A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202005286

Link to VoR: https://doi.org/10.1002/anie.202005286

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COMMUNICATION

Direct Umpolung Morita-Baylis-Hillman like α-Functionalization of Enones via Enolonium Species

Shlomy Arava,[a]§ Sourav K. Santra,[a]§ Gulab K. Pathe,[a] Raja Kapanaiah,[a] and Alex M. Szpilman*[a]

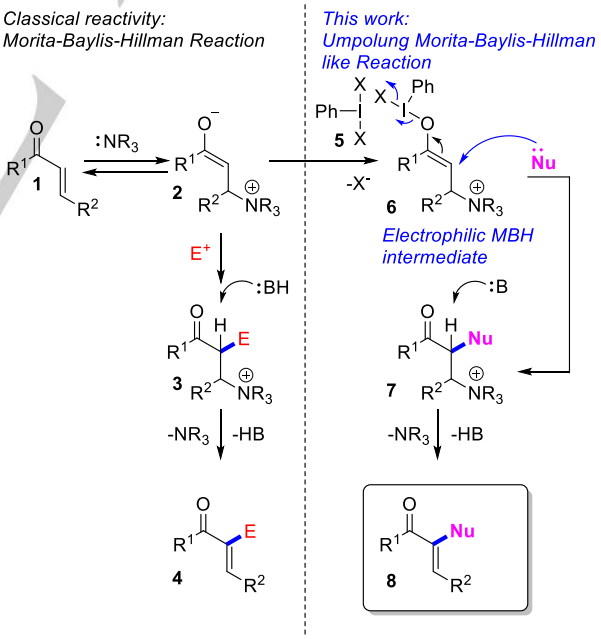
This paper is dedicated to Professor Mario D. Bachi

Abstract: Herein we report the on Umpolung of Morita-Baylis-Hillman type intermediates and application to the α-functionalization of enone C-H bonds. This reaction gives direct access to α-chloro-enones, 1,2-diketones and α-tosyloxy-enones. The latter are important intermediates for cross-coupling reaction and, to the best of our knowledge, cannot be made in a single step from enones in any other way. The proposed mechanism is supported by spectroscopic studies. The key initial step involves conjugate attack of an amine (DABCO or pyridine), likely assisted by hypervalent iodine acting as a Lewis acid leading to formation of an electrophilic β-ammonium-enolonium species. Nucleophilic attack by acetate, tosylate or chloride anion is followed by base induced elimination of the ammonium species to give the noted products. Hydrolysis of α-acetoxy-enones lead to formation of 1,2-diketones. The α-tosyl-enones participate in Negishi coupling reactions under standard conditions.

The development of new methods that defy the constraints of classical reactivity is an important goal in order to further the science of chemistry. Reactivity umpolung, a revolutionary concept originally defined by Seebach is one of the ways this goal may be attained.[1]

The classical Morita-Baylis-Hillman (MBH) reaction gives unique access to α-functionalized enones.[2],[3] The reaction takes place through attack of a tertiary phosphine[2a] or amine[2b] at the β-position of an enone **1** leading to an β-ammonium or β-phosphino enolate zwitterion like **2** (See Scheme 1).[3] This in turn reacts with an electrophile, such as an aldehyde to give an intermediate **3** followed by base assisted elimination of the ammonium or phosphonium group to reestablish the alkene bond and give product **4**. A wide range of electrophiles have been utilized in the reaction leading to a diverse range of products.[3] We envisioned that if the intermediate species **2** could be trapped by a suitable oxidant such as an Iodine(III) reagent **5** this would afford a new electrophilic species **6**. This would result in a novel mechanistic possibility namely reaction with nucleophiles. Obviously, this paradigm would make possible the development of numerous new reactions only limited by imagination and the type of compatible oxidants and nucleophiles available. Herein we describe the successful umpolung of a Morita-Baylis-Hillman intermediate (i.e. **6**, Scheme 1) and its reaction with three different nucleophiles namely anionic oxygen nucleophiles acetate and tosylate as well as chloride anion.

Recently, we reported the first characterization of ketone and hypervalent iodine[4] derived enolonium species.[5] The mechanistic insight gained from this study led to the development of a series of new C-C,[5-6] and C-N[7] bond forming reaction. We envisioned that if a Lewis acidic iodine(III) reagent[8] **5** could be combined with a tertiary N- or P-nucleophile this would drive the formation of an intermediate enolonium species **6** (R = PhI(III)-X) from enones **1**. Of course alkenes are readily oxidized by hypervalent iodine reagents[9] **5** as are nitrogen or phosphorous nucleophiles. In addition, the desired nucleophile might compete with the ligands (X) on iodine(III) **5** as well as the tertiary base. These potential side reactions would have to be avoided by the judicious choice of iodine(III) oxidant **5**, tertiary nucleophile (NR_3) and final nucleophile (Nu) (Scheme 1). The relative ease of oxidation of phosphines lead us to focus on tertiary amines as activators for the enone system **1**.



Scheme 1. Classical versus the Umpolung MBH reaction.

As expected, numerous combinations of hypervalent iodine reagents, tertiary amines and nucleophiles failed to give any product at all. Combinations tested including iodine(II) reagents such as Koser's reagent, [Bis(trifluoroacetoxy)iodo]benzene, or iodosobenzene in combination with typical amines used as MBH

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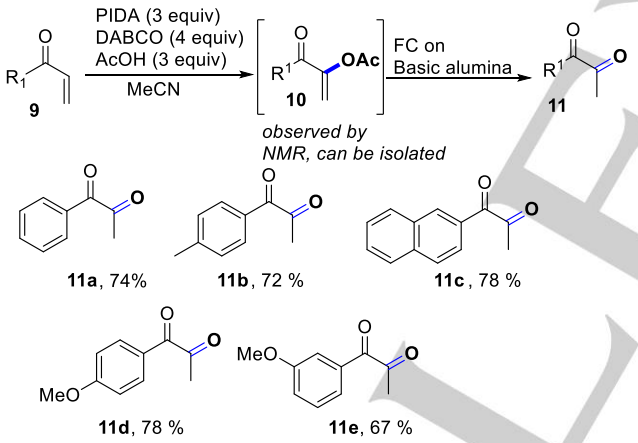
catalysts including pyridine, methoxy-pyridines, DMAP, and DABCO. These were tested both in the presence and absence of Lewis acids, including boron trifluoride etherate. A variety of solvents such as dichloromethane, DMF and acetonitrile were examined.

For successful proof of concept, we initially found it necessary to reduce the number of potential side-reactions by using phenyliodine(III) diacetate (PIDA) as both the oxidant **5** and the source of the eventual nucleophile acetate i.e. Nu=X in Scheme 1. This also eliminated the issue of compatibility between the nucleophile and the oxidant. DABCO proved to be the best amine in combination with PIDA. Even though DABCO is slowly oxidized by PIDA it was found possible to successfully carry out an umpolung MBH reaction with enones **9**, PIDA and DABCO in which acetate anion originating from PIDA functioned as the nucleophile leading to formation of α-acetoxy-enones **10** (Scheme 2). Compound **10** (R^1=Ph) could be observed by NMR as a clean single product under these conditions. However, purification by flash chromatography on silica gel was found to sometimes lead to low yields of products **10**. This is presumably due to the electron-withdrawing nature of the α-keto enol group. Attempts to hydrolyze the α-acetoxy-enones on purpose by contact with wet silica gel was not fruitful and basic hydrolysis lead to side products including benzoic acids. However, we succeeded in purposely cleaving the acetate to give the free 1,2-diketones **11a** (R^1=Ph) in 74% yield (Scheme 2) on basic alumina which also provided the solid phase for chromatographic purification.



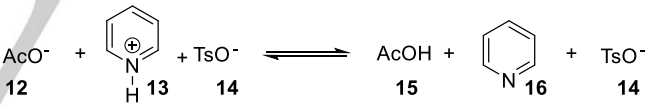
Scheme 2. Umpolung MBH α-acetoxylation and hydrolysis to give 1,2-diketones.

We prepared a number of additional 1,2-diketones to ensure this result was not a chance occurrence before embarking on establishing generality of the concept (Scheme 2). The products, 1,2-dicarbonyl compounds are important intermediates in the synthesis of heterocycles such as pyrazines and quinoxaline that are often found in biologically active substances, cycloadditions and many other transformations.[10]

Both a 4-methyl-phenyl substituent and a naphthyl group as the R^1 group (Scheme 2) were tolerated and the products **11b** and **11c** were isolated in 72% and 78% respectively. A methoxy-substituent in both para and meta position on the phenyl group was also tolerated. The corresponding products **11d** and **11e** were isolated in 78 and 67% yield respectively.

To demonstrate the versatility of the umpolung MBH concept we were interested in testing the reaction of other nucleophiles with enones via ammonium enolonium species **6** (Scheme 1). Using tosylate as the nucleophile would result in the formation of α-tosyl enones. Vinyl tosylates are highly useful reactants in e.g. Kumada-,[11] Heck-,[12] Negishi-,[13] Stille-,[14] Suzuki-,[15] and Sonigashira couplings,[13, 16] as well as C-S, [17] and C-P[18] cross-couplings. However, the preparation of α-tosyloxy enones remains a difficult undertaking.

In addition to address the challenges noted in the introduction, the planned transformation would be troubled by the fact that tosylate anion is a much weaker nucleophile (pKa of toluene sulfonic acid ca. -2.6) than acetate anion (pKa of acetic acid 4.76). Unsurprisingly reaction under the original conditions, but in the presence of different tosylate salts invariably led to formation of α-acetoxy-enones (**10**) as the main product as determined by NMR of the reaction mixtures. Substituting PIDA for Koser's reagent or other Iodine(III) reagents in the presence of tosylate or triflate salts did not lead to formation of the desired α-tosyl-enone product in satisfactory yields. However, it occurred to us that the basicity of acetate anion relative to tosylate anion could be used to overcome the higher nucleophilicity of acetate anion simply by turning it into the less nucleophilic acetic acid by adding a mild Brønsted acid. This we surmised would establish a series of equilibria in which protonation of acetate anion (**12**) by pyridinium salt (**13**) takes place to give acetic acid (**15**) while leaving tosylate anion (**14**) free (Scheme 3). This it was hoped would lead to tosylate acting preferentially in the reaction and afford α-tosyl enones since tosylate anion is a better base/nucleophile than acetic acid.



Scheme 3. Simplified depiction of equilibria between pyridinium (pKa ca 5), acetate anion (**12**, pKa of acetic acid ca. 4.76) which allow tosylate anion **14** (pKa of toluene sulfonic acid ca. -2.8) to be the predominant nucleophile in the reaction shown in Scheme 4.

Indeed, adding pyridinium toluenesulfonate (3.5 equiv) as a combined Brønsted acid and source of tosylate to a mixture of PIDA and enone (17) results in formation of product **18**. The compound **18a** may be observed by NMR as the only product in the reaction (See supporting information). Upon addition of triethylamine as a base, **18a** is quantitatively converted into the desired α-tosyl enone **19a** as shown by NMR. Compound **19a** is isolated in 80% yield. See the supporting information Figure S1 and S2 for the spectra of the reaction mixture containing **18a** and **19a**). Due to the much lower nucleophilicity of triflate (pKa of triflic acid is -14) a 5:4 mixture of α-acetoxy ketone **10** (R_1=Ph) and triflate **19** (R_1=Ph, R^2=H, OTf instead of OTs) resulted when pyridinium triflate was used instead of pyridinium tosylate (See Supporting Information).

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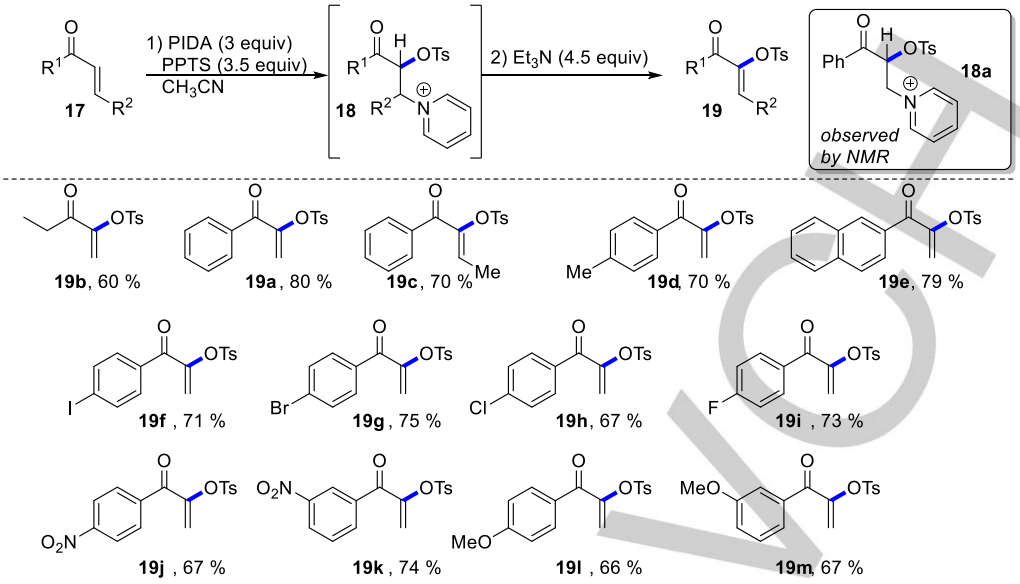
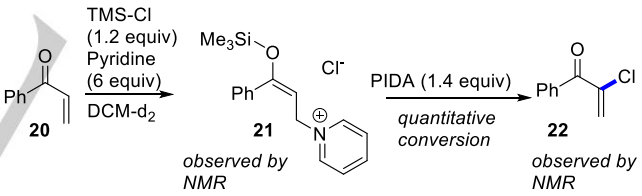


Scheme 4. Umpolung MBH α-sulfonylation. The anion for **18** is presumably tosylate.

The tosylation reaction is not restricted to aryl-enones as α-tosyloxy enone **19b** may be prepared in 60% yield starting from the corresponding enone under the same conditions (Scheme 4). In contrast methyl-vinyl ketone affords mainly the known dimerization product,[3a] In the case of highly hindered *tert*-butyl-vinyl-ketone no reaction takes place at all. These are not limitations inherent only to this specific method, but are well-known general problems of the Morita-Baylis-Hillman reaction of α-substituted vinyl-ketones with amine catalysts.[3a,b] In fact even phenyl vinyl ketones **17a, 17d-m** (i.e. R^1=Ar, R^2=H) can be difficult substrates in the classical Morita-Baylis-Hillman reaction requiring long reactions times and/or cooperative catalysis for successful product formation.[3a, d-f] The more surprising therefore that in this method the alkene function need not be terminal. Thus, methyl-substituted enone **17c** reacts to give **19c** in 70% yield (Scheme 4). As in the reactions shown in Scheme 2, a 4-methyl-phenyl and a naphthyl are compatible with the reaction conditions (Scheme 4). Products **19d** and **19e** encompassing these substituents are isolated in 70% and 79% yield respectively. All the halogen substituted aryl-vinyl ketones are compatible with the reaction conditions as may be gathered from the fact that compounds **19f**, **19g**, **19h** and **19i** can be prepared by this reaction in 67%-73% yield. The strongly electron withdrawing nitro group does not interfere with the reaction either whether in the para or meta position relative to the enone (Scheme 4). Finally, electron-donating methoxy groups are also tolerated with **19l** and **19m** prepared in 66% and 67% yield respectively.

We now had in our hand evidence for formation of two different products of the proposed Umpolung MBH reaction namely acetoxy enone **10** (Scheme 2) and tosyl-enone **19** (Scheme 4). In addition, we had evidence that an intermediate like **7** (Scheme 1) was in the pathway of the formation of **19** in the form of observing compound **18a** and its conversion into **19a** upon addition of base by NMR (Scheme 4, Figure S1 and S2). Delivering evidence for fleeting and highly reactive intermediates like **6** (Scheme 1) would likely be impossible. However, if a stable analogue of **2** could be converted into a Umpolung MBH product **8** (Scheme 1) this would further support the intermediacy of **6**.



Scheme 5. In situ preparation of TMS-trapped MBH intermediate **21** and reaction with PIDA to give α-chloro-enone **22**. Se Figure S3 and S4 for the NMR spectra.

Cazeau *et al.* reported that it is possible to prepare trimethylsilyl enol ethers like **21**, essentially trapped and stable MBH intermediates of type **2** (Scheme 1) by reaction of an enone with trimethylsilyl chloride and pyridine.[19] Thus, we prepared known compound **21**[19] in situ in CD_2Cl_2 and the NMR of the reaction mixture was recorded (Scheme 5 and supporting information). Upon treatment of **21** with PIDA (1.4 equiv) compound **21** was converted quantitatively into known α-chloro-enone **22**[20] as observed by NMR.[21] While this work was in revision a paper[22] by the Wengryniuk group appeared which reports the arylation of substrates like **21** to give ortho-aryl products presumably via the rearrangement reported by Shafir.[23] This further supports the proposed mechanism.

To demonstrate that α-tosyl enones would be substrates for coupling reactions we carried out a preliminary investigation of

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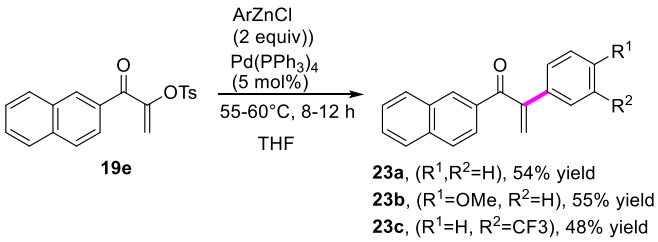
19e in the Negishi coupling reaction using the simplest available catalyst palladium tetrakis(triphenylphosphine) (Scheme 6). Compound **19e** reacted with three electronically different, *in situ* prepared, aryl-zinc reagents to give the coupling products **23a**, **23b** and **23c** in similar yields (Scheme 6). These results show that oxidative addition step works for substrate **19e** even with $Pd(PPh_3)_4$ and thus indicates the potential of substrates **19** in other coupling reactions.[11-17]



Scheme 6. Unoptimized conditions for Negishi coupling of α-tosyl-enones with *in situ* prepared arylzinc reagents with electron donating-, electron withdrawing and neutral substituents.

In summary, we have demonstrated a new reactivity principle in the umpolung of MBH intermediates to form electrophilic ammonium enolonium species (**6**, Scheme 1) allowing reaction with nucleophiles. Intriguingly the umpolung MBH like reaction works well for vinyl-ketones that do not work well in the classical amine catalyzed MBH reaction.[3a] This is possibly due to cooperative assistance of the Lewis acidic hypervalent iodine reagent in the formation of intermediate **6** (Scheme 1).[8] We have demonstrated proof of principle using three nucleophiles, acetate anion, tosylate anion and chloride. Resulting in formation of 1,2-diketones, α-tosyl-enones and a α-chloro-enone. NMR studies underpin the proposed reaction mechanism. Many more applications of this novel concept should be expected in the future.

Acknowledgements

This research was supported by an Israel Science Foundation Individual Science Grant (no 870/19)

Keywords: Umpolung • enones • Ketones • Morita-Baylis-Hillman • Hypervalent iodine

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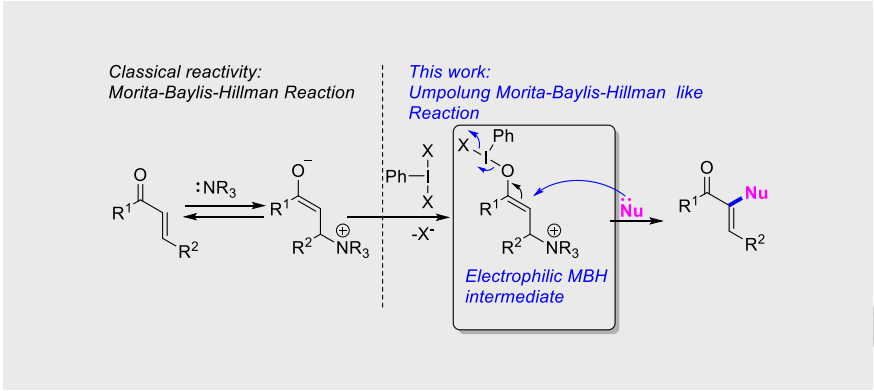

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TEXT for TOC:

The hypervalent iodine reagent PIDA in combination with a nucleophilic amine (DABCO or pyridine) induces α-functionalization of enones with three different nucleophiles. The reaction is proposed to proceed via the Umpolung of Morita-Baylis-Hillman type intermediates. The proposed mechanism is supported by spectroscopic studies that details the conversion of several reaction intermediates into products.