
11	$Pd(dba)_2$	**L1**	1.0/1.0	$LiN(SiMe_3)_2$	95(94)[c]
12	$Pd(dba)_2$	**L1**	0.5/0.5	$LiN(SiMe_3)_2$	77

[a] Reactions conducted on a 0.1 mmol scale using 1 equiv of **1a**, and 1.5 equiv of **2a**. [b] Assay yields determined by ^1H NMR spectroscopy of the crude reaction mixtures. [c] Isolated yield after chromatographic purification.

$PdCl_2(COD)$, $Pd(NCPh)_2Cl_2$, $[Pd(2\text{-methylallyl})Cl]_2\}$ and four solvents [THF, CPME, DME, and toluene] with $LiN(SiMe_3)_2$ at 65 °C for 1 h. The two top Pd/solvent combinations from this screen were $[PdCl(allyl)]_2$/CPME and $Pd(dba)_2$/CPME. Scaling to 0.1 mmol resulted in 74% ($[PdCl(allyl)]_2$) and 88% ($Pd(dba)_2$) assay yields (entries 6 and 7, respectively).

The Pd:NIXANTPHOS ratio was next examined. Changing the Pd/ligand ratio from 1:1.5 to 1:2 resulted in no change in AY (entry 8). When a 1:1 Pd/L ratio was employed, however, the AY increased to 96% (entry 9). This increase in activity is likely due to inhibition by excess ligand.[7] Under identical reaction conditions, with the exception of substitution of $NaN(SiMe_3)_2$ for $LiN(SiMe_3)_2$, only a 60% AY was obtained (entry 10), highlighting the important role of the counterion in DCCPs with NIXANTPHOS. Further reducing the catalyst loading to 1 mol % provided a 95% AY and 94% isolated yield (entry 11). Attempts to further reduce the amount of the catalyst to 0.5 mol % resulted in a drop in the AY (77%, entry 12).

Table 2. Scope of Vinyl Bromides in α-Alkenylation of 4-Pyridylmethyl Ethyl Ether 1a[a]

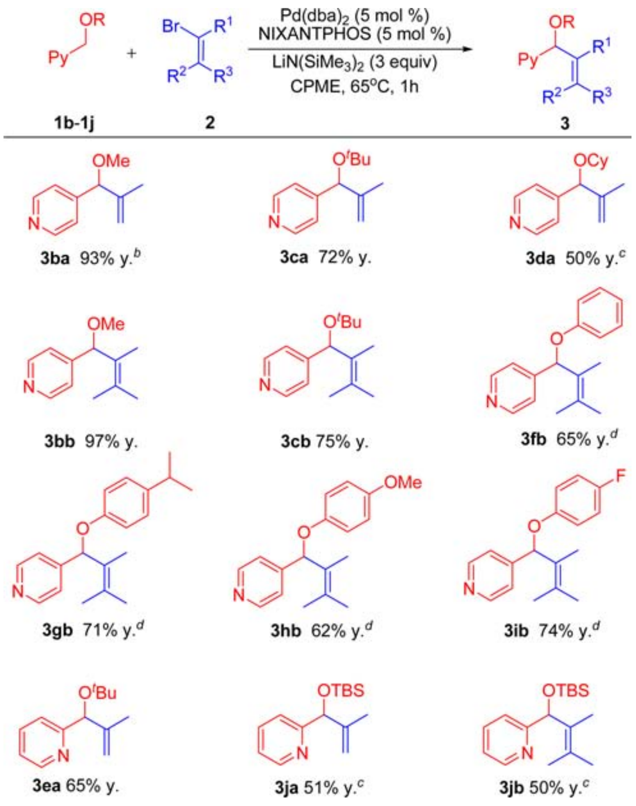


[a] Reactions conducted on 0.2 mmol scale using 1 equiv of **1a** and 1.5 equiv of vinyl bromide **2**. Isolated yields after chromatographic purification. [b] 2.5 mol % Pd loading. [c] 10 mol % Pd loading, 3 h reaction time. [d] 0.5 h reaction time. [e] 3 h reaction time.

Starting from the optimized conditions in Table 1 (entry 11), we explored the alkenylation of 4-pyridylmethyl ethyl ether **1a** with a variety of vinyl bromides (Table 2). In general, at a 1 mol % catalyst loading, alkenylated products were formed with very good yields with no product isomerization observed by ^1H NMR of the crude reaction mixtures. As noted, 2-bromoprop-1-ene **2a** rendered product **3aa** in 94% yield. Trisubstituted 2-bromo-3-methylbut-2-ene **2b** provided product in 91% yield under standard conditions. Coupling of **1a** with *trans*- and *cis*-2-bromobut-2-ene (**2c** and **2d**) delivered **3ac** and **3ad** in 92% and 80% yields using a 2.5 and 1 mol % catalyst loading, respectively. We observed that the geometries of products were retained in each case. 1-Bromo-2-methylprop-1-ene **2e** and (bromomethylene) cyclohexane **2f** were successfully coupled with **1a** to afford **3ae** and **3af** in 71% and 70% yields, respectively. Vinyl bromides with aryl substituents (1-bromovinyl)benzene (**2g**) and hindered bromotriphenylethylene (**2h**) afforded **3ag** and **3ah** in 80% and 53% yields at 1 and 10 mol % Pd loadings, respectively. Finally, (1-bromovinyl)trimethylsilane successfully coupled with **1a** furnishing the product **3ai** in 65% yield (1 mol % catalyst).

We next examined the alkenylation of 4- and 2-pyridylmethyl ethers bearing different ether O−R substituents (Table 3). In general, all the pyridylmethyl alkyl or aryl ethers exhibited a good to excellent yield with no isomerization products observed (^1H NMR). The 4-pyridylmethyl methyl ether (**1b**) coupled with 2-bromoprop-1-ene (**2a**) to give product **3ba** in 93% yield with a 1 mol % catalyst loading. 4-Pyridylmethyl *tert*-butyl ether (**1c**) underwent alkenylation with 2-bromoprop-1-ene (**2a**) providing a 72% yield. Alkenylation of 4-pyridylmethyl cyclohexyl ether (**1d**) with a 5 mol % catalyst loading gave a 50% yield after 10 h. 4-Pyridylmethyl alkyl ethers, including methyl ether (**1b**) and *tert*-butyl ether (**1c**), underwent coupling with 2-bromo-3-methylbut-2-ene (**2b**) to give products **3bb** and **3cb** in 97% and 75% yields under the standard conditions. Furthermore, 4-pyridylmethyl aryl ethers, including phenyl (**1f**), 4-isopropylphenyl (**1g**), 4-methoxyphenyl (**1h**), and 4-fluorophenyl (**1i**), were coupled with 2-bromo-3-methylbut-2-ene (**2b**) (10 mol % catalyst), leading to products **3fb**, **3gb**, **3hb**, and **3ib** in 65%, 71%, 62%, and 74% yields, respectively.

Table 3. Scope of Pyridylmethyl Ethers in Alkenylation with Vinyl Bromides[a]



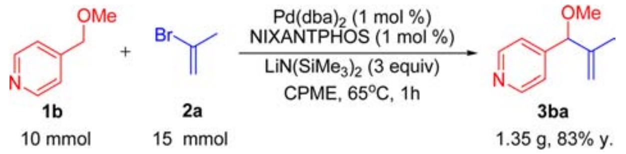
[a] Reactions conducted on a 0.2 mmol scale using 1 equiv of pyridylmethyl ethers **1** and 1.5 equiv of vinyl bromides **2**. Isolated yield after chromatographic purification. [b] 1.0 mol % Pd loading. [c] 10 h reaction time. [d] 10 mol % Pd loading, 5 h reaction time.

As mentioned earlier, 2-picoline derivatives are less acidic than 4-picolines by a factor of about 100. This difference in acidity is reflected in the reduced suitability of 2-pyridylmethyl ethers in this chemistry. The 2-pyridylmethyl *tert*-butyl ether (**1e**) and *tert*-butyldimethylsilyl ether (**1j**) underwent coupling with 2-bromoprop-1-ene (**2a**) and 2-bromo-3-methylbut-2-ene (**2b**) to provide the corresponding products **3ea**, **3ja**, and **3jb** in 65%, 51%, and 50% yields, respectively. Other 2-pyridylmethyl ethers exhibited poor yields.

Finally, we evaluated the scalability of our method. Conducting the alkenylation of **1b** with 2-bromoprop-1-ene **2a** on a 10 mmol scale with a 1.0 mol % Pd loading (Scheme 2) provided product **3ba** in 83% yield (1.35 g).

In summary, we have developed an efficient and versatile palladium-catalyzed alkenylation of pyridylmethyl ethers with vinyl bromides. The screening of ligands indicated that a (NIXANTPHOS)Pd-based catalyst exhibited the highest reactivity. Under our reaction conditions, a range of pyridylmethyl ethers underwent coupling with vinyl bromides in good to excellent yields. Importantly, no product isomerization or sequential Heck reactions were observed. These observations suggest that an enantioselective version may be possible. Efforts to develop enantioselective catalysts for this reaction are currently being pursued.

Scheme 2. Gram Scale Preparation of 4-(1-Methoxy-2-methylallyl)pyridine (3ba)



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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Procedures, characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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