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Nucleophilic Acylation of *o*-Quinone Methides: An Umpolung Strategy for the Synthesis of α-Aryl Ketones and Benzofurans

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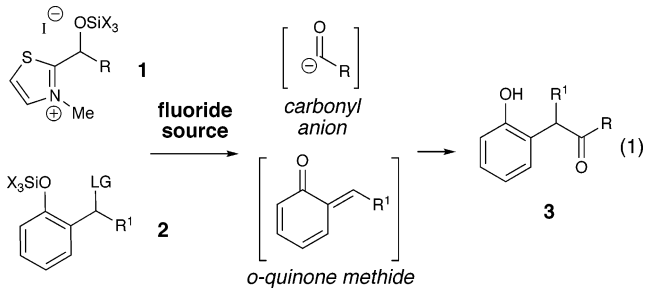
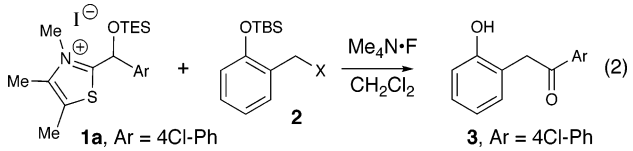
The inversion of normal reactivity patterns, or umpolung, enables the development of unconventional bond-forming strategies for the synthesis of biologically active target molecules.[1] The generation of acyl anion equivalents by the polarity reversal of carbonyl functional groups is one valuable umpolung tactic. Given our interest in unconventional bond-forming strategies,[2] we decided to concentrate on developing an acyl anion approach to synthesize α-aryl ketones. The preparation of α-aryl ketones is a challenging goal, and the majority of recent progress has focused on the development of transition-metal-catalyzed couplings of enolates and aryl halides.[3] Herein, we report the direct synthesis of α-aryl ketones (**3**) by the fluoride promoted addition of protected thiazolium carbinols (**1**) to quinone methides that are generated in situ from silyl protected phenols (**2**, eq 1).



We recently disclosed that fluoride promotes the nucleophilic acylation of nitroalkenes when stable *O*-silyl thiazolium carbinols (**1**) are employed as carbonyl anion precursor.[4] Interestingly, Rokita has reported that *O*-silylated phenols (such as **2**) produce *o*-quinone methides when exposed to fluoride.[5,6] We envisioned that combining compounds with the general structures of **1** and **2** with an appropriate fluoride source would simultaneously generate the corresponding carbonyl anion and *o*-quinone methide species *in the same reaction flask*. The subsequent combination of the nucleophilic carbonyl anion and electrophilic *o*-quinone methide should provide the desired α-aryl ketones (**3**) in a single operation.[7] The main challenge with this approach is the simultaneous generation of two highly reactive intermediates.

Our investigations of this new coupling strategy focused on the addition of protected thiazolium carbinol **1a** to *o*-quinone methide precursor **2** in the presence of tetramethylammonium fluoride (Table 1, eq 2).[8] The exposure of **1a** and **2a** to this fluoride source at −50 °C afforded an encouraging 43% yield of the desired α-aryl ketone **3** (entry 1). Optimization of the reaction conditions revealed that the best yields of **3** are obtained with lower temperatures (−78 °C, 23 h) followed by slowly warming to 23 °C (entry 2).[9,10] Another important factor affecting the yield of the reaction is concentration: the optimal value of 0.1 M affords 72% of **3** (entries 2−4). Although bromide leaving groups on the *o*-quinone methide precursor gives the highest yields, the corresponding benzylic chloride (**2b**) is also a suitable reaction partner (entry 2 vs entry 5), albeit in reduced yield (53%).[11] To lend support to the intervention of an *o*-quinone methide, a competition experiment was conducted with 1 equiv each of **1a**, **2a**, and 2-methoxybenzylbromide in the presence of 2 equiv of $Me_4N{\cdot}F$. Using the reaction conditions from Table 1, *only* aryl ketone **3** is observed with none of the methyl ether product that would arise from direct alkylation of the carbonyl anion.[10]

Table 1. Optimization of Carbonyl Anion Additions[a]



entry	temp (°C)	X	concentration	yield[b]
1	−50 to 23	Br (**2a**)	0.1 M	43%
2	−78 to 23	Br (**2a**)	0.1 M	**72%**
3	−78 to 23	Br (**2a**)	0.3 M	23%
4	−78 to 23	Br (**2a**)	0.05 M	45%
5	−78 to 23	Cl (**2b**)	0.1 M	53%

[a] See Supporting Information for details. [b] Isolated yield.

With the optimal parameters established for this umpolung reaction, we turned our attention to investigating the scope of the process (Table 2, eq 3). A brief survey of protected thiazolium carbinols reveals the reaction accommodates additional aromatic substituents (entries 1−3). When carbinols derived from alkyl and α,β-unsaturated aldehydes are employed as the acyl anion precursor, the desired α-aryl ketones are formed in moderate yields (not shown 40−53%). While these observations are encouraging, further investigations of this new strategy are necessary to accommodate these particular substrates.

An examination of the *o*-quinone methide component of the reaction indicates that variously substituted protected phenols are competent electrophile progenitors. In addition to the unsubstituted methides (e.g., derived from **2**), alkyl and aryl substitution at R^1 provides good yields of the corresponding acylated products (60% and 68%, entry 5). Substitution on the phenyl ring is also well tolerated. The quinone methide precursor derived from *o*-vanillin was able to produce the desired α-aryl ketone in 68% yield (entry 6). A high yield of product was also observed when the quinone methide precursor **2f** was subjected to the reaction conditions (75%, entry 7). For certain structures, the benzylic bromide reactants are unstable and could not be easily isolated. For these cases, the corresponding benzylic chlorides can be successfully employed in the reaction (entries 5 and 7).

This fluoride-induced umpolung strategy can be extended beyond *o*-quinone methides. For example, α-indoyl ketone compounds such as **12** can be accessed in good yield (70%) from the combination of a silyl protected gramine derivative **11** and thiazolium carbinol **1a** in the presence of 2.5 equiv of $Me_4N{\cdot}F$ (Scheme 1).[12]

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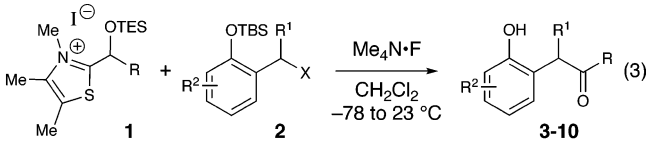
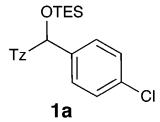
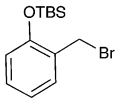
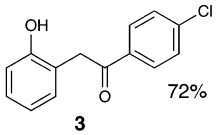
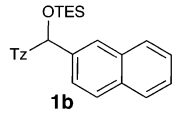
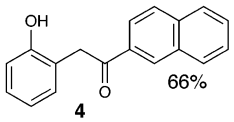
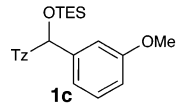
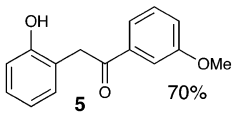
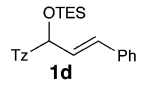
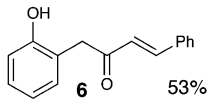
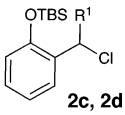
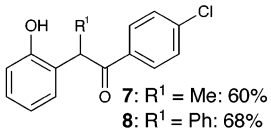
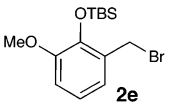
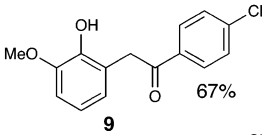
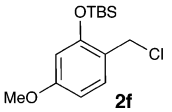
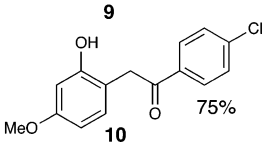
Table 2. α-Aryl Ketones Prepared from Thiazolium Carbinols (**1**) and Silylated Phenols (**2**)[a]



entry	carbinol[b]	halide	aryl ketone
1	 **1a**	 **2a**	 **3** 72%
2	 **1b**	**2a**	 **4** 66%
3	 **1c**	**2a**	 **5** 70%
4	 **1d**	**2a**	 **6** 53%
5	**1a**	 **2c, 2d**	 **7**: R^1 = Me: 60% **8**: R^1 = Ph: 68%
6	**1a**	 **2e**	 **9** 67%
7	**1a**	 **2f**	 **10** 75%

[a] See Supporting Information for reaction details. [b] Tz = 2-substituted 3,4,5-trimethylthiazol-3-ium iodide.

This new bond-forming process facilitates a total synthesis of the naturally occurring aromatase inhibitor, demethylmoracin I.[13] In the key step, highly substituted α-aryl ketone **14** is prepared in 62% yield from thiazolium carbinol **13**[9] and **2f** with Me_4N·F. The acid-catalyzed cyclization to the corresponding benzofuran **15** is accomplished in 79% yield. The prenyl group is installed using a Stille cross coupling reaction and global demethylation with lithium diphenylphosphanide[14] in refluxing THF affords demethylmoracin I. (Scheme 2).

In summary, the synthesis of α-aryl ketones via the direct nucleophilic acylation of *o*-quinone methides has been reported. In this umpolung process, a reactive carbonyl anion and *o*-quinone methide are generated in the same flask by the addition of fluoride ion and then undergo productive bond formation to yield the desired adducts. Investigations into the utility and applications of thiazolium carbinols as unique acyl anion precursors are ongoing in our laboratory.

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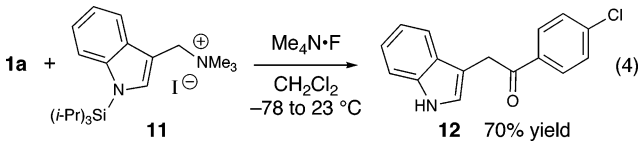
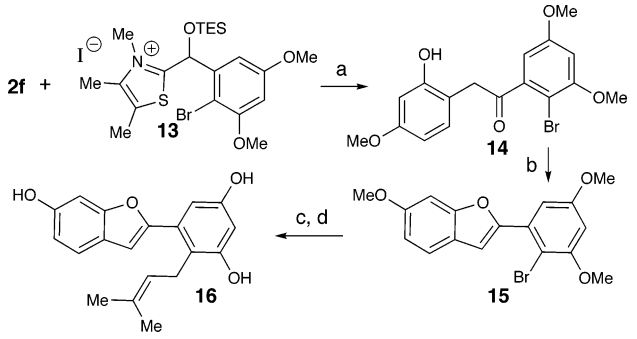
Scheme 1



Scheme 2. Synthesis of Demethylmoracin I[a]



[a] Conditions: (a) Me_4N·F, CH_2Cl_2, −78 to 23 °C, 62%; (b) Amberlyst 15, 4 Å Sieves, CH_2Cl_2 79%; (c) prenyl tributyltin, $PdCl_2$(dppf), DMF, 100 °C, 76%; (d) *n*BuLi, $PHPh_2$, THF, 61%.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The yield of **3** is lower (45%) when incubating the reaction at −78 °C for 1 h (vs. 23 h) followed by warming to 23 °C.
(10) See Supporting Information for details.
(11) The combination of **1a** and Me_4NF with benzyl bromide affords only low yields of benzyl ketone under the best conditions from Table 1.
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