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Tetrahedron Letters 44 (2003) 4403–4406

TETRAHEDRON
LETTERS

Differentiating allylic and vinylic leaving groups for Pd catalysis. The use of vinyl iodide to facilitate room temperature activation of a vinyl C–X bond in the presence of allyl carbonate

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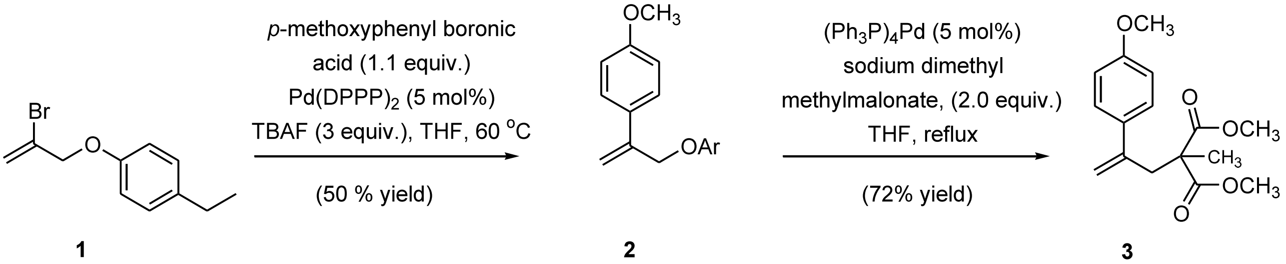
Received 24 March 2003; revised 3 April 2003; accepted 3 April 2003

Abstract—Ionization of allylic, stabilized leaving groups by Pd catalysis is a very facile process at or below room temperature, whereas oxidative addition of many vinyl or aryl C–X bonds requires heating. There are only a handful of examples in the literature where a vinyl leaving group can be activated in a competitive fashion in the presence of a suitable allylic one. In this report a series of polyfunctional olefin building blocks have been constructed that allow vinyl halides to be selectively and routinely activated in the presence of highly active allylic leaving groups. This differentiation is dependent solely on the bond strengths of the leaving groups involved and shows no temperature dependence to differentiate the two processes. © 2003 Elsevier Science Ltd. All rights reserved.

Our research group is interested in the development of small, polyfunctional olefin building blocks (templates) for use in modular organic synthesis using transition metal catalysis to affect sequential transformations of one, or of more than one mechanism.[1,2] For such olefin compounds, allylic leaving groups are generally considered to be much more readily activateable than the corresponding vinyl group (i.e. halides or pseudo halides).[3,4] For example the allylic bromide of 2,3-dibromo-1-propene is activated cleanly in the presence of the vinyl halide at rt and can be substituted with a number of suitable nucleophiles. The remaining vinyl halide can then be activated readily, albeit at elevated temperature (e.g. refluxing THF), and cross coupled with a variety of organometallic reagents.[1] We demonstrated for the first time that this reactivity profile can be reversed in a general, non-substrate specific manner.[5] That is, an olefin substrate (**1**) was designed with a vinyl halide that was activated preferentially by Pd in the presence of a suitable allylic leaving group (Scheme 1). In this case, the selectivity of the catalyst toward the vinyl bromide of **1**, when compared with 2,3-dibromo-1-propene, can be reasoned by the bond strengths of the leaving groups involved. This can be made practical for the synthetic chemist by considering the pK_a values of their corresponding acids.

While the development of olefin template **1** allowed us to change the order of Pd-mediated reactions involving polyfunctional olefins as we desired, and to demon-



Scheme 1.

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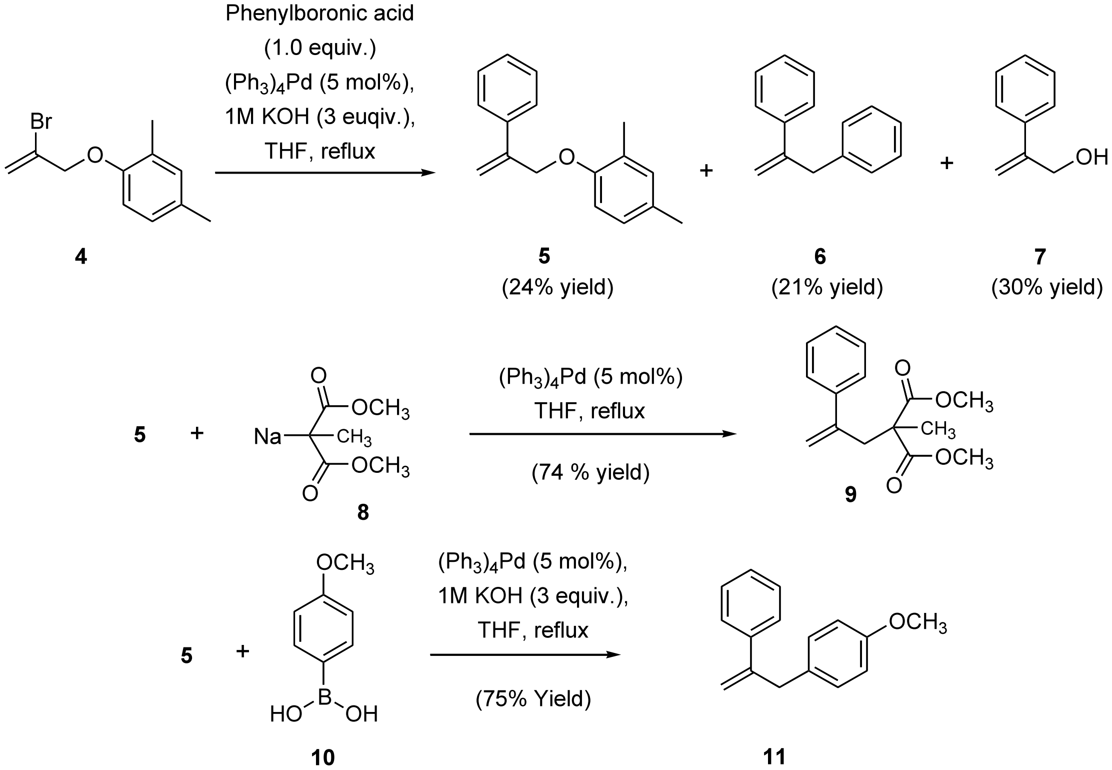
doi:10.1016/S0040-4039(03)00881-5

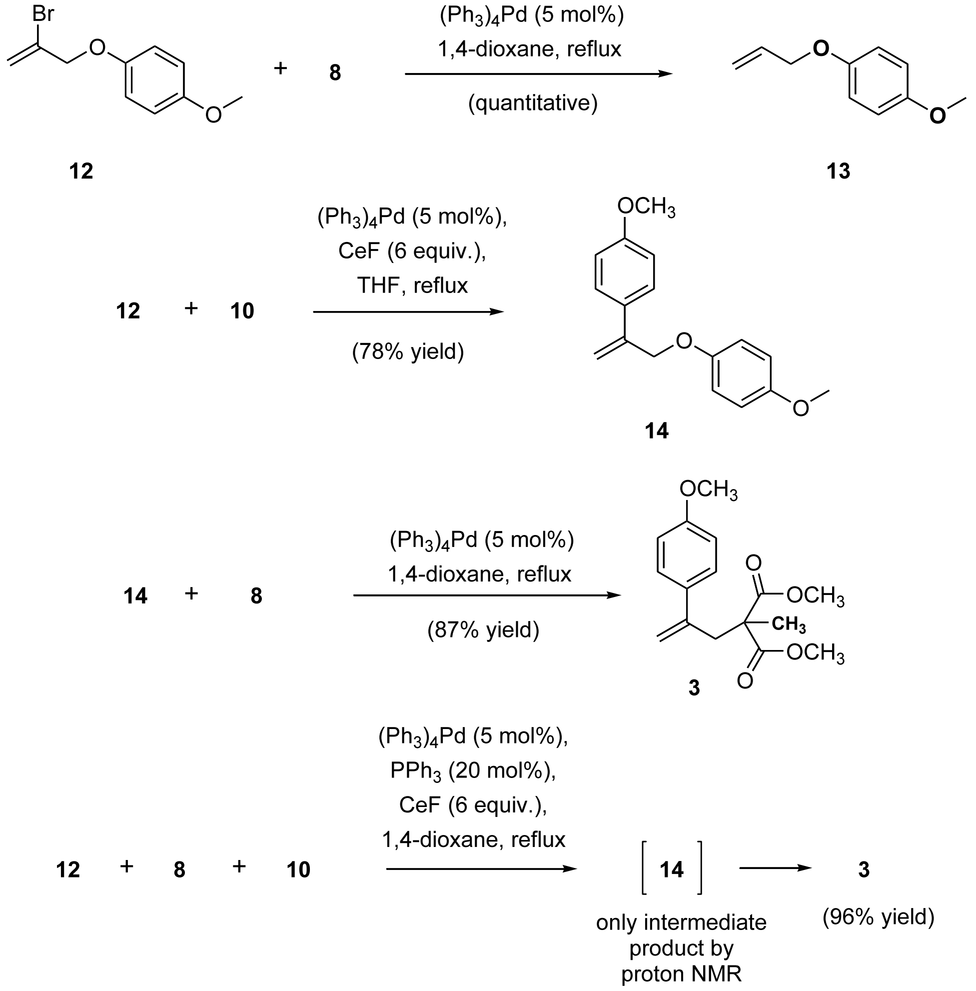
strate the application of this methodology synthetically,[5] the reactions still had to be monitored closely. With compound **1**, it was important that the temperature not exceed 60°C in the first step to ensure that no undesired allylic ionization was occurring. We sought to develop a second generation olefin template that was equipped with a suitable allylic leaving group such that the two competing Pd-mediated pathways (i.e. vinylic oxidative addition and allylic ionization) were energetically well separated so that close monitoring of temperature between reactions was not necessary. This would make olefin template use increasingly practical for the synthetic community.

In designing the new olefin template, there were two possibilities: increase the electron richness of the leaving group (i.e. increase the pK_a of its' conjugate acid) or decrease the bond strength of the vinyl substituent. In light of our initial success with phenoxide leaving groups, we opted first to adjust the substituent(s) on the phenol ring to diminish its leaving group ability. Olefin template **4** was prepared and treated to Suzuki coupling conditions[6] (Scheme 2). From the product distribution, and by monitoring the reaction's progress by NMR spectroscopy, it is clear that vinyl Br activation is the first event that takes place. However, ionization of the 2,4-dimethylphenoxide group and coupling of the Br are a closely related process energetically resulting in the formation of **6** and **7** from **5**. The phenol moiety on **5** was then activated by Pd to give either the product of nucleophilic substitution (**9**) or Suzuki coupling (**11**). Although an exhaustive set of compounds has yet to be made, it appears that simple alkyl groups are not electron rich enough to allow Pd to adequately differentiate allylic and vinylic leaving group activation.

The 2-bromo olefin template was re-equipped with the more electron-rich 4-methoxyphenol substituent (**12**) and subjected to an allylic substitution reaction in refluxing 1,4-dioxane (Scheme 3). Under these conditions, the phenol group did not ionize visibly and the major product (**13**) arose from oxidative addition of the vinyl bromide.[7] Next, the Br in **12** was cross coupled to give **14** in refluxing THF, again with no apparent activation of the phenol moiety. Compound **14** was reacted subsequently at ~100°C with malonate (**8**) to provide **3**. In a separate reaction, all three components (i.e. **12**, **8** and **10**) were put into the same flask in 1,4-dioxane at reflux and the reaction's progress followed by proton NMR spectroscopy. The cross coupling completed first selectively in ~20 min (**14**), which was followed in situ by the allylic substitution to give the final product (**3**). Thus, the reaction components can assemble themselves in a controllable fashion based on their inherent reactivities which can prove very useful synthetically. This result confirmed that a change in temperature was no longer necessary to differentiate the reaction pathways as all events took place in the same solvent at the same temperature.



Scheme 2.



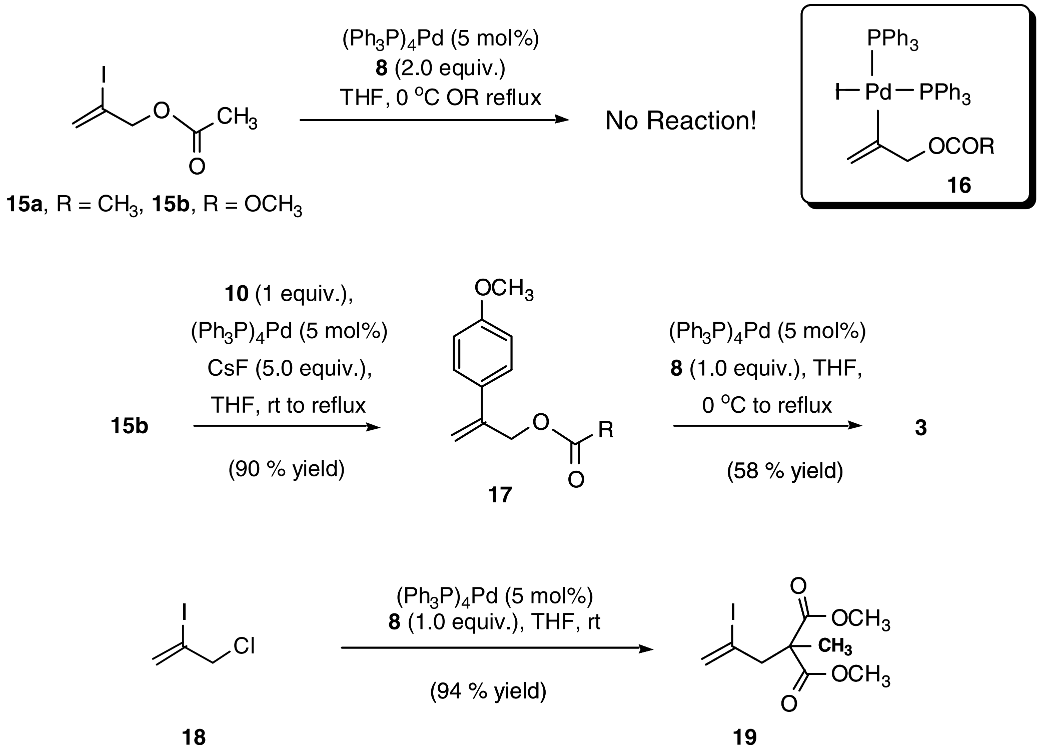
Scheme 3.

While the reaction pathways were now well differentiated electronically, we still wanted to have an allylic group that could be activated at a lower temperature to improve the method's general application. Thus, we turned our attention to the functional group on the olefin and replaced the bromide with an iodide. We discovered that we could now differentiate the vinyl position from the allylic position at rt (Scheme 4). When **15a** or **15b** were reacted under allylic substitution conditions, it appeared as though no reaction took place despite that fact that carboxylates and carbonates ionize at, or well below 0°C. In fact, oxidative addition had taken place and we identified intermediate **16** by proton and carbon NMR spectroscopy and mass spectroscopy.[8] In the absence of a suitable organometallic partner (i.e. not sodium malonate), the reaction could proceed no further. When we tried to cross couple **15b** at rt, metal–metal exchange was now the rate-limiting step and no reaction took place. However, heating to reflux allowed smooth conversion to **17** which was subsequently reacted with malonate (**8**) and substituted at the allylic position to yield **3**. Thus, once again we have a template in hand that not only allows us to change the order of reactivity of the catalyst from allylic ionization to oxidative addition of a vinyl halide, but to do so under very mild reaction conditions. It is interesting to note that when the leaving group of **15** was modified to a halide (i.e. **18**) that reactivity was then switched back to the allylic site, once again at rt.

In summary, we have developed a series of difunctional olefin templates that allow us to switch the regioselectivity of the Pd catalyst from the allylic site to the vinylic site of these useful 3-carbon building blocks. The selectivity is solely on the basis of electronic features, i.e. bond strength and anion stability. Hence, the pairings of functional groups will provide reliable reactivity when applied to other related systems.

Acknowledgements

Support for this research came from NSERC (Canada) and the Ontario Research and Development Challenge Fund (Ontario).



Scheme 4.

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5. Organ, M. G.; Arvanitis, E. A.; Dixon, C.; Cooper, J. T. *J. Am. Chem. Soc.* **2002**, *124*, 1288–1294.
6. All compounds in this report were characterized by proton and carbon NMR spectroscopy, infrared spectroscopy and high-resolution mass spectroscopy and/or combustion analysis.
7. Reduction product **13** was substituted subsequently with malonate under the identical reaction conditions which suggests that the malonate in the initial reaction was consumed in the reduction of **12**.
8. There are many examples of such stable Pd(II) complexes which can be reviewed on the Cambridge Crystallographic Data Base.