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J. K. Sader, B. A. Molder & J. E. Wulff

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A Chan–Evans–Lam Approach to Trisubstituted Vinyl Ethers

Jonathan K. Sader,[a] Bryce A. Molder [a] and Jeremy E. Wulff *[a]

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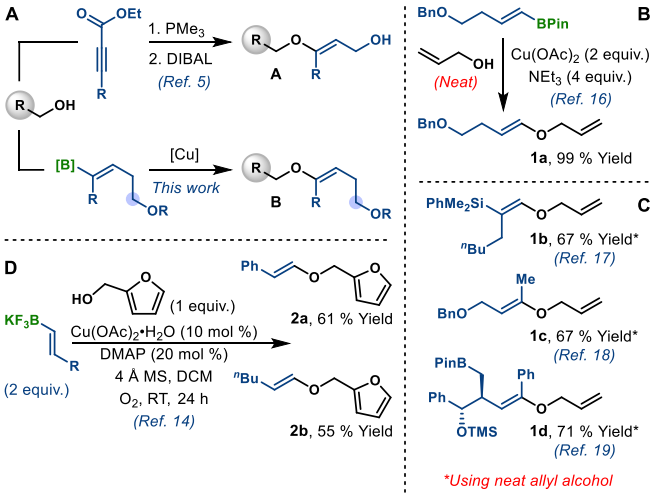
Trisubstituted vinyl ethers were accessed via Chan–Evans–Lam coupling of vinyl trifluoroborates and primary aliphatic alcohols. This approach complements prior methods that required the use of neat liquid alcohol coupling partners. A palladium-catalyzed redox-relay Heck reaction was used to convert several vinyl ethers into aldehyde-functionalized 1,3-dihydroisobenzofurans.

Vinyl ethers are electron-rich alkenes that possess great value in complex molecule synthesis. For example, recent syntheses of diverse polyalkyl furans,[1a] complex *abeo*-steroids,[2] tetracyclic meroterpenoids,[3] and pimarane natural products,[4] have all capitalized on the use of complex vinyl ether intermediates. Previously, our lab has developed an efficient, iterative (oligo)vinyl ether synthesis[5] that was leveraged for the synthesis of oxygen-containing juvenile hormone mimics,[5c] Claisen rearrangements,[5d] and cascading radical cyclizations.[5a,5b] This earlier approach, which hinges upon the trimethylphosphine-catalyzed conjugate addition of alcohols to alkynoates (Scheme 1A),[6] can be regarded as a formal hydroalkoxylation of activated alkynes. The addition/reduction sequence leading to vinyl ether **A** is exemplary in regard to its high efficiency, excellent atom economy, high stereoselectivity, and broad scope of alcohol coupling partners. In spite of these advantages, the use of the three-carbon alkynoate building block inherently limits the scope of accessible products. We became motivated to prepare trisubstituted linear vinyl ethers of type **B** without recourse to a one-carbon homologation reaction from **A** (Scheme 1A). We sought a general and modular approach to **B** that would complement recently reported hypervalent iodine-mediated vinyl ether syntheses.[7]

Conceptually, the direct hydroalkoxylation of an unactivated alkyne would be the most favorable approach to **B**. However, considering that this mode of reactivity remains largely confined to intramolecular systems for the synthesis of dihydropyrans and exocyclic vinyl ethers,[8] we instead opted for an intermolecular transition metal-mediated coupling between an alcohol and a stereodefined vinyl halide- or boronate building block. The success of this strategy has been documented by several groups. Nordmann and Buchwald demonstrated a copper-catalyzed coupling of allylic alcohols and vinyl iodides as part of a domino C–O coupling-Claisen rearrangement cascade.[9] Stoltz and co-workers adopted a similar strategy for an intramolecular nickel-catalyzed cycloetherification.[10] Notwithstanding the success of vinyl halide-based approaches, we were particularly drawn to the prospect of a copper-mediated Chan–Evans–Lam coupling[11] between an alcohol and a vinyl boronate. A wealth of methods for the stereoselective synthesis of vinyl boronates, the use of cheap copper salts, and mild reaction conditions are appealing features of this chemistry.[12] Additionally, it is worth noting that aryl (pseudo)halides are preserved under the Chan–Evans–Lam manifold, which provides an avenue for orthogonal reactivity.



Scheme 1 A) Our plan for a Chan–Evans–Lam vinyl ether synthesis. B) Merlic's synthesis of allyl vinyl ether **1a**. C) Trisubstituted linear vinyl ethers prepared via Chan–Evans–Lam coupling, using neat allyl alcohol as the coupling partner. D) Quach and Batey's vinyl ether synthesis.

[a] *Department of Chemistry, University of Victoria, PO Box 3065 STN CSC, Victoria, British Columbia, Canada, V8W 3V6. E-mail: wulff@uvic.ca*

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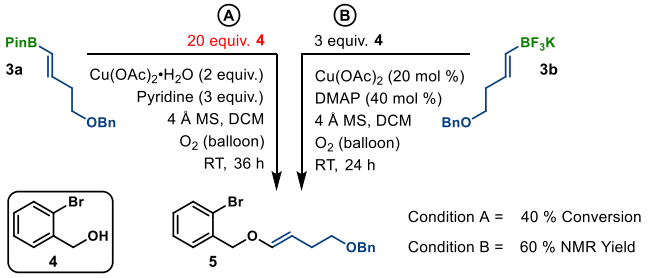
Pioneering studies from the groups of Lam,[13] Batey,[14] and O'Shea[15] demonstrated the feasibility of the Chan–Evans–Lam approach, albeit exclusively for the synthesis of simple mono- or disubstituted vinyl ethers. In 2010 Merlic and co-workers reported high-yielding, stereospecific syntheses of various allyl-, 2-chloroethyl-, and 2-trimethylsilylethyl vinyl ethers from disubstituted vinyl boronate coupling partners.[16] This was exemplified by the synthesis of allyl vinyl ether **1a**, which was isolated in 99 % yield (Scheme 1B). The groups of Sun,[17] Carretero,[18] and Chen[19] have capitalized on this methodology for the synthesis of complex trisubstituted allyl vinyl ethers **1b**, **1c**, and **1d**, respectively (Scheme 1C). To the best of our knowledge, these three compounds are the *only* trisubstituted linear vinyl ethers that have been prepared via Chan–Evans–Lam coupling,[20] and in each case the alcohol coupling partner was used as the solvent for the reaction. This requirement—while permissible for the synthesis of allyl vinyl ethers—precludes access to vinyl ethers derived from more complex alcohol coupling partners. In their seminal report about the use of organotrifluoroborates in the Chan–Evans–Lam reaction,[14] Quach and Batey reported the syntheses of furfuryl vinyl ethers **2a** and **2b** in 61 % and 55 % yield, respectively (Scheme 1D). Despite the relative simplicity of these vinyl ethers, it is noteworthy that these products were obtained when only 2 equivalents of the trifluoroborate coupling partner were used. Herein, we describe our efforts to build upon these advances to develop a more broadly applicable Chan–Evans–Lam coupling for the synthesis of trisubstituted vinyl ethers.

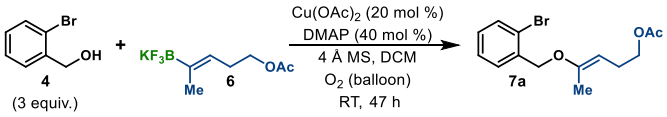
We began our investigation with the attempted coupling of 2-bromobenzyl alcohol (**4**) and disubstituted vinyl boronate **3a** using modified conditions from the Merlic group.[16] This coupling did not proceed efficiently even with the use of stoichiometric $Cu(OAc)_2$ and 20 equivalents of **4**. At best, we observed 40 % conversion of **3a** to vinyl ether **5** (Scheme 2). Conversely, when using trifluoroborate **3b** under modified conditions from Quach and Batey,[14] **5** was produced in 60 % NMR yield (Scheme 2). In contrast to Quach and Batey's conditions, we deemed it more practical to use the trifluoroborate as the limiting reagent. We attempted to make an analogous vinyl boronic acid coupling partner to **3b**, but found that this reagent was significantly more difficult to work with.[21] Furthermore, we empirically confirmed the necessity of powdered 4 Å molecular sieves, dichloromethane as the optimal solvent,[14] and oxygen as the preferred atmosphere.[22]



Scheme 2 Preliminary scouting experiments for the synthesis of disubstituted vinyl ether **5**.

Having confirmed optimal conditions for the synthesis of disubstituted vinyl ether **5**, we progressed towards the synthesis of the more challenging trisubstituted vinyl ether **7a** (Table 1). When the reaction was performed on 0.2 mmol scale, **7a** was produced in 43 % NMR yield (Entry 1). When performed on 1 or 2 mmol scale, **7a** was isolated in 51 % or 48 % yield, respectively (Entries 2 and 3). The addition of $CaCO_3$ had little effect on the reaction efficiency (Entry 4). The isolated yield could be slightly increased by adding trifluoroborate **6** in a portion-wise manner (Entry 5), although this was not generally adopted in favour of operational simplicity. After screening a variety of copper salts (Entries 6–8) and *N*-heterocyclic ligands,[23] we confirmed that the pairing of $Cu(OAc)_2$ and DMAP was ideal. Decreasing the catalyst loading led to a precipitous drop in yield (Entry 9). Conversely, by doubling the catalyst loading, no substantial improvement was observed (Entry 10).

Table 1 Selected optimization experiments for the synthesis of trisubstituted vinyl ether **7a**.



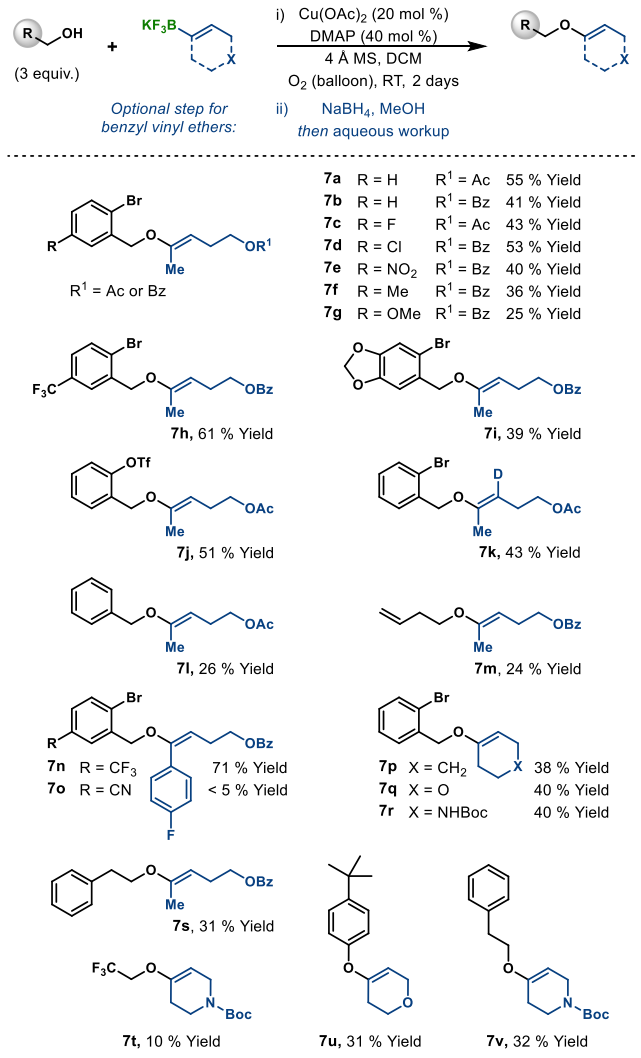
Entry	Deviation from Standard Conditions	Yield [a]
1	None	(43 %)
2	1 mmol scale [b]	51 %
3	2 mmol scale [c]	48 %
4	$CaCO_3$ (3 equiv.) additive; 1 mmol scale [d]	47 %
5	Portion-wise trifluoroborate addition [e]	55 %
6	$Cu(TFA)_2•xH_2O$ instead of $Cu(OAc)_2$	(10 %)
7	$Cu(OTf)_2$ instead of $Cu(OAc)_2$	(13 %)
8	CuTC instead of $Cu(OAc)_2$	(18 %)
9	10 mol % $Cu(OAc)_2$; 20 mol % DMAP	(11 %)
10	40 mol % $Cu(OAc)_2$; 80 mol % DMAP [f]	(44 %)

[a] Yields were determined by ^1H NMR using 4-bromoanisole as internal standard. Isolated yields are shown without parentheses. Unless specified, reactions were performed on 0.2 mmol scale. [b] Reaction was run for 36 h. [c] Reaction was run for 39 h. [d] Reaction was run for 45 h. [e] Reaction was performed on 0.7 mmol scale. [f] Reaction was performed on 1.3 mmol scale.

With functional conditions in hand, we explored the reaction scope (Table 2). Under the reaction conditions, benzyl alcohol substrates underwent a minor background oxidation to afford the corresponding benzaldehydes;[24] in many cases, these side products were difficult to separate from the desired vinyl ethers. On several occasions we tried removing the benzaldehyde impurity as a bisulfite adduct[25] by treatment with aqueous sodium bisulfite, but this resulted in vinyl ether decomposition. In contrast, rapid and quantitative benzaldehyde removal could be achieved by treating the crude, filtered reaction mixture with a sub-stoichiometric quantity (50–80 mol %) of sodium borohydride. A variety of trisubstituted vinyl ethers were prepared in synthetically useful yields. Despite using only 3 equivalents of the alcohol coupling partner, complex benzyl vinyl ethers **7h** and **7n** were isolated in 61 % and 71 % yield, respectively. The use of a deuterated

trifluoroborate enabled the synthesis of vinyl ether **7k** in 43 % yield. As illustrated by much of the scope, aryl bromides were well-tolerated as were an aryl chloride (**7d**) and an aryl triflate (**7j**). Cyclic trifluoroborates (**7p**–**7r**; **7t**–**7u**) also proved to be competent coupling partners. While the reaction worked best with benzyl alcohol coupling partners, homoallyl- (**7m**), 2-phenylethyl- (**7s**, **7v**), 2,2,2-trifluoroethyl- (**7t**), and 4-*tert*-butylphenyl (**7u**) vinyl ethers could also be accessed, albeit in diminished yield. Of practical consideration, this methodology was amenable to the use of solid alcohols, and in most cases, the excess alcohol could be recovered by column chromatography. Several limitations of the methodology are worth noting. Secondary alcohols, hindered primary (neopentyl) alcohols, and electron-deficient trifluoroborates were all incompatible in this reaction.[23] In stark contrast to **7n**, the benzonitrile-containing vinyl ether **7o** was inaccessible on preparative scale. This might be due to the known non-innocence of nitriles under Chan–Evans–Lam conditions.[26]

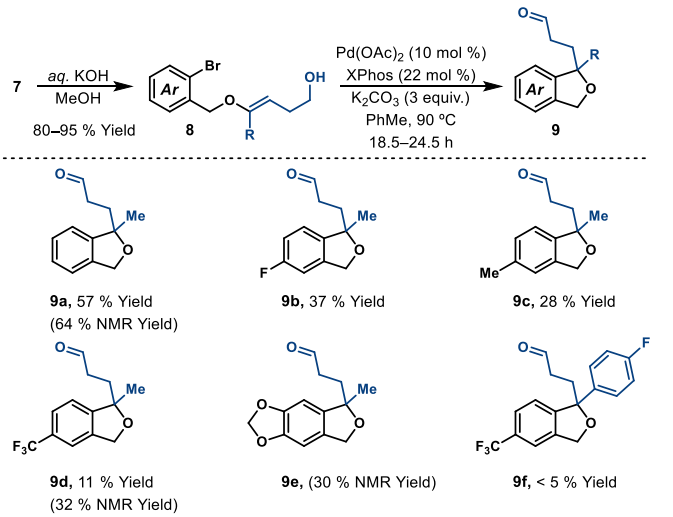
Table 2 Scope of the vinyl ether synthesis.[a]



[a] Reactions were performed on 0.3–1.4 mmol scale. Yields refer to purified products isolated after column chromatography.[23]

Aryl halide-tethered vinyl ethers can engage in palladium-catalyzed cyclization reactions to provide oxa-cyclic structures,[1b] including 1,3-dihydroisobenzofurans. This heterocyclic motif is present in many bioactive natural products and drug molecules, including the antidepressant Citalopram.[27] The Sigman lab has recently shown that vinyl ethers can participate in palladium-catalyzed redox-relay Heck reactions.[28] We sought to convert our vinyl ethers into aldehyde-functionalized 1,3-dihydroisobenzofurans by adopting Sigman's redox-relay strategy. To this end, the acetate group of **7a** was cleaved to unveil primary alcohol **8a**.[23] After surveying several palladium pre-catalysts, phosphine ligands, and bases, we identified successful conditions for the redox-relay Heck reaction (Table 3). Alcohol **8a** underwent the desired transformation to afford dihydroisobenzofuran **9a** in 64 % NMR yield and 57 % isolated yield. The use of XPhos as ligand was essential to the success of the reaction. Moreover, the aryl bromide was necessary for a clean reaction profile; use of the analogous aryl triflate afforded complex mixtures.[23] Fluoro- (**9b**) and methyl-substituted (**9c**) products were isolated in 37 % and 28 % yield, respectively. The trifluoromethyl-substituted product (**9d**) was produced in 32 % NMR yield and 11 % isolated yield after column chromatography. The low isolated yields resulted from the difficulty of purifying the relatively labile aliphatic aldehydes. Though not isolated, the electron-rich product **9e** could be observed (30 % NMR yield) on a small scale. Unfortunately, dihydroisobenzofuran **9f**, with a sterically demanding 4-fluorophenyl substituent, was inaccessible. Despite these modest results, it is worth noting that this transformation results in a rapid increase in complexity. In addition to the formation of the 1,3-dihydroisobenzofuran nucleus, a quaternary center is formed in concert with a synthetically useful aldehyde handle. This transformation also complements other 1,3-dihydroisobenzofuran syntheses.[29]

Table 3 Exploration of a redox-relay Heck reaction.[a]



[a] Reactions were performed on 0.1–0.4 mmol scale.[23] Unless specified, yields refer to purified products isolated after column chromatography. ^{1}H NMR yields were determined using trimethyl 1,3,5-benzenetricarboxylate as internal standard.

Building upon previous advances,[14] we have developed an operationally simple Chan–Evans–Lam coupling of vinyl trifluoroborates and primary aliphatic alcohols that delivers trisubstituted vinyl ethers in synthetically useful yields. Prior Chan–Evans–Lam syntheses of trisubstituted linear vinyl ethers mandated the use of neat allyl alcohol as both the coupling partner and the solvent.[17–19] In contrast, our reaction conditions are amenable to the use of more complex primary alcohols (including solids) using dichloromethane as the solvent. The reaction is particularly well-suited for the synthesis of complex benzyl vinyl ethers. Access to trisubstituted vinyl ether target compounds bearing aryl bromide substituents enabled us to demonstrate an intramolecular redox-relay Heck reaction for the synthesis of aldehyde-functionalized 1,3-dihydroisobenzofurans.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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