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Zn(II)-Catalyzed Addition of Aromatic/Heteroaromatic C(sp^2)–H to Azoalkenes: A Polarity-Reversed Arylation of Carbonyl Compounds

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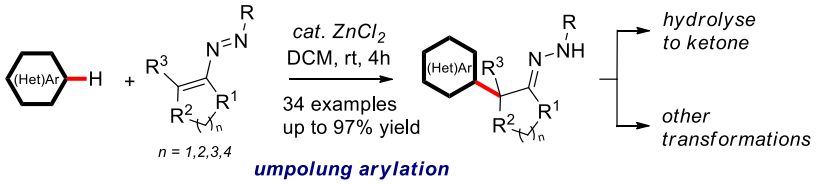
Supporting Information Placeholder



ABSTRACT: An umpolung α-(hetero)arylation strategy that involves the Michael-type reaction between electron-rich (hetero)aromatic substrates and azoalkenes is developed. The reaction proceeds under very mild conditions at room temperature and in the presence of inexpensive, non-toxic $ZnCl_2$ catalyst to provide access to otherwise inaccessible hydrazone structures. Subsequent hydrolysis of these latter to ketones, as well as the other valuable synthetic transformations to a variety of heterocyclic scaffolds demonstrate the usefulness of this protocol.

The direct installation of an aryl/heteroaryl substituent into the α-position of ketone has proven to be a transformation of great utility in pharmaceutical, agrochemical and organic synthesis.[1] As result, there is an ever-growing number of methods reported in literature,[2–4] most of them involving the addition of organometallic species or preformed enolates/azaenolate to halide/pseudohalide. Despite significant advances in transition metal promoted carbon-carbon bond-forming reactions have been made over the years, a general catalytic arylation/heteroarylation exploiting the C−H bonds of (hetero)aromatics,[5] the most abundant moiety in organic molecules, remains elusive. From the viewpoints of efficiency, sustainability, atom- and step-economy, the replacement of C−X with C−H bonds that are unreactive under traditional approaches is therefore highly appealing.

A polarity-reversed strategy[6] to introduce aryl substituents into the α-position of carbonyl compounds would employ unconventional reactivity patterns, such as azoalkenes[7–9] ("umpoled" carbonyl compounds) in the context of a Michael addition. With this objective, the transformation of a carbonyl group into a hydrazone functionality (d^2-*to*-a^2) represents an intriguing alternative to conventional strategies (Figure 1). Realizing the need for a practical and more sustainable catalytic arylation/heteroarylation method, we report herein the first Lewis acid-catalyzed addition of activated (hetero)aromatic C−H substrates[10] (π nucleophiles) to azoalkenes.[11]

This protocol is remarkable in its efficiency and selectivity upon employing available non-preactivated starting materials such as arenes or heterocycles themselves. In addition, it avoids the use of strong bases, oxidants and precious/toxic transition metals such as palladium and nickel, making this reaction an attractive complementary approach to produce α-aryl ketone surrogates in mild reaction conditions.

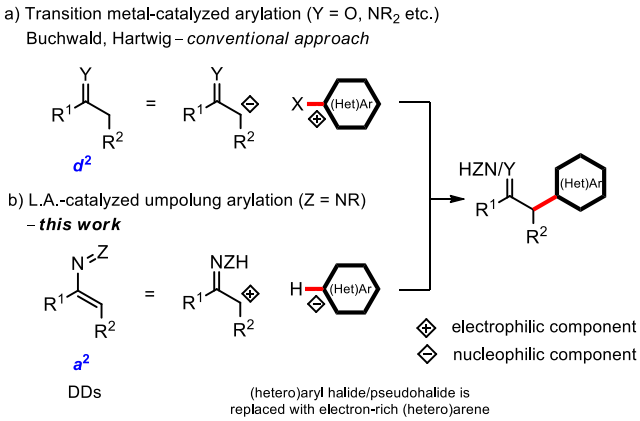
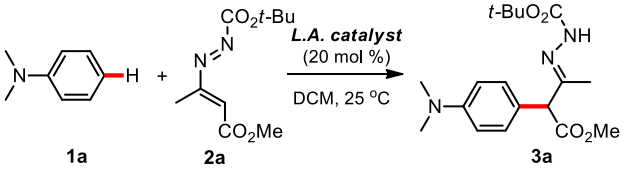


Figure 1. Comparison of component polarization in conventional and umpolung α-arylation reaction.

To test the feasibility of our idea, we began with the model reaction between *N*,*N*-dimethylaniline (**1a**) and azoalkene **2a**, which was screened with common Lewis acid catalysts in CH_2Cl_2 (Table 1). Notably, no product was detected in the absence of catalyst over 48 hours at room temperature (Table 1, entry 1). Gratifyingly, the reaction was productive with different Zn(II) salts. Among them, low cost $ZnCl_2$[12] catalyst was found to be superior affording a yield of 64% for **3a** (entry 4). We observed that the efficiency of the reaction was improved to 78% yield when 1.3 equiv. of azoalkene **2a** was used (entry 12). On the other hand, lowering the catalyst loading from 20 to 10 mol% resulted in a decrease in yield, giving **3a** in a 67% yield (entry 13). Interestingly, in the presence of other Lewis acids such as $InBr_3$, $FeCl_3$, CuI, $Cu(OTf)_2$, $Bi(OTf)_3$ and $Sc(OTf)_3$, no product or significantly lower yields were obtained.

Table 1. Michael Addition of *N*,*N*-Dimethylaniline (1a) with Azoalkene 2a.[a]



entry	catalyst	time (h)	yield (%)[b]
1	–	48	0
2	$InBr_3$	48	0
3	$Zn(OAc)_2$	48	< 5
4	$ZnCl_2$	1.0	64
5	$ZnBr_2$	4.0	46
6	$FeCl_3$	18	< 5
7	CuI	48	0
8	$Cu(OTf)_2$	0.4	0
9	$Zn(OTf)_2$	5.0	61
10	$Bi(OTf)_3$	48	5
11	$Sc(OTf)_3$	24	23
12[c]	$ZnCl_2$	1.0	78
13[c,d]	$ZnCl_2$	1.0	67

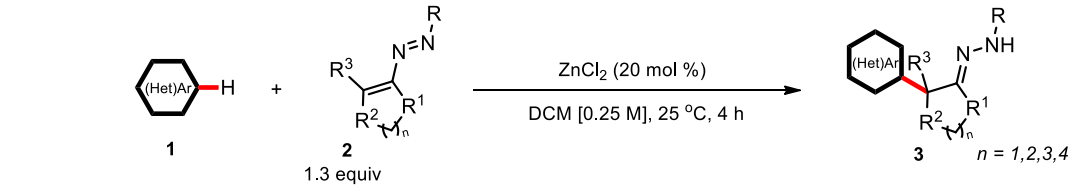
[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), cat. (0.1 mmol, 20 mol %), DCM (2.0 mL), 25 °C for the indicate time. [b]Isolated yields. [c]1.3 equiv of **2a** was used. [d]10 mol % cat. was used.

With the optimized reaction conditions in hand, we next focused our attention on the substrate scope (Scheme 1). In all cases, the reaction reached completion within 4 hours at room temperature, and the exclusive *para*-substitution was observed. As highlighted in Scheme 1A, aromatic and heteroaromatic substrates were employed as nucleophiles in Michael reaction to give the corresponding compounds **3a–o**. For example, good yields were obtained when simple arenes such as *N*,*N*-diethylaniline (**1b**) and *N*-methyl-*N*-(prop-2-yn-1-yl)aniline (**1c**) were coupled with azoalkene **1b** to give **3b** and **3c**, respectively. The use of *N*,*N*-dimethyl-1-naphthyl-amine (**1d**) generated the product **3d** in excellent yield (95%). Furthermore, *N*,*N*-dimethylaniline **1e** and **1f** bearing electron-donating substituents such as methyl and methoxy on the phenyl ring performed very well to give the desired products (**3e** and **3f**, 73% and 86%, respectively).

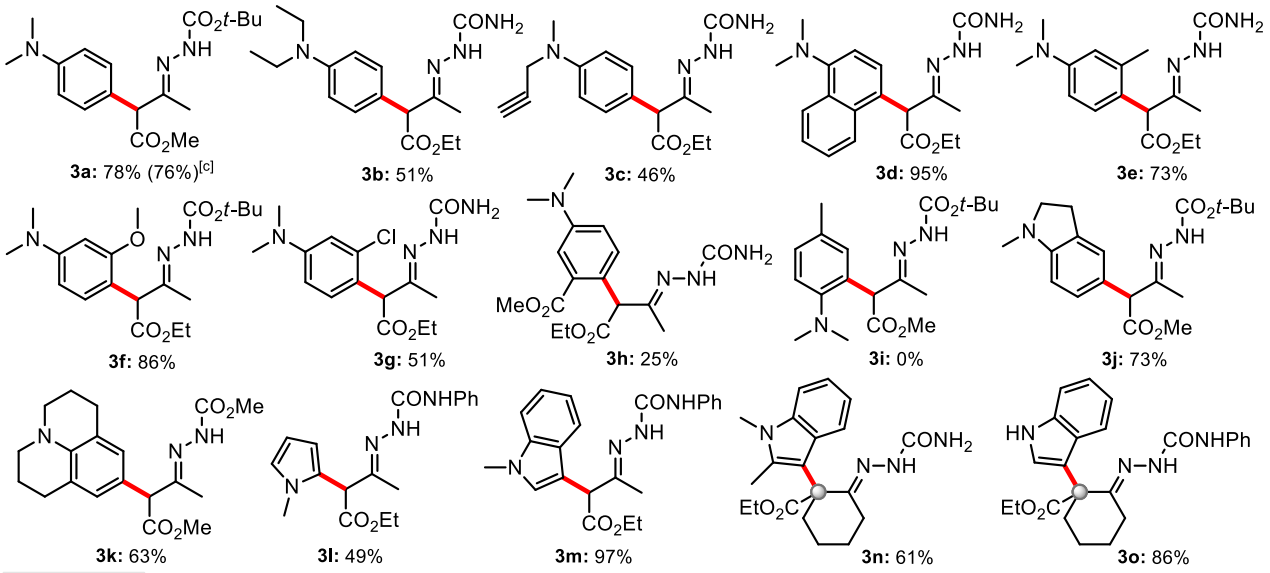
In comparison, the reaction of electron-withdrawing chlorine and ester *N*,*N*-dimethylanilines exhibited lower reactivity, affording products **3g** (51%) and **3h** (25%) in lower yields, presumably due to their reduced nucleophilicity. Notably, when *N*,*N*-dimethyl-*p*-toluidine (**3i**) was used as a substrate, no *ortho*-substitution was observed. Also, (hetero)cyclic reactants e.g., *N*-methylindoline (**1j**), julolidine (**1k**), *N*-methylpyrrole (**1l**), *N*-methyl-indole (**1m**), *N*-methyl-2-methyl-indole (**1n**), and *N*H-indole (**1o**) were readily converted into the desired Michael adducts **3j–o** in satisfied isolated yields (49–97%).

Next, we examined the scope of the azoalkene partners. As revealed in Scheme 1B, the reaction was applicable to differently acyclic and cyclic substituted azoalkenes **2a–w** (R = COY; Y = OMe, OEt, O*t*-Bu, OBn, NH_2, NHPh; R^1 = Me, Pr; R^2 = H, CO_2Et; R^1–R^2 = $(CH_2)_{3\text{-}6}$; R^3 = COX; X = OMe, OEt, O*i*-Pr, O*t*-Bu, NMe_2, NEt_2; $PO(OMe)_2$; Ph). Thus, a remarkably broad range of substituents can be accommodated to the hydrazone products, and importantly, it also provides access to synthetically challenging α-quaternary centers (e.g., **3n**, **3o**, **3ab**, **3ac**, **3ad**, **3ae**, and **3ai**). Also, incorporation of a five-, six-, seven-, and eight-membered ring in the hydrazone structure was also well tolerated. Regarding the *N*-protecting groups for the *N*1 atom of azoalkenes, it was found that better results were obtained in the cases of alkoxycarbonyl groups than aminocarbonyl groups (Scheme 1, **3a** *vs.* **3u**, **3e** *vs.* **3af** and **3f** *vs.* **3ag**). Finally, our reaction was performed on a gram scale, yielding 1.33 g of the desired product **3a** without loss of yield (76%). It should be noted that no detectable formation of the bis-adducts were observed in all cases.[10d]

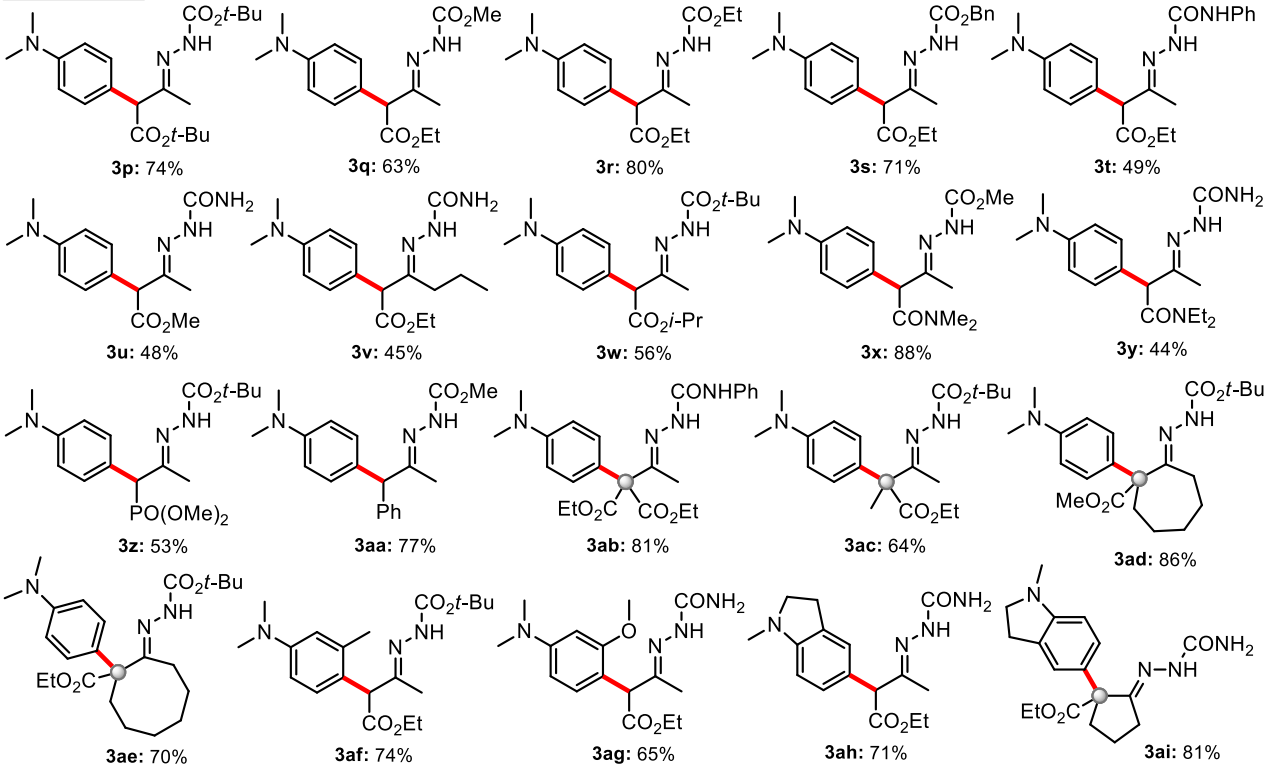
Scheme 1. Substrate Scope.[a,b]



A: arenes/heteroarenes



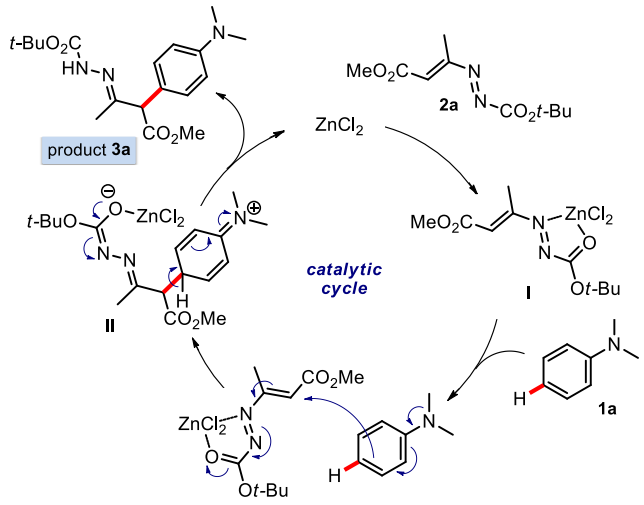
B: azoalkenes



[a]Reaction conditions: **1** (0.5 mmol), **2** (0.65 mmol), $ZnCl_2$ (0.1 mmol, 20 mol %), DCM (2.0 mL), 25 °C, 4 h. [b]Isolated yields. [c]**3a** (1.33 g) was obtained in 5.0 mmol scale.

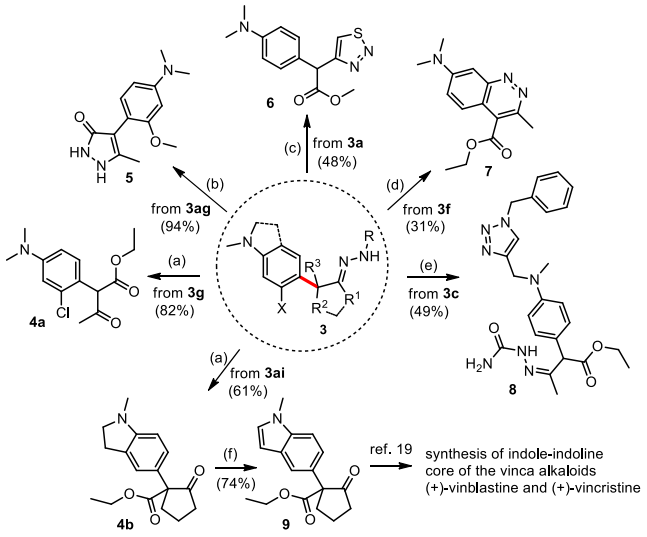
A possible mechanism for the $ZnCl_2$-catayzed Michael addition reaction between *N*,*N*-dimethylaniline (**1a**) with azoalkene **2a** is depicted in Scheme 2. **2a** was activated upon chelation to Zn(II) to generate intermediate **I**,[13] which undergoes a nucleophilic addition of *N*,*N*-dimethylaniline (**1a**) from the *para* position to form intermediate **II**. Subsequent rearomatization and protonation of the hydrazone via [1,5-H] shift, lead to adduct **3a** with regeneration of the Zn(II) catalyst.

Scheme 2. Proposed Mechanism for $ZnCl_2$-Catalyzed Michael reaction.



To demonstrate the utility of these ketone hydrazones as building blocks in syntheses, various transformations were investigated (Scheme 3).

Scheme 3. Synthetic Applications.[a]



[a]Reaction conditions: (a) Amberlyst-15H, $(CH_3)_2CO/H_2O$ 9:1, reflux, 2 h. (b) K_2CO_3, EtOH, reflux, 3 h. (c) $SOCl_2$, DCM, rt, 2 h. (d) $Cu(OAc)_2{\cdot}H_2O$, toluene, reflux, 1.5 h. (e) Benzyl azide, $Cu(OAc)_2{\cdot}H_2O$, sodium ascorbate, DCM/H_2O 1:1, rt, 3.5 h. (f) Pd/C, toluene, reflux, 6 h.

As a preliminary test of these, regeneration of carbonyl function[14] (path a) from representative hydrazones **3g** and **3ai** to give ketones **4a** and **4b**[15] respectively, was conducted. Cyclization of hydrazone **3ag** under basic condition furnished 1*H*-pyrazol-3(2*H*)-one **5** in 94% yield (path b). Also, transformation of **3a** into 1,2,3-thiadiazole **6** via Hurd–Mori-type reaction was realized using thionyl chloride (path c).[16] Subsequent six-membered heterocyclization of **3f** afforded cinnoline **7** in the presence of $Cu(OAc)_2{\cdot}H_2O$ as a promoter (path d).[17] Then a further functionalization with participation of an alkyne-group by CuAAC (azide-alkyne cycloaddition)[18] of **3c** with benzyl azide yielded the 1,2,3-triazole derivative **8** in 49% yield (path e). Finally, the synthetic potential of this arylation method was tested carrying out the preparation of compound **9** (from **4b**[15]) as precursor of bis-indoles related to the core of (+)-vinblastine and (+)-vincristine (path f)[19].

In conclusion, we have developed an efficient, practical and scalable approach to the synthesis of α-(hetero)aryl-hydrazones including those with an α-quaternary center. This umpolung arylation/heteroarylation reaction requires the simple combination of an electron-rich (hetero)aromatic substrate and an azoalkene, and proceeds in a highly *para*-selective manner. The method enables unprecedented, atom-economical access to a variety of simple α-aryl carbonyl surrogates directly from readily available starting materials (no preactivation of (hetero)aryl reagents is needed) avoiding the use of expensive/toxic catalysts, high temperatures and minimizing the production of salts waste. We are sure that this transformation, that overcomes the limits/complications associated with traditional α-(hetero)arylation, represents a robust alternative to existing methods. Furthermore, synthetic usefulness of these challenging synthons, were demonstrated. Studies directed toward the asymmetric version of this transformation are underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental details, procedures, and characterization of all compounds (PDF).

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Notes

The authors declare no competing financial interest.

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