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Phosphine Catalyzed α-Arylation of Enones and Enals Using Hypervalent Bismuth Reagents: Regiospecific Enolate Arylation via Nucleophilic Catalysis

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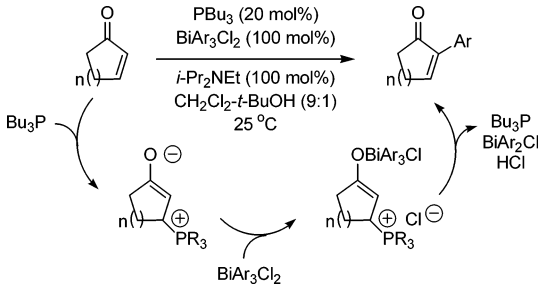
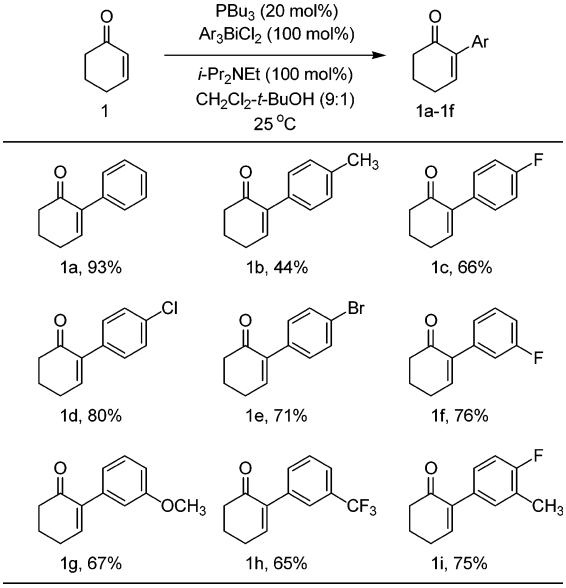
The development of catalytic methods for the regiospecific generation and capture of enolates via tandem conjugate addition−electrophilic trapping is currently under investigation in our lab. Here, enone hydrometallation (1,4-reduction),[1] enone carbometallation (1,4-addition),[2] and nucleophilic catalysis[3] have been applied to the regiospecific generation of enolate nucleophiles, which are found to engage in subsequent additions to aldehyde,[1a−c] ketone,[1d,e,2] ester,[2c] nitrile,[2c] activated alkene,[1a,b,3a,b] and Pd(II)-π-allyl[3c] partners. Further development based on this enone-electrophile template is potentially enabled through the use of *arenes* as terminal electrophiles. Indeed, while considerable effort has been devoted to transition metal catalyzed enolate arylation by way of ketone pronucleophiles,[4,5] general catalytic methods for the α-arylation of enones have not been described.[6,7] Here, we report a method for the regiospecific α-arylation of enones and enals under the conditions of nucleophilic catalysis. Specifically, exposure of cyclic enones or enals to 1 equiv of $BiAr_3Cl_2$ and Hunig's base in the presence of substoichiometric tributylphosphine results in aryl transfer to afford the corresponding α-aryl enones and α-aryl enals in good to excellent yield.

Scheme 1. Proposed Mechanism for Catalytic Enone α-Arylation under the Conditions of Nucleophilic Catalysis



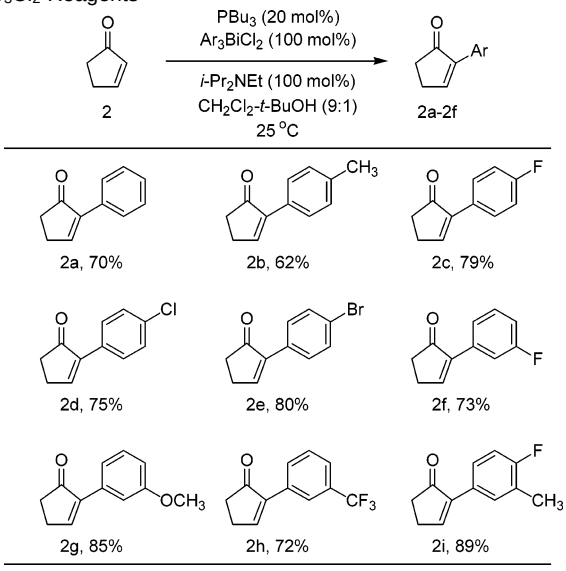
Triarylbismuth(V) reagents[8] such as $BiPh_3Cl_2$ are well-known to effect the arylation of alcohols[9] and amines,[10] as well as the C-arylation of phenols,[11] β-dicarbonyl compounds,[12] preformed alkali-enolates,[13] and enol silanes.[14] A catalytic mechanism for enone α-arylation under the conditions of nucleophilic catalysis using triarylbismuth(V) reagents is easily envisioned (Scheme 1). However, the feasibility of phosphine catalyzed enone α-arylation using triarylbismuth(V) reagents requires compatibility between tributylphosphine, a Lewis base, with the triarylbismuth(V) reagent, a Lewis acid. Additionally, Bi(V)-mediated phosphine oxidation should be slow with respect to aryl transfer pathways. To assess the feasibility of applying nucleophilic catalysis to the α-arylation enones, cyclohexenone **1** (100 mol %) was exposed to $BiPh_3Cl_2$ (100 mol %) in the presence of tributylphosphine (20 mol %) and Hunig's base (100 mol %) at ambient temperature in CH_2Cl_2-^{t}-BuOH solvent. Gratifyingly, the α-arylation product **1a** was obtained in 93% isolated yield as a single regioisomer, as determined by ^{1}H NMR analysis. Under these conditions, the

Table 1. Phosphine Catalyzed Arylation of Cyclohexenone Using $BiAr_3Cl_2$ Reagents[a,b]



[a] See Supporting Information for a detailed experimental procedure. [b] Isolated yields after purification by silica gel chromatography.

Table 2. Phosphine Catalyzed Arylation of Cyclopentenone Using $BiAr_3Cl_2$ Reagents[a,b]



[a] See Supporting Information for a detailed experimental procedure. [b] Isolated yields after purification by silica gel chromatography.

catalytic α-arylation of cyclohexenone **1** (Table 1) and cyclopentenone **2** (Table 2) was explored using diverse triarylbismuth(V) dichlorides. As demonstrated by the formation of α-arylation

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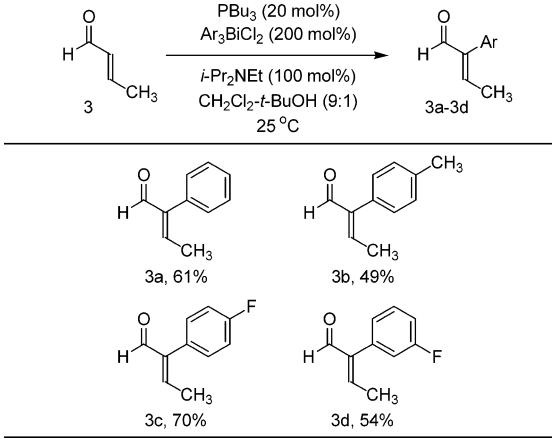
Table 3. Phosphine Catalyzed Arylation of Crotonaldehyde Using $BiAr_3Cl_2$ Reagents[a,b]



[a] See Supporting Information for a detailed experimental procedure. [b] Isolated yields after purification by silica gel chromatography.

products **1b**−**e** and **2b**−**e**, aryl transfer proceeds readily using para-substituted triaryl bismuth(V) dichlorides. However, it was found that strong π-donating substituents in the para-position diminish the efficiency of aryl transfer. For example, transfer of para-methoxy-substituted arenes occurs in greatly diminished yield. As demonstrated by the formation of α-arylation products **1f**−**h** and **2f**−**h**, meta-substituted triaryl bismuth(V) dichlorides transfer efficiently, even in the case methoxy-substituted systems. Finally, the transfer of disubstituted arenes is illustrated by the formation of α-arylation products **1i** and **2i**.

To further probe the scope of this transformation, alternative pronucleophiles were examined. The collective experiments reveal the pronucleophile must be substituted at the β-position, because of competitive anionic polymerization. Additionally, it appears that the pronucleophile must readily achieve an *s-trans*-conformation. For example, whereas cyclic enones such as cyclohexenone and cyclopentenone undergo arylation in good yield, corresponding acyclic systems provide α-arylated products in greatly diminished yield. Gratifyingly, it was found that β-substituted enals, such as crotonaldehyde **3**, participate in aryl transfer to provide the α-arylated enals **3a**−**d** in modest to good yields.

In summation, cyclic enones and β-substituted enals undergo regiospecific α-arylation under the conditions of nucleophilic catalysis using triarylbismuth(V) dichlorides. This approach complements related Pd-catalyzed methods for enolate arylation in several respects. Specifically, the use of enones as latent enolates enables regiospecific enolate generation, bromo-substituted arenes are readily transferred, and finally, preservation of the enone moiety in the product facilitates subsequent elaboration of the arylated products. Future studies will focus on the development of related reagents for aryl transfer under the conditions of nucleophilic catalysis and the application of such methods toward the total synthesis of therapeutically relevant target molecules.

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Supporting Information Available: Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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