THE ENOLONIUM ION: UMPOLUNG STRATEGIES FOR THE α–FUNCTIONALIZATION OF CARBONYLS

Reported by Sydney McKee October 22, 2020

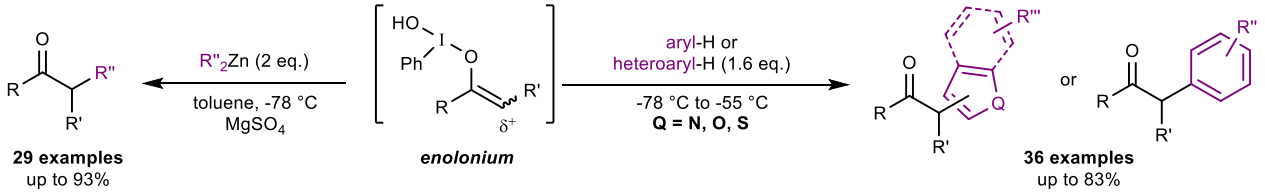
INTRODUCTION

The carbonyl functional group is a versatile chemical handle in organic synthesis. The acidic nature of its α–protons allows for deprotonation to form an enolate, and subsequent attack of an electrophile furnishes a plethora of potential functionalizations. The advent of transition metal/organocatalysis and chiral auxiliaries permits stereoselective transformations. However, transition metals are often expensive and toxic, chiral auxiliaries mandate a final cleavage step, and incorporation of heteroatoms necessitate their prior masking as an electrophile. An alternative approach, originally coined by Wittig and later popularized by Seebach and Corey, is the notion of umpolung chemistry – the reversal of polarity.[1] Historically, this technique generated acyl anion equivalents with dithiane, and more modern methods employ *N*-heterocyclic carbenes (NHCs).[1] Conversely, hypervalent iodine I(III) reagents or pyridine *N*-oxides either in the presence of activated amides or alkynes produce the "enolonium ion" that reacts with nucleophiles at the now electrophilic α–position. This alternative approach offers safer handling of I(III) species and orthogonal functional group tolerance.

ALKYLATIONS AND ARYLATIONS

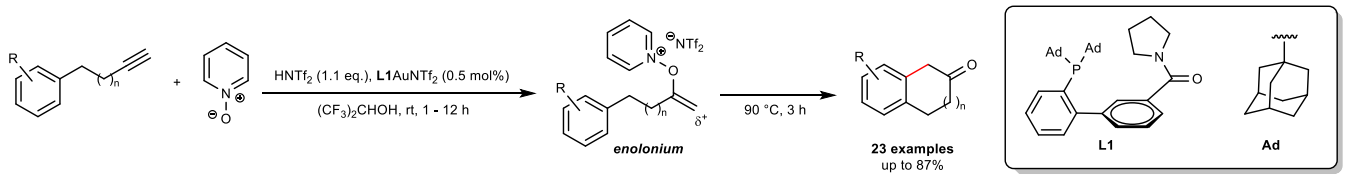
In 2015, Szpilman and coworkers achieved α–alkylation through oxidative umpolung of 1,3-bis carbonyl and simple ketone substrates with I(III) reagents.[2] That same year, they described repurposing Evans chiral auxiliary for the stereoselective alkylation of a limited scope of β–ketoimides, which reported enhanced stereoselectivity compared to traditional methods.[3] Furthermore, this lab established a method for α–arylation of ketones under similar conditions with heteroarenes and arenes, which showed an identical regioselective pattern to electrophilic aromatic substitution (Scheme 1).[4]

Scheme 1. Alkylation and arylation strategies by the Szpilman group with I(III) reagents[2,4]



Just this year, Sousa e Silva et al. expanded umpolung arylation to cyclic enones with I(III) reagents and included heterocyclic, electron-poor, and electron-rich arenes in their scope.[5] As noted, generation of an enolonium ion is not limited to I(III) species. The gold-catalyzed addition of pyridine *N*-oxides into unactivated terminal alkynes to form *N*-alkenoxypyridinium salts, as described by Xu et al., allowed for the one-pot synthesis of fused medium-ring ketones with tethered arene nucleophiles (Scheme 2).[6]

Scheme 2. Gold catalyzed synthesis of *N*-alkenoxypyridinium salts for umpolung arylation[6]



INCORPORATION OF HETEROATOMS

In 2019, Maulide and coworkers leveraged chemoselective activation of amides with triflic anhydride; subsequent addition of 2,6-lutidine *N*-oxide generated enolonium species.[7] Addition of TBAT as the nucleophilic fluorine source furnished α–fluorinated amides with substrates containing olefins, alkynes, nitriles, and other carbonyl groups. The same year, Martín-Matute et al. developed an umpolung strategy for the regioselective synthesis of α–alkoxy ketones with iridium enolates using I(III) reagents to promote the polarity reversal.[8] Although the carbonyl substrate scope was extensive, the incorporated alkoxy group was largely constrained to methoxy. Lastly, Mizar and Wirth attempted a stereoselective umpolung strategy with I(III) reagents and silyl enol ether tethers containing various unmasked heteroatom nucleophiles.[9] Synthetically useful enantioselectivity was not achieved until after the implementation of a chiral I(III) reagent in stoichiometric quantities. Albeit these examples demonstrate that chemoselective, regioselective, and stereoselective transformations are attainable individually via umpolung, rarely does a strategy encompass all three.

SUMMARY AND OUTLOOK

While classical methods incorporating alkyl groups, aryl groups, and heteroatoms will never lose relevance, umpolung is an alternative strategy to consider, especially in the context of functional group tolerance and safer handling of I(III) reagents over transition metals. However, substrate scopes are often biased and only include one enolizable position or mandate prior functionalization to control regioselectivity. For *N*-alkenoxypyridinium salts, the resulting carbonyl is necessarily a ketone, which must arise from a terminal alkyne. Additionally, stereoselective versions are scarce and usually require either the utilization of a chiral auxiliary or stoichiometric chiral hypervalent iodine reagents. For this technique to become more popularized, variations that reflect the importance of selectivity are essential. To accomplish this, more robust mechanistic studies must be undertaken.

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