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Transition-Metal-Free α-Arylation of β-Keto Amides via an Interrupted Insertion Reaction of Arynes

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ABSTRACT

Direct α-arylation reactions of secondary β-keto amides with arynes, generated by fluoride-induced elimination of *ortho*-silyl aryltriflates, are described. The transformation proceeds via an interrupted insertion reaction of arynes and leads to densely functionalized aromatic compounds exhibiting a chiral 'all carbon' quaternary center under transition-metal-free conditions. An organocatalytic asymmetric version of the reaction also proved possible, affording the proof of concept that arynes can be involved in enantioselective transformations.

Functionalized aromatic compounds are ubiquitous in drugs and biologically active natural products. The synthesis of functionalized aromatic compounds can traditionally be realized through Friedel–Crafts alkylation reactions with electron-rich substrates.[1] In the past two decades, a complementary approach has been developed with the α-arylation of carbonyl compounds, most often relying on efficient transition-metal catalysts.[2] More recently, several useful metal-free equally efficient organocatalytic systems have also been developed for these transformations.[3] Noncatalyzed nucleophilic additions of enolates (or synthetic equivalents) to electrophilic Bi(V),[4a–c] Pb-(IV),[4d,e] and I(III)[4f,g] aromatic derivatives have also successfully been examined, and recently, the Maulide group reported an interesting sulfoxide mediated α-arylation of carbonyl compounds.[5]

In 2005, the Stoltz group reported their postulate that arynes,[6] gently generated from *ortho*-silyl aryltriflates **1** in

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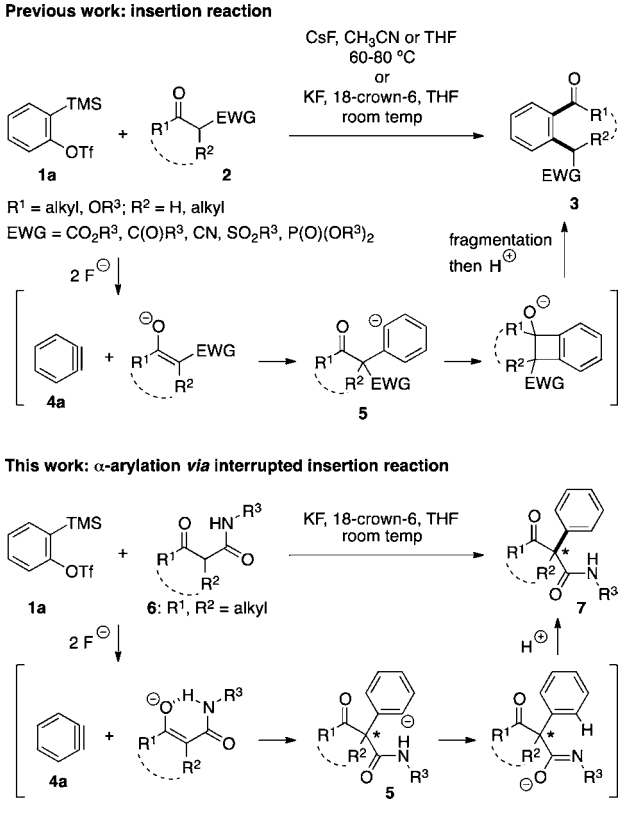
the presence of an excess of nucleophilic fluoride ions,[7] could serve as α-arylation reagents for β-keto esters **2** (R^1 = alkyl, EWG = CO_2R^3). Unexpectedly, their studies have actually shown that benzyne (**4a**, and other arynes **4**) reacts with β-keto esters to give the acyl-alkylation product **3** resulting from a net insertion of a benzene into the α,β-C−C bond of the activated carbonyl compound **2** (Scheme 1, top).[8] This valuable reaction was presumed to proceed via an initial nucleophilic addition of the enolate derived from **2** to benzyne (**4a**) to give the intermediate aryl anion **5**. In the absence of a proton source, **5** rearranges via a formal [2 + 2] cycloaddition/fragmentation sequence to give **3**. Since, the method has been generalized to many activated carbonyl compounds **2**, including 1,3-diesters, 1,3-diketones,[9a] β-keto cyanides,[9b] β-keto sulfones,[9c] β-keto phophonates,[9d] cyanomethyl diphenylphosphine oxide,[9e] malonitrile, and *p*-toluenesulfonyl acetonitrile[9f] (Scheme 1, top). Only in a few cases, minor amounts of the α-arylation product could be detected in these reactions.

Scheme 1. Reactions of 1,3-Dicarbonyls with Arynes: State of the Art and Novelty



Our research program on the stereocontrolled creation of chiral 'all carbon' quaternary centers[10] has recently allowed the identification of secondary β-keto amides **6**[11] as a very promising class of pronucleophiles.[12] The particularity of these substrates is that they exhibit two distinct acidic protons: the C−H proton at the α-position and the N−H proton of the secondary amide group. Capitalizing on Stoltz's original idea, we surmised that this particular class of substrates would actually be suitable for an efficient net α-arylation reaction. This plan relied on the rapid transfer of the secondary amide N−H proton to the transient intermediate aryl anion **5**, thereby interrupting the normal insertion reaction of arynes with 1,3-dicarbonyls and analogs (Scheme 1, bottom). Related intramolecular proton transfers were postulated in the *C*-arylation of β-enamino esters and ketones with arynes.[13] Very recently, the Mhaske group independently reported the α-arylation of malonamide esters with arynes,[14] and this article has triggered the report of our own results in this field.

We report herein direct α-arylation reactions of rationally designed secondary β-keto amides with arynes generated by fluoride-induced elimination of *ortho*-silyl aryltriflates. The transformation leads to densely functionalized aromatic compounds exhibiting a chiral 'all carbon' quaternary center under transition-metal-free conditions. Importantly, the proof of concept for such an asymmetric organocatalytic direct arylation has been obtained, which represents the first enantioselective reaction with an aryne.

Based on our background, we presumed that *N*-aryl secondary β-keto amides would be the most suitable substrates for our objective because of the significantly higher acidity of their N−H protons when compared to *N*-alkyl secondary β-keto amides.[12] Our first attempt involved the reaction of the simple *N*-phenyl secondary β-keto amide **6a**, using the KF/18-crown-6 system in THF for the generation of benzyne (**4a**) from 2-(trimethylsilyl)phenyl triflate (**1a**). Rewardingly, the

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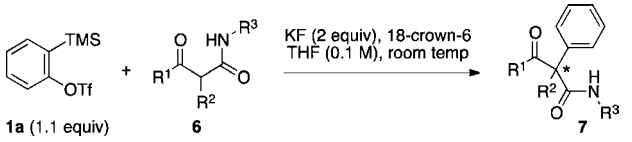
reaction provided, after hydrolysis, the expected α-arylation product **7a** in 82% yield (Table 1, entry 1). The scope of the reaction was then evaluated under these fine conditions with a variety of secondary β-keto amides **6b**−**r**, and as can be seen from Table 1, the reaction was found to be very general, allowing for the efficient α-arylation of a number of secondary β-keto amides **6**. The reaction was not significantly influenced by the nature of the amide, tolerating various cyclic and acyclic substrates, with the R^3 aryl group nicely allowing electron-withdrawing (e.g., entries 4, 5, and 8), -neutral (e.g., entries 1, 2, and 11), and -donor substituents (e.g., entries 10 and 13), amenable to further selective chemical manipulation. The structure of the α-arylation product **7b** was secured by X-ray diffraction analysis (Figure 1). However, when the reaction was performed with the *N*-alkyl secondary β-keto amides **6q,r** (entries 17 and 18), somewhat lower yields of the α-arylation products were observed. Especially, in the reaction of **6r**, bearing an electron-donor *tert*-butyl substituent, the benzene insertion side-product **3r** was obtained in 36% yield together with the expected α-arylation product **7r** (entry 18; see Supporting Information). This limit of reactivity is presumed to reflect the lower acidity of the N−H proton in this substrate,[12] resulting in a less efficient interruption of the insertion reaction.

Table 1. Arylation of Secondary β-Keto Amides with Benzyne



entry	6	R^1, R^2	R^3	7, yield[a]
1	**6a**	$CH_2C(CH_3)_2CH_2$	C_6H_5	**7a**, 82%
2	**6b**	$CH_2C(CH_3)_2CH_2$	4-H_3C-C_6H_4	**7b**, 78%
3	**6c**	$CH_2C(CH_3)_2CH_2$	2,4,6-$(H_3C)_3$-C_6H_2	**7c**, 90%
4	**6d**	$CH_2C(CH_3)_2CH_2$	4-O_2N-C_6H_4	**7d**, 92%
5	**6e**	$CH_2C(CH_3)_2CH_2$	4-F_3C-C_6H_4	**7e**, 80%
6	**6f**	$CH_2C(CH_3)_2CH_2$	4-Br-C_6H_4	**7f**, 95%
7	**6g**	$CH_2C(CH_3)_2CH_2$	2-Br-C_6H_4	**7g**, 78%
8	**6h**	$CH_2C(CH_3)_2CH_2$	4-F-C_6H_4	**7h**, 88%
9	**6i**	$CH_2C(CH_3)_2CH_2$	2-I-C_6H_4	**7i**, 74%
10	**6j**	$CH_2C(CH_3)_2CH_2$	2-H_3CO-C_6H_4	**7j**, 83%
11	**6k**	$CH_2C(CH_3)_2CH_2$	2-naphthyl	**7k**, 87%
12	**6l**	$(CH_2)_3$	4-Br-C_6H_4	**7l**, 92%
13	**6m**	$(CH_2)_3$	3,5-$(H_3CO)_2$-C_6H_3	**7m**, 82%
14	**6n**	$(CH_2)_4$	4-Br-C_6H_4	**7n**, 82%
15	**6o**	CH_3, CH_3	4-F-C_6H_4	**7o**, 74%
16	**6p**	CH_3, CH_3	4-Br-C_6H_4	**7p**, 92%
17	**6q**	$CH_2C(CH_3)_2CH_2$	allyl	**7q**, 68%
18	**6r**	$CH_2C(CH_3)_2CH_2$	*t*-Bu	**7r**, 32%[b]

[a] Isolated pure product obtained after chromatographic purification. [b] In that case, 36% of the benzene insertion side-product **3r** were additionally isolated.

Also, the regioselectivity issue of the reaction was examined with 1,2-naphthalyne generated from 1-trimethylsilyl naphthalen-2-yl triflate (**1b**).[15] The illustrative reaction of **6f** with **1b** pleasingly afforded the expected α-arylation product **7s** in high yield and with excellent regioselectivity (the other regioisomer was not detected, Scheme 2).

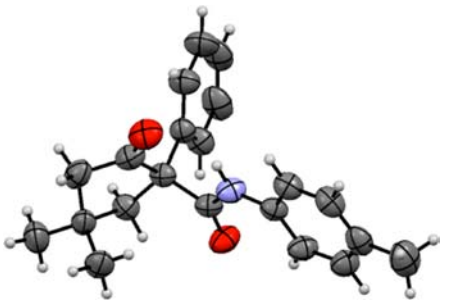
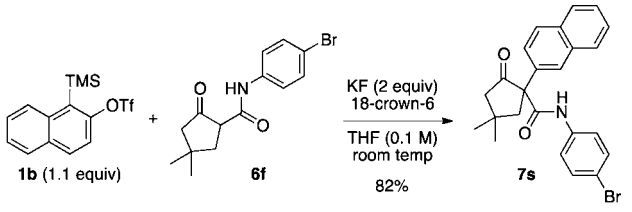


Figure 1. Structure of **7b** by X-ray diffraction analysis. Ellipsoids are drawn at the 50% probability level, and hydrogen atoms are represented as fixed-size spheres of radius 0.15 Å. See Supporting Information for details.

Scheme 2. Regioselective α-Arylation



Finally, we briefly tested the possibility of performing the above-described α-arylation reactions in the asymmetric series. For our early trials, we selected the bifunctional *N*-aryl thiourea/tertiary amine catalyst **8** described by Takemoto,[16] a catalyst that operates *via* noncovalent interactions. In the model reaction of **1a** with **6d** using the previously developed conditions in the presence of 10 mol % of the organocatalyst **8**, the product **7d** was obtained in good yield but without any detectable enantioselectivity (Table 2, entry 1), and a similar result was obtained at lower temperature (entry 2). However, using cesium fluoride or tetra-*n*-butyl ammonium fluoride as the fluoride anion source, some encouraging enantioselectivities could be observed in the α-arylation reaction of **6d** (entries 3 and 4, respectively). These preliminary results importantly demonstrate that, for the first time, asymmetric reactions of arynes are possible.

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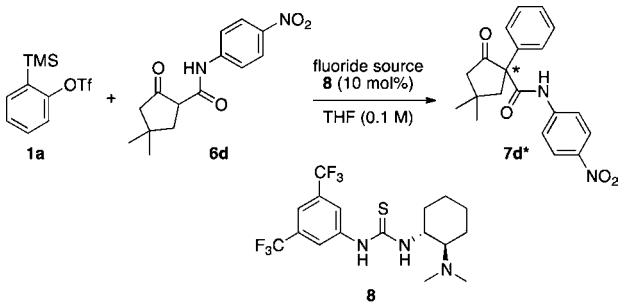
(16) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.

Table 2. Enantioselective Organocatalytic α-Arylation



entry	fluoride source	temp	yield[a]	ee **7d**[b]
1	KF, 18-crown-6rt	rt	92%	0%
2	KF, 18-crown-6	0 °C	82%	0%
3	CsF	rt	85%	12%
4	TBAF	rt	76%	21%

[a] Isolated pure product obtained after chromatographic purification. [b] Determined by HPLC on chiral stationary phase from the enantiomeric ratio.

In conclusion, a transition-metal-free direct and practical α-arylation reaction of secondary β-keto amides with arynes has been developed that leads to densely functionalized chiral 'all carbon' quaternary centers. From a mechanistic point of view, this reaction interrupts the normal insertion reactivity of arynes with 1,3-dicarbonyls, likely due to the acidic properties of the N−H protons of secondary β-keto amides. Unprecedentedly, a highly regioselective version of the reaction proved possible with a nonsymmetrical aryne, and importantly, the feasibility of an organocatalytic asymmetric version could be evidenced with a bifunctional thiourea/tertiary amine catalyst. The reactivity of arynes described herein opens up new opportunities for their applications in organic synthesis, and further studies on this exciting reaction are ongoing in our laboratory.

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Supporting Information Available. full experimental details, CIF for **7b**, and characterization data for all compounds.This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.