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Letter

A Regioselective, One-Pot, Transition-Metal-Free α-Alkylation of Quinone Monoacetals for Various Organic Transformations

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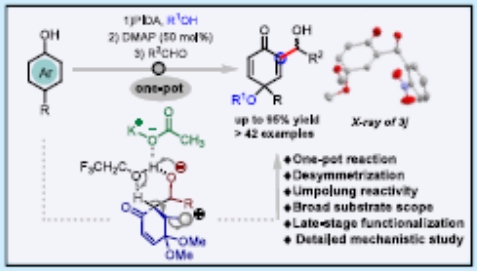
ABSTRACT: Regioselective reactions of biologically significant quinones are challenging. An unprecedented advancement in quinone monoacetal (QMA) chemistry is proposed for constructing regioselective and less explored α-alkylated QMAs through the Morita−Baylis−Hillman (MBH) reaction. Electrophilic QMAs were transformed to nucleophilic umpolung reagents for aldol-type condensation with several electrophiles. Mechanistic studies reveal that solvent (TFE:water (1:1)) and in situ-generated potassium acetate accelerate the reaction. The ensuing MBH adducts were scalable and underwent several post-synthetic transformations and late-stage functionalization.



Quinone-type compounds are highly important in organic synthesis because they are ubiquitous in the skeletons of natural products, pharmaceuticals, and functional materials, and are also valuable as synthetic intermediates.[1] Due to the presence of unsaturated enone structures, they are used mainly as versatile electrophiles in organic synthesis. However, including two carbonyl functionalities and enone units in one molecule causes several chemo- and regioselectivity issues with the electrophilic ring carbons, limiting the use of quinones in organic synthesis. *p*-Quinone monoacetals (QMAs) or 4,4-dimethoxycyclohexa-2,5-dienones, which are desymmetrized derivatives of *p*-benzoquinone, can be ideal candidates to explore regioselective reactions on quinone type compounds. The bifunctionality arising from enone and allyl-ketal moieties renders them versatile intermediates for making key polycyclic intermediates in natural product synthesis via acetal displacement,[2] 1,2-additions to carbonyls,[3] 1,4-nucleophilic addition,[4] allylic substitutions[5] with a variety of nucleophiles, Diels−Alder reaction,[6] tunable desymmetrization of cyclohexadienones,[7] and constructing a bridged cyclic framework[8] (Scheme 1A). The majority of the reactions reported for QMAs utilize them as electrophiles. The Morita−Baylis−Hillman (MBH) reaction[9] is an atom-economical, metal-free, base-catalyzed α-alkylation of activated alkenes (acting as nucleophilic partners) with aldehydes (acting as electrophilic partners). This reaction is generally catalyzed by nucleophilic bulky Lewis bases, such as tertiary amines and phosphines, and leads to the formation of a new carbon−carbon σ-bond, a stereogenic center, and provides small polyfunctionalized compounds.[9] Interestingly, the MBH reaction offers a means of converting electrophilic α,β-unsaturated carbonyl compounds, like QMA, to nucleophilic umpolung reagents. This reaction offers a simple route to further expand the activity of QMAs for the rapid construction of less explored α-alkylated quinones, leading to more complex structures, natural products, and potent drugs. *o*-Hydroxybenzyl alcohols have recently been recognized as versatile building blocks for constructing several natural products and biologically relevant heterocycles, utilizing *o*-quinone methide (*o*-QM) as intermediates.[10] *o*-Hydroxybenzyl alcohols are conventionally synthesized from the Grignard reaction or reaction of organolithium reagents with salicylaldehydes.[11]

All of these methods involve toxic and costly metal catalysts and ligands like *N*-heterocyclic carbenes (NHC). Carreño et al. recently reported α-alkylation of 4-hydroxy-4-substituted cyclohexadienones (*p*-quinols) to synthesize 4-hydroxy-2-(hydroxy(phenyl)methyl)-4-methylcyclohexa-2,5 dienones *via* MBH reactions (Scheme 1A).[12] The results suggested an essential role of the OH group of the *p*-quinol systems to initiate the MBH process, since a parallel reaction of *p*-quinol methyl ether (4-methoxy-4-methyl-2,5-cyclohexadienone), lacking the free OH, afforded the unchanged substrate with DABCO or DMAP. α-Alkylation of QMAs *via* the MBH reaction has not been explored so far. Therefore, dearomatization of low-cost and abundant phenols with hypervalent iodine(III) followed by MBH reaction may offer a metal-free,

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